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CME ARTICLE

Cutaneous metastases: From epidemiology to therapy

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Summary
Cutaneous metastases are seen in up to 10% of all oncology patients and can occur in different locations depending on the entity. Cutaneous metastases are often associated with a high psychological burden and, especially in the case of exulceration, with shame and social withdrawal. This review discusses the diagnostic and therapeutic options. The most common tumor entities in which cutaneous metastases are observed are discussed, and local and systemic treatment options are presented according to the current state of research.

KEYWORDS
cutaneous metastases, dermato-oncology, oncology, palliative care, tumor therapy

INTRODUCTION

Skin metastases occur in up to 10% of cancer patients and are often indicators of advanced cancer.[1] In a study with 724 patients, Brownstein et al. analyzed the distribution of skin metastases in both genders.[2] In men, the most common primary malignancies developing skin metastases were lung carcinomas (24%), colorectal carcinomas (19%), melanomas (13%), and oral squamous cell carcinomas (12%), whereas in women, skin metastases originated from breast carcinomas (69%), colorectal carcinomas (9%), melanomas (5%), and ovarian carcinomas (4%).[2] The occurrence of cutaneous metastases is often correlated with a poor prognosis.[1] In addition to classical systemic therapies, local therapeutic procedures are available. In some instances, these may also be administered in combination. This article aims at providing an overview of the current approach in the diagnosis and therapy of cutaneous metastases.

DEFINITION AND EPIDEMIOLOGY

Skin metastases are disseminations of primary skin tumors or malignant tumors of other organs developing both in

a lymphogenic and hematogenic manner. Skin metastases occur in 0.6%–10% of all malignant tumors. They represent approximately 2% of all malignant skin tumors.[3–6] In literature, the frequencies of primary tumors developing cutaneous metastases differ. While Brownstein et al. showed that lung carcinoma is the most common primary tumor developing cutaneous metastases in men, Alcaraz et al. specified malignant melanoma as the most common original tumor of skin metastases. Both groups described breast carcinoma as the most common primary for cutaneous metastases in women.[3,6]

Skin metastases are disseminations of primary skin tumors or malignant tumors of other organs developing both in a lymphogenic and hematogenic manner.

Cutaneous metastases occur most often on the trunk and the head and neck region, followed by the extremities.[7,8]

CLINICAL AND HISTOLOGICAL FEATURES

Skin metastases may be the first evidence for an unknown tumor disease or demonstrate the progression of a known tumor. Clinical features usually do not allow specific assignment to a primary tumor, hence diagnosis is largely based on histological findings. Well-differentiated metastases often present with typical morphological features of the primary tumor. Localization and clinical manifestation of skin metastases may, however, guide the initial assignment to a corresponding primary tumor (Figure 1).[6,9,10]

Clinically, cutaneous metastases often present as solitary or multiple papules, nodules, infiltrated plaques, or ulcers. Histologically, a lacking connection to epidermis and skin appendages indicates the presence of a skin metastasis as opposed to a primary cutaneous tumor. Immunohistological methods play a central role in the histological diagnosis (Table 1a, b).[6,9,10]

Clinically, cutaneous metastases often present as solitary or multiple papules, nodules, infiltrated plaques, or ulcers.

Approximately 60% of the cutaneous metastases are derived from adenocarcinomas, especially breast, lung, colorectal, stomach, and, in rare cases, also ovarian and prostate carcinomas.[9]

In many tumors, there is a close anatomical proximity of the skin metastasis to the primary. In addition, cutaneous metastases may occur in surgical scars, drainage ducts, and in the area of a stoma.[6,9,10] It should also be noted that cutaneous metastases may be infected by various pathogenic and/or opportunistic bacteria (for example, *Staphylococcus aureus*, *Pseudomonas aeruginosa*) resulting in discomfort, pain, offensive odor, and other complications.[11,12]

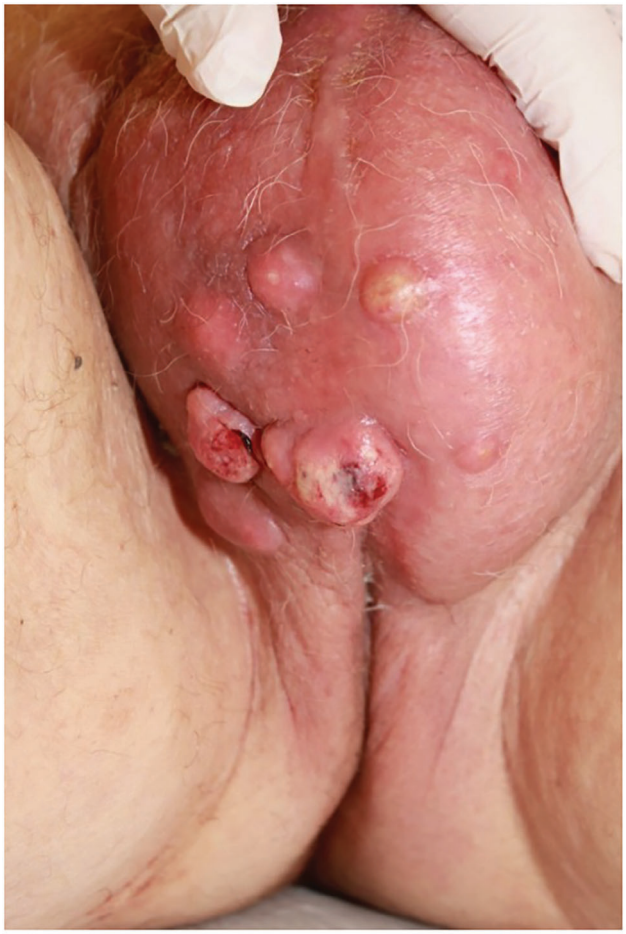

FIGURE 1 Skin metastases of a penile carcinoma: on the scrotum, multiple, partly centrally ulcerated erythematous papules and nodules.

DERMATOSCOPY OF CUTANEOUS METASTASES

Dermatoscopy is a widely used method in clinical practice, mostly to examine benign and malignant melanocytic lesions. A study by Christoph Sinz et al. from 2017 suggested that it also improves the diagnosis and management

TABLE 1a Immunohistochemical markers in the diagnosis of cutaneous metastases from primary cutaneous malignancies (adapted from Moll et al.[9]).

Origin	Immunohistochemical markers *positive*	Immunohistochemical markers *negative*
Malignant melanoma	HMB45, melan A, S-100, SOX10, vimentin	CK7, CK20, CK5, GCDFP-15, ER
Cutaneous squamous cell carcinoma	p63, p40, CK5/6	CK20, GCDFP-15, ER, TTF-1, vimentin, BerEp-4
Merkel cell carcinoma	CK20	CK7, CK5, GCDFP-15, ER, TTF-1, vimentin

TABLE 1b Immunohistochemical markers in the diagnosis of cutaneous metastases from non-primary skin tumors (adapted from Alcaraz et al.[6]).

Origin	Histology	Immunohistochemical markers positive	Immunohistochemical markers negative
Breast	Ductal	CK7, GCDFP-15, CEA, c-erbB-2, mammaglobin, E-cadherin, ER	CK20, CK5/6
	Lobular	CK7, estrogen receptor (ER), progesterone receptor (PR), GCDFP-15, CEA, EMA, mammaglobin	S100, E-cadherin, podoplanin, P63
	Erysipelas carcinomatosa	CD31, podoplanin	
Lung	Squamous cell carcinoma	CK5/6	CK7, CK20, TTF-1, CEA
	Adenocarcinoma	CK7, TTF-1, Ber-EP4, CEA, surfactant, apoprotein A	CK5/6, CK20
	Mesothelioma	CK5/6, calretinin, vimentin	CEA, TTF-1, S100, CD31
	Small-cell lung carcinoma	TTF-1, CAM5.2, CK8/18, Ber-EP4, ENS	CK7, CK20, CD99
Colorectal	Adenocarcinoma	CK20, CEA, mucin, CDX2	CK7
Small intestine	Squamous cell carcinoma	CK20, EMA, AE1/AE3	CK7
	Adenocarcinoma	CEA, EMA	
Stomach	Adenocarcinoma	CK20, CEA, EMA, CDX2, HIK1083	$CK7^+$/CK72
Esophagus	Squamous cell carcinoma/adenocarcinoma	CK5/6, Ber-EP4	CK7, CK20
Oral cavity	Squamous cell carcinoma	Ber-EP4	
Liver	Hepatocellular carcinoma	Alpha-fetoprotein, polyclonal CEA, Hep Par1, arginase-1	Pancytokeratin, EMA, monoclonal CEA
Biliary system	Adenocarcinoma	CK7, CK20	CDX2
Pancreas	Adenocarcinoma	CA19.9, CK7, CK8, CK18, CK19	CK20
Kidney	Renal cell carcinoma	AE1/AE3, MNF116, CD31, RCC-Ma (>2/3), vimentin, CD10, EMA, S-100, adipophilin, PAX8	Inhibin, melan-A, TTF-1, CK7, CK20
Bladder/urethra	Urothelial carcinoma	CK7, CK19, CK20, CK14 (50%), thrombomodulin, uroplakin III, CD10	
Prostate	Adenocarcinoma	PSA, PAP, AMACR (p504s), ERG transcription factor	CK7, CK20, thrombomodulin
Testicles	Chorionic carcinoma	Beta-HCG	
Ovaries	Carcinoma	CA125, CK7, PAX8	CK20 (except some mucinous variants)
Cervix and vagina	Carcinoma	CK7, EMA^+/EMA^-	CK20, CEA
Endometrium	Carcinoma	CK7, PAX8	CK20, P63, podoplanin
Thyroid	Papillary	Thyroglobulin, TTF-1, PAX8 (50%)	
	Follicular		
	Anaplastic	$Thyroglobulin^+$/$Thyroglobulin^-$	
	Medullary	Calcitonin	Thyroglobulin, PAX8

of non-pigmented skin tumors and should be used to supplement the basic examination of suspicious lesions.[12,13]

