# Sebaceous carcinoma: evidence-based clinical practice guidelines

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**Sebaceous carcinoma usually occurs in adults older than 60 years, on the eyelid, head and neck, and trunk. In this Review, we present clinical care recommendations for sebaceous carcinoma, which were developed as a result of an expert panel evaluation of the findings of a systematic review. Key conclusions were drawn and recommendations made for diagnosis, first-line treatment, radiotherapy, and post-treatment care. For diagnosis, we concluded that deep biopsy is often required; furthermore, differential diagnoses that mimic the condition can be excluded with special histological stains. For treatment, the recommended first-line therapy is surgical removal, followed by margin assessment of the peripheral and deep tissue edges; conjunctival mapping biopsies can facilitate surgical planning. Radiotherapy can be considered for cases with nerve or lymph node involvement, and as the primary treatment in patients who are ineligible for surgery. Post-treatment clinical examination should occur every 6 months for at least 3 years. No specific systemic therapies for advanced disease can be recommended, but targeted therapies and immunotherapies are being developed.**

## Introduction

Sebaceous carcinoma is an uncommon but potentially aggressive cutaneous malignancy. Periocular sebaceous carcinoma arises from the sebaceous glands, whereas extraocular sebaceous carcinoma has an indeterminate origin. Periocular and extraocular tumours behave differently and have different genetic signatures.[1,2] No standardised treatment yet exists. In this Review, we present guidelines for the diagnosis and management of sporadic sebaceous carcinoma (panel 1; panel 2), based on expert assessment of data derived from a systematic review of the literature. Management of Muir-Torre syndrome—a variant of Lynch syndrome with cutaneous neoplasms—has been described elsewhere.

## Guideline development

Experts in sebaceous carcinoma were identified by JLO, BW, NK, and MA through relevant publication history, national clinical reputation, involvement in previous cancer guidelines, and peer nomination. Key stakeholder specialties were included. The panel was composed of people specialising in general dermatology (seven specialists), cutaneous oncology (29), ocular oncology (four), surgical oncology (three), medical oncology (three), dermatopathology (three), radiation oncology (two), general radiology (one), plastic surgery (one), statistics (one), and research methodology (three). The expert committee reviewed data tables extracted from the published literature to answer the question, "in individuals without a genetic predisposition, what are the best practices for diagnosis, risk assessment, and management of extraocular and periocular sebaceous carcinoma?" The consensus process was through teleconferences and an in-person meeting at the American Society for Dermatologic Surgery Annual Meeting in Phoenix, AZ, USA, in October, 2018. The guidelines were collaboratively revised in four rounds until consensus on key recommendations was achieved. All panellists reviewed the final manuscript. A flow diagram of the study screening process can be found in figure 1.

### Grading of recommendations

We graded recommendations in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group. We also reported National Comprehensive Cancer Network Evidence Grading and Consensus categories. For the purposes of these guidelines, recommendations with category 2A indicate unanimous consensus, whereas category 2B indicates at least 90% of the panel voted in favour of the recommendation.

### Guideline update plan

These guidelines will be reviewed for revision every 5 years to ensure the recommendations reflect up-to-date evidence. When new practice-changing studies emerge, an interim update might be issued.

### Method for calculating surgical margins

Case-level data for presurgical and postsurgical margins were extracted, primarily from studies using margin-controlled techniques. Recurrent or incompletely excised cases were excluded. From the mean and standard deviation of the margin that resulted in complete tumour clearance, a Q–Q plot showed whether or not population-wide data would approximate a normal distribution.

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***Panel 1*: Principles of sebaceous carcinoma management**

**Overall considerations**

- The primary goal of the treatment of sebaceous carcinoma is complete excision with clear surgical margins and preservation of function and cosmesis. All treatment decisions should be personalised according to clinical presentation, medical history, and patient preference.
- No specific systemic therapy for advanced disease can be recommended. Distant metastasis is an uncommon outcome.

**Screening for Muir-Torre syndrome**

- Cutaneous sebaceous carcinoma mismatch repair protein immunohistochemistry is moderately sensitive and not specific for reliable detection of Muir-Torre syndrome when compared with genetic testing initiated by clinical criteria (GRADE B).
- Individuals can be selected for genetic testing using the Mayo risk score (GRADE B). Young patients (aged <50 years) who have extraocular sebaceous carcinoma can be considered for tumour tissue mismatch repair protein immunohistochemistry testing (GRADE D).

**Extraocular sebaceous carcinoma**

- Margin-controlled techniques such as Mohs micrographic surgery or complete circumferential peripheral and deep margin assessment (CCPDMA) by intraoperative frozen or permanent sections and en face sectioning might provide the lowest chance of recurrence. Wide local excision with adequate margins cannot be compared with Mohs micrographic surgery or CCPDMA because current comparisons involve a single, small retrospective cohort (GRADE B).
- Alternatively, wide local excision with 1 cm radial (peripheral) margins with resection to the deep fascial plane can be considered in anatomical areas where this is feasible. Radiotherapy cannot be recommended as first-line therapy (GRADE C).
- Staging by sentinel lymph node biopsy or elective lymphadenectomy is not recommended (GRADE C). Adjuvant radiotherapy to the affected nodal basin can be considered to assist with regional control (GRADE D).

**Periocular sebaceous carcinoma**

- Surgery by CCPDMA or Mohs micrographic surgery is first-line treatment. Where there is pagetoid spread or diffuse conjunctival spread, conjunctival mapping biopsies might help determine the extent of disease to assist with preoperative planning. Wide local excision is not indicated (GRADE B).
- Topical mitomycin or cryotherapy can be helpful for focally positive conjunctival margins, or local conjunctival recurrence after repeat CCPDMA or Mohs micrographic surgery, or diffuse pagetoid spread on the bulbar conjunctiva (GRADE C).
- Eyelid tumours stage T2c or higher by the eighth edition of the American Joint Committee on Cancer staging system can be considered for sentinel lymph node biopsy (GRADE B).
- Completion lymph node dissection or radiotherapy can be considered to supplement resection of involved sentinel lymph nodes (GRADE C). Close clinical follow-up and ultrasonography of the nodal basin are recommended to monitor for recurrence of disease (GRADE C).

GRADE recommendation categories are indicated next to each recommendation unless otherwise specified. GRADE=Grading of Recommendations, Assessment, Development, and Evaluation

Data were positively skewed. A logarithmic normal distribution was created to model the 95% cutoff margin for tumour clearance.

### Guideline disclaimer

These guidelines are provided by the Committee on Invasive Skin Tumor Evidence-Based Recommendations (CISTERN) to assist clinical decision making. We made an effort to review the most recent information available as of the publication date and to implement a rigorous expert consensus process. When relevant, recommendations in these guidelines are followed by explanatory notes. However, these guidelines do not establish a standard of care. No clinical actions are mandated or prohibited. New evidence might emerge after the guidelines are published. Treating physicians can select courses of action other than those suggested here when they judge these to be most appropriate for specific patients. CISTERN assumes no responsibility and makes no warranty, express or implied, regarding the information provided.

## Clinical presentation and tests for sebaceous carcinoma

### Epidemiology

Recommendation 1: a biopsy of a suspicious extraocular lesion using shave, punch, or excisional techniques should include deep dermis; eyelid biopsies do not require depth for diagnosis; and atypical chalazion or chronic unilateral blepharitis in adults older than 60 years should prompt consideration of sebaceous carcinoma (GRADE B; category 2A).

In 61 studies that met the inclusion criteria (panel 3), mean age for extraocular sebaceous carcinoma was 67·9 years (SD 7·8; 16 019 patients). Approximately 9291 (58%) of these patients were men. For periocular sebaceous carcinoma, 2934 patients from 95 studies had a mean age of 67·7 (8·3) years and were predominantly women (1857 [63·3%]). The most frequently affected ethnic groups were white people (8568 [87·0%] of 9844 patients with extraocular sebaceous carcinoma and 302 [42·1%] of 717 with periocular sebaceous carcinoma), and people from Asia-Pacific islands (202 [2%] of

### *Panel 2*: Principles of radiotherapy for sebaceous carcinoma

**Overall considerations**

- Consultation with a radiation oncologist familiar with sebaceous carcinoma is recommended, given the weak evidence for dosing of radiotherapy.
- When radiotherapy is selected, protracted fractionation is associated with improved cosmesis and should be considered, especially for poorly vascularised areas.
- Contraindications to radiotherapy include previous irradiation of the field and genetic conditions that predispose patients to cutaneous malignancy (eg, xeroderma pigmentosum). Radiotherapy should be used with caution in patients with connective tissue diseases.

