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Tumor recurrence of keratinocyte carcinomas judged appropriate for Mohs surgery using Appropriate Use Criteria

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Abstract

Background—Use of Mohs micrographic surgery (MMS) has increased greatly to treat basal cell and cutaneous squamous cell carcinomas (keratinocyte carcinoma, KC), and consensus-based Appropriate Use Criteria (AUC) were developed to identify tumors for which MMS is appropriate.

Objective—In tumors judged appropriate for MMS, to compare recurrence rates after different treatments.

Methods—We used data from an observational prospective cohort study, and retrospectively categorized consecutive tumors as appropriate for MMS according to the AUC. Among appropriate tumors, we used survival analyses to compare 5-year recurrence rates after treatments.

Results—Among tumors appropriate for MMS (N=1483), adjusted 5-year recurrence rates were 2.9% [1.4–4.3] after MMS, 5.5% [3.1–7.9] after excision, 4.0% [0.6–7.2] after destruction, and 5.9% [1.5–10.2] after other treatments. In tumors treated only with MMS or excision (the most similar subgroups), the adjusted hazard of 5-year recurrence after MMS was 0.6 [0.3,1.0] (P=0.06).

Limitations—Uncertain generalizability, lack of randomization, unmeasured characteristics.

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IRB Approval – This study was approved by the local Institutional Review Boards.

Attachments – Supplemental figure, IRB approval letter, Research protocol, Survey instrument, STROBE checklist, Statistical analysis plan

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Conclusions—The AUC identified tumors for which recurrence would be less common after MMS than after excision, but the absolute difference in recurrence rates is small.

Keywords

basal cell carcinoma; cutaneous squamous cell carcinoma; keratinocyte carcinoma; Mohs micrographic surgery; Appropriate Use Criteria; outcomes research

INTRODUCTION

Skin cancer treatments in the US increased around 50% from 1996 to 2008,¹ but the use of Mohs micrographic surgery (MMS) increased 400% from 1995 to 2009.^{2,3} Few rigorous studies have compared recurrence outcomes after different treatments for basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC), (keratinocyte carcinoma [KC]). In a randomized clinical trial of high-risk BCCs on the face, ten-year tumor recurrence rates were somewhat lower after MMS than after excision (4.4% vs 12.2%, respectively, $P=0.100$) but for most primary KCs, no empiric study has demonstrated for which tumors MMS is superior.⁴⁻⁷

To guide clinicians, Appropriate Use Criteria (AUC) for MMS were developed by the American Academy of Dermatology and dermatological surgery societies.³ Using a modified Delphi exercise,⁸ a 17-member panel reviewed 270 clinical scenarios that contained different patient and skin cancer characteristics, and rated them as appropriate, inappropriate, or uncertain for MMS.³ The AUC define MMS *as one appropriate treatment for such tumors, but the document acknowledges that other acceptable approaches may also exist.*

We sought to learn if the AUC would identify KCs for which MMS is superior to other treatments in preventing tumor recurrence. We applied the AUC to a large consecutive cohort of patients with KC, to determine, among tumors judged appropriate for MMS, if tumor recurrence differed after different treatments. We hypothesized that in this more targeted subgroup, recurrence rates after MMS would be significantly lower than after other treatments.

METHODS

Design, Setting, Patients, Baseline Data

This study was nested within a prospective cohort study of all patients with KC in 1999 or 2000 treated at a university-based dermatology clinic (UNIV) or the affiliated Veterans Affairs (VA) dermatology clinic. The parent study compared outcomes after different therapies of all tumors diagnosed over the two-year period; the current study was limited only to tumors judged appropriate for MMS using the AUC. This study was approved by local Institutional Review Boards. We obtained patient informed consent when required.

The parent study has been previously described in detail.⁴ In brief, eligible patients for this study were histopathologically diagnosed with BCC or SCC at a primary skin site. Date of

diagnosis was the date of biopsy of the initial KC. Treatment with MMS and excision occurred during specialized clinics.

