Basal cell carcinoma

Brief S2k guidelines – Basal cell carcinoma of the skin

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Background

Epidemiology and clinical appearance

Statements

• Basal cell carcinoma (BCC) of the skin is the most commonly occurring non-benign tumor in human beings. The aggressive tumor exhibits local infiltration and destructive growth. Metastasis is extremely rare.
• In Germany, the incidence of BCC is approx. 170 new reports per 100,000 inhabitants per year.
• Basal cell carcinoma arises de novo without a precancerous lesion.
• Predilection sites are chronically sun-exposed areas of the skin (face, head, neck, upper chest).
• Pre-disposing genetic factors play a role in disease.
• Patients often have multiple tumors simultaneously or over a span of years or decades.

Basal cell carcinoma (formerly also known as “basalioma”) is a locally destructive epithelial neoplasm with basaloid differentiation. It is the most common cancer in the United States and Australia [1, 2]. In Central Europe basal cell carcinoma is also among the most common malignant tumors. In Germany the incidence is about 170/1 new reports per 100,000 inhabitants annually. The average age is 60 years. Both sexes are affected, but the disease occurs more frequently in men. Approx. 80% of basal cell carcinomas occur in the head and neck region. The most important etiological factors are a genetic pre-disposition with light skin pigmentation and cumulative UV exposure. Basal cell carcinomas can also occur in conjunction with hereditary diseases such as (nevoid) basal cell carcinoma syndrome (Gorlin-Goltz syndrome), xeroderma pigmentosum, and albinism. Additional risk factors include exposure to arsenic and long-term immunosuppression. Tight scar tissue and nevi sebacei are also predisposing factors [3].

Diagnosis and histology

Recommendations

• A biopsy with histological evaluation should be performed on any cutaneous lesion of uncertain benign/malignant nature.

• The diagnosis of basal cell carcinoma is generally made clinically and confirmed by histology. Exceptions are multiple superficial basal cell carcinomas and Gorlin-Goltz syndrome. Light microscopy can help to increase the certainty of a clinical diagnosis.
• In addition to inspecting the tumor, the initial clinical examination should include an inspection of the entire skin surface.
• Along with the diagnosis, histological findings should contain the following information:
  – Histological type
  – Histological depth (maximal vertical tumor diameter in mm)
  – Microscopic examination of resection margins showing no tumor cells / virtually no tumor cells, possibly with minimum distance of the tumor from the resection margin / incomplete resection.
• Imaging studies to rule out metastasis are not generally recommended. They should only be performed if there is clinical suspicion of metastasis or for very advanced primary tumors.
Basal cell carcinoma

The diagnosis is generally made on the basis of clinical findings. Dermatoscopy may be helpful for differential diagnosis [4]. To confirm the diagnosis, it is necessary to obtain a histological analysis; depending on tumor size and treatment approach, this may be with an incision biopsy, excision biopsy, or therapeutic excision [5]. An exception may be made for multiple, superficial tumors or basal cell carcinoma syndrome. Subclinical spread of disease often evades certain detection, and even with modern non-invasive diagnostic techniques can only be detected with microscopy. For pigmented lesions, basal cell carcinoma as well as melanoma must be differentiated. Rather than a biopsy, a complete resection should be performed. For destructive basal cell carcinomas and/or clinical suspicion of infiltration of deep structures, additional imaging studies may be needed for diagnosis.

Basal cell carcinomas are characterized by a large clinical spectrum. Tumors tend to arise on sun-exposed areas of the skin, without any pre-cancerous lesions. The most common subtype, a solid (syn.: nodular) basal cell carcinoma, begins as a flat elevated, circumscribed, yellow-red papule with a string-of-pearl-like margin and typical dilated blood vessels extending from the border into the center of the tumor. There are also other variants such as basal cell carcinoma of the trunk (superficial type) which presents with erythematous plaques and cicatrional basal cell carcinomas which resemble scars. Later erosions and ulcerations can occur. A typical clinical sign of basal cell carcinoma is recurrent, usually punctate bleeding. Histogenetically, basal cell carcinomas arise from cells in the basal cell layer and/or the outer root sheath of the hair follicles. Sometimes they exhibit differentiation resembling certain features of the adnexa (follicles, sebaceous glands, eccrine, or apocrine sweat glands). The histological subtypes of basal cell carcinoma are based on the different patterns of differentiation which are also found in the current WHO histological classification. The following classification has proven useful in clinical practice:

