


Cutaneous metastases of internal malignancies: a single-institution experience

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Cutaneous metastases of internal malignancies: a single-institution experience

Aims: Cutaneous metastases of internal malignancies occur in 1–10% of cancer patients. The diagnosis can sometimes be challenging, especially in cases with an unknown primary cancer.

Materials and methods: A retrospective case review was performed including all cases of skin metastases from primary internal malignancies diagnosed at the Department of Pathology at the Maastricht University Medical Centre+ from 2007 to 2021. The clinicopathological data were collected and immunohistochemical and molecular diagnostic tests were performed to confirm the primary origin of the metastases.

Results: We identified 152 cases (71 female; 31 male patients) of cutaneous metastases of internal malignancies. 28 patients (20 women and 8 men) were diagnosed with multiple cutaneous metastases. Among the female patients, the most common primary tumour was breast cancer (50% of the cases), followed by lung (13.6%), gynaecological (7.3%), and

gastrointestinal origin (7.3%). Among the male patients, the most common primary sites were gastrointestinal and lung origin (altogether, 50% of the cases). In 19 patients, the cutaneous metastasis was the first presentation of a clinically silent internal malignancy (18.6%), of which most (78.9%) represented metastatic lung carcinomas. Finally, metastasizing patterns were different across tumour types and gender.

Conclusion: Breast, lung, gastrointestinal, and gynaecologic cancers are the most common primary tumours demonstrating skin metastases. Infrequently, cutaneous metastases can be the first clinically visual manifestation of an underlying not yet diagnosed internal malignancy; therefore, occasional broad immunohistochemical profiling, molecular clonal analysis, and a continuous high level of awareness are necessary for a precise diagnosis of cutaneous metastases of internal malignancies.

Keywords: breast, colon, cutaneous metastasis, internal malignancy, lung, skin

Introduction

The skin is the largest organ of the human body, with a total area of approximately two square meters.

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It has a unique medical significance because of cutaneous manifestations of numerous systemic conditions.^{1,2} Skin metastases represent a challenging issue in clinical practice, since their detection demands a high level of clinical suspicion.³ Moreover, the distinction between a primary skin carcinoma and a metastatic adenocarcinoma of a primary breast, lung, or other origins can be challenging.⁴

Skin metastases can be divided into three different groups.⁵ The first and largest group represents

cutaneous metastases originating from primary cutaneous malignant tumours, such as primary skin melanoma, squamous cell carcinoma, Merkel cell carcinoma, and adnexal carcinomas. The second group is the metastases of internal malignancies.^{6–8} The last group is manifestations of systemic haematological neoplasms (leukaemia and lymphomas) in the skin. Since skin metastases reflect systemic dissemination of a primary malignancy, they are associated with poor prognosis.⁹ In rare cases thus diagnostically challenging—cutaneous metastases can be the first presentation of an internal malignancy, which occurs in 1% to 10% of cancer patients in published studies, depending on the inclusion criteria.¹⁰

Despite case reports, small case series, and review articles having already been published, only a few cohort studies have been presented in the literature concerning this topic. This study aims to evaluate the clinicopathological features of cutaneous metastases of internal neoplasms, diagnosed in the Department of Pathology of an academic hospital, and to examine the diagnostic challenges.

Materials and Methods

CASE SELECTION

In this retrospective single-centre cohort study, histopathological specimens and clinicopathological data over a period of 15 years were collected from the archive of the Department of Pathology, Maastricht University Medical Centre+ (MUMC+), Maastricht, the Netherlands. The collected clinical data included age and gender, location of the skin metastasis, and the interval between diagnosis of the primary tumour and the skin metastasis. All histological and immunohistochemical slides were independently reviewed by at least two experienced pathologists (A.V., X.L., V.W., I.S.).

The study was approved by the Medical Ethics Review Committee of the MUMC+ (METC-number: 301320). All tissue samples were collected and studied according to the protocol of the Dutch Code of Conduct for Observational Research with Personal Data (2004) and Tissue.¹¹

Only skin metastases of internal organ malignancies were included in this study. Therefore, skin metastases from primary cutaneous tumours, direct tumour invasion, and skin metastases in the postoperative surgical scar were excluded from this study. Systemic haematological neoplasms (leukaemia and lymphomas) and sarcomas extending secondarily to the skin were included if a primary cutaneous haematological neoplasms or sarcoma was excluded.

The skin specimens included biopsies and excisions, reaching the dermis and/or subcutis.

Cutaneous metastases of nonlymphoproliferative neoplasms were classified into locoregional and distant metastases. The definitions used of locoregional metastases per organ (system) are described in Table 1. These definitions were based on the anatomical features, regional lymph nodes, and previously published data.^{9,12–14}

IMMUNOHISTOCHEMISTRY AND MOLECULAR DIAGNOSTICS

Immunohistochemistry (IHC) was performed on 4- μ m thick, buffered formaldehyde 4%-fixed, paraffin-embedded tissue sections. A list of the used primary

