In-Transit Metastasis From Squamous Cell Carcinoma

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BACKGROUND In-transit metastasis from cutaneous squamous cell carcinoma (SCC) is an uncommon form of metastasis through lymphatics and occurs more commonly in immunosuppressed patients.

OBJECTIVE To identify cases of in-transit SCC and determine patient characteristics, tumor features, management, and prognosis.

METHODS AND MATERIALS A multicenter case series treated by Australian and New Zealand clinicians.

RESULTS In 31 patients, median age was 72 years (range 52–99) and 68% were immunocompetent. Tumors occurred on the head and neck in 94% of cases, with 71% of all tumors occurring on the scalp, forehead, or temple. The median time to presentation with in-transit SCC from treatment of the initial tumor was 5 months. Management included surgery (94%), radiotherapy (77%), chemotherapy (10%), and reduction of immunosuppression (3%). Median follow-up was 12 months. Overall survival at 3 and 5 years were 27% and 13%, respectively.

CONCLUSION In-transit metastases are described in 31 patients, of whom the majority was immunocompetent. The scalp, forehead, and temple were the most common sites. New clinical and histological diagnostic criteria are proposed. Prognosis was poor with 5-year survival of 13%. Recommended management is a combination of surgery and adjuvant radiotherapy. Reduction of any iatrogenic immunosuppression should be considered.

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Cutaneous squamous cell carcinoma (SCC) is the second most common type of skin cancer, and may have an annual incidence of over 700,000 cases in the United States and 118,000 cases in Australia.1–3 Despite the high incidence in these countries, cancer registries collect limited data on SCC.4

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Cutaneous SCC commonly arises on locations exposed to ultraviolet light such as the head and neck. Tumor features that increase the risk of metastasis include diameter >2 cm, Clark Level IV, thickness >2 mm, location on the ear or lip, location on the temple, poor histological differentiation, perineural invasion, lymphovascular invasion, and immunosuppression.\(^5\)\(^-\)\(^7\) In-transit metastasis is an uncommon type of metastasis. It occurs when SCC spreads through lymphatics to dermal or subcutaneous tissue before the first group of regional lymph nodes.\(^8\)\(^,\)\(^9\)

Few case series\(^8\) and reports\(^10\)\^-\(^17\) have described in-transit metastases of cutaneous SCC. In addition, most of these cases have occurred in immunocompromised patients. Thus, there are limited data on the features and prognosis of in-transit SCC, and metastases that occur in immunocompetent patients. The aim of the study was to identify cases of in-transit SCC and determine patient characteristics, tumor features, management, and prognosis.

**Materials and Methods**

In-transit metastases were defined as foci of SCC originating within dermal or subcutaneous tissue, clinically distinct from the initial cutaneous tumor, and occurring before the first echelon of regional lymph nodes.\(^8\)\(^,\)\(^9\) Patients were excluded if they were diagnosed with nodal disease before in-transit metastasis because these patients already had more advanced disease with a worse prognosis.

Cases of in-transit SCC were identified by Australian and New Zealand dermatologists, pathologists, plastic surgeons, and radiation oncologists. The following data were retrieved: patient demographics, medical history, initial tumor and metastasis features, investigations, management, and patient outcome. Institutional review board ethics approval was obtained.

The initial SCC were staged using the 2010 American Joint Committee on Cancer (AJCC) staging system\(^6\) and the 2013 alternative T staging system proposed by Jambusaria-Pahlajani and colleagues.\(^18\) The AJCC system defines Stage T1 as tumor ≤2 cm in greatest dimension, and Stage T2 as tumor >2 cm in dimension or tumor with ≥2 high-risk features. The high-risk features are >2 mm thickness, Clark Level IV, perineural invasion, site on the ear or lip, and poor histological differentiation.\(^6\) The alternative system defines Stage T1 as 0 risk factors, T2a as 1 risk factor, and T2b as 2 to 3 risk factors. The risk factors are diameter ≥2 cm, poor differentiation, perineural invasion, and invasion beyond subcutaneous fat.\(^18\)

Overall survival was estimated using the Kaplan–Meier method, and the log-rank test was used to compare survival between groups. Cox proportional-hazards regression was also used. Statistical tests were performed using SPSS 22 (IBM Corp, Armonk, NY), and \(p < .05\) (2-tailed) was considered significant.

