

## A Eleven-Year Retrospective Study of Metastatic Carcinomas of the Skin: Own Experience

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**SUMMARY** A brief overview of some metastatic carcinomas of the skin is given. The basic principles of the metastatic process, the distribution of metastases and clinical features of the most common metastatic carcinomas of the skin are presented, along with an account of our own data based on the records of Dermatohistology Registry of the University Department of Dermatology and Venereology, Zagreb University Hospital Center, for the 1994-2004 period and presentation of 22 cases of cutaneous metastases from this eleven-year period.

**KEY WORDS:** metastatic carcinoma of the skin, site of distant skin metastasis, type of skin metastasis

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### INTRODUCTION

Metastasizing is defined as development of secondary implants (metastases) which are no longer in contact with primary tumor, and can be found in distant tissues. The ability to metastasize is the most important property of malignant tumors. Not all malignant tumors metastasize. Exceptions are basal cell carcinomas and some primary central nervous system tumors (1).

Cutaneous metastases are defined as cancer involving the dermis or subcutaneous tissue that was not contiguous with the primary neoplasm (2). Malignant tumors spread into the skin *per continuitatem*, by lymphatic or hematogenous dissemination (1). Metastases to the skin can appear many years after extirpation of the primary tumor (3).

In previous autopsy series the frequency of cutaneous metastases ranged from 0.7% to 4.4%

(2,4-7), but a more recent study reports 9.0% (8). In previous reports, Lookingbill *et al.* have reported an overall frequency of 4.7% for skin metastases in patients with carcinoma, excluding melanoma (9). However, in a more recent study the same authors noted cutaneous metastases in 420 of 4020 (10.4%) patients with metastatic disease (2). According to Braun Falco *et al.*, between 3% and 10% of cancer patients have cutaneous metastases (10).

### The metastatic sequence

Metastatic process is very complex, and consists of several steps (11). Detachment from the primary tumor is the initial phase. It is believed that tumor cells are more easily separable from each other than normal ones. Invasion of tissue and in-

travasation of vessel is very similar and proceeds in the following sequence: attachment to matrix or basement membrane receptors, secretion of hydrolytic enzymes to degrade the matrix, and finally movement of tumor cells into the region of degraded matrix. Upon entering the circulation, tumor cell either remains and proliferates at the site of invasion and releases emboli, or detaches from the vessel wall and circulates. Once tumor cells enter the circulation, both hematogenous and lymphatic dissemination should be considered, due to extensive communications between blood and lymph vessels.

Whatever the distribution pattern, stasis of an embolic cell in the recipient tissue and extravasation must occur. Extravasation and invasion of target organ consist of a sequence similar to that in intravasation (attachment to vessel wall, enzymatic degradation of vessel wall, and finally tumor cell moving out). The final step in the metastatic process is tumor cell proliferation in the recipient tissue. There are several mechanisms involved to enable successful proliferation: 1) presence of organ specific growth factors, to which tumor cells are responsive; 2) increased or decreased sensitivity of tumor cells to growth factors or growth inhibitors; 3) production of autocrine growth factors; and 4) production of angiogenic factors.

### Distribution of metastases

There are three major distribution patterns in metastatic disease (11). The first one is mechanical implantation, which accounts for 50%-60% of all cases. Multicellular emboli, which can be homotypic or heterotypic (includes not only tumor cells but also platelets, lymphocytes, etc.), are being arrested in capillary bed due to their size. Examples of this type of distribution are head and neck cancers as well as melanoma, although melanoma also has a tendency to metastasize to specific organs such as lung, liver, brain, etc. Another distribution pattern is organ specific, which occurs *via* organ specific receptors on tumor cells, adhesion molecules, chemotaxis, or simply enhanced tumor cell proliferation within a given organ. Examples of nonspecific or random pattern of metastasizing are some highly aggressive metastatic tumors that are capable of adhering to vessel wall of many different organs and proliferate in various tissues. Autocrine growth factors are produced by tumor cells and provide a stimulus for cell growth and proliferation regardless of the local environment, and local growth factors favor nonspecific metastases.

