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Research Article

How Can We Best Manage Patients With Oligometastatic Disease In Head And Neck Cancer?

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Abstract:

Background: Oligometastatic disease in head and neck cancer is a new entity that is beginning to gather significant attention. It is a concept that is defined as <5 lesions with control of the primary lesion.

Methods: In this paper, we explore the literature for the presentation and management of patients presenting with oligometastatic disease in the head and neck from non-head and neck primaries.

Results: The most common infraclavicular primary tumours to metastasise to the head and neck are breast, lung and renal carcinomas. Management of these oligometastatic lesions is currently very variable and surgery and/or ablative therapies can in fact be associated with good survival outcomes or locoregional control compared to patients with widespread metastatic disease.

Conclusion: The recommendations in this paper will help towards establishing clear guidelines in the future for surgical and ablative therapies for these patients.

Key Words: head and neck neoplasms, neoplasm metastasis

Introduction:

Oligometastasis was a term first proposed by Hellman and Weichselbaum in 1995 to identify a group of patients with limited 'few' metastatic deposits (1). They attempted to broadly fit this group of patients in between those with localised lesions, with potentially good prognosis, and those with widespread metastatic disease, with typically very poor prognosis. Over time, this definition has been debated and refined, and the current generally accepted definition of oligometastatic disease refers to <5 lesions with control of the primary lesion (2).

The importance of this concept, and why its treatment has generated significant research recently, is because of the potentially curative intent of malignancy for this group of patients. Traditionally, patients with metastatic disease are associated with poor prognosis and have treatment options limited to systemic chemotherapy and molecular targeted therapy to improve or prolong quality of life. It has been shown that metastatic disease burden is negatively correlated to prognosis in many cancers (3, 4), so it stands to reason that patients with oligometastases have better survival outcomes compared to patients with widely-disseminated metastatic disease. Research has focused on both detection and treatment modalities for these patients. Detection modalities including CT, MRI, PET-CT and bone scintigraphy scans have been explored in relation to timing, detection rates and histological subtypes (5). Treatment modalities have centred on locally ablative therapies such as stereotactic body radiotherapy and radiofrequency ablation (6) to curative surgical resections. This shift in thinking has allowed patients to greatly benefit, but has also given clinicians a potential new problem with new treatment options without robust guidelines present.

Biological basis of Oligometastases:

Before we explore the potential benefits of treatment an individual with oligometastatic disease, it is important to explore the biology behind its development. Cancer development and pathogenicity had always been thought of in a traditional 'seed and soil' hypothesis (7) whereby 2 distinct states existed at time of diagnosis. The patient either had localised disease, or systemic disease with positive lymph nodes and a high probability of metastasis. These two groups of patients were seen as entirely distinct entities, with different treatment options offered and subsequent survival

outcomes. It wasn't until the aforementioned Hellman and Weichselbaum proposed their oligometastatic theory that the progression of cancer was thought to be multi-stepped. It was proposed that a cancer's full metastatic potential hadn't been reached yet, but was limited to certain receptive sites of the body. Four factors have been found to favour an oligometastatic state over a widespread polymetastatic state: (5)

1. *A long time interval between the surgical removal/treatment of the primary tumour and the appearance of a single metastasis.*
2. *A single metastasis that is slow growing with a large difference in volume between it and any others.*
3. *A single metastasis in the presence of a larger primary tumour*
4. *Chemotherapy that has wiped out effectively any micrometastatic burden.*

Additionally, microRNA sampling and detection has identified certain clustered microRNA patterns in patients with polymetastatic disease compared to oligometastatic disease. For example, in breast cancer, clusters of miR-200c were found in the metastatic population, and subsequently in mouse models this was able to convert oligometastatic models to polymetastatic models. (8) There is sufficient evidence to class oligometastatic disease as a separate entity from metastatic disease both on a genomic and a phenotypic level. As such, further research and a better understanding of the molecular and biological frameworks involved in oligometastatic disease development and progression is needed to allow more evolved and robust treatment options to be developed.

Oligometastatic disease in other cancers:

Colorectal, prostate, lung, renal, sarcoma and renal cancers have all been found to predispose to an oligometastatic state. Radiotherapy and surgical managements remain the primary focus of research for treatment options for these patients. Metastasectomy is a procedure that involves surgical resection of isolated metastases, and is one that been increasing in incidence and in efficacy over the last 2 decades. (9) Colorectal, lung, breast cancer and melanoma are the most common indications for metastasectomy. Resection of colorectal liver metastases is well known and has led to increased long-term survival benefit in these patients, with 5-year survival rates up to 50% and 3-year local recurrence free survival rates up to 95% (10). Additionally, pulmonary metastasectomy has been increasing in practice over the last decade, and colorectal metastases in the lung remain its primary indication. However, despite its widespread use there remains a lack of sufficient evidence advocating its benefits. Its use is based on retrospective case series and follow-up studies (11). Of note, there has only been one randomised controlled trial, PulMiCC (12), but this was stopped due to low recruitment. However, it did report an increased estimated survival of 9% over the control group. Evidence-based surgical practice appears not to have been as thorough with this particular group of patients, perhaps due to the fact that these oligometastatic patients would traditionally have been given palliation treatments rather than those aiming for locoregional control. Thomford et al (13) first proposed the Thomford criteria for selecting metastatic patients to undergo surgical treatment, and over the years it has been refined. The generally accepted consensus, for patients with pulmonary metastases at least is: i) controlled primary tumour ii) no extrapulmonary lesions. By extension, these fit the criteria for oligometastatic patients, and significant research on surgical resections need to be explored both in multiple other primary cancers and in resections in other locations.