**Radiotherapy as monotherapy**

- Radiotherapy as monotherapy is reserved for surgery-ineligible patients or for palliation (GRADE C).
- Extraocular sebaceous carcinoma: 50–70 Gy in 2 Gy fractions and 2 cm margin can be considered (GRADE C).
- Periocular sebaceous carcinoma: 56–70 Gy given in 2 Gy fractions can be considered. The margin is based on adjacent anatomy. Substantial ocular toxicity might result, especially for the upper eyelid and with high doses (GRADE C).

**Postoperative adjuvant therapy**

- Extraocular sebaceous carcinoma: radiotherapy might possibly be considered if there is perineural invasion or if postsurgical margins are positive (GRADE C).
- Periocular sebaceous carcinoma: 50–60 Gy in 2 Gy fractions can be considered for perineural invasion, with margin based on adjacent anatomy (GRADE C).
- Regional lymph nodes: particularly for periocular disease, patients with positive sentinel lymph node dissections can receive radiotherapy to the nodal basin instead of completion lymph node dissection (GRADE C). For patients with clinical evidence of regional lymph node metastasis, regional radiotherapy can be considered after therapeutic lymphadenectomy (GRADE D).

**Local recurrence after first-line therapy**

- Adjuvant radiotherapy can be considered after re-excision (GRADE D).

GRADE recommendation categories are indicated next to each recommendation unless otherwise specified. GRADE=Grading of Recommendations, Assessment, Development, and Evaluation.

9844 with extraocular sebaceous carcinoma and 402 [56%] of 717 with periocular sebaceous carcinoma).

Extraocular sebaceous carcinoma typically presents as a painless, red-yellow to red-brown ulcerated papule, usually on the head or neck. Benign sebaceous neoplasms, basal cell carcinoma with focal sebaceous differentiation, and clear-cell squamous cell carcinoma can mimic sebaceous carcinoma. Data from the systematic review showed that to distinguish sebaceous carcinoma from basal cell carcinoma and squamous cell carcinoma, cytological features of sebocytes are helpful, and immunohistochemical markers (described later) are often used. Furthermore, extraocular sebaceous carcinoma tumours were present in study patients 1–2 years before diagnosis, had a mean largest dimension of 1·4 cm (SD 0·3), and nine (14%) of 65 tumours were recurrent at presentation.

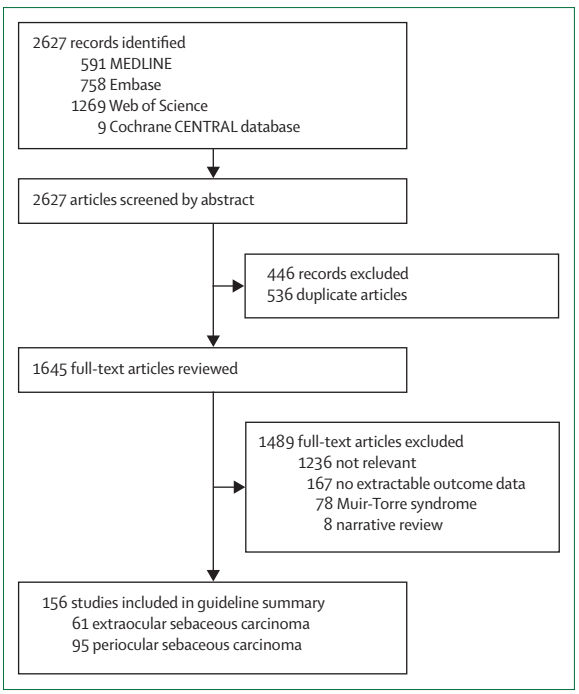


*Figure 1:* **Study inclusion flow diagram**

Because periocular sebaceous carcinoma can resemble benign lesions such as chalazia, blepharitis, or blepharoconjunctivitis, diagnosis might be delayed, resulting in poor outcomes.[3] For the data we reviewed, the mean time to diagnosis was 1·7 years (SD 1·1), mean lesion size was 1·40 cm (0·64), and the upper eyelid (789 [31·8%] of 2482 cases) was the most frequently affected area. Other affected areas were the lower lid (409 [16·5%] cases), cornea (15 [0·6%]), conjunctiva (13 [0·5%]), caruncle (13 [0·5%]), medial canthus (11 [0·4%]), lateral canthus (five [0·2%]), and diffuse sebaceous carcinoma (including the bilateral eyelid; 22 [0·9%]). In 1113 (44·8%) patients the exact location on the eyelid was not specified, and in 92 (3·7%) the exact location in the orbit was not specified. In 89 of 95 periocular studies, partial-thickness or full-thickness eyelid biopsy was used for diagnosis.[4–9]

## Tumour profiling and assessment

Recommendation 2: at the time of biopsy or diagnosis, a full cutaneous examination and lymph node examination of relevant nodal basins should be done; for periocular tumours, assessment for restricted ocular mobility, proptosis, globe displacement, and pupillary abnormalities is recommended (GRADE D; category 2A).

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***Panel* 3: Worldwide demographics of sebaceous carcinoma based on published cases**

The US National Institutes of Health racial and ethnic categories are reported. Other ethnic subgroups not listed might comprise some of the total number of patients.

**Extraocular sebaceous carcinoma**
- 16 019 total patients
- Mean age 67·9 years (SD 7·8)
- Women: 42·0%

*Ethnic groups*
- White: 87·0%
- African American: 1·4%
- Asia-Pacific islander: 2·0%
- Hispanic or Latino: 0·01%
- Native American: 0·09%
- Not specified: 9·5%

**Periocular sebaceous carcinoma**
- 2934 total patients
- Mean age 67·7 years (SD 8·3)
- Women: 63·3%

*Ethnic groups*
- White: 42·1%
- African-American: 0·5%
- Asia-Pacific islander: 56·1%
- Hispanic or Latino: 1·3%
- Native American: 0·0%

Although no studies show the benefit of physical examination, examination of a lesion that is suspicious for cutaneous carcinoma begins with full cutaneous examination and examination of relevant nodal basins.

## Pathological diagnosis and immunohistochemistry

Recommendation 3: an immunohistochemistry profile positive for nuclear factor XIIIa (clone AC-1A1 mouse monoclonal), androgen receptor, and adipophilin and perilipin, with or without BerEP4, can help to identify sebaceous carcinoma with indeterminate features (GRADE B; category 2A).

In the studies we reviewed, the usual histopathological pattern of extraocular sebaceous carcinoma was an infiltrative, uniformly nested or lobular, vacuolated sebaceous neoplasm in the dermis. On cytological examination, the malignant cells were foamy, with scalloped nuclei, atypia, and mitoses. Sebaceous carcinoma in situ or with pagetoid spread, overlying or adjacent to the primary lesion, was often reported. Primary in-situ tumours were uncommon. Most extraocular sebaceous carcinomas showed dermal invasion, rarely penetrating to subcutaneous tissue and muscle.[10–13] Of 2249 patients with sebaceous carcinoma for which the degree of differentiation was reported, 754 (33·5%) were well differentiated, 630 (28·0%) were moderately differentiated, and 865 (38·5%) were poorly differentiated.

By contrast, periocular sebaceous carcinoma had multiple histopathological patterns: lobular (274 [48%] of 576 carcinomas), comedo-acinar (136 [24%]), papillary (37 [6%]), and mixed (129 [22%]). 182 (21%) of 871 periocular sebaceous carcinomas were well differentiated, 408 (47%) were moderately differentiated, and 281 (32%) were poorly differentiated. Pagetoid spread was present in 208 (24%) of 870 cases. Pagetoid tumours were more likely than non-pagetoid tumours to be poorly differentiated,[14] recurrent,[15] and require orbital exenteration;[15,16] pagetoid tumours were also at higher risk for metastasis.[17,18]

For extraocular sebaceous carcinoma, positive immunohistochemical markers, as reported in a total of 38 studies, included nuclear factor XIIIa (AC-1A1), EMA (positive in squamous cell carcinoma), cytokeratin AE1 and AE3 (positive in squamous cell carcinoma), androgen receptor, adipophilin, and perilipin. Markers that were mostly negative in sebaceous carcinoma included carcinoembryonic antigen, S100, HMB45, SOX10, CD5, GCDFP-15, D2-40, and Ber-EP4.[19,20] Alternative markers used to identify extraocular sebaceous carcinoma include PGRMC1, ABHD5, SQS, CA15-3, CA19-9, CK8, and CK19.[21] Although immunohistochemistry is often used to definitively establish a diagnosis of sebaceous carcinoma, it is not required when histopathological findings are typical.

