

Narrative review on minimally invasive metastasectomy for head and neck malignancies

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Background and Objective: Head and neck cancer (HNC) is the 7th most common malignancy globally, with the lungs being the most common site of distant metastases. Pulmonary metastasectomy (PM) has traditionally been performed using open techniques. Since the advent of thoracoscopy, these procedures have increasingly been performed using minimally invasive techniques. We review available evidence on outcomes of PM for HNC, with a focus on minimally invasive PM.

Methods: A PubMed search was performed using the search combination: metastasectomy, metastases, head cancer, head carcinoma, neck cancer, and neck carcinoma. All relevant articles published between the years 2000 and 2023 were identified. Case reports, reviews, and articles lacking relevance to the study were excluded. A total of 15 original articles were selected for this narrative review.

Key Content and Findings: PM for HNC confers a survival benefit when compared to non-surgical treatment in carefully selected patients. The favorable prognostic factors for PM include a disease-free interval (DFI) >12 months, female sex, non-squamous cell cancer (SCC) histology, younger age, R0 resection, and an extra-oral site for the primary HNC. Currently, minimally invasive options for PM seem to be associated with superior short and similar long-term outcomes to thoracotomy.

Conclusions: PM is associated with favorable survival outcomes for metastatic HNC when compared to non-operative therapy. Minimally invasive PM seems to be a safe and feasible option for PM with superior short and similar long-term outcomes to conventional open PM.

Keywords: Pulmonary metastasectomy (PM); head and neck cancer (HNC); thoracoscopy; minimally invasive

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Introduction

Background

Head and neck cancer (HNC) is the 7th most common malignancy globally and carries a significant morbidity and mortality burden (1). The lungs are the most common site of distant metastases for HNC (2,3). Pulmonary metastasectomy (PM) is commonly performed for the

management of metastatic HNC to the lungs in carefully selected patients.

Rationale and knowledge gap

PM has traditionally been performed using open surgical techniques. However, with the advent of minimally invasive techniques, thoracic surgeons have increasingly performed

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Table 1 The search strategy summary

Items	Specification
Date of search	09/15/2023 to 03/01/2024
Databases searched	PubMed
Search terms used	(Head and neck cancer AND pulmonary metastasectomy) OR (metastatic head and neck cancer and pulmonary resection) OR (thoracoscopic, thoracotomy, metastasectomy, survival)
Timeframe	2000–2023
Inclusion criteria	Retrospective studies, search limited to articles published in English language
Selection process	The study authors, A.C.S., R.M., and A.B., independently reviewed all articles identified following the initial query, and subsequently collectively selected relevant papers for inclusion in this study

these procedures using thoracoscopic techniques. The outcomes of PM for metastatic HNCs using minimally invasive techniques as compared to conventional thoracotomy are yet to be established.

Objectives

The aim of this paper is to review available evidence on outcomes of PM for HNC. Furthermore, we sought to appraise outcomes of minimally invasive as compared to open PM in this patient population. We present this article in accordance with the Narrative Review reporting checklist (available at <https://vats.amegroups.com/article/view/10.21037/vats-23-66/rc>).

Methods

A PubMed search was performed using the search combination: (head and neck cancer AND pulmonary metastasectomy) OR (metastatic head and neck cancer and pulmonary resection) OR (thoracoscopic, thoracotomy, metastasectomy, survival). The database was queried to identify all articles published in English language between the years 2000 and 2023. This search yielded a total of 784 articles. Case reports, reviews, and articles lacking relevance to the study were excluded. The study authors, A.C.S., R.M., and A.B., independently reviewed all articles identified following the initial query, and subsequently collectively selected relevant papers for inclusion in this study. A total of 12 original manuscripts were used in writing this narrative review. See *Table 1* for further information.

Discussion

Oncologic principles of PM

The current oncologic criteria for PM are: (I) the primary cancer needs to be controlled or controllable; (II) the absence of extrathoracic metastasis that is not controlled or controllable; (III) all of the tumor must be resectable with adequate pulmonary reserve; and (IV) an absence of alternative medical treatment options with lower morbidity (4). For PM, the necessity of achieving microscopically negative resection margins (R0) guides the extent of resection. The optimal technique allows for parenchymal sparing with a lobectomy occasionally being indicated. A pneumonectomy is hardly ever appropriate, and is questionable as a surgical option for patients with pulmonary metastases.

