For many malignant skin tumors, exposure to ultraviolet radiation is a strongly etiologic factor in addition to genetic factors. Since UV stress of the skin has increased through people’s leisure time behaviors, the incidence of malignant skin tumors has risen. In northern Europe it has reached 140 tumors per 100,000 population per year for basal cell carcinomas (1). More than 80% of these tumors occur in the head-neck area. Because they are so common in the facial area they are an esthetic as well as functional issue. The aim of treatment – local, radical excision – is necessary because recurring tumors in the head and neck area cause serious problems for the patient because they cause extensive destruction and because repeated treatments incur follow-on costs.

Sometimes striking subclinical tumor growth occurs at the cellular level and is not visible intraoperatively. Often this growth is asymmetric and forms a narrow strand, the width of a few cell layers. Pre-therapeutically, these growths cannot be caught in their complete extent, even with the most modern methods. Only histologic investigation enables diagnosis of continual tumor strands in the periphery.

Normally, conventional histologic cross-sectional investigation is performed so as to assess the tumor; topographic marking is best to relate parts of the tumor in the margin. The fewer incisions are made across the tissue that is to be excised the greater the danger that tumor strands are histologically not exposed and the findings seem to be R0 resections (histologically in the healthy/normal spectrum) (diagram 1). This mistake can be reduced only by a larger number of histologic incisions. This, however, increases the work for the laboratory and diagnosis. And more diagnostic gaps remain the more tissue is to be excised. Histologic procedures that expose the tumor excision margins in three dimensions, without diagnostic gaps, are notably more sensitive and enable rather more successful microscopically controlled surgery.

SUMMARY

Introduction: Microscopically controlled surgery is defined as histologically complete tumor excision in three dimensions, or "3D-histology," without diagnostic gaps. This must be distinguished from the conventional histopathologic procedure of sequential sections leaving diagnostic gaps, which can mimic the appearances of an R0 (histologically normal) resection.

Methods: Selective literature review in medline. Results: 3D histology has high sensitivity in detecting cord-like, locally resectable tumor strands. This allows for selective, tissue conserving resection with good functional and esthetic results after reconstruction. Standardizing this technique via routine paraffin-based processing allows for widespread, convenient application.

Discussion: Recurrence rates are low using this method for basal cell and squamous cell carcinomas of the skin, of lentiginous melanomas, dermatofibrosarcoma protuberans and some adnexal tumors. Whether the technique may prove useful in other non dermatological tumors is not yet clear.

Key words: microscopically controlled surgery, micrographic histographic surgery, 3D histology, skin cancer
Histologically complete tumor excision in three dimensions – 3-D histology

In 1941, the American dermatologist Mohs introduced a type of continuous histologically controlled chemosurgery by means of zinc chloride and named this "microscopically controlled surgery" (2). In 1962, the German maxillofacial surgeon Drepper published the method of systematic histologic control of the tumor base with paraffin based excision (3). Burg and Konz in 1971 established the procedure in Europe and developed the frozen technique (4, 5, 6). In 1986, Brunninger published the method of "control of excision margins by conventional histopathologic techniques in the treatment of skin tumours" (7), which uses paraffin-based excision as a routine procedure. As a short name for all similar procedures, "3-D histology" has become internationally recognized (8). The therapeutic superiority of 3-D histology compared with conventional histology has been shown in large comparative overviews (9) (table) and is plausible because there are no diagnostic gaps.

Processing methods

In processing the excision margins of an excised tumor, the aim is to expose its three-dimensional margins completely, in two-dimensional histologic slides. The additional effort involved in this should be as negligible as possible. Important for all preparations is easy to follow topographic marking. A standard has become established by which this marker is always put at 12 o'clock, in relation to the body axis, with a suture or deep incision. This enables exact, topographically correct allocation of later histologic incisions. If more than one area is to be excised or there are deviations, sketches and further markings become necessary. For the purposes of plastic reconstruction, a vertical incision for the lateral tumor resection is appropriate. In this case, the edges of the excised tissue are dissected as strips, and the base. By straightening the outsides of these strands into one level, the three-dimensional external margins are converted into a two-dimensional histologic excision level.
The size of the routine cassette determines the division of the external margin and the base. The image shows a piece of excised tissue measuring 28 mm x 21 mm, which with its complete outer margins fits into two cassettes in four parts. In making the diagnosis, attention has to be paid only to tumor incisions. In small amounts of excised tissue, the margins and base fit into one cassette, and the evaluation of the complete excision margins can be done in a single section. This type of processing is also possible on a fixated excision section, e.g., after tumor tissue has been sent away (7).

