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Revised Mohs surgery care guidelines for squamous cell carcinoma *in-situ* are overdue

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Abstract

The treatment of cutaneous squamous cell carcinoma in situ by Mohs micrographic surgery is currently deemed as appropriate by the Mohs Appropriate Use Criteria. However, squamous cell carcinoma in situ is a very superficial, indolent, low-risk tumor amenable to destructive and non-surgical treatments. It is uncommon for squamous cell carcinoma in situ to have progressed to invasive malignancy subsequent to definitive management. The suggestion that squamous cell carcinoma in situ on certain anatomic locations has a poorer prognosis is widely assumed but lacks an evidence base. We recommend that most primary squamous cell carcinoma in situ in non-immunosuppressed patients be scored inappropriate or uncertain for Mohs micrographic surgery by the Mohs Appropriate Use Criteria. Multiple other efficacious treatment options exist for managing squamous cell carcinoma in situ, including curettage and cryotherapy, curettage and electrodessication, and topical therapies.

Keywords: Mohs micrographic surgery; squamous cell carcinoma in situ; Mohs surgery appropriate use criteria

Introduction

Mohs micrographic surgery (MMS) is often unnecessary and frequently inappropriate for primary cutaneous squamous cell carcinoma in-situ (SCCis) tumors. However, its use is deemed appropriate in most circumstances by the Mohs Surgery Appropriate Use Criteria (MAUC), [1]. We discuss the rationale for a change in the MAUC for SCCis.

Discussion

Cutaneous SCCis is a common, intra-epidermal, low-risk, indolent malignancy [2, 3]. Many involve the superficial hair follicle [4]. However, risk of progression to invasive SCC is only 3-5%, and SCCis has a negligible risk of metastasis [5, 6]. This low risk of progression to SCC and metastasis exists despite the reported presence of invasive SCC in 9.8% of biopsies diagnosed as SCCis [7]. Chang et al. step-sectioned 726 MMS excisional specimens of cases diagnosed as SCCis and found only 3.3% contained invasive SCC [8]. There was no significant difference in the presence of invasive SCC based on anatomic site, including the head and neck [8]. Eimpunth et al. found that 16.3% of 566 biopsy-proven SCCis treated with MMS contained evidence of invasive SCC on frozen section slides [9]. Ear, nose, lips and eyelid location, preoperative

Abbreviations

C&C – curettage and cryotherapy
C&E – curettage and electrodessication
MAUC – Mohs Surgery Appropriate Use Criteria
MMS – Mohs micrographic surgery
NCCN – National Comprehensive Cancer Network
PDT – Photodynamic therapy
SCC – squamous cell carcinoma
SCCis – squamous cell carcinoma in situ
TG – treatment guidelines

diameter >1.0cm, and biopsy pathology reports mentioning transection of the base were significant indicators of upstaged SCCis. Lee et al. found no evidence of invasive SCC in 173 cases of auricular SCC treated with MMS [10]. Thus, studies of the incidence of invasive SCC within excisional specimens of tumors diagnosed as SCCis is not consistent and assumptions of increased invasiveness may lead to over-treatment and increased cost of treatment. Moreover, the high cure rates reported with alternative treatments, when the same degree of SCC foci would be expected, suggests this is not a factor in treatment results.

There is a paucity of evidence on the appropriateness of MMS for SCCis. There is only one retrospective study comparing MMS to alternative treatments. Inherent selection bias complicates retrospective studies as only cases of SCCis referred for MMS were included [11]. Thus, MAUC recommendations for SCCis are based on insufficient studies to be considered properly evidence-based. As a result, the reviewers creating the MAUC were forced to determine final consensus scores partially based on personal clinical experience. The authors later acknowledged that, "many cases of … Bowen disease may be treated by other modalities [12]."