Table 1. Definitions of locoregional cutaneous metastases

Primary tumour	Locoregional metastasis
Breast	<ul style="list-style-type: none"> • Ipsilateral axilla • Ipsilateral anterior chest wall (inferior to the clavicle, lateral to the sternal midline, medial to the midaxillary line, and superior to the costodiaphragmatic angle) • Presternal skin
Lung	<ul style="list-style-type: none"> • Ipsilateral anterior chest wall (see above) • Ipsilateral posterior suprascapular region
Colorectum, stomach, liver	<ul style="list-style-type: none"> • Anterior abdominal wall (inferior to the costodiaphragmatic angle, including epigastric, umbilical, hypogastric regions, and bilateral lumbar and iliac regions)
Pancreas	<ul style="list-style-type: none"> • Anterior abdominal wall (see above)
Oesophagus	<ul style="list-style-type: none"> • Bilateral anterior chest wall (see above) • Epigastric abdominal wall
Sinonasal space, salivary gland, oral cavity	<ul style="list-style-type: none"> • Face, excluding scalp • Neck
Oropharynx, larynx, thyroid	<ul style="list-style-type: none"> • Neck
Retroperitoneal / intra-abdominal sarcoma	<ul style="list-style-type: none"> • Anterior abdominal wall (see above) • Subdiaphragmatic dorsum
Kidney	<ul style="list-style-type: none"> • Ipsilateral posterior and anterior lumbar region
Urinary bladder and gynaecologic system	<ul style="list-style-type: none"> • Anterior abdominal wall (see above) • Groin

antibodies is shown in Supplementary Table S1. The identification of the primary tumour origin was based on an IHC evaluation (Table S2). Detection of primary antibodies was carried out in the DAKO automatic immunostainer (Agilent Technologies, Palo Alto, CA, USA) using the avidin-biotin peroxidase technique and diaminobenzidine as chromogen according to the manufacturer's protocol (DAB Detection Kit; DAKO, Agilent Technologies).

According to the guidelines,^{15,16} analysis of ERBB2 *HER2/NEU* gene copy number by FISH was performed in metastatic breast carcinomas, following the manufacturer's instructions (Pathvision, Abbott Molecular, Abbott Park, IL, USA). In some cases, the molecular clonal analysis, including either loss of heterozygosity analysis (LOH) or targeted next-generation sequencing (NGS) DNA analysis (Illumina, San Diego, CA, USA), was performed. The data on the patient's medical history was available via the Dutch National Pathology Registry (PALGA).¹⁷

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS Statistic 27 (IBM, Armonk, NY, USA). The *P*-values were calculated using Pearson chi-square (χ^2) test and Fisher's exact test. Results are reported as mean and range. Statistical significance was considered if $P \leq 0.05$.

Results

Of the 75,686 skin biopsy and small resection specimens registered in the database of the Department of Pathology, 152 cases (0.2%) were cutaneous metastases of internal malignancy, obtained from 71 women and 31 men with a mean age of 68.5 years (range, 29 to 95 years). 28 patients (20 women and 8 men) were diagnosed with multiple cutaneous metastases during the follow-up period.

Histological evaluation revealed that all skin metastases were located in the dermis and subcutis. None of them showed epidermotropism. The skin appendages were spared in all cases.

PRIMARY ORIGIN OF CUTANEOUS METASTASES IN MEN AND WOMEN

The mean age of the 31 male patients was 71.5 years (range 29–95 years) and included 42 cases of cutaneous metastases. The mean age of the 71 women was 67 years (range 42–94 years). This group covered 110 cases of cutaneous metastases

(Table 2). Eight male patients (25.8%) and 20 female patients (28.2%) were diagnosed with multiple cutaneous metastases. In men, the most common primary site was the gastrointestinal tract (29.0%; 9/31 patients), followed by lung (25.8%; 8/31 patients), head and neck (including thyroid) (9.7%; 3/31 patients), and urinary system (9.7%; 3/31 patients). The most common primary origin in women was the breast (47.9%; 34/71 patients), followed by lung (18.3%; 13/71 patients), gynaecological malignancy (8.5%; 6/71 patients), head and neck (including thyroid) (8.5%; 6/71 patients), and gastrointestinal tract (7.0%; 5/71 patients).

Breast carcinomas were the most prevalent primary tumour in women, compared to men ($P < 0.001$). In contrast, in men cutaneous metastases originated more often from the gastrointestinal tract or haematolymphoid neoplasms, compared to women ($P < 0.01$). However, when eliminating the breast cases from the statistical analysis, the differences in primaries between men and women failed to reach statistical significance.

In nine male (9/31; 29.0%) and ten female patients (10/71; 14.1%), the cutaneous metastases were the first sign of a yet-unknown internal malignancy. The histopathological and clinical data of these patients ($n = 24$ cases) are presented in Table 3.

GASTROINTESTINAL TRACT TUMOURS

Cutaneous metastases of gastrointestinal tract tumours (Figure 1) were identified in 14 patients (13.7%; 14/102 patients, including nine men and five women) (Table 2). The primary sites included mostly the colorectum, followed by the oesophagus, stomach, pancreas, and liver. The most common sites for skin metastases in this group were head/scalp (31.6%; 6/19 cases), abdomen (26.3%; 5/19 cases), umbilicus (15.8%; 3/19 cases), and groin/perineum (15.8%; 3/19 cases). All cutaneous metastases of colorectal carcinoma expressed CK20 (6/6 tested cases) and CDX2 (5/5 tested cases), whereas only one was positive for CK7 (1/5 tested cases). Both cases of metastatic pancreatic adenocarcinomas showed strong immunoreactivity for CK7 and weak positivity for CK20 and CDX2.

BREAST TUMOURS

Breast carcinoma was the most frequent primary cancer, associated with skin metastasis in our cohort of female patients (Table 2). One male patient presented with two cutaneous metastases of breast carcinoma.

