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# Dissemination patterns and chronology of distant metastasis affect survival of patients with head and neck squamous cell carcinoma

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ABSTRACT

*Objectives:* To define metastatic categories based on their prognostic significance. We hypothesized that oligometastasis in patients with head and neck squamous cell carcinoma (HNSCC) is associated with better post-distant metastasis disease specific survival (post-DM DSS) compared to patients with polymetastasis. Furthermore, the impact on survival of synchronous versus metachronous distant metastasis (DM) occurrence was assessed.

*Materials and methods:* Retrospective cohort study in which patients with DM were stratified into three groups: oligometastasis (maximum of 3 metastatic foci in ≤2 anatomic sites), explosive metastasis (≥4 metastatic foci at one anatomic site) and explosive-disseminating metastasis (spread to ≥3 anatomic sites or >3 metastatic foci in 2 anatomic sites). In addition, patients were divided into synchronous versus metachronous DM.

*Results:* Between January 1, 2006 and December 31, 2013, a total of 2687 patients with HNSCC were identified, of which 324 patients developed DM. In this group, 115 (35.5%) patients had oligometastasis, 64 (19.8%) patients had explosive metastasis and 145 (44.8%) patients had explosive-disseminating metastasis. Their median post-DM DSS were 4.7 months, 4.1 months and 1.7 months respectively ($p < .001$). Synchronous DM was associated with more favorable survival rates in univariable and multivariable analyses than metachronous DM with recurrence of the index tumor (6-month post-DM DSS probability of 0.51 vs 0.17, $p < .001$).

*Conclusion:* Oligometastasis in HNSCC signifies a better prognosis than a polymetastatic pattern. Metachronous DM occurrence with recurrence of the primary index tumor is associated with an unfavorable prognosis.

## Introduction

Head and neck cancer accounts for more than 850,000 cases worldwide per year [1]. The vast majority of these cases are squamous cell carcinomas (SCC). Distant metastasis (DM) occurs in 10% to 24% of all SCC cases, affecting primarily the lungs, bones and liver [2–4]. Once DM is discovered, survival is often poor with a median survival of 3–8 months [5,6]. Substantial heterogeneity however appears to exist in survival between patients with DM i.e. patients with fewer metastatic foci seem to have better overall survival (OS) rates in comparison to

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patients with polymetastasis [7,8]. This is in line with the concept of "oligometastasis" (OM) proposed by Hellman and Weichselbaum in 1995 [9]. This concept suggests that metastasis should not be regarded as a binary state (metastases either do or do not exist), but rather as a spectrum of metastatic disease. In this concept, OM is a state in which metastases are still limited in number and location. This concept allows to create more nuance in terms of prognosis of patients with metastatic disease. In head and neck squamous cell carcinomas (HNSCC), however, it remains undefined as to what number of metastatic foci and locations constitute OM.

In the past, studies have considered metastatic foci ranging from 2 to 5 and confined to 1 to 3 anatomic site(s) as OM [7,8,10,11]. Sinha et al. [10] defined patterns of DM for p16-positive oropharyngeal SCC, with OM defined as metastasis to 1 or 2 anatomic site(s) or $\leq$3 metastatic foci in one anatomic site, "explosive" metastasis as $\geq$4 foci of metastasis at one anatomic site and "disseminating" metastasis as spread to more than 2 anatomic sites. A limitation of this approach is that the demarcation of the categories fails to include all possible metastatic patterns (e.g. more than 3 metastatic foci in 2 anatomic sites).

Given that OM yields better survival rates than polymetastasis, we hypothesized that a gradation of metastatic disease can be defined for all HNSCC. The primary aim of this study was therefore to define categories for DM, including OM, in HNSCC and to determine whether there were any significant differences in prognosis.

In non-head and neck tumors, such as renal cell and colorectal carcinomas, patients presenting with synchronous metastatic disease at the time of diagnosis (i.e. diagnosed with a local tumor and metastasis simultaneously), have unfavorable prognosis compared to patients who develop metachronous DM [12–15]. In HNSCC, this distinction is ill-defined. Our secondary aim was therefore to establish whether there were significant prognostic differences between patients with synchronous versus metachronous DM in HNSCC.

