Updates in Cutaneous Oncology

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Skin cancer diagnosis is now aided by expanding dermoscopic knowledge, total body photography, and emerging machine-learning technologies.

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Abstract

Cutaneous oncology is currently a rapidly evolving field. Dermoscopy, total body photography, biomarkers, and artificial intelligence are affecting the way skin cancers, especially melanoma, are diagnosed and monitored. The medical management of locally advanced and metastatic skin cancer is also changing. In this article, we will discuss recent developments in cutaneous oncology with a particular focus on treatment of advanced cancers.

Epidemiology

Melanoma incidence had been rising for decades in the United States,[1] although mortality is falling due to earlier detection and improved treatment options for locoregional and metastatic melanoma. In recent years incidence has stabilized and been falling by approximately 1% annually for people under 50-years old.[1] A similar pattern has occurred for cutaneous squamous cell carcinoma, with incidence increasing in the 2000s and mid-2010s in the US but stabilizing in recent years.[2,3] These changes may be related to changes in occupational and recreational sun exposure, tanning bed use, sun-protection behaviors, and skin cancer detection.

Diagnosis and Biomarkers

Dermoscopy has become a widespread and important tool for dermatologic diagnosis. Dermoscopy, also called epiluminescent microscopy or dermatoscopy, uses magnification with or without light polarization to enhance visualization of subcorneal skin structures. In experienced hands, dermoscopy in combination with traditional exam can improve sensitivity for diagnosing melanoma.[4] Photography with sequential tracking of dermoscopic images may be particularly useful for early detection of melanoma, since early melanomas may lack typical dermoscopic features and the most concerning feature is often longitudinal change.[5–7]

Total body photography (TBP) is gaining traction, mostly at academic centers, to longitudinally track patient's skin exams. TBP images nearly the entire skin surface to allow detection of new lesions or changes in existing lesions. Data suggests that it may facilitate earlier detection of melanoma and reduce the number of benign lesions biopsied.[8,9] Some total body photography systems incorporate convolutional neural networks (CNNs) to identify lesions that may warrant close inspection by the clinician. The best CNNs have shown

Table 1. Biomarkers for Monitoring Merkel Cell Carcinoma Patients

Biomarker	Utility	Specimen	Availability	Turnaround Time	Comment
MCC small-T antigen oncoprotein antibody (AMERK)	Primarily used to monitor for recurrence	Blood	Send-out test to the University of Washington	3-4 weeks	Antibody titers correlate with tumor volume. They fall in response to treatment and rise with recurrence. High predictive value. Only positive in 41-48% of MCC patients. Must obtain at baseline. Often done at each follow up visit. Detects recurrence before radiology in some patients.
Tumor-informed circulating cell-free tumor DNA (ctDNA)	Primarily used for monitoring for recurrence	1st test: FFPE and blood All subsequent tests: Blood	Available via Natera and Gaurdant360	1st test: 2-3 weeks. Subsequent tests: 5-7 days.	ctDNA levels correlate with tumor volume. Used similarly to AMERK, but useable in all MCC patients. Newer and less established in MCC management than AMERK.

AMERK – anti-merkel cell antibody, ctDNA – circulating cell-free tumor DNA, FFPE – formalin-fixed paraffin-embedded tissue.

accuracy similar to board-certified dermatologists for differentiating benign from malignant lesions.[10] However, there is variability between CNNs and they have been particularly weak in skin of color,[10] perhaps due to a relative lack of skin of color images in training sets. Oversensitivity is a common problem with the CNNs used with TBP, but criteria to call out a lesion can be adjusted by the user. Use of TBP will initially require time of both staff and the physician. As familiarity with the software grows, it may expedite exams of high-risk patients. Clinic staff will have to be trained on how to use the system, and some basic equipment, such as photography backgrounds and lighting, are often used. Outside of TBP, CNNs are not yet used in routine practice, but they are receiving growing interest for skin cancer diagnosis.

Biomarkers are becoming increasingly utilized in cutaneous oncology as predictors of treatment response and for surveillance (Table 1). The most well established is $BRAF^{V600}$ mutation testing, which determines eligibility for treatment with combination BRAF and MEK inhibitors for locoregional or metastatic melanoma. Merkel cell polyomavirus (MCPyV) small T oncoprotein antibodies have become well established as powerful tools for monitoring for recurrence in Merkel cell carcinoma (MCC) patients, and are now included in the NCCN guidelines and used at the University of Missouri.[11] These antibodies are sensitive markers of recurrence and provide positive predictive values as high as 97% and negative predictive values as high as 99%.[12,13] Their major limitation is that they are only present in 41-48% of MCC patients.[13–16] Tumor-informed circulating cell-free tumor DNA (ctDNA) has emerged as a biomarker performing largely the same role as MCPyV oncoprotein antibodies, but can be used in all MCC patients and is growing in popularity. It is also being used in some centers for melanoma.