Table 2. Cutaneous metastases in 102 patients (number of specimens = 152)

Primary tumour	Number of cases (%) in men (n = 42)	Number of cases (%) in females (n = 110)	P-value (Pearson χ^2)	Site of the skin metastasis (number of specimens)	Primary diagnosis (number of specimens)	Interval time (mean, [range], months)
Breast	2 (4.8)	55 (50.0)	<0.001* (26.540)	Anterior chest wall (32); Dorsum (8); Axilla (4); Abdomen (3); Head/scalp (2); Neck (2); Arm/hand (2); Groin/perineum (1); Unknown (3)	Invasive carcinoma NST (32); Invasive lobular carcinoma (23)	124.9 [1–348] ¹
Lung	10 (23.8)	15 (13.6)	0.13 (2.289)	Head/scalp (7); Anterior chest wall (6); Dorsum (3); Groin/perineum (2); Arm/hand (2); Neck (1); Leg (1); Abdomen (1); Unknown (2)	Adenocarcinoma (18); Atypical carcinoid (4); Small cell carcinoma (2); Large cell NEC (1)	16.5 [1–60] ^{1,2}
Gastrointestinal tract	11 (26.2)	8 (7.3)	0.002* (9.945)	-	-	43.9 [1–156] ^{1,2}
Colorectum	7 (16.7)	4 (3.6)	-	Groin/perineum (3); Abdomen (3); Head/scalp (2); Umbilicus (2); Leg (1)	Intestinal type adenocarcinoma (11)	-
Oesophagus	2 (4.8)	0 (0)	-	Abdomen (2)	Intestinal type adenocarcinoma (2)	-
Stomach	0 (0)	3 (2.7)	-	Head/scalp (3)	Adenocarcinoma (Lauren: intestinal type – WHO: tubular type) (3)	-
Pancreas	2 (4.8)	0 (0)	-	Head/scalp (1); Umbilicus (1)	Ductal adenocarcinoma (2)	-
Liver	0 (0)	1 (0.9)	-	Dorsum (1)	Cholangiocarcinoma (1)	-
Gynaecologic system	0 (0)	8 (7.3)	NA	Abdomen (4); Umbilicus (3); Unknown (1)	(Extra)ovarian high grade serous adenocarcinoma (5); Carcinosarcoma (2); (Extra)ovarian endometrioid adenocarcinoma (1)	43.4 [1–295] ¹
Head and neck	3 (7.1)	17 (15.5)	0.175 (1.838)	-	-	39.0 [1–212] ¹
Sinonasal space	1 (2.4)	0 (0)	-	Axilla (1)	Intestinal type adenocarcinoma (1)	-
Larynx	1 (2.4)	0 (0)	-	Abdomen (1)	Neuroendocrine carcinoma (1)	-
Oropharynx	0 (0)	1 (0.9)	-	Arm/hand (1)	HPV-related SCC (1)	-
Salivary gland (parotitis)	1 (2.4)	2 (1.8)	-	Head/scalp (2); Neck (1)	Epithelial-myoepithelial carcinoma (2); Poorly differentiated carcinoma (1)	-

Table 2. (Continued)

Primary tumour	Number of cases (%) in men (n = 42)	Number of cases (%) in females (n = 110)	P-value (Pearson χ^2)	Site of the skin metastasis (number of specimens)	Primary diagnosis (number of specimens)	Interval time (mean, [range], months)
Oral cavity	0 (0)	9 (8.2)	-	Head/scalp (4); Dorsum (3); Anterior chest wall (1); Unknown (1)	Mucoepidermoid carcinoma (8); SCC (1)	-
Thyroid	0 (0)	5 (4.5)	-	Neck (3); Anterior chest wall (1); Dorsum (1)	Follicular carcinoma (4); Papillary carcinoma (1)	-
Urinary system	3 (7.1)	2 (1.8)	0.130 ³	-	-	87.8 [24–132]
Kidney	2 (4.8)	2 (1.8)	-	Head/scalp (1); Abdomen (1); Dorsum (1); Arm/hand (1)	Clear cell RCC (3); Papillary RCC (1)	-
Urinary bladder	1 (2.4)	0 (0)	-	Dorsum (1)	Poorly differentiated UCC (1)	-
Sarcoma	3 (7.1)	3 (2.7)	0.348 ³	Head/scalp (4); Abdomen (1); Dorsum (1)	High grade leiomyosarcoma (6) of the intra-abdominal region/retroperitoneum	49.7 [17–116]
Haematopoietic system	6 (14.3)	2 (1.8)	0.006 ^{3*}	Dorsum (3); Neck (1); Leg (1); Abdomen (1); Groin/perineum (1); Arm/hand (1)	DLBCL (3); Systemic follicular lymphoma (2); ALCL, ALK positive (2); Plasmacytoma (1)	54.3 [1–216] ^{1,2}
Unknown	4 (9.5)	0 (0)	NA	Head/scalp (3); Neck (1)	Poorly differentiated carcinoma (4)	-

ALCL: anaplastic large cell lymphoma; DLBCL: diffuse large B-cell lymphoma; NA: not assessed; NEC: neuroendocrine carcinoma; NST: no special type; RCC: renal cell carcinoma; SCC: squamous cell carcinoma; UCC: urothelial cell carcinoma; WHO: World Health Organization.

¹Some skin metastases were synchronous with the primary tumour.

²In one or several of the patients the skin metastasis was the first presentation of primary tumour.

³These P-values were calculated Fisher's exact test. The other P-values were calculated using Pearson's χ^2 -test.

*The P-value is significant (<0.05).