## Materials and methods

### *Patient selection*

The Erasmus Medical Center ethics committee approved this retrospective study (MEC-2016-751). All patients diagnosed with HNSCC between January 01, 2006 and December 31, 2013 were retrospectively analyzed and included in this study. Distant metastasis number of foci and anatomic locations were determined through radiological imaging, cytological or histological sampling and clinical examination when applicable. In case of uncertainty between distant metastasis or second primary cancer, biopsies were performed to determine the origin of the tumor through loss of heterozygosity analyses. Patients with synchronous tumors outside the head and neck region at the time of DM were excluded from this study, except if the metastasis was pathologically proven to be of the same entity as the HNSCC. Patients were also excluded if the diagnosis of DM was for the first time at post-mortem examination, in case of non-HNSCC related death or if records were missing to determine the pattern of DM.

Patients were selected from the Rotterdam Oncology Documentary (RONCDOC), a database comprising all patients with head and neck cancer treated at the Erasmus MC Cancer Institute since 1995. Patient and tumor specific data were obtained from patient records and integrated with data from the Netherlands Comprehensive Cancer Organization. The variables age, gender, index site classification, treatment of metastatic foci, and chronology of DM were collected as we believed them to be potential confounders in the relation between post-DM DSS and patterns of DM.

### *Endpoints and definitions*

The primary endpoint was post-DM disease-specific survival rates (post-DM DSS) in relation to patterns of DM. Post-DM DSS was calculated from the date of diagnosis of DM to the date of death or last follow-up.

Patterns of DM were characterized based on a modified classification of Sinha et al. [10]. DM with a maximum of 3 metastatic foci in $\leq$2 anatomic sites were considered to be OM. Explosive metastasis (EM) was defined as $\geq$4 metastatic foci at one anatomic site. The remainder of the DM patterns fell under the explosive-disseminating metastasis (EDM) category, which constituted spread to $\geq$3 anatomic sites or >3 metastatic foci in 2 anatomic sites.

Skeletal metastases were considered to be distinct anatomic sites in the case of spread to separate bones.

The date of DM detection was defined as the date when the discovered metastatic foci had been for the first time clinically regarded as such, i.e. the date of radiological imaging or histological sampling. The pattern of DM was recorded as found at the time of DM detection. Further progression of DM at later time intervals were not taken into account.

In case of DM without local, regional or locoregional tumor recurrence, the last primary HNSCC was set as the original index site classification.

At our center, patients presenting for the first time with a head and neck tumor underwent a CT-scan of the thorax and abdomen as part of the work-up. If deemed necessary, additional radiological imaging was performed. After treatment, CT-scans of the thorax and abdomen were performed in the follow-up in case of suspicion of recurrent disease. Radiological imaging of other anatomical areas were only performed in case of clinical symptoms. In this cohort, Positron Emission Tomography scans were not part of the standard protocol.

Patients diagnosed with a tumor in the head and neck region and DM simultaneously were considered to have synchronous DM. Metachronous DM was defined as any DM occurring after completion of curative treatment of the primary tumor. In case of metachronous DM, a further distinction was made in regard to recurrence of the index tumor in the head and neck region.

### *Treatment*

At our center, treatment for all distant metastatic HNSCC is solely offered in a palliative setting which focuses on comfort care on a case by case basis. Systemic therapy in the form of chemotherapy or immunotherapy is considered with the aim of prolonging survival and alleviation of symptoms. On the other hand, local (non-systemic) therapy in the form of radiotherapy or if applicable, surgery, is offered with the goal of symptom relief of either the head and neck tumor or metastatic foci. In the present study, treatment was defined as any therapy (local or systemic) or a combination thereof on the metastatic foci.

### *Statistical analysis*

Statistical analyses were conducted using SPSS (IBM SPSS Statistics, version 24.0.0.1). Post-DM DSS were estimated with the Kaplan-Meier method. Cox proportional hazard regression model was applied using the enter method to calculate the multivariable hazard ratios (HR) by adding all covariates simultaneously. Heterogeneity between groups was assessed using the Chi-squared test and Fisher's exact test when appropriate. Two-tailed significance levels of $\leq$5% were used for all analyzes. For frequencies and proportions, descriptive statistics were used.

