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A Case of a Discrepancy Between a Highly Staged Cutaneous Squamous Cell Carcinoma Using Standard Staging Systems and 40-Gene Expression Profile Testing (Decisiondx SCC)

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Abstract

Cutaneous squamous cell carcinoma (CSCC) is a prevalent nonmelanoma skin cancer primarily affecting light-skinned individuals. Most patients with CSCC experience favorable outcomes following surgical clearance; however, a subset faces local recurrence, nodal metastasis, and disease-specific deaths. With the increasing incidence of nonmelanoma skin cancer, staging systems are crucial for managing high-risk CSCC cases. The American Joint Committee on Cancer 8th edition (AJCC 8) and Brigham and Women's Hospital (BWH) staging systems are the current standards, but they have limitations in risk stratification. This paper presents a clinical case of CSCC initially staged with AJCC 8 and BWH systems, which were categorized differently due to perineural invasion. The DecisionDx-SCC test, employing a 40-gene expression profile and RT-PCR technology, classified the lesion as Class 1 with low risk of metastasis. The study explores the discrepancies between current staging systems and gene expression profiling in predicting metastasis risk.

Keywords: SCC; Nonmelanoma Skin Cancer; Cancer Staging; Mohs Surgery; Adjunctive tool

Abbreviations: CSCC: Cutaneous Squamous cell Carcinoma; NMSC: Nonmelanoma Skin Cancer; BWH: Brigham and Women's Hospital; AJCC 8: American Joint Committee on Cancer 8th edition; PNI: Perineural Invasion; PPV: Positive Predictive Value; HNSCC: Head and Neck SCCS; NPV: Negative Predictive Value

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most prevalent nonmelanoma skin cancer (NMSC) that largely affects light-skinned individuals [1]. The majority of individuals who undergo surgical clearance of CSCC have a highly favorable prognosis. Nevertheless, there is a small population of patients that experience local recurrence, nodal metastasis, and disease-specific deaths [2,3]. It is estimated that the incidence of NMSC will continue to rise until 2040 and because of this, staging is a useful tool for the care of patients with CSCC, especially those with high-risk features [2]. To date, the two most common tools for staging CSCC are the American Joint Committee on Cancer 8th edition (AJCC 8) and the Brigham and Women's Hospital (BWH) staging systems. The DecisionDX-SCC test (Castle Biosciences) utilizes a 40-gene expression profile (40-GEP) and RT-PCR technology to screen for specific tumor markers in primary tumor tissue biopsies [3]. This test allows for adjuvant information regarding risk of metastasis within 3 years. In turn, the DecisionDX SCC test could also serve as a patient-specific prognostic tool and help with disease management decisions. We present this clinical case of CSCC with a highly staged CSCC, using the standard available staging systems, that was subsequently tested with the gene expression profile test, DecisionDx-SCC, in order to show the oncology community that this method provides an independent predictive tool to help stratify risk of metastasis when compared to the standard available staging systems. This case also reflects the discrepancy that can exist between current standard staging

systems and gene expression profile testing, with regards to risk of metastasis.

Case Presentation

A 74-years old male presented with a 3.5 x 3.0cm scaly plaque on his mid occipital scalp (Figure 1). Biopsy of the lesion showed a well-differentiated CSCC. The patient underwent excisional surgery with subsequent clear surgical margins. The tumor had evidence of "extensive" perineural invasion of nerves greater than or equal to 0.1mm. Based on their respective criteria, AJCC 8 was classified as a stage T3 and BWH classified it as a stage T2b. The DecisionDx-SCC gene expression profile test then classified this lesion as a Class 1 with low risk of metastasis within three years.

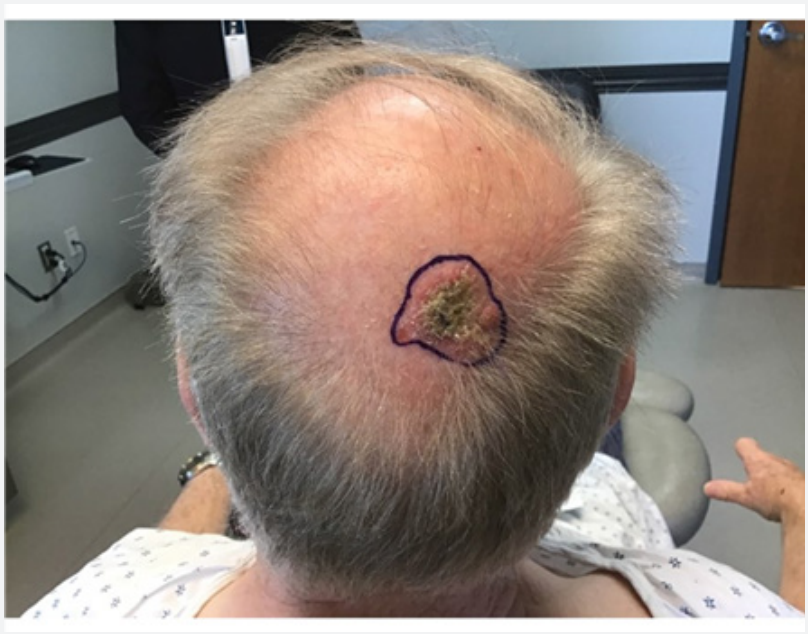

Figure 1: Patient presentation of occipital lesion.

Table 1: Current staging methods for AJCC8 and BWH [6].