Radiotherapy has largely focused on localised ablation therapies for oligometastatic patients. One of these methods is stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), which involves using external beam radiotherapy to target sites with high-dose radiation while sparing the surrounding healthy tissue. Again, use of this has largely focused on colorectal cancers, with retrospective studies showing a 2-year local control rate of greater than 80% for liver metastases in colorectal cancer (10), without the morbidity associated with surgery. In breast cancer, 2-year progression free survival and 2-year local control rates of 97% have been achieved in SBRT trials with oligometastatic patients. (8) In lung cancer, many phase II and III RCTs are currently in progress exploring a combination of metastasectomy vs SBRT vs systemic therapy (14). Some of these trials have already been stopped or modified for showing a significant improvement in progression-free survival in SBRT over systemic therapy in oligometastatic patients. Clearly, this field of therapy hold significant interest and could lead to many solid evidence-based recommendations for the treatment of oligometastatic patients based on site and primary tumour.

Oligometastatic disease in Head and Neck cancers:

Within head and neck cancer, research into oligometastatic disease has remained fairly less extensive than some of the cancers discussed above. Cancers of this group are comprised of many different tumours within the head and neck region, with the most common being of these five subtypes:

1. Laryngeal and hypopharyngeal cancers
2. Nasal cavity and paranasal sinus cancers
3. Nasopharyngeal cancers
4. Oral and oropharyngeal cancers
5. Salivary gland cancers.

Of these, the most predominant histology is squamous cell carcinomas (SCCHN). It is the sixth most common malignancy in the world, and up to 40% of patients may have metastases during their surveillance (15, 16). Analysis of the national cancer database revealed that metastatic patients who received both systemic therapy and high-intensity local therapy had a 13% improvement in 2-year survival over those with systemic therapy alone (17). Similarly, a retrospective study in Germany revealed a significant survival benefit in oligometastatic patients who received local therapy over those matched controls who didn't, irrespective of site of the metastases (18). Regarding metastasectomy, in HNSCC patient, pulmonary resection for limited lung metastatic has yielded 5-year survival rates of 59%, which is similar to those with non-metastatic disease (19). A recent RCT called SABR-COMET (SABR Therapy for the comprehensive treatment of oligometastatic tumours) (20) evaluated the use of SABR/SBRT on oligometastatic patients, including HNSCC patients. The HNSCC cohort reported a 5-year survival overall survival of 42%, which is significantly higher than those undergoing no treatment and similar to those undergoing metastasectomy.

Despite these promising signs, the retrospective nature of these studies needs to be taken into context, and more data from RCTs and clinical trials will provide stronger evidence to guide future management. In particular the heterogenic nature of head and neck cancers will make this difficult, and a deeper analysis into each subtype is required.

Oligometastatic disease to the head and neck:

Metastatic disease to the head and neck from non-head and neck primaries is infrequent. Less than 1% of all head and neck cancers has been estimated to be attributable to infraclavicular primary malignancies (21). Oligometastatic disease to the head and neck, in fact, remains far more infrequent than this. 10 years ago, Barnes et al (22) identified lung, breast, kidney and skin (melanoma) to be the most common primary tumours. Even at this time, solitary metastases were found to have unexpectedly good prognosis. To date, there remains no large review in literature exploring oligometastatic disease to the head and neck, and its impact on survival and treatment options.

Aim:

Due to the increased recognition of oligometastatic disease and the potential curative benefit, or significantly improved survival benefit, therapeutic options for these patients are being explored. As such, there is an increasing number of patients presenting with metastases in the head and neck area with primaries elsewhere. This poses a clinical challenge for many ENT surgeons, clinical oncologists and radiologists.
There remains a dearth of high-level evidence for these groups of patients, so it is essential to explore what is currently present in literature both in terms of the primary tumour and of the metastatic location in the head and neck to best guide future management.

Methodology:

A literature search was performed on English Medline between 1995 until 2020 on the following key words or combinations:

Oligometstat*, head and neck, single/isolated/solitary metast*

Articles only from 1995 onwards were selected because this is the date this term was first proposed by Hellman and Weichselbaum. Retrospective and prospective studies were included, along with case series and case reports. Squamous cell carcinomas were excluded.

The results were then subdivided into the nature of the primary tumour. Only the most common cancers to the head and neck were selected:

Breast, renal/kidney, lung.

Skin (BCC/SCC/melanoma), colorectal and ovarian were also explored, but not included in this review due to very few numbers.

Due to the heterogenous nature of head and neck cancers, these results were further split up into location with the head and neck region.

1. Breast cancer presenting in the Head and Neck:

Breast cancer is the most common cancer in women worldwide. 4-6% of women with breast cancer initially present with distant metastases at the time of diagnosis (8, 23), and the majority of mortality in these patients is attributed to distant metastases or recurrence with a 5-year survival of 26%. The rate of recurrence at distant sites is very high, with 20-30% in literature (24). The most common subtype is invasive ductal carcinoma, compromising up to 80% of all breast cancers. Breast cancer commonly metastasise to the lungs, bones, brain and liver.

Spread to the head and neck is rare, but has been identified in literature with multiple case series and reports. In fact, breast carcinoma is one of the most common tumours to metastasise to the head and neck, and has been shown to comprise up to 15-20% of all metastases in this region (25). Table 1 has been collated to show all the identified reports in literature, since 1995, with oligometastases to the head and neck region from a primary breast tumour. Studies with significant missing information for the chosen columns were excluded.