**Results**

Thirty-one cases of in-transit SCC were identified, presenting between 2001 and 2015.

**Patient Characteristics**

Median age was 72 years (range 52–99). Twenty-six (84%) patients were male. Twenty-one (68%) were immunocompetent. Causes of immunosuppression included chronic lymphocytic leukemia (\(n = 3\)), chronic myeloid leukemia (\(n = 1\)), myelodysplasia (\(n = 1\)), non-Hodgkin lymphoma (\(n = 1\)), B-cell lymphoma (\(n = 1\)), mucosa-associated lymphoid tissue lymphoma (\(n = 1\)), tacrolimus use in an organ transplant recipient (OTR) (\(n = 1\)), and prednisolone and hydroxychloroquine use in a patient with systemic lupus erythematosus (\(n = 1\)). Twenty-one patients have developed other skin cancers in their medical history. One patient had been exposed to nuclear radiation in the past.

**Characteristics and Management of Initial Squamous Cell Carcinoma**

The initial SCC occurred on the scalp (\(n = 12\)), forehead (\(n = 5\)), temple (\(n = 5\)), nose (\(n = 2\)), nasolabial fold (\(n = 1\)), cheek (\(n = 1\)), medial canthus (\(n = 1\)), ear (\(n = 1\)), neck (\(n = 1\)), wrist (\(n = 1\)), and leg (\(n = 1\)). Eighteen tumors occurred on the left side of the body, 7 on the
Characteristics and Management of In-Transit Metastases

The median time to presentation with in-transit SCC from treatment of the initial tumor was 5 months (range 0–34). Multiple metastases occurred in 16 (52%) cases. Macroscopically, tumors were commonly described as nodules (Figures 3 and 4). Median maximum diameter was 1.5 cm (range 0.4–6.0). Twenty-nine (94%) cases were excised, of which 4 underwent MMS. Figures 5–7 show the histology of an initial SCC and the corresponding in-transit metastasis. Twenty-four (77%) cases underwent radiotherapy, of which 6 received radiotherapy to the neck and 1 to the axilla. Three patients were treated with chemotherapy (2 carboplatin, 1 cisplatin). The OTR ceased taking tacrolimus as part of management and was switched to prednisolone. Acitretin was used in 1 patient for chemoprevention of further SCC. Imaging modalities used included computed tomography (CT) \( (n = 24) \), positron emission tomography \( (n = 6) \), magnetic resonance imaging (MRI) \( (n = 3) \), and whole-body bone scan \( (n = 1) \). Neck dissection was performed in 9 patients, and parotidectomy in 7 patients.

Patient Outcome

Median follow-up was 12 months (range 0–117). Twelve (39%) patients were deceased at follow-up. Overall survival at 3 and 5 years were 27% and 13%, respectively (Figure 8). There were no significant differences in survival between
immunocompetent and immunosuppressed patients ($p = .35$), or between surgery only and a combination of surgery and ART ($p = .34$). In addition, there was no significant association between time to presentation with in-transit SCC and survival ($p = .52$). At least 10 (32%) patients had developed nodal or distant metastases at follow-up.

**Pathology Reporting of In-Transit Squamous Cell Carcinoma**

The pathology reports of 13 in-transit SCC were reviewed to identify the terminology initially used to describe the tumors. Terminology included: metastasis ($n = 7$), tumor deposit ($n = 6$), recurrence ($n = 5$), in-transit metastasis ($n = 1$), and satellite nodule ($n = 1$).

**Discussion**

The authors report a large series of 31 patients with in-transit SCC on which there have been limited data in the literature (Table 2). This series comprised a large group of immunocompetent patients ($n = 21$). The previous large case series reported by Carucci and colleagues contained 21 patients, of whom only 5 were immunocompetent.

