Defining skin cancer local recurrence

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Definitions of skin cancer recurrence are variable and nonstandardized, which can lead to inconsistent and potentially inappropriate management of tumors of uncertain recurrence status. Defining recurrence is important given the potential association with metastasis in both melanoma and nonmelanoma skin cancer. A review of the literature across multiple disciplines involved in the care of skin cancer patients reveals that although criteria for recurrence are provided in the majority of cases, most are vague and inconsistent. Given the presumably increased morbidity and mortality associated with recurrent tumors, accurate identification and appropriate management is paramount. In addition, value-based health care necessitates validated and relevant outcome measures that are standardized and, thus, enable tracking of comparable and corresponding outcomes. A universal definition of localized skin cancer recurrence would ultimately allow for improved surveillance and informed therapeutic strategies to decrease morbidity and mortality of patients afflicted with skin cancer, the most common cancer nationwide. (J Am Acad Dermatol 2019;81:581-99.)

Key words: melanoma; Mohs; nonmelanoma skin cancer; recurrence; skin cancer.

Overall, skin cancer is the most common cancer in the United States. Nonmelanoma skin cancers, predominantly comprising basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are the most common cancers in the United States, with >5 million estimated cases per year, and rates continue to rise.[1,2] Melanoma is the fifth most common cancer in the United States, according to the Surveillance, Epidemiology, and End Results database, but is the skin cancer with the highest attributed mortality. Although the case-fatality rate is only ~1%, national nonmelanoma skin cancer mortality figures equal or exceed those for melanoma, which is far more lethal but less common.[3] There are also several high-risk features that have been reported to elevate morbidity and mortality risk in skin cancer, including its characterization as a recurrent tumor.[4,5]

In a longitudinal analysis of 210 patients with SCC, locally recurrent lesions were significantly larger than nonrecurrent (de novo) lesions and were more often characterized by high-risk features.[3] Rates of perineural, lymphovascular, and deep invasion beyond subcutaneous tissues are significantly more common in recurrent than nonrecurrent lesions.[3] These features confer a tumor with high-risk status, which eventuates in increased potential for destructive local disease, local spread to lymph nodes, and metastatic spread to organs, such as the lung, brain, and bone. In melanoma, recurrent tumors are significantly more likely to be upstaged and lead to higher morbidity and mortality.

Thus, given the poorer outcomes correlated with recurrent tumors, it is imperative to detect and treat them swiftly and appropriately. Classifying and researching recurrent tumors becomes difficult without a standardized method for the identification of what is and what is not considered a recurrent tumor. A background search of the current scientific and medical literature revealed that although the majority of manuscripts report criteria for recurrence, it is often inconsistent, vague, and thus nonreproducible. These inconsistencies place patients at risk of inappropriate management for an exceedingly

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common and morbid disease. To address this issue, we sought to review the literature in hopes of identifying inconsistencies and to make recommendations for standardization of the criteria to define local recurrence across medical disciplines.

METHODS

A comprehensive review was performed to evaluate definitions of skin cancer recurrence. A PubMed search was conducted for articles published during 1982-2017 by using the key words "skin cancer" ("melanoma," "squamous cell carcinoma," and "basal cell carcinoma") AND "radiology," "radiation," "radiation oncology," "ophthalmology," "immunology," "pathology," "oncology," "ear nose and throat," "head and neck surgery," "dermatology," "plastic surgery," "oculoplastic," "oral, maxillofacial, and reconstructive surgery," "Mohs surgery" AND "recurrence." A total of 103 manuscripts were reviewed for inclusion in the study. In total, 27 manuscripts were excluded for lack of information on recurrence. A total of 76 manuscripts were identified that reported recurrence rates for cutaneous carcinoma. The primary data extracted from these manuscripts was the definition or criteria used to identify mentioned recurrences. Lack of such definitions was also noted.

CAPSULE SUMMARY

- Definitions of skin cancer recurrence are variable and nonstandardized throughout the scientific and medical literature, which can lead to inconsistent and potentially inappropriate management of aggressive tumors.
- We comprehensively review the literature to elucidate inconsistencies and propose a standardized algorithm for determination of tumor recurrence status across disciplines.

RESULTS

A total of 76 manuscripts were included for review and spanned the fields of medical and surgical oncology, radiology, plastic and reconstructive surgery, general dermatology, dermatologic surgery, craniofacial and oral maxillofacial surgery, ophthalmology, oculoplastics, head and neck surgery, and otolaryngology (ear, nose, and throat). Of these 76 manuscripts, 72 (95%) included some definition of recurrence (Table I).[6-77] In only a minority of studies (5%, 4/76) were specific and reproducible criteria reported for identifying recurrences.

The studies that included specific and reproducible recurrence criteria included a 2017 retrospective cohort study and a 2015 experimental study by Armstrong et al, a 2017 study by Stuart et al, and a prospective cohort study by Brantsch et al.[6,20,30,53] The manuscripts by Armstrong et al in the plastic surgery literature indicated that BCC recurrences were identified with guidelines created in consultation with a senior pathologist that included key lesion and tissue sample characteristics.[6,30] These characteristics included lesion location, microscopic findings (dermal scarring and hypertrophic changes), lesion subtype, and clinical history attached with the pathology samples.[6,30] In another review from the dermatology literature, Stuart et al provide a set of criteria for defining recurrences.[20] The authors defined a tumor as recurrent if the tumor type (BCC or SCC) and body location were identical to those of the primary tumor as noted in clinical notes, maps, and diagrams in the record, and the lesion was described by the clinician as recurrent or previously treated.[20] In the prospective cohort by Brantsch et al, a recurrence was defined by comparable histology and by the tumor appearing within the area of the scar from prior SCC extirpation.[53]