Collection of Outcome Data

The primary source of data on recurrence was the medical record, reviewed by dermatologic nurse practitioners at a median of 9.0 years after initial treatment. Typically, they were not aware of treatment when reviewing pathology records, although they may have learned the treatment as they reviewed the record. Consenting patients were re-examined by a dermatologist blinded to treatment type at a median of 8.6 years after initial treatment. If either the record review or examination indicated a tumor recurrence, the record was reviewed again by a dermatologic clinician blinded to the original review (to validate the outcome). Follow-up ended at the last date when the patient received care. A patient was lost to follow-up if there was no record of care after treatment.

Measures

Primary Outcome—A tumor was defined as recurrent if either of these criteria was met: 1) if the tumor type (BCC or SCC) and body location were identical to those of the primary tumor, and the lesion was described by the clinician as recurrent or previously treated or 2) if the tumor type was identical to the primary tumor and the tumor location was very close to or the same as the original body site, using clinical notes, maps, and diagrams in the record.⁴ The date of recurrence was the date of the biopsy of the recurrent lesion.

Patient and Tumor Characteristics—The primary source for patient and tumor characteristics was the medical record; data on comorbidity was obtained by patient survey. We collected data on age, sex, prior KCs, number of tumors at presentation, care site, genetic syndromes (Basal Cell Nevus syndrome), immunosuppression (human immunodeficiency virus [HIV] infection, organ transplantation, hematologic malignancy, pharmacologic immunosuppression), and prior radiation exposure. Comorbidity was measured by an adapted Charlson instrument.^{9,10} We also counted each patient's visits to dermatology throughout follow-up. Tumor characteristics included size (diameter), body location (Area H, M, or L, according to the AUC criteria),³ histopathological categories (aggressive BCC, superficial/nodular BCC, invasive SCC, SCC in situ) and noted histopathological features considered high risk for recurrence using National Comprehensive Cancer Network (NCCN) criteria.¹¹ These features included, for example, notation of morpheaform, sclerosing, mixed infiltrative, or micronodular features for BCC and moderate or poor differentiation, adenoid, adenosquamous, or desmoplastic features for SCC.

AUC Categorization—Patient and tumor characteristics were used to categorize each tumor as appropriate, inappropriate, or uncertain for MMS, based on the AUC.³ This review was blinded to treatment type. Judgment was required for classification of seven patients, because they could have been classified into two AUC categories. In these situations we classified patients into the category in which recurrence was more likely. For example, patients who were both immunocompromised and had prior radiation were classified as “prior radiation.” Similarly, judgment was required for classification of some tumors, because records did not contain information required for categorization, or tumors fell into

two categories. For example, tumor size was missing for 206/1483 tumors (13.9%), but assumption of the largest or smallest criterion for size did not change the AUC categorization for any tumor; for tumors with missing size, we used multiply imputed tumor sizes as described in Analytic Strategy below. Breslow depth was not noted on the pathology reports for any tumor; Clark level was noted in the charts for only 3% of SCCs.

Analytic Strategy

Statistical analyses were performed using SAS version 9.4. Our overall strategy was, within the group of tumors judged appropriate for MMS, to describe differences in patients and tumors treated with MMS or other treatments, to compare patient, tumor, and treatment characteristics in tumors that recurred or did not recur after treatment, and to compare 5-year recurrence rates after different treatments in unadjusted and adjusted models.

We compared treatment with or without MMS using chi-square tests for categorical characteristics, and non parametric Wilcoxon tests for continuous characteristics.

We performed adjusted Cox models to calculate 5-year recurrence rates after adjustment for characteristics likely related to recurrence. Cumulative incidence plots (with data right-censored at the last date of care) were used to display cumulative incidence of tumor recurrence. Potential predictors of recurrence included in the models were age, sex, care site, annual number of dermatology visits, history of prior KC, history of HIV, number of tumors at presentation, tumor histopathological category (aggressive BCC, superficial/nodular BCC, invasive SCC, SCC in situ), tumor body location, and tumor size. Pathological records noted NCCN histopathological risk factors for recurrence much more commonly at UNIV than the VA; this variable was co-linear with care site and was not included in the models. We also performed similar models with fewer predictors; because the results were similar we present the more comprehensive models.¹² A Cox proportional hazard model was developed in the tumors treated with excision or MMS, because the indications for these treatment methods are similar,¹¹ and because patients and tumors treated with other modalities were different.⁴ The Huber-White method was used to adjust for intra-patient correlation in the Cox models (for those with more than one tumor).