Study	Number of patients	Time from diagnosis to metastasis	Site of metastasis	Presentation	Treatment	Outcome
Tracy et al. 2017 (23)	4	Not specified	Maxillary sinus Submandibular gland Skull base	Nasal obstruction Neck swelling Hoarseness	Not specified	Not specified
Gondim et al. 2017 (25)	25	Mean 10.9 years 3 patients not previously diagnosed breast cancer	Neck lymph nodes (8 patients) and orbital soft tissue (5), followed by oral cavity (3), skull base (3), Mastoid sinus (2), nasal cavity (1), palatine tonsil (1), facial skin (1), and paratracheal soft tissue (1).	Not specified	Not specified	Not specified
Madabhavi et al. 2020 (26)	1	0	Maxilla	Pain + swelling	Palliative chemoradiotherapy + aromotase inhibitor.	Alive at 13 months.
Friedrich et al. 2010 (27)	18	14/18 - not specified 4/18 - not previously diagnosed breast cancer	Facial skeleton (12)- mainly mandible. Cervical lymph node, oral mucosa, cheek,	Not specified	Only grouped data available	Only grouped data available
Muttagi et al. 2011 (28)	5	Mean 42.7 months	Mandible	Pain + parathesia. 2 fungating masses	Surgery + palliative chemoradiotherapy	3 died
Ghias et al. 2019 (29)	1	2 years	Thyroid	Hoarseness + dysphagia	Surgery- right thyroid lobectomy + vocal cord injection	Patient developed brain metastasis.

Bauer et al. 2017 (30)	85	Not specified	Parathyroid	Not specified	Not specified	Not specified
Rotolo et al. 2012 (31)	1	10 years	Tracheostomy site	Persistent cough	Surgery- laser resection + stent.	Died 6 months later
Morris et al. 2001 (32)	1 (Male)	7 years	Mandible	Submental swelling	Chemotherapy	Died 1 year later
Adelson et al. 2005 (33)	1	8 years	Oral	Mass	Surgery	Referred for palliative chemo
Zhou et al. 2017 (34)	8	Median interval 76.5 months	Thyroid	Not specified	3 surgery 5 chemotherapy	2 alive 4 alive
Emanuelli et al. 2018 (35)	1	16 months	Parotid	Not specified	Surgery- total parotidectomy	Died within 23 months
Agrawal et al. 2015 (36)	1	1 year	Nasopharynx	Recurrent sinusitis	Palliative chemo	Died
Raut et al. 2001 (37)	1	15 years	Parotid	Dysphagia	Surgery	Alive
Roberts et al. 2015 (38)	1	7 years	Paranasal sinus - ethmoid sinus, then sphenoid sinus	Gradual loss of taste, and smell, sinus pain, obstructive nasal symptoms, and proptosis	Initially radiation then endoscopic debulking surgery	Alive
Tiwari et al. 2014 (39)	1	Not specified	Sphenoid + maxillary sinus	Mass effect	Radiation	Alive
Bayon et al. 2013 (40)	1	Not specified	Hypopharynx - piriform sinus	Severe dysphagia	Surgery- microlaryngoscopy + excision of mass	Alive
Vessecchia et al. 1995 (41)	1	2 years	Submandibular gland	Mass effect	Surgery	Alive
Xiong et al. 2017 (42)	1	5 years	Sphenoid sinus	Numbness, pain + impaired vision in right eye	Chemoradiotherapy	32 months
Horakova et al. 2018 (43)	2	5 years	Skull base	Dysphagia Progressive diplopia and blurred vision	Surgical biopsy + palliative radiotherapy	18 months
Varghese et al. 2014 (44)	1	2 years	Mandible	Swelling	Radiotherapy	Not specified
Szymański et al. 2002 (45)	2	15 years	Parotid	Swelling + pain	Surgery	<6 months
Liao et al. 2010 (46)	1	4 years	Nasal cavity	Recurrent epistaxis + nasal obstruction	Surgical resection	Alive
Tueche et al. 1999 (47)	1	24 years	Tonsil	Recurrent haemoptysis	Tonsillectomy	Not specified
Staton et al. 2003 (48)	1	1 year	Mandible (cystosarcoma phyllodes)	Mass effect	Palliative radiotherapy	Dead
Bar et al. 2011 (49)	1	2 years	Tonsil (breast haemangiosarcoma)	Haemorrhage	Tonsillectomy + IR embolisation of left lingual artery	Alive
Sadri et al. 2015 (50)	3	Not specified	Mandible	Not specified	Not specified	Not specified

Kmeid et al. 2016 (51)	1	6 years	Parotid	Swelling + facial palsy	Parotidectomy + radiotherapy (because of additional microscopic tumour left behind around nerve).	Not specified
Davey et al. 2012 (52)	1	2 years	Nasopharynx + sphenoid + ethmoid sinus	Left sided facial weakness + partial nasal obstruction	Palliative radiotherapy	Died
Servato et al. 2013 (53)	3	10-21 months	Cervical lymph nodes (IV and V)	Not specified	1 surgery 1 radiotherapy	1/3 alive with disease
Goldernberg et al. 2016 (54)	1	10 years	Thyroid	Hoarseness + difficulty speaking	Patient declined treatment	Died
Jakharia-Shah et al. 2019 (55)	1	8 years	Parotid	Painless lump	Total parotidectomy with a posterolateral neck dissection	Alive
Owosho et al. 2016 (56)	5	Not specified	4 mandible 1 base of tongue	Not specified	Not specified	2/5 alive
Sagheb et al. 2017 (57)	18	Mean 8 years	8 to mandible/maxilla 2 to submandibular gland	Not specified	Surgery +/- chemo/radiotherapy 3 surgery + 1 radiotherapy + 1 palliative	Not specified Not specified
Mclure et al. 2013 (58)	5	Not specified	Mandible	Not specified	Not specified	Not specified
Daley et al. 2011 (59)	5	Not specified	3 mandible 2 oral	Not specified	Not specified	Not specified

Table 1- *Literature review of breast carcinoma oligometastases to the head and neck:*

It is already well established that breast carcinoma has a predilection for bony metastases, the second most common site after the lungs. Within the head and neck region, this translates to the mandible and maxilla being the most common site, a finding that is supported by table 1. In fact, Hirshberg et al (60) found in a large retrospective study that up to 40% of female metastatic lesions to the jaw were breast metastases to the mandible, and up to 20% overall. However, interestingly, breast cancer metastases have been reported in virtually all of the subsites of the head and neck. Salivary glands, in particular parotid, was relatively common in table 1, as well as paranasal sinuses.