The remaining reports on recurrence had definitions that were notably vague. In most studies, recurrence was reported exclusively on the basis of the subjective surveillance of the patient or physician (51%, 39/76). A 2017 retrospective study from the surgical literature reports "patients were followed up on regular basis to ensure early identification of recurrence."[16] A 2017 manuscript from the ophthalmology literature reports that "no recurrence was observed during a 22-month follow-up."[10] In a 2016 manuscript from the otolaryngology literature, it is reported that follow-up ranged 1.3-39.2 months and that 5 patients developed a recurrence.[25] However, none of these manuscripts provided additional details on the criteria used to diagnose recurrences, which is problematic given the well-known variability in physician assessments.[78] The poor interrater reliability between physicians has been attributed at least in part to concepts such as differential salience (ie, the differential value placed on different aspects of the assessment) and criterion uncertainty (ie, the variable or unclear criteria utilized in assessing a clinical scenario).[78]

Some studies involved supplemental diagnostic tests in the evaluation of potential recurrences. These tests included biopsy with histopathology, radiographic imaging, and impression cytology. In the studies utilizing histopathologic evaluation of biopsy specimens taken from the vicinity of the prior skin

Abbreviations used:

BCC: basal cell carcinoma
SCC: squamous cell carcinoma

cancer, the specifics regarding where the biopsy was performed relative to the prior lesion was mentioned in only a minority.* When proximity to prior resection scar or tumor margins is cited, approximate and inconsistent language is often utilized.[29,50,53] For example, when describing a potential BCC recurrence, authors of a case study in the surgical literature reported a "lump along the inferior portion of the prior resection scar" and "at the inferior border of the scar" at different points in the manuscript.[29] From this language, it is unclear if the lump abuts the scar, or if it is in close proximity to the scar. Furthermore, in several studies, recurrence was defined via visualization of malignant features on various forms of radiographic imaging, including computed tomography, magnetic resonance imaging, or positron emission topography scans.[18,19,23,27,28,36,80] In other studies, surveillance laboratory tests were used to track and define recurrences.[28,36] In another, surveillance impression cytology was used in the case of ocular SCC, with impression cytology serving as a means to remove the superficial layers of the ocular surface epithelium.[32] In another study, recurrence was defined via the results of sentinel lymph node biopsy.[43] However, in these cases, it is important to differentiate local recurrence, or recurrence of the skin tumor at the primary site in the skin, from in-transit metastasis, regional metastasis, and distant metastasis of the original tumor.

Even still, other studies provided even fewer comprehensive definitions of skin cancer recurrence. In a 2017 review from the dermatology literature, dermatoscopic surveillance of the primary BCC location was used to identify recurrences.[9] The disappearance of dermatoscopic criteria for BCC (arborizing vessels, ulceration, maple leaf–like areas, and spoke-wheel areas) after local therapy was reported to predict histopathologic resolution, and the presence of some dermatoscopic clues (ie, multiple blue-grey globules) suggested persistent tumor or recurrence.[9]

Another case report from the ophthalmology and plastic surgery literature identifies recurrence via clinical proximity to a prior lesion. Histopathologic examination of the slide from the prior surgical excision demonstrated sebaceous carcinoma with involved margins.[50] The involved margins of the primary tumor in addition to the clinical proximity of the second tumor to the primary site appears to imply an incompletely treated or persistent lesion rather than a true recurrence.[50]

Of the manuscripts that do not include an objective criterion or definition for recurrence, the majority reference recurrences with no definition provided, and others leave the definition to be implied from provided information. Use of the term recurrence without mention of how it is defined predominantly occurred in case series and review manuscripts. In a 2017 case series from the ophthalmology literature, features of periocular BCC predictive of recurrence were assessed.[11] In this study, the recurrence rate was identified as one of the study's primary outcomes without any mention as to what classifies a tumor as recurrent.[11] In a 2014 review article, the authors state total skin electron irradiation should be used "as a primary therapy to recurrent/refractory or extensive lesions," although no definition is provided for recurrent or refractory tumors.[81] In another manuscript from the immunology-oncology literature, different medication regimens were provided to patients on the basis of the presence of disease recurrence, although disease recurrence was never defined.[82]

Other studies leave the recurrence definition to be implied. A recent 2017 manuscript from the radiology literature reports on locally recurrent versus second primary tumor in head and neck cancer.[83] The report states that "tumors were classified as SP [second primary] when they originated >2 cm away from the original tumor site or when patients had been in complete remission for at least 24 months," leaving it to be implied that locoregional recurrence was defined as tumors that arise within 2 cm of the original tumor and within 24 months of complete remission.[83]

DISCUSSION

Skin cancer recurrence is characterized by presumed elevated morbidity and mortality. Precise research and appropriate management of these recurrences is contingent upon appropriate classification that any given tumor is, or is not, an actual recurrence. Thus, the American College of Mohs Surgery Registry and Outcomes Committee has proposed and previously published a standardized definition of recurrence developed via a modified-Delphi process.[84] Local recurrence of skin cancer has been defined by the American College of Mohs Surgery Registry and Outcomes Committee as a tumor that has comparable histology, contiguity with the

*[15,17,19,22,24,33-35,37,58,77,79]