## Results

A total of 2687 patients with HNSCC were identified in the period between January 01, 2006 and December 31, 2013. Out of these patients, 332 (12.4%) patients either had or developed DM. Three patients were excluded due to synchronous non-HNSCC at the time of DM, two patients were excluded due to non-HNSCC related cause of death,

another two patients were excluded due to missing records and one patient was excluded as DM was found at post-mortem examination. In total 324 (12.1%) patients with DM were included in this study, see Table 1.

DM dissemination occurred to a cumulative total of 606 anatomic sites. The most commonly affected anatomic site was the lung, with spread being present in 187 patients (57.7%). Other prominent anatomic sites included the mediastinal and/or hilar lymph nodes (50.6%), the skin (20.4%) and the skeletal system (19.1%), see Table 2.

The majority of the oropharynx and oral cavity patients had an EDM pattern. The same was observed in nasopharyngeal cancers and cancers of unknown primary. Compared to other head and neck sub sites, OM spread was more common in glottic, supraglottic and sinonasal carcinomas, see Table 3.

The median and mean post-DM DSS of all 324 patients were respectively 3.2 months (IQR 1.3–6.8) and 6.3 months (95% CI 5.2–7.4 months). In our cohort, all patients died, with the exception of three patients (0.9%) who remained alive at the date of last follow-up.

The majority of the DM spread showed an EDM pattern (44.8%), while OM and EM accounted for 35.5% and 19.8% respectively. The median post-DM DSS of the EDM group was 1.7 months (IQR 0.9–4.4), whereas the OM and EM had more optimistic rates of 4.7 months (IQR 2.8–10.3) and 4.1 months (IQR 1.5–7.5) respectively ($p < .001$).

In univariable analyses, all variables, except age at DM detection and gender, showed a statistically significant relationship with post-DM DSS. Significantly longer post-DM DSS was observed in the OM group, with a 3-month post-DM DSS of 71.3%, whereas patients in the EM group had a 3-month post-DM DSS of 59.4%. Patients in the EDM group had the worst 3-month post-DM DSS, with a survival rate of 35.2% (Table 4 and Fig. 1, $p < .001$). Furthermore, a clear distinction existed in post-DM DSS in regard to DM chronology. Patients who had DM at first presentation had more optimistic survival rates (64.2% at 3 months), compared to patients who developed DM as recurrence with or without local, regional or locoregional index tumor recurrence (45.4% and 53.4% at 3 months respectively, Fig. 2, $p < .001$).

Sub-analysis of treatment frequencies per metastatic category showed no significant difference between the groups. The patients who had no treatment on DM foci accounted for 69.6%, 82.8% and 73.8% in the OM, EM and EDM categories respectively ($p = .344$).

For metachronous DM, the median time to DM from index tumor diagnosis – recurrence free survival (RFS) – was 9.9 months (range 2.3–75.7 months). No significant association existed between the RFS and the patterns of DM ($p = .512$).

Sub analysis of 44 patients with known human papillomavirus (HPV) p16 status showed no significant difference in metastatic patterns. In both the p16-negative group and the p16-positive group, metastatic spread occurred most often with an EDM pattern (48.5% and 54.5% respectively, $p = .665$). In addition, no significant difference was observed in chronology of DM, with metachronous DM without recurrence accounting for 60.6% in the p16-negative group and 72.7% in the p16-positive group ($p = .879$). The median survival in both groups was 3.5 months (range 1.6–5.3 months) and 4.2 months (range 2.6–5.9 months) respectively, $p = .456$.