There are different proposed mechanisms for this spread:

1. **Batson Venous Plexus:**
   This is a low-pressure valveless network of veins connecting the deep pelvic veins and the thoracic veins (intercostal veins, vena cava and azygous system) to the internal vertebral venous plexus. Therefore, blood can be diverted away from the caval venous system and can go into this valveless system. This provides a direct route for breast cancer cells (and other thoracic, abdominal and pelvic) tumours to spread directly into the head and neck region, bypassing the other sites of metastases (61). Oligometastatic disease, in the form of solitary lesions within the head and neck, can therefore develop from breast carcinomas.
2. **Direct haematogenous:**
   Another possibility for oligometastatic disease to the head and neck is via a direct haematogenous route. Breast tumour cells can directly extend into the caval system and into the subsequent head and neck arterial system. To reach the paranasal sinuses, the cells can travel up to the pterygoid plexus and cavernous sinus. This in particular explains why the maxillary sinus was the most common site out of the paranasal sinuses because they are very highly vascularised through branches of the external carotid which communicate with the pterygoid plexus. It has also been hypothesised that the Valsalva manoeuvre or increased intrathoracic pressure may help push the tumour emboli through the pterygoid plexus into the paranasal sinuses (62).
3. **Lymphogenous route:**
   Another route involves tumour emboli from regional lymph nodes flowing into the thoracic duct. They are then able to reach the head and neck through retrograde flow via intercostal, mediastinal or supraclavicular lymph vessels.

These different mechanisms for oligometastatic disease can create avenues for different treatment options by targeting isolated head and neck metastases.

Strikingly, in the cases identified in literature, there appears to be quite a large time interval between the primary breast cancer diagnosis and detection of the head and neck lesion. The largest such lag identified was 24 years (47), but the mean reported time in literature appears to be 10-11 years. It is already established that in breast cancer oestrogen and progesterone receptor positivity and human epidermal growth factor 2 (HER2) positivity are very strong risk factors for local or distant recurrence after 5 years (63). Clearly, this presents a problem because it implies that despite control of the primary tumour, there is still a chance for oligometastatic recurrence in other sites. This raises new questions of regular active surveillance within the head and neck region for patients

with previously thought to be controlled/remitted breast carcinomas, particularly for those with strong risk factors for distant recurrence.

Interestingly, there were at least 7 identified cases in table 1, where the head and neck lesions were the first diagnostic specimen of breast carcinoma. Clearly this presents a challenge to head and neck pathologists because they have to be aware of breast carcinomas in this region as the initial presenting lesion. Special immunohistochemical stains, not routinely tested in head and neck specimens, such as pankeratin, mammaglobin, GATA binding protein 3, erbB-2 (61) as well as receptors for oestrogen and progesterone can help histopathologists identify oligometastases of breast origin.

a.Management options:

There is no clear guidance for the treatment of oligometastatic breast carcinoma in the head and neck. As evidenced in table 1, the treatment options varied immensely with very different survival outcomes. Treatment options varied particularly due to the site of the lesion. Treatment options fell into one of 3 arms for these groups of patients: chemotherapy, radiotherapy and surgery.

Chemotherapy, for this subset of patients, tended to be palliative, and in fact survival outcomes were not great. Due to the sparsity of this group, it is difficult to extrapolate any meaningful conclusions about the effective of chemotherapy for this subset over metastatic breast cancer patients. It is worth conducting large scale retrospective studies comparing the survival outcomes of both groups to guide future chemotherapy use in oligometastatic breast cancer patients.

Biological agents are another avenue that can be explored, particularly with anti-VEGF treatments such as Bevacizumab having shown significant progression free survival and objective response rates when used in combination with chemotherapy. This is a treatment option worth exploring in oligometastatic breast carcinoma to the head and neck.

Radiotherapy has also tended to be preferred as a palliative option in these patients thus far. Stereotactic body radiotherapy (SBRT) has been explored in breast cancer patients, and studies have shown a 74% overall 2 year survival (8). In fact, bone metastases were found to be particularly sensitive to SBRT, with one study reporting no rates of recurrence and no grade 3 toxicity in bone compared to 10/68 lesions recurring at other sites. Mandible and maxilla breast metastases may be particularly amenable to SBRT, and RCTs involving this or comparing SBRT to surgery seems the next logical step.

The benefits of surgery in liver metastasectomy and pulmonary metastasectomy have already been discussed. Within the head and neck, curative resections were performed for many patients identified in table 1. Particularly with oligometastatic disease to the thyroid, parathyroid and major salivary glands, curative resections are a treatment option. The patients that had good survival outcomes lacked any other significant disease burden, and hence fit the oligometastatic mould. Oligometastatic disease to the paranasal space is more contentious. Palliative surgery is not an overly familiar concept. Endoscopic sinus surgery in this regard is a low morbidity-associated operation that has been shown to significantly improve patient comfort by reducing proptosis and sinonasal complaints from oligometastatic disease to the sinuses (38). However, there are very few indications for it being curative, even in the oligometastatic setting, possibly due to the tumour disease burden present to breach into the pterygoid plexus and into the paranasal sinuses.

Tabaee et al (64) were able to take one further step and establish criteria for palliative surgery in their group of patients.

1. A reasonable expectation of improvement
2. Possible prolongation of life
3. Survivability of anaesthesia.

This is a criteria that ENT surgeons can adapt for patients with oligometastatic disease, as a significant proportion of them will be fit patients that can survive anaesthesia, and so surgical options should be explored despite there being a lack of understanding of cure. Of course, this is a decision that requires significant input from the rest of the multi-disciplinary team.