Treatment

Gene expression profiling (GEP) is seeing use for diagnosis, prognosis, and testing for $BRAF^{V600}$ mutations in melanoma. GEP quantifies mRNA levels and uses artificial intelligence (AI) to predict outcomes for melanocytic tumors. However, clinicopathologic risk stratification in melanoma is relatively accurate,

Table 2. Medical Therapies for Advanced Skin Cancers

Cancer	Treatment	Comments
Melanoma	Nivolumab Pembrolizumab	Immunotherapy should generally be first-line over targeted therapy in *BRAF*^{V600}-mutant melanoma
	Nivolumab with relatlimab	Higher PFS than nivolumab monotherapy. Lower rate of adverse events than nivolumab with ipilimumab
	Nivolumab with ipilimumab	
	Vemurafenib with cobimetinib	Vemurafenib may cause photosensitivity. BRAF inhibitors may cause benign and malignant cutaneous squamous tumors.
	Dabrafenib with trametinib	Dabrafenib may cause febrile episodes
	Encorafenib with binimetinib	Encorafenib may cause hepatotoxicity
	Atezolizumab with vemurafenib and cobimetinib	Uncommonly used
	Talimogene laherparepvec	Later-line therapy
Squamous cell carcinoma	Cemiplimab	
	Pembrolizumab	Less frequent infusions than cemiplimab – every 3 weeks rather than every 2 weeks
	Cetuximab	Approved for head and neck squamous cell carcinoma
	Chemotherapy	Includes cisplatin ± 5-FU, carboplatin ± paclitaxel, may be used with radiotherapy
Basal cell carcinoma	Vismodegib	
	Sonidegib	Not approved for metastatic BCC, only locally advanced disease, due to poor ORR in metastatic BCC in the BOLT trial
	Cemiplimab	Approved for BCC previously treated with a hedgehog inhibitor

PFS – progression-free survival, ORR – overall response rate

creating a high bar for GEP to clear. GEP AI tools were trained on old data samples that are not consistent with prognoses in the era of targeted and immune therapies. Some clinicians find continuous GEP results difficult to interpret and communicate to the patient. Dichotomous results are provided to solve this problem, but dichotomization attenuates predictive ability. Inaccuracy is a major limiting factor. Marchetti et al. performed a meta-analysis of seven studies on GEP used to predict recurrence for stage I and II melanoma. DecisionDx-Melanoma correctly predicted only 29% of recurrences in stage I melanoma – a 71% false negative rate.[17] For stage II disease it had a 56% false-positive rate.[17] MelaGenix had a 68% false-negative rate for stage I disease and 57% false-positive rate for stage II disease.[17]

Medical management of locoregional and metastatic skin cancers remains dynamic. The LAG-3 inhibitor relatlimab was approved with nivolumab in March 2022 for patients 12-years-old and older with unresectable or metastatic melanoma. The RELATIVITY-047 trial of relatlimab with nivolumab vs. nivolumab monotherapy showed a median progression-free survival (PFS) of 10.1 months for the combination and 4.6 months for nivolumab monotherapy (p=0.006).[18] PFS at 12 months was 47.7% for relatlimab with nivolumab and 36.0% for nivolumab.[18] Treatment-related adverse events occurred in 81.1% of relatlimab with nivolumab patients and 69.9% of nivolumab patients.[18] CTCAE Grade 3-4 adverse events occurred in 18.9% of relatlimab with nivolumab patients and 9.7% of nivolumab patients.[18] Head-to-head data is lacking, but PFS is comparable between relatlimab-nivolumab and nivolumab-ipilimumab.[19] However, relatlimab-nivolumab may be safer than nivolumab-ipilimumab. As noted, 18.9% of patients receiving relatlimab-nivolumab suffer severe adverse events.[18] In contrast 55.0% of nivolumab-ipilimumab patients suffer severe adverse events,[19] a 2.9-fold increase. We are still waiting on important data, since RELATIVITY-047 excluded patients with untreated brain metastases. The immunotherapy doublet is being evaluated in patients with active brain metastases in a study at

MD Anderson Cancer Center. Overall survival (OS) data for relatlimab-nivolumab is not yet published, but the regimen is likely to find a prominent place in treatment of metastatic melanoma.