To include all observations in the Cox models we used multiple imputation for tumor size.¹³ Specifically, tumor size was predicted using a linear regression on age, sex, location in the H Zone of the face,¹⁴ prior history of KC, histopathological type, histopathological category, and number of tumors at presentation. We used 100 imputed data sets to ensure estimates had acceptably small levels of Monte Carlo error.

RESULTS

Patient, Tumor, and Care Characteristics

Of the 1992 tumors in the cohort, 1483 tumors (74%) were classified as appropriate, 121 (6%) as uncertain and 388 (19%) as inappropriate for MMS (eFigure). Of the entire cohort, 34% were treated with MMS. Of tumors classified as appropriate, 45% were treated with MMS.

Compared with other patients, patients whose tumors were treated with MMS were much more likely to be female and to be treated at UNIV ($P<.0001$). Compared with other tumors, tumors treated with MMS were smaller and more likely to be located in the H area³ ($P<.0001$). They were also more likely to be aggressive BCCs than nodular or superficial BCCs. Most SCCs were treated by other treatments, although MMS was more likely to be used for invasive SCCs than for SCC in situ ($P<.0001$). Overall, MMS was more likely for tumors for which NCCN histopathological risk factors for recurrence were noted ($P=0.0006$) (Table I).

Tumor Recurrence

Follow-up was available for over 90% of tumors at a median of 7.4 years (3.0–8.8) after treatment.⁴ Duration of follow-up did not differ ($P=0.2$) among treatment groups. Throughout the observation period, 57 tumors recurred after treatment. Table II reports patient, tumor, and care characteristics of tumors that recurred. Tumors were more likely to recur ($P<0.03$) in patients with prior KC, or with more than one tumor at presentation, or with a history of HIV, or who visited dermatology more often than other patients. Tumors that recurred were somewhat smaller ($P=0.05$) but otherwise were similar to tumors that did not recur.

The Figure depicts the adjusted cumulative incidence of recurrence, and Table III reports unadjusted and adjusted 5-year recurrence rates in treatment groups. Variables in adjusted models were age, sex, history of HIV, prior KC, number of tumors at presentation, care site, annual number of dermatology visits, tumor location in the H-Zone of the face,¹⁴ tumor size (missing values multiply imputed as described above), and histopathological category. The presence of NCCN histopathological risk factors for recurrence was not retained in the models because it was collinear with UNIV site. Adjusted 5-year recurrence rates were 2.9% [1.4–4.3] after MMS, 5.5% [3.1–7.9] after excision ($P=0.040$), 4.0% [0.6–7.2] after destruction, and 5.9% [1.5–10.2] after other treatments.

Hazard of tumor recurrence at 5 years after MMS compared to excision

Table IV reports the final multivariable model of 5-year tumor recurrence in the subsample of tumors treated with MMS or excision. Tumors were more likely to recur in patients who were infected with HIV [Hazard Ratio [HR] 4.6 (1.2, 17.5)] and who had more than one tumor at presentation [HR 2.2 (1.1, 4.2)]. Larger tumors were somewhat less likely to recur ($P=0.06$), and the hazard of tumor recurrence after MMS compared to excision was 0.6 [0.3, 1.0], $P=0.06$.

DISCUSSION

In this application of the Appropriate Use Criteria to a prospective cohort of 1536 consecutive patients with 1992 keratinocyte carcinomas, 74% of tumors were classified as appropriate for Mohs micrographic surgery. Of tumors judged appropriate for MMS, overall the 5-year recurrence rate after treatment was 3.1% ($N=57$); in tumors treated with either MMS or excision, the hazard of tumor recurrence after MMS was somewhat less than after excision (0.6 [0.3, 1.0]), $P=0.06$.