### ETIOLOGY AND PATHOGENESIS

Cutaneous metastasis may represent the first sign of a tumor, the first sign of tumor spread from its primary organ, or the first sign of recurrence of a cured tumor (10). The most common tumors are the most common sources of skin metastases. According to a retrospective study in 4020 patients, performed by Lookingbill *et al.*, the most common were skin metastases caused by melanoma, breast cancer, nasal sinus cancer, cancer of the larynx, endocrine gland cancer, oral cavity cancers, followed by esophageal cancer, urinary bladder cancer, cancer of unknown primary site, gallbladder and bile duct cancer, and liver cancer (2). Considering the origin of skin metastases according to sex, the most common sources of skin metastases in men were melanoma, lung, colon and rectum cancer, oral cavity cancers, larynx, kidney, upper digestive tract, breast, nasal sinus, urinary bladder, esophagus, endocrine gland, stomach, pancreas and liver (2). In women, breast cancer was by far the most common primary site of skin metastasis, followed by melanoma, ovary, oral cavity, lung, colon and rectum, endometrium, urinary bladder, uterine cervix, stomach, bile duct, pancreas and endocrine glands (2). It was noted that tumor of unknown primary site was rather frequently the source of skin metastases in both men and women.

### TYPES OF SKIN METASTASES

As noted by other investigators, most skin metastases appear as nodules (12). The color differs and rarely provides useful diagnostic information. Melanoma metastases may be pigmented, while the ones originating from renal cell carcinoma are frequently red or purple, mimicking hemangiomas (13,14). Inflammatory skin metastases are most frequently caused by breast cancer (15). However, cancers from other sites can produce this type of metastases, such as cancer of the pancreas (16), rectum (2), lung (2), ovary (17), parotid glands (18) as well as melanoma (19). Cicatricial metastasis is usually caused by breast carcinoma, but may also arise from renal cell carcinoma. Bullous lesions were described in some patients with breast cancer (2), and sometimes a zosteriform pattern of bullous distribution has been reported (20). Melanomatosis is seen in patients with malignant melanoma who have an increased production of melanin that is spread hematogenously to all areas of the skin, resulting in slate-gray skin color as well as in urine discoloration (10).

**Table 1.** Sites of distant skin metastases (modified from Lookingbill *et al.* (2))

Primary site	Sites of distant skin metastases
Breast	Back, scalp, upper extremities, abdomen, neck, shoulders, lower extremities, flank, chest*, buttocks, face
Melanoma	Chest, lower extremities, upper extremities, neck, scalp, abdomen, back, face, shoulders, buttocks, flank, genitalia
Unknown	Lower extremities, abdomen, neck, scalp, face, back, upper extremities, genitalia, flank, chest
Lung	Chest, abdomen, scalp, neck, back, face, upper extremities, lower extremities
Oral cavity	Neck, scalp, face, chest, back, upper extremities
Colon and rectum	Chest, back, abdomen, scalp, face, genitalia
Urinary bladder	Chest, flank, abdomen
Ovary	Abdomen, lower extremities
Larynx	Chest, abdomen
Kidney	Scalp, face, neck, chest, upper extremities
Esophagus	Chest, abdomen, scalp, shoulders, upper extremities, lower extremities
Nasal sinuses	Scalp, neck, back, abdomen
Endometrium	Abdomen, scalp, upper extremities, lower extremities
Endocrine glands**	Scalp
Uterine cervix	Chest, abdomen, genitalia
Pancreas	Chest, abdomen, upper extremities
Stomach	Chest

\*contralateral chest wall involvement without ipsilateral involvement; \*\*site not specified in one

### Breast cancer

Carcinoma of the breast is a common cancer in women, and may frequently involve the skin as well. According to some authors, 23.9% of patients with breast cancer have cutaneous metastases (2). Also, the most interesting parts of history tackle breast carcinoma and its cutaneous involvement (21). So, Velpeau in 1838 described "cancer en cuirasse", the name chosen because of the resemblance to the metal breastplate of a cuirassier (21). Paget described persistent breast eczema with breast cancer in 1874, and the disorder has been named after him (21). In 1893, Hutchinson described carcinoma erysipelatoides (inflammatory metastatic carcinoma of the breast): "The erythematous infiltration of the skin was very superficial, and was attended simply by redness with a slight degree of induration. Until touched by the finger the condition might easily have been taken for a slightly-marked form of erysipelas, the spreading edge presenting much more vivid congestion than the rest of the patch" (21).