In dermatoscopy, vascular structures as sign of neovascularization are found remarkably often in cutaneous metastases. A case series by Chernoff et al., for example, showed different vascular patterns in 88% of non-pigmented metastases. The most common findings were serpentine-like (linear irregular) and arborizing vessels, as well as a polymorphic vascular pattern with a chaotic display of mostly different linear vessel types. While dot-shaped vessels were less common in cutaneous metastases, their presence was a highly specific indicator of a melanocytic origin (positive predictive value 90%).[14,15] However, vascular patterns are not exclusive characteristics of cutaneous metastases, but are also classical features of primary cutaneous tumors, especially epithelial tumors.[15]

Other dermatoscopic signs of cutaneous metastases are unstructured areas, white lines, and the presence of

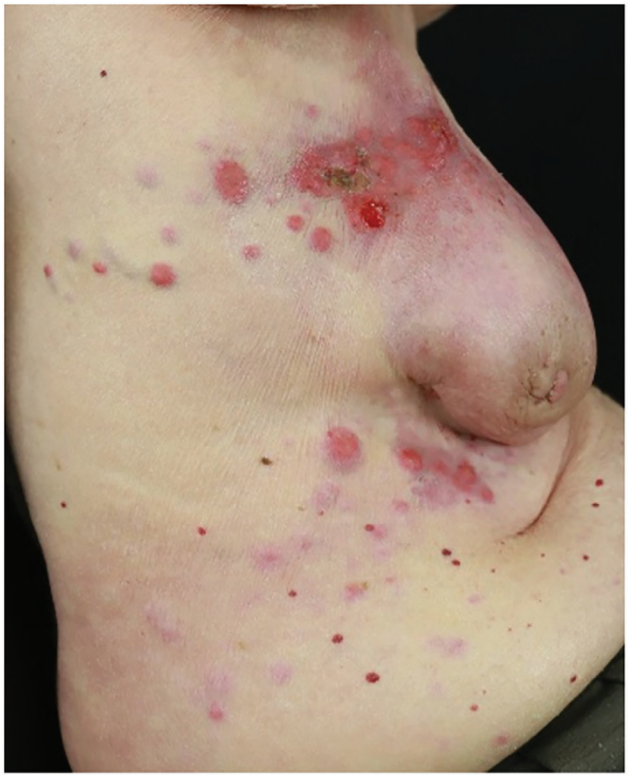

FIGURE 2 Skin metastases of a multicentric breast carcinoma: On the right thoracic wall there are disseminated rough, partly confluent and ulcerated, erythematous papules and nodules.

peripheral globules or spots. Discoloration (hyperpigmentation, pink, yellow, and orange macules) has also been described.[12]

Dermatoscopy should supplement the diagnosis of cutaneous metastases.

BREAST CARCINOMA

Cutaneous metastases from breast carcinoma are the underlying cause in most female cases and occur predominantly on chest wall and abdomen. Typically, they present as skin-colored to reddish, solid, mostly asymptomatic nodules with a size of 1–3 cm (Figure 2).[6,9,10]

Histologically, invasive ductal mamma carcinoma, the most common form, presents mostly with solid dermal tumor cell infiltrates with surrounding fibrosis in form of trabeculae and tubules. Usually, E-cadherin, keratins 7 and 19, mammaglobin, gross cystic disease fluid protein 15 (GCDFP-15), as well as estrogen and progesterone receptors are detected by immunohistochemistry. In contrast, invasive lobular mamma carcinomas tend to be negative for E-cadherin (Figures 3a–c).[6,9]

Alopecia neoplastica is a special form of cutaneous metastasis on the scalp with mamma carcinoma as primary tumor in 84% of the cases (Figure 4). It presents as solitary or multiple, hairless, sharply demarcated, oval, erythematous plaques without scaling.[6,9,10] This cutaneous metastasis is probably caused by hematogenic and not by lymphogenic spreading. The alopecic areas are usually painless, nonpruritic and well-defined. They may resemble discoid lupus erythematosus, lichen planus pilaris, pseudopelade, or morpheaform basal cell carcinoma.[6]

Another noteworthy form of cutaneous metastasis is *carcinoma en cuirasse* that occurs mostly in lobular breast carcinomas, but also in prostate carcinomas (Figure 5a, b). It presents as indurated erythematous plaque infiltrating the chest wall. Erysipelas carcinomatosum is another typical form of skin metastasis derived from breast carcinoma (Figure 6). This is a sharply demarcated, sometimes erosive, reddish macule or plaque that resembles erysipelas in its clinical features and may be interfused by lymphedema. Based on the clinical appearance, this effect is referred to as *peau d'orange*.[6,10,16]

Cutaneous metastases from breast carcinoma occur predominantly on thorax and abdomen and present mostly as reddish, solid, asymptomatic nodules.

LUNG CANCER

Skin metastases from lung carcinoma resemble cutaneous metastases from breast carcinoma and are usually also localized on chest, abdomen, and back. In small-cell lung carcinoma, the tumor cells have a highly diverse histological appearance, and they often show a low level of differentiation and a nodular or infiltrative configuration. In immunohistology, they are almost always positive for thyroid transcription factor-1 (TTF-1) and Cell Marque cytokeratin 5.2 (CAM5.2). In most cases, they are, however, negative for cytokeratins 7 and 20.[6,9,10]

COLORECTAL CARCINOMA AND RENAL CELL CARCINOMA

Skin metastases from colorectal carcinomas mostly occur on perineum, abdomen, and especially in the periumbilical region. Umbilical and periumbilical cutaneous metastases, typically derived from a primary malignancy in the abdomen, are also called "Sister Mary Joseph nodules". Interestingly, skin metastases from colon and prostate carcinomas are not only found on the abdomen, but also on the scalp (Figure 7).[6,9,16]

Umbilical and periumbilical cutaneous metastases, typically derived from a primary malignancy in the abdomen, are also called "Sister Mary Joseph nodules".

Cutaneous metastases from renal cell carcinomas are actually most frequently localized in the head and neck region and share common clinical and histological features with other clear-cell carcinomas. The differentiation from primary cutaneous clear-cell tumors, such as sebaceous gland

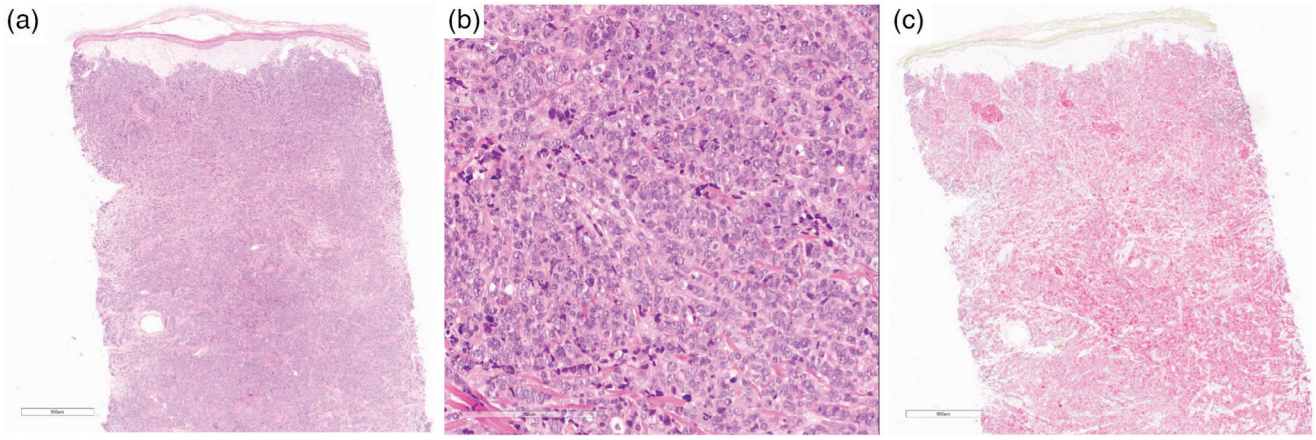

FIGURE 3 (a) Skin metastasis of a breast carcinoma, hematoxylin-eosin stain, overview: Localized tumor infiltrates are found in the dermis. (b) HE, magnification. The tumor cells have large, pale nuclei. Mitoses are visible in large numbers. (c) Skin metastasis of a breast carcinoma: immunohistochemistry: strong positivity for CK7 is shown (illustrations: T. Cunha, UKGM Marburg).

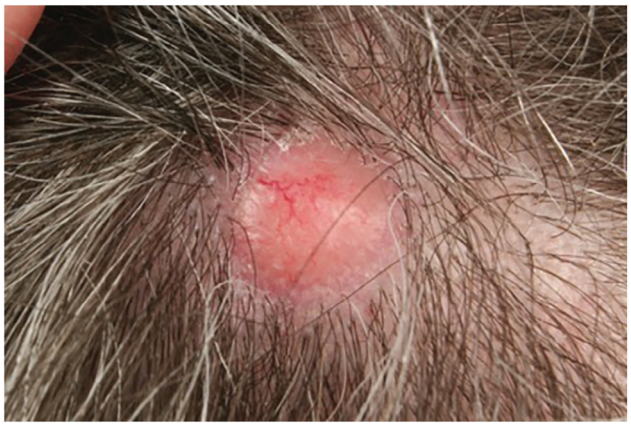

FIGURE 4 Alopecia neoplastica: solitary hairless, sharply demarcated, oval erythematous plaque in the hairy capillitium in a patient with metastatic breast carcinoma.

carcinoma, is facilitated by the determination of keratin 5 that is almost always present in primary cutaneous tumors.[9]

CUTANEOUS SQUAMOUS CELL CARCINOMA

The differentiation of cutaneous squamous cell carcinoma from a cutaneous metastasis derived from a primary squamous cell carcinoma of the skin is often challenging. Again, the absent contact to the epidermis is evidence for a metastasis. In addition, cutaneous squamous cell carcinomas develop more often in UV-exposed areas, such as head and neck region and hands, than metastases (Figure 8).[7]

The differentiation of cutaneous squamous cell carcinoma from a cutaneous metastasis derived from a primary squamous cell carcinoma of the skin is often challenging.