For periocular sebaceous carcinoma, based on a total of 40 studies, positive markers included EMA, adipophilin, BerEP4 (usually negative but occasionally positive),[19] BRST1, and CAM5.2. Aberrant expression of retinoid receptors was also shown.[22,23] Pagetoid spread was associated with EMA-negative, p16-positive, and p53-positive tumours,[24] whereas invasive periocular sebaceous carcinomas were adipophilin negative[25] and androgen receptor positive.[26,27]

## Risk stratification

Recommendation 4: for periocular sebaceous carcinoma, little evidence exists to suggest that a high ALDH1 or androgen receptor index by immunohistochemistry predicts an increased chance of recurrence or metastasis; this association has not been explored in extraocular sebaceous carcinoma. Perineural invasion has an uncertain effect on clinical outcomes (GRADE C, category 2A).

The following predisposing factors should be considered at diagnosis, because they might affect the choice of treatment for sebaceous carcinoma: location of the tumour, whether the patient is immunosuppressed, previous radiotherapy, pathological features, and perineural involvement.

### *Location of the tumour*

Three studies in our review concluded that periocular sebaceous carcinoma had an equivalent 5-year survival,[28] a non-statistically significant lower hazard ratio (HR) of

survival,[29] but a significantly higher (nearly five-times) proportion of patients with metastases than extraocular sebaceous carcinoma.[10] Other studies showed that eyelid tumours,[10] especially those of the lower eyelid[30] or with orbital extension,[31] were associated with higher mortality than tumours in other locations.

*Immunosuppression*

The effect of immunosuppression on sebaceous carcinoma is unclear,[32,33] but solid organ transplantation is estimated to increase the risk of sebaceous carcinoma by 90 times,[34] possibly because of iatrogenic immunosuppression-induced microsatellite instability.[32] Other immunosuppressed states, such as in lymphoma, might predispose individuals to periocular sebaceous carcinoma.[35]

*Previous radiotherapy*

The data we reviewed showed that 14 patients had periocular sebaceous carcinoma following remote radiotherapy for retinoblastoma or facial acne.[3,16,36] One study reported that periocular sebaceous carcinoma was diagnosed at a median age of 14 years (range 8–30) in patients who had radiotherapy, and at a median of 11 years (5–26) after radiotherapy.[36] Previous radiotherapy was not linked to extraocular sebaceous carcinoma.

*Pathological features*

Poorly differentiated tumours seem to be associated with higher mortality than are tumours that are well differentiated.[3,10] In individual studies, immunohistochemistry marker positivity has been correlated with recurrence and metastasis in periocular tumours. High androgen-receptor staining index, defined as more than 50% staining with at least moderate intensity, has been associated with increased risk of recurrence (odds ratio [OR] 7·0) and metastasis (7·2) for periocular sebaceous carcinoma.[26] Overexpression of ALDH1 might also be associated with increased risk of metastasis (5·68).[37] Ki-67 positivity was more common in poorly differentiated tumours,[38] and PD-1-expressing tumour cells tended to have a higher T stage than those not expressing PD-1.[39] These markers have not been explored in extraocular sebaceous carcinoma. The significance of higher EGFR expression in extraocular sebaceous carcinoma is uncertain.[40]

*Perineural involvement*

The effect of perineural invasion or lymphovascular invasion on prognosis is uncertain because of their low incidence in extraocular and periocular sebaceous carcinoma. Of 1313 patients with extraocular sebaceous carcinoma in the studies we reviewed, four (0·3%) had perineural invasion and three (0·2%) had lymphovascular invasion. For periocular sebaceous carcinoma, 34 (2·7%) of 1263 patients had perineural invasion, 49 (3·9%) had lymphovascular invasion, and three (0·2%) had both. No studies we reviewed addressed whether larger nerve calibre (>0·1 mm) imposes a greater risk of metastasis, as is the case in cutaneous squamous cell carcinoma.[41]

## Staging

Recommendation 5: the eighth edition of the American Joint Committee on Cancer (AJCC) staging system for eyelid carcinoma is used for periocular sebaceous carcinoma. The eighth edition of the Union for International Cancer Control TNM staging system for skin carcinomas can be used for extraocular sebaceous carcinoma (GRADE B, category 2A).

No specific staging criteria exist for extraocular sebaceous carcinoma. Because periocular sebaceous carcinoma is primarily an eyelid carcinoma, it is subject to the eighth edition of the AJCC guidelines (panel 4). Modifications in the eighth edition of these guidelines define T2 tumours as those larger than 10 mm, and T4 tumours as those that substantially invade adjacent structures. Each tumour grade is stratified by no invasion of eyelid margin or tarsal plate (a), invasion of eyelid margin or tarsal plate (b), or full-thickness eyelid involvement (c). Pagetoid intraepithelial neoplasia is not used for staging but should be noted because it is important prognostically. Validation studies of staging by T and N categories using the eighth edition of the AJCC system have shown better stratification than previous editions.[15,42]

***Panel 4*: T categories for staging of periocular sebaceous carcinoma reproduced from the eighth edition of the American Joint Committee on Cancer staging form supplement**

- Tx: primary tumour cannot be assessed
- T0: no evidence of primary tumour
- Tis: carcinoma in situ
- T1: tumour at least 10 mm in greatest dimension
  - T1a: no invasion of the tarsal plate or eyelid margin
  - T1b: invasion of the tarsal plate or eyelid margin
  - T1c: involves the full thickness of the eyelid
- T2: tumour 10–20 mm in greatest dimension
  - T2a: no invasion of the tarsal plate or eyelid margin
  - T2b: invasion of the tarsal plate or eyelid margin
  - T2c: involves the full thickness of the eyelid
- T3: tumour 20–30 mm in greatest dimension
  - T3a: no invasion of the tarsal plate or eyelid margin
  - T3b: invasion of the tarsal plate or eyelid margin
  - T3c: involves the full thickness of the eyelid
- T4: any tumour that invades the ocular, intraocular, or facial structures
  - T4a: invasion of ocular or intraocular structures
  - T4b: invasion of the bony orbit, extension to the paranasal sinus, nasolacrimal system, or brain

### Imaging

Recommendation 6: ultrasonography or CT scan of the nodal basin can be considered to delineate recurrent tumours or clinically palpable regional lymph nodes. Imaging should be considered for periocular tumours of stage T2c or higher, poorly differentiated pathology, pagetoid spread, or perineural invasion. Enlarged lymph nodes should be sampled, typically by fine-needle aspiration or image-guided core needle biopsy. Evaluation for distant metastases with CT or PET–CT scans should be considered only for confirmed nodal metastasis (GRADE B, category 2A).

Imaging protocols for direct tumour extension, regional lymph nodes, or distant metastases are not established and data for extraocular and periocular sebaceous carcinoma are scarce. Nodal spread and metastasis are uncommon. Clinically detected lymphadenopathy in extraocular sebaceous carcinoma has been assessed with ultrasonography and CT scans.[43–45]

For periocular sebaceous carcinoma, potential direct extension into the orbit, orbital nerves, temporal fossa, parotid gland, or skull base evaluated by MRI revealed that advanced tumours with higher T stages were more likely to have nodal spread than tumours with lower T categories.[46–50] Clinically detected lymphadenopathy has been evaluated with CT-guided biopsy[8,17,46,49,51–55] or ultrasonography with fine-needle aspiration or core needle biopsy.[15,48] When regional lymphadenopathy was not clinically detected, and the tumour was stage T2c or higher, high grade (ie, poorly differentiated, or with perineural invasion, or pagetoid spread), or recurrent, imaging of draining nodal basins with ultrasonography or CT has been considered.[15]

When distant disease was suspected, CT or total body PET–CT have been most frequently used, although two studies advocated the use of baseline chest radiography.[53,55] Surveillance imaging for detection of recurrence in high-risk tumours is discussed separately in the follow-up section.