2. Lung cancer presenting in the head and neck:

Lung cancer is currently the second most common cancer worldwide, and the leading cause of cancer-related deaths in both men and women (65). It is responsible for 1.3 million deaths worldwide every year. It currently has a 10-year survival rate of 10% in the UK (66). The most common histological subtype is non-small cell carcinoma, which compromise of squamous cell, adenocarcinoma and large cell lung cancer. Small cell carcinomas make up the remaining 15-20% of lung cancers, and are generally associated with the most metastatic potential and worst survival outcomes. In fact, the majority of small cell carcinomas have metastatic disease at the time of initial presentation (67) . Lung cancers are also prone to paraneoplastic syndromes, which increase patient morbidity and mortality.

Lung cancer has a tendency to metastasise to the liver, brain, bones and adrenal glands. Small cell and adenocarcinomas tend to metastasise to the brain preferentially, while liver metastases almost never arise from adenocarcinomas exclusively (68). Lung cancer oligometastatic disease to the head and neck is rare but has been reported in literature. However, it remains the second most common after breast oligometastatic disease (69). Table 2 has been collated to show all the identified reports in literature, since 1995, with oligometastases to the head and neck region from a primary lung tumour. Studies with significant missing information for the chosen columns were excluded. It is also worth noting that a lot of the lung cancer patients, in particular small cell carcinoma, had widespread disseminated metastatic disease at presentation and so were excluded.

Study	Number of patients	Time from diagnosis to metastasis	Site of metastasis	Presentation	Treatment	Outcome	Histology
Sagheb et al. 2017 (57)	8	0.5 months	7 Bone (mandible/maxilla)	Lesion	Not specified	Not specified.	Not specified
Mcclure et al. 2013 (58)	10	Not specified	2 parotid 8 mandible	Mass Mass	Parotidectomy +/- chemoradiotherapy	Not specified.	3 small cell, 2 adenocarcinoma, 5 non-small cell

Cui et al. 2019 (70)	1	Undiagnosed lung cancer	Parotid	Painless mass + facial paralysis grade III	Total parotidectomy + neck dissection + adjuvant chemotherapy	Ongoing	Small cell
Chen et al. 2019 (71)	1	Undiagnosed	Tonsil	Haemoptysis + productive cough	Wide excision + EGFR inhibitor	No local recurrence 6 months post-op	Adenocarcinoma
Nuyen et al. 2016 (72)	1	Undiagnosed	Maxilla	Indurated, non-ulcerating lesion	Palliative radiotherapy	Died	Adenocarcinoma
Wong et al. 2017 (73)	1	10 months	Internal auditory meatus (temporal bone)	Hearing loss + vertigo	Palliative chemotherapy	Died	Adenocarcinoma
Hu et al. 2014 (74)	1	2 years	Nasopharynx	Mass	Chemotherapy	Alive	Squamous
Wong et al. 2011 (75)	1	2 months	Nasopharynx	Haemoptysis + nasal blockage	Radiotherapy	Disease-free for 10 years	Adenocarcinoma
Tajima et al. 2015 (76)	1	10 years	Tonsils	Mass	Right-sided tonsillectomy + chemotherapy	Not specified.	Squamous
Hain et al. 2012 (77)	1	10 days	Bony EAC (temporal bone)	Bleeding ear	Chemotherapy	Died 6 months later	Small cell
Veerappan et al. 2003 (78)	1	Undiagnosed	Zygoma	Mass	Chemoradiotherapy	Not specified	Squamous
Vasileiadis et al. 2013 (79)	1	Undiagnosed	EAC	Swelling + sudden-onset hearing loss	Chemoradiotherapy	Died 7 months later	Adenocarcinoma
Borg et al. 2004 (80)	1	Undiagnosed	Parotid	Fungating mass	Radiotherapy	Disease-free for 3 years	Squamous
Chen et al. 2015 (81)	20	11-102 months	Thyroid	Mass	2 patients received thyroidectomy - both had survival > 10 months. Rest had combination of chemo +/- radiotherapy.	2-31 months	8 adenocarcinomas, 5 squamous, 4 small cell. 1 sarcomatous, 1 giant cell, 1 non-small cell
Emanuelli et al. 2018 (35)	8	1 had recurrence 12 months after, rest not specified.	Parotid	Mass +/- facial palsy	Total parotidectomy.	< 23 months	2 small cell, 1 squamous, 2 adenocarcinoma, 1 large cell, 1 neuroendocrine
Shen et al. 2009 (21)	5	Not specified	2 x gingiva, 3 x mandible	Mass, bleeding, numbness	Not specified	Not specified	4 squamous, 1 adenocarcinoma
Yildiz et al. 2011	1	Undiagnosed	Temporal bone (facial canal)	Facial palsy	Chemoradiotherapy	Died 4 months later	Small cell
Zaubitzer et al. 2019 (68)	1	Undiagnosed	Tonsil	Mass	Chemoradiotherapy	Alive	Adenocarcinoma

Preuss et al. 2005 (82)	1	2 years	Thyroid	Hoarseness of voice	Resection + radiotherapy	Alive + disease-free	Squamous
Noel et al. 2020 (83)	1	2 years	Tonsil	Pharyngeal discomfort	Chemotherapy	Died 6 months later	Mixed neuroendocrine/ squamous lung
Friederich et al. 2010 (27)	11	5 were undiagnosed	8 to mandible/maxilla	Mass	Not specified	Not specified	Not specified
Oshima et al. 2019 (84)	1	Undiagnosed	Medial pterygoid muscle	Severe trismus	Palliative radiotherapy	Died 5 months later	Not specified
Franzen et al. 2016 (85)	3	2 were undiagnosed, 1 patient was a few months	Parotid	Mass	Total parotidectomy + chemoradiotherapy	2 died within.6 months, 1 alive and disease free for 5 years (squamous)	2 small cell, 1 squamous