Of the total 57 cases, 32 were cutaneous metastases to the anterior chest wall (56.1%), exclusively identified in women. Twenty-one of these anterior chest wall metastases were ipsilateral, five contralateral, four on the midline (presteral), and in the remaining two cases comparison was not possible. In all, 58.2% of the cases were metastases of an invasive breast carcinoma of no special type (NST) (Figure 2A), followed by invasive lobular carcinoma (41.8%) (Figure 2B). The metastases showed retained expression of the oestrogen receptor in 44/44 tested cases and of the progesterone receptor in 19/44 tested cases, as compared with the hormone receptor status of the primary tumour (data not shown). *HER2/neu* amplification by FISH was identified in 7/41 tested cases and gain in HER2 receptor expression was present in two of the tested cases (7.7%; 2/26).

LUNG TUMOURS

Cutaneous metastasis of lung carcinoma was diagnosed in 21 patients (13 women and 8 men; with 25 cases) and was the second most frequent type of cutaneous metastases in both men and women. Lung cancer was also the most frequent primary neoplasm in which the cutaneous metastasis was the first sign of malignancy (71.42%; 15/21 patients; Table 3). The most common sites for skin metastases were head/scalp (28.0%; 7/25 cases) and anterior chest wall (24.0%; 6/25 cases). The majority of the cases were classified as adenocarcinoma (16 patients) (Figure 3A,B). The other cases were atypical carcinoids (two patients) (Figure 3C,D); small cell carcinomas (two patients); and large cell neuroendocrine carcinomas (one patient). Interestingly, TTF1 was negative in 50% of the metastatic lung adenocarcinomas, and even in 63.6% if the cutaneous metastasis was diagnosed prior to the primary tumour, while CK7 was expressed in almost all tested cases (93.3%; 14/15 tested cases). A mutation in *KRAS* was found in 50% of metastases (6/12 tested cases). None of the cases had an *EGFR* mutation.

ANATOMIC PATTERNS OF CUTANEOUS METASTASES IN MEN AND WOMEN

The anatomic patterns of cutaneous metastases were significantly different between men and women (Table 4, Figure 4). In men, the most common location for the cutaneous metastases was head/scalp (31.0% of the cases), followed by the abdominal wall (16.7%) and dorsum (11.9%). In women, the most common location was the anterior chest wall (34.5%

of the cases), followed by the dorsum (15.5%), head/scalp (13.6%), and abdominal wall (9.1%). These differences could be explained by the prevalence of metastatic breast cancer in women. Interestingly, skin metastases in the umbilicus were associated with gastrointestinal tumours in men and gynaecological malignancy in women. The distant metastases of the nonlymphoproliferative neoplasms were seen in 63.9% (23/36 cases) in men and 42.6% (46/108 cases) in women. The locoregional metastases comprised 25.0% (9/36 cases) in men and 46.3% (50/108 cases) in women. Male patients had a significantly higher relative prevalence of distant metastases compared to female patients ($\chi^2 = 5.544$; $P = 0.019$).

Discussion

Despite cutaneous metastases of internal malignancies being infrequent, they may represent a diagnostic challenge, especially if a primary tumour did not manifest clinically at the time of cutaneous presentation.^{3,10} The results of our study show that breast carcinoma, lung carcinoma, and gynaecological and gastrointestinal tumours are the most common primary tumours of the cutaneous metastases in women. Lung carcinoma and gastrointestinal tumours are the most frequent source for skin metastases in men. The anatomic patterns of cutaneous metastases were different between men and women, which is mainly explained by the high number of metastatic breast carcinoma in female patients. Moreover, in 18.6% of the patients the cutaneous metastasis was the first presentation of a yet clinically silent primary malignancy, of which almost 80% appeared to be lung tumours.

Our findings are in line with previously published data.^{8,13,18–20} However, metastases of breast carcinomas were less frequent in our study (50% of the cases in women) compared to other studies (ranging 62.5%–70%).^{8,13,18–20} This difference may be due to the Dutch screening program for breast carcinoma.^{21,22} Almost 42% of the breast cutaneous metastases were invasive lobular carcinomas, although they comprise only 5%–10% of the breast carcinomas.^{23,24} Expression of hormone receptors in breast carcinomas has been shown to change in the course of metastasising.²⁵ In our study, all tested cases retained the expression of the oestrogen receptor, but almost 48% lost expression of the progesterone receptor. In two meta-analyses, up to 49.4%^{15,16} of the metastases had a loss of progesterone receptor expression and up to 23%^{15,16} loss of oestrogen receptor expression. The gain in HER2

Table 3. Histopathological and clinical data of the 19 patients with primary tumour diagnosed subsequent to cutaneous metastasis ($n = 24$ specimens)