Comparison with Past Studies

Previous applications of the AUC to university dermatology practices had similar percentages of appropriate, inappropriate, and uncertain categorizations and of the tumors deemed appropriate, similar percentages of referral for MMS.^{15,16} To our knowledge no previous study has compared tumor recurrence outcomes after different treatments in the subgroup of tumors judged appropriate for MMS.¹⁷ Rigorous cohort and randomized studies comparing recurrence of primary KC after different treatments have consistently demonstrated lower, although typically not statistically significantly lower, recurrence rates after MMS.⁴⁻⁷ For example, unadjusted, adjusted, and propensity-adjusted analyses of the complete cohort from which the current data were derived demonstrated HRs for 5-year recurrence after MMS compared to excision of around 0.6, but with confidence limits that always crossed 1.⁴ In prospective studies, reduction in recurrence rates after MMS compared to excision has been of borderline statistical significance in certain clinical subgroups of tumors. In a randomized controlled trial in high-risk primary BCCs of the face, 10-year recurrence rates were 4.4% after MMS and 12.2% after excision ($P=0.1$).⁷ Similarly, in the complete cohort from which the current data were derived, for tumors in the H-zone of the face, recurrence was less likely after MMS than after excision (1.2% vs. 6.3%, respectively, $P=0.05$) at the university site.⁴

The AUC sought to “provide guidance for the rational use of MMS in the practice setting” but not to dictate a standard of care.³ Also the AUC did not include other treatment modalities.³ The current results demonstrate that in a sample of KCs judged appropriate for MMS using the AUC, tumor recurrence over median follow-up of 7.4 years was somewhat lower in tumors treated with MMS than in those treated with excision.

Our findings inform this guidance provided by the AUC on the use of MMS in the practice setting. We noted a 2% point difference in unadjusted 5-year recurrence rates between MMS and excision; i.e., 50 KCs would need to be treated with MMS rather than excision to prevent a single tumor recurrence at 5 years. The clinical significance of this 2% point difference depends on individual patient characteristics and patient preferences.

Potential Limitations

This study was not randomized to treatment, and treating dermatologists may have used MMS for higher risk tumors whose characteristics were unmeasured, and could have affected the risk of recurrence. Although propensity adjustments did not alter conclusions in the parent study,⁴ this selection bias may have decreased any observed benefit of MMS. By judging any tumor that was not classifiable as one for which recurrence was more likely, the study sample may contain more tumors that would not recur regardless of how they were treated. This situation was likely very uncommon, however, since the overall number of tumors judged appropriate for MMS (74%) is almost identical to that reported elsewhere.¹⁵ The study was conducted at two sites within one dermatology department in a single city, which could affect generalizability. Also, we did not detect increased risk of recurrence in tumors with some features conventionally believed to increase risk (e.g., tumors in the H-zone of the face¹⁴), which may be due to insufficient power, since recurrence rates overall

were low. Finally, the AUC were guided not only by the goal of reducing recurrence rates, but also for tissue conservation, which was not considered in this study.

CONCLUSIONS

We tested and confirmed the ability of the Appropriate Use Criteria for Mohs surgery to identify KCs for which recurrence rates will be lower than after excision. The absolute difference in recurrence rates between treatments is small, however. New studies should determine more specifically the subgroups of patients and tumors for which tumor recurrence rates after MMS are substantially improved. Echoing the explicit statement of the Task Force that composed the AUC, we hope that our work will guide future reassessments and refinements of the criteria.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AUC	Appropriate Use Criteria
BCC	basal cell carcinoma
HIV	human immunodeficiency virus
HR	Hazards Ratio
KC	keratinocyte carcinoma
MMS	Mohs micrographic surgery
NCCN	National Comprehensive Cancer Network
SCC	squamous cell carcinoma
UNIV	university-based dermatology clinic
VA	Veterans Affairs dermatology clinic

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Figure. Cumulative incidence plots of the probability of tumor recurrence over time after different treatments

Cumulative incidence of recurrence were adjusted for age, sex, history of HIV, prior history of KC, number of tumors at presentation, care site, number of dermatology visits per year, tumor location in the H-Zone,¹⁴ tumor size (with missing values multiply imputed as described in the text), and histopathological category (aggressive BCC, superficial/nodular BCC, invasive SCC, SCC in situ).