Table 2- *Literature review of lung carcinoma oligometastases to the head and neck:*

As evidenced in table 2, a significant proportion of these patients had undiagnosed primary lung carcinomas at their time of presentation. Synchronous metastasis are generally those defined as presenting within 6 months of the initial lesion, while metachronous lesions are defined as greater than 6 months. Lung oligometastases to the head and neck tend to favour a synchronous nature whilst breast tended to be metachronous with a relatively long time interval. In fact, even in histologies other than small cell carcinoma, the head and neck lesion was the first presenting lesion of the primary lung carcinoma. This presents a challenge for clinicians because it is essential to investigate for lung primaries with appropriate immunostaining and imaging as a part of staging, and there have been reports of lung metastases being misdiagnosed as primary head and neck tumours, especially in small cell and squamous cell carcinomas (85, 86).

a. Mechanism of spread:

Unlike for breast cancer, Batson's plexus, which traditionally bypasses the lung is therefore not thought to be involved in the spread of lung cancer to the head and neck region. The highly vascularised microenvironment of the lungs makes it very easy for distant spread, especially with central lesions. The exact nature of this spread is not clearly defined and is believed to involve the major head and neck vessels en route to brain metastases.

a. Lymphogenous route:

The lymphatic route is thought to be of relevance in lung cancer due to pattern of distribution of oligometastatic sites, with the parotid gland and tonsils being very common. The concept of retrograde lymphatic flow to the head and neck is one that is explored in literature (68, 76, 78). It suggests that as a result of involvement of cervical lymph nodes, there is a higher down-stream pressure in the lymph vessels which then causes an inversion of flow. There is usually a mechanism to inhibit retrograde flow involving bi-leaflet vales but their function becomes defective as a result of tumour cell adhesion. This is particularly the mechanism that has been described for the palatine tonsils as they lack afferent lymphatic vessels. In combination with this, is pagetoid spread, which is the concept of invasion of the upper epidermis from below. This was noted by Tajima et al (76) in microscopic findings, and suggests that there does not need for there to be direct continuity with the epithelium of the primary tumour. This could allow even small pulmonary adenocarcinoma to metastasise to the cervical lymph nodes, and then subsequently onto the palatine tonsils.

b. Direct implantation:

Another theory proposed for the spread of oligometastatic disease to the head and neck, unique to lung cancer is direct implantation. It is known that metastases prefer sites of trauma, and lung cancer patients undergo bronchoscopic procedures either for diagnostic purposes with biopsies or interventional therapeutic purposes with debulking. There is a risk of damage particularly to the oropharynx and the tonsils, and this has been reported in literature (68, 74) with patients developing tonsillar metastases after rigid bronchoscopies. In fact, this has been shown in other conditions too, particularly with port-site metastases secondary to instruments in laparoscopic surgery and percutaneous endoscopic gastrostomy sites. These isolated lesions tend to have good survival outcomes after surgical resections.

b. Management Options:

Survival outcomes in table 2 for lung oligometastatic disease to the head and neck tended to be poorer than for primary breast carcinomas. This is in a large part due to the fact that significantly more patients presented with the head and neck metastasis as their presenting lesion with an as of yet undiagnosed primary lung carcinoma. Despite not having widespread disseminated metastatic disease at time of presentation, their primary had most likely remained untreated for a prolonged length of time. Treatment options varied in the literature depending on site of the lesion and on the primary histology.

Small cell carcinomas had the worst survival outcomes. Small cell oligometastatic disease to the parotids had a survival life expectancy of less than 10 months (70), while mandible oligometastases had a mean survival of 7-16.6 months (72). Patients with metastases of small cell origin had chemotherapy regimes due to the sensitivity of the primary small cell carcinoma in the lung to chemotherapy. However, despite this, the majority of patients received palliative regimes and had very poor survival outcomes. Combination with radiotherapy yielded marginally better results, and in fact Wong et al (75) proposed solitary nasopharyngeal metastases from primary lung tumour to be a separate entity entirely. This form of tumour responded preferentially well to radiotherapy despite an advanced stage of primary lung cancer, and the patient remained disease free for over 10 years. Clearly, further research is needed on palliative chemoradiotherapy regimes in patients with advanced lung primaries and oligometastatic disease to best optimise

patient comfort and provide an improvement to quality of life as well as possible overall survival.

Newer biological therapies have also been tried in primary lung cancer and metastatic disease. Molecular profiling studies have allowed the identification of many genomic alterations and oncogenes that are histology specific and potential therapeutic targets. In adenocarcinoma particularly, many exist and one such target is the EGFR (epidermal growth factor receptor) which exhibits tyrosine kinase activity. Hence this can be inhibited with EGFR-tyrosine kinase inhibitors, and large scale RCTs have shown higher response rates and longer progression free survival compared to platinum-based chemotherapy (87)**.** This finding has in fact been translated into oligometastatic disease too, and both Chen et al (71) and Kim et al (88) were able to demonstrate partial tumour response with EGFR-tyrosine kinase inhibitor in patients with lung adenocarcinoma metastases to the tonsils and bilateral internal auditory canal respectively. However, despite this, studies have so far failed to demonstrate an improvement in overall survival, although this has been argued that this is due to the high level of treatment crossover as disease progresses. Other therapeutic targets such as FGR-1 (fibroblast growth factor receptor 1) gene in squamous cell carcinomas are still being investigated (89), and they can perhaps play a major role in as treatment options in lung oligometastatic disease to the head and neck if identified early.

