Nonmelanoma skin cancers (NMSCs), which encompass a variety of cutaneous malignancies, are frequently managed with surgery, radiation therapy, cytotoxic chemotherapy, systemic immunotherapy, and active surveillance. In this tumor board–style forum, a panel of experts used several case studies as a basis to review these approaches and to describe existing clinical challenges. The current NCCN Guidelines for NMSC, which reflect the most up-to-date, evidence-based data relating to the evaluation and management of NMSCs, also provide key considerations and recommendations for the treatment of this patient population.

A wide range of approaches exist for treating aggressive nonmelanoma skin cancers, including surgery, radiation therapy (RT), cytotoxic chemotherapy, systemic immunotherapy, and active surveillance. Selecting an appropriate therapeutic approach, however, largely depends on the clinicopathologic presentation and patient factors. At the NCCN 2022 Annual Conference, 3 experts explored the key considerations in managing these patients through a tumor board–style presentation of several case studies. Panelists included Valencia D. Thomas, MD, MHCM, Professor, Department of Dermatology; Michael K. Wong, MD, PhD, Professor, Department of Melanoma Medical Oncology; and Andrew J. Bishop, MD, Assistant Professor, Department of Radiation Oncology, all from The University of Texas MD Anderson Cancer Center.

Cutaneous Squamous Cell Carcinoma

“As we discuss squamous cell carcinoma [SCC], we have essentially 3 classifications,” Dr. Thomas commented, “which are classified as well-differentiated, moderately differentiated, or poorly differentiated.”

Well-differentiated SCCs, which arise from the epidermis, make keratin well and are characterized by mild to moderate cytologic atypia. They often show abundant pink cytoplasm and prominent keratinization. “The well-differentiated SCCs grow rapidly because they’re full of keratin protein that expands the tumor almost like a balloon,” she explained.

The moderately differentiated variant of SCC is characterized by focal keratinization; however, the foci are not as diffuse as well-differentiated tumors. SCCs classified as poorly differentiated show minimal keratinization, or cellular dedifferentiation. There is a high nuclear-to-cytoplasmic ratio, and the nuclei meet the morphologic definition of being anaplastic.

NCCN, the American Joint Committee on Cancer (AJCC), and Brigham and Woman’s Hospital have all developed guidelines for staging SCC. The current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Squamous Cell Skin Cancer, in particular, provide an outline for patient stratification based on risk factors for local recurrence, metastases, and death from disease (Figure 1). “There are so many characteristics and elements that we must take into consideration that there are conflicting stages [among the 3 major staging systems],” Dr. Thomas explained. “[However,] one thing all 3 groups agree on [is that] there are particular aggressive subtypes we should always pay attention to, and those are the desmoplastic and adenosquamous subtypes, [as well as] carcinomas associated with scarring.”

Case 1: Therapeutic Strategies for SCC

The first case presentation focused on a 63-year-old man who was diagnosed in 2016 with SCC of the right side of the forehead and scalp. Histologic analysis after Mohs surgery revealed moderately differentiated disease, with deep dermis involvement and a depth of invasion of ≥3 mm; at this point, according to Dr. Wong, the margins were clear.

In 2017, the patient experienced disease recurrence at the 6 o’clock margin. Biopsy revealed moderately differentiated disease with a depth of invasion ≥3.7 mm. There appeared to be no lymphovascular invasion or epidermal connection, but perineural invasion was reported. After undergoing excisional surgery, the patient was found to have positive bone involvement.
“When we think about the role of adjuvant RT, we are trying to identify the patients who we think are at an increased risk of local recurrence,” Dr. Bishop explained. “In this patient [with] perineural invasion, bone invasion, and recurrent disease, adjuvant RT should be considered.” The patient underwent RT and experienced a clinical complete response (CR). Thereafter, he was placed under surveillance. “You [should] be very careful with [this patient] because his biology has already told you what could happen,” Dr. Wong commented.