- Basal cell carcinoma of the skin develops over months or years. The lesions later become ulcerative (rodent ulcer) and can also destroy deep tissue structures (ulcus terebrans). If uninhibited growth reaches vital structures (frontal skull base, carotid artery, etc.) the disease can be fatal. Metastasis of basal cell carcinoma is extremely rare. Similar to squamous cell and other carcinomas of the skin, the current staging of basal cell carcinoma is based on the UICC classification. It is useless for clinical practice, however. The T classification is too unspecific and the N and M categories rarely apply to this type of tumor. To ensure the quality of treatment, the following information is useful:
  - Clinical tumor size (horizontal tumor diameter)
  - Localization
  - Histological type
  - Histological spread in depth (vertical tumor diameter in mm)
  - Therapeutic safety margin (for resection or radiation treatment or cryotherapy)
  - Resection margins microscopically without tumor cells/nearly without tumor cells/incomplete resection. This information assumes that the histopathological preparation method of the tumor specimen is also documented.

Therapy

Recommendations

- Surgical treatment with histological control of the complete removal of the tumor with no remaining cells at the resection margins should be offered as the first-line therapy. Surgery may be done with systematic control of the margins (microscopically controlled surgery) or with a tumor-adapted safety margin and conventional histologic examination. For superficial basal cell carcinomas, horizontal excision (shave excision) with conventional histology is also possible (Table 1).

- For local tumors that cannot be removed in sano, as well as for inoperable patients, an interdisciplinary treatment concept is warranted. Usually radiation treatment is performed in such situations (Table 2).
- Patients with basal cell carcinoma syndrome should not be treated with ionizing radiation.
- Alternative treatment procedures – for multiple or superficial basal cell carcinomas, and in inoperable patients – as well as locally destructive procedures (electrodessication, curettage, cryotherapy, laser therapy, and photodynamic therapy as well as local drug treatments with imiquimod or 5-fluorouracil) may be considered (Table 2).
- Until approved, systemic treatment with Hedgehog inhibitors (Vismodegib, LDE225) should be considered in the framework of clinical trials for selected patients with inoperable or metastatic basal cell carcinoma.

Surgical treatment with histological confirmation is the standard procedure for treatment of basal cell carcinoma. If tumor removal is incomplete, all surgical possibilities for re- excision should be exhausted as long as they are feasible given the patient’s overall condition and the tumor spread. This applies in particular to all infiltrative and cicatrional basal cell carcinomas and for infiltration of deeper structures that are not limited to the skin. There is a vast array of treatments, including radiation therapy as well as curettage, cryotherapy, laser therapy, and photodynamic therapy and local drug treatments such as imiquimod and 5-fluorouracil. The disadvantage of these procedures is lacking histological control of the treatment result and a higher rate of recurrence compared to surgery [3]. An overview of risk-associated treatment recommendations is presented in Tables 1 and 2.

In very elderly or multimorbid patients with asymptomatic or low-risk basal cell carcinoma, aggressive treatment approaches no longer seem warranted. The approach should be palliative without a curative intention. Local tumor removal or radiation therapy may be performed to ensure local tumor control and/or improve quality of life in the short-term.
Microscopically controlled surgery

Microscopically controlled surgery is the conservative surgical excision of a tumor (2–4 mm safety margin) with markings followed by a complete histopathological evaluation of lateral and basal margins of the excised material [6]. This allows for topographical classification of subclinical residual tumor and targeted re-excisions if needed, until the surface of the excised material is negative for residual tumor. Even for small unproblematic tumors, the procedure may have advantages. Given the high diagnostic certainty, healthy skin can be spared and only histologically confirmed tumor cells are excised. Processing may be done with cryostat or paraffin sections. Paraffin sections are superior to cryostat sections in terms of the information they can provide.