Recently, we received FDA approval for pembrolizumab for stage IIB and IIC melanoma based on improved recurrence-free survival (RFS) in KEYNOTE-716.[20] Multiple immunotherapies and dabrafenib-trametinib had received approvals for adjuvant treatment for stage IIIA and higher melanoma, but it is known that stage IIC disease has worse RFS and OS compared to IIIA disease.[21] 26.5% of stage IIC melanoma patients will be recurrence-free at five years, compared to 44.8% of stage IIIA patients.[21] Similarly, stage IIC melanoma has a 71.0% 5-year OS, compared to 81.0% for stage IIIA.[21] In the KEYNOTE-716 trial of adjuvant pembrolizumab vs. placebo for stage IIB or IIC melanoma, RFS at 20.9 months of follow up was 85% in the pembrolizumab group and 76% in the placebo group.[20] OS data from KEYNOTE-716 are not yet reported. Risk prediction tools can be helpful when considering adjuvant therapy. AJCC-8 staging is useful but is limited by including only tumor-level data and excluding factors such as mitotic index and prior treatment. Melanomarisk.org.au and melanomaprognosis.net are two risk calculators to help inform patient discussions and treatment decisions (Table 2).

For $BRAF^{V600}$-mutant metastatic melanoma it was unclear for years whether first-line targeted therapy or immunotherapy performed better. Preliminary results of the DREAMseq trial were presented at the American Society of Clinical Oncology meeting in November 2021 and first-line nivolumab-ipilimumab demonstrated superior two-year OS compared to first-line dabrafenib-trametinib in stage III-IV disease.[22] Two-year OS for patients receiving first-line nivolumab-ipilimumab was 72% compared to 52% for patients receiving first-line dabrafenib-trametinib.[22] The OS difference caused the data safety and monitoring committee to recommend halting enrollment early and offer patients on first-line targeted therapy a switch to immunotherapy. Median duration-of-response was not reached in the immunotherapy arm but was 12.7 months in the targeted therapy arm – another favorable finding for first-line nivolumab-ipilimumab. Dabrafenib-trametinib had a higher PFS until six6 months and higher OS until 10-months, but longer-term outcomes favored immunotherapy. Patients were able to switch to the second regiment if they progressed on first-line treatment, and dabrafenib-trametinib performed equally well in the first and second lines. In contrast, 46% of patients on first-line nivolumab-ipilimumab responded, but only 30% responded to second-line immunotherapy. The major limitation of DREAMseq is that first-line immunotherapy is more commonly PD-1 monotherapy rather than doublet nivolumab-ipilimumab, and a monotherapy arm did not exist in this trial. Van Breeschoten et al. used the Dutch Melanoma Treatment Registry to examine first-line PD-1 inhibitor monotherapy against BRAF-MEK targeted therapy in a propensity-score matched cohort of 584 $BRAF^{V600}$-mutant melanoma patients.[23] Patients receiving first-line PD-1 inhibition had median OS of 42.3 months and 2-year OS of 65.4%.[23] First-line BRAF-MEK inhibition had a median OS of 19.8 months and two-year OS of 41.7%.[23] Both the Dutch registry study and DREAMseq trial suggest that first-line immunotherapy is generally preferred over targeted therapy in BRAF-mutant melanoma. Exceptions include patients with contraindications to immunotherapy and when a rapid response is needed and pseudoprogression may be dangerous, such as with symptomatic brain metastases.

For years completion lymph node dissection was standard management of melanoma with sentinel lymph node positivity or clinically detectable locoregional disease. However, two large trials evaluating completion lymph node dissection against observation found no improvement in overall survival or disease-specific survival.[24,25] One did find the three-year disease-free survival to be 5% higher in the dissection group (68% v. 63%, p=0.05).[24] In recent years, multiple studies have shown overall survival and recurrence-free survival benefit from adjuvant immunotherapy and targeted therapy regimens, and this has led to adjuvant treatment usurping completion lymph node dissection for management of locoregional melanoma in many centers.[26–31] A trial comparing ipilimumab against placebo in resected stage IIIA-C melanoma with a tumor deposit of at least 1 mm found five-year OS in the ipilimumab group was 65.4% and in the placebo group was 54.4%