Table I. Manuscripts providing an objective definition of skin cancer recurrence

Authors	Year	Title	Journal	Patient population	Definition provided
Armstrong et al[6]	2017	Risk factors for recurrence of facial basal cell carcinoma after surgical excision: A follow-up analysis	J Plast Reconstr Aesthet Surg	Plastic surgery	Histologic evaluation: To accurately identify recurrent lesions, a guideline using key lesion and tissue sample characteristics was created in consultation with a senior pathologist. These characteristics included lesion location, microscopic findings (dermal scarring and hypertrophic changes), lesion subtype and clinical history attached with pathology samples (these features were located in patient records). All potentially recurrent lesions were identified and assessed by the principle researchers by using these criteria.
Bu W et al[7]	2017	Preliminary results of comparative study for subsequent photodynamic therapy versus secondary excision after primary excision for treating basal cell carcinoma	Photodiagnosis Photodyn Ther	Dermatology	Clinical surveillance and patient report: Evaluation was performed by patient and clinicians. "Follow-up for at least 8 months was conducted by combining outpatient visits with telephone inquiries. We recorded the rate of clinical relapses…"
Cooper LK et al[8]	2017	Basal cell carcinoma arising in a congenital melanocytic naevus in an adult	BMJ Case Rep	Dermatology	Clinical surveillance: "At 6-month follow-up, there was no evidence of local recurrence…"
Diluvio L et al[9]	2017	Dermoscopic monitoring of efficacy of ingenol mebutate in the treatment of pigmented and non-pigmented basal cell carcinomas	Dermatol Ther	Dermatology	Clinical surveillance: "The disappearance of dermoscopic criteria for BCC (arborizing vessels, ulceration, maple leaf—like areas, and spoke-wheel areas) after local therapy was proven to predict histopathologic resolution, while the persistence or new appearance of some clues (multiple blue-grey globules) suggest persistence or recurrence."
Yazici BG et al[10]	2017	Thermal Burn Scar-Related Squamous Cell Carcinoma in the Eyelid	Ophthal Plast Reconstr Surg	Ophthalmology	Clinical surveillance: "No recurrence was observed during a 22-month follow-up."
Furdova A et al[11]	2017	Periocular Basal Cell Carcinoma Predictors for Recurrence and Infiltration of the Orbit	J Craniofac Surg	Ophthalmology	Clinical surveillance: "During the 7-year observership, the authors have seen 13 recurrences."

Fife D et al[12]	2017	Vismodegib Therapy for Basal Cell Carcinoma in an 8-Year-Old Chinese Boy with Xeroderma Pigmentosum	Pediatr Dermatol	Dermatology	Clinical surveillance: "Because a repeat biopsy was declined after therapy, subclinical BCC recurrence cannot be excluded."
Shi Y et al[13]	2017	Ocular basal cell carcinoma: a brief literature review of clinical diagnosis and treatment	Onco Targets Ther	Ophthalmology	Clinical surveillance: "A 5-year follow-up was performed." "With a mean follow-up time of 38 months, only 1 patient relapsed." "No evidence of clinical recurrence."
Bhatnagar A et al[14]	2016	High-dose Rate Electronic Brachytherapy: A Nonsurgical Treatment Alternative for Nonmelanoma Skin Cancer	J Clin Aesthet Dermatol	Oncology, dermatology	Clinical surveillance: "Median follow-up times at the various centers ranged 4-16 months, and results yielded an extremely low recurrence rate of <1%." "Locally recurrent (previously treated)"
Karabulut GO et al[15]	2017	Imiquimod 5% cream for the treatment of large nodular basal cell carcinoma at the medial canthal area	Indian J Ophthalmol	Ophthalmology, plastic surgery	Clinical surveillance and histologic evaluation: With biopsy of suspicious sites and histopathologic assessment, "patients were followed up for at least 3 years without tumor recurrence, and the biopsies taken from the suspected area were found to be tumor free."
Jerjes WZ et al[16]	2017	Photodynamic therapy in the management of basal cell carcinoma: Retrospective evaluation of outcome	Photodiagnosis Photodyn Ther	Head and neck surgery	Clinical surveillance: "Patients were followed up on regular basis to ensure early identification of recurrence, need for further intervention, and assessment of outcome."
Kristensen RN et al[17]	2017	Lip carcinoma: clinical presentation, surgical treatment, and outcome: a series of 108 cases from Denmark	J Plast Surg Hand Surg	Plastic surgery	Clinical surveillance or histologic evaluation: Recurrence was defined as tumor growth at the location of the primary surgery after a disease-free period or as histologically verified lymph node metastases.
Martin JW et al[18]	2017	Multipoint Thermal Sensors Associated with Improved Oncologic Outcomes Following Cryoablation	J Endourol	Urology, radiology	Radiologic evaluation: Contrast-enhanced CT or MRI was used to evaluate for the presence or absence of recurrence at the most recent follow-up (at least 3 months after cryoablation). Tumor recurrence was defined by the presence of enhancement at the ablation zone on follow-up contrast-enhanced CT or MRI. All recurrences were confirmed by the radiology report and independently by authors.

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Table I. Cont'd

Authors	Year	Title	Journal	Patient population	Definition provided
Papastefanou VP et al[19]	2017	Secondary Resistance to Vismodegib After Initial Successful Treatment of Extensive Recurrent Periocular Basal Cell Carcinoma with Orbital Invasion	Ophthal Plast Reconstr Surg	Oncology	Clinical surveillance with histologic evaluation: Left upper eyelid BCC was excised several years earlier, with recent biopsies of left eyebrow and temple confirming infiltrative BCC. CT and MRI scans were used to confirm extensive orbital disease.
Stuart SE et al[20]	2017	Tumor recurrence of keratinocyte carcinomas judged appropriate for Mohs micrographic surgery using Appropriate Use Criteria	J Am Acad Dermatol	Dermatology	Medical record review with subjective definition: The primary source of data on recurrence was the medical record, which was reviewed by dermatologic nurse practitioners at a median of 9.0 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. 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, as indicated by clinical notes, maps, and diagrams in the record.
Williams HC et al[21]	2017	Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: 5-Year Results of the SINS Randomized Controlled Trial	J Invest Dermatol	Dermatology	Medical record review: The recurrence data were retrieved from at least 1 and (more often than not) all of the following 3 sources: (1) hospital histopathology records from each center and follow-up of the general practitioner (2) and hospital records (3).