**Table 1**
Baseline characteristics of the included patient population.

| Characteristic | | No. (%) |
|---|---|---|
| Gender | Male | 239 (73.8) |
| | Female | 85 (26.2) |
| Mean age at DM detection in years ± SD | | 64.3 ± 9.5 |
| Mean time to metachronous DM from diagnosis in months ± SD | | 13.8 ± 12.3 |
| Index site classification | Oropharynx | 86 (26.5) |
| | Oral cavity | 83 (25.6) |
| | Hypopharynx | 51 (15.7) |
| | Glottic | 33 (10.2) |
| | Supraglottic | 25 (7.7) |
| | Unknown primary | 20 (6.2) |
| | Nasopharynx | 10 (3.1) |
| | Nasal cavity and paranasal sinuses | 10 (3.1) |
| | Subglottic | 3 (0.9) |
| | Lip | 3 (0.9) |
| Chronology of DM | Synchronous with index tumor | 53 (16.4) |
| | DM as 1st recurrence | 197 (60.8) |
| | DM as 2nd recurrence | 63 (19.4) |
| | DM as 3rd recurrence | 9 (2.8) |
| | DM as 4th recurrence | 2 (0.6) |
| Index tumor recurrence at time of DM | No recurrence | 174 (53.7) |
| | Local | 27 (8.3) |
| | Regional | 48 (14.8) |
| | Locoregional | 22 (6.8) |
| Treatment of metastatic foci | No treatment | 240 (74.1) |
| | Local therapy (surgery or radiotherapy) | 65 (20.1) |
| | Systemic therapy | 13 (4.0) |
| | Local and systemic therapy | 6 (1.9) |
| Pattern of DM | Oligometastasis | 115 (35.5) |
| | Explosive | 64 (19.8) |
| | Explosive-disseminating | 145 (44.8) |

Abbreviations: SD, standard deviation; DM, distant metastasis.

**Table 2**
Affected anatomic sites of distant metastasis.

| Anatomic sites | No. (% of patients) |
|---|---|
| Lungs | 187 (57.7) |
| Mediastinal and/or hilar lymph nodes | 164 (50.6) |
| Skin | 66 (20.4) |
| Skeletal system | 62 (19.1) |
| Liver | 45 (13.9) |
| Brain | 7 (2.2) |
| Adrenal glands | 7 (2.2) |
| Parotid glands | 5 (1.5) |
| Spleen | 5 (1.5) |
| Kidneys | 5 (1.5) |
| Pancreas | 1 (0.3) |
| Other anatomic sites | 52 (16.0) |

**Table 3**
Distant metastasis pattern per sub site.

| Index site | Oligometastasis – No. (%) | Explosive – No. (%) | Explosive-disseminating – No. (%) |
|---|---|---|---|
| Oropharynx | 26 (30.2) | 18 (20.9) | 42 (48.8) |
| Oral cavity | 32 (38.6) | 14 (16.9) | 37 (44.6) |
| Hypopharynx | 14 (27.5) | 19 (37.3) | 18 (35.3) |
| Glottic | 14 (42.4) | 3 (9.1) | 16 (48.5) |
| Supraglottic | 11 (44.0) | 8 (32.0) | 6 (24.0) |
| Unknown primary | 7 (35.0) | 0 (0.0) | 13 (65.0) |
| Nasopharynx | 1 (10.0) | 2 (20.0) | 7 (70.0) |
| Nasal cavity and paranasal sinuses | 7 (70.0) | 0 (0.0) | 3 (30.0) |
| Subglottic | 1 (33.3) | 0 (0.0) | 2 (66.7) |
| Lip | 2 (66.7) | 0 (0.0) | 1 (33.3) |

**Table 4**
Univariable analysis assessment of impact on post-distant metastasis disease-specific survival.

| Variable | 3-month post-DM DSS probability | 6-month post-DM DSS probability | P value, log rank |
|---|---|---|---|
| Pattern of DM | | | **p < .001** |
| Oligometastasis | 0.71 | 0.44 | |
| Explosive | 0.59 | 0.38 | |
| Explosive-disseminating | 0.35 | 0.17 | |
| Index site classification | | | **p = .020** |
| Oropharynx | 0.56 | 0.33 | |
| Oral cavity and lip | 0.42 | 0.22 | |
| Hypopharynx | 0.65 | 0.37 | |
| Glottic | 0.46 | 0.33 | |
| Supraglottic and subglottic | 0.68 | 0.43 | |
| Unknown primary | 0.50 | 0.20 | |
| Nasopharynx | 0.50 | 0.30 | |
| Nasal cavity and paranasal sinuses | 0.50 | 0.20 | |
| Gender | | | p = .216 |
| Male | 0.57 | 0.33 | |
| Female | 0.41 | 0.22 | |
| Age at DM detection | | | p = .668 |
| <65 y | 0.55 | 0.32 | |
| ≥65 y | 0.50 | 0.29 | |
| Chronology of DM | | | **p < .001** |
| Synchronous with index tumor | 0.64 | 0.51 | |
| Metachronous DM without index tumor recurrence | 0.53 | 0.32 | |
| Metachronous DM with index tumor recurrence | 0.45 | 0.17 | |
| Treatment of metastatic foci | | | **p < .001** |
| No treatment | 0.44 | 0.22 | |
| Local therapy | 0.74 | 0.52 | |
| Systemic therapy | 0.92 | 0.62 | |
| Local and systemic therapy | 1.00 | 0.67 | |

Abbreviations: DM, distant metastasis; DSS, disease-specific survival; y, years.

