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What is This?
Head and Neck Mucoepidermoid Carcinoma: A Curious Association with Second Primary Malignancy

Richie Chiu-Lung Chan, MBBS, MRCS (Ed), MMedSc¹, and Jimmy Yu-Wai Chan, MS, MRCS, FCSHK¹

Abstract

Objective. We noticed that a significant proportion of our patients with head and neck mucoepidermoid carcinoma (HNMEC) had second primary malignancies. To our knowledge, such an association has never been described. The aim of our study is to elucidate the association between second primary malignancies and HNMEC.

Study Design. Case series with chart review.

Setting. Tertiary referral center.

Subjects and Methods. We included all patients with histologically proven HNMEC managed in the Department of Surgery, Queen Mary Hospital, from January 2003 through December 2013. Medical records were retrospectively reviewed and analyzed.

Results. Fifty-seven patients with HNMEC were identified. Fourteen (24.6%) had second primary malignancies. The commonest second primary malignancy was nasopharyngeal carcinoma, followed by carcinoma of the thyroid. Second primary malignancies developed before HNMEC in 7 patients, with a mean interval of 196 months. Five patients had second primary malignancies after development of HNMEC, with a mean interval of 65 months. Two patients had synchronous second primary malignancies. Clinical patterns of patients with HNMEC with and without second primary malignancies were compared. Major salivary glands were more frequently affected among patients with second primary malignancies, while minor salivary glands were more frequently affected among those without secondary primary malignancies \((P = .032)\). Development of second primary malignancy was not found to affect the survival.

Conclusion. About one-fourth of patients with HNMEC had a second primary malignancy. Major salivary glands were more frequently affected among patients with second primary malignancies. Development of second primary malignancy did not affect survival.

Keywords

MEC, HNMEC, mucoepidermoid carcinoma, second primary malignancy, second primary tumor

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Background

Salivary gland cancers account for less than 5% of all head and neck malignancies.¹ They represent a heterogeneous group of diseases, and head and neck mucoepidermoid carcinoma (HNMEC) is one of the most frequent histologic types. The commonest clinical presentation is an isolated, painless, hard, and slow-growing mass in the major salivary glands (eg, parotid glands) or in the minor salivary glands in the oral cavity. Histologic grade has been shown to be an important prognostic indicator.² Other features, such as advanced age, larger tumor size, extraparenchymal extension, presence of positive lymph nodes, and distant metastases, have also been suggested to be associated with decreased survival.²

Rather intriguingly, we noticed that a significant proportion of our patients with HNMEC had a second primary malignancy. To our knowledge, such an association has not been described or studied in the literature apart from a few case reports.³⁻⁵ Very scarce data were available in the literature regarding the association between HNMEC and second primary malignancies. Most of these studies described HNMEC as a secondary malignancy that develops years after the treatment of hematologic malignancies in the pediatric age group. However, we noticed that a significant proportion of our patients with HNMEC did not have such medical histories.

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We reviewed our experience in patients with HNMEC in an attempt to elucidate the association between second primary malignancies and HNMEC and to investigate its impact on survival.

**Methods**

A computer search was performed to identify all patients who have been treated under the Division of Head and Neck Surgery, Department of Surgery, Queen Mary Hospital, from January 2003 through December 2013 with histologically proven HNMEC. Individual records were reviewed manually and electronically to retrieve details on clinical history, presentations, investigations, pathologic results, treatment details, and survival outcome. Approval was granted by the institutional review board of the University of Hong Kong–Hospital Authority Hong Kong West Cluster before data collection.

The entire medical record of each patient was thoroughly reviewed to identify the presence of a second primary malignancy and to retrieve relevant details, including its location, chronological relationship to HNMEC, history of radiotherapy in the same field, and history of chemotherapy.

Data were analyzed with SPSS version 18.0 (SPSS, Inc, an IBM Company, Chicago, Illinois). Patient demographics and clinicopathologic details were presented.

Univariate comparisons were performed with the \( \chi^2 \) test for nominal variables and logistic regression for continuous variables. A \( P \) value of .05 or less was considered significant.

**Results**

Table 1 summarizes the demographics and clinical characteristics of the 57 patients included. The median age was 49 years (range, 17-87 years), and there was a slight female preponderance. The commonest site of the tumor was the parotid gland (47.4%), followed by the oral cavity (42.1%), oropharynx (5.3%), skin (3.5%), and submandibular gland (1.8%). Nodal metastasis (11.3%) and/or distant metastasis (1.9%) were uncommon at presentation. The mean size (largest diameter) of the tumor was 24.9 ± 17.8 mm. More than half of the tumors (54.2%) were low-grade lesions.