MERKEL CELL CARCINOMA

The immunohistochemical examination plays a central role in the differentiation from various neuroendocrine and small-cell tumors, as well as lymphomas. Analogous to primary Merkel cell carcinoma, cytokeratin 20 is expressed in metastases derived from Merkel cell carcinomas, but not in metastases derived from lung carcinomas and lymphomas (Figures 5, 9a–c).[6,9]

MALIGNANT MELANOMA

Cutaneous metastases from malignant melanoma may be pigmented or non-pigmented and occur as satellite, in-transit, or distant metastases. Apart from the skin, metastases may also manifest in mucous membranes (Figure 10a–d). Regional tumor disseminations forming at a distance of less than 2 cm from the primary are called satellite metastases. In contrast, skin metastases occurring at a distance greater than 2 cm from the primary, but within the locoregional lymph drainage area, are called in-transit metastases. Beyond the locoregional lymph drainage area, they are distant cutaneous metastases.[17,18]

In contrast to other skin tumors, metastases derived from melanoma may be localized in epidermis, dermis, and subcutaneous tissue. In immunohistochemistry, they are positive for S100, melan A, HMB45, and SOX10 (Figure 11a–c).[9]

Diffuse melanosis cutis should be mentioned as a rare special form of cutaneous metastasis in malignant melanoma characterized by blue-gray discoloration of skin and mucous membranes.[19]

In histology, metastases from primary skin tumors usually have no contact to the epidermis.

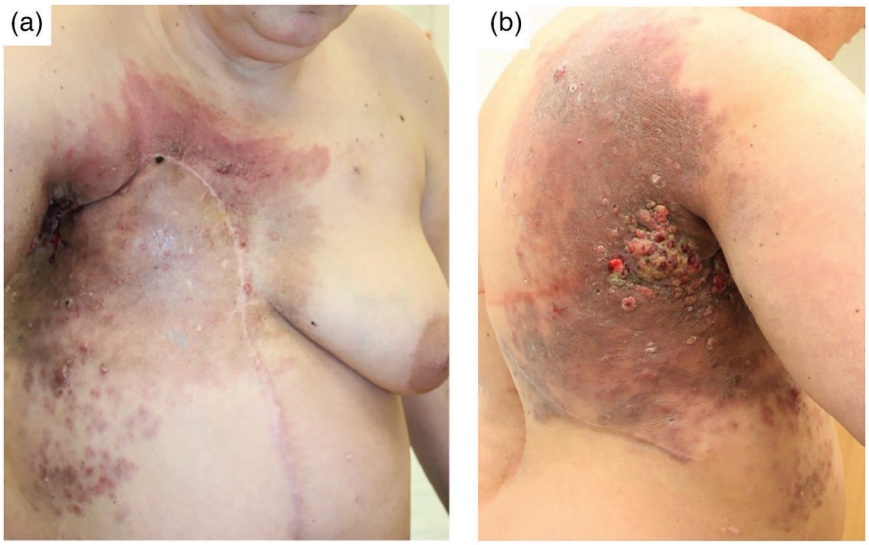

FIGURE 5 (a, b) *Cancer en Cuirasse*: clinically, a rough indurated plaque with incipient ulceration and nodule formation of the entire right thoracic wall.

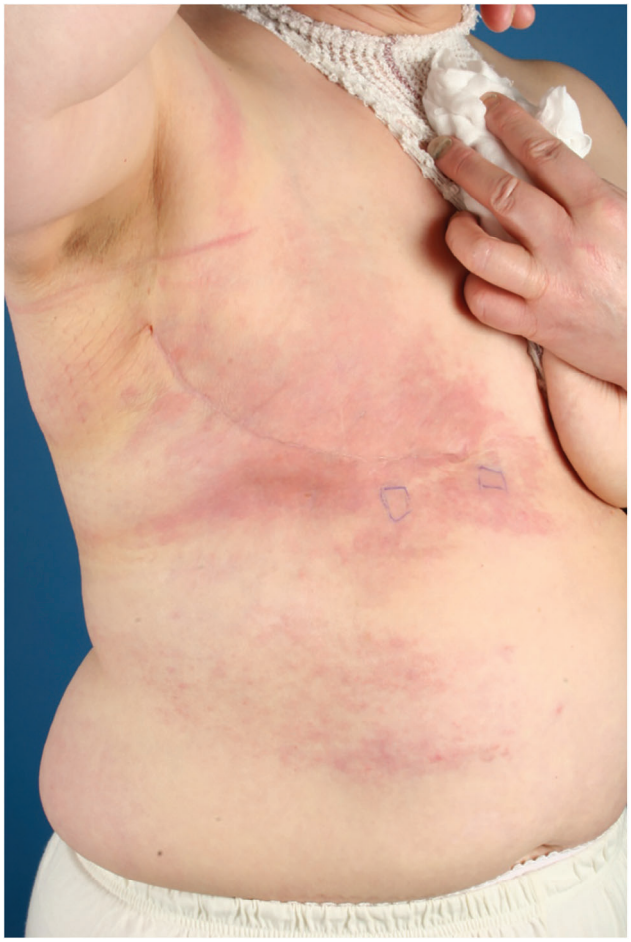

FIGURE 6 Erysipelas carcinomatosa: There is a blurred erythema with extensions on the right flank in a patient with breast carcinoma.

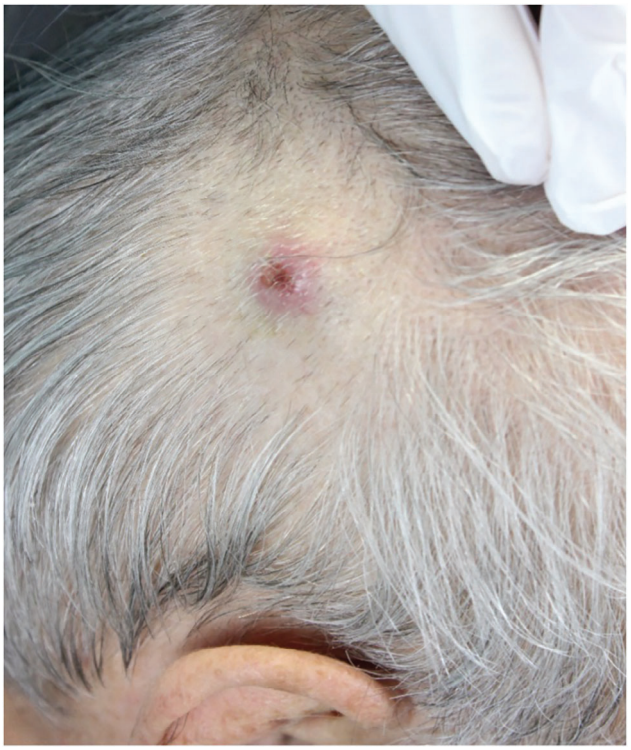

FIGURE 7 Skin metastasis of a colon carcinoma: There is a parieto-temporal central ulcerated erythematous nodule on the right side.

THERAPY OF SKIN METASTASES

The treatment of skin metastases is diverse and depending on various factors. Important aspects are localization, characteristics of the metastasis, tumor entity, age of the patient, potential comorbidities, and the general health of the patient. Based on these factors, both local and systemic therapies or their combinations may be used. It is important to note that, to date, only talimogene laherparepvec (T-VEC) is approved for the local treatment of melanoma metastases, whereas all other medical local treatment methods are used *off label*.

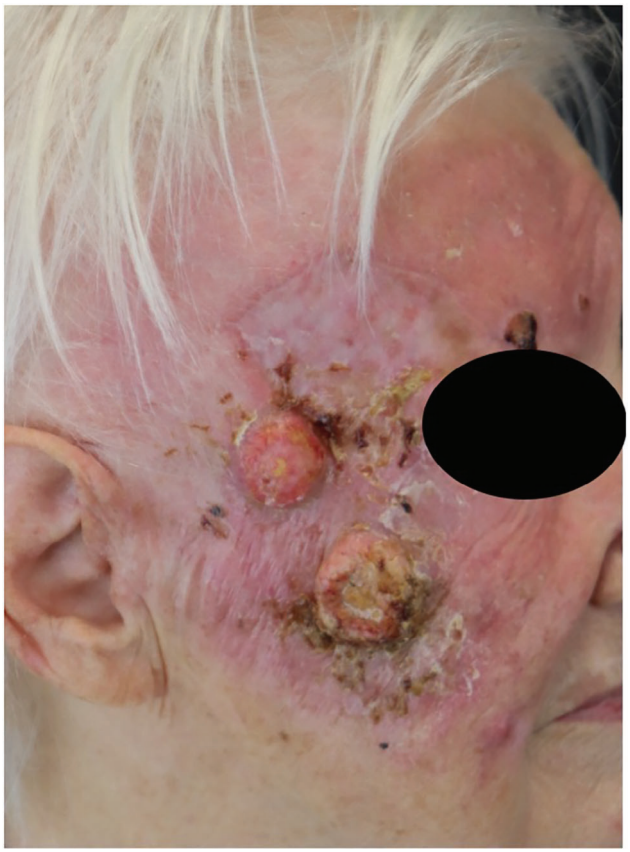

FIGURE 8 Cutaneous metastases of a primary cutaneous squamous cell carcinoma: Clinically, two ulcerated erythematous nodules with circumscribed blurred surrounding erythema and hemorrhagic crusts appear under radiotherapy. The split-thickness skin graft of the former primary at the right temple is well visible.

LOCAL THERAPEUTIC PROCEDURES

Given the usually advanced tumor stage and the associated physical, psychological, and localization-specific problems, the locoregional, often palliative treatment approaches are of major importance.

Surgery

If there is no evidence of distant metastasis – in case of perspective R0 resectability of the skin metastases – the aim should be the surgical treatment as curative approach. Apart from the number and localization of skin metastases, potential functional deficits should be considered, in particular, when making the decision. The aim is always a complete excision with control of the resection margins.[20,21]

If there is no evidence of distant metastasis – in case of perspective R0 resectability of the skin metastases – the aim should be the surgical treatment as curative approach.

This is followed by entity-specific, adjuvant therapy based on guideline recommendations.[20,21]

Radiotherapy

Radiotherapy refers to the use of ionizing radiation with the aim to create DNA-damaging free radicals in the tumor cells.

