**GUIDELINE IMPLEMENTATION IN MERKEL CELL CARCINOMA: AN EXAMPLE OF A RARE DISEASE**


**SUMMARY**

Introduction: Little is known about the implementation of guidelines in rare diseases which, because of low incidence, are often based on a low level of evidence. Merkel cell carcinoma is an aggressive skin malignancy which provides an example. Methods: A questionnaire survey relating to treatment of Merkel cell carcinoma between 1998 and 2004, the time since publication of the first version of the guidelines was sent to 47 hospitals. Data were solicited on epidemiology, tumour grade and stage, treatment and clinical course. Results: Replies were received for 150 patients. The analysis suggests that guideline adherence is patchy. There were particularly strong variations in practice relating to adjuvant radiotherapy. This is important because guideline conformity in this area is associated with fewer recurrences. Discussion: The example of Merkel Cell carcinoma illustrates that the mere publication of guidelines is insufficient to ensure that best evidence is put into practice. Dtsch Arztebl 2006; 103(42): A 2791–6.

Key words: Merkel cell carcinoma, neuroendocrine carcinoma of the skin, sentinel lymph node biopsy

**Maria cell carcinoma** is an aggressive malignant tumor of the skin with neuroendocrine differentiation. With an incidence of 0.1 to 0.3 new cases per 100,000 persons per year, it is one of the rarer skin tumors (1, 2). The average age of newly diagnosed patients is between 65 and 70 years (1). Merkel cell carcinomas are typically reddish or purple, solid, painless, cutaneous or subcutaneous tumors (figure a). They are often hemispherical or nodular, though plaque-like variants are seen as well. They are histologically characterized as a poorly differentiated, small-cell carcinoma of the dermis that may extend into the subcutaneous fat (3). The tumor cells are often arranged in strands and solid cell complexes that give rise to trabecular formations (figure b).

The clinical course is typified by a high local recurrence rate and by sequential metastasis. It is usually not possible to determine whether a local recurrence represents a persistent tumor or a satellite metastasis. As many as one-third of patients already have locoregional lymph node involvement at the time of diagnosis, and the lymph nodes are involved at some point in the course of the disease in more than 60%. More than 30% of patients develop systemically disseminated disease, which usually leads to death within a few months (4). Precise data on the five-year disease-related survival rate of patients with Merkel cell carcinoma are lacking, both because of the low incidence of the disease and because of the high comorbidity of the affected patients. The most commonly used clinical staging scheme has...
three stages. In stage I, the primary tumor is the only evidence of disease; patients with
lcoregional metastases are in stage II, while those with distant metastases are in stage III.

The low incidence of Merkel cell carcinoma also accounts for the lack of controlled
prospective studies, and therefore for the lack of high-level, evidence-based recommendations
for its diagnosis and treatment. Both the consensus statement on the diagnosis and treatment
of Merkel cell carcinoma that was in effect in Germany from 1998 to 2004 (5) and the recently
updated version of the guidelines that it contained (6) are based on single case reports,
retrospective studies (mostly on a small scale), and the authors’ clinical experience.

The 1998 guidelines recommended an initial diagnostic assessment of the extent of
disease with ultrasonography of the draining lymph nodes and of the abdomen, and a chest
x-ray. In case of suspicion of distant metastases, a directed, organ-specific, computer
tomographic (CT) or magnetic resonance imaging (MRI) study was recommended. The
1998 guidelines made no mention of sentinel lymph node biopsy for staging purposes (5).

According to the 1998 guidelines, the treatment of choice for the primary tumor is
surgical excision with a 3 cm safety margin. In case of local recurrence or lymph node
metastasis, too, curative surgical intervention should be attempted. Because these tumors
are highly radiosensitive, a further recommendation was for adjuvant postoperative
radiation therapy of the excision site with a 3 cm margin, as well as of the regional draining
lymph nodes, with an overall dose up to 50 Gy (5).