All but 2 of our patients (96%) underwent radical surgery with wide excision of the tumor (as described earlier). One patient was treated conservatively due to distant metastasis on presentation. Treatment detail was missing in the other patient. Neck dissection was performed in only 6 patients. Adjuvant radiotherapy was employed in 22 patients. Only 4 patients received adjuvant chemotherapy. None of our patients was treated with upfront radiotherapy.

The median follow-up time was 51.5 months (range, 2-344 months). The median overall survival was 213 months. One-year and 5-year overall survival were 89.0% and 47.8%, respectively.

During our study period, 14 (24.6%) patients had second primary malignancies with a median age of 49.5 years and a slight female preponderance. Their clinical characteristics are summarized in Table 2. The commonest second primary malignancy was nasopharyngeal carcinoma, followed by carcinoma of the thyroid. Second primary malignancies developed before HNMEC in 7 patients, with a mean interval of 196 months. Five patients had second primary malignancies after development of HNMEC, with a mean interval of 65 months. Two patients had synchronous second primary malignancies.

Clinical patterns of patients with HNMEC with and without second primary malignancies were compared (Table 3). Both groups had similar median age and female preponderance. Major salivary glands were more frequently affected among patients with second primary malignancies while minor salivary glands were more frequently affected among those without secondary primary malignancies (\( P = .032 \)). There was no significant difference in tumor size, nodal stage at presentation, distant metastasis at presentation, and tumor grades between the 2 groups of patients. Development of a second primary malignancy was not found to affect the overall survival (\( P = .058 \)) or disease-specific survival (\( P = .761 \)).

**Discussion**

The risk of developing second primary malignancies in patients with head and neck malignancies have been reported to range from 8% to 17%. In a pooled analysis of 99,257 patients from 13 cancer registries, for all cancer sites combined, the standardized incidence ratio of second primary malignancies was 1.86, and the 20-year cumulative risk was 36%. It should be noted, however, that most of these studies were based on squamous cell carcinomas of
the upper aerodigestive tracts and may not be applicable to patients with HNMEC.

Very scarce data were available in the literature regarding the association between HNMEC and second primary malignancy. Most of these studies described HNMEC as a secondary malignancy that develop years after the treatment of hematologic malignancies in the pediatric age group. A French study on HNMEC in the pediatric population reported that 11 of 18 cases (61%) had a prior second primary malignancy.3 All had been treated by radiotherapy and/or chemotherapy for a first malignant tumor. There are also case reports on the development of parotid HNMEC in patients who were previously treated for hematologic malignancies4 or heavily radiated for thyroid malignancies.5 While the high incidence of a second primary malignancy (24.6%) is concerning, the exact reason for this phenomenon remains unclear. In our cohort of patients, 7 patients developed a second primary malignancy before HNMEC. Their first malignancies were either nasopharyngeal carcinomas, hematologic malignancies, or thyroid cancers. These patients had previous exposure to ionizing radiation from radioactive iodine or external local radiotherapy, which has been suggested to increase the risk of second primary malignancies.9 Chemotherapy and other forms cytotoxic treatment may also cause second primary malignancies.3,10 However, these do not explain the remaining 7 patients who had either a synchronous second primary malignancy or a second primary malignancy that developed after HNMEC. In particular, the second tumors of all 5 patients (8.8% of the study population) who developed a second primary malignancy after HNMEC were located outside the head and neck region. None received chemotherapy for the treatment of HNMEC. Thus, cytotoxic treatments in the form of radiotherapy or chemotherapy are unlikely to be accountable for these second primary malignancies. Another possible explanation is posttreatment surveillance bias. However, even in a much larger study of thyroid cancer with 1106 patients and a 104-month median follow-up interval, the nonsynchronous second primary malignancy rate after the diagnosis of thyroid cancer was only 8.3%, and most of these patients received radioactive iodine therapy.11 Posttreatment surveillance bias alone does not explain our observed incidence of second primary malignancy in patients with HNMEC. Other possible explanations include genetic predisposition, environmental factors, and/or dietary factors. However, investigations of these factors were beyond the scope of this study.