Kobayashi T et al[22]	2016	Aggressive Digital Papillary Adenocarcinoma With Multiple Organ Metastases: A Case Report and Review of the Literature	Am J Dermatopathol	Dermatology	Clinical surveillance with histologic evaluation: Scout biopsy of suspicious lesions was performed. On histologic examination, both the primary and locally recurrent tumors were found to be composed of discrete and well-circumscribed solid nodules, lacking cystic space. All tumors presented with a pattern of fused back-to-back tubular structures and myoepithelial differentiation confirmed by immunohistochemical examination.
Lee SY et al[23]	2016	The Relationship between the Size and the Invasion Depth of Tumors in Head and Neck Cutaneous Squamous Cell Carcinoma	Arch Plast Surg	Plastic and reconstructive surgery	Clinical surveillance and radiographic imaging: ''Follow-up was conducted on an outpatient basis… Macroscopic examination and computed tomography were performed to examine recurrence and sequelae.''
Luz FB et al[24]	2016	Analysis of effectiveness of a surgical treatment algorithm for basal cell carcinoma	An Bras Dermatol	Dermatology	Clinical surveillance and scout biopsy of suspicious lesions: ''Patients were followed-up and reviewed for clinical, dermatoscopic, and histopathologic detection of possible recurrences.''
Day KE et al[25]	2016	Parotid gland metastasis in Merkel cell carcinoma of the head and neck: A series of 14 cases	Ear Nose Throat J	Otolaryngology	Clinical surveillance: ''Follow-up ranged 1.3-39.2 months… 5 patients developed a recurrence.''
Guyon A et al[26]	2016	Retrospective Outcome Analysis of 39 Patients Who Underwent Lip Surgery for Cutaneous Carcinoma	J Maxillofac Oral Surg	Plastic surgery, dermatology	Surveillance by the patient: ''The oncologic, functional, and aesthetic outcome were collected by phone call for each patient at least 1 year after surgery….The oncologic outcomes were defined as a local or nodal recurrence after primary surgical treatment (yes vs no, time since surgery)… Among all patients, only 2 experienced a local recurrence over the 38-month follow-up period.''
Mena E et al[27]	2016	18F-FDG PET/CT and Melanoma: Value of Fourth and Subsequent Posttherapy Follow-up Scans for Patient Management	Clin Nucl Med	Radiology	Clinical surveillance and radiologic imaging: ''18F-FDG PET-CT scans in the follow-up of patients with melanoma were performed after the completion of the primary treatment with or without clinical signs suggestive of disease'' recurrence.

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Table I. Cont'd

Authors	Year	Title	Journal	Patient population	Definition provided
Podlipnik S et al[28]	2016	Performance of diagnostic tests in an intensive follow-up protocol for patients with American Joint Committee on Cancer (AJCC) stage IIB, IIC, and III localized primary melanoma: A prospective cohort study	J Am Acad Dermatol	Radiology, dermatology	Combination: Routine surveillance or regular self-examination, clinical examination, laboratory test, and imaging studies. Lymph node sonography was used to confirm suspicious findings detected on palpation. If any of the test results were equivocal, additional strategies including histologic examination were performed to confirm the diagnosis.
Sleightholm RL et al[29]	2016	Bilateral Lymphatic Spread of Metastatic Basal Cell Carcinoma	Plast Reconstr Surg Glob Open	Surgery	Clinical surveillance with biopsy and histopathology of suspicious lesions: "The decision was made to observe the area (upper back) for any signs of recurrent disease. One year later, the patient complained of a new, persistent lump in his right axilla… On exam, he had a hard, mobile, 2.5 × 2.0−cm lump in his right posterior axilla and a 1.5 × 1.5−cm lump along inferior portion of prior resection scar… biopsies from both the axilla and scar were consistent with recurrent/metastatic disease."
Armstrong LT et al[30]	2015	The Role of Embryologic Fusion Planes in the Invasiveness and Recurrence of Basal Cell Carcinoma: A Classic Mix-Up of Causation and Correlation	Plast Reconstr Surg Glob Open	Plastic surgery	Pathologic: Pathology criteria were established to recognize recurrent lesions. Lesion location and lesion description, macroscopic and microscopic examination (hypertrophic changes and dermal scarring), and lesion subtype were criteria used to establish lesion recurrence. Lesions with the potential to be recurrent were analyzed in conjunction with a senior pathologist.
Mizoguchi N et al[31]	2015	Carbon-ion radiotherapy for locally advanced primary or postoperative recurrent epithelial carcinoma of the lacrimal gland	Radiother Oncol	Radiology	Clinical surveillance: "Of the 21 subjects enrolled, all patients were followed for >6 months and analyzed…Local recurrence was observed in 5 patients…"