Because of the lack of treatment options for stage III disease, follow-up at close intervals
is essential so that recurrent tumors can be detected while curative surgical intervention is
still possible. The 1998 guidelines suggested clinical re-examination, including local and
regional ultrasonography, every six weeks for the first year, thereafter quarterly and, finally,
semiannually (5). Abdominal ultrasonography and chest x-rays were recommended once a
year, and follow-up was to be continued for at least five years (5).
Before the present study was performed, it was not known to what extent physicians actually followed the 1998 guidelines for the diagnosis and treatment of Merkel cell carcinoma (5) in clinical practice. It has become increasingly clear that influencing physicians' routine behavior through the publication of guidelines is a difficult matter indeed (7, 8), even though guidelines are generally issued by expert committees and thus ought to reflect the best clinical practice based on the available data. Mere "passive" publication of guidelines is not enough; they must also be incorporated into the medical school curriculum, specialty training, and continuing medical education programs (7–9) if they are to take root in clinical practice.

**Patients and Methods**

From June 2004 to January 2005, a questionnaire on the diagnosis, treatment, and follow-up of patients with Merkel cell carcinoma after the publication of the initial guidelines in 1998, which was developed in Würzburg with the support of the German Working Group on Dermatological Oncology (Arbeitsgemeinschaft Dermatologische Onkologie, ADO), was sent to 47 hospitals in the German-speaking countries (Austria, Germany, Switzerland). Data were collected on the patients' age and sex, on tumor size and histology, and on staging tests, treatment, and the course of the disease. Replies were obtained from 15 of the hospitals to which questionnaires were sent (32%); the number of patients reported on by each hospital ranged from 2 to 31. It must also be assumed that variable percentages of the patients treated in each institution were represented in the study, because only a few of these hospitals maintain systematic registries. The collected questionnaires were entered into a computer and analyzed with Microsoft Access and Statview software (Microsoft Corp., Redmont, WA, USA; Statview for Windows, SAS Institute, Inc., Cary, NC, USA).

**Results**

Information on a total of 150 patients had been collected by mid-March 2005 (table 1). The mean age at diagnosis was 74 years, with a female-to-male ratio of 1.6 : 1. At the time of diagnosis, the mean horizontal tumor diameter was 1.97 cm, and the mean tumor thickness 1.81 cm. Women seemed to have slightly smaller tumors at diagnosis than men (1.74 ± 0.20 cm versus 2.30 ± 0.38 cm), but this difference was not statistically significant (p=0.16 by the unpaired t-test). Specific information on the histologic type of tumor was provided for 68 patients: the carcinoma was trabecular in 44%, intermediate in 32%, and of small-cell type in 24%. The overall rate of recurrence was similar for the three histologic types, ranging from 25% to 31.8%. 75 tumors were immuno-histologically tested for cytokeratin 20: 72 of these tests were positive, and only 3 were negative.

**Primary staging**

With regard to primary staging (diagram 1a), 56 of the 150 patients underwent primary staging in conformity with the 1998 guidelines, including a chest x-ray and abdominal and lymph node ultrasonography. 18 further patients underwent not only these tests but also, in addition, a CT or MRI of the abdomen or chest, already as part of their initial staging. Among the 56 patients whose primary staging conformed fully to the guidelines, 32 went on to undergo CT or MRI because of unclear findings on at least one of the initial tests, i.e., the primary staging was intensified in 32 of these 56 patients. 33 of the total group of 150 patients underwent a CT scan or, more often, an MRI of the head as part of their initial staging. CT was performed more commonly than MRI to examine the abdomen and chest. Furthermore, 20.7% of patients underwent somatostatin receptor scintigraphy, and 24.7% had a sentinel lymph node biopsy. 46 out of 150 patients underwent only a limited, and therefore inadequate, primary staging. For 30 patients, no information was provided on the type and extent of the tests that were performed. The stage of Merkel cell carcinoma on initial diagnosis was reported for 143 patients: stage I in 118, stage II in 23, and stage III in 2 (diagram 1b). For 68 patients, information was provided both on the tumor stage at initial diagnosis and on the histologic type. The percentage of patients who were already in stage II upon diagnosis was 6.7% (2/30) among those with trabecular tumors, 31.8% (7/22) among those with intermediate tumors, and 18.8% (3/16) among those with small-cell tumors.
Primary treatment
Responses to the questionnaire revealed that the primary treatment of Merkel cell carcinoma was generally less extensive than recommended in the guidelines. The mean width of the safety margin around the primary tumor was 1.86 cm (median: 2 cm). The width of the safety margin varied depending on the site of the tumor, from 1.40 cm (median: 1 cm) on the head to 1.87 cm (median: 2 cm) on the trunk and 2.01 cm (median: 2 cm) on the limbs.