**TABLE**

<table>
<thead>
<tr>
<th>Publications</th>
<th>No of patients/tumors</th>
<th>Postoperative observational period</th>
<th>Local recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigel et al. (11) 1981</td>
<td>2,960 BCC</td>
<td>5 years</td>
<td>Primary tumor: 1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrence: 3.4</td>
</tr>
<tr>
<td>Roenigk et al. (12) 1986</td>
<td>1,620 BCC</td>
<td>Up to 4 years</td>
<td>29% 3-D histology:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primary tumor: 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrence: 4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71% conventional:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Primary tumor: 2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrence: 15.5.</td>
</tr>
<tr>
<td>Dinehart et al. (13) 1992</td>
<td>1,050 patients</td>
<td>5 months to 10.7 years</td>
<td>Primary tumor: 2.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrence: 7.4</td>
</tr>
<tr>
<td>Miller et al. (14) 1992</td>
<td>2,265 patients</td>
<td>1 to 6 years</td>
<td>BCC: 0.88</td>
</tr>
<tr>
<td></td>
<td>with 2,614 BCC,</td>
<td></td>
<td>SCC: 1.41</td>
</tr>
<tr>
<td></td>
<td>711 SCC and 30 other</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leibovitch et al. (15, 16)</td>
<td>BCC 3,370</td>
<td>5 years</td>
<td>BCC primary: 1.4</td>
</tr>
<tr>
<td></td>
<td>SCC 381</td>
<td>5 years</td>
<td>BCC recurrence: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SCC primary: 2.6</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>SCC recurrence: 5.9</td>
</tr>
</tbody>
</table>

**Figure:** Complete exposure of the three-dimensional excision margins of a 28 mm excised tumor with only two prepared sections. a) Basal cell carcinoma on the cheek with marked excision margin and 12 o’clock position; b) prepared excised tissue with incision at 12 o’clock; c) severance of the edges of the excision margin and the tumor center; d) severance of the base; the three-dimensional excision margins are leveled out below; e) the 4 sections are inserted into two routine cassettes for further processing; f)3-D histology after 20 hours; only two prepared sections; tumor strand at 12–1 o’clock.
In the case of "Mohs’s micrographic surgery" and the frozen technique, the excised tissue is taken out in a bowl shape and processed by the cryostatic method. That makes leveling easier (diagram 1c). But by doing it this way, the junctional zone is exposed at an angle, tumor parts are more often found in the excision margin, and only relatively small pieces can be processed. Additionally, the excision margin has to be straightened out before a plastic closure. A modified version, which also enables processing of the vertical margins, has been described by Konz and Burg (6). With the cryostatic technique, the diagnostic findings are available very quickly, but more staff is required.

The paraffin-based technique has the advantage of being a routine procedure and offering a better quality of section, which is required for most tumor entities. By fixating the tissue quickly, for two hours in a formalin solution at 60 degree Celsius, the sections may be ready after 20 hours. 3-D histology can be used only in soft tissues. In bone infiltrations,
a complete exposure of the resection margins can be done only after decalcification. Only these techniques of completely exposing the excision margins fulfill the conditions of "histographic or micrographic surgery," as mentioned in the German Procedure Classification (OPS) catalogue and the doctors’ fee scale (Einheitlicher Bewertungsmaßstab, EBM).

As a result of the complete exposure of the resection margins, the sensitivity of 3-D histology in exposing tumor strands is very high. The excision safety margins can therefore be kept small if needed so that healthy skin is spared. After a sparing excision, however, targeted follow-on surgery becomes necessary more often on average. Diagram 2 (10) shows this likelihood for basal cell carcinomas. If flap grafts become necessary to cover the defect it is better to cover the defect with a temporary wound covering, such as wound strips, fat gauze, or polyurethane film.

Since a surgeon and, as a rule, a histopathologist, participate in the procedure, the division of processing steps has to be agreed in each individual case scenario. Either the surgeon processes the material at the operating table and puts it into cassettes for histopathologic examination, or s/he delegates this to the pathologist. The effort involved in 3-D histology with the paraffin-based technique is not necessarily higher than in conventional histologic preparation, but increases notably in the cryostatic technique. The overall effort in tumor removal, however, increases after excision with tissue sparing, because follow-on surgery is required more frequently. Healthy skin, however, can be spared, which is useful in special anatomic locations of the face.