SBAR (Stereotactic ablative radiotherapy)/SBRT (Stereotactic body radiation therapy) has gathered significant attention in role of treating lung oligometastases. This is particularly in relation to non-small cell carcinomas, which are much less likely to present with widespread metastatic dissemination. A recent systematic review has revealed 4 prospective phase II randomized trials, 4 prospective non-randomized studies and eleven retrospective studies that have been fully completed and published results (90). Despite including head and neck sites, it is difficult to draw out any meaningful conclusions about the effect of SBAR on oligometastases to the head and neck because of the way the data has been grouped. However, overall, these studies have thus far demonstrated prolonged progression-free survival and overall survival compared to systemic therapy (chemotherapy +/-biological therapy). There are currently many ongoing phase III trials (90, 91), and once these are published, they will give a better idea of whether SBAR/SBRT is a feasible management option. However, there is no identifiable phase II/III trial looking at the use of SBAR in head and neck oligometastases only. This is something that can be established relatively easily in line with the current trials, and can provide good evidence-based guidance for future use of ablative radiotherapy for lung oligometastases in the head and neck.

Surgical resections in lung oligometastases were performed in the literature, and these had the potential to be either curative or of symptomatic benefit. This particularly applied to tonsillar metastases. Some advocate for a tonsillectomy in view of a biopsy regardless (68), and the mechanism of tonsillar spread as a form of direct implantation post-bronchoscopy favours it being an isolated lesion without any further tissue involvement. However, whether this translates into direct overall survival benefit is difficult to see with the low number of cases in literature. Certainly tonsillar oligometastases of other origin, in particular renal carcinoma, has demonstrated curative benefit after tonsillectomies, and this advocates this practice as a management option for oligometastases of lung origin.

Surgical management for parotid lesions from lung oligometastases is a bit more contentious. Some have advocated for parotidectomies with negative margins and preservation of the facial nerve in the presence of single parotid metastasis (35). However, in the literature, no cases of surgery to the parotid alone has resulted in curative treatment. Addition with chemo/radiotherapy may yield a greater overall survival benefit. In fact, Cui et al (70) revealed that with small cell metastases to the parotid gland, the life expectancy is less than 10 months, due to its aggressive nature. In addition to having an estimated 5 year survival rate of 10%, this means that curative or radical parotidectomies cannot be realistically performed in this population cohort. Combining parotidectomies with radiotherapy however, will allow greater symptom control such as preventing morbidity associated with fungating masses and nerve invasion, and allow greater locoregional control. Ipsilateral neck dissections have been performed in some cases in literature, but this is thought to be unnecessary because the metastasis is much more likely to have originated via the haematogenous route rather than the lymphatic route (70). It is not recommended because it avoids the morbidity associated with neck dissections and does not impact on locoregional control.

Metachronous oligometastatic disease tended to have better surgical outcomes than synchronous disease. This is especially well demonstrated in metastases to the thyroid (81). Squamous cell carcinomas also tended to present with metachronous disease. However, it can be argued whether synchronous disease can be included in the criteria of oligometastatic disease in the first place because there is no control of the primary lesion, and this has the potential to negatively impact upon the state of the lesion within the head and neck. Certainly for small cell carcinomas, many of the patients had very poor survival outcomes because despite locoregional control with surgery, there was limited control of the primary lung tumour and this would have led to metastases uncovered later that contributed to the patients' deaths. The question of whether better surgical outcomes are associated with longer time intervals between initial diagnosis of the primary lesion and diagnosis of the metastatic lesion is one that needs to be answered, and retrospective analyses of national cancer databases can help establish this.

3. Renal cancer presenting in the head and neck:

Renal carcinomas (RCC) are the 9th most common worldwide (92) and commonly metastasise to the lungs, bone and liver. However, they are in fact the third most common infraclavicular tumour to metastasise to the head and neck (93). 85% of all malignant renal tumours are comprised of the clear cell subtype (94). It has a very high risk of metastatic disease, primarily because of haematogenous spread due to its frequent invasion of the local vascular renal network. The most common sites to the head and neck involve the bone, skin, subcutaneous tissue and lymph nodes (92). Table 3 has been collated to show all the identified reports in literature, since 1995, with oligometastases to the head and neck region from a primary renal tumour that are of significant clinical relevance in terms of management. Studies with significant missing information for the chosen columns were excluded.

Study	Number of patients	Time from diagnosis to metastasis	Site of metastasis	Presentation	Treatment	Outcome
Gottlieb et al. 1998 (94)	3	Undiagnosed 20 years Undiagnosed	Nasal cavity Thyroid Thyroid	Proptosis + mass Mass Mass	Transethmoidal excision Excision Palliative radiotherapy	No recurrence after 62 months No recurrence after 70 months

						Died within 3 weeks
Lieder et al. 2017 (93)	22	Mean - 27 months	Various- 1 parotid, 1 mandible, 1 sinus, 2 thyroid, 1 tongue		Surgical excision. 14 received adjuvant radiotherapy, 9 received chemotherapy or targeted therapy.	Mean time 38 months
Marcotullio et al. 2013 (95)	1	3 years	Tonsil	Mass	Surgery + adjuvant radiotherapy	No recurrence at six months
Bayne et al. 2020 (92)	1	7 years	Hypopharynx	Mild dysphagia	Immunotherapy + palliative radiotherapy	Alive at 1 month
Stanczyk et al. 2006 (96)	1	11 months	Tonsil		Surgery	Died 16 months post treatment- developed bony + pulmonary metastases.
Nishii et al. 2020 (97)	1	7 years	Maxilla + maxillary sinus	Mass	Vascular embolisation + subtotal maxillectomy	Died 17 months - developed pulmonary metastases.
Menauer et al. 1998 (98)	1	10 years	Tonsil		Surgery	Not specified
Massaccesi et al. 2009 (99)	1	3 years	Tonsil		Radiotherapy	Died 15 months later- developed bony/ pulmonary metastases
Ross et al. 2020 (100)	1	15 years	Tonsil (had recurrence in tonsil x 2 after tonsillectomy)	Mass	TORS + left buccal artery myomucosal flap reconstruction	Died 3 months later due to unrelated pathology
Liou et al. 2018 (101)	266	47% < 1 year; 23% years 1-5; 30% > 5 years	Various	Not specified	Surgery performed in 68% of patients	60 months for those that underwent metastasectomy. 36 months for those that didn't.