The study data available for the treatment of skin metastases from malignant melanoma demonstrate a good response, although smaller skin metastases show a better response with longer lasting remission.[20,22–24] Superficial tumors are preferentially irradiated with fast electrons and deep tumors with photons. Depending on the prognosis, a dosage of 5 x 4 Gy, 10 x 3 Gy, or 20 to 25 x 2 Gy is chosen.[20,25] Additional hyperthermia, that is, warming of the patient to 43 °C for 60 minutes, can increase the complete response rate to up to 62%.[20,26]

In a study with 46 patients, local control by pulsed brachytherapy (2 settings at an interval of 4 weeks with total doses of 38–50 Gy) was also shown for skin metastases derived from breast carcinoma in 89% with a median follow-up of 16 months.[27]

Case reports are available showing a good clinical response of skin metastases derived from tumors of the urogenital system (urothelial carcinoma, renal cell carcinoma).[28,29]

Apart from its "therapeutic" use, radiotherapy is of major importance in the palliative care of patients. Skin metastases often cause pain due to the space-occupying effect and result in bleeding and malodor due to tumor infiltration or degradation. In this indication, treatment in the form of hypofractionation with higher individual doses (3.0 – 4.0 – 8.0 Gy), while keeping the treatment duration as short as possible, is preferred.[30]

The analgesic effect of radiotherapy does not require complete regression of metastases and is already observed after dosages from 8 Gy, with a maximum effect 2–4 weeks after radiotherapy has been completed.[30] It can be achieved in 60%–80% of the irradiated patients and persists for months to years.[31]

Radiotherapy can often be used to alleviate pain.

Electrochemotherapy

Electrochemotherapy was first described in France at the end of the 1980s and has since then become an integral part of the palliative symptom control of advanced inoperable skin metastases (as well as primary tumors).[32,33]

Mode of action is the combination of a cytostatic drug administered intravenously or intratumorally with the application of electrical impulses. Electroporation is the active principle: The applied electrical impulses result in changes of the transmembrane potential, stimulation

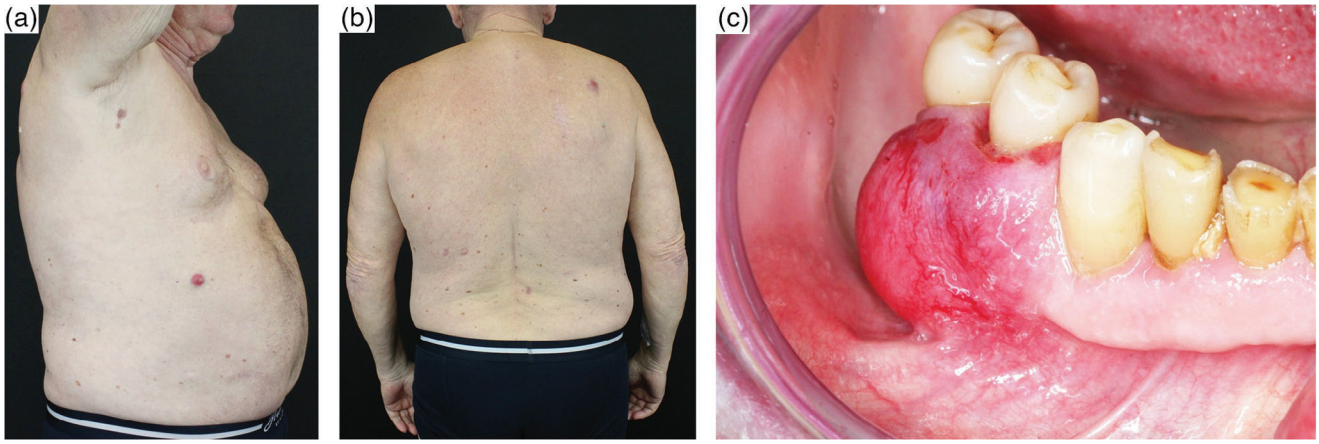

FIGURE 9 (a, b) Cutaneous metastases of Merkel cell carcinoma: Solitary erythematous-livid rough nodules are seen on the trunk and extremities. (c) Mucosal metastasis of Merkel cell carcinoma: The same patient shows a perimolar erythematous nodule with continuous spread into the alveolar mucosa.

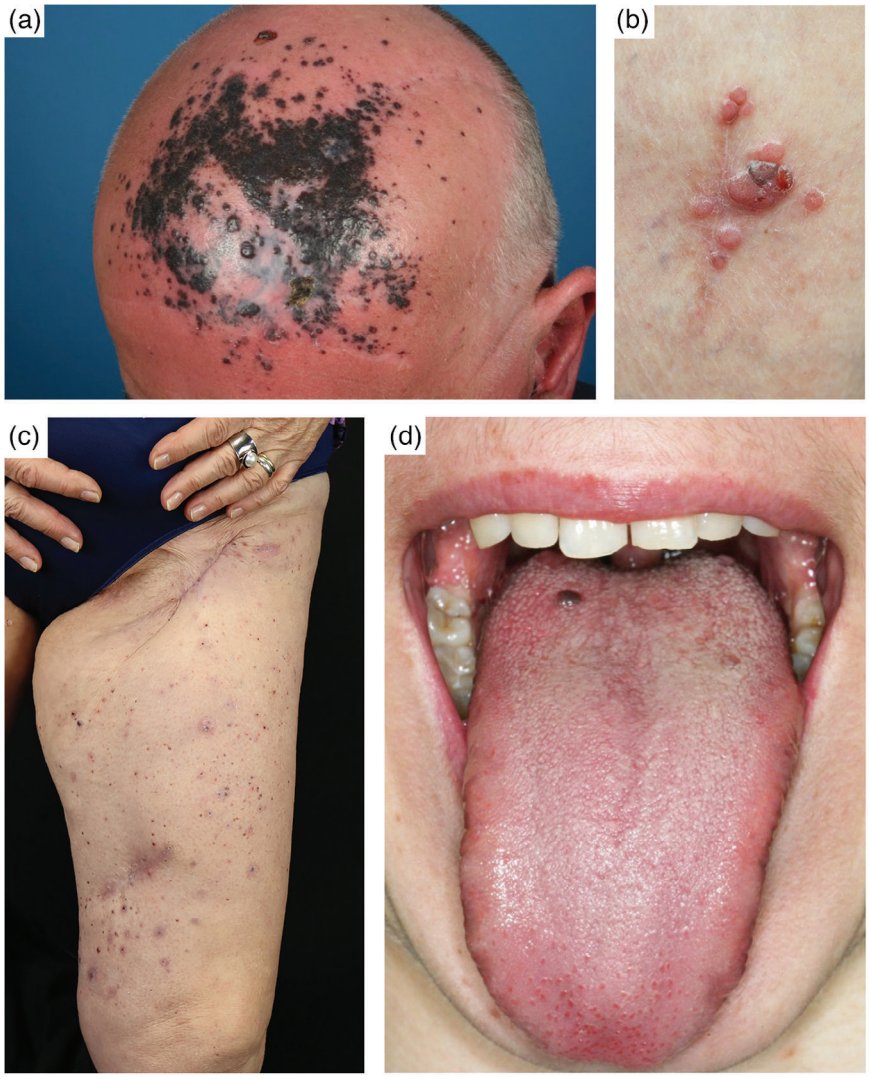

FIGURE 10 (a) Pigmented skin metastases of a malignant melanoma: frontoparietal livid to black round macules and papules on both sides, confluent centrally to form a plaque. (b) Depigmented satellite metastases of malignant melanoma: Grouped erythematous nodules are seen in the area of the primary scar. (c) Pigmented and depigmented in-transit metastases of malignant melanoma: Clinically, both pinhead-sized disseminated reddish papules and pigmented nodules appear in the lymphatic drainage area of the primary on the left ventral thigh. (d) Metastasis of the base of the tongue in a metastasized malignant melanoma: A 5 mm large bluish shimmering nodule is seen at the junction of the corpus linguae and the radix linguae.

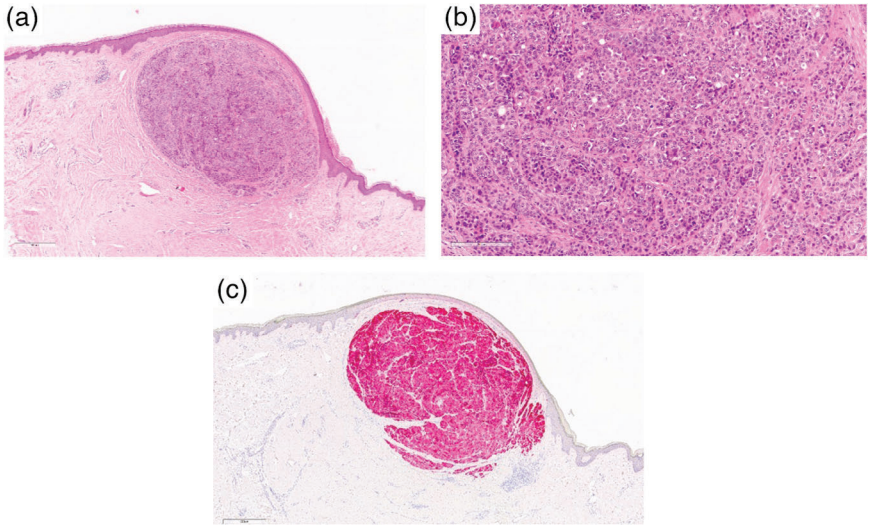

FIGURE 11 (a, b) Skin metastasis of a malignant melanoma, hematoxylin-eosin stain: dermally, a well-demarcated nodule consisting of nests of different sizes, with marked nuclear polymorphism and strong mitotic activity. (c) Skin metastasis of malignant melanoma, immunohistochemistry. Positivity for melan A (illustrations: T. Cunha, UKGM Marburg).

of the cell, and consecutively to an opening of the cell membrane.[34] The latter is responsible for the improved uptake and thus effectiveness of the cytostatic drug. For intravenously or intratumorally administered cisplatin, the effectiveness is increased by a factor of up to 80, and for the intravenously administered bleomycin even by a factor of up to 8,000 due to its molecular size.[35] Depending on size, number, and region of the metastases, electrochemotherapy should be performed under local or general anesthesia.[36]

Electrochemotherapy is implemented according to the standardized ESOPE (*European Standard Operation Procedure for Electrochemotherapy*) protocol.[37]

Local side effects include – apart from pain resembling sore muscles – bleeding, necroses, or infections and occur in 5%–16% of the patients.[35,37] Therapy-related side effects include, in particular, the dreaded bleomycin-induced interstitial pneumonia with pulmonary fibrosis; after administration of cisplatin, primarily nausea and vomiting are observed.[36]

Reproducible data show objective response rates of up to 85% and up to 73.7% of complete remissions for highly diverse tumor entities. While no significant differences in response were found based on tumor entity and size of metastases, differences were observed based on localization (trunk > extremities > head/neck).[38] Apart from the shrinking of metastases, especially a rapid reduction of clinical symptoms such as exudate production, malodor, and bleeding has been observed (Figure 12a, b).