**Indication for 3-D histology**

3-D histology is most commonly used in the surgical treatment of basal cell carcinomas of the head and neck area (box). Especially for such tumors, its utility with regard to the certainty of achieving complete excision has been well documented. Large studies show low recurrence rates (table) (11–16). Evidence level III has thus far not been exceeded in the literature, however, and rival procedures are described with numbers that vary tenfold and shorter postoperative observation periods – which means selection bias. Only one randomized study has been reported, with small numbers, a short postoperative observation period, and a questionable study design. The difference between conventional histology and 3-D histology is complex – also with regard to the smaller excision margins in micrographic surgery and the associated opportunities for sparing tissue – and has not been worked up in randomized studies.

Tumor recurrences are more common in relapses, so that tumor treatment with 3-D histology is of particular importance in the treatment of the primary tumor. Tissue sparing allows good esthetic results of reconstructive surgical techniques, which is important especially in the head and neck area (diagram 3). Similar results (83%) have been reported in a study with a very small number of subjects (n=97) for photodynamic therapy, which has a higher recurrence rate. By comparison, randomized proven surgery with conventional histology shows notably worse results in the “good” and “very good” assessment ranges (41%) (18).

The second most common tumor is the squamous cell carcinoma of the skin, which is effectively surgically managed with this technique (14, 16). Squamous cell carcinomas of the desmoplastic type, however, have a significantly higher rate of recurrence even with this method (19). 3-D histology is well suited also for the treatment of the rare but recurrence-prone dermatofibrosarcoma protuberans. In this tumor, microscopically small strands – sometimes several centimeters long – can be excised topographically precisely while sparing healthy tissue. Excision steps of 5–10 mm are recommended. The recurrence rates are clearly below those of conventional histology (20) with larger excision margins (21).

A further indication are lentigo maligna and acral lentiginous melanomas, because, in contrast to superficial and nodular melanomas, they have a continual centrifugal subclinical spread (22). Lentigo maligna and lentigo maligna melanomas are often located in the head-neck area, and the acral lentiginous melanomas located on palms, soles, and under the nails. In both scenarios, highly sensitive 3-D histology can help spare healthy tissue without increasing local recurrence rates (23). Acrail amputations are therefore nowadays hardly ever necessary in melanoma cases. The excision margins in the first operation can start at a few millimeters, depending on the individual situation. Follow-on operations are done only on tumor positive sections of the margin. This is also the case for the rare adnexal tumor, extramammary Paget’s disease. The latter does not require histological examination of the
base of the excised tissue. The tumor may also have a substantial horizontal subclinical spread, of a few centimeters. Excision steps of 5–10 mm are therefore recommended (24). This technique is also helpful in perianal and genital Bowen’s disease. The utility has not been confirmed for Merkel cell carcinoma, but a reduced expanse of the operation seems possible without increasing the rate of recurrence (25).

**Conclusion**

3-D histology in the context of microscopically controlled surgery is a technique that enables, for a multitude of malignant skin tumors, the highest degree of certainty in proving a real, and not just a seeming, R0 resection. The process can be varied by surgeon and histologist. The procedure’s high sensitivity allows tissue sparing surgery. After sparing excision, however, more targeted follow-on surgery is required on average. This may increase the overall effort used to remove the tumor and has to be considered on an individual basis. 3-D histology does, however, offer a technique that satisfies the demands for high recurrence-free intervals and good reconstructive results. Only 3-D histology satisfies the conditions of the histographic or micrographic microscopic surgery as mentioned in the OPS catalogue and the EBM scale. Studies are needed into whether complete exposure of the excision margins of excised tissue with 3-D histology might be useful in the context of other solid, non-dermatologic tumor entities.

**Conflict of Interest Statement**

The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.

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**REFERENCES**


Corresponding author
Prof. Dr. med. Helmut Breuninger
Universitäts-Hautklinik
Eberhard-Karls-Universität Tübingen
Liebermeisterstr. 25, 72076 Tübingen, Germany
www.medizin.uni-tuebingen.de/mkc
helmut.breuninger@med.uni-tuebingen.de

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