A significantly longer RFS was observed in p16-positive patients, with a median RFS of 17.4 months (range 14.8–20.1 months) compared to 8.0 months (range 7.0–8.9 months) in the p16-negative patients (p = .006).

Multivariable Cox regression analysis was performed to assess how the variables performed simultaneously. All variables, except age and gender, remained statistically significant in the multivariable Cox model, see Table 5. A metastatic spread of EDM had the greatest impact on post-DM DSS in the multivariable analysis, with an HR of 2.53 (95% CI 1.94–3.31).

Chronology of DM remained to have an impact on post-DM DSS. Patients with metachronous DM with recurrence of the index tumor had a worse prognosis compared to patients who developed DM synchronously with the index tumor (HR 1.94, 95% CI 1.33–2.84). Metachronous DM without index tumor recurrence, however, did not appear to impact post-DM DSS significantly more than DM synchronous with the index tumor (HR 1.33, 95% CI 0.94–1.86).

In regard to index site classification, DM originating from the oral cavity and lip (HR 1.77, 95% CI 1.29–2.42) or from the nasal cavity and paranasal sinuses (HR 2.07, 95% CI 1.03–4.14) showed significantly worse post-DM DSS in comparison to DM originating from other subsites.

### *Long term survivors*

Three patients remained alive at the time of last follow up with all three of them having an OM pattern. Two patients with a hypopharynx and an oropharynx tumor as primaries had undergone a wedge excision of the lung for a suspicious long nodule. Loss of heterogeneity analyses showed that the excised lung nodules and the primary HNSCC emerged from the same entity. In both patients, no adjuvant therapy was given and there was no evidence of disease at the time of inclusion three years post metastasectomy. The other patient presented with a HPV p16-negative T4aN1 oropharyngeal tumor with three suspicious nodules in the lungs on the diagnostic CT-scan. The patient received palliative radiotherapy to the primary tumor and the neck without systemic therapy, and remained alive six years after diagnosis with stable metastatic disease in the lungs.

