Introduction

Despite rapid progress in the field of oncology, metastatic disease remains challenging to treat. Recently, with the advent of treatments for various types of malignancies, the concept of oligometastasis has been proposed (1). Local therapy might be curative for certain patients with distant metastases. Generally, the lung is regarded as the main organ of metastases derived from various malignancies, and pulmonary metastasectomy (PM) is performed in carefully selected patients with pulmonary-limited metastases in clinical practice (2,3). Because there are no randomized studies that have validated the survival benefit of PM, the surgical outcome of PM is controversial (4-6). The advent of systemic therapies could play a significant role in the treatment of pulmonary metastasis.

Criteria for PM were recently proposed by Kondo et al. (7). The major indications for PM are as follows: (I) the patient is a good candidate for surgical intervention; (II) the primary cancer can be controlled; (III) no other extrapulmonary metastases are present, or if present, they can be controlled by surgery or another treatment modality; and (IV) the pulmonary metastasis is considered to be completely resectable. Additional indications include (I) there is an effective systemic chemotherapy as a combined modality; (II) difficulty with the differential diagnosis from primary lung cancer; (III) no other effective treatments available other than resection; and (IV) presence of symptoms due to the pulmonary metastasis, e.g., pneumothorax or hemoptysis (7).
Characteristics of pulmonary metastasis from head and neck (HN) cancers

HN cancers include mainly oral, pharyngeal, laryngeal, and thyroid cancers. The epidemiology, biological behavior, and treatments differ depending on the anatomical site of the HN cancer. Therefore, the primary cancer site should be taken into consideration when deciding treatment for HN cancers (8). The incidence rate of distant metastasis from HN cancers is 4.2–58.8% and that of HN squamous cell carcinoma 1.5–16.8% (9). Patients with metastasized HN cancers are considered to have an extremely poor prognosis.

According to the site of metastasis from head HN cancers, the lung is the most common (66%), followed by bone (22%) and liver (10%) (10). A nationwide database study showed that 53.1% of distant metastases from HN cancers develop in the lung (11). On the other hand, previous studies on pulmonary metastasis from HN malignancies had a small number of objectives (10,12-21). Due to the insufficient data, the value of PM for pulmonary metastasis from HN cancer has not been clarified. The National Comprehensive Cancer Network guidelines, version 2.2019, which do not specifically address treatment of pulmonary metastasis, proposed the following: surgery, radiotherapy, or systemic therapy with or without radiotherapy is recommended for patients who have only distant metastasis and a performance status of 0 or 1 (8). Therefore, PM may be an optional treatment for select patients with pulmonary metastases (8).

Because the knowledge on PM for pulmonary metastasis from HN cancers is insufficient and the optimal management of this disease unclear, the aim of this review is to summarize the published studies on, and assess the role of PM for, pulmonary metastasis from HN cancers.

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication year</th>
<th>Pulmonary metastasectomy</th>
<th>N</th>
<th>Overall survival</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter* (10)</td>
<td>2008</td>
<td>(+)</td>
<td>67</td>
<td>20.9% (5 years)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(-)</td>
<td>67</td>
<td>6.0% (5 years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miyazaki (19)</td>
<td>2013</td>
<td>(+)</td>
<td>24</td>
<td>90.0% (1 year)</td>
<td>0.01</td>
</tr>
<tr>
<td>(-)</td>
<td>45</td>
<td>35.0% (1 year)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*, patients with versus without pulmonary metastasectomy were compared using matched pair analysis.

Outcomes of patients with pulmonary metastasis from HN cancer after PM

Patients with pulmonary metastasis from HN cancer who underwent PM have a better prognosis than those who did not. Table 1 shows overall survival data from two studies that compared patients with pulmonary metastasis who underwent PM and those who did not. Although the results should be interpreted cautiously due to selection bias, the patients who underwent PM had a better prognosis (10,19). The median overall survival was 19.4 months for the patients who underwent PM versus only 5.0 months for the patients who did not undergo PM (10).