### Screening for Muir-Torre syndrome

Recommendation 7: genetic testing for Muir-Torre syndrome in patients presenting with extraocular sebaceous carcinoma is recommended for individuals with a Mayo Muir-Torre syndrome risk score of 2 or higher. Muir-Torre syndrome screening is not recommended for periocular sebaceous carcinoma (GRADE B, category 2B).

Recommendation 8: young patients (aged <50 years) with their first sebaceous carcinoma, with loss of mismatch repair protein expression on the immunohistochemistry profile, and not otherwise meeting the Mayo Muir-Torre syndrome risk score threshold, might benefit from genetic testing to stratify their risk for Lynch syndrome-related cancers (GRADE D, category 2A).

The Mayo Muir-Torre syndrome risk score is a clinical screening tool for Muir-Torre syndrome.[56] Although extraocular sebaceous carcinoma occurring below the neck is strongly associated with Muir-Torre syndrome, universal screening by immunohistochemistry with follow-up germline testing for this syndrome is inefficient.[57] Analysis of the Surveillance, Epidemiology, and End Results (SEER) database could not detect the link between sporadic periocular sebaceous carcinoma and increased risk of internal malignancy.[58,59] Mismatch repair protein loss shown by immunohistochemistry in extraocular sebaceous carcinoma has 81–85% sensitivity and 48% specificity compared with 92–94% sensitivity and 88–100% specificity for colorectal cancer. Lower sensitivity and specificity for immunohistochemistry in identifying Muir-Torre syndrome-associated sebaceous carcinoma limits its usefulness for screening. Evidence regarding Muir-Torre syndrome does not favour screening for periocular sebaceous carcinoma.

## Management: extraocular sebaceous carcinoma

A clinical algorithm for the management of extraocular sebaceous carcinoma is provided in figure 2.

### Local treatment

Complete circumferential peripheral and deep margin assessment (CCPDMA), Mohs micrographic surgery, wide local excision, and radiotherapy were specified for 1233 patients in our systematic review. CCPDMA is defined as surgical excision followed by pathologist-rendered margin assessment using either en-face analysis (a specific sectioning technique whereby the tissue is placed epidermis side down and sectioned circumferentially) or other methods. Mohs micrographic surgery refers to surgical excision followed by surgeon-rendered evaluation of en-face tangential frozen sections.

#### *Superficial and destructive techniques*

Recommendation 9: superficial and destructive techniques for treating extraocular sebaceous carcinoma are not recommended (GRADE C, category 2B).

Superficial and destructive techniques have rarely been used for treatment, and their utility is uncertain.[29,60]

#### *Wide local excision*

Recommendation 10: when CCPDMA or Mohs micrographic surgery is not available, and wide local excision is chosen as the surgical approach, a peripheral surgical margin of 1 cm down to the fascial plane is recommended. When immediate margin assessment is unavailable, staged excision might increase the likelihood of clear margins before reconstruction (GRADE C, category 2A).

The data we reviewed showed that, of 1226 patients treated primarily with surgery, 1074 (87·6%) had wide local excision. Using study-level data from 84 patients (57 [68%] had wide local excision, 24 [29%] had Mohs micrographic surgery),[61–64] complete peripheral margin clearance would be expected with mean margins of 0·54 cm (95% CI 0·19–0·88). Using Z scores

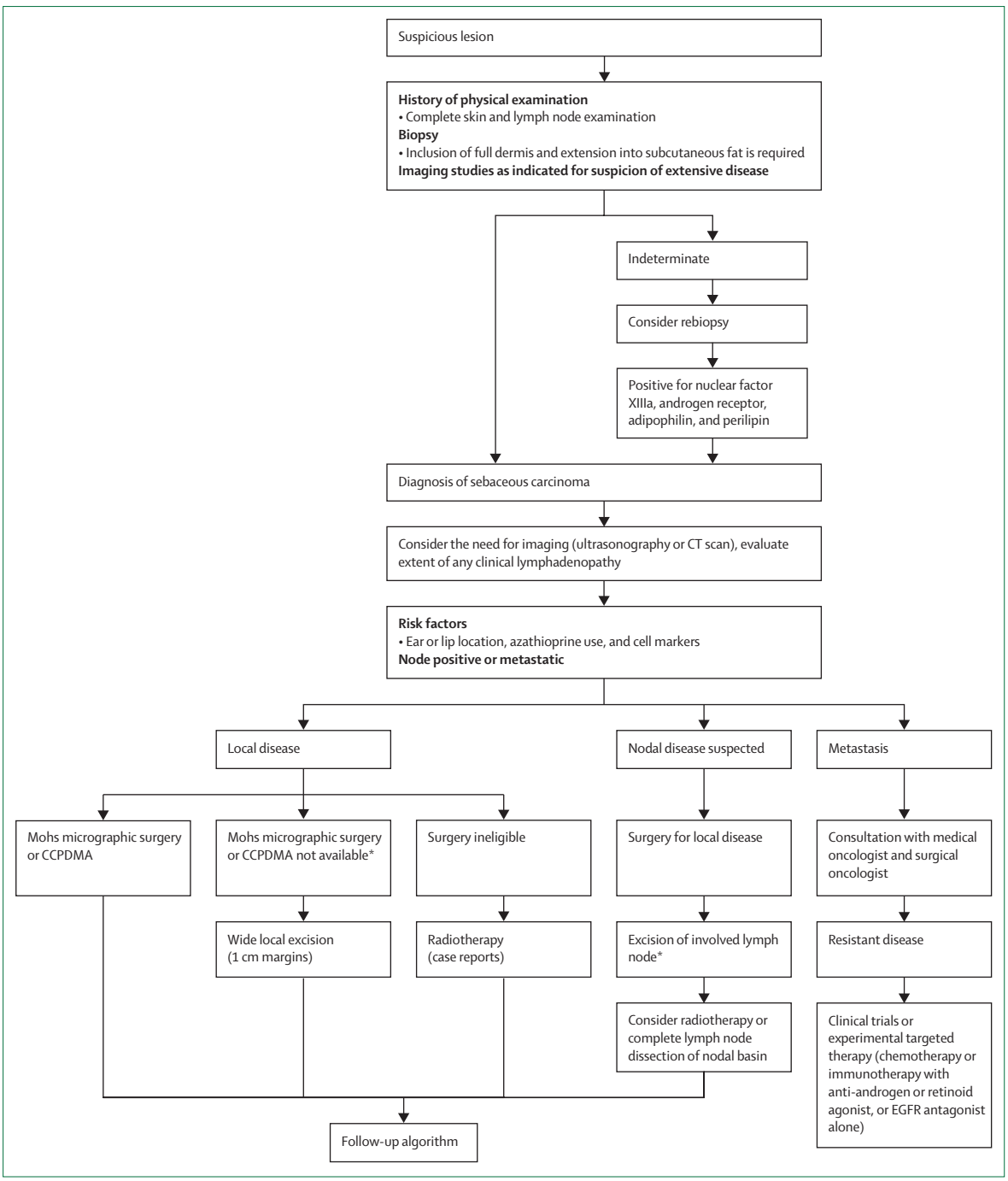


***Figure 2:*** **Diagnosis and initial treatment of extraocular sebaceous carcinoma**
Radiotherapy doses for monotherapy are limited to case reports. CCPDMA=complete circumferential peripheral and deep margin assessment. *Although the expert panel recommends margin-controlled surgery, comparative studies between margin-controlled surgery and wide local excision are unavailable.

derived from presurgical and postsurgical margins of 25 patients without recurrences, a logarithmic normal distribution model predicted that 95% of tumours would be cleared with a 1·0 cm margin (appendix p 1). However, this model might underestimate the margins needed for large tumours and requires validation because it is based on a subset of complete case-level data.[61]

### *Margin-controlled surgery*

Recommendation 11: local treatment for extraocular sebaceous carcinoma should focus on complete

See **Online** for appendix

histological margin control. Although few comparative studies have been done, Mohs micrographic surgery, CCPDMA, or similar techniques might minimise the risk of recurrence (GRADE B, category 2B).