(p=0.001). The five-year RFS was 40.8% and 30.3%, respectively (p<0.001). However, 54.1% of patients in the ipilimumab group experienced grade three to four adverse events, so the risk-benefit ratio must be carefully considered. Two trials of adjuvant nivolumab vs. ipilimumab in stage III or IV melanoma found superior RFS with nivolumab, with markedly lower risk of immune-related adverse events.[28,29] One found a comparable, although slightly higher, four-year OS with nivolumab compared to ipilimumab that was not statistically significant (77.9% vs. 76.6% p=0.31). In a trial of adjuvant nivolumab with ipilimumab vs. nivolumab vs. placebo for resected stage IV melanoma with no evidence of disease, one-year RFS in the nivolumab with ipilimumab group was 75%, in the nivolumab group it was 52% and in the placebo group it was 32%. Treatment-related grade three to four adverse events occurred in 71% of the doublet immunotherapy group and 27% of the nivolumab group. Adjuvant dabrafenib with trametinib vs. placebo in stage III melanoma with tumor deposits > 1 mm demonstrated superior three-year OS (86% vs. 77% p=0.006) and RFS (58% vs. 39%, p<0.001).[31] These data clearly favor adjuvant medical management over completion lymph node dissection for improved OS and disease-free survival. Risk of immune-related adverse events must be considered and discussed with the patient and contrasted with the risk of lymphedema and surgical complications from completion dissection. Lymphedema occurs in approximately 24% of melanoma patients after completion lymph node dissection.[24] Multiple studies excluding stage IIIA patients with nodal tumor deposits < 1 mm in diameter weakens support for adjuvant treatment in this lower-risk population. In some of these patients, completion dissection will increase their stage from IIIA to IIID, since completion dissection does provide more complete staging information compared to sentinel-lymph node biopsy.

There is interest in adjuvant and neoadjuvant cemiplimab for high-risk cutaneous squamous cell carcinoma, and there are ongoing trials for both. There is also interest in neoadjuvant immunotherapy and targeted therapy for melanoma. Neoadjuvant therapy may allow for reduced extent of surgery. It also allows for pathologic assessment of immunotherapy response and pathologic complete or partial response is a predictor of improved RFS.[32] Neoadjuvant therapy can often be given without delaying surgery,[33] but severe immune-related adverse events can delay surgery if they occur. The clinical context must be considered.

In 2021 the FDA approved cemiplimab for locally advanced and metastatic basal cell carcinoma (BCC) in patients previously treated with a hedgehog inhibitor. The approval was based on response rate in locally advanced BCC patients who had previously progressed on or not tolerated a hedgehog inhibitor. Objective response rate was 26%, with 6% achieving a complete response and 25% a partial response.[34] Prior to this approval, the hedgehog inhibitors vismodegib and sonidegib were the only agents approved for locally advanced or metastatic BCC. Many patients are unable to tolerate hedgehog pathway inhibition due to muscle spasms, dysgeusia, alopecia, and weight loss, so having a third agent available is important for these rare but challenging cancers. Grade 3-4 adverse events were documented in 48% of patients, with the most common side effects being fatigue, musculoskeletal pain, diarrhea, rash, and pruritus. Cemiplimab was approved for locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC) in 2018. In 2020 pembrolizumab was approved for recurrent or metastatic cSCC or cSCC not curable by surgery or radiation. Given the complexity of management of these patients, a multidisciplinary cutaneous oncology tumor board is a valuable tool that we are fortunate to have at the University of Missouri.

Conclusion

Cutaneous oncology is a rapidly changing field. Skin cancer diagnosis is now aided by expanding dermoscopic knowledge, total body photography, and emerging machine-learning technologies. Biomarkers are increasingly prevalent and are most useful currently for guiding treatment (as with $BRAF^{V600}$ mutation testing) and surveillance. As GEP and other biomarkers develop, they may develop a larger niche in diagnosis and risk stratification. LAG-3 inhibitors recently entered the market with relatlimab's approval for melanoma, adding an effective regiment for these patients. Adjuvant immunotherapy replacing completion lymph node dissection for locoregional melanoma is improving survival in these patients.

Nonmelanoma skin cancer is also seeing new developments with the approval of PD-1 inhibitors in BCC and cSCC. We are excited to be offering these advances to our patients via our cutaneous oncology program at the University of Missouri and can expect the field to remain dynamic in coming years.

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Disclosure

None reported.

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