A Systematic Review of Treatment Modalities for Primary Basal Cell Carcinomas

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Objective: To systematically review the literature for studies reporting on recurrence rates of basal cell carcinomas (BCCs) after different therapies.

Design: We reviewed all studies published in English, French, German, Dutch, Spanish, or Italian between 1970 and 1997 that prospectively examined recurrence rates for at least 50 patients with primary BCCs treated for at least 5 years after treatment with Mohs micrographic surgery, surgical excision, curettage and electrodesiccation, cryosurgery, radiotherapy, immunotherapy with interferon or fluorouracil, or photodynamic therapy.

Setting: Department of Dermatology, University Hospital Maastricht, Maastricht, the reference center for dermatologic oncology and Mohs micrographic surgery in the Netherlands.

Main Outcome Measures: The recurrence rates after different therapies for BCCs, resulting in the development of guidelines for the treatment of these disorders.

Results: Of 298 studies found in several electronic databases, only 18 met the requirements and could be used for analysis. Tumors treated with Mohs micrographic surgery show the lowest recurrence rates after 5 years, followed in order by those treated with surgical excision, cryosurgery, and curettage and electrodesiccation.

Conclusions: Recurrence rates for different therapies could not be compared because of a lack of uniformity in the method of reporting, so evidence-based guidelines could not be developed. We surmise that Mohs micrographic surgery should be used mainly for larger, morphea-type BCCs located in danger zones. For smaller BCCs of the nodular and superficial types, surgical excision remains the first treatment of choice. Other treatment modalities can be used in patients in whom surgery is contraindicated. Immunotherapy and photodynamic therapy are still investigative.

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Basal cell carcinoma (BCC) is the most common non-melanoma skin cancer in the world, with incidence rates varying between 146 and 317 per 100,000 in the United States and 1 per 100 in tropical regions in Australia. Even in western Europe, with the Netherlands used as a reference point, almost 30,000 new cases of BCC (200 per 100,000) are diagnosed a year. The tumor develops from the basal layer and epidermal appendages, and the malignant character depends on the destructive growth of the primary tumor, rather than on metastasis.

The tumor is seen especially in people of white ethnicity. Its prevalence is related to increasing age and frequent exposure to UV light, and most of the BCCs develop on facial areas, where substantial disfigurement can result. Basal cell carcinomas occurring in younger persons and those with immunodeficiency syndromes usually are more aggressive. Patients who have been treated for BCC show a higher risk for another BCC developing.

See also pages 1171 and 1255

Basal cell carcinoma is a slowly growing tumor that can generally be cured easily by standard office-based surgical methods. In about 10% of patients with BCC, treatment is not so simple. Sometimes the tumors show strong destructive behavior, high recurrence rates, and even metastasis.

Because BCCs can present in many different ways and situations, several thera-
METHODS

TREATMENT MODALITIES

We systematically reviewed studies that reported recurrence rates after the treatment of primary BCC by MMS, SE, CS, CE, RT, immunotherapy, and photodynamic therapy. The validity of each study was examined, and the data concerning recurrence rates were analyzed.

DATA SEARCH

The MEDLINE standard computer database (US National Library of Medicine, Bethesda, Md), the EMBASE computer database (Elsevier Science BV, Amsterdam, the Netherlands), the MEDLINE advanced (Internet) database, and the CANCERLIT database (US National Library of Medicine; this also includes unpublished articles and meeting abstracts) were searched for articles from 1970 through 1997. The following key words (including analogs and derivatives) were used: basal cell carcinoma, basocellular, or epithelium in combination with (surgical) excision, surgery, Mohs (micrographic) surgery, cryotherapy, cryosurgery, electrodesiccation, curettage, radiation therapy, radiotherapy, immunotherapy, interferon, 5-fluorouracil, photodynamic therapy, δ-aminolevulinic acid, and skin cancer.

The yearbooks of dermatology that were published between 1978 and 1996 were manually screened for studies. Finally, textbooks, reviews, editorials, existing guidelines, and the references of the studies found were checked for further information.

INCLUSION AND EXCLUSION CRITERIA

We included prospective studies reporting the recurrence rates of MMS, SE, CS, CE, RT, immunotherapy, and photodynamic therapy as treatment of all subtypes—superficial, nodular, micronodular, adenoid, morphea, and metatypical—of previously untreated BCCs. The follow-up had to be for at least 5 years for each tumor treated. Studies published in English, French, German, Dutch, Italian, and Spanish were included.