Radiation treatment

Radiation treatment is indicated for primary inoperability, as well as following incomplete surgical resection (R1, R2) if re-excision is not possible. Radiotherapy is contraindicated in patients with basal cell carcinoma syndrome (Gorlin-Goltz syndrome). In 84–96 % of patients the sole use of radiation therapy to treat basal cell carcinoma can lead to a long-term cure, but it is a more time-consuming method. Radiotherapy of R1 and R2 resections can significantly decrease the rate of local recurrences. Indications also include lacking willingness to undergo surgery, general or local inoperability, R1 or R2 situations and recurrences. In modern treatment concepts, radiation treatment of basal cell carcinoma is mainly done with electrons of adequate energy in individual dosages ranging from 2.0 to 3.0 Gy. For definitive radiation therapy, total dosages of 60 to 70 Gy are used. Postoperatively, total doses of 50 to 60 Gy (R1) or 60 to 70 Gy (R2) may be used. Radiation treatment methods using orthovolt therapy with higher individual doses (e. g., 5 Gy) with a lower total dose can also achieve high rates of tumor control [7–10].

Other treatment methods

Given the local infiltration of basal cell carcinomas, conventional surgery with less precise histological control leaves more residual tumor – depending on the safety margin 5–34 % (Table 3). To prevent recurrences with conventional surgery, larger safety margins must be used, even for small tumors (0.3–1 cm), which puts a greater burden on the patient. Cryotherapy is performed using liquid nitrogen with either a contact or open

Table 1: Recommendations for surgical treatment of basal cell carcinoma (with histological control) by tumor type, localization, and risk of recurrence.

<table>
<thead>
<tr>
<th>Surgical and histological procedures</th>
<th>Recommended indications</th>
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<tr>
<td>Surgery with systematic control of margins (histographic/micrographic surgery)</td>
<td>“Problem localizations” on the face (e. g., lids, lip, nose, and ear) in conjunction with size and histological type as well as recurrent lesions</td>
</tr>
<tr>
<td>Surgery with tumor-adapted safety margin and conventional histology</td>
<td>Small tumors at any localization Larger tumors on the trunk and extremities,</td>
</tr>
<tr>
<td>Horizontal excision with conventional histology</td>
<td>Multifocal, superficial BCC, especially on the trunk and extremities</td>
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Table 2: Therapy alternatives for surgical treatment (without histological control).

<table>
<thead>
<tr>
<th>Type of treatment and indication</th>
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<tr>
<td>Radiation therapy for primary inoperability, as well as after incomplete surgical removal (R1, R2), if re-excision is not possible. Contraindicated in basal cell carcinoma syndrome (Gorlin-Goltz syndrome)</td>
</tr>
<tr>
<td>Cryotherapy: smaller superficial tumors, e. g., on the eyelids. Especially in elderly patients in whom surgery would be a significant burden.</td>
</tr>
<tr>
<td>Immunological treatment with imiquimod, photodynamic therapy (PDT) and local chemotherapy with 5-fluorouracil, especially for superficial BCC and basal cell carcinoma syndrome (Gorlin-Goltz syndrome)</td>
</tr>
<tr>
<td>Hedgehog inhibitors (Vismodegib; LDE225) should only be used in clinical studies on patients with inoperable basal cell carcinoma or metastatic BCC until the drug is approved</td>
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Table 3: Percentage of residual tumor components that may be expected for a given safety margin and tumor type.

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<tr>
<th>Tumor type</th>
<th>Safety margin</th>
<th>Probability of residual tumor components</th>
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<tr>
<td>Basal cell carcinoma</td>
<td></td>
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<tr>
<td>with diameter &lt; 20 mm</td>
<td>3 mm</td>
<td>15 %</td>
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<td></td>
<td>4–5 mm</td>
<td>5 %</td>
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<tr>
<td>Infiltrative BCC</td>
<td>3 mm</td>
<td>34 %</td>
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<td></td>
<td>5 mm</td>
<td>18 %</td>
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<tr>
<td></td>
<td>13–15 mm</td>
<td>5 %</td>
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</table>
spray procedure at ~196 °C; there is no histological control, but for small and superficial tumors, especially in elderly patients, it may be an alternative to surgery [11]. In certain situations, especially in patients with multiple superficial basal cell carcinomas, it may be appropriate, especially for tumors on the trunk or extremities. With thermal destruction techniques, the healing and aesthetic results are poorer than with conventional excision. Other methods, such as curettage with electrodesiccation and tangential removal (shave excision) of basal cell carcinomas, should be reserved for use in only a limited number of patients due to lacking histological control.