Arora T et al[32]	2015	Bilateral recurrent ocular surface squamous cell cancer associated with epidermodysplasia verruciformis	BMJ Case Rep	Ophthalmology	Clinical surveillance with periodic impression cytology: The patient did not show any signs of recurrence at 4 years of follow-up. Repeat impression cytology failed to show any evidence of squamous dysplasia.
Eftekhari K et al[33]	2015	Local Recurrence and Ocular Adnexal Complications Following Electronic Surface Brachytherapy for Basal Cell Carcinoma of the Lower Eyelid	JAMA Dermatol	Oculoplastic surgery	Clinical surveillance and biopsy of suspicious lesions: Suspicious lesion within the area in which he had received radiation therapy (for prior BCC) was noted. A biopsy specimen of the new lesion on the left lower eyelid showed recurrent infiltrative BCC.
Erickson BP et al[34]	2015	Recurrent Dermatofibrosarcoma Protuberans Masquerading as a Lacrimal Sac Neoplasm: A Case Report and Review	Ophthal Plast Reconstr Surg	Ophthalmology	Corroboration of histopathology from medical records and current biopsy: Patient had indolent growth of left medial canthus. H&E staining demonstrated spindle cells in a storiform pattern. A subsequent investigation revealed patient had lesion removed from forehead 5 years prior. At the time, the pathologist noted fibroblastic characteristics but did not obtain immunostaining.
Alabiad CR et al[35]	2014	En bloc resection of lacrimal sac tumors and simultaneous orbital reconstruction: surgical and functional outcomes	Ophthal Plast Reconstr Surg	Ophthalmology, oncology	Clinical surveillance and biopsy of suspicious lesions with histopathology
Baker JJ et al[36]	2014	Routine restaging PET/CT and detection of initial recurrence in sentinel lymph node positive stage III melanoma	Am J Surg	Surgical oncology	Medical record: Recurrences were identified from the medical record and categorized into 1 of 4 groups: 1) local recurrence, defined as that occurring within 2 cm of the primary tumor, 2) in transit, 3) regional lymph node basin, and 4) distant soft tissue, distant lymph node basin, or visceral.
Notz G et al[37]	2014	Perineural invasion of cutaneous squamous cell carcinoma along the zygomaticotemporal nerve	Ophthal Plast Reconstr Surg	Otolaryngology, head and neck surgery, neuro-ophthalmology	Clinical surveillance with imaging and biopsy of suspicious lesions with histopathology: Patient with history of SCC on the temple reported persistent headache. CT demonstrated bony abnormality suggestive of erosion. Exploratory surgery and biopsy with frozen-section control confirmed recurrent SCC.

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Table I. Cont'd

Authors	Year	Title	Journal	Patient population	Definition provided
Karatas D and Erten S[38]	2014	Pinkus tumor at the nostril floor	J Craniofac Surg	ENT	Clinical surveillance: "The patient is being monitored for any possible local recurrence."
Qassemyar A et al[39]	2014	Orbital exenteration and periorbital skin cancers	J Oral Maxillofac Surg	Plastic and reconstructive surgery	Clinical surveillance: "Clinical follow-up was performed until July 2012. Recurrences were identified through direct contact with the dermatologists."
Mulay K et al[40]	2014	Periocular sebaceous gland carcinoma: do androgen receptor (NR3C4) and nuclear survivin (BIRC5) have a prognostic significance?	Acta Ophthalmol	Ophthalmic pathology	Clinical surveillance (chart review) and histopathology: "Patients without sufficient tissue samples, necessary clinicopathological information and follow-up <9 months were excluded."
Kilic C et al[41]	2014	Nonmelanoma facial skin carcinomas: methods of treatment	J Craniofac Surg	Otorhinolaryngology	Recurrences were identified by retrospective chart review.
Trani MM et al[42]	2014	Giant-cell tumor of the tendon sheath in the external auditory canal	Ear Nose Throat J	Otolaryngology, ENT	Clinical surveillance: "No recurrence was detected at 2 years of clinical follow-up."
Pfeiffer ML et al[43]	2013	Sentinel lymph node biopsy for eyelid and conjunctival tumors: what have we learned in the past decade?	Ophthal Plast Reconstr Surg	Ophthalmology, head and neck surgery	Sentinel lymph node biopsy
Sahai P et al[44]	2013	Recurrent sebaceous carcinoma of the scalp in a young male treated with adjuvant radiotherapy	J Cancer Res Ther	Radiation oncology	Clinical surveillance: "…the patient developed local recurrence after an interval of 4 months ….was successfully treated with no evidence of any local recurrence seen after a follow-up period of 1 year."
Rishi P et al[45]	2013	Cutaneous vitiligo following management of uveal melanoma in 6 patients	JAMA Ophthalmol	Ophthalmology and ocular oncology	Clinical surveillance: "There was no local tumor recurrence during the 71-month mean follow-up."
Patel SS et al[46]	2013	Incomplete removal of basal cell carcinoma: what is the value of further surgery?	Oral Maxillofac Surg	Oral and facial department	Clinical surveillance: "…3 have been lost to follow-up and 4 show no evidence of recurrence 18(+) months post primary excision."