The following criteria were used for excluding data (Table 1): studies reporting on cutaneous malignant lesions other than BCC if the results were not described separately for each cancer; recurrent BCCs; retrospective analyses; a follow-up shorter than 5 years; the results of fewer than 50 tumors and patients; the effectiveness of the therapy, as proved by excision and histopathologic study several months after treatment; and cosmetic results only.

Duplicate publications, reviews on certain therapies, and reports on combinations of 2 or more therapies were also excluded.

STUDY SELECTION AND DATA EXTRACTION

For each patient series included, the treatment modality, number of BCCs treated, recurrence rates, and duration of follow-up were recorded. Initially, the histologic subtype, size and location of the tumors, number of tumors per patient, and the number and reasons for dropouts were not analyzed. This provided an adequate number of studies to make a comparison between the different treatments.

The studies were categorized into 3 groups according to the number of tumors treated (50-99, 100-250, and >250).

DATA ANALYSIS

If possible, the study size–weighted recurrence rates for all groups of tumors were calculated by dividing the total number of recurrences by the total number of tumors treated (raw recurrence rate) and the total number of patients observed for at least 5 years (3-year recurrence rate). The mean weighted recurrence rates for each treatment modality were also calculated 2 ways. Finally, the life-table cumulative 5-year recurrence rates were either recorded from the articles or calculated in cases in which sufficient data for these calculations were available.

RESULTS

LITERATURE SEARCH

In total, 298 patient series, published between 1970 and 1997, were identified in the several databases. Of these, 153 were found in the MEDLINE standard database and an additional 70 in the MEDLINE advanced database, 28 in the EMBASE database, and 47 in the CANCERLIT database.

A screening of reference lists, abstract books, and yearbooks of dermatology revealed no additional stud-
ies. Only 51% of all studies were found in the MEDLINE standard database, the database most frequently used worldwide. Only 18 of the 298 studies found were large, prospective studies of primary BCC with a follow-up longer than 5 years. Table 1 shows the reasons for exclusion in order of importance for each treatment modality. Initially, 29 studies written in a language other than those previously mentioned, 25 duplicate publications, and 13 reviews were excluded. Also excluded were 16 series reporting on the histopathologic verification of a treatment modality several months after therapy. Finally, 1 study reporting on the cosmetic results only and another 51 series reporting on different criteria—comparison between 2 or more therapies (n = 16), etiologic studies (n = 9), a review of the treatment of BCC in general (n = 7), a combination of 2 or more treatment modalities (n = 7), primarily wound care (n = 3), a meeting abstract without exact data (n = 2), follow-up after incomplete excision (n = 2), a discussion of excision margins (n = 2), radiotherapy as adjuvant therapy (n = 2), and a case report (n = 1)—were excluded.

After the main exclusion criteria (not confined to BCCs, includes recurrent BCCs, retrospective studies, follow-up shorter than 5 years, and patient series <50 in Table 1) were applied to the 133 remaining series, 18 patient series were included. The main reasons for exclusion were a follow-up shorter than 5 years (59/229 [25.8%]) and that the studies were retrospective (33/229 [14.4%]). In 22 series (9.6%), no differentiation was made between the treatment of primary or recurrent BCCs, and 16 series (6.9%) reported on the results of the treatment of cutaneous tumors in general (BCCs, squamous cell carcinomas, and precancerous lesions). In another 15 series (6.6%), the number of tumors treated (<50) was considered too small.

The final total of 18 patient series included reports on the treatment of 9930 primary BCCs (Table 2). Some patients were observed for more than 5 years; the exact figures could not be calculated because several studies mentioned only the recurrence rates without the absolute number of patients with BCC observed for more than 5 years. Six patient series reported on 4212 tumors treated with CE. Three reported on 1303 patients with BCCs treated with SE, and another 3 reported on 2660 patients with BCCs treated with MMS. Four series reported on 798 patients with BCCs treated with CS, and only 1 series reported on 862 patients with BCCs treated with RT.

Among the investigational treatment modalities, 1 series reporting on 95 patients with BCCs heated by immunotherapy was included. For photodynamic therapy, no patient series was included because the follow-up was too short in all studies.