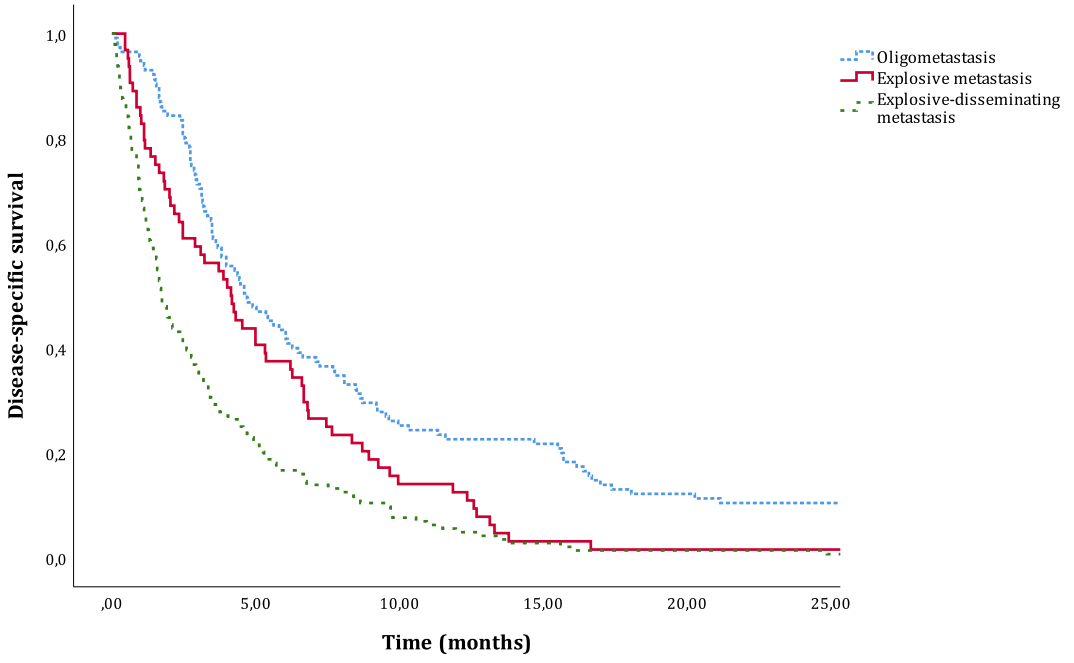


**Fig. 1.** Kaplan-Meier curve of post-distant metastasis disease-specific survival by distant metastasis pattern (log-rank test p < .01).

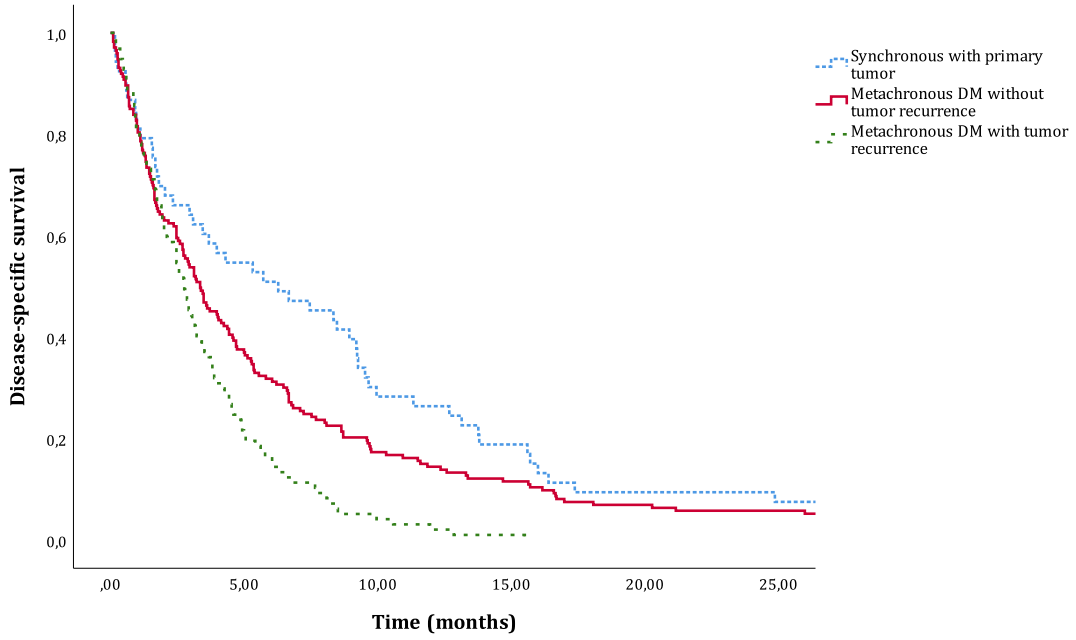


**Fig. 2.** Kaplan-Meier curve of post-distant metastasis disease-specific survival by distant metastasis chronology (log-rank test $p < .01$).

## Discussion

In this study, we observed that patients with an OM pattern had longer post-DM DSS rates in comparison to patients with a poly-metastatic pattern. Furthermore, patients with multiple (≥4) metastatic foci at one anatomic site showed more promising survival rates than patients with disseminated spread. For oropharyngeal cancer, similar findings have been reported by other authors [8,10,11].

A median difference in RFS of 9.5 months was observed in HPV p16-positive patients. This is comparable to the observations by Sinha et al., where p16-positive patients were also found to develop DM later in their course than p16-negative patients (3.6 months difference, $p = .002$) [10].

In our series, not only were patterns of metastasis associated with survival, but also chronology of DM. Patients with synchronous DM (with local tumor) at first presentation had more favorable survival rates than those who developed DM as recurrence. In multivariable analysis, the difference in survival remained significant compared to patients who developed metachronous DM with recurrence of the index tumor. However metachronous DM without recurrence of the index tumor showed a similar HR to patients with synchronous DM. In non-head and neck regions, it remains controversial whether there is a clear prognostic significance regarding synchronous versus metachronous metastasis detection [13,16].