Recommendation 12: discovery of sebaceous carcinoma in a misclassified tumour during Mohs micrographic surgery treatment should prompt submission of tumour debulk for histopathological review (GRADE D, category 2A).

Mohs micrographic surgery was the primary surgical method in 152 (12·4%) of 1226 patients with 1·4 stages (mean margin unknown) needed on average to achieve tumour clearance. A retrospective cohort of 37 patients with predominantly extraocular, sporadic sebaceous carcinoma reported recurrence-free survival for individuals treated with Mohs micrographic surgery (26 patients) versus wide local excision (11 patients) at 1 year (88% *vs* 67%), 3 years (88% *vs* 45%), and 4 years (59% *vs* 45%).[65] Although this study had a small sample size, the findings suggest that Mohs micrographic surgery has superior outcomes compared with wide local excision. The consensus of the expert panel was that margin control by Mohs micrographic surgery or CCPDMA is most likely to give the greatest chance of tumour clearance and reduce the risk of recurrence. However, we cannot conclude on the basis of a small retrospective cohort that wide local excision is inferior to Mohs micrographic surgery or CCPDMA when sufficient margins are taken. Prospective or sufficient retrospective cohort data would probably be needed to reach a conclusion because randomised controlled trials are unlikely to be done on this subject.

## Lymph node sampling or dissection

Recommendation 13: routine use of sentinel lymph node biopsy is not recommended for extraocular sebaceous carcinoma. Because insufficient data are available regarding the value of completion lymph node dissection after a biopsy of a suspicious lymph node or a sentinel lymph node biopsy, clinical judgment and multidisciplinary consultation are suggested to guide management (GRADE C, category 2A).

Of 1070 extraocular sebaceous carcinoma cases in the SEER database, ten (0·9%) had positive lymph nodes,[10] and location on the lip and ear increased the risk of having a positive lymph node (HR 1·68 for lip and 1·24 for ear, compared with periocular sebaceous carcinoma).[29] For extraocular sebaceous carcinoma, 1% of patients within cohort studies had a sentinel lymph node biopsy, among whom only 1·2–1·7% had regional lymph node involvement, thus limiting the usefulness of sentinel lymph node biopsies in this disease.[10] Nodal biopsies of clinically enlarged lymph nodes (done in 43 patients) were positive in 16 (37%) patients, of which 50% (eight of 16) were regional.[10,29] Most patients with extraocular sebaceous carcinoma with positive sentinel lymph node biopsies had completion lymph node dissection, with uncertain benefit.

## Radiotherapy

Recommendation 14: radiotherapy as monotherapy is not recommended (GRADE C, category 2A); however, radiotherapy might be appropriate for patients who are medically inoperable or have tumours or nodal metastases that are surgically unresectable (GRADE D, category 2A).

Recommendation 15: if completion lymph node dissection is done, adjuvant radiotherapy of the involved nodal basin could be considered; multidisciplinary consultation is recommended (GRADE D, category 2A).

Recommendation 16: the effect of adjuvant radiotherapy on overall survival and local and regional control is unclear; radiotherapy can be considered in individual cases (GRADE C, category 2A).

### *Radiotherapy as monotherapy*

Evidence is insufficient to support or refute the effectiveness of radiotherapy as monotherapy for extraocular sebaceous carcinoma. In the studies we reviewed, radiotherapy as monotherapy was used in eight patients to treat tumours not amenable to surgery.[30,63] Case reports have shown the use of 50–70 Gy doses of radiotherapy in 25–35 fractions and 2 cm margins to control extraocular sebaceous carcinoma.[66]

### *Adjuvant radiotherapy*

Postsurgical adjuvant radiotherapy was used in 95 (6·6%) of 1438 patients with extraocular sebaceous carcinoma in the studies we reviewed. Consistent with this, SEER data showed that 5·3% of patients with sebaceous carcinoma receive a combination of surgery and radiotherapy.[28] Tumours treated with this combination therapy included locally advanced primaries and those with positive margins or perineural invasion. Data about radiotherapy for perineural invasion are too scarce to draw firm conclusions about its efficacy.[28,30,61,67–70]

Recurrences were reported after adjuvant radiotherapy for positive margins in the studies examined, but these recurrences could be related to extent of disease, technique, or dose.[30,44,61,67,70] Further studies are needed to help define the role of radiotherapy in local management of extraocular sebaceous carcinoma. Radiotherapy to the nodal basin for confirmed lymph node involvement is reported, but outcome data are scarce.[44,61,67]

## Recurrent disease

Of the 246 patients with reported follow-up in the studies we examined, 35 patients (14%) had recurrent disease. The mean time to recurrence (data available for 78 patients) was 19·4 months (SD 20·4). 19 studies (275 patients) recorded both treatment method and recurrence. For Mohs micrographic surgery, there were five studies (78 total patients) with a mean follow-up of 28·7 months (21·8); for wide local excision there were

16 studies (total 186 patients) with a longer mean follow-up of 44·6 months (30·7). No disease recurrences occurred in patients treated with Mohs micrographic surgery; 14 of 16 studies of wide local excision reported at least one recurrence. The disparity between the number of patients whose data were reported for Mohs micrographic surgery and wide local excision might introduce some selection bias.

*Surgical management*

Recommendation 17: for recurrent extraocular sebaceous carcinoma, complete histological margin control with Mohs micrographic surgery or CCPDMA might be considered over wide local excision (GRADE C, category 2A).

The data we reviewed showed that most recurrences were treated surgically with wide local excision or Mohs micrographic surgery. Of five studies that included lesions that were recurrent on presentation,[12,43,44,62,69] the only patients who had subsequent second recurrences had been previously treated with wide local excision.[44,69] The reliability of this finding was limited by the shorter mean follow-up time for Mohs micrographic surgery (29 months *vs* 45 months for wide local excision), the unavailability of descriptive data regarding tumour characteristics in each group, and the absence of any direct comparisons between techniques.

*Radiotherapy*

Recommendation 18: radiotherapy is of uncertain utility for recurrent extraocular sebaceous carcinoma (GRADE D, category 2A).

Data on the use of radiotherapy for recurrent extraocular sebaceous carcinoma are insufficient. In the studies we reviewed, only a single patient received radiotherapy for a recurrent lesion and they had no further recurrence.[69]

## Management: periocular sebaceous carcinoma

A clinical algorithm for the management of periocular sebaceous carcinoma is provided in figure 3.

### Local treatment

Periocular sebaceous carcinoma has usually been managed surgically (1520 [86·9%] of 1749 patients reviewed) with wide local excision, CCPDMA, Mohs micrographic surgery, or another unspecified method. Adjuvant superficial and destructive techniques have been used in 70 (4·6%) patients with periocular sebaceous carcinoma.

*Superficial and destructive techniques*

Recommendation 19: focally positive surgical margins can be treated with adjuvant double freeze–thaw cryotherapy or topical mitomycin (GRADE C, category 2A).

As a primary treatment method for periocular sebaceous carcinoma, topical mitomycin has been used in 14 patients, including for pagetoid disease.[31,71,72] Topical mitomycin has been an adjuvant treatment in 21 patients and cryotherapy has been an adjuvant treatment in 13 patients, when surgical margins were positive or pagetoid disease was observed.[16,73–76] Some studies have suggested scouting biopsies or clinical observation for residual pagetoid disease, and have described spontaneous resolution after resection of the invasive component.[75]

*Wide local excision*

Recommendation 20: if complete margin assessment cannot be done or is unavailable, staged excision with delayed reconstruction can be considered, although this treatment might result in increased morbidity in cases of pagetoid spread and multicentric tumour origin (GRADE B, category 2A).

417 (27·4%) of 1520 patients treated surgically were treated with wide local excision with paraffin-embedded sectioning. Two studies (21 patients) reported patient-level data, with surgical margins averaging 0·66 cm (99% CI 0·06–1·26). A logarithmic normal distribution model estimated that margins of 1 cm would clear 54% of tumours, and margins of 2 cm would clear 95% (appendix p 1). Wide local excision has not been compared directly with CCPDMA or Mohs micrographic surgery, but given the calculated margins, wide local excision seems to be an impractical surgical strategy for periocular sebaceous carcinoma.

*Margin-controlled surgery*

Recommendation 21: periocular sebaceous carcinoma should be managed surgically (CCPDMA or Mohs micrographic surgery) with full margin assessment (GRADE B, category 2A).