The exclusion of a few studies needs further explanation. The article by Emmett, reporting on the results of SE on 2539 BCCs, was not included because the author described a surgical technique with wide resection margins (≤10 mm) and frozen section analysis of the excised tissue. If the free margins in the frozen paraffin sections were too small according to the histologic subtype of the BCC, a re-excision was performed. This technique will absolutely decrease the risk of recurrence of a BCC, and the results cannot be compared with those of surgical techniques reported on in other studies.

Also excluded from this review was the article by Breuninger et al, reporting on the results of SE on 2016 BCCs using the so-called flounder technique. This implies a 3-dimensional histologic control of the excised tissue, evaluating some cross-sections, 2 additional edge sections, and the undersurface. The principles of this technique, and maybe the results, are comparable to MMS, with only 1 difference: MMS is aimed at removing all the cancerous tissue and saving as much healthy tissue as possible, whereas the flounder technique does not include the second aspect of saving healthy tissue. This might lead to less favorable cosmetic results. The flounder technique was developed and performed by Breuninger only, so the results of that study cannot be compared with the others.

An impressive study by Dinehart et al, reporting on the difference in the presentation of BCCs and the results of MMS for BCC in younger patients compared with older patients, was not included because the follow-up

### Table 1. Number of Studies Excluded Using Fixed Exclusion Criteria of 298 Studies Found*

| Fixed Exclusion Criteria† | MMS | SE | CS | CE | RT | IM | PDT | Total |
|---------------------------|-----|----|----|----|----|----|-----|-------|
| Language                  | 1   | 9  | 10 | 1  | 5  | 2  | 1   | 29    |
| Not confined to BCCs      | 1   | 7  | 3  | 0  | 5  | 0  | 0   | 16    |
| Includes recurrent BCCs   | 5   | 6  | 2  | 1  | 8  | 0  | 0   | 22    |
| Retrospective studies     | 4   | 15 | 2  | 2  | 10 | 0  | 0   | 33    |
| Follow-up <5 years        | 2   | 13 | 13 | 5  | 6  | 10 | 10  | 59    |
| Patient series <50        | 2   | 1  | 3  | 0  | 9  | 0  | 0   | 15    |
| Duplicate publications    | 1   | 6  | 6  | 3  | 6  | 3  | 0   | 25    |
| Histopathologic studies   | 0   | 0  | 1  | 1  | 0  | 13 | 1   | 16    |
| Reviews                   | 3   | 1  | 2  | 2  | 2  | 3  | 0   | 13    |
| Report on cosmetic results| 0   | 0  | 0  | 0  | 1  | 0  | 0   | 1     |
| Total                     | 19  | 58 | 42 | 15 | 52 | 31 | 12  | 229   |

* A total of 51 studies were excluded for other reasons described in the “Literature Search” subsection of the “Results” section. MMS indicates Mohs micrographic surgery; SE, surgical excision; CS, cryosurgery; CE, curettage and electrodesiccation; RT, radiotherapy; IM, immunotherapy; PDT, photodynamic therapy; and BCCs, basal cell carcinomas.

† Given in order of importance.
was too short (median, 4.2 and 4.4 years, respectively; range, 3 months to 10.7 years).

Glatt et al\textsuperscript{48} reported the results of SE in 236 primary and recurrent periocular BCCs, but these tumors were resected under conventional frozen section control, implying a lower recurrence rate than for “simple” SE. The study was excluded for that reason.

In the category RT, large studies such as the ones by Schneiter and Krebs\textsuperscript{39} and Reymann and Kopp\textsuperscript{50} were excluded because the results were analyzed retrospectively. The studies by Lippert and Wiskemann\textsuperscript{51} and Petrovich et al\textsuperscript{52} failed to report the results of the treatment of primary BCCs separate from those of recurrent BCCs and were excluded.

**EFFECTIVENESS OR RECURRENCE RATES**

The results of the literature search are summarized in Table 3. Because most authors used different statistical methods for calculating the results of their therapies, we were unable to give an overall mean recurrence rate for each treatment modality.

The real recurrence rate will be somewhere between the estimated weighted recurrence rate for BCCs after 5 years follow-up and the estimated weighted recurrence rate for all BCCs treated from the start of the study.