Clinical patterns were generally similar between patients with and without second primary malignancies in our cohort of patients (Table 3). Both groups had a median age in the late 40s and a slight female preponderance. However, major salivary glands appeared to be much more frequently affected among patients with second primary malignancies

### Table 2. Clinical Characteristics of Patients with a Second Primary Malignancy (n = 14).

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age, y</th>
<th>Anatomical Location</th>
<th>Size, mm</th>
<th>Histologic Grade</th>
<th>Second Primary</th>
<th>Chronological Relationship to MEC</th>
<th>History of Radiotherapy</th>
<th>History of Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>46</td>
<td>Parotid</td>
<td>45</td>
<td>High</td>
<td>CA pancreas</td>
<td>19 mo after MEC</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>77</td>
<td>Oral cavity</td>
<td>10</td>
<td>Low</td>
<td>CA stomach</td>
<td>20 mo after MEC</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>17</td>
<td>Parotid</td>
<td>20</td>
<td>Low</td>
<td>ALL</td>
<td>156 mo before MEC</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>67</td>
<td>Oral cavity</td>
<td>60</td>
<td>High</td>
<td>NPC</td>
<td>540 mo before MEC</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>50</td>
<td>Parotid</td>
<td>8</td>
<td>Low</td>
<td>CA breast</td>
<td>48 mo after MEC</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>49</td>
<td>Submandibular</td>
<td>15</td>
<td>Low</td>
<td>Multiple myeloma</td>
<td>1 mo before MEC</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>46</td>
<td>Parotid</td>
<td>22</td>
<td>Low</td>
<td>APL</td>
<td>32 mo before MEC</td>
<td>None</td>
<td>Yes^d</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>64</td>
<td>Parotid</td>
<td>18</td>
<td>Low</td>
<td>CA thyroid^b</td>
<td>136 mo before MEC</td>
<td>Yes, dosage unknown</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>38</td>
<td>Parotid</td>
<td>UNK</td>
<td>UNK</td>
<td>CA corpus</td>
<td>197 mo after MEC</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>68</td>
<td>Oral cavity</td>
<td>30</td>
<td>Low</td>
<td>CA sigmoid</td>
<td>43 mo after MEC</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>42</td>
<td>Parotid</td>
<td>10</td>
<td>Intermediate</td>
<td>NPC</td>
<td>85 mo before MEC</td>
<td>72 Gy given</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>73</td>
<td>Skin</td>
<td>UNK</td>
<td>High</td>
<td>NPC</td>
<td>420 mo before MEC</td>
<td>66 Gy given</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>41</td>
<td>Parotid</td>
<td>20</td>
<td>Intermediate</td>
<td>CA thyroid^b</td>
<td>Synchronous</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>71</td>
<td>Parotid</td>
<td>30</td>
<td>Intermediate</td>
<td>NPC</td>
<td>Synchronous</td>
<td>Irrelevant</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic lymphoma; APL, acute promyelocytic leukemia; CA, carcinoma; MEC, mucoepidermoid carcinoma; NPC, nasopharyngeal carcinoma; UNK, unknown.

^aOnly considered relevant if radiotherapy was given between 2 malignancies; history of radiotherapy was deemed irrelevant when the 2 malignancies occurred in a different anatomical region or synchronously; no patient received radiotherapy before development of first malignancy for any other reason.

^bBoth cases were papillary carcinoma of the thyroid.

cDetails unknown.

dTretinoin, danorubicin, and idarubicin were given for APL.
(71.4% vs 41.9%), while minor salivary glands were more frequently affected among those without secondary primary malignancies (55.8% vs 21.4%; \( P = .032 \)). Tumor sizes and histologic grades were similar in both groups. Patients without second primary malignancies presented with nodal metastasis and distant metastasis slightly more frequently, although this did not reach a statistical difference. We found that the survival outcome was not affected by the presence of a second primary malignancy, in concordance to the previous findings in the literature.\(^3,4\) Nevertheless, patients with second primary malignancies did appear to have worse overall survival that approached a statistical significance level (178.8 vs 224.7 months; \( P = .058 \)). Such associations can perhaps be elucidated in future larger studies.

To our knowledge, this is the first study to investigate the association between HNMEC and a second primary malignancy. While we do not have a plausible explanation to the observation, we believe this peculiarly high frequency (24.6%) of second primary malignancy in our predominantly adult population of patients with HNMEC is noteworthy and demands further investigation.

**Conclusion**

Around one-fourth of patients with HNMEC had a second primary malignancy. Major salivary glands were more frequently affected among patients with second primary malignancies, while minor salivary glands were more frequently affected among those without secondary primary malignancies. Development of a second primary malignancy did not affect overall survival or disease-specific survival. Further studies should be carried out to investigate these observations.

**Author Contributions**

Richie Chiu-Lung Chan, conception of study design, data collection, drafting manuscript, final approval of the version to be published; Jimmy Yu-Wai Chan, conception of study design, revising manuscript, final approval of the version to be published.

**Disclosures**

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**References**