A high proportion of patients with pulmonary metastases also have metastases to extrathoracic sites. Previous reports have estimated that only 15–25% of patients with pulmonary metastases have lesions confined to the lungs and meet criteria for metastasectomy, highlighting the importance of appropriate staging using standard modalities to identify extrathoracic disease prior to consideration of PM (4).

Epidemiology of HNCs

HNC is the 7th most common cancer globally and accounts for over 660,000 new cases and 325,000 deaths annually (1). Approximately 90% of HNCs are head and neck squamous cell cancers (HNSCCs) that arise from the epithelial lining of the oral cavity, pharynx, and larynx (1). HNSCC is

predominantly a loco-regional disease, but distant metastasis is a major determinant of management and prognosis. The incidence of distant metastases at presentation for HNSCC is relatively low when compared to other malignancies (2). Using the Surveillance, Epidemiology, and End Results (SEER) database, Kuperman *et al.* reported a 2.8% prevalence of distant metastasis at presentation in the largest published series of 73,247 HNSCC patients (3). The lungs are the most common site of distant metastases for HNSCC, with a frequency of 70–85% in most series (2,3).

Other less common histologic types of HNCs include malignant salivary gland tumors (MSGTs), melanoma of the head and neck, lymphoma of the head and neck, sinonasal adenocarcinoma, sinonasal neuroendocrine carcinoma (SNEC), and sinonasal undifferentiated carcinoma (SNUC). The most common histologic subtypes of MSGT are adenoid cystic carcinoma, acinic cell carcinoma, and mucoepidermoid carcinoma. Similar to HNSCC, the lungs are the most common site of distant metastases for MSGT (5).

Outcomes of PM for head and neck malignancies

Metastatic HNCs have historically been treated with systemic therapy, radiation therapy, or PM. Contrary to metastatic breast and colon cancer, only few reports have studied the clinical outcomes of PM in HNC patients. Current available data are largely from case series and retrospective studies with a lot of heterogeneity. Another challenge is the difficulty in differentiating between primary SCC of the lung and lung metastasis from a HNSCC using standard clinical and histopathologic techniques. Although, loss of heterozygosity analysis and microRNA profiling have been used to differentiate primary lung SCC and metastases, there is currently no gold standard histologic technique for differentiation.

Shiono *et al.*, in a retrospective review of 114 patients with HNSCC that underwent PM, reported a post-resection 5-year overall survival of 26.5%. Some predictors of poor outcomes were male sex, oral cavity cancers, lymph node metastasis, disease-free interval (DFI) of 24 months or less, and an incomplete resection (6). Similarly, Chen *et al.* published a retrospective study on a cohort of 20 patients that underwent PM for mixed histology HNC pulmonary metastases. The overall survival at 5 and 10 years were 59.4% and 47.5%, respectively. A DFI ≥ 12 months rendered a favorable prognosis ($P=0.02$ for overall survival), while SCC histology and male sex were negative predictors

of survival (7).

In another retrospective review of 33 patients that underwent resection of pulmonary tumors from metastatic HNC, the overall 1- and 3-year survival rates were 76% and 43%, respectively. On univariate analysis, a DFI ≤ 2 years, tongue carcinoma, and SCC histology adversely affected survival. On multivariable analysis, tongue carcinoma was found to most strongly affect survival, and the most frequent pattern of initial recurrence after pulmonary resection was distant metastasis (64%) (8). Haro and colleagues retrospectively reviewed 25 patients with malignant HNC who underwent PM over a period of 27 years in a single institution and found that the 3- and 5-year survival rates after a metastasectomy were 53.3% and 50.0%, respectively. In their study, age >60 years ($P=0.019$) and pulmonary metastases from SCC of the oral cavity or pharynx ($P=0.0002$) were identified as adverse prognostic factors. All patients with SCC of the oral cavity or pharynx died within 2 years of PM (9).

These studies all demonstrate differences in survival outcomes after PM based on the underlying histology of the primary tumor, with SCC demonstrating worse outcomes compared to non-SCC histologies. Although there is the possibility that the lower observed survival with metastatic HNSCC in the above reports may actually be related to misdiagnoses of primary SCC of the lung.

In patients with lung metastases from extrathoracic sites, intrathoracic lymph node involvement is a poor prognostic factor. In the past, thoracic surgeons had rarely performed lymphadenectomy for metastatic disease. More recently, there seems to be a change in practice patterns towards lymphadenectomy in the setting of metastatic disease as reflected in a recent European Society of Thoracic Surgeons (ESTS) report (10). Although there is no evidence that mediastinal lymphadenectomy renders a therapeutic effect, expert consensus guidelines recommend that lymph node sampling/dissection be considered at the time of PM (11).