In addition to the classical electrochemotherapy with bleomycin and cisplatin, other substances such as calcium electroporation (Ca-EP) are currently being investigated. This presents a novel form of therapy that has, however, characteristics similar to electrochemotherapy. Here, the intracellular calcium concentration is increased by electroporation resulting in increased ATP consumption and a loss in ATP production resulting in apoptosis.[39] Àgoston et al. studied the efficacy of calcium electroporation compared to bleomycin-based electrochemotherapy. In this double-blind, randomized, controlled phase II trial, up to ten measurable cutaneous metastases per patient were separately block randomized for a single treatment to administer either calcium or bleomycin intratumorally followed by reversible electroporation. The response of the tumor was evaluated clinically and histologically 6 months after treatment. Serious adverse events were not registered. Ulceration and hyperpigmentation were observed more frequently after bleomycin-based electrochemotherapy than after Ca-EP. Calcium electroporation was non-inferior to electrochemotherapy and should, therefore, be considered a feasible, effective, and safe treatment option.[39]

Electrochemotherapy is suitable for local control of inoperable tumors.

LOCAL IMMUNOTHERAPIES

Interleukin-2

Intralesionally delivered interleukin-2 results in tumor lysis and apoptosis via formation of lymphokine-activated killer cells. Compared to the systemic administration, local administration is more tolerable.[40] A clinical trial with 51 patients could show response rates of more than 80% with 79% complete remissions of treated metastases. For this purpose, interleukin-2 was administered two to three times a week over a period of 2 to 57 weeks (3–18 MIU/session) according to the individual tolerability. Local reactions, but also flu-like symptoms, fatigue, and, occasionally, gastrointestinal symptoms were predominantly reported as side effects.[41] In Germany, interleukin-2 is approved as subcutaneous or intravenous injection for the treatment of metastatic renal cell carcinoma.[42] The intratumoral administration is an *off-label* therapy.

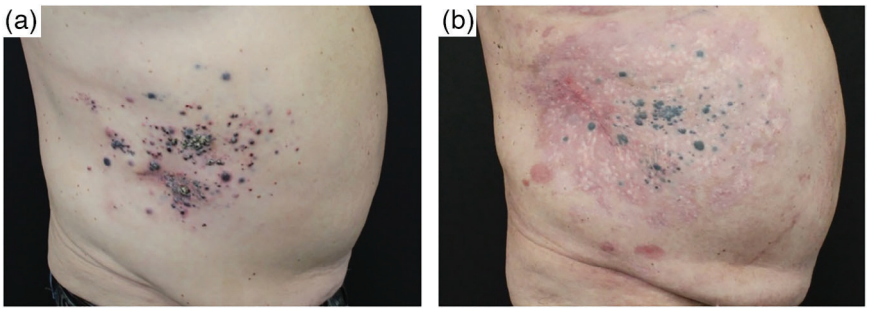

FIGURE 12 (a) Multiple inoperable in-transit metastases in malignant melanoma on the right flank before ECT. (b) Condition after two cycles of ECT with 15 mg/m^2 BSA: There is a clear fading of the pigment as well as a flattening of the nodes without evidence of new metastases. The puncture channels of the hexagonal probe heads and the erythema after treatment are clearly visible.

In Germany, interleukin-2 is approved as subcutaneous or intravenous injection for the treatment of metastatic renal cell carcinoma.

Imiquimod

In Germany, the toll-like receptor 7 agonist imiquimod is approved for the topical therapy of actinic keratosis and superficial basal cell carcinoma. Numerous case reports are available for the monotherapy of melanoma metastases with topical imiquimod applied predominantly 5 times a week under occlusive conditions for a period of 8 to 22 weeks. In a review of Sisti et al., this topical therapy proved to be an effective and safe treatment option with complete remission in 82.3% of the cases, although the published case series certainly represent a positive selection.[43]

In combination with interleukin-2 (daily application of imiquimod for 4 weeks, followed by intralesional interleukin-2 administration one to three times a week), response rates of approximately 50% were demonstrated for skin metastases from malignant melanoma in a phase I/II trial.[44]

Miltefosine

Topical therapy with 6% miltefosine solution may be discussed specifically for the treatment of cutaneous metastases from breast carcinoma "in findings with minor spreading".[21] This substance is currently used predominantly systemically as antiprotozoal agent; it is applied locally and results in significantly less tumor progression of flat and micronodular metastasis.[45,46] In Germany, however, miltefosine solution as a finished product (Miltex® solution, Baxter Oncology) was withdrawn from the market in 2011.

Dinitrochlorobenzene (DNCB)/ diphenylcyclopropenone (DCP)

Application of a 2% dinitrochlorobenzene solution can significantly increase the effectiveness of intravenous dacarbazine therapy by triggering an obligatory contact allergy with associated immune stimulation. Already in 1997, Strobbe et al. described response rates of up to 37% (12% partial remission [PR], 25% complete remission [CR]).[47] A retrospective survey involving nine German skin tumor centers revealed an objective response rate of even 62% for patients in stage III.[48] Overall, this combined treatment option has been pushed somewhat into the background in recent years due to the decreasing use of chemotherapy for malignant melanoma.

Talimogene laherparepvec

Talimogene laherparepvec (T-VEC) is a genetically engineered herpes simplex virus type I selectively replicating in tumor and producing GM-CSF (granulocyte macrophage colony-stimulating factor).[49] In a randomized, *open-label* phase III trial with melanoma patients in stage IIIB–IV, a response rate of 26.4% with 10.8% complete remissions was shown.[50] The oncolytic virus was approved in 2016 for patients with unresectable malignant melanoma with local or distant metastases without bone, brain, lung, or visceral metastases (Figure 13a, b).

The oncolytic virus was approved in 2016 for patients with unresectable malignant melanoma with local or distant metastases without bone, brain, lung, or visceral metastases.

Unfortunately, the results of a large phase III trial on the combination of T-VEC therapy with the PD-1 inhibitor pembrolizumab for patients with malignant melanoma were disappointing. The combination showed no significant improvement of progression-free survival or overall survival.[51]

A good response to the intralesional therapy with T-VEC was also reported for other tumor entities with skin involvement (squamous cell carcinoma, Merkel cell carcinoma, cutaneous lymphoma, sarcoma).[52]

Overall, the therapy is very well tolerated, with fatigue, fever, and chills as most common side effects.

Isolated (hyperthermal) limb perfusion

The option of isolated limb perfusion should be considered especially for multiple melanoma metastases with rapid recurrence that are limited to the arm or leg.[20] Isolated

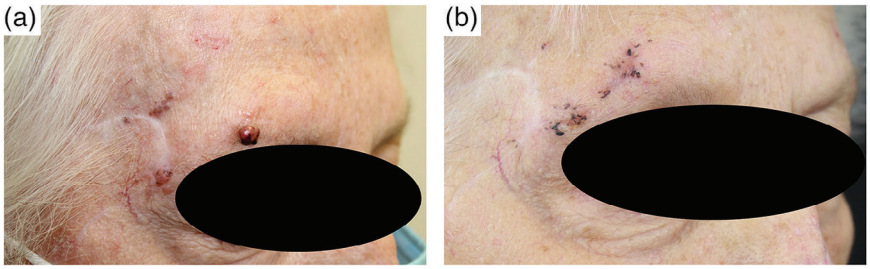

FIGURE 13 (a) Satellite metastases in malignant melanoma: Small livid-bluish papules appear around the scar of the primary. (b) Already after five injections of T-VEC, the metastases are no longer clinically detectable, only residual pigment is still visible above the right eyebrow.

limb perfusion is a technically very complex procedure involving the vascular isolation and subsequent perfusion of the respective limb with melphalan, optionally in combination with rhTNF-α (recombinant human tumor necrosis factor-α), under mild tissue hyperthermia at 39–40 °C.

A large review with more than 2,000 patients with malignant melanoma showed a median response rate of 90.35% with a median complete response in 58.2%. The combination of both therapeutic agents resulted in a significantly higher response (46.5% vs. 68.9%).[53]

Apart from locoregional consequences (erythema, overheating, blister formation, desquamation, lymphedema, but also a potential compartment syndrome with loss of the extremity), potential side effects include rhabdomyolysis or cardiac stress when using TNF-α.

In addition to its use for in-transit and satellite metastases from malignant melanoma, isolated limb perfusion is often used in sarcomas. Theoretically, however, it is also a good – albeit complex – therapeutic option for metastases of other tumors limited to one extremity.[54]

Cryotherapy

The term cryotherapy refers to the use of freezing techniques with the aim of remodeling pathologically altered tissue. Nitrogen with an evaporation temperature of –195.8 °C is mostly used in practice resulting in formation of extracellular and intracellular ice crystals with secondary cell death. Moreover, the coldness is responsible for a disturbed microcirculation resulting in tissue anoxia and additional necrosis.[55]

Although cryotherapy is mentioned in the guidelines as therapeutic option, only small case series are available for the treatment of skin metastases from melanoma with cryotherapy. Grotmann et al. treated 30 patients with metastatic malignant melanoma and could demonstrate a mean remission time of 36 months with markedly improved quality of life.[56,57] Advantages are the simple implementation, the good repeatability, and the very rare contraindications (Figure 14).

(CO_2) laser ablation

The CO_2 laser is the classical ablative laser system for the treatment of melanoma metastases.[20,58] It emits light with a wavelength of 10,600 nm resulting in ablation of the epidermal and upper dermal portions of the skin.

Accordingly, smaller skin metastases (diameter < 1 cm) can be directly vaporized, while larger metastases are first encircled before the center is removed with forceps.[59]

In a series of 16 treated patients with 559 ablated melanoma metastases, Kandamany et al. showed complete clinical remission in 62.5% of the patients, which still persisted after 12 months.[59]

Analogous to cryotherapy, ablative laser therapy is a safe and effective option for palliative treatment of skin metastases derived from melanoma, especially for small superficial metastases.