**COMMENT**

Systematic reviews in clinical research are based on simple principles: systematically searching out and, when possible, quantitatively combining the results of all studies that have addressed a similar research question.\textsuperscript{33} The literature on treatment modalities for primary (previously untreated) BCCs and recurrence rates following therapy is massive. By systematically searching the available literature, we tried to compare the recurrence rates for several therapies. However, recurrence rates for different therapies could not be compared because of a lack of uniformity in the methods of reporting. From a statistical point of view, the recurrence rates are the results of calculating several types of survival curves. The most precise ones are the Kaplan-Meier survival curve\textsuperscript{54} and the life-table survival curve according to Cutler and Ederer.\textsuperscript{55} in which all information about survival times is included. In this way, “survival time” means the period in which a patient is free of recurrences. Unfortunately, only a few of the selected studies provided sufficient data to calculate the cumulative 5-year recurrence rates according to the life-table method. Most of the (short-term) studies reported a recurrence rate based on the total number of patients with recurrent BCC divided by the total number of patients with initial tumors treated (raw recurrence rate). This method ignores the patients unavailable for follow-up and artifically lowers the recurrence rates reported. Thus, a recurrence rate of 5% actually would be slightly higher if life-table analysis had been used. In contrast, the long-term studies reported a recurrence rate based on the total number of patients with recurrent BCC divided by the total number of patients with tumors who were observed for at least 5 years (strict 5-year recurrence rate). This method artifically raises recurrence rates because it excludes patients with tumors who were observed for less than 5 years. The actual recurrence rate might be between these 2 values and best calculated by using the 5-year life-table method. Therefore, an important initial conclusion of this review is that the results of different treatment modalities for BCC cannot be compared based on the recurrence rates in the articles.

In theory, the aggregation of data from multiple studies should enhance the precision and the accuracy of any pooled result. But combining data requires a leap of faith that the differences among studies are primarily due to chance. In fact, differences in treatment results are caused by other—often subtle—factors such as differences in populations, outcome measures, study design, and study quality.\textsuperscript{56} Thus, systematic reviews may generate misleading results by ignoring meaningful heterogeneity among studies, entrenching the biases in individual studies, and introducing further biases through the process of finding studies and selecting the results to be pooled.\textsuperscript{37}

Another goal of a systematic review is to possibly explain the variation in the results of equivalent therapies performed by different authors by looking at the factors that cause this heterogeneity among the studies.\textsuperscript{58} For the studies of treatments of BCC, the heterogeneity is large. From the literature, it is known that the risk for the recurrence of a treated BCC depends not only on the

| Treatment Modality                      | PS | T | PS | T | PS | T | PS | T | Total |
|----------------------------------------|----|---|----|---|----|---|----|---|-------|
| Mohs micrographic surgery              | 0  | ... | 1  | 145 | 2  | 2515 | 3  | 2660 |
| Surgical excision                      | 0  | ... | 0  | ... | 3  | 1303 | 3  | 1303 |
| Cryosurgery                            | 1  | 61 | 1  | 214 | 2  | 521 | 4  | 796  |
| Curettage and electrosclerisisation    | 1  | 91 | 1  | 210 | 4  | 3911 | 6  | 4212 |
| Radiotherapy                           | 0  | ... | 0  | ... | 1  | 862 | 1  | 862  |
| Immunotherapy                          | 1  | 95 | 0  | ... | 0  | ... | 1  | 95   |
| Photodynamic therapy                   | 0  | ... | 0  | ... | 0  | ... | 0  | ...  |
| **Total**                              | 3  | 247 | 3  | 569 | 12 | 9112 | 18 | 9928 |

* Ellipses indicate not applicable.
treatment modality but also on the location\textsuperscript{59,60}; on the size and histologic subtype of the tumor\textsuperscript{61,62}; and to a lesser degree, on patient-specific aspects such as age, immune status, and sex.\textsuperscript{63} Especially with the micronodular, adenoid, and morphea subtypes of BCC and tumors localized in the H figure (danger zone) of the face, those larger than 2 cm are associated with a higher risk for recurrence. These factors were initially left out of consideration, but after the included studies had been analyzed, it was obvious that they account for some of the high recurrence rates in several studies. Fraunfelder et al,\textsuperscript{37} for example, reported on the recurrence rate for BCCs on the eyelid, with those larger than 10 mm having nearly 4 times the recurrence rate of smaller BCCs in the same location. The 2 studies by Mohs et al\textsuperscript{29} and Mohs\textsuperscript{30} were performed on BCCs located in a specific anatomic site, namely, on and around the external ear and on the eyelid. Tumors located around the ear are known to have a higher risk for recurrence, so this might explain why the recurrence rate in the study by Mohs et al was 3 times that in the second study.