Patient	Gender (M = male; F = female), age (years)	Site of the skin metastasis (number of specimens)	Type of malignancy	Primary tumour site	Relevant IHC and molecular results (+ = positive staining; - = negative staining)	Relevant additional data
#1	M, 72	Anterior chest wall (1)	Poorly differentiated adenocarcinoma	Lung	TTF1- , CK7+ , CK20-, CDX2- NGS: <i>KRAS</i> mutation.	MRI: mass-forming lesion in the upper lobe of the right lung.
#2	M, 75	Neck (1), Leg (1)	Poorly differentiated adenocarcinoma	Lung	TTF1- , CK7+ , CK20-, CDX2-, CK19+, PSA-, PAX8-, GCDFP15- <i>HER2/neu</i> FISH: <i>Her2/neu</i> amplification	MRI: mass-forming lesion in the upper lobe of the right lung.
#3	F, 60	Abdomen (1)	Adenocarcinoma	Lung	TTF1- , CK7+ , CK20-, CDX2+ (weak), Napsin A-, CKAE1/AE3+, PAX8- NGS: <i>KRAS</i> mutation	MRI: mass-forming lesion in the upper lobe of the left lung.
#4	F, 59	Head/scalp (1)	Adenocarcinoma	Lung	TTF1- , CK7+ , GATA3-, hormone receptors- NGS: <i>KRAS</i> mutation	MRI: mass-forming lesion in the upper lobe of the right lung.
#5	F, 82	Anterior chest wall (1)	Adenocarcinoma	Lung	TTF1- , CK7+ , CK20-, CDX2+ (weak), Napsin-A+, GCDFP-, PAX8-, hormone receptors-	MRI: mass-forming lesion in the upper lobe of the left lung.
#6	F, 42	Unknown (1)	Adenocarcinoma	Lung	TTF1- , CK7+ , CK20-, hormone receptors-, <i>EGFR</i> FISH: <i>EGFR</i> amplification	MRI: mass-forming lesion in the lower lobe of the left lung.
#7	M, 83	Groin/perineum (1)	Poorly differentiated carcinoma	Lung	TTF1- , CK7- , CK20-, CDX2-, Napsin A-, CKAE1/AE3+, CK5/6-	MRI: mass-forming lesion in the upper lobe of the right lung.
#8	M, 63	Anterior chest wall (1)	Adenocarcinoma	Lung	TTF1+ , CK7+ , CK20-, CDX2-, Thyroglobulin-	MRI: mass-forming lesion in the left lung lingula.
#9	M, 83	Arm/hand (1)	Adenocarcinoma	Lung	TTF1+ , CK7+ , CK20+, CDX2-, PSA-	MRI: no primary tumour in any organs
#10	F, 67	Anterior chest wall (1)	Adenocarcinoma	Lung	TTF1+ , CK19+, hormone receptors-, PAX8- NGS: <i>BRAF</i> and <i>TP53</i> mutation	MRI: mass-forming lesion in the upper lobe of the right lung.
#11	F, 47	Anterior chest wall (1)	Adenocarcinoma	Lung	TTF1+ , CK7+ , CK20-, Thyroglobulin-, hormone receptors-	No further clinical data on primary tumour.

Table 3. (Continued)

Patient	Gender (M = male; F = female), age (years)	Site of the skin metastasis (number of specimens)	Type of malignancy	Primary tumour site	Relevant IHC and molecular results (+ = positive staining; - = negative staining)	Relevant additional data
#12	M, 49	Head/scalp (2)	Atypical carcinoid	Lung	Neuroendocrine markers+, TTF1+, CK7+, Calcitonin-	MRI: mass-forming lesion in the upper lobe of the right lung.
#13	F, 51	Dorsum (1)	Atypical carcinoid	Lung	Neuroendocrine markers+, TTF1+, CK7-, CKAE1/AE3+, CK20-	
#14	F, 66	Head/scalp (1)	Small cell neuroendocrine carcinoma	Lung	Neuroendocrine markers+, TTF1+, CK7-, CKAE1/AE3+	
#15	M, 63	Groin/perineum (1)	Large cell neuroendocrine carcinoma	Lung	Neuroendocrine markers+, TTF1+, CK20-, CKAE1/ AE3+	MRI: mass-forming lesion in the middle lobe of the right lung.
#16	M, 73	Umbilicus (1)	Adenocarcinoma	Pancreas	CK7+, TTF1- , CDX2+ , PSA-	MRI abdomen: pancreatic mass. Colonoscopy: no GI tumour.
#17	F, 60	Groin/perineum (1)	Lymphoma	Systemic DLBCL	No MYC or BCL2 gene rearrangement	Clinically multiple pathologic lymph nodes
#18	F, 74	Hand/arm (1)	Lymphoma	Systemic follicular B cell lymphoma	BCL2 gene rearrangement	
#19	M, 79	Head/scalp (3), neck (1)	Poorly differentiated carcinoma	Unknown	CK7+, TTF1- , CK20-, CDX2-, BerEP4+, GATA3+, EMA+, neuroendocrine markers-, hormone receptors-, CEA-, S100-, CD117-, p40-, PSA-, PAX8- Molecular clonal analysis: very probable clonal relation between skin lesions and the lesion in parotid. NGS: Mutations in <i>AKT3</i> , <i>BRAF</i> , <i>KRAS</i> and <i>TP53</i> .	Clinically multiple skin lesions and a lesion in a parotid gland. No other tumour detected by MRI.

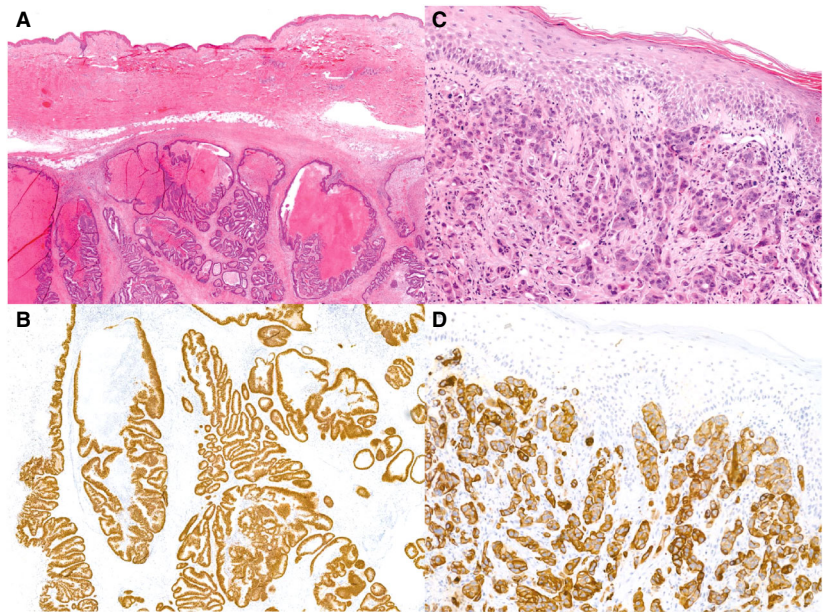
DLBCL: diffuse large B-cell lymphoma; IHC: immunohistochemistry; NGS: next-generation sequencing.