Somayaji G et al[47]	2013	Recurrent Pindborg tumor of the maxilla: a case report and review of the literature	Ear Nose Throat J	ENT, head and neck surgery	Clinical surveillance with radiographic imaging and biopsy with histopathology of suspicious lesion: "Examination revealed… recurrence of her earlier Pindborg tumor… CT identified… radiopaque mass lesion… Histopathology identified polyhedral epithelial cells arranged in sheets and strands that exhibited nuclear pleomorphism and variable hyperchromasia without mitosis. There were numerous homogenous calcified bodies that were positive on Congo red staining. Based on these findings, a histopathologic diagnosis of CEOT was made." "During 9 years of follow-up, the patient was asymptomatic and recurrence free."
Bertelmann E and Rieck P[48]	2012	Relapses after surgical treatment of ocular adnexal basal cell carcinomas: 5-year follow-up at the same university centre	Acta Ophthalmol	Ophthalmology	Clinical surveillance: "On follow-up… functional and cosmetic outcome and relapses were documented."
Hoguet AS et al[49]	2012	Syringocystadenocarcinoma papilliferum of the eyelid	Ophthal Plast Reconstr Surg	Ophthalmology	Clinical surveillance: "3 months after complete excision of the tumor, the patient remains well with no evidence of local recurrence."
Priyadarshini OB et al[50]	2010	Neoadjuvant chemotherapy in recurrent sebaceous carcinoma of eyelid with orbital invasion and regional lymphadenopathy	Ophthal Plast Reconstr Surg	Ophthalmic plastic surgery	Clinical surveillance with imaging (CT) and fine-needle aspiration of suspicious lesions
Skaria AM[51]	2010	Recurrence of basosquamous carcinoma after Mohs micrographic surgery	Dermatology	Dermatology	Clinical surveillance: "Retrospective study… mean follow-up time was 59.55 months… recurrence rate of epidermal tumors in this study was ~2.5%"
Pugliano-Mauro M and Goldman G[52]	2010	Mohs surgery is effective for high-risk cutaneous squamous cell carcinoma	Dermatol Surg	Dermatology	Clinical surveillance: "Retrospective study… mean follow-up was 3.9 years… there were 3 local recurrences"

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Table I. Cont'd

Authors	Year	Title	Journal	Patient population	Definition provided
Brantsch KD et al[53]	2008	Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study	Lancet Oncol	Dermatology	"If metastasis, local recurrence, or new skin cancers were suspected, patients were invited to department for further investigation. Biopsies were taken if ultrasonography of the regional lymph nodes confirmed suspicion of metastasis, and metastases were diagnosed by histopathology. Tumors newly arising in the area of a scar from a resected SCC included in this study were either resected or had a biopsy taken. Histopathological confirmation of SCC tissue led to diagnosis of local recurrence."
Missotten GS et al[54]	2008	Merkel cell carcinoma of the eyelid review of the literature and report of patients with Merkel cell carcinoma showing spontaneous regression	Ophthalmology	Ophthalmology	Clinical and histopathologic surveillance: "Retrospective case series and literature review… after local excision, none of the MCCs demonstrated local recurrence, without regional or distant metastases."
DeMartelaere SL et al[55]	2008	Neoadjuvant chemotherapy-specific and overall treatment outcomes in patients with cutaneous angiosarcoma of the face with periorbital involvement	Head Neck	Ophthalmology, head and neck surgery	Clinical surveillance: "…the mean follow-up time from diagnosis to the date of last contact was 51.9 months… The 5-year recurrence-free rate for the entire cohort was 31.9%."
Farhi D et al[56]	2007	Incomplete excision of basal cell carcinoma: rate and associated factors among 362 consecutive cases	Dermatol Surg	Dermatology	Medical records: Tumor occurring after "first or multiple treatments"
Villalon-Lopez et al[57]	2006	Supraestructure maxillectomy and orbital exenteration for treatment of basal cell carcinoma of inferior eyelid: case report and review	J Cancer Res Ther	Surgical oncology	Clinical surveillance: "The patient was followed without evidence of tumoral activity for 8 months, but a relapse was detected by the presence of a raised, ulcerated hemorrhagic lesion."
Leibovitch I et al[58]	2005	Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I. Experience over 10 years	J Am Acad Dermatol	Dermatology, surgery, ophthalmology	Clinical surveillance (in addition to histopathologic assessment): Tumor within an area "previously treated with non-Mohs procedures."

Innocenzi D et al[59]	2005	Morpheaform extra-ocular sebaceous carcinoma	J Surg Oncol	Dermatology, plastic surgery	Clinical surveillance: "There was no evidence of recurrence or metastasis after a follow-up period of 3 years."
Murthy R et al[60]	2005	Neoadjuvant chemotherapy in the management of sebaceous gland carcinoma of the eyelid with regional lymph node metastasis	Ophthal Plast Reconstr Surg	Oncology	Clinical surveillance: "Ten months later, vision remained 20/20 OU, and there was no evidence of recurrence."
Wilson AW et al[61]	2004	Surgical management of incompletely excised basal cell carcinomas of the head and neck	Br J Oral Maxillofac Surg	Maxillofacial surgery	Clinical surveillance: "…retrospective audit of all basal cell carcinomas…of the 140 cases managed by observation, 21% recurred."
Malhotra R et al[62]	2004	The Australian Mohs database, part II: periocular basal cell carcinoma outcome at 5-year follow-up	Ophthalmology	Ophthalmology	Clinical surveillance: "5-year follow-up was based on a questionnaire sent to the participating surgeons."
Lydiatt W[63]	2003	Management of lower lip cancer: a retrospective analysis of 118 patients and review of the literature	Arch Facial Plast Surg	Plastic and reconstructive surgery	Medical records: "clinical data and postoperative follow-up findings… are presented."
Batra RS and Kelley LC[64]	2002	A risk scale for predicting extensive subclinical spread of nonmelanoma skin cancer	Dermatol Surg	Dermatology	Clinical surveillance or patient reported: "Recurrence status was based on patient history or repeat treatment required during the 3 years of follow-up."
Kumar P et al[65]	2002	Incomplete excision of basal cell carcinoma: a prospective multicentre audit	Br J Plast Surg	Plastic surgery	Clinical surveillance: "prospective audit… 3 forms were designed for data collection. The first was completed by the operating surgeon at the time of surgery and included data on the age and sex of the patient, the site and size of the lesion, whether it was a recurrent lesion…"
Dieu T and Macleod AM[66]	2002	Incomplete excision of basal cell carcinomas: a retrospective audit	ANZ J Surg	Oral and facial	Medical records: "Data were collected from a computerized auditing system and patients' files… Of the 223 BCC, 151 had no documented history of past treatment at the site… Of the remaining 72 lesions, 62 were recurrent BCC."