In 2018, the patient presented with eye symptoms and pain. He was diagnosed with an advanced local supraorbital recurrence based on an MRI scan of the face and brain. Exenteration of the orbit and RT were offered; however, the patient declined due to concerns regarding vision preservation. “This is somewhat of a challenging place to deliver a definitive dose of RT,” Dr. Bishop explained. “Therefore, there might be a bit of tumor that would get underdosed if RT were the recommended [definitive] strategy [in order to minimize toxicity risk to the eye].”

The patient subsequently underwent systemic therapy with the anti–PD-1 immune checkpoint inhibitor cemiplimab-rwlc infused every 3 weeks. He reported an improvement in his vision and a decrease in pain after the second infusion. By the fourth infusion, he was pain-free and his vision remained intact; no high-grade toxicities were observed. He continued cemiplimab for 18 months and remained in a high-quality unmaintained CR for >30 months from the end of therapy. “This reflects a ‘fairy tale’ of what we can do with immunotherapy in this disease,” Dr. Wong commented.

Case 2: Considerations for Carcinomas With Nodal Metastases

According to Dr. Wong, nodal metastasis is not uncommon in patients with skin cancer. The current NCCN Guidelines provide recommendations for the clinical staging, preoperative assessment, and primary treatment of patients with palpable regional lymph nodes or abnormal lymph nodes identified by imaging studies. Of particular interest, considerations for surgical evaluation are included (Figure 2).

The second case presentation focused on a patient with a stage IV skin malignancy affecting the left upper extremity—there appeared to be lung metastases and axillary involvement. The vast majority of SCC and basal cell carcinomas (BCCs) are superficial lesions definitively managed in the dermatologist’s office, but in those rare instances of advanced disease, both SCC and BCC may present in this manner. Therefore Dr. Wong and Dr. Bishop took an agnostic approach to evaluate its management.

“SCCs and BCCs are fairly radiosensitive … so RT is a good tool in conjunction with immunotherapy or other systemic therapies to try to provide some sort of long-term control in patients who are not surgical candidates,” Dr. Bishop explained. With the emergence of novel
therapies such as immunotherapy, Dr. Wong added that surgery might eventually be feasible in patients with a similar clinical presentation. Thus, multidisciplinary management is key.

Case 3: Management of PD-1–Refractory SCC
The third case presentation focused on a woman with metastatic SCC to lung and axilla who underwent cemiplimab therapy. After 4 cycles, a smaller lung mass disappeared; however, according to Dr. Wong, disease progression occurred in the axilla after 6 cycles of immunotherapy. The patient was admitted to the ICU with a large, bulky, fungating PD-1–refractory mass. “RT in this scenario … can often provide palliative benefit, as well as shrink the mass down,” Dr. Bishop remarked. “If we can escalate the dose in a safe way, avoiding some of the nearby structures, we can get these large fungating tumors to cytoreduce and provide a [durable tumor control] benefit.”

According to Dr. Wong, the patient experienced a high-quality response to local therapy in the axilla. The axillary mass shrunk to a scarred 4-cm nodule, and the lungs remained clear. Because the patient remains in a state of disease stability, now at the 1 year mark, immunotherapy has not been reinitiated.

Role of Immunotherapy
According to Dr. Wong, Hedgehog inhibitors (HHI) have been the “cornerstone” of targeted therapy for BCC. The objective response rate is in the 60% range for patients with locally advanced disease and between 17% and 49% for those with metastatic disease who undergo oral therapy with these agents.3

The most frequently reported adverse events for HHI include alopecia, muscle spasms, dysgeusia or ageusia, and weight loss.4,5 “The struggle here is to understand how to best manage these patients and maintain them on dose and schedule,” Dr. Wong explained. However, despite these toxicities, there are options for this population. In patients with locally advanced BCC who experienced disease progression with or were intolerant to previous Hedgehog inhibition, cemiplimab therapy resulted in a durable disease control rate of 60%, and 85% of patients remained in response at 12 months.6 Importantly, 6% of these HHI-refractory/intolerant patients on cemiplimab achieved a complete response.

