**ABSTRACT**

Patients with nasopharyngeal carcinoma may present with a normal-appearing nasopharynx (nonexophytic NPC). These patients have been reported to have higher risk of nodal and distant metastasis.

We investigated the immunohistochemical expression of E-cadherin, survivin and VEGF in 30 patients with nonexophytic NPC and compared them with 30 patients with exophytic NPC.

The majority of nonexophytic NPC patients had late stage disease (Stage I: 13.3%, II: 23.3%, III: 33.3%, IV: 30%), even though 67% had T1 disease of the nasopharynx. A significant result was obtained for cytoplasmic E-cadherin, with positive expression in 12% of nonexophytic NPC patients compared to 35.7% of exophytic NPC patients (p=0.045).

Reduced cytoplasmic E-cadherin suggests downregulation and provides a possible explanation for the higher risk of nodal and distant metastasis in nonexophytic NPC.

**INTRODUCTION**

Nasopharyngeal carcinoma (NPC) has a high incidence rate in Southeast Asia, as the 6th most common cancer among males (6.4 per 100 000). Certain populations are particularly affected, including the Singapore Chinese, Malaysian Sarawak Bidayuh, and Southern Chinese from Hong Kong and Guangdong, with Incidence rates ranging from 12.5 – 31.5 per 100 000.

Although the majority of NPC presents with an exophytic mass in the nasopharynx, some patients present with a normal-appearing nasopharynx (non-exophytic NPC). These patients present with a higher frequency of advanced lymph node and distant metastasis. However, they have similar treatment outcomes compared to patients with exophytic NPC (Loh, 2011).

We aimed to explain this phenomenon through immunohistochemical staining with the following markers:

<table>
<thead>
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<th>Marker</th>
<th>Role</th>
<th>Association with NPC</th>
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<tr>
<td>E-cadherin</td>
<td>Mediator of intercellular adhesion</td>
<td>Increased nodal metastasis (Huang, 2001)</td>
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<tr>
<td>Survivin</td>
<td>Inhibitor of apoptosis, regulation of cell proliferation and angiogenesis</td>
<td>Increased expression leads to poorer survival and increased distant metastasis. (Li, 2008)</td>
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<tr>
<td>VEGF</td>
<td>Main growth factor involved in tumor angiogenesis</td>
<td>Increased expression leads to poorer survival. (Li, 2008)</td>
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</tbody>
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**METHODS AND MATERIALS**

From 2003 to 2011, 30 patients with nonexophytic NPC were diagnosed in a single institution. Thirty patients diagnosed with exophytic NPC were selected for comparison, matched for age, gender and TNM stage.

Expressions of E-cadherin, survivin and VEGF in tumor tissues were investigated by immunohistochemistry. Expression levels were evaluated by a pathologist blinded to the clinical data, using a semiquantitative scoring scheme.

**RESULTS**

The majority of nonexophytic NPC patients had late stage disease (Stage I: 13.3%, II: 23.3%, III: 33.3%, IV: 30%), even though 67% had T1 disease of the nasopharynx.

The expression profiles for the three markers are detailed in Table 2.

A significant result was obtained for cytoplasmic E-cadherin, with positive expression in 12% of nonexophytic NPC patients compared to 35.7% of exophytic NPC patients (p=0.045, chi-square test). There was no difference in overall expression of survivin and VEGF between both groups (p=0.757 and p=0.653 respectively, Mann-Whitney U test).

**DISCUSSION**

E-cadherin levels have been found to be inversely proportional to disease progression in NPC. Furthermore, E-cadherin mRNA levels in metastatic NPC tumors are downregulated compared to primary tumors (Li, 2004).

The lack of expression of cytoplasmic E-cadherin in 88% (22 of 25) of nonexophytic NPC tumors in our study suggests a downregulation of E-cadherin, and explains the increased nodal and distant metastasis observed. Possible mechanisms include aberrant methylation of the E-cadherin gene promotor and downregulation of the cadherin-catenin complex essential for maintaining cell-cell adhesion.

Reduced expression of E-cadherin has also been shown to predict lymph node metastasis and poor outcome in other head and neck squamous cell carcinomas.

**CONCLUSIONS**

Reduced cytoplasmic E-cadherin provides a possible explanation for the high nodal and distant metastasis in nonexophytic NPC. Further studies on the E-cadherin gene promotor and the cadherin-catenin complex should be considered to explain this phenomenon.

**REFERENCES**