Diagnosing in-transit metastasis can be challenging, and requires clinicopathological correlation to distinguish it from local recurrence and perineural spread of tumor. New diagnostic criteria, incorporating clinical...
and histological features, are proposed (Table 3). As noted in this series, in-transit metastasis specimens may initially be reported as local recurrence. In some cases, this may be due to histological similarities between in-transit metastases and local recurrences such as the presence of scarring in the submitted tissue and the absence of overlying epidermal tumor. Similar difficulties in classification of cutaneous melanoma metastases have previously been described. It may also be challenging to distinguish perineural spread of tumor from in-transit metastasis which is spread through lymphatics. Perineural spread may be more likely if tumor is observed exclusively in perineural locations in tissue sections. Although the initial SCC was not identified in a few of the previously reported cases of in-transit metastasis, the initial tumor should ideally be identified to demonstrate that the potential in-transit SCC lies between the initial tumor and draining lymph nodes.

In this series, hematologic malignancy was the most frequent cause of immunosuppression, occurring in 80% of immunosuppressed patients. This supports hematologic malignancy as a risk factor for developing in-transit SCC. It has previously been shown that in patients with hematologic malignancy, non-melanoma skin cancers tend to follow a more aggressive course. Consistent with this, one of the immunosuppressed patients had an initial tumor with a small diameter of 0.3 cm.

Most of the initial SCC (94%) occurred on the head and neck, consistent with the previous large case series (n = 21). Initial SCC occurred on the scalp, forehead, or temple in 71% of the cases and in 10 of the 19 cases in the previous case series. These sites are exposed to high levels of sun damage and may be at higher risk of metastasis. However, these sites are not categorized as high risk in the AJCC staging system or 2013 system. Using both staging systems, most initial SCCs were Stage T2 or higher. This confirms that in-transit SCC arises from more aggressive tumors.

After a diagnosis of in-transit metastasis, CT or MRI staging of the draining lymph nodes should be performed. Sentinel lymph node biopsy to identify occult nodal metastases may also be considered.

Based on the limited cases in the literature (Table 2), management of in-transit SCC often includes a combination of surgery and ART. The addition of ART is likely to improve outcomes for in-transit SCC. This is because ART has been shown to improve locoregional control of nodal disease, and both in-transit and nodal metastases spread through lymphatics. However, the sample size may have limited the ability to demonstrate this. It has been suggested that ART can be delivered to in-transit SCC in a similar way to Merkel cell carcinoma. Radiotherapy may be delivered with a field of at least 1 cm and up to 5 cm, and encompass the primary site, in-transit site, and the first

Figure 7. Circumscribed nodule of in-transit metastatic squamous cell carcinoma involving the deep dermis and subcutis of sun-damaged skin. There is no epidermal connection, adjacent scar, associated lymph node, or perineural spread (H and E x25).

Figure 8. Kaplan–Meier overall survival curve for in-transit squamous cell carcinoma.
Given the poor prognosis of in-transit SCC, adjuvant systemic chemotherapy may be considered. Other management options include reduction in iatrogenic immunosuppression and oral retinoids. The epidermal growth factor receptor inhibitor cetuximab has produced a good response in a few cases of in-transit SCC.12 Greater intensity and duration of immunosuppression in OTRs are associated with development of SCC.29,30 In addition, the prognosis of in-transit SCC in OTRs may be worse than in immunocompetent patients.8 In OTRs who develop multiple skin cancers per year or high-risk cancers, reduction in immunosuppression has been suggested as part of the management strategy.22 Where the skin cancer is life threatening, a large reduction in immunosuppression, even to the extent of risking allograft failure, may be appropriate.22 In the previous case series of in-transit SCC, 76% of patients were alive at mean follow-up of 24 months, whereas 61% of the patients were alive at median follow-up of 12 months. This suggests that this case series contains more aggressive cases. Our documented prognosis of in-transit SCC was poor with 3-year overall survival of 27%. In contrast, non-metastatic SCCs have 3-year survival rates of 70% to over 90%.31,32 Given the poor prognosis of in-transit