receptor expression was present in our study in two of the tested cases (7.7%; 2/26), comparable to the previously published study.^{12,16} This stresses again the importance of redetermination of the hormone receptor status in case of a metastasis.^{15,16}

According to the literature, most skin metastases are locoregional.^{9,10,12–14,18} However, in our study,

in the male patients, more than 60% were distant metastases. In women, almost half of the cutaneous metastases were locoregional. This difference was statistically significant and could be attributed to the frequent locoregional skin metastases of breast carcinomas in women, which is in concordance with other studies.¹² The lymphatic system in the breast,

Figure 1. Microscopic pictures of two cutaneous metastases of the gastrointestinal tract. A and B: Cutaneous metastasis of a colonic adenocarcinoma (A: Haematoxylin-eosin stain, 10× magnification; B: CDX2 immunohistochemistry, 20× magnification). C and D: Cutaneous metastasis of a pancreatic adenocarcinoma (C: Haematoxylin-eosin, 100× magnification; D: CK7 immunohistochemistry, 100× magnification).



which makes connections to the axillary, parasternal, intercostal, and clavicular lymph nodes and their respective dermal lymphatic vessels can probably be accounted for these locoregional metastases.¹²

Thirty-one percent of the cases were metastases to the head and scalp, especially metastatic lung and gastrointestinal tumours, but also some metastatic leiomyosarcomas and head and neck tumours. It has been suggested that the vertebral venous system, which can supplement blood to the scalp and which parallels and partially bypasses the portal, caval, and pulmonary veins, plays a role in head and scalp metastases from abdominal internal malignancies.^{10,26} Some studies also showed that lung cancers in the upper lobes were more frequently associated with cutaneous metastases, perhaps due to the differentiated blood and lymphatic flow in the different lobes.^{26,27} In our study as well, 60% of the cutaneous

metastases originated from a lung carcinoma in the upper lobes. In six cases (three gastrointestinal tract and three gynaecologic tumours), the cutaneous metastases were located in the umbilical region (Sister Mary Joseph nodules). Tumour cells might reach the umbilicus through the umbilical artery and the urachus, and in rare cases through the lymphatics and other hematogenic pathways.⁵

The cutaneous metastasis was the first manifestation of a yet-undiagnosed internal malignancy in 18.6% of the patients, which was comparable to other studies (5.2%–16.1%).^{9,13,18,20} In these patients, lung cancer was the most frequent primary tumour and in 63.6% TTF1 was negative, making the diagnosis challenging. In these cases, a broad IHC panel and the correlation with radiological findings are necessary (Table 5A). In a recent study, about 70% of the skin metastases of lung adenocarcinomas

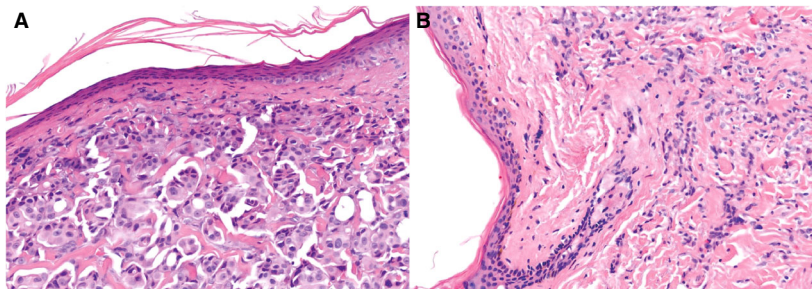


Figure 2. Microscopic pictures of two cutaneous metastases of breast carcinomas. A: Cutaneous metastasis of an invasive carcinoma of no special type (NST) (Haematoxylin-eosin stain, 200× magnification). B: Cutaneous metastasis of an invasive lobular carcinoma (Haematoxylin-eosin stain, 200× magnification).