*Adjusted for age, sex, care site, number of dermatologic visits per yer, prior history of NMSC, histopathological type, history of HIV, number of tumors at presentation, location in H Zone, tumor size with imputed missing.

Table I

Patient and tumor characteristics for tumors judged appropriate for MMS, according to whether the tumor was treated with MMS or not.

	Treated with MMS	Not treated with MMS	P Value
Characteristics of Patients (n=1207)	(N=555)	(N=652)	
Age, mean	66.4 ± 14.9	68.4 ± 14.3	0.03
Sex, male	371 (66.8%)	511 (78.4%)	<.0001
Comorbidity (Charlson Index) *			
< 3	253 (75.1%)	256 (69.0%)	0.07
3	84 (24.9%)	115 (31.0%)	
History of HIV	12 (2.2%)	25 (3.8%)	0.09
Prior history of KC at Presentation	300 (54.1%)	379 (58.1%)	0.2
Proportion with >1 Tumor at Presentation	113 (20.4%)	125 (19.2%)	0.6
Care site			
VA	162 (29.2%)	341 (52.3%)	<.0001
UNIV	393 (70.8%)	311 (47.7%)	
Mean number of visits to dermatology/year **	2.2 ± 3.2	2.1 ± 2.4	0.5
Characteristics of Tumors (n=1483)	(N=672)	(N=811)	
Size (mean Diameter in cm) ***	2.1 ± 1.0	2.4 ± 1.1	<.0001
Tumor Location ****			
L	14 (2.1%)	155 (19.1%)	<.0001
M	158 (23.5%)	275 (33.9%)	
H	500 (74.4%)	381 (47.0%)	
Histopathological Category			
BCC Aggressive	284 (42.3%)	211 (26.0%)	<.0001
BCC Superficial/Nodular	251 (37.4%)	349 (43.0%)	
SCC Invasive	92 (13.7%)	120 (14.8%)	
SCC In Situ	45 (6.7%)	131 (16.2%)	
NCCN histopathological risk factor noted in pathology report			
Yes	199 (29.6%)	177 (21.8%)	0.0006
No	473 (70.4%)	634 (78.2%)	

* Data were missing for 499 patients

** Eighty-one patients had no subsequent visits to dermatology.

*** Data on size were missing for 206 tumors (13.9%).

**** As defined by the AUC criteria³

Table II

Patient and tumor characteristics for tumors judged appropriate for MMS, according to whether the tumor recurred over the entire observation period.

Characteristics of Patients (n=1207)			
	No Recurrence N=1164 patients	Tumor Recurred N=43 patients	P Value
Age, mean	67.5 ± 14.7	67.1 ± 12.4	0.5
Sex			
Male (73.1%)	848 (72.9%)	34 (79.1%)	0.4
Female (27.7%)	316 (27.1%)	9 (20.9%)	
Comorbidity (Charlson Index) *			
< 3	489 (71.8%)	20 (74.1%)	0.8
3	192 (28.2%)	7 (25.9%)	
History of HIV			
Yes	33 (2.8%)	4 (9.3%)	0.02
No	1131 (97.2%)	39 (90.7%)	
Prior history of KC at Presentation			
Yes	647 (55.6%)	32 (74.4%)	0.01
No	517 (44.4%)	11 (25.6%)	
>1 Tumor at presentation			
Yes	224 (19.2%)	14 (32.6%)	0.03
No	940 (80.8%)	29 (67.4%)	
Care site			
VA	484 (41.6%)	19 (44.2%)	0.7
UNIV	680 (58.4%)	24 (55.8%)	
Median dermatology visits/year (Interquartile range) **	1.5 (0.4–2.8)	2.2 (1.2–3.2)	0.005
Characteristics of Tumors (n=1483)			
	No Recurrence N=1426 tumors	Tumor Recurred N=57 tumors	P Value
Size (mean, SD, N) in cm ***	2.2 ± 1.0	1.9 ± 0.9	0.05
Tumor location ****			
L	162 (11.4%)	7 (12.3%)	0.9
M	418 (29.3%)	15 (26.3%)	
H	846 (59.3%)	35 (61.4%)	
NCCN histopathological risk factor noted in pathology report			
Yes	365 (25.6%)	11 (19.3%)	0.3
No	1061 (74.4%)	46 (80.7%)	