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Photodynamic therapy (PDT)

In photodynamic therapy, photosensitizing substances are used (usually topically) that accumulate selectively in the diseased epidermis and are activated by exposure to light of an appropriate wavelength. This causes the production of reactive oxygen species resulting in cell damage and cell death.[60]

In a large meta-analysis comparing skin-directed therapeutic procedures, four studies on photodynamic therapy were included. In 36 included patients (one patient each with adenocarcinoma of submandibular gland, colon, and breast, all remaining patients with breast carcinoma), complete remission of cutaneous metastases was demonstrated for 75.9%.[61]

OUTLOOK ON LOCAL PROCEDURES

Against the background of increasingly effective systemic therapies, combination studies of systemic therapies and intratumoral injection of immune modulators are expected to improve the effectiveness for accessible skin lesions, especially for the entity of malignant melanoma. Individual substances, such as the oncolytic peptide LTX-315 or the oncolytic virus RP-1 to mention just two examples, are currently being tested in clinical trials for this purpose.[62–64]

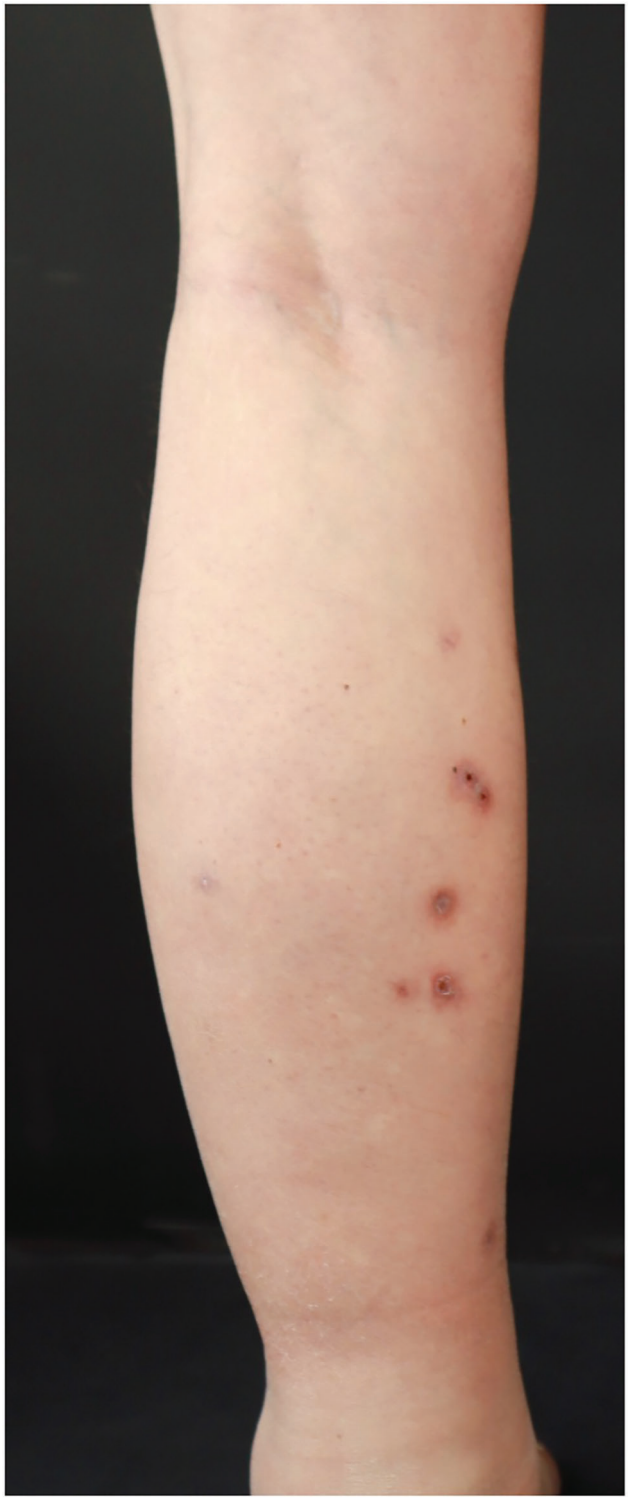

FIGURE 14 Development of in-transit metastasis in the course of pT2a pN3c M0: The clinical picture of the metastases on the dorsal lower leg is shown after two rounds of spray cryotherapy under ongoing systemic therapy with pembrolizumab. The surrounding erythema and the flattening of the pigmented metastases as a sign of response to the combined therapy are clearly visible.

Initial data of phase I/II trials on the safety and efficacy of topically applied submicron particle paclitaxel (SPP) as ointment showed that the treatment is safe and well tolerated and provided first evidence for pain reduction and stabilization of metastases derived from breast carcinoma.[65]

Another therapeutic approach in cutaneous metastatic breast carcinoma are chimeric antigen receptors (CARs). These are synthetic molecules giving new specificities to T cells. While they are successful in treating hematologic malignancies, there is still insufficient evidence for the efficacy of CAR-T cells in solid tumors. Tchou et al. discovered that the cell surface molecule c-Met is expressed in approximately 50% of breast tumors prompting the researchers to develop a CAR-T cell that is specific for c-Met and halted tumor growth in immunocompetent mice with tumor xenografts.[66]

SYSTEMIC THERAPY FOR CUTANEOUS METASTASES

Depending on tumor entity and tumor burden, a specific systemic therapy is available, in principle, that may be combined with local procedures as needed. For the majority of tumor entities, the respective guidelines can be consulted for practical use.

ERIBULIN AS STUDIED SUBSTANCE FOR CUTANEOUS METASTASES IN BREAST CANCER

While eribulin suppresses the replication of tumor cells by inhibiting microtubule dynamics, it does not cause depolymerization of existing tubules.

In an observational study, La Verde et al. analyzed the response rates of cutaneous breast cancer metastases treated with eribulin.[67] Overall, 23 patients were included in the study. Of these, 43% exhibited a partial response, 35% stable disease, and 22% progressive primary disease. With respect to the skin response, 26% obtained complete response, 22% partial response, 39% stable disease, and 13% no response. The research team could demonstrate an improvement of symptoms, infiltration, and ulceration. With a median follow-up of 6 months, the median progression-free survival was 4.3 months and the median overall survival was 9.1 months.[67] In Germany, eribulin is approved as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer progressing after at least two chemotherapies. Previous therapies should have included one anthracycline and one taxane, unless these treatments were unsuitable for the patient.

SYSTEMIC THERAPY OF MALIGNANT MELANOMA

Checkpoint inhibitors and tyrosine kinase inhibitors

Data from prospective studies on response rates of cutaneous metastases to anti-PD1 antibodies and tyrosine kinase inhibitors are lacking or poorly presented. In a retrospective analysis of melanoma patients, Zaremba et al. showed a comparatively poor efficacy of anti-PD1 monotherapy in stage IIIC patients with unresectable skin metastases on the leg. The authors suggest the cause to be a special tumor immunology that restricts tumor spreading to locoregional metastases for a long time, but also reduces the response to PD1 inhibitors.[68]

Novel therapeutic approaches: Combination of systemic therapies with local procedures

ECT and checkpoint inhibitors: In a study of Campana et al., it was shown that the combination of PD1 inhibitor and electrochemotherapy achieved a higher response rate in cutaneous melanoma metastases than treatment with checkpoint inhibitor alone.[69] Given that electrochemotherapy is known to induce immunogenic cell death, its combination with immune checkpoint inhibitors might be beneficial. In this matched retrospective cohort analysis, the scientists studied the efficacy of electrochemotherapy in cutaneous melanoma metastases in combination with pembrolizumab. For this purpose, three different cohorts of melanoma patients in stage IIIC–IV were compared: pembrolizumab alone, pembrolizumab plus electrochemotherapy, and electrochemotherapy as monotherapy. The groups were comparable with respect to age, gender, performance status, and size of skin metastases. The local objective response rate (ORR) was higher in the group with pembrolizumab plus electrochemotherapy than in the pembrolizumab group (78% and 39%, respectively, $p < 0.001$). The 1-year rates for local progression-free survival were 86% and 51%, respectively ($p < 0.001$), and the 1-year rates for systemic progression-free survival were 64% and 39%, respectively ($p = 0.034$). The 1-year overall survival rates were 88% and 64%, respectively ($p = 0.006$). These results indicate that the skin-directed therapy with electrochemotherapy improves superficial tumor control in melanoma patients treated with pembrolizumab (Figure 15a, b). Interestingly, the colleagues observed a longer progression-free and overall survival in the group with pembrolizumab plus electrochemotherapy than in the group with pembrolizumab monotherapy.[69]

The combination of immune checkpoint inhibitors with electrochemotherapy results in a higher response rate.

T-VEC and checkpoint inhibitors: Intralesional therapy with T-VEC in combination with ipilimumab was studied in patients with advanced melanoma (stage IIIB–IV) in a phase Ib trial with 19 patients.[64,70] No dose-limiting toxicities were observed. The objective response rate was 50%. A durable response (more than 6 months) was obtained in 44% of the patients. Progression-free survival and overall survival were 50% and 67%, respectively.[70] In another phase II trial, 198 patients with stage IIIB–IV melanoma were randomized to T-VEC plus ipilimumab versus ipilimumab alone.[64,71] The study reached its primary endpoint, a significantly higher objective response rate in the combination group compared to the ipilimumab group (39% vs. 18%; odds ratio, 2.9; 95% confidence interval: 1.5–5.5; $p = 0.002$). Compared to the arm with ipilimumab monotherapy, more patients in the combination arm experienced side effects of all grades (98% vs. 95%) and of grade ≥ 3 (45% vs. 35%).[64,71]

In a phase Ib trial on T-VEC with pembrolizumab in patients with advanced melanoma (stage IIIb–IV), 21 patients were treated.[64,72] There was an objective response rate of 62% (complete response rate 33%) without dose-limiting toxicity. In the subsequent phase III trial, patients ($n = 713$) with stage IIIB to IVM1c melanoma were treated with pembrolizumab with or without T-VEC. However, Chesney et al. could show that the combination did not significantly improve progression-free or overall survival compared to the monotherapy.[51] The same combination is studied as neoadjuvant therapy in patients with resectable stage III cutaneous melanoma with clinically palpable lymph node metastases (NCT03842943).