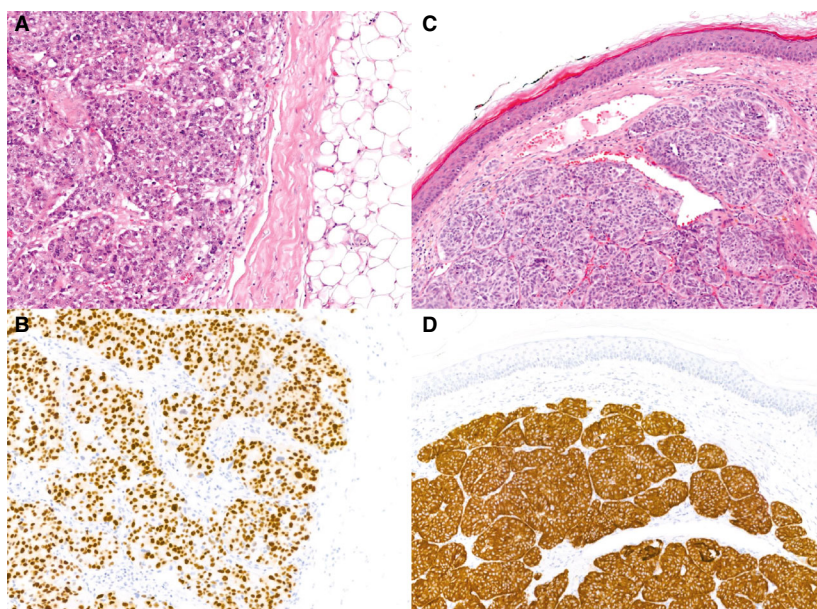


Figure 3. Microscopic pictures of two cutaneous metastases of lung carcinomas. **A and B:** Cutaneous metastasis of a lung adenocarcinoma (**A:** Haematoxylin-eosin stain, 100× magnification; **B:** TTF-1 immunohistochemistry, 100× magnification). **C and D:** Cutaneous metastasis of an atypical carcinoid (**C:** Haematoxylin-eosin stain, 100× magnification; **D:** CK7 immunohistochemistry, 100× magnification). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 4. Site of the cutaneous metastases in male patients ($n = 42$ specimens) and in female patients ($n = 110$ specimens)

Site of the cutaneous metastases	Number of specimens in male (%)	Number of specimens in female (%)	Primary tumour's location (number of specimens)	<i>P</i> -value (Pearson χ^2)
Head/scalp	13 (31.0%)	15 (13.6%)	Lung (7), gastrointestinal tract (6), head & neck tumour (5), sarcoma (retroperitoneum/intra-abdominal) (4), breast (2), urinary system (1), unknown primary (3)	0.014* (6.065)
Abdomen	7 (16.7%)	10 (9.1%)	Gastrointestinal tract (5), gynaecological system (4), breast (3), sarcoma (retroperitoneum/intra-abdominal) (1), lung (1), urinary system (1), head & neck tumour (1), haematopoietic neoplasm (1)	0.248 ¹
Neck	4 (9.5%)	6 (5.5%)	Head & neck tumour (5), breast (2), lung (1), haematopoietic neoplasm (1), unknown primary (1)	0.464 ¹
Dorsum	5 (11.9%)	17 (15.5%)	Breast (8), head & neck tumour (4), lung (3), haematopoietic neoplasm (3), urinary system (2), sarcoma (intra-abdominal) (1), gastrointestinal tract (1)	0.578 (0.309)
Leg	3 (7.1%)	0 (0%)	Lung (1), gastrointestinal tract (1), haematopoietic neoplasm (1)	NA
Groin/perineum	3 (7.1%)	4 (3.6%)	Gastrointestinal tract (3), lung (2), haematopoietic neoplasm (1), breast (1)	0.396 ¹
Anterior chest wall	2 (4.8%)	38 (34.5%)	Breast (32), lung (6), head & neck tumour (2)	$P < 0.001^*$ (13.905)
Arm/hand	2 (4.8%)	5 (4.5%)	Breast (2), lung (2), head & neck tumour (1), urinary system (1), haematopoietic neoplasm (1)	1.000 ¹
Umbilicus	2 (4.8%)	4 (3.6%)	Gynaecological system (3), gastro-intestinal tract (3)	0.668 ¹
Axilla	1 (2.4%)	4 (3.6%)	Breast (4), head & neck tumour (1)	1.000 ¹
Unknown	–	7 (6.4%)	Breast (3), Lung (2), gynaecological system (1), head & neck tumour (1)	NA

¹These *P*-values were calculated Fisher's exact test. The other *P*-values were calculated using Pearson's χ^2 -test.

*The *P*-value is significant (<0.05). NA: not assessed.