We assume that the choice for a specific treatment modality was also influenced by the features—location, size, and histologic subtype—of the specific tumor to be treated. The studies we analyzed did not randomize treatment as patients came in because this was not practical or ethical. On the other hand, randomization is the only way to avoid tumor selection bias. This kind of selection bias can be seen especially in retrospective studies, usually performed without previously drafted treatment protocols. For this reason, retrospectively analyzed studies were excluded in this review. Also important for the recurrence risk might be the period in which the treatment was performed. The equipment needed for a particular treatment and the way in which some of the treatment modalities (especially CS and CE) are performed today might be more refined and precise compared with the treatments performed ear-

| Study                         | Comments | No. of Patients | >5-y Follow-up | Unavailable for Follow-up | Absolute No. of Patients | Raw Rate† | Strict Rate‡ | Cumulative 5-y Rate§ |
|-------------------------------|----------|----------------|----------------|---------------------------|--------------------------|-----------|--------------|----------------------|
| Julian and Bowers,\textsuperscript{28} 1997 | 1981-1995 | 145 | 117 | 28 | 1 | 0.7 | 0.8 | ... |
| Mohs et al,\textsuperscript{28} 1988 | Ear | 1032 | 748 | 284 | 13 | 1.3 | 1.7 | ... |
| Mohs,\textsuperscript{28} 1986 | Eyelid | 1483 | 1124 | 359 | 7 | 0.5 | 0.6 | ... |
| Recurrence rate, mean         |          |                |                |                           |                          | 0.8 (21/2660) | 1.1 (21/1989) | ... |
| Baur et al,\textsuperscript{25} 1977 | High number unavailable | 443 | 74 | 369 | 6 | 1.4 | 8.1 | 8.0 |
| Germann et al,\textsuperscript{26} 1992 | | 272 | ... | ... | 8 | 2.9 | ... | 3.2 |
| Silverman et al,\textsuperscript{29} 1992 | 1955-1982 | 588 | 289 | 299 | ... | ... | ... | 4.8 |
| Recurrence rate, mean         |          |                |                |                           |                          | ... | ... | 5.3† |
| Nordin et al,\textsuperscript{24} 1997 | Nose, >10 mm | 61 | 50 | 11 | 1 | 1.6 | 2.0 | ... |
| Lindgren and Larke,\textsuperscript{26} 1997 | Eyelid | 214 | 140 | 64 | 0 | 0 | 0 | 0 |
| Anders et al,\textsuperscript{26} 1995 | Eyelid | 254 | 202 | 52 | 7 | 2.8 | 3.5 | 3.5 |
| Fraunfelder et al,\textsuperscript{28} 1984 | Eyelid, ≤10 mm | 181 | 115 | 66 | 6 | 3.3 | 5.2 | 4.7 |
| Fraunfelder et al,\textsuperscript{28} 1984 | Eyelid, >10 mm | 88 | 49 | 39 | 10 | 11.4 | 20.4 | 16.5 |
| Recurrence rate, mean         |          |                |                |                           |                          | 3.0 (24/798) | 4.3 (24/556) | ... |
| Kopf et al,\textsuperscript{38} 1977 | 1958-1962 | 597 | ... | ... | 108 | 18.1 | ... | 18.8 |
| Kopf et al,\textsuperscript{38} 1977 | 1970 | 91 | ... | ... | 7 | 7.7 | ... | 9.6 |
| Kopf et al,\textsuperscript{38} 1977 | 1962-1973 | 210 | ... | ... | 8 | 3.8 | ... | 5.7 |
| Launis,\textsuperscript{39} 1993 | 356 | ... | ... | 22 | 6.2 | ... | ... |
| McDaniel,\textsuperscript{40} 1983 | Curettage only | 644 | 328 | 318 | 28 | 4.3 | 8.5 | ... |
| Silverman et al,\textsuperscript{41} 1991 | 1955-1982 | 2314 | 1110 | 1204 | ... | ... | 13.2 |
| Silverman et al,\textsuperscript{42} 1992 | 1955-1982 | 862 | 470 | 392 | ... | ... | 7.4 |
| Immunotherapy                 |          |                |                |                           |                          | ... | ... | ... |
| Reymann,\textsuperscript{43} 1979 | 1966-1968 | 95 | 56 | 39 | 12 | 12.6 | 21.4 | ... |