Regarding radiation therapy, stereotactic ablative radiotherapy (SABR) has been increasingly performed for metastatic HNC, particularly for patients with extensive comorbidities that preclude surgery. A recent study reported comparable short-term survival outcomes to PM after SABR for patients with metastatic HNC (12). Others have reported superior survival outcomes with PM when compared to chemoradiation and radiation (13). However, there are no prospective studies that compare both modalities in patients with metastatic HNC.

Platinum-based chemotherapy remains the backbone of

Table 2 Survival outcomes after PM for HNC and prognostic factors

Author (reference)	Study design	Year of publication	Number of patients	5-year survival (%)	Negative prognostic factors
Shiono <i>et al.</i> (6)	Retrospective	2009	114	26.5	Male sex; oral cavity cancers; LN metastasis; incomplete resection
Chen <i>et al.</i> (7)	Retrospective	2008	20	59.4	DFI <12 months; SCC; male sex
Daiko <i>et al.</i> (8)	Retrospective	2010	33	NA	Tongue carcinoma
Haro <i>et al.</i> (9)	Retrospective	2010	25	50	Age >60 years; SCC of oral cavity or pharynx
Schlachtenberger <i>et al.</i> (13)	Retrospective	2022	33	53.4	None
Winter <i>et al.</i> (17)	Retrospective	2008	67	20.9	Incomplete resection; peri-operative complications; adjuvant therapy of the primary tumor
Miyazaki <i>et al.</i> (18)	Retrospective	2013	24	NA	Recurrence of primary ahead of lung metastasis; DFI \leq 21.4 months
Dudek <i>et al.</i> (19)	Retrospective	2021	44	41	Larger tumor size >1.4 cm
Alshammari <i>et al.</i> (20)	Retrospective	2020	56	71.7	Histologic subtype

PM, pulmonary metastasectomy; HNC, head and neck cancer; LN, lymph node; DFI, disease-free interval; SCC, squamous cell cancer; NA, not available.

chemotherapeutic treatment for recurrent disease with the addition of immunotherapy or monoclonal antibodies (14). With the recent success of KEYNOTE-048, there has been a shift in treatment of HNSCC and recurrent HNSCC towards programmed death 1 inhibitors (15,16). Even with advances in non-operative management of recurrent and metastatic disease, there have been minimal investigations into the outcomes of PM to chemoimmunotherapy.

Only two reports have comparatively assessed the outcomes of PM to chemotherapy. Winter *et al.* performed a matched-pair analysis that compared patients undergoing PM to conservative management for metastatic HNC. In this study, a total of 80 patients underwent surgery but only 67 of them were histologically confirmed to be HNC metastases. The median overall survival after PM was longer when compared to non-operative management (19.4 *vs.* 5.0 months, $P < 0.001$). On multivariable analysis, incomplete resection of the pulmonary lesions, postoperative complications, and adjuvant therapy of the primary tumor were independently associated with worse survival. Multiple or bilateral pulmonary metastases, when resectable, did not seem to negatively impact survival (17).

In another retrospective study on 69 patients with metastatic HNC to the lungs, 24 patients in their cohort underwent PM and 45 were treated with chemotherapy

and supportive care. Overall, the PM group experienced an improvement in survival when compared to the non-surgical group (1-year survival: 90% *vs.* 35% and 3-year survival: 67% *vs.* 15%, respectively). Compared to other histologies, SCC histology negatively impacted survival (1-year survival: 47% *vs.* 91% and 3-year survival: 17% *vs.* 82%, respectively). In the PM group, a local recurrence of the primary tumor ahead of lung metastasis ($P = 0.006$) and a DFI ≤ 21.4 months; ($P = 0.046$) were significant negative prognostic factors on univariate analysis, but no independent prognostic factors were identified on multivariable analysis (Table 2) (18).

Despite the obvious limitations, available data suggest that PM results in significantly better survival when compared to chemotherapy. Furthermore, due to the difficult preoperative differentiation between primary lung cancer and pulmonary metastases resection is warranted. In addition, favorable prognostic factors for PM include: a DFI >12 months, female sex, non-SCC histology, younger age, complete resection (R0), and extra-oral site of the primary HNC.