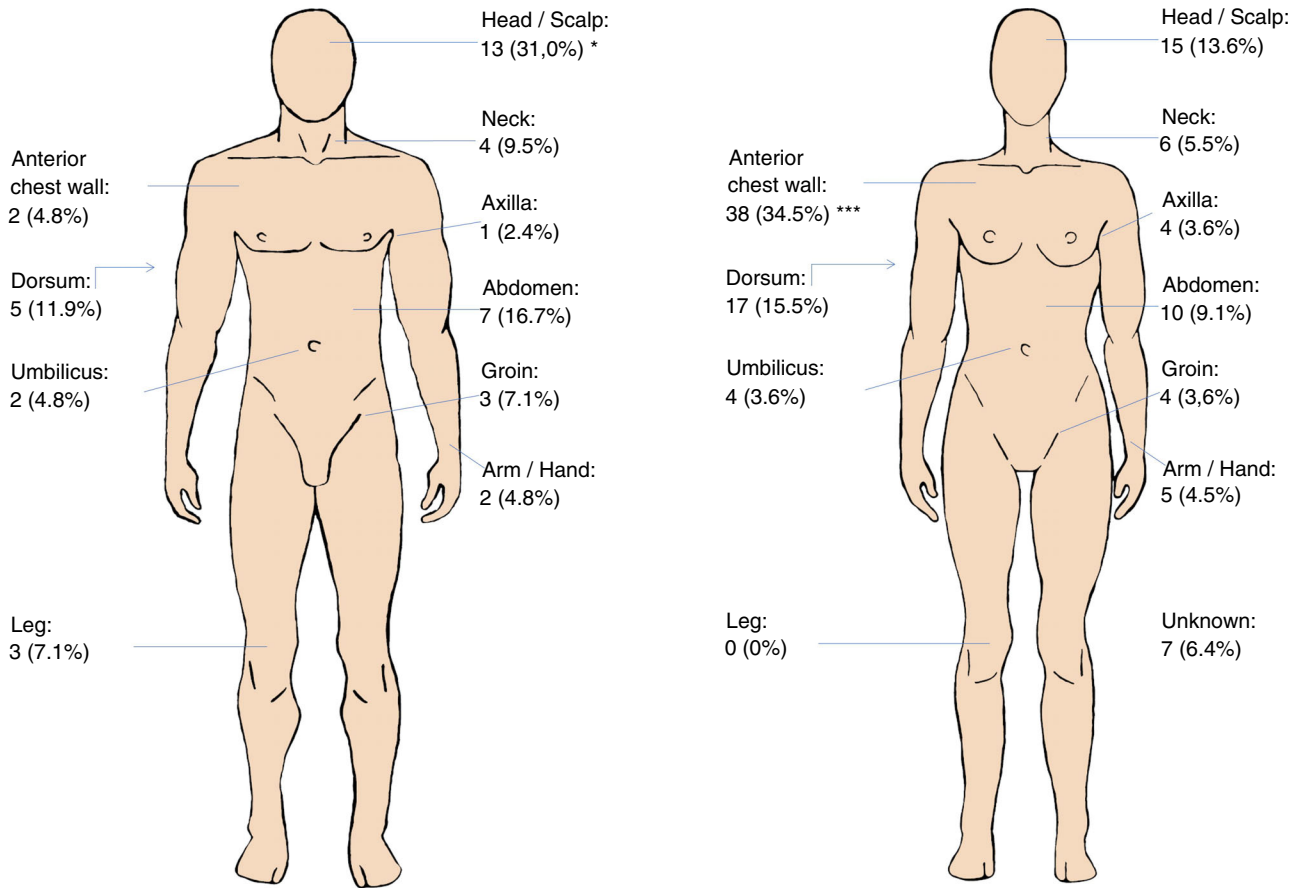


Figure 4. Anatomical patterns of cutaneous metastases in male (left) and female patients (right). * $P < 0.05$; *** $P < 0.001$. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 5. Immunohistochemical panels for selected cutaneous metastases

Compared tumours		Recommended immunohistochemistry	References
5A Differential diagnoses for metastasized lung cancers			
TTF1 positive lung adenocarcinoma	Thyroid cancer	<ul style="list-style-type: none"> • PAX8 • Thyroglobulin 	1
TTF1 negative lung adenocarcinoma	Adenocarcinomas of different primaries	<ul style="list-style-type: none"> • Broad immunohistochemical panel, targeting several differentiation lines 	28,29
Neuroendocrine carcinoma	Medullary carcinoma	<ul style="list-style-type: none"> • Calcitonin 	1
	Merkel cell carcinoma	<ul style="list-style-type: none"> • CK 20 	1
5B Distinction between metastatic breast carcinoma, salivary gland carcinoma and primary cutaneous adnexal carcinoma			
Metastatic breast carcinoma	Primary sweat gland carcinoma	<ul style="list-style-type: none"> • CK 5 • CK 14 • CK 17 • p63 • Mammaglobin 	32
Metastatic breast carcinoma	Metastatic salivary duct carcinoma	<ul style="list-style-type: none"> • CEA • Oestrogen receptor 	31
Metastatic adenocarcinoma	Primary adnexal tumour	<ul style="list-style-type: none"> • p63 • CK 15 • D2-40 	4

were negative for TTF1, which might be due to the frequent poorly differentiated nature of the adenocarcinoma in skin metastases.³⁰

The distinction between primary skin adnexal carcinoma and metastatic adenocarcinoma, especially breast and salivary gland, can be challenging because these tumours can exhibit similar morphological patterns and immunohistochemical profiles.^{28,31} Depending on the tumour type, several IHC panels are recommended (Table 5B). Some histomorphological features can also increase the suspicion of a metastatic carcinoma, such as a prominent deep dermal component, and the presence of tumour necrosis, inflammation, lymphovascular invasion, and tumour cells following dermal collagen bundles. There is also usually a tumour-free zone under the epidermis, which is usually not involved in the metastasis. Also, the lack of a benign or premalignant component can support metastatic carcinoma.^{7,9,29} Finally, molecular analysis can aid in challenging cases.

In summary, skin metastases of internal malignancies are infrequent and can be a true diagnostic challenge, especially in cases of a yet undiagnosed primary tumour. In our cohort, breast, lung, and gastrointestinal tract were the most common primary sites for cutaneous metastases. More research is necessary to address the diagnostic challenges, but also the metastasizing pattern of internal malignancies, which shows remarkable differences across tumour types and gender.

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Authors' contributions

Conceptualization, V.W. and I.V.S.; methodology, G.R., B.K., E.J.S., A.z.H., V.W. and I.V.S.; investigation, A.V., X.L., V.W. and I.V.S.; writing—original draft preparation, A.V., X.L. and I.V.S.; writing—review and editing, G.R., E.J.S., B.K., A.z.H., V.W. and I.V.S.; visualization, A.V., and I.V.S.; principal investigator, supervision, and project administration, V.W. and I.V.S. All authors have read and agreed to the published version of the article.

Conflict of Interest

The authors disclose no potential conflict of interest.

Data availability statement

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

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Primary antibodies.

Table S2. Immunohistochemical approach to predict the primary site of the cutaneous metastases.