Breast carcinoma shows eight different clinicopathologic types of skin involvement (22).

**Inflammatory metastatic carcinoma (carcinoma erysipelatoides).** Superficial lymphatic metastases elicit an intense inflammatory re-

sponse mimicking erysipelas. There are irregular erythematous bands (10).

**Cancer en cuirasse** shows a diffuse morphealike induration of the skin. It is rarely seen in some other metastasizing malignancies such as lung, gastrointestinal tract, kidney, etc. (2,12,21-23). It usually begins as scattered, firm, lenticular papulonodules overlying an erythematous or red-blue smooth cutaneous surface (22).

**Telangiectatic metastatic breast carcinoma** presents with violaceous papulovesicles resembling lymphangioma circumscriptum (21).

**Nodular metastatic carcinoma** usually appears as multiple papulonodules or nodules. Sometimes they may be solitary, rarely ulcerated or bullous (2,9,24-26).

**Alopecia neoplastica** is caused by haematogenous rather than lymphatic spread, unlike the previously mentioned forms (21,27-30). It often presents as circular areas of alopecia like alopecia areata, is painless, nonpruritic, well-demarcated, of red-pink color with smooth surface (13). Since alopecia neoplastica might be the first sign of a metastatic breast cancer, breast examination and lesion biopsy should be performed in adult women showing this clinical picture (21).



**Figure 1.** Alopecia neoplastica in a patient with breast cancer.

**Paget's disease** is a sharply demarcated eczema on the nipple or areola, usually but not always associated with underlying breast cancer (21). Nipple biopsy should be obtained in a woman with a history suspect of Paget's disease, because the cured Paget's disease still indicates underlying breast cancer (21,31).

**Breast carcinoma** of the inframammary crease is characterized by a cutaneous exophytic nodule resembling primary cutaneous squamous or basal cell carcinoma (32,33).

**Metastatic mammary carcinoma** of the eyelid with histiocytoid histology (21) appears as painless eyelid swelling with induration, or as a nodule.

### Melanoma

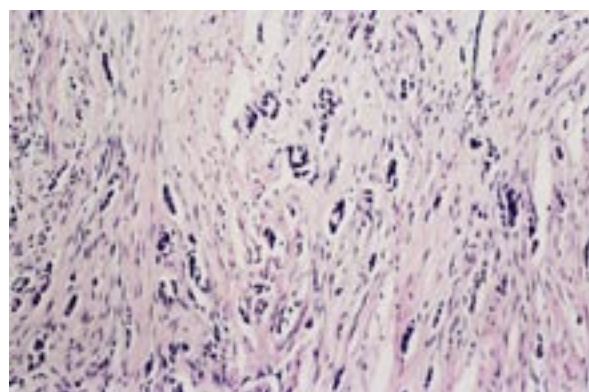
Melanoma is the third most common cause of skin metastases (24). They are usually heavily pigmented, although there are cases of amelanotic ones, too. They present as a few or showers of nodules (21).

### Renal cell carcinoma

Very often skin metastases are the first sign of renal cell carcinoma (13,34) but they may also appear 10 years after the initial cancer diagnosis (35). The metastases appear as well-circumscribed nodules of flesh-, violaceous, or blue-colored, but also as a cutaneous horn (34,36).

### Carcinoma of the lung

Skin metastases may appear, as a localized cluster of cutaneous nodules, on any cutaneous surface, although the most common sites are the chest wall and posterior abdomen. Oat cell carcinoma of the lung usually metastasizes to the skin of the back (2,21).



**Figure 1a.** Histopathology of the same patient. The tumor cells form small groups of single rows between fibrotic and thickened collagen bundles. (H&E, x75)



**Figure 2.** Cutaneous metastases in a patient with renal cell carcinoma.

noma of the lung usually metastasizes to the skin of the back (2,21).