Continued

Table I. Cont'd

Authors	Year	Title	Journal	Patient population	Definition provided
Snowden RT et al[67]	2001	Superficial leiomyosarcoma of the head and neck: case report and review of the literature	Ear Nose Throat J	ENT, head and neck surgery	Clinical surveillance with radiographic imaging and biopsy with histopathology of suspicious lesion: "3-week history of a rapidly growing mass… patient had earlier undergone 2 local resections of the tumor at the site… CT revealed the presence of a soft tissue mass… an incisional biopsy was suspicious for a fibrohistocytic neoplasm."
Wenzel CT et al[68]	2001	Second malignant neoplasms of the head and neck in survivors of retinoblastoma	Ear Nose Throat J	Surgery, ENT, head and neck surgery	Clinical surveillance with radiographic imaging, fine-needle aspiration, and biopsy with histopathology of suspicious lesions: "At the age of 31 months, the girl developed a recurrent retinoblastoma… developed a left upper lid chalazion that was followed clinically. When the lesion did not resolve, the girl underwent an excisional biopsy… 6 months later, the patient developed a left preauricular mass…. findings on fine-needle aspiration were consistent with a sebaceous gland carcinoma"
de Visscher JG et al[69]	1998	Surgical treatment of squamous cell carcinoma of the lower lip: evaluation of long-term results and prognostic factors—a retrospective analysis of 184 patients	J Oral Maxillofac Surg	Oral maxillofacial surgery	Medical records: "Retrospective study…. follow-up was 2 years… local recurrence and regional metastasis occurred in 9 and 10 patients, respectively… Recurrent disease was defined as tumor growth at the same site within 5 years after completion of initial therapy."
Holmkvist KA et al[70]	1998	Squamous cell carcinoma of the lip treated with Mohs micrographic surgery: outcome at 5 years	J Am Acad Dermatol	Dermatology	Clinical surveillance and histologic evaluation: Data recorded for "recurrence at the tumor site… In all cases with recurrence, the fresh-frozen, hematoxylin-eosin—stained sections obtained during the first MMS were reviewed… If follow-up data were not available in the patient's chart, the patients, their families, or outside physicians were contacted for further information regarding recurrence…"

Julian CG and Bowers PW[71]	1997	A prospective study of Mohs' micrographic surgery in two English centres	Br J Dermatol	Dermatology	Clinical surveillance: "Presence or absence of recurrence at yearly postoperative consultations"
Park AJ et al[72]	1994	Basal cell carcinomas: do they need to be followed up?	J R Coll Surg Edinb	Plastic surgery	Medical records: "Retrospective study was performed using the case notes… overall recurrence rate was 5.1%."
Silverman MK et al[73]	1992	Recurrence rates of treated basal cell carcinomas. Part 3: Surgical excision	J Dermatol Surg Oncol	Dermatology	Medical records: "In the NYU Oncology Section computerized database, there were 588 biopsy-proved, primary (previously untreated) BCCs… First, we compared the recurrence rates of previously treated (recurrent) BCCs with primary BCCs."
Crowley NJ and Seigler HF[74]	1990	Late recurrence of malignant melanoma. Analysis of 168 patients	Ann Surg	Surgery	Clinical surveillance: "A retrospective computer-aided search identified 168 patients who had a disease-free interval of ≥10 years, with a subsequent recurrence."
Rowe DE et al[75]	1989	Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma	J Dermatol Surg Oncol	Dermatology	Medical records: Previous treatment
Lang PG, Jr, and Maize JC[76]	1986	Histologic evolution of recurrent basal cell carcinoma and treatment implications	J Am Acad Dermatol	Dermatology, pathology	Histologic evaluation: Histologic sections from the original lesion and from each subsequent recurrence, as well as the chemosurgical specimens, were examined.
Dzubow LM et al[77]	1982	Risk factors for local recurrence of primary cutaneous squamous cell carcinomas. Treatment by microscopically controlled excision	Arch Dermatol	Dermatology	Clinical surveillance and histologic evaluation: "All diagnoses of previously untreated or recurrent carcinomas were made by biopsy performed either by the referring physician or a member of our unit. Pathology slides were not always available for our review when the biopsy was performed by a referring physician."

18F-FDG PET-CT, Positron emission tomography with ^{18}F-labeled fluoro-2-deoxyglucose and computed tomography; *BCC*, basal cell carcinoma; *CEOT*, calcifying epithelial odontogenic tumor; *CT*, computed tomography; *ENT*, ear, nose, and throat; *H&E*, hematoxylin and eosin; *MCC*, Merkel cell carcinoma; *MMS*, Mohs micrographic surgery; *MRI*, magnetic resonance imaging; *NYU*, New York University; *OU*, oculus uterque; *SCC*, squamous cell carcinoma.