Only 60 of 150 patients (40%) received radiation therapy as part of their primary treatment. Among the 118 patients in stage I, the fraction of patients receiving radiation therapy as part of their primary treatment was even lower (41 patients, 34.7%). 34 patients underwent at least local radiation therapy, 17 underwent irradiation of the lymphatic drainage area, and 14 underwent irradiation of the regional lymph nodes. 19 of the 23 patients initially in stage II underwent radiation therapy.

Sentinel lymph node biopsy
A total of 37 patients underwent sentinel lymph node biopsy. A definitive histological diagnosis was indicated in 33 cases; the lymph nodes were positive for tumor in 24.2%. 7 of the 8 patients with positive sentinel lymph nodes went on to undergo lymph node dissection, yet 2 of them nonetheless had a later recurrence of regional lymph node metastases (98 and 261 days after the initial diagnosis). Among the 6 patients who were found to have tumor-positive sentinel lymph nodes but did not go on to develop locoregional recurrences, 4 received radiation therapy of the lymph nodes. Among the patients with negative sentinel lymph nodes, 3 patients (9.1%) went on to develop regional lymph node metastases in the later course of their disease (199, 240, and 240 days after the initial diagnosis). One of these three patients had undergone adjuvant radiation therapy (locally, to the lymphatic drainage area, and to the regional lymph nodes). Among all patients with negative sentinel lymph nodes, 9 underwent adjuvant radiation therapy. 2 of the patients who had undergone sentinel lymph node biopsy later developed distant metastases; both had originally had tumor-negative sentinel lymph nodes. Local recurrences developed in 2 patients with tumor-positive and 4 patients with tumor-negative sentinel lymph nodes.

Recurrence rate
Our poll confirmed the high recurrence rate of Merkel cell carcinoma. 56 of 150 patients (37%) suffered a recurrence of tumor during the period for which data were collected. 29 patients (19.3%) had local recurrences, 33 (22%) had locoregional metastases, and 22 (14.7%) had distant metastases. Among those with distant metastases, 22.7% also had a local recurrence, 45% had lymph node metastases, and 18.2% had both a local recurrence and lymph node metastases.

| TABLE |
|---|---|---|
| Epidemiologic data* | Women | Men |
| Number (n) | 92 | 58 |
| Mean age | 73 | 74 |
| Site of primary tumor | | |
| Head | 29 (32 %) | 16 (28 %) |
| Limbs | 58 (63 %) | 32 (55%) |
| Trunk | 5 (5 %) | 10 (17 %) |
| Tumor diameter (n = 81) | | |
| Mean | 1,74 ± 0,20 cm | 2,30 ± 0,38 cm |
| Median | 1 cm | 1,45 cm |
| Tumor thickness (n = 18) | | |
| Mean | 1,33 ± 0,21 cm | 2,05 ± 0,46 cm |
| Median | 1 cm | 1,5 cm |

* There were no significant differences between women and men (by the paired t-test) with respect to tumor diameter or thickness.
Tumor recurrence was significantly correlated with the chosen safety margin for primary excision (diagram 2a). The safety margin was documented for 90 patients. It lay between 0 and 1 cm in 28 patients, between 1 and 2 cm in 28, and between 2 and 3 cm in 34 patients. 39% of the patients in the first group developed recurrent tumors (3 local recurrences, 9 loco-regional metastases, and 4 distant metastases), in contrast to 17.9% in the second group (2 local recurrences, 2 locoregional metastases, and 2 distant metastases) and only 8.8% in the third group (2 local recurrences, 1 locoregional metastasis, and 1 distant metastasis).

The purpose of adjuvant radiation therapy is to lower the recurrence rate. The data that we collected in fact confirmed a lower rate of local recurrence after radiation therapy \( (p=0.012 \text{ by the chi-square test, diagram 2b}). \) Irradiation of the lymphatic drainage area and/or the regional lymph nodes was not associated with any improvement of the locoregional recurrence rate in this patient collective \( (p=0.388 \text{ by the chi-square test, diagram 2c}). \) This finding may be due in part to the necessary exclusion from this portion of the data analysis of patients who had undergone not only locoregional irradiation, but also an elective lymph node dissection, a sentinel lymph node biopsy, chemotherapy or immunotherapy. The relevant patient group was too small for multivariate analysis.