Recommendation 22: surgical planning for periocular sebaceous carcinoma can be assisted by conjunctival mapping biopsies for patients with pagetoid spread on initial biopsy, probable subclinical spread beyond visible margins, or gross involvement of conjunctiva (GRADE B, category 2A).

459 (30·2%) of 1520 patients with periocular sebaceous carcinoma were treated with CCPDMA with or without permanent sectioning.[77] In 154 (33%) of 459 patients, a 3–5 mm margin was specified. Mohs micrographic surgery was used in 35 (2·3%) of 1520 patients with an average of 2·01 stages (99% CI 0·95–3·06) and unspecified margins. One study showed significantly lower recurrence at a median follow-up of 5 years with Mohs micrographic surgery (15·7%) compared with wide local excision (39·6%) and an HR of 0·42 through multivariate analysis.[78]

Conjunctival mapping biopsies assisted surgical planning by delineating conjunctival involvement for tumours with pagetoid spread on initial biopsy, probable subclinical spread beyond visible margins, or gross conjunctival involvement. In one cohort of 129 patients, 16% of conjunctival mapping biopsies were positive for distant pagetoid spread.[31] Several mapping techniques have been described, mainly differing in the number of

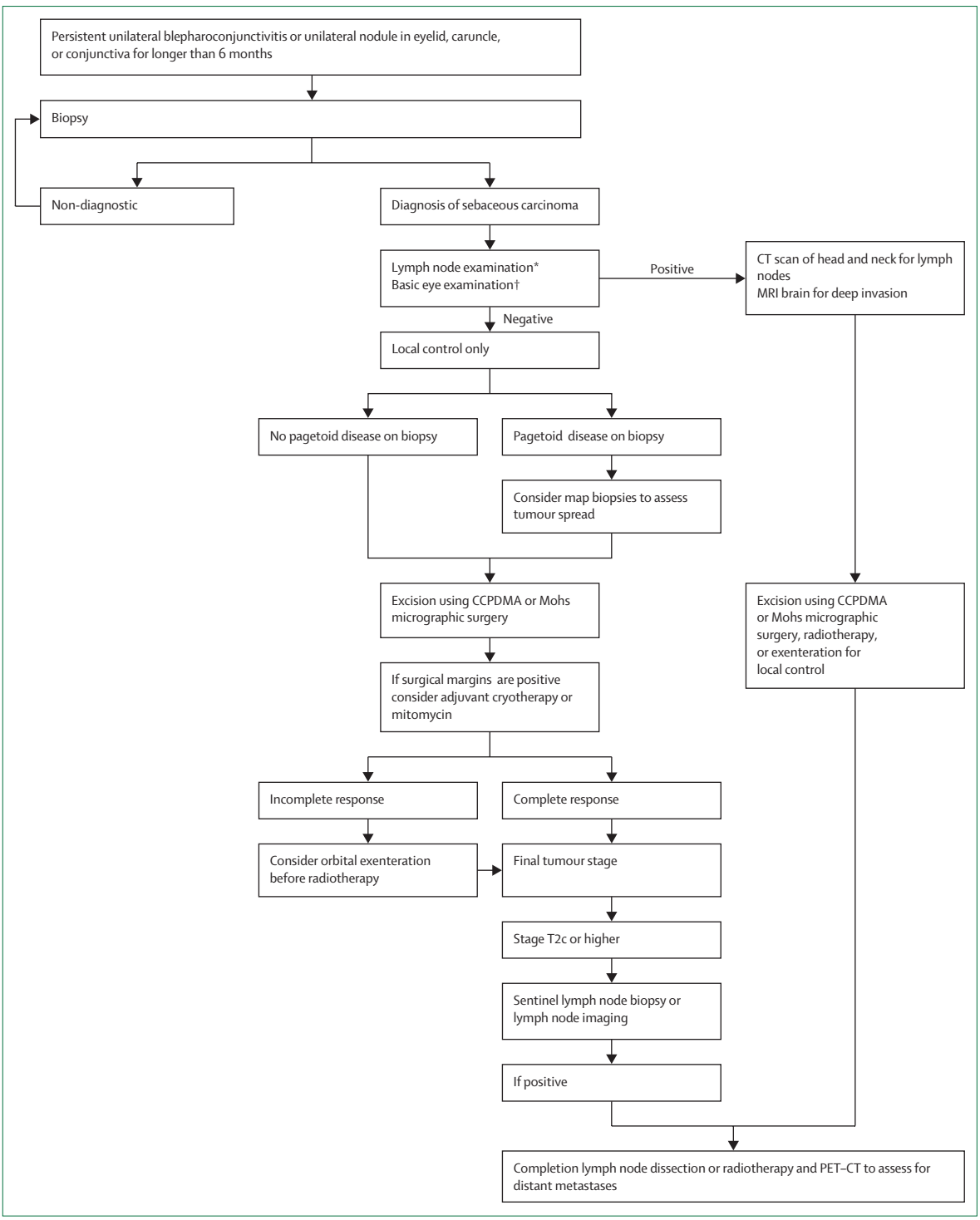


***Figure 3:*** **Diagnosis and initial treatment of periocular sebaceous carcinoma**
CCPDMA=complete circumferential peripheral and deep margin assessment. *Lymph node examination includes assessment of relevant basins. †Eye examination includes evaluation of sensation and position, extraocular muscle assessment, and pupillary dilatation.

circumferential biopsies taken from palpebral and bulbar conjunctivae.[79,80] Further study is required to confirm the usefulness of this method. Some experts argue that most pagetoid disease can be diagnosed from examination of the primary tumour specimen.[81] Posterior lamellar resection, a surgical technique that

entails removing the entire tarsal plate and palpebral conjunctiva, has been described as having lower morbidity and fewer metastases than lumpectomy.[82]

*Exenteration*

Recommendation 23: orbital exenteration is reserved for when other treatments are unsuccessful and there is extensive involvement of orbital or periorbital anatomy (GRADE B, category 2B).

Orbital exenteration was used in 119 (7·8%) of 1520 patients whose carcinoma involved the orbit, globe, or paranasal sinuses when there was extension to retrobulbar structures, extraocular muscles, bulbar conjunctiva, or sclera.[83,84] In a retrospective study, exenteration improved disease-free survival.[85] An eyelid and orbicularis sparing exenteration has been suggested to allow quick healing of the socket and earlier prosthetic fitting.[58] Orbit-sparing surgery seems to be possible when both eyelids are involved, but is technically difficult, and exenteration might be preferred. As an alternative to exenteration, plaque brachytherapy[86] or mitomycin with double freeze–thaw cryotherapy has been used in patients with advanced orbital or lacrimal system involvement.[80]

## Lymph node sampling or dissection

Recommendation 24: sentinel lymph node biopsy with or without imaging of the nodal basin can be considered for periocular sebaceous carcinoma at stage T2c or higher (GRADE B, category 2A).

Recommendation 25: completion lymph node dissection or radiotherapy can be considered for microscopic regional metastasis (GRADE C, category 2B).

Sentinel lymph node biopsy for periocular sebaceous carcinoma is supported by early evidence from approximately 100 patient cases published by centres with expertise in the procedure for sebaceous carcinoma.[87–89] The effect of positive sentinel lymph node biopsy on disease-specific survival and overall survival is not known. In another study from an institution with extensive experience with sentinel lymph node biopsy, no biopsies were positive, but two (20%) of ten patients with negative biopsies for periocular sebaceous carcinoma developed nodal disease.[51] However, a follow-up study suggested that at least five (15%) of 30 tumours at stage T2c or higher had positive sentinel lymph node biopsies.[15] A negative biopsy does not obviate the need for close clinical follow-up and metastasis surveillance.

Of 502 patients with positive lymph nodes (by sentinel lymph node biopsy or fine-needle aspiration), 44 had lymph node dissection. In patients in whom additional positive nodes were identified on lymph node dissection, adjuvant radiotherapy was done in selected cases (see section on adjuvant radiotherapy). Lymph node dissection has been done for regional metastasis, with overall poor outcomes.[80,90] The effect of lymph node dissection on survival is unknown.