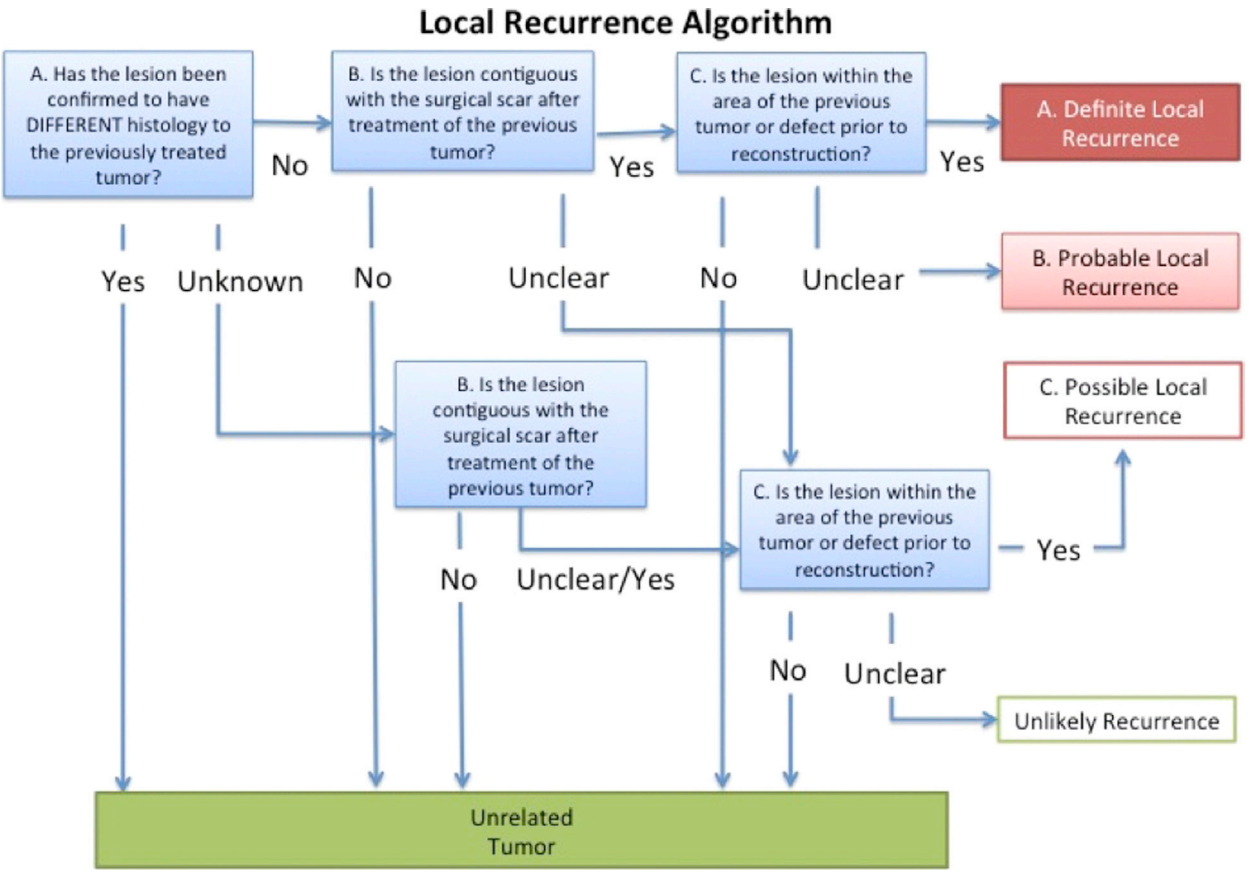

Fig 1. Local recurrence algorithm.

surgical scar after treatment, and arises within the area of the previously treated tumor (Fig 1).[84] Comparable histology means that the postoperative diagnosis of tumor type must match but the histologic pattern might vary. Of note, the original definition has been amended since the initial publication for improved clinical application in cases where the pathology of the initial tumor might be unknown (Fig 1). Contiguity with the surgical scar means that the tumor abuts the 3 dimensional surgical scar at the epidermal, dermal, or subcutaneous tissue. The within-the-area component of the objective recurrence criteria is estimated by using a photo overlay of the original postoperative surgical defect when available. If the original photo overlay is unavailable, the previously treated area is approximated by radially diagramming the greatest radius of the final defect measured from the estimated center of the original wound. In the event that clinical recurrence is suspected, a biopsy should be performed to confirm comparable histology whenever possible. In addition, it is important to differentiate an incompletely treated or persistent tumor from a true recurrence. In order for a tumor to be considered recurrent, it must have undergone definitive treatment with the intent for cure, and in the case of surgical management, there should be clear surgical margins.

This review demonstrates the lack of the use of a standardized definition for recurrence in the skin cancer literature and inconsistencies within manuscripts that provide a published definition. Of the few studies that provided the specific criteria used to define recurrence in their specific study, only 1 manuscript proposes a definition with elements similar in nature to those proposed by the authors who sit on the American College of Mohs Surgery Registry and Outcomes Committee.[53] Brantsch et al describes a tumor as recurrent if it appears in the area of the prior lesion's scar and has comparable histology.[53] No studies, however, report recurrence criteria with the level of specificity and reproducibility as those previously proposed by the authors. This discrepancy in the literature breeds large variability in recurrence criteria and thus limited comparability of recurrences and associated outcomes across and within medical specialties. This is problematic given the high prevalence of skin cancer in the United States.

Dermatologists and skin cancer surgeons tend to rely on physical examination and clinical assessments of previous clinicians to guide further workup for local recurrence, and medical and radiation oncologists tend to use imaging more readily to evaluate for local, regional, and distant disease. However, the use of various imaging modalities, such as positron emission topography–computed tomography, computed tomography alone, and ultrasound are being used with increasing frequency for postoperative surveillance and detection of recurrent disease in high-risk tumors in dermatology.[85,86] Ultimately, once recurrence is suspected, utilization of objective criteria for defining local recurrence in skin cancer, including histologic evaluation, will enable increased transparency and improved comparability within the literature. In addition, it might improve communication and coordination of care between the several different medical specialties that treat cutaneous carcinoma. We believe standardization of the definition of local recurrence in skin cancer has great potential to improve outcomes and quality of care in skin cancer patients. Validation of these criteria and prospective studies are needed to standardize this definition of skin cancer recurrence.

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