* Ellipses indicate that data are unavailable.
† Raw recurrence rate: absolute number of patients with recurrence divided by number of patients with primary BCCs at the start of study.
‡ Strict recurrence rate: absolute number of patients with recurrence divided by number of patients with primary BCC observed for at least 5 years.
§ Life-table cumulative 5-year recurrence rate: values are recorded from the cited article. Ellipses indicate that data are unavailable.
# The number of patients with primary BCC at the start of study is not mentioned (total number of patients with BCC minus the number with treated recurrent BCC, observed for >5 years).
¶ Calculated.
# Small group (number < 50).
lier. This could explain the high recurrence rates after CE, both in the first group of tumors reported on by Kopf et al (treated between 1958 and 1962) and in the study performed by Silverman et al, who described less favorable results in tumors treated in the earlier years (1955-1963). This explanation is only a hypothetical one because other tumor-specific factors could have attributed to these results. Nevertheless, to restrict the influence of the accuracy of the treatment in earlier decades, we analyzed only the studies published after the 1960s.

Ten years ago, Rowe et al performed a meta-analysis on the recurrence rates for treatment modalities of primary BCCs. They also compared the recurrence rates after a follow-up of shorter than 5 years with those of a follow-up of longer than 5 years. Nearly two-thirds of all recurrent tumors seemed to appear in the first 3 years after treatment, and 18% appeared between 5 and 10 years after treatment. According to this article, the reporting of recurrence rates for BCC should be standardized, using 5-year life-table analyses. We mostly agree with this statement; these 5-year cumulative recurrence rates can best be compared in prospective studies, without a tumor selection bias. Nevertheless, studies reporting on treatment results after a follow-up of shorter than 5 years might give unrealistically low recurrence rates. For this reason, these studies were not included in our search.

Systematic review, in general, has made and continues to make major contributions to medical research, clinical decision making, and standards of research reportage; but it is no panacea. When considering all the aspects mentioned earlier and shown in Table 3, MMS appears to be the treatment modality with the lowest recurrence rate, even for BCCs localized in anatomic sites at risk for recurrences. Several years ago, MMS was a time-consuming surgical method, but it can now be done efficiently. It was also thought to be an expensive treatment modality, but recently Cook and Zitele demonstrated near-equivalent cost of MMS vs standard SE with permanent section control and even lower cost of MMS vs SE with frozen section control. Treating all BCCs with MMS should certainly lead to overtreatment, especially in patients with smaller (<2 cm) BCCs of the nodular type located outside the H region of the face. These BCCs can be treated successfully with primary SE.

According to the results of our analysis, the recurrence rates with CS and CE are higher than with surgical methods. No conclusions can be drawn from our results whether certain small tumors with less aggressive histologic subtypes localized on some areas of the body are treated better with CS or CE. Further large, prospective comparative studies should be performed to analyze this. The recurrence rate for RT has been based on a solitary study, so it is difficult to draw a conclusion for this treatment modality. Because of the less favorable cosmetic results more than 5 years after therapy, this treatment modality should not be used as primary treatment in relatively young patients. Finally, the long-term cure after immunotherapy, so far based on the results of I study, is not promising.

### CONCLUSIONS

From this systematic review, it is not possible to propose general guidelines for the treatment of BCCs. Several characteristics of the tumor and the patient should be taken into account before deciding how to treat this specific tumor. If surgery is not contraindicated, SE remains the treatment modality of first choice for BCCs. For the larger BCCs in the H region of the face and those with more aggressive growth patterns, MMS is recommended. Because the number of dermatologic surgeons capable of performing MMS is still low, special training in this surgical technique should be an important consideration for dermatologic surgeons.

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