Merkel Cell Carcinoma
Merkel cell carcinoma (MCC) is a neuroendocrine tumor of the skin, with a 5-year mortality rate of 41% to 77%.7,8 Risk factors for this disease include exposure to ultraviolet light and Merkel polyomavirus.

MCC is histologically distinct, as it is made up of small, round, “blue” cells on standard tissue stains. According to Dr. Thomas, there are frequent mitoses. The cells stain positive for low-molecular-weight keratin (CK20) in a distinctive paranuclear pattern, as well as several other markers for neuroendocrine tumors.

Case 4: Therapeutic Strategies for MCC
Dr. Bishop presented the case of a 79-year-old man with a history of cutaneous tumors who underwent a shave biopsy for a painless growing bump on his left index finger. Pathology demonstrated an MCC measuring approximately 5 mm with 2 mm of invasion. There seemed to be
evidence of vascular invasion and positive margins. Systemic workup was negative for metastatic disease. A wide local excision with a sentinel lymph node biopsy was performed, and the pathologic analysis revealed clear margins and 2 mm of residual disease. Neither of the 2 evaluated lymph nodes were involved.

“When we look at surgical management, sentinel node biopsy is strongly recommended in the NCCN Guidelines,” Dr. Thomas commented. “The guidelines [also] recommend consideration of a peripheral and deep en-face margin assessment, with 100% of the margin assessed using horizontal sections.” She noted that patients undergoing surgery alone are more likely to develop a regional recurrence than those who undergo surgery and RT; however, wide excision should still be considered when RT is not possible.

MCC is a radiosensitive tumor. However, according to Dr. Bishop, tumor risk factors should be considered when selecting patients for adjuvant RT, which include tumors measuring ≥ 1 cm in diameter, positive margins, and lymphovascular invasion.

“This was a small tumor, and that typically wouldn’t be an indication for postoperative RT,” Dr. Bishop remarked. “[However,] because of the location on the index finger, widely negative margins were not able to be achieved, and so adjuvant RT was recommended for this patient.” After undergoing adjuvant RT to the primary tumor, the patient elected for surveillance. However, 13 months later, he developed unresectable extensive adenopathy of the left axilla with vascular encasement. The patient subsequently underwent immunotherapy with avelumab and achieved a radiographic partial response—this, according to Dr. Bishop, was enough of a response to render the tumor resectable. Sixteen lymph nodes were removed during axillary lymph node dissection and were negative for any viable metastatic carcinoma, resulting in a pathologic CR.

According to Dr. Wong, several ongoing trials are evaluating the role of adjuvant immunotherapy in stage III disease and advanced MCC (ClinicalTrials.gov identifiers: NCT04291885, NCT02196961, NCT03798639, NCT03271372). Although much of these data are not yet available, he noted that this patient was administered adjuvant immunotherapy because of his “great” immunologic response and high risk of recurrence. “Oftentimes, RT is used in the adjuvant setting for bulky adenopathy or extracapsular extension,” Dr. Bishop commented. “[However,] given the CR here, I might omit RT from his treatment … [and] opt for [close] observation.”

Pathologic Features of Dermatofibrosarcoma Protubera\n
Dermatofibrosarcoma protubera\n
Case 5: Management of DFSP

A 40-year-old man presented with a small painless nodule in the left groin; however, he developed a painless nodular lesion in the inguinal and suprapubic regions after more than a decade of slow continuous growth. Based on punch biopsy, the patient was diagnosed with DFSP without any evidence of fibrosarcomatous transformation.

Due to the tumor size and proximity to his genitalia, the patient was administered neoadjuvant imatinib, which he continued for approximately 1 year. The patient achieved a radiographic partial response. “In this case, there was some discussion of [incorporating] RT [into the local management due to the large tumor size and abutment of the genitalia, which would limit the surgical margins],” Dr. Bishop explained. “However, given his partial response to imatinib and his young age, we opted for wide local excision alone.” Negative margins were achieved, and he remains without evidence of disease.

References