Previous studies of PM for pulmonary metastasis from HN cancers showed the outcomes after PM. Published studies on the survival and prognostic factors of patients with pulmonary metastasis from HN cancers treated with PM since 1999 are summarized in Table 2. The 5-year overall survival rate after PM in those studies was 20.9–59.4% (10,12-21). Regarding the factors predicting a worse prognosis after PM, incomplete resection was associated with poor survival of patients with pulmonary metastasis from HN cancers (10,11,17), suggesting that complete resection during PM is essential for curative treatment. Some of the studies showed that a short disease-free interval (DFI) also predicted a worse prognosis in patients with pulmonary metastasis from HN cancers after PM (11,15,18-21); in addition, other studies showed a shorter DFI after PM from other primary sites (2,3). However, as the patients who receive PM are often highly selected patients, it is possible that patients with a shorter DFI were excluded from those studies. Furthermore, patients with slowly growing tumors tend to have longer DFIs, potentially leading to longer survival times, and the
follow-up duration and modalities used for postoperative monitoring are additional factors that influence the DFI. Therefore, the role of the DFI as a prognostic factor might be controversial. The histology of HN cancers can also affect patient survival, with pulmonary metastasis from HN squamous cell carcinoma considered to predict a worse prognosis (15-18,20,21). Especially, overall survival after PM for pulmonary metastasis from oral floor (17) and tongue (18,22) primary sites were much worse compared with other primary sites. Based on those studies, the indications for PM treatment of pulmonary metastasis from oral floor and tongue cancers might be controversial. Lu et al. showed that the 2-year survival rates after PM for adenoid cystic, thyroid, nasopharyngeal, and HN squamous cell carcinomas were 100%, 88.2%, 71.4%, and 59.2%, respectively (23). A study of PM for pulmonary metastasis from adenoid cystic carcinomas reported a 5-year overall survival rate of 84% (14). Despite the small number of studies (n=14), the prognosis of resected pulmonary metastasis from adenoid cystic carcinomas might be promising.

In addition to curative resection, DFI, and histology, older age (11,16,20), male sex (15,17), and recurrence before PM (19,21) have been reported as prognostic factors after PM in patients with pulmonary metastasis from HN cancers. However, those studies were retrospective evaluations of select patient populations, and the patients in those studies had various types of HN cancers, which have different biological behaviors. Moreover, almost all were single-center studies with long study periods.

### Chemotherapy for pulmonary metastasis from HN cancers

Systemic therapy is recommended for metastatic HN cancers (8). Compared with platinum-based chemotherapy plus fluorouracil alone, cetuximab plus platinum-fluorouracil chemotherapy improved overall survival when given as a first-line treatment to patients with recurrent or metastatic HN squamous cell carcinoma (24). As HN cancers often express the epidermal growth factor receptor (EGFR), and expression of EGFR is associated with a poor outcome, cetuximab plus platinum–fluorouracil chemotherapy might improve the overall survival of patients with recurrent or metastatic HN squamous cell carcinoma (24).

Nivolumab, which is an anti-programmed death 1 monoclonal antibody, is a promising treatment for advanced diseases, and it resulted in a longer overall survival compared with standard single-agent therapy in patients with recurrent HN carcinoma (25). Using immune checkpoint inhibitors could drastically change the treatment strategy for metastatic HN cancers.

Many clinical trials to study the efficacy of neoadjuvant

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Table 2: Studies published since 1999 on survival and prognostic factors after pulmonary metastasectomy for pulmonary metastasis from head and neck cancers

<table>
<thead>
<tr>
<th>First author</th>
<th>Publication year</th>
<th>Study period</th>
<th>N</th>
<th>5-year survival</th>
<th>Factors predicting a worse prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu (14)</td>
<td>1999</td>
<td>1966–1995</td>
<td>83</td>
<td>50.0%</td>
<td>Age &gt;50 years, DFI ≤24 months, incomplete resection</td>
</tr>
<tr>
<td>Winter (10)</td>
<td>2008</td>
<td>1984–2006</td>
<td>67</td>
<td>20.9%</td>
<td>Incomplete resection, postoperative complications, adjuvant therapy for primary tumor</td>
</tr>
<tr>
<td>Chen (15)</td>
<td>2008</td>
<td>1991–2007</td>
<td>20</td>
<td>59.4%</td>
<td>Male, Sq, DFI &lt;1 year</td>
</tr>
<tr>
<td>Haro* (16)</td>
<td>2010</td>
<td>1981–2008</td>
<td>25</td>
<td>50.0%</td>
<td>Age ≥60 years, Sq (oral cavity, pharynx)</td>
</tr>
<tr>
<td>Shiono (17)</td>
<td>2009</td>
<td>1980–2006</td>
<td>114</td>
<td>26.5%</td>
<td>Male, Sq, oral cavity cancer, lymph node metastasis, incomplete resection</td>
</tr>
<tr>
<td>Daiko (18)</td>
<td>2010</td>
<td>1992–2006</td>
<td>33</td>
<td>43.0% (3-year survival)</td>
<td>DFI ≤2 years, Sq, tongue primary</td>
</tr>
<tr>
<td>Miyazaki (19)</td>
<td>2013</td>
<td>1999–2009</td>
<td>24</td>
<td>68.0% (3-year survival)</td>
<td>DFI ≤21.4 months, recurrence before surgery</td>
</tr>
<tr>
<td>Yotsukura (20)</td>
<td>2015</td>
<td>1986–2013</td>
<td>34</td>
<td>57.9%</td>
<td>Age, Sq, DFI ≤26 months</td>
</tr>
<tr>
<td>Oki (21)</td>
<td>2019</td>
<td>1992–2013</td>
<td>77</td>
<td>54.0%</td>
<td>DFI &lt;18 months, Sq, recurrence before surgery, tumor size &gt;2.5 cm</td>
</tr>
</tbody>
</table>