**Supercificial basal cell carcinomas**

There are also other treatment options for superficial basal cell carcinomas. Photodynamic therapy may be used for topical treatment. First, a specific substance (e.g., delta aminolevulinic acids and its esters) is applied to the tumor which causes synthesis of a photosensitizer in the tumor tissue (protoporphyrin IX). Next the patient is exposed to intense light with a wavelength in the absorption spectrum of the photosensitizer. This treatment acts largely selectively on tumor tissue and must be performed twice per treatment cycle [12]. Local treatment with imiquimod 5 % cream may also be used to treat superficial basal cell carcinomas [13, 14], primarily for multiple BCC. In the drug approval study, imiquimod was applied once daily 5 ×/weekly for 6 weeks; the rate of histologically controlled, complete healing of superficial basal cell carcinoma was ca. 80 % [15]. The cyrosstatic agent 5-fluorouracil (5 % in cream) may also be used. 5-Fluorouracil is given topically daily for 4–6 weeks. Prospective randomized studies on treatment results are still being awaited, however.

**Hedgehog inhibitors**

For basal cell carcinoma syndrome (Gorlin-Goltz syndrome) as well as various sporadically occurring basal cell carcinomas, mutations have been shown in the Sonic hedgehog signal transduction pathway which are relevant for the development of basal cell carcinoma.

In 2009 the results were published from an early clinical study with 33 patients who were given a Hedgehog inhibitor (GDC-0449), an inhibitor of SMO (smoothened). Eighteen out of 33 patients in the dose-escalation study had complete or partial remission of their non-resectable and previously irradiated, and sometimes metastatic, basal cell carcinomas [16]. A worldwide phase II study with Vismodegib (as of January 2012 in the framework of an Early Access Program (EAP). Another inhibitor of the Sonic hedgehog signal transduction pathway (LDE225; Novartis) is currently being tested in clinical studies on patients with basal cell carcinoma.

**Follow-up care, primary and secondary prevention**

**Recommendations**

- Patients with basal cell carcinoma should undergo follow-up at least once a year for three years, given that the majority of local recurrences occur within two years.
- Given the frequency of second tumors, patients with basal cell carcinoma should undergo regular screening.
- Patients who have local recurrences or non in toto resectable tumors, as well as patients with a higher risk of new tumors (immunosuppression, genetic pre-disposition, prior multiple basal cell carcinomas), should be more closely monitored and possibly undergo lifelong follow-up.
- Patients should be instructed in regular self-inspection techniques in order to detect basal cell carcinoma as early as possible.
- Patients with basal cell carcinoma – especially basal cell carcinoma syndrome or chronically immunosuppressed patients – should protect themselves against excessive exposure to sunlight.

After micrographic surgery, despite the low rate of recurrence, primary tumors should be followed-up given that new tumors can occur in ca. 30 %. With other procedures, recurrences after undetected subtotal excision are usually clinically apparent within three years (ca. 70 %), but may be identified even after ten years [3]. Annual follow-up with clinical inspection of the entire skin surface is advisable for at least three years. Patients with local recurrences or incomplete resection, as well as those with a higher risk of new tumors (immunosuppression, genetic pre-disposition) should be more closely monitored and possibly undergo lifelong follow-up. It is important to thoroughly inform the patient and carefully instruct him or her in performed regular self-inspections.

**Psycho-oncology**

The effects of basal cell carcinoma on various psychosocial dimensions and quality of life, as well as the related need for support, have not yet been systematically studied.

A comparative study on patients with basal cell carcinoma and a matched sample from the general population failed to find any difference in regard to psychosocial problems [17]. One study focusing on basal cell carcinoma syndrome in particular reported marked symptoms of depression in 50 % [18].

Based on the S3 guidelines on malignant melanoma and the S3 guidelines (work in progress) for patients with various tumors entitled "Psycho-oncological diagnosis, counseling and treatment of cancer patients", for basal cell carcinoma as well, an assessment of the individual burden and health-related quality of life are advisable.
### Conflicts of interest

<table>
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<tr>
<th>Declaration of conflicts of interests</th>
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References