Several other trials are ongoing combining T-VEC with various agents, for example, with the chemotherapeutic melphalan administered by isolated limb perfusion (NCT03555032), with dabrafenib and trametinib in BRAF-mutated melanoma (NCT03088176), and with autologous CD1c (BDCA-1) positive myeloid dendritic cells (NCT03747744).[64]

In addition, other therapy combinations are being studied in clinical trials.[73] These include the identification of new immune checkpoint inhibitors (anti-LAG3, GITR agonist, and anti-TIGIT), adoptive cell therapy, vaccines, TCR therapy, IL-2 agonists, new targets for targeted therapies (new MEK or RAF inhibitors, inhibitors of HDAC, IDO, ERK, Axl, ATR, and PARP). In many cases, only preliminary efficacy data from early-phase studies are available that need to be confirmed in larger patient cohorts. Ongoing studies will further clarify the exact roles of these agents.[64]

NOVEL THERAPEUTIC APPROACHES: COMBINATION OF SYSTEMIC THERAPIES WITH LOCAL PROCEDURES IN MERKEL CELL CARCINOMA

Agonists of toll-like receptors and genetically engineered viruses are other remarkable immune therapeutic strate-

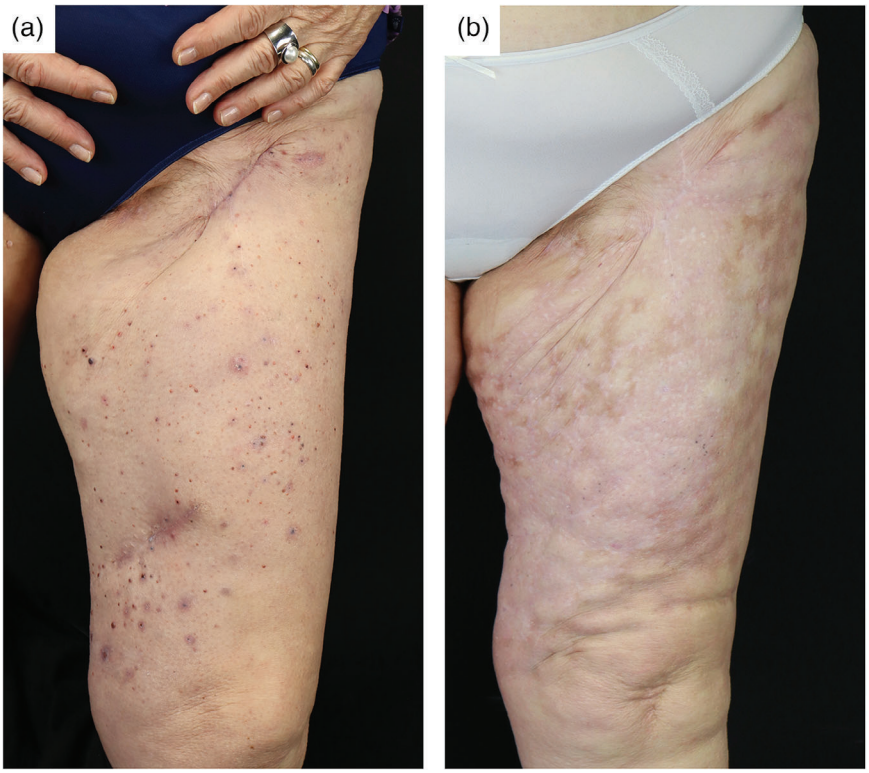

FIGURE 15 (a) Development of pigmented and depigmented in-transit metastases in malignant melanoma under adjuvant immunotherapy with pembrolizumab. This was followed by a sequential combined therapy: ECT with bleomycin 15 mg/m^2 BSA followed by a combination immunotherapy with ipilimumab/nivolumab. (b) Clinical findings 24 months after two cycles of ECT and during ongoing immunotherapy: Clinically, there is a complete remission of the in-transit metastases. Incidental findings show residual erythema and depigmented areas corresponding to the puncture channels of the hexagonal probe.

gies studied in Merkel cell carcinoma. Toll-like receptor agonists promote inflammatory changes in the microenvironment of the tumor by increasing the infiltration of $CD8^+$ and $CD4^+$ T cells and antigen-presenting cells, as well as the expression of chemokines and cytokine-related genes to reverse immunosuppressive mechanisms and facilitate local and systemic immune responses. These agents can promote the regression of the tumor prior to surgery and/or radiotherapy. In a pilot study, intratumoral G100, an agonist of toll-like receptor 4, showed promising results in patients with locoregional tumors with respect to the response and regression of the tumor.

In patients with localized or locally advanced Merkel cell carcinoma, administration of T-VEC prior to surgery and/or radiotherapy is investigated as monotherapy or in combination with immune checkpoint inhibitors to determine response rates and immunological changes in the microenvironment of the tumor (NCT02819843, NCT02978625, NCT03458117).[74]

In addition, therapeutic vaccines targeting tumor-associated antigens or viral oncoproteins are also being developed, as they may be interesting in the perioperative phase of skin cancers like Merkel cell carcinoma to reduce the tumor volume, eliminate potential micrometastases, and, ultimately, to prevent recurrence.[74] Clinical trials are currently underway to investigate vaccines in metastatic or locally advanced Merkel cell carcinoma (NCT04160065, NCT04246671). Interestingly, IFx-Hu2.0 is an experimental intralesional vaccine inducing the expression of the emm55 gene by tumor cells leading to a broad immune response that may overcome the primary and secondary resistance against immune checkpoint inhibitors in patients with advanced skin cancer including Merkel cell carcinoma (NCT04853602).[74]

SYSTEMIC THERAPY FOR CUTANEOUS METASTASES FROM LUNG CARCINOMA

Individual, solitary skin metastasis is usually treated by surgery alone or in combination with chemotherapy. If required, the treatment may also be combined with radiation. It has, however, been shown that patients with skin metastases originating from lung carcinoma have a poorer outcome despite treatment with a combination of these methods.[75]

Resection is not possible if multiple cutaneous lesions are present. In such a case, chemotherapy is the primary treatment option. Specific substances, such as cisplatin, cyclophosphamide, adriamycin, mitomycin, interferon-beta, etoposide and carboplatin, are used for chemotherapy.[75] Radiation is usually not effective in patients with skin metastases derived from lung cancer. Coslett et al. and Hidaka et al. investigated the treatment of three patients with radiation alone. In these studies, the survival time was between 1.8 months and one year and thus significantly shorter than after surgery or chemotherapy.[75–77]

For the treatment of skin metastases, the attending physician should follow the directives for systemic therapies specified in the guidelines. The choice of

the systemic therapy depends on various factors including the presence of driver mutations, PD-L1 expression, ECOG status, histological subtype, and previous therapies.[78]

SYSTEMIC THERAPY IN SQUAMOUS CELL CARCINOMA

Approximately 80% of the metastases derived from cutaneous squamous cell carcinomas occur locoregionally as satellite metastases, in-transit metastases, or locoregional lymph node metastases. For locoregional metastases detected at an early stage, the option of R0 resection exists. Apart from local therapeutic procedures, systemic therapies specified in the current guidelines are available for inoperable situations.[60]

Novel therapeutic approaches for cutaneous squamous cell carcinoma

Several clinical trials are currently ongoing, for example, with combinations of checkpoint inhibition and EGFR inhibition (DRKS00017255). Moreover, intralesional administration of PD-1 inhibitors in locally advanced squamous cell carcinoma is investigated in trials (NCT03889912). Another therapeutic approach is the combination of an anti-PD1 antibody with RP1, an oncolytic herpes simplex virus (NCT05220748, NCT03767348). In addition, other combination strategies are currently being investigated: RM-1995 photoimmunotherapy in combination with pembrolizumab (NCT05220748) or NKTR-255 in combination with cetuximab (NCT04616196). NKTR-255 is a cytokine intended to regulate the activation and proliferation of T cells and natural killer cells in order to support their anti-tumor effect.

ASPECTS OF PALLIATIVE CARE

Skin tumors and cutaneous metastases from various primary tumors showing exophytic growth are observed in 5%–10% of the patients in a palliative situation, especially in the final months of life.[79] Palliative care often requires other standards, especially because the affected patients usually suffer from several distressing symptoms.[80] Cutaneous metastases are often associated with high psychological burden and reduce the quality of life, in particular in case of ulcerative disintegration of the tumors or if they cause cosmetic defects, produce exudate, or become infected (Figure 16). These conditions may generate a putrid, feculent odor, while bleeding and pain may develop as complications.[81,82] Given that exulcerating wounds have a negative impact on self-esteem, they often result in social withdrawal, concealment of disease severity, and avoidance of physical contact. Disgust and shame towards the own body is not uncommon. Social withdrawal may increase anxiety, and patients may despair to such an extent that they wish to end their own lives. Accordingly, the care of these critically ill patients requires a high level of empathy, sensitivity, as well as communicative and professional competence.[83–85]

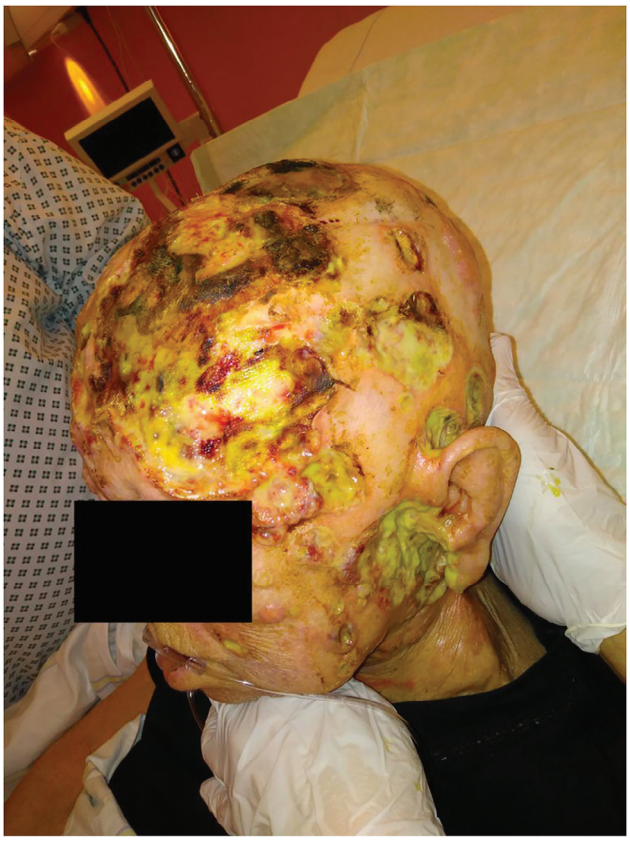

FIGURE 16 Locally advanced cutaneous squamous cell carcinoma with multiple exulcerated cutaneous in-transit metastases and lymph node metastases. There are clinically clearly evident exulcerated tumor nodules accompanied by pronounced odor formation. The patient refused conventional medical treatment and had received palliative care for symptom control.