The MAUC was created primarily to define clinical presentations that did not merit MMS and scores of "uncertain" (4-6) or "appropriate" (7-9) are deemed to justify insurance reimbursement [1, 12]. These criteria, by design, do not compare the appropriateness of MMS to other treatments [1, 13]. It is unfortunate that no studies performed outside the United States were considered, despite valuable published studies performed in Europe and Australia [1, 14, 15]. The National Comprehensive Care Network (NCCN) treatment guidelines (TGs) for SCC were used as a resource and their principles embodied in the MAUC [12, 16]. Although the NCCN TGs report that the risk of metastasis for SCCis is negligible and alternative therapies are suggested, the MAUC score all SCCis in MAUC Areas H and M as appropriate for MMS. Additionally, several other national TGs also do not recommend MMS for many SCCis [17–20]. For instance, the British Association of Dermatologists' guidelines recommended MMS only for of digital and certain genital cases of SCCis [2]. Thus, reliance on MAUC for determining appropriate treatment of SCCis can be reasonably expected to lead to overuse of MMS. The MAUC's authors acknowledged that the MAUC "is intended as a living revisable document that will need to be reviewed and modified as new data become available" [1]. The time for review and revision is overdue.

Efficacy of MMS

Given the paucity of studies comparing the effectiveness of MMS for SCCis to other treatments, we undertook a literature search of the terms "squamous cell in situ" and "Mohs" using the PubMed database [3, 5]. Studies were limited to those with greater than 30 subjects. Leibovitch et al. retrospectively evaluated 270 SCCis treated with MMS [14]. The average number of MMS stages to clearance was 2.0 and 5-year recurrence rates were 2.5%. Malhotra et al. noted a 5% recurrence rate in periocular SCCis treated with MMS with an average of 77.4 months follow-up and average stages to clearance of 2.1 [21]. The average number of stages to clearance for all non-melanoma skin cancers has been reported to be 1.2 to 1.9 [22, 23]. Hansen et al. evaluated 406 SCCis in a retrospective comparative study and found an overall 5-year recurrence rate of 4.0%, though it is important to note over 50% of these cases were themselves recurrent tumors [11]. Recurrence rates were 5.5% for elliptical excision, 6.3% for MMS, 6.5% for curettage and electrodesiccation (C&E), 9% for shave excision, 9% for topical 5-fluoruracil, and 13.4% for cryotherapy. Based on this data, MMS may not be the most appropriate treatment choice for SCCis as compared to other treatments such as standard excision and C&E.

High-Risk Anatomic Areas

Squamous cell carcinoma location on the lip, ear, and temple are considered high-risk factors for recurrence and metastasis [24, 25]. Although some studies report a higher recurrence rate for SCCis on the head and neck, none found this to be statistically significant [26]. There has been no reported statistically significant correlation between anatomic location of SCCis and increased rates of metastases or recurrence [26]. Yet, both the MAUC and NCCN TG state that SCCis in these locations are high risk tumors [1, 27]. As the evidence

for SCCis risk based on location is inconclusive, MMS is likely overused as treatment of SCCis in these reportedly high-risk areas for SCC.

Immunosuppression

Patients with certain hematologic malignancies, organ transplants, HIV, pharmacologic immunosuppression, and certain genodermatoses are at higher risk of developing SCC [28–31]. Moioli et al. recently noted a non-significant, but higher percentage of residual SCCis or SCC in serially sectioned excision specimens of biopsy- proven SCCis from immunosuppressed patients [32]. The rate of complete tumor clearance after biopsy was significantly lower in immunosuppressed patients than in immunocompetent patients. Metchnikoff et al. reported a 5-year recurrence rate of 4% for SCCis in organ transplant patients treated primarily with non-excisional treatments [29]. In a single retrospective study, recurrence of SCCis after surgical excision was 9% in immunocompromised patients, compared to 3% in immunocompetent patients [33]. In a retrospective review of 18 SCCis studies, Matsumoto et al. suggest that immunosuppression represents "a statistically significant association for SCCis recurrence" [26]. Thus, SCCis arising in immunosuppressed patients in MAUC areas H and M should continue to be scored "appropriate" for treatment with MMS [1]. Whether MMS is the optimal treatment modality is not clear, owing to a lack of comparative studies in this patient population, and a surgical margin of 5mm or alternative therapies may suffice.