**Follow-up intervals**

Information on the frequency of follow-up examinations after primary treatment (diagram 3) was obtained for 93 patients. 11 of these patients (11.8%) were seen in follow-up once
follow-up until the submission of the questionnaire was 887 days (standard deviation: 98 days). Death was reported for 17 patients (11.3%).

Discussion

The distribution of sites of Merkel cell carcinoma that we found in this study was comparable to that seen in other large, retrospective case series (10). The sex distribution, with a female-to-male ratio of 1.6 : 1, differed from that seen in some other studies, though a number of studies have shown a higher incidence among women (11, 12). With regard to tumor histology, there was a surprisingly large number of trabecular tumors (44%); it should be remarked, however, that the respondents to our questionnaire had no opportunity to indicate mixed variants. The high mitotic rate is similar to that found by other researchers (1, 10). The distribution of disease stages at the time of diagnosis (82.5% in stage I, 16.1% in stage II, and 1.4% in stage III) corresponds to the combined results of 4 other studies, as summarized by Goessling et al. (1). The results of our questionnaire thus seem to be consistent with previously available data on the epidemiology, histology, and stage distribution of Merkel cell carcinoma at the time of diagnosis. This consistency strengthens the validity of the further findings of our study with respect to diagnostic and therapeutic measures.

The German guidelines for the diagnosis and treatment of Merkel cell carcinoma that were issued in 1998 (5) recommended excision of the primary tumor with a 3 cm safety margin. Our poll shows that this recommendation is usually not followed. Data stratification by tumor site reveals that, on average, wider margins are obtained at primary excision if the tumor lies in an area of the body where a wide margin can be taken without causing a functional deficit, yet even these wider margins are still considerably narrower than recommended. Similarly, adjuvant radiotherapy was given to only 34.7% of patients. Stricter adherence to the guidelines would certainly be desirable, as the current study once again shows that adequate surgical margins and adjuvant radiation lead to a lower rate of recurrence.

The tests most commonly performed for primary staging are ultrasonography of the draining lymph nodes and abdomen and chest x-rays, as recommended by the guidelines. Additional tomographic images were obtained, however, in a considerable number of cases. The questionnaire did not ask whether this was always done because of a suspicion of distant metastases. It is worth pointing out here that the current literature, as far as we are aware, contains no systematic investigation regarding the question of which types of imaging study are useful for primary staging purposes. In Germany, according to our data, there is a marked tendency to use tomographic techniques (CT, MRI), which provide
improved organ-specific diagnosis, but at a higher cost. This extended form of primary staging nonetheless resulted in an "upstaging" of the tumor (i.e., a change to a higher tumor stage because of improved detection) in only a very small number of cases.

Sentinel lymph node biopsy is discussed in the literature as a possibly beneficial method of diagnosis and prognostication, or even of treatment (4, 13). The replies to our questionnaire reveal that it is already being practiced in many hospitals. 37 of the 150 patients who were reported on underwent a sentinel lymph node biopsy, and there was a trend toward the more frequent performance of biopsies in the later years of the study. The 24.2% positivity rate of sentinel lymph nodes indicates the value of the technique, but the results of our study do not show whether sentinel lymph node biopsy enables the formulation of a more accurate prognosis. Although we did find that patients with tumor-positive sentinel lymph nodes went on to develop lymph node metastases more frequently than patients with tumor-negative nodes (25% versus 9.1%), the number of patients was so small that this percentage difference was not statistically significant.

In summary, it can be concluded that the currently operative guidelines for the diagnosis and treatment of Merkel cell carcinoma are not fully adhered to in everyday clinical practice. There are major discrepancies, in particular, with respect to adjuvant radiation therapy and the interval between follow-up examinations. Nonetheless, the large number of sentinel lymph node biopsies performed and the data showing the effect of adjuvant radiation on the recurrence rate give us reason to hope that the care of patients with Merkel cell carcinoma can be made more effective than it is at present. In any case, more accurate data on the results that are obtainable with different methods of diagnosis and treatment are still urgently needed, and these data can only be derived from future controlled, prospective studies.

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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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