American Joint Committee on Cancer 8th Edition	
• T1 <2 cm in greatest diameter • T2 ≥2 cm but <4cm in greatest diameter • T3 ≥ cm diameter or single high-risk factor*	• High Risk Factors: ○ Bone invasion ○ PNI ≥ 0.1mm, tumor cells in nerve sheath of nerve lying deeper than the dermis ○ Deep invasion, beyond subcutaneous fat or > 6mm
Brigham and Women's Hospital T stage	
• T1 0 high-risk factors • T2a 1 high-risk factors • T2b 2-3 high-risk factors • T3 4 high-risk factors or bone invasion	• High Risk Factors: ○ Tumor diameter ≥ 2cm ○ Poorly differentiated ○ PNI ≥ 0.1mm in caliber ○ Invasion beyond subcutaneous fat

Discussion

The AJCC 8 describes cutaneous carcinomas into 8 different T categories based on tumor size, bone erosion/invasion, perineural invasion, deep invasion (invasion beyond the subcutaneous fat or >6mm) [4]. The T stages vary from TX - the primary tumor cannot be assessed, T3 - tumor >4cm/minor bone erosion/ perineural invasion/deep invasion, or at its highest T4 - tumor with gross cortical bone and marrow, skull base invasion and/or skull base foramen invasion (Table 1). Based on our patient's presentation the ACCJ8 staging method categorized this CSCC as T3 because of its perineural invasion (PNI) measuring 0.1mm and initial size being greater than 2 cm. PNI refers to the invasion of tumor cells

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into nerve sheaths that spreads along the connective tissue of the fascicles [1]. PNI has shown an elevated risk of local recurrence, mortality and a 35% increased risk of regional and distant metastasis.1 Despite this increased risk, there have been studies that show no correlation between large-caliber PNI and poor prognosis [1].

The BWH staging system was developed to address the tumor stratification discrepancies in the T2 category of the AJCC7 staging system [2]. The BWH staging system includes the T1, T2a, T2b, and T3 categories, which are based on the number of high-risk factors present (Table 1). Based on our patient's presentation, the BWH categorized the CSCC as T2b, with high risk factors based on its PNI measuring nerves of calibers equal to or larger than 0.1 mm and the initial size being greater than 2 cm. The addition of the T2b category allows for more detailed tumor stratification. An investigation of the AJCC8 system has suggested a lack of distinction between the AJCC8 T2 and T3 categories has resulted in equivalent outcomes among these categories, given that poor differentiation is not considered a high-risk factor in this staging system [3]. In fact, the study compared the AJCC and BWH studies and revealed that the risk of poor outcomes is lower in the AJCC8 T3 category compared to the BWH T2b category, because the AJCC T3 category is only required to have one of three high risk factors, while the BWH T2b category requires two to three high-risk factors [4]. The exclusion of poor differentiation in the AJCC8 T3 high risk features is a major limitation of this staging system. Another major limitation of the AJCC8 staging system is that it includes only head and neck SCCS (HNSCC) [5]. A large study analyzing the validity of four CSCC staging systems for HNSCCs, including the AJCC8 and BWH systems, indicated that the BWH system had the highest specificity and c-index, while the AJCC8 had a higher negative predictive value (NPV); however, all systems had low positive predictive value (PPV), calling attention to the need for further improvements to the CSCC staging systems [6]. Tumor staging systems with low PPV, or those that poorly predict risk of metastasis, can lead to wide variability in patient care, surveillance cadences and treatment recommendations by inaccurately staging tumors at risk of metastasis. Thus, we present the DecisionDx-SCC gene expression profile test which has been proven to independently predict the risk of metastasis in high-risk CSCC.

The DecisionDx-SCC gene expression profile test was developed to more specifically identify high-risk CSCC with potential for metastasis. Whereas the AJCC and BWH systems rely on clinicopathologic risk factors, the 40-gene expression profile (40-GEP) testing system utilizes RT-PCR technology to screen for specific tumor markers in primary tumor tissue biopsies [3]. Utilizing this technology, the patient presented was tested as a Class 1 category, indicating a low risk of metastasis within 3 years of diagnosis. Under the guidance of the AJCC8 and BWH systems, our patient's CSCC was labeled as a high-risk tumor; yet the DecisionDx-SCC gene expression profile test placed our patient's CSCC in a low-risk category, which allows for a reassessment of further managements, recommendations and surveillance measures for this patient and other similar patients.

In a study analyzing the impact of this technology on clinical management, 402 dermatologists were surveyed on expectant management of high and low-risk CSCC-GEP staged tumors. A lower risk result led to a significant decrease in the fraction of dermatologists who recommended more invasive interventions such as postoperative adjuvant radiation, chemotherapy, and sentinel lymph node biopsy [7]. This study emphasizes the difference genomic testing can make on a patient's treatment plan and can perhaps guide the oncology community towards integrating GEP-based systems into daily practice.

While the role of the AJCC 8 and BWH are seen as the standard of care for CSCC staging, the DecisionDx-SCC 40-GEP test shows promise as an independent predictor of metastatic events within 3 years and should be used in conjunction with information provided in current staging systems. Of note, it is not the authors' opinion that the DecisionDx-SCC gene expression profile test replace current staging systems or NCCN guidelines but rather serve as an adjunctive tool for more patient-specific management of patients with high risk CSCC. This case is evidence that there are discrepancies between the current staging systems; DecisionDx-SCC should be considered as a tool to bridge the gap that current clinicopathologic staging systems have. It is the authors' opinion that the use of gene expression profile testing for high-risk CSCC to screen for specific tumor markers allows for a more effective predictor of metastasis compared to the currently available clinicopathologic risk factors utilized in the two other standard staging systems, AJCC8 and BWH. It is also our opinion that this case report will enlighten other oncologists, head and neck surgeons, surgical oncologists, dermatologists and Mohs surgeons to the benefits of the DecisionDx-SCC test in the patient-specific care of patients with highly staged CSCC.

Conflict of Interest

CGM is a Speaker and Share Holder for Castle Biosciences.

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