Lesion Size

For some skin cancers the MAUC considers lesion size to be a determining factor for scoring tumors to be "acceptable" for MMS [1]. Although some studies do report higher recurrence rates in larger SCCis tumors (greater than 2cm or 3cm), others suggest no correlation between tumor size and recurrence [5]. Therefore, data on tumor size as an independent risk factor is conflicting and inconclusive; treatment recommendations cannot be made based on evidence.

Alternative Treatments

The documented presence of SCC in reexamined biopsy and MMS tissue and potential growth down adnexa are common arguments against using non-MMS treatments for SCCis in Areas H and M. Alternative treatment results do not support this position and no studies have correlated these findings with recurrence [26]. Overmark et al. retrospectively evaluated 263 SCCis treated with excision, curettage followed by cryotherapy (C&C), or photodynamic therapy (PDT) with a mean follow-up of 66 months [34]. Recurrence rates for surgical excisions with 0–5mm margins were 0.8% (1/125 cases). No recurrences were noted in 42% (53/125 cases) for excisions using ≤2 mm margins. Recurrence rates were 4.7% for C&C and 18% for photodynamic therapy. Nordin and Stenquist report no recurrences in 100 SCCis cases at 5 years with treatment using C&C [35]. In a randomized trial, Morton et al. treated 225 cases of SCCis, showing an 80% complete response rate with PDT, 67% with cryotherapy, and 69% and with topical fluorouracil [36]. In this study, recurrence rates at 12 months was lowest at 15% for PDT, 17% for topical fluorouracil, and 21% for cryotherapy. For C&E, most reports found recurrence rates of 1.9 to 9.6%, with one outlier study reporting 18.8% [3, 37, 38]. MacFarlane and Tal treated 31 SCCis with cryosurgery followed by imiquimod (average follow-up 43.5 months) and found no recurrences [39]. Given current data, treatment of SCCis with PDT has lower comparative cure rates and monotherapy with topical 5-FU may best be reserved for infirmed or aged populations who might not tolerate alternative treatments.

The 2017 NCCN TGs state that low-risk SCCis may be treated with non-excisional modalities, though cure rates may be lower [27]. As discussed, with the exception of immunosuppression, the distinction between high-risk and low-risk SCCis is not evidence-based and current evidence does not suggest significantly different cure rates. With some reported 5-year recurrence rates lower for elliptical excision than for MMS and with MMS and C&E cure rates being essentially equal, MMS should not be considered a primary treatment modality for most SCCis [40]. This conclusion is further supported by

other national TGs, which do not recommend MMS as primary treatment for many SCCis [6, 17–20, 41].

We suggest the appropriate first line treatment for many SCCis lesions is either curettage and cryotherapy (C&C) or curettage and electrodessication (C&E). In certain circumstances SCCis can be managed with topical chemotherapeutic agents such as 5-fluorouracil. Photodynamic therapy has lower cure rates and concerning recurrence risks. Clinically concerning lesions, or recurrent lesions may be sampled again to diagnose invasive SCC. MMS is appropriate for the management of SCCis in immunocompromised patients.

Conclusion

The MAUC state, ''an appropriate treatment modality is one in which the anticipated clinical benefit combined with clinical judgment exceeds the possible negative consequences for a specific indication" [1]. The MAUC authors acknowledged that "a most important point is the rating of 'appropriate' for a particular defined scenario signifies MMS is generally considered acceptable and does not imply that MMS is preferred or absolutely indicated for management" [13]. MAUC uses scores of "uncertain" for scenarios in which there is insufficient data for definitive categorization or there is varying agreement regarding MMS appropriateness. Current data evaluating MMS for SCCis, except in immunosuppressed patients, merits a score of at best "uncertain."

The treatment of most primary SCCis with MMS is not indicated nor appropriate based on current evidence. Without evidence-based studies demonstrating that SCCis is more aggressive in certain anatomic sites or in patients with certain comorbidities, the current MAUC have likely supported overtreatment of these indolent lesions of epithelial origin [42]. New evidence-based treatment guidelines should focus on global evidence-based studies rather than on anecdotal experience. We eagerly await new guidelines and further comparative studies to illuminate the most appropriate and efficacious treatment modalities for SCCis.

Potential conflicts of interest

The authors declare no conflicts of interests.

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