Schwartz et al. compared the survival of synchronous and metachronous second cancers in head and neck tumors. No significant difference in survival was observed in both groups, with a post-2nd cancer 5-year survival of 7.2% and 8.5% respectively ($p = .97$). Nevertheless, no sub-analysis of the DM group was performed in their study [17]. To our knowledge, no studies in literature exist comparing synchronous versus metachronous DM detection for head and neck tumors.

In the synchronous group, five patients developed DM during treatment of the primary tumor. Three developed DM after finishing surgery but before the start of the post-operative radiotherapy, whereas two patients developed DM during (primary) radiotherapy. Due to the small numbers, no meaningful statistical analyses could be performed. Despite the fact that this sub-group is generally associated with an unfavorable prognosis, the synchronous group remains to have significantly longer post-DM DSS than the metachronous categories.

In this study, we considered skeletal metastases to be distinct anatomic sites in case of spread to separate bones instead of one organ. Up until now, it remained undefined in literature how spread to the skeletal system is to be classified. In our view, tumor metastasis to two separate bony structures (e.g. scapula and rib) has different clinical implications than when there are two metastatic foci in one bone (e.g. only rib). We therefore presumed that (bony) anatomic sites should be classified based on their underlying blood supply.

### *Long term survivors*

In our cohort, the median and mean post-DM DSS were 3.2 months and 6.3 months respectively, this is comparable to survival rates reported by other authors [5,6,18].

Three patients remained alive at the time of last follow-up. One of these patients (with OM) had received only palliative radiotherapy to the primary tumor in the head and neck, but remained to have stable metastatic disease six years after diagnosis.

There is increasing evidence that radiotherapy can induce a systemic immune response, resulting in the regression of tumor fields outside of the irradiated target volumes. This phenomenon is the so-called "abscopal effect" (from the Latin ab scopus, away from the target) [19]. The theory behind the abscopal effect is that radiotherapy is capable of inducing a tumor-specific immune-mediated response through the release of tumor associated antigens (TAA). These TAAs will in turn be presented to T-cells by dendritic cells in the lymph nodes, causing the T-cells to exit the lymph nodes and kill malignant cells outside the irradiated tumor site [20]. A theory for the long-term survival in this patient could therefore be that the palliative radiotherapy to the head and neck has halted the progression of the metastatic disease through the abscopal effect.

### *Treatment and mechanisms of (oligo)metastasis*

Metastasis of cancer is a complex and multi-step process that involves a number of fundamental biological processes. The metastatic process includes epithelial-mesenchymal transition (EMT), detachment from the primary tumor site and mesenchymal-epithelial transition (MET), after which a metastatic lesion begins to grow in a colonized distant environment [21]. However, two questions still remain; (1) what causes OM to occur rather than more aggressive spread?,(2) why does

**Table 5**
Multivariable Cox regression analysis - impact on post-distant metastasis disease-specific survival.

| Variable | Hazard Ratio (exp β) | P value | 95% confidence interval |
|---|---|---|---|
| Pattern of DM | | | |
| Oligometastasis | 1.000 | **p < .001** | |
| Explosive | 1.754 | | 1.25–2.46 |
| Explosive-disseminating | 2.534 | | 1.94–3.31 |
| Index site classification | | | |
| Oropharynx | 1.000 | **p = .001** | |
| Oral cavity and lip | 1.765 | | 1.29–2.42 |
| Nasopharynx | 1.910 | | 0.93–3.91 |
| Hypopharynx | 0.866 | | 0.61–1.24 |
| Nasal cavity and paranasal sinuses | 2.067 | | 1.03–4.14 |
| Glottic | 1.128 | | 0.74–1.73 |
| Supraglottic and subglottic | 0.868 | | 0.56–1.35 |
| Unknown primary | 1.255 | | 0.76–2.09 |
| Gender | | | |
| Male | 1.000 | p = .494 | |
| Female | 1.096 | | 0.84–1.42 |
| Age at DM detection | | | |
| Mean age (64.3) | 1.000 | p = .132 | |
| Above* | 0.990 | | 0.98–1.00 |
| Chronology of DM | | | |
| Synchronous with index tumor | 1.000 | **p = .001** | |
| Metachronous DM without index tumor recurrence | 1.325 | | 0.94–1.86 |
| Metachronous DM with index tumor recurrence | 1.941 | | 1.33–2.84 |
| Treatment of metastatic foci | | | |
| No treatment | 1.000 | **p < .001** | |
| Local therapy (surgery or radiotherapy) | 0.481 | | 0.36–0.65 |
| Systemic therapy | 0.329 | | 0.18–0.61 |
| Local and systemic therapy | 0.472 | | 0.20–1.09 |