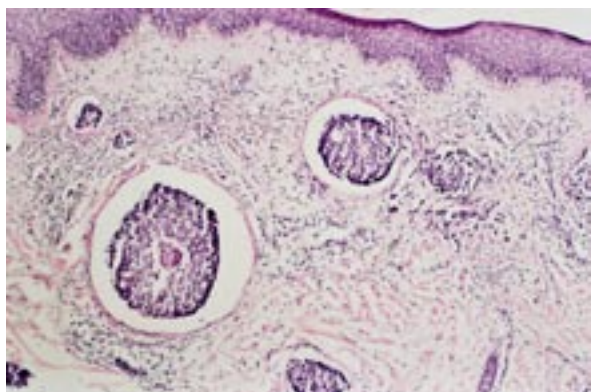
### Sister Mary Joseph nodule

Sister Mary Joseph was an operating room nurse at The Mayo Clinic. She was the first one to report that patients with umbilical nodule she noticed during preparation for surgery usually had intra-abdominal metastases. Some tumors of the gastrointestinal system (stomach, colon and pancreas) may give metastases to the umbilicus (10).

### HISTOPATHOLOGY

Histologic pattern in cutaneous metastatic disease may be specific or nonspecific. Some clinical and histologic features may indicate a primary tumor. Specific histologic stains as well as the use of immunohistochemistry and electron microscopy techniques are enormously helpful in the diagnosis of cutaneous metastatic diseases (37).





**Figure 3.** Breast carcinoma metastatic to the skin – histopathology. Diluted lymphatics contain groups of tumor cells. (H&E, x40)

### DIFFERENTIAL DIAGNOSIS

As discussed under clinical appearance, skin metastases may mimic a wide variety of disorders such as erysipelas, alopecia areata, eczema, various primary carcinoma cutis, etc. Careful examination and thorough patient history should be undertaken to avoid misdiagnosis.

### TREATMENT

Depending on the type of tumor, symptoms, and degree of tumor burden, treatment options include chemotherapy, radiotherapy, and excision. Cutaneous metastases can serve as a marker of response to systemic therapy (38). The presence of cutaneous metastases usually urges the need of change in therapy for primary tumor.

### COURSE AND PROGNOSIS

Skin metastases represent a poor prognostic sign, especially in patients suffering from cancers of the lung, ovary, upper respiratory tract or upper digestive tract (2).

### PRESENTATION OF 22 PATIENTS WITH METASTATIC CARCINOMAS OF THE SKIN 1994-2004: OWN DATA

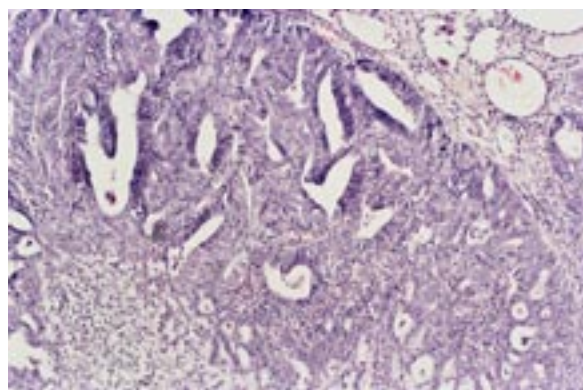
Twenty-two patients with histologically verified diagnosis of metastatic skin disease were recorded at our Department during the 1994-2004 period. There were five men and 17 women, age range 46-84 in men and 42-88 in women. In men, the primary tumor site was lung in 2 cases, whereas in the remaining three cases primary tumor was unknown at the time of histologic diagnosis (Table 2). In women, breast cancer was by far the most common cause of skin metastases (n=12), in

three cases the primary site was unknown, whereas malignant melanoma and primary gynecologic tumor were found in one case each (Table 3).

As for clinical manifestations, metastases of lung cancer appeared as noduli located on the abdomen, back, and extremities. Cutaneous metastases of breast cancer appeared as carcinoma *en cuirasse*, carcinoma erysipelatoides, cicatricial alopecia (Fig. 1), different types of noduli and papules, erythema, exanthema and edema. Carcinoma of the ovary presented as tumorous lesions in the region of abdominal wall and thorax (Fig. 3). Malignant melanoma skin metastases showed a clinical picture of elephantiasis of the extremity, with erythematous, papular infiltrate.