### TABLE 2. Management of In-Transit Squamous Cell Carcinoma and Patient Outcomes in the Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Immune Status (n)</th>
<th>Management (n)</th>
<th>Proportion Alive</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study, n = 31</td>
<td>CPT (21), SUP (10)</td>
<td>Excision (29), radiotherapy (24), chemotherapy (3), reduce immunosuppression (1)</td>
<td>19/31</td>
<td>12 (median)</td>
</tr>
<tr>
<td>Carucci and colleagues,8 n = 21</td>
<td>CPT (5), SUP (16)</td>
<td>Excision (15), radiotherapy (19), chemotherapy (2), reduce immunosuppression (7), amputation (1), and retinoids (3)</td>
<td>16/21</td>
<td>24 (mean)</td>
</tr>
<tr>
<td>Copcu and colleagues10</td>
<td>CPT (2)</td>
<td>Excision, radiotherapy</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Weidner and colleagues11</td>
<td>SUP (1), u (1)</td>
<td>Excision, radiotherapy, amputation</td>
<td>1/2</td>
<td>11, 6</td>
</tr>
<tr>
<td>Bauman and colleagues12</td>
<td>CPT (1), u (1)</td>
<td>MMS, cetuximab</td>
<td>2/2</td>
<td>6, 4</td>
</tr>
<tr>
<td>Wain and colleagues13</td>
<td>CPT (1)</td>
<td>Radiotherapy</td>
<td>0/1</td>
<td>5</td>
</tr>
<tr>
<td>Wollina and colleagues14</td>
<td>CPT (1)</td>
<td>MMS, radiotherapy, cetuximab</td>
<td>1/1</td>
<td>3.5</td>
</tr>
<tr>
<td>Padmavathy and colleagues15</td>
<td>u (1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Kocaturk and colleagues16</td>
<td>u (1)</td>
<td>—</td>
<td>0/1</td>
<td>2</td>
</tr>
<tr>
<td>Altunay and colleagues17</td>
<td>u (1)</td>
<td>—</td>
<td>0/1</td>
<td>2</td>
</tr>
<tr>
<td>Neoh and colleagues19</td>
<td>SUP (1)</td>
<td>Radiotherapy</td>
<td>0/1</td>
<td>25</td>
</tr>
<tr>
<td>Mahieu-Renard and colleagues20</td>
<td>u (1)</td>
<td>Chemotherapy</td>
<td>1/1</td>
<td>24</td>
</tr>
</tbody>
</table>

CPT, immunocompetent; SUP, immunosuppressed; u, unspecified.

### TABLE 3. Diagnostic Criteria for In-Transit Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Histological criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis should lie separate from scars of previous treatment (excluding donor site for flaps)</td>
<td>Deposit should lie separate from scars of previous treatment (excluding flaps)</td>
</tr>
<tr>
<td>Metastasis should lie between the initial tumor and possible draining lymph nodes</td>
<td>Deposit should not have epidermal origin</td>
</tr>
<tr>
<td>Tumor should not be present exclusively in perineural locations</td>
<td>Tumor metastasis should bear at least focal histological similarity to initial tumor</td>
</tr>
</tbody>
</table>
SCC, appropriate investigations and treatment should be performed in a timely manner.

A limitation of this case series is its retrospective nature and the possibility of case selection bias. Prospective studies are required to overcome this bias but these may be difficult to establish for this uncommon disease. Secondly, SCC staging may be underestimated as not all tumor features were explicitly reported. Lastly, the small sample size limited the statistical power.

Diagnosis of in-transit SCC relies on clinicopathologic correlation. Immunosuppression and location on the scalp, forehead, and temple may be predisposing factors. Prognosis was poor with 5-year overall survival of 13%. However, localized disease may still be salvageable so curative treatment options should be explored. After diagnosis, investigations for regional and systemic metastases should be performed. Recommended treatment is a combination of surgery and ART. Reduction in any iatrogenic immunosuppression should be considered.

References


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