Abbreviations: DM, distant metastasis.
* Hazard ratio per year increase.

metachronous DM lead to worse survival rates than synchronous DM?

Two possibilities concerning the development of OM have been suggested. These two extreme possibilities state that OM either occurs due to a less aggressive genomic milieu, or that OM is merely an early stage in the sequential development of polymetastatic disease [8,22]. In oligometastatic samples of tumors originating from non-head and neck regions, multiple over-expressed tumor-suppressor micro-RNAs have been found. This suggests that tumor-suppressor micro-RNAs may cause negative regulatory loops in oligometastatic lesions, preventing the formation of more extensive metastatic disease [22].

Furthermore, as discussed above, EMT is a fundamental transformation in the metastatic process, necessary for the escape from the primary tumor. The process of EMT encompasses the loss of epithelial morphology and markers, leading to a mesenchymal cell phenotype [23]. A number of well-known regulators of the EMT mechanism have been identified in oligometastatic samples, such as mir-200cc, mir-29c and mir-665, which suppress EMT through distinct regulatory pathways [24–26]. As an answer to the first question, it is therefore likely that oligometastatic disease, and thus limited metastatic spread, is partially dependent on the suppression of the EMT process and the over-expression of tumor-suppressor micro-RNAs.

On the other hand, cancer stem cells (CSCs) are a small subpopulation within cancer cells with the capability of self-renewal and multipotent differentiation [23]. CSCs portray a mesenchymal cell phenotype and it is believed that CSCs may play a role in cancer relapse, especially post-radiotherapy [27]. Studies have shown that ionizing radiation can induce certain molecular signaling factors, such as TGF-β, which in turn promote EMT and enhance the CSC phenotype of normal tumor cells [23,28]. In addition, carcinoma-associated fibroblasts are believed to be "activated" by ionizing radiation, causing it to secrete various cytokines which induce cancer progression [29]. Moreover, an in vitro study of hepatic carcinomas showed that the secreted cytokines promote the survival and metastasis of CSCs and increase the number of circulating tumor cells [23,30]. In patients with cancer of the oral cavity, higher levels of interleukin-6 cytokines were detected in cases of recurrent cancer than in primary tumors [23]. A possible explanation to the second question is that pre-treated HNSCC, specifically with radiotherapy, can lead to a more aggressive metastatic recurrence which in turn leads to a more unfavorable prognosis.

### *Study strengths and limitations*

Our study paves the way for a more individualized prognostic prediction in patients with DM. In our center, an internally and externally validated prognostic model (OncologIQ) was developed over the last two decades to estimate the OS of patients with HNSCC through tumor- and patient specific factors [31–33]. The new insights from this study allow the addition of the metastatic patterns and DM chronology to the OncologIQ model as independent prognosticators for survival, as it has been shown that patients prefer receiving prognostic information in case of a poor prognosis [34]. To our knowledge, this study is the first of its kind which assesses the significance of oligometastatic cancers and DM chronology for all sites of the head and neck region.

However, beyond its retrospective nature, one substantial limitation in our study is the unavailability of all HPV-p16 and Epstein-Barr virus statuses. Furthermore, besides the covariates accounted for in the multivariable cox regression analysis, it is possible that other factors, such as comorbidity, may also influence the post-DM DSS.

## Conclusion

This study demonstrated that an oligometastatic pattern is associated with more favorable survival rates compared to an explosive-disseminating pattern. Moreover, a middle group of metastatic pattern has been identified in which multiple metastatic lesions are confined to one anatomic site, showing relatively comparable survival rates to the oligometastatic group. Patients with DM at first presentation concomitant with their primary tumor portend a better prognosis than metachronous DM. These distinct patterns of DM will be of value in prognostication and counseling.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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