Skin tumors and cutaneous metastases from various primary tumors showing exophytic growth are observed in 5%–10% of the patients in a palliative situation, especially in the final months of life.

In this context, these lesions may generally be referred to as malignant wounds, defined as "malignant lesions of the skin caused by a primary skin tumor, a skin metastasis from another primary tumor, or the penetration of a tumor from deeper tissue layers".[86] A comprehensive wound-specific history is also required in the palliative situation and should include the resulting social and psychological consequences. Consultation of a wound expert for assessment and treatment planning is recommended. Given that malignant wounds may cause severe pain, this aspect should receive special attention and should be considered, in particular, during dressing change, for example, by administration of a short-acting opioid (Table 2).[86]

TABLE 2 Treatment of malignant wounds in the palliative situation (summary from[83,86]).

Psychosocial aspects	- The patient should not be reduced to the wound - Self-management and sense of control should be strengthened - Personal and interpersonal changes and consequences should be actively addressed
Pain relief	- Wound care should be performed in an atraumatic manner (for example, non-adhesive dressings, avoidance of mechanic irritation, tension-free application of dressings) - Administration of a short-acting analgesic before dressing change - Local analgesic therapy, if necessary - Lymphatic drainage in case of associated lymphedema, if necessary
Reduction of odor	- Careful and gentle cleansing, use of wound antiseptics - Consider local or systemic use of metronidazole (for wounds with anaerobic colonization) or local use of chlorophyll solution - Use wound dressings with activated carbon or antiseptic components - In case of strong exudation, absorbent secondary dressings should be applied - Consider surgical necrosectomy - Consider odor absorption or aromatization in the room
Prevention and management of bleeding	- Atraumatic dressing change (for example, use of non-adhesive wound dressings, moistening of dressing material prior to removal) - Assessment of anticoagulant medication - Preparation of an emergency plan for potential lethal bleeding and its communication with all parties concerned - Take local (cooling and hemostyptics) and, if necessary, systemic (antifibrinolytics) measures

The analgesic therapy should be performed in consensus with palliative healthcare professionals or pain therapists and should be adapted to the quality of pain (nociceptive and/or neuropathic).[87] Local treatment procedures (for example, electrochemotherapy or radiotherapy, as mentioned above) may also be suitable for therapy.[33] Psychosocial problems of patients or relatives should be actively addressed by the treatment team, and specialist support, for example by psycho-oncologists, should be offered. In this context, the preservation and promotion of social integrity are paramount.[83] Accordingly, the care of palliative patients with malignant wounds should be performed by a multi-professional team while continuously re-evaluating the wishes of those affected.[33,79]

Palliative care of patients with malignant wounds often requires interdisciplinary cooperation and a high level of empathy.

CONCLUSION

Irrespective of their entity, cutaneous metastases present a challenge in medical care. Local procedures may be combined with systemic therapies. In addition, novel procedures are being investigated in trials. Good cooperation between primary care physicians and dermato-oncologists is of crucial importance to provide patients with adequate therapy.

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CONFLICT OF INTEREST STATEMENT

None.

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CME QUESTIONS/ LERNERFOLGSKONTROLLE

1. Welche Aussage zu kutanen Metastasen ist richtig?
   a. Das Kolonkarzinom metastasiert häufig in die Haut des Kopf-Hals-Bereiches.
   b. Das maligne Melanom ist der häufigste Tumor bei der Frau, der kutane Metastasen setzt.
   c. Kutane Metastasen, die im lokoregionären Abflussgebiet entstehen, werden als Satellitenmetastasen bezeichnet.
   d. Kutane Metastasen, die in der Umgebung des Primarius nicht mehr als 2 cm entfernt auftreten, sind In-Transit-Metastasen.
   e. Kutane Filiae beim malignen Melanom sind stets pigmentiert.

2. Welche Aussage ist **falsch**?
   a. Die Immunhistochemie ist ein wichtiger Bestandteil zur Differenzierung der Metastasen.
   b. S 100, Melan A und HMB45 ist klassische Marker für das maligne Melanom.
   c. Das Merkelzellkarzinom zeigt sich deutlich positiv für TTF1 in der Immunhistochemie.
   d. CK 20 ist ein typischer Marker zur Differenzierung zwischen dem kleinzelligen Bronchialkarzinom und dem Merkelzellkarzinom.
   e. Das kleinzellige Bronchialkarzinom weist eine Positivität für TTF-1, CAM5.2, CK8/18, Ber-EP4 auf.

3. Welche Aussage triff zu?
   a. Die Dermatoskopie ist diagnostisches Mittel der Wahl zur Differenzierung kutaner Metastasen.
   b. In der Dermatoskopie kutaner Metastasen finden sich selten vaskuläre Strukturen als Zeichen der Neovaskularisation.
   c. Die Dermatoskopie kann unterstützend zur Diagnostik kutaner Metastasen herangezogen werden.
   d. Es finden sich selten serpentinenartige (lineare-irreguläre) und arborisierende Gefäße.
   e. Punktförmige Gefäße finden sich immer bei kutanen Metastasen.

4. Welche Aussage zur Therapie der kutanen Metastasen beim malignen Melanom trifft zu?
   a. Es gibt keine zugelassenen Substanzen zur lokalen Therapie.
   b. Lokale Immunmodulatoren sind Therapie der Wahl bei disseminiertem Befall.
   c. Die Kombination von Elektrochemotherapie und PD1-Antikörpertherapie ist der Monotherapie überlegen.
   d. T-VEC ist in allen Stadien (M1a–M1d) zugelassen.
   e. Miltefosin ist eine mögliche lokale intraläsionale Therapieoption

5. Welche Aussage zur Therapie von Mammakarzinommetastasen ist richtig?
   a. T-VEC ist eine zugelassene Therapieoption.
   b. Die Elektrochemotherapie ist eine gute Therapieoption im palliativen Setting.
   c. Miltefosin ist in der Leitlinie als lokale Therapieoption genannt und ist in Deutschland verfügbar.
   d. Eribulin ist in Deutschland als First-Line-Monotherapie für die Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Brustkrebs zugelassen.
   e. Die Elektrochemotherapie wird als kurative Intention eingesetzt.

6. Welche Aussage zur Klinik von kutanen Metastasen ist **falsch**?
   a. Die Schleimhaut kann auch ein Manifestationsort für Metastasen sein.
   b. Kutane Melanommetastasen können pigmentiert oder depigmentiert sein.
   c. Klinisch imponieren Metastasen beim Mammakarzinom immer als derbe Knoten.
   d. Das Erysipelas carcinomatosa ist eine Sonderform der Metastasierung beim Mammakarzinom.
   e. Die Alopecia neoplastica kann bei Patienten mit Mammakarzinom auftreten.

7. Welche Aussage zur Elektrochemotherapie ist richtig?
   a. Paclitaxel ist das Chemotherapeutikum der ersten Wahl.
   b. Cisplatin kann gemäß ESOPE-Protokoll sowohl intratumoral als auch intraläsional verabreicht werden.
   c. Das Wirkprinzip stellt die Elektroporation dar.
   d. Die ECT ist nur zugelassen für das maligne Melanom.
   e. Muskelkaterartige Schmerzen sind eine sehr seltene Nebenwirkung.

8. Welche Aussage zu T-VEC ist richtig?
   a. Ist zur Behandlung von kutanen Metastasen im Stadium M1d zugelassen.
   b. Kann in kutane, subkutane oder lokoregionäre

Lymphknotenmetastasen beim malignen Melanom appliziert werden.
c. Stellt eine Off-Label-Therapie beim malignen Melanom dar und muss bei der Kasse beantragt werden.
d. Wird bei allen Injektionstagen in derselben Dosierung verabreicht.
e. Ist eine Standardtherapie zur Behandlung kutaner Metastasen des Kolons.

9. Welche Aussage für die Betreuung von Palliativpatienten ist **falsch**?
   a. Psychosoziale Probleme können durch exulzerierende Tumoren und Metastasen entstehen.
   b. Schmerzen sind keine Komplikation maligner Wunden.
   c. Für eine letale Blutung sollte ein Notfallplan erstellt werden.
   d. Die Gabe eines kurzwirksamen Analgetikums vor einem Verbandswechsel sollte erwogen werden.
   e. Starke Geruchsbildung durch zerfallende Tumoren kann zum Verlust des Selbstwertgefühls führen.

10. Welche Aussage zur Versorgung von malignen Wunden ist richtig?
    a. Das Hinzuziehen eines Wundexperten ist in der palliativen Erkrankungssituation nicht mehr notwendig.
    b. Nichtadhäsive Wundauflagen bieten keinen Vorteil für einen schmerzarmen Verbandswechsel.
    c. Ein Ulcus cruris ist *per definitionem* eine maligne Wunde, da meist komorbide eine schwere Herzinsuffizienz vorliegt.
    d. Psychosoziale Probleme sollten aktiv durch das Behandlungsteam angesprochen werden.
    e. Maligne Wunden sind eines der häufigsten Probleme bei Palliativpatienten.

Liebe Leserinnen und Leser, der Einsendeschluss an die DDA für diese Ausgabe ist der 30.September 2024.

Die richtige Lösung zum Thema "Okkludierende kutane Vaskulopathien als Ursachen chronischer Unterschenkelulzerationen" in Heft 4/2024 ist:
1d, 2b, 3a, 4c, 5b, 6b, 7d, 8e, 9a, 10a

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