## Radiotherapy

Recommendation 26: radiotherapy as monotherapy can be considered in patients with periocular sebaceous carcinoma when there is extensive orbital involvement, although this treatment is probably inferior to exenteration. Adjuvant radiotherapy can be considered in tumours manifesting perineural invasion. Radiotherapy or completion lymph node dissection can be considered for microscopic regional metastasis (GRADE C, category 2B).

*Radiotherapy as monotherapy*

The data we reviewed showed that of 1747 patients with periocular sebaceous carcinoma, 85 had radiotherapy as the primary treatment method at doses of 30·0–70·4 Gy given in 22–37 fractions. One meta-analysis showed that doses greater than 55 Gy were associated with improved local control.[91] The largest study of radiotherapy as monotherapy included 78 patients (74 treated with electron beam, four treated with x-ray), with a 5-year disease-free survival of 54% overall and 74% in patients with T1 or T2 tumours. 31 (40%) of 78 patients had recurrence of their tumours after radiotherapy.[92]

*Adjuvant radiotherapy*

Adjuvant radiotherapy was used in 28 patients with tumours with positive postsurgical margins or with poorly differentiated tumours, most often within 4–6 weeks of surgery, using external beam doses of 45–65 Gy. For tumours extending into the lacrimal system or involving the orbit, plaque brachytherapy (50 Gy) has been used instead of exenteration.[86,93] Adjuvant radiotherapy has been used with unclear benefit to manage perineural invasion and to treat the

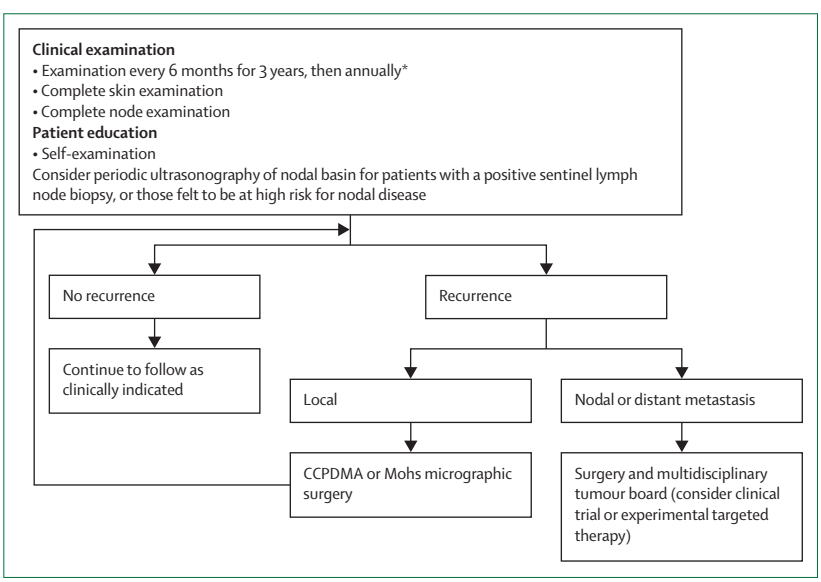


***Figure 4:*** **Follow-up algorithm for extraocular sebaceous carcinoma**
CCPDMA=complete circumferential peripheral and deep margin assessment. *The follow-up schedule can be modified on the basis of individual patient factors concerning their disease course and perceived risk of recurrence.

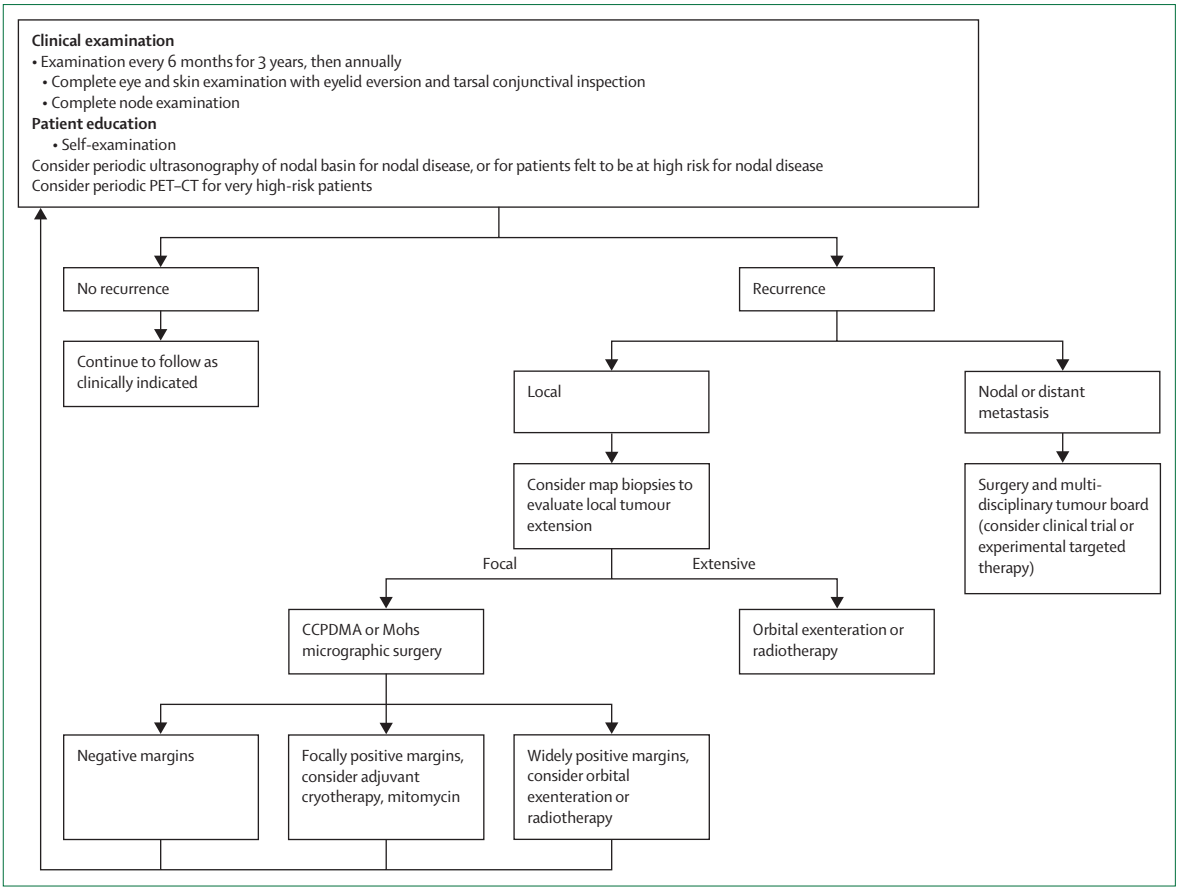


***Figure 5:*** **Follow-up algorithm for periocular sebaceous carcinoma**
The follow-up schedule can be modified on the basis of individual patient factors concerning their disease course and perceived risk of recurrence. CCPDMA=complete circumferential peripheral and deep margin assessment.

nodal basin after lymph node dissection has identified additional positive lymph nodes.[46] The appropriate nerve calibre for radiotherapy has not been studied.

## Recurrent disease

Periocular sebaceous carcinoma has a high recurrence. Of 1020 patients with reported follow-up data, 120 (11·8%) had local recurrence, 68 (6·7%) had recurrence with regional lymph node involvement, and 56 (5·5%) had recurrence with distant metastases. The risk factors associated with tumour recurrence are poorly understood. Most recurrences in the data we reviewed were in patients with cancers of a T category higher than T2.[15] Lymph node recurrences involved either preauricular, cervical, or parotid lymph nodes, most often levels I, II, and III.[3,80] Few data are available about the management of locally recurrent disease.

### *Surgical management*

Recommendation 27: patients with recurrent disease can be treated with margin-controlled surgery. Mapping biopsies can be done to assess the extent of recurrence. Patients with focally positive margins after surgery can receive adjuvant cryotherapy or topical mitomycin (GRADE D, category 2A).

Local recurrences of periocular sebaceous carcinoma have typically been managed surgically.[3,30,80,90] Most reported patients with recurrent disease were treated with margin-controlled surgery. Conjunctival mapping biopsies have been used to assess local tumour spread and to plan surgery.[80] Bulbar conjunctival or other orbital involvement has been managed with adjuvant superficial or destructive methods to avoid orbital exenteration.[80,90,94] Radiotherapy has been used when neither surgery nor destruction were desirable or feasible, such as when the patient had medical comorbidities or locally advanced tumour.[30,94]

### *Radiotherapy*

Recommendation 28: when surgery is not indicated, radiotherapy can be considered for locally recurrent disease. For recurrence with extensive involvement, including broad involvement of the bulbar conjunctiva, some data suggest exenteration or radiotherapy can be considered.[30,94] Completion lymph node dissection or radiotherapy can be considered for lymph node

involvement, but have uncertain benefit (GRADE D, category 2A).