Outcomes of minimally invasive PM for HNCs

Prior practice patterns for the intervention of pulmonary metastases were highly variable, but PM was traditionally

performed using open surgical technique due to the advantage of bimanual palpation (21,22). With the improvements in preoperative imaging, there is less of a need for palpation to identify smaller nodules. It is well documented throughout the literature that sublobar resection is an acceptable approach to PM. Sublobar resection through a minimally invasive approach such as video-assisted or robotic-assisted thoracoscopic surgery is extensively performed.

Mutsaerts *et al.* showed in 2002 that thoracoscopic resection of solitary peripherally located nodules is safe with long-term outcomes comparable to thoracotomy (23). Additionally, a review of retrospective data by Greenwood *et al.* in 2013, concluded that in comparison to open surgery, thoracoscopic resections were associated with better short-term outcomes—shorter hospital stay, shorter chest drainage duration, and fewer perioperative complications (24). Furthermore, there were no survival differences identified with either approach (24). In reference to satisfaction, Numan *et al.* concluded that VATS is the preferable approach for pulmonary metastasis due to superior quality of life and functional outcomes (25).

In regards to HNC specifically, there is limited data comparing outcomes between approaches. Dudek *et al.* explored factors influencing 5-year survival among 44 patients undergoing PM for HNC. Thoracotomy was the more common approach (79.5%). The authors found no statistical difference in overall survival based on surgical approach (19). Another study by Schlachtenberger *et al.* showed that of 33 patients undergoing PM for metastatic HNC, 73.4% underwent VATS wedge resection, 9.5% underwent open segmentectomy, and 17.1% underwent open lobectomy. Two of the VATS cases were converted to thoracotomy for dense adhesions. All patients had an R0 resection and the 5-year overall survival was 53.4% for patients. No direct comparisons were made based on surgical approach. However, all patients treated with PM had superior 1-, 3-, and 5-year survival rates than those who were managed non-operatively with chemotherapy, chemoradiation, or radiation therapy (13).

In the retrospective study by Winter *et al.* in 2008, 81 PM were performed between 1984 and 2006. Eighty-five percent of patients underwent thoracotomies and 15% had thoracoscopic pulmonary resections. They reported an 80% complete resection rate with thoracotomy but did not evaluate for this outcome in the thoracoscopy group. Overall, their data suggested that an incomplete resection was a negative prognostic factor for survival (17).

More recently, a retrospective analysis by AlShammari and colleagues evaluated the effectiveness of PM. They examined 56 patients that underwent PM over a 16-year period from 2000 until 2016. In terms of surgical approach, there were 43 thoracotomies, 12 thorascopies, and a sternotomy with all patients successfully having an R0 resection. Interestingly, sublobar pulmonary resections were most performed despite the relatively large number of thoracotomies. Their outcomes and conclusions support the currently reported literature (20).

The role of segmentectomies in the management of PM is another area of research interest. Since the goals of PM are to accomplish a complete (R0) resection while preserving as much pulmonary function as possible in the event of a need for future resections for metachronous tumors, segmentectomies should be considered the first option for patients with tumors that are not amenable to wedge resection. There is also extensive evidence to suggest that segmentectomies can be performed safely with acceptably low morbidity and mortality (26). Awake, non-intubated thoracoscopic techniques have been used to perform complex pulmonary resections with comparable outcomes to intubated VATS (27). The widespread adoption of these techniques for procedures such as PM would require careful patient selection, surgical planning, and close collaboration between the surgical and anesthesia teams.

Other relevant studies on PM in patients with metastatic HNC failed to specify their surgical approach. In addition, due to the low incidence of surgically resectable metastatic HNC, the available evidence is based solely on retrospective reports. Despite these limitations, it is prudent to assume that the universal principles that seem to drive favorable outcomes for PM performed via thoracotomy in HNC patients would apply to minimally invasive surgery. When feasible, we advocate for performing PM utilizing minimally invasive approaches in the setting of a DFI exceeding 12 months and the ability to obtain an R0 resection.

Conclusions

The lungs are the most common site of distant metastases for HNC. PM is associated with a survival benefit when compared to non-surgical treatment in carefully selected patients. The favorable prognostic factors for PM in this patient population include a DFI >12 months, female sex, non-SCC histology, younger age, R0 resection, and an extra-oral site for the primary HNC. Currently, minimally invasive options for PM seem to confer superior short and

similar long-term outcomes to thoracotomy.

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Footnote

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