**Figure 4.** Cutaneous metastases in a patient with primary carcinoma of the ovary.



**Figure 4a.** Tumor tissue consists of atypical glandular formations which are covered by atypical cylindrical epithelial cells. (H&E, x75)

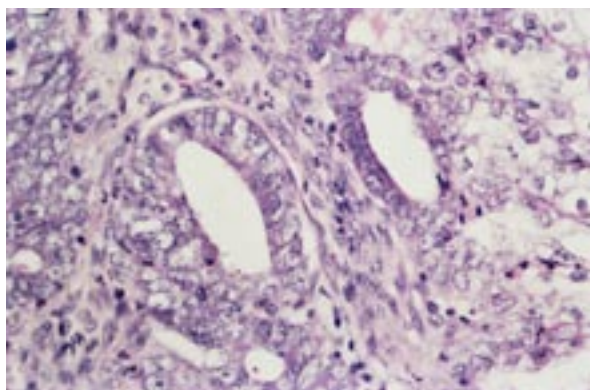


Figure 4b. Detail, (H&E, x100)

## CONCLUSIONS

Dermatologists are nowadays encountering cutaneous metastases not only from primary melanomas and squamous cell carcinomas but also from other cancers giving rise to skin metastases. According to recent literature, between 3% and 10% of cancer patients have cutaneous metastases. We report on 22 patients with metastatic skin disease during a 11-year period (1994-2004). The incidence of various tumors that are metastatic to the skin correlated well with the prevalence of primary malignant tumors in each sex. Breast cancer was most common in women and lung cancer in men.

**Table 2.** Cutaneous metastases in our patients

Patient No.	Age (yrs)	Sex	Primary tumor	Metastasis
1	61	M	Unknown	Abdominal noduli
2	66	M	Unknown, bone metastasis, right axilar metastasis, abdominal tumorous infiltrates in which malignant cells were cytologically verified	Scalp – 3 infiltrated lesions, with central erosions and crusts
3	84	M	Unknown	Umbilical and periumbilical red elevated lesions, crusted
4	46	M	Carcinoma pulmonum	Abdominal noduli, with lymph discharge, 2 infiltrates on the back
5	68	M	Carcinoma pulmonum	Brown-livid noduli on left thigh, left forearm and right hand
6	59	F	Carcinoma mammae	Papulous exanthema under right breast, and on the right side of abdomen. Carcinoma en cuirasse in obs.
7	60	F	Unknown	Edema of right breast and neighboring parts of the chest wall as well as of complete right arm. Skin is red, there are scattered groups of herpetiform vesicles
8	74	F	Carcinoma mammae	Small noduli in the scar area
9	50	F	Carcinoma mammae	Dermatitis papulosa
10	88	F	Unknown	Hand tumors
11	87	F	Carcinoma mammae	Papule on the back
12	67	F	Carcinoma mammae	Erythema in the scar region, on the sternum
13	59	F	Carcinoma mammae	Infiltratio regionalis mammae l. sin. and mammae dex.
14	46	F	Carcinoma mammae	Livid tumorous lesion above scar, with vesicles of pinpoint size on the surface. On the back annular lesions with elevated edge
15	45	F	Carcinoma ovarii metastaticum, primary tumor unknown	Lymphoedema of both legs. Erythematous-livid infiltrate in pubic area
16	65	F	Carcinoma mammae	Trophic ulcer on the left side of the back
17	71	F	Melanoma malignum	Elephantiasis of the left leg, indurated erythematous, edematous infiltrate with papuli
18	63	F	Adenoacanthoma endometrii, Adenocarcinoma ovarii	Tumorous lesions in the region of abdominal wall and thorax. Some lesions of walnut size are exulcerated
19	61	F	Unknown, histologically: Carcinoma mammae	Several white-yellowish half-sphere lesions up to a pea size in the scalp
20	47	F	Carcinoma mammae	Carcinoma erysipelatoides mammae l. sin.
21	42	F	Carcinoma mammae	Noduli in the scalp, nuchal area as well as in the right labium majus
22	45	F	Carcinoma mammae	Cicatricial alopecia in the occipital region

Since skin metastases sometimes represent the first sign of the extranodular spread of primary tumor, the role of dermatologist in the early detection and establishing an accurate diagnosis becomes very important. It is of great importance to diagnose metastatic cutaneous carcinomas as early as possible in order to provide for appropriate treatment of primary cancer, which is very often modified when skin metastases are found.

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