Characteristics of Patients (n=1207)			
	No Recurrence N=1164 patients	Tumor Recurred N=43 patients	P Value
Histopathological category			
BCC Aggressive	479 (33.6%)	16 (28.1%)	0.2
BCC Superficial/Nodular	577 (40.5%)	23 (40.4%)	
SCC Invasive	206 (14.4%)	6 (10.5%)	
SCC In Situ	164 (11.5%)	12 (21.1%)	

* Data were missing for 499 patients.

** Eighty-one patients had no subsequent visits to dermatology.

*** Data were missing for 206 tumors.

**** As defined by the AUC criteria³

Table III

Five-year tumor recurrence rates for KCs judged appropriate for MMS, according to treatment received.

Treatment Received	N = 1483	Unadjusted 5yr Rate (95% CI)	* Adjusted 5yr Rate (95% CI)
MMS	672	2.8 (1.5 – 4.0)	2.9 (1.4 – 4.3)
Excision	523	4.8 (2.8 – 6.7)	5.5 (3.1 – 7.9)
ED&C	139	4.4 (0.8 – 8.0)	4.0 (0.6 – 7.2)
Other Treatment **	149	7.1 (2.0 – 11.9)	5.9 (1.5 – 10.2)

* Adjusted for age, sex, history of HIV, prior history of KC, number of tumors at presentation, care site, number of dermatology visits per year, tumor location in the H-Zone of the face, tumor size (with missing values multiply imputed as described in the text), and histopathological category (aggressive BCC, superficial/nodular BCC, invasive SCC, SCC in situ).

** Other treatments were cryotherapy, laser, and none.

Table IV

Hazard ratios of recurrence after treatment with MMS compared to excision, in tumors judged appropriate for MMS by AUC.

	Adjusted* Hazard Ratio and [95% CI]	P Value
Characteristics of Patients		
Age	1.0 [1.0, 1.0]	0.54
Sex, male	1.0 [0.4, 2.2]	0.94
HIV, yes	4.7 [1.1, 19.5]	0.03
Prior history of KC at Presentation, yes	1.6 [0.8, 3.2]	0.15
>1 Tumor at Presentation	2.2 [1.1, 4.3]	0.02
Care Site, UNIV comparison VA	0.9 [0.5, 2.0]	0.92
> 2 Dermatology Visits/Year	1.1 [0.9, 1.2]	0.31
Characteristics of Tumors		
Tumor Size, > 2 cm	0.7 [0.5, 1.0]	0.06
Body Location, vs L**		
M	0.6 [0.2, 2.5]	0.49
H	0.9 [0.2, 3.1]	0.81
Histopathological Category, vs BCC Aggressive		
BCC Superficial / Nodular	1.5 [0.7, 3.0]	0.32
SCC Invasive	1.0 [0.3, 3.1]	0.96
SCC In Situ	2.1 [0.8, 5.5]	0.13
Treatment Type		
Mohs comparison Excision	0.6 [0.3, 1.0]	0.07

* Adjusted for age, sex, history of HIV, prior history of KC, number of tumors at presentation, care site, number of dermatology visits per year, tumor location, tumor size (with missing values multiply imputed as described in the text), and histopathological category (aggressive BCC, superficial/nodular BCC, invasive SCC, SCC in situ).

** As defined by the AUC criteria³