Few data support radiotherapy for locally recurrent disease, which is best managed surgically in the opinion of some experts. Radiotherapy for regionally metastatic disease has been used as monotherapy,[80,94] or in combination with lymph node dissection,[30] without a clear benefit relative to its morbidity.

## Management of metastasis

### Systemic therapy

Recommendation 29: conventional chemotherapy, immunotherapy, or targeted therapies, including antiandrogen, retinoid receptor ligands, and EGFR inhibitors, can be considered for management of metastatic disease. When available, tumour profiling using next-generation sequencing or other methods can guide selection of appropriate therapies. Multidisciplinary consultation and management are strongly recommended (GRADE C, category 2B).

74 (1·8%) of 4176 extraocular sebaceous carcinomas and 128 (12·5%) of 1020 periocular sebaceous carcinomas were reported as having metastasised during the disease course.[10,28–30,43–45,61,68,70,95–98] Of those, 56 (75%) extraocular and 64 (50%) periocular sebaceous carcinomas metastasised to regional or distant nodes, with the remainder developing pulmonary, hepatic, osseous, or cerebral metastases. Disease-specific mortality at 3–5 years was 18% for extraocular sebaceous carcinoma, and 25·6% for periocular sebaceous carcinoma, although reporting bias probably led to overestimation.[3,79,90,94] No histological or clinical risk factors were reproducibly associated with metastasis.

Systemic therapy for metastatic sebaceous carcinoma is not well described. Treatments for metastatic disease have included chemotherapy with anthracycline-based or platinum-based regimens.[53,67] Whether or not platinum-based chemotherapy affects progression-free survival is unclear. Possible investigational approaches based on tumour sequencing include the use of agents targeting RAR-β, androgen receptor, mTOR, or EGFR,[1,99] and have been reviewed elsewhere.[100] PD-1 inhibitors, such as nivolumab, which is approved by the US Food and Drug Administration for microsatellite-unstable malignancies of any tissue origin, might be effective in microsatellite instability-related sebaceous carcinoma. Immunotherapy has been used in metastatic periocular sebaceous carcinoma with early success.[101]

## Follow-up

Recommendation 30: in the first 3 years following treatment, clinical surveillance is recommended every 6 months. Thereafter, annual visits or visits at a frequency tailored to the individual patient can be considered (GRADE D, category 2A).

Recommendation 31: close clinical observation of the primary site and draining nodal basin is appropriate for most patients. Periodic ultrasonography imaging of nodal basin or cross-sectional imaging (CT or PET–CT) can be considered as clinically indicated, based on disease stage (GRADE D, category 2A).

Recommendation 32: periodic lymph node basin ultrasonography can be considered for periocular sebaceous carcinoma (GRADE C, category 2A); the benefit for extraocular sebaceous carcinoma is less certain (GRADE D, Category 2A).

Clinical algorithms are provided for extraocular sebaceous carcinoma (figure 4) and periocular sebaceous carcinoma (figure 5). For both tumour sites, little guidance is available on follow-up practices that improve patient outcomes. For extraocular sebaceous carcinoma, mean follow-up across 23 studies including 9447 patients was 40·1 months (SD 27·4). Mean time to recurrence was 19·4 months (20·4). Most of the recurrences occurred within 6 years of surgery.[70] Most disease-specific deaths occurred 3–5 years after diagnosis.

For periocular sebaceous carcinoma, mean follow-up time for 1889 patients from 44 studies was 44·1 months (SD 23·8). Mean time to recurrence was 20 months (13·6) and most carcinomas recurred within 2 years of surgery. Overall disease-attributable mortality was 6·85% (across 30 studies).[16,31,74]

Evidence was insufficient regarding the frequency or type of imaging studies in patients with systemic or advanced disease. The expert panel, however, felt that the benefits of periodic ultrasonography of the lymph node basin outweighed the risks, especially for high-risk periocular sebaceous carcinoma.

### Search strategy and selection criteria

We searched MEDLINE, Web of Science, Embase, and Cochrane CENTRAL database for articles published between Jan 1, 1990, and June 30, 2019, for "sebaceous carcinoma", "Meibomian gland carcinoma", "tarsal gland carcinoma", and "Zeis gland carcinoma". We chose the year 1990 as the earliest date because historical approaches from before this time might differ from modern practice. We narrowed our search results by title, abstract, and full-text review, and we evaluated the reference lists of review articles for additional eligible studies. We extracted studies related to sebaceous carcinoma diagnosis, investigations, treatment, or follow-up. Articles that described fewer than three patients, management related to Muir-Torre syndrome, or those that contained no original data were excluded. 61 articles met the search criteria for extraocular sebaceous carcinoma, and 95 articles met the search criteria for periocular sebaceous carcinoma (figure 1). During data extraction, when possible, case-level outcomes were preserved. All included studies were systematically assessed for bias using the ROBINS-I tool (appendix pp 2–11). In accordance with ROBINS-I methods, non-randomised studies were classified as those with at least a moderate risk of bias.

## Conclusions

The main aim in the management of sebaceous carcinoma, whether extraocular or periocular, is complete surgical removal with clear histological margins. Immunohistochemical stains might be required to exclude histological mimics in uncertain cases before treatment. Margin-controlled surgery techniques, such as Mohs micrographic surgery or CCPDMA, that conserve normal tissue are preferred when available. Adjuvant radiotherapy and lymphadenectomy are not routinely recommended for most patients because of insufficient evidence. Planning treatment of advanced disease, regardless of location, is suggested to occur in conjunction with multidisciplinary consultation. Continued prospective data are needed to confirm high-risk tumour features and to further clarify the management of this potentially aggressive cancer.

#### Contributors

JLO, NK, and BW contributed equally to this manuscript and are the lead authors. JLO, NK, BW, and RCK were on the data team. MA was the Guidelines Chair. JLO, NK, BW, and MA had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MA, JLO, NK, BW, and EP were responsible for the concept and study design. All authors collected, analysed, and interpreted the data. MA, JLO, NK, BW, and RCK drafted the manuscript. All authors critically revised the manuscript for important intellectual content. TR did the statistical analysis. JLO, NK, BW, and EP provided administrative, technical, or material support. MA supervised the study. All authors had access to the information and certify its accuracy.

#### Declaration of interests

NCZ has received personal fees from Genetech, Sanofi/Regeneron, Biofrontera, and Sun Pharma; and grants from Sun Pharmagrants and Biofrontera, outside the submitted work. DB has received personal fees from Abbvie and Pelle Pharm, outside the submitted work. MA has received personal fees from Pulse Biosciences, outside the submitted work. CAB has received grants from Elekta, University of California San Francisco, Australia and New Zealand Melanoma Trials Group, Merck, and Amgen; personal fees from National Comprehensive Cancer Network, American College of Radiation Oncology, University of Rochester, University of Florida, Elsevier, University of Colorado, Charlotte Area Health Education Center, American Academy of Dermatology, University of Florida Health Center Orlando, Driver Group, Weill Cornell Medical Center, Patient Resource, and Pfizer; and non-financial support from National Comprehensive Cancer Network, American College of Radiation Oncology, University of Rochester, University of Florida, University of Colorado, Charlotte Area Health Education Center, American Academy of Dermatology, University of Florida Health Center Orlando, Driver Group, Pfizer, American Head and Neck Society, and Alpha Tau Medical, outside the submitted work. TMK has received grants from Tempus, outside the submitted work. MLC has received personal fees from Allergan, MD Outlook, Medline Industries, and Sanofi Genzyme/Regeneron, outside the submitted work. HD reports personal fees from Castle Biosciences and Immunocore, outside the submitted work. EHL has received personal fees from UpToDate, outside the submitted work. TMS has received grants from Regeneron, outside the submitted work. SYL is a health affairs coordinator for Cardinal Health, outside the submitted work. The remaining authors declare no competing interests.

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