Integrating the 40-Gene Expression Profile (40-GEPS) Test into Management of High-Risk Cutaneous Squamous Cell Carcinoma

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SYNOPSIS

- Cutaneous squamous cell carcinoma (cSCC) is the 2nd most common skin cancer, with ~1,000,000 cases diagnosed per year in the U.S. Incidence is growing rapidly (>5-fold increase in past 30 years) and it surpasses the incidence of invasive melanoma.
- Regional metastasis rates of 13% have been reported, with most studies reporting 6% and most events occurring within 2-3 years of initial diagnosis and treatment. Disease-specific mortality is 1.5-2% and the number of deaths from cSCC per year is similar to that from melanoma.3,7
- National Comprehensive Cancer Network (NCCN) guidelines accommodate a broad range of treatment plan options for high-risk patients and recommend risk-directed implementation. These guidelines and the American Joint Committee on Cancer (AJCC) and Brigham and Women’s Hospital (BWH) staging systems have low positive predictive value (PPV) for identifying patients at high risk for metastasis (NCCN 15%; AJCC 14-17%10-11; BWH 24-38%11-12).
- Improved stratification for risk-appropriate treatment plans for patients with NCCN-defined high-risk cSCC is needed.
- Integration of the recently validated 40-gene expression profile (40-GEPS) test with AJCC or BWH T stage criteria into management of NCCN high-risk cSCC patients may be key to identifying those high-risk patients who would most benefit from aggressive treatment strategies, while concomitantly reducing unnecessary interventions for those who are low risk for poor outcomes.

OBJECTIVE:

To integrate a validated, prognostic 40-gene expression profile test into clinical decision making for risk-appropriate management of NCCN high-risk cSCC patients

METHODS

- The 40-gene expression profile (40-GEPS) test was developed and validated to stratify a patient’s risk for regional or distant metastasis at 3 years after diagnosis as low (Class 1), high (Class 2A), or highest (Class 2B) risk for metastasis (Figures 1 and 2).9
- As NCCN high-risk cSCC patients are the intended population for the 40-GEPS test, cases categorized as such (n=300, Table 1) were used to analyze the effects of integration of 40-GEPS risk stratification into patient management decision making. All cases were staged according to either AJCC or BWH staging system criteria for T stage. The numbers of patients in each Class/T stage combination along with metastasis rates were reported and used to align each patient group with risk-appropriate management recommendations.
- Risk-aligned management recommendations based on 40-GEPS results and T stage were developed for low, moderate, and high intensity management within the boundaries of acceptable NCCN patient management approaches for patients with high-risk localized disease. Metastasis rates of <10%, 10-50%, and >50% were aligned with low, moderate, and high intensity management recommendations, respectively.

RESULTS

Table 1. Cohort demographics of 300 NCCN high-risk cSCC cases

<table>
<thead>
<tr>
<th>Feature of Modeling Cohort (% of Cohort)</th>
<th>40-GEPS Class</th>
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<tbody>
<tr>
<td>Age: Median years (range)</td>
<td>70 (34-95)</td>
</tr>
<tr>
<td>Sex: Male</td>
<td>219 (73%)</td>
</tr>
<tr>
<td>Immune deficient</td>
<td>76 (25%)</td>
</tr>
<tr>
<td>Located on H&amp;N</td>
<td>201 (67%)</td>
</tr>
<tr>
<td>Tumor diameter: mean cm (±2 cm)</td>
<td>1.85 (36%)</td>
</tr>
<tr>
<td>Tumor thickness*: mean mm (≥6 mm)</td>
<td>3.90 (16%)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>36 (12%)</td>
</tr>
<tr>
<td>Clark Level I/V</td>
<td>62 (21%)</td>
</tr>
<tr>
<td>PNI present</td>
<td>36 (12%)</td>
</tr>
<tr>
<td>Subcutaneous fat invasion</td>
<td>43 (14%)</td>
</tr>
</tbody>
</table>

Figure 3. Integration of 40-GEPS prognostication into patient management decisions for NCCN high-risk cSCC patients (n=300)

A. Cohort stratification and metastasis rate by 40-GEPS Class and T Stage

B. Management intensity determined by risk for metastasis

Figure 4. Risk-aligned management recommendations based on 40-GEPS and T stage prognostics

CONCLUSIONS

- Integration of the 40-GEPS test into risk-directed management plans for NCCN high-risk cSCC patients identified a group of patients (Class 1, T1/T2) with risk approaching that of the general population, thereby warranting a low intensity management strategy and sparing these patients unnecessary procedures and potential adverse effects.
- Conversely, those patients with rates of metastasis surpassing 50% (Class 2B) warrant a high intensity strategy that increases follow-up visits, utilizes imaging and/or biopsies for nodal assessment, and offers adjuvant treatments and clinical trials for probable metastatic events.
- The data presented herein support integration of the 40-GEPS into management of NCCN high-risk cSCC patients for implementation of risk-appropriate treatment plans for these patients.

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