Table 3- *Key literature review of renal carcinoma oligometastases to the head and neck.*

There are three proposed mechanisms in literature for renal cancers to metastasise to the head and neck. Haematogenous spread seems to the be most important mechanism, and this is relatively easy to explain because of the nature of invasion of the local vessels surrounding the kidney. Anatomically, this would however mean that lung metastases develop before head and neck oligometastases do. The concept of micro-seeding of the lungs proposed by Gottlieb et al (94) can help explain this phenomenon. In most likely case, oligometastatic disease of the head and neck is accompanied by microscopic seeding of the lungs which is not picked up on routine imaging, and explains why many of the patients with poor survival outcomes die as a result of pulmonary metastases. The other mechanisms are by Batson's venous plexus and retrograde lymphatic flow, both of which have been explained.

a. Management options:

Survival outcomes in table 3 demonstrate better outcomes than for breast oligometastases. Additionally, there are far fewer patients presenting with synchronous disease, and the time interval between diagnosis of primary tumour and oligometastatic lesion can even range up to 20 years. Lieder et al (93) demonstrated a rate of metastatic disease to the head and neck from RCC of 3.3% (22/671 patients) of all patients they treated with RCC, which they felt was sufficient enough to recommend for neck to be included in staging investigations for RCC. Liou et al (101) in a systematic review found a much higher rate of 14-16%, and so this advocates this recommendation even further. Crucially, metastases to the head and neck can result in severe morbidity and mortality involving airway obstruction, haemorrhage and airway obstruction, and for this reason both screening and treatment can be advocated.

RCC is a radioresistant tumour, and therefore radiotherapy is not often used as a treatment option. However, with metastatic lesions, SBAR has demonstrated significant progression-free and overall survival benefit with bone and brain metastases (102). Studies exploring its use within head and neck metastases have yet to sufficiently conclude or yield any significant results so far. A number of phase III trials with new immunotherapies such as bevacizumab + IFNα have demonstrated better response rates and progression-free survival over current regimes and this is something that can be explored in the oligometastatic cohort of patients.

To achieve locoregional control, surgery is still considered by many to be the definitive management option. There is a lot more evidence supporting surgical resections for oligometastases of renal origin than for breast and lung. A systematic review of 266 patients found that median overall survival of renal oligometastatic disease to the head and neck was 36 months. 68% of these patients underwent a metastasectomy. Interestingly, the median survival for those treated with complete metastasectomy was significantly higher at 60 months compared to 12

months for those with incomplete or no metastasectomy. It is however important to consider that the cohort of patients selected for surgery may have been fitter in the first place. However, after multivariate analysis to consider for cofounders, surgical metastasectomy remained associated with a reduced risk of death. Even in terms of locoregional control, recurrence only occurred in 16% of those treated with complete metastasectomy in this review and a local control rate of over 90% for oral cavity oligometastases of RCC origin in another review (97). Surgery is therefore advocated both for improved survival and for locoregional control.

The major complication with surgery for RCC in the head and neck is haemorrhage and this is why there may be a lot of hesitancy amongst ENT surgeons for performing them. Renal metastases have a rich blood supply, and this is of particular concern with oral cavity lesions. Involvement of interventional radiology with vascular embolisation of feeding vessels is a technique that has yielded successful results (97).

Recommendations/ Future studies:

Based on this review, the following can be recommended with regards to management of patients with oligometastatic disease to the head and neck.

1. If patients are fit, surgical options should be considered for locoregional control and/or survival benefits.
2. Palliative surgery should be explored as an option, particularly in view of low morbidity operations such as endoscopic sinus surgery. However, clear criteria should be established and palliative care teams should be involved.
3. Regardless of whether surgery or local ablative therapies are suitable, MDT discussions should be offered to best optimise their management.
4. Retrospective analyses of relationship between time of primary diagnosis and time of diagnosis of metastatic lesions vs survival – look at national cancer databases.
5. The origin of the primary tumour can influence management:
    a. Breast:
        i. Regular active surveillance for recurrence in head and neck in patients with breast cancer in remission particularly for those with strong risks factors for distant recurrence (oestrogen and progesterone receptor positivity and human epidermal growth factor 2 (HER2) positivity)
        ii. Retrospective studies comparing chemotherapy vs biological agents in oligometastatic breast cancer.
        iii. RCTs comparing surgery to SBRT/SBAR for bony metastases in head and neck of breast origin.
    b. Lung:
        i. Phase II/III trials for SBAR in head and neck lung oligometastases.
        ii. Study exploring the role of biological targeted therapies in lung oligometastases to head and neck- particularly in adenocarcinomas.
        iii. Parotidectomy can be performed for locoregional control- no need for ipsilateral neck dissection.
        iv. Small cell carcinomas will tend to present with synchronous disease and have poor survival outcomes regardless of treatment.
    c. Renal:
        i. Surgery is advocated for both locoregional control and for survival benefit.
        ii. Involve MDT and interventional radiologists in planning for surgical resections.
        iii. Phase II/III trials looking at SBAR + immunotherapies.

Conclusion:

Oligometastatic disease in head and neck cancer is a new entity that is beginning to gather significant attention. The most common infraclavicular primary tumours to metastasise to the head and neck are breast, lung and renal carcinomas. Management of these oligometastatic lesions is currently very variable and surgery and/or ablative therapies can in fact be associated with good survival outcomes or locoregional control. The recommendations in this paper will help towards establishing clear guidelines in the future for surgical and ablative therapies for these patients.

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