* This study included thyroid cancer as a primary site. Sq, squamous cell carcinoma; DFI, disease-free interval; NA, not available.
therapy for HN cancers are ongoing. PD-L1 positivity, high tumor mutation burden, and infiltration of NK cells, CD8, CD26 and Tim3 positive lymphocytes are considered to be related with response to the treatment (26). Neoadjuvant therapy will become the promising treatment for metastatic HN cancers.

**Diagnosis of pulmonary metastasis from HN cancers**

The clinical and morphological diagnoses of pulmonary metastasis from HN cancers are often difficult. If the preoperative radiological diagnosis is lung cancer, a definitive diagnosis of pulmonary metastasis from HN cancers might not be obtained by pathological evaluation alone. The criteria for diagnosis of pulmonary metastasis from HN cancers used by Winter et al. were a history of advanced-stage HN cancer, peripheral tumor location, multiple lesions, and a DFI of <36 months (10). However, these criteria are considered arbitrary.

Smoking is a common risk factor for laryngeal and lung cancer. The relative risk of lung cancer developing in patients with a history of HN squamous cell carcinoma is three to six times higher than that in a healthy population (27). In addition, the pathological findings are similar between pulmonary metastasis from HN cancers and primary squamous cell lung cancer. A reliable method for differential diagnosis of pulmonary metastasis from primary squamous cell carcinoma of lung cancer is being explored.

Ichinose et al. showed the usefulness of a diagnostic algorithm based on immunohistochemical patterns for differentiating between pulmonary metastasis derived from HN squamous cell carcinoma and primary squamous cell lung cancer (28). Immunochemistry using three types of antibodies (CK19, MMP3, and P13) showed a sensitivity of 96%, specificity of 44%, and accuracy of 65% for diagnosing pulmonary metastasis, suggesting that immunohistochemistry is a promising diagnostic method (29). Because of the higher prevalence of well-differentiated tumors among HN squamous cell carcinoma cases, Ichinose et al. suggested that the degree of cell differentiation also helps differentiate HN squamous cell carcinoma from lung squamous cell carcinoma. Geurts et al. differentially diagnosed HN squamous cell carcinoma from primary lung cancer using a loss of heterozygosity (LOH) analysis (29). In their study, survival after PM for HN squamous cell carcinoma was similar to that after lung resection for metachronous primary squamous cell lung cancer (29).

However, given the cost and time, LOH analysis is not a realistic approach for differential diagnosis. For molecular diagnosis, sufficient specimens should be obtained preoperatively by needle or transbronchial biopsy. Since pulmonary metastatic lesions tend to be small on computed tomography, it is questionable whether this technique can be put to practical use. More rapid and reliable diagnostic methods are needed in daily clinical practice.

**Surgical strategy for pulmonary metastasis from HN cancers**

Due to the difficulty with pathological diagnosis, preoperative definitive diagnosis is challenging. Radiological diagnostic methods can be used to differentiate pulmonary metastases from primary lung cancers, as pulmonary metastases tend to comprise multiple lesions with a round shape and smooth surface; however, not all such lesions have the same characteristics. According to the indications for PM proposed by Kondo et al., PM is warranted for differential diagnosis of primary lung cancers in some cases (7).

A key question is which patients with a history of HN cancer will benefit from PM. According to previous studies, patients with a DFI >2 years, non-oral cancer, and resectable pulmonary metastasis are good candidates for PM. Because the 5-year overall survival after PM is approximately 30–40%, PM is a treatment option for certain patient populations.

In conclusion, pulmonary metastasis from HN cancers is a common type of metastatic HN cancer. A histology of squamous cell carcinoma, incomplete resection, a short DFI, and the oral cancer have been identified as factors predicting worse survival of patients with pulmonary metastasis from HN cancers. Considering the difficulties associated with preoperative differential diagnosis of pulmonary metastases from primary lung cancers, performing PM is warranted to determine the diagnosis and achieve complete resection. Novel chemotherapeutic and other treatments for metastatic HN cancers will improve the survival of this patient population.

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**Footnote**

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declare.

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**References**