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ORIGINAL ARTICLE

Distant metastases in squamous cell carcinoma of the pharynx and larynx: a population-based DAHANCA study

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ABSTRACT

Background: In head and neck cancer, distant metastases may be present at diagnosis (M1) or occur after treatment (DM). It is unknown whether M1 and DM follow the same clinical development and share prognosis, as population-based studies regarding outcomes are scarce. Therefore, we investigated the incidence, location of metastases and overall survival of patients with M1 and DM.

Materials and methods: Patients diagnosed with squamous cell carcinoma of the pharynx and larynx in Denmark 2008–2017 were identified in the Danish Head and Neck Cancer Group (DAHANCA) database. We identified 7300 patients, of whom 197 (3%) had M1 and 498 (8%) developed DM during follow-up.

Results: The 5-year cumulative incidence of DM was 8%. 1- and 2-year overall survival for DM (27% and 13%) vs. M1 (28% and 9%) were equally poor. There was no significant difference in location of metastases for M1 and DM and the most frequently involved organs were lungs, bone, lymph nodes and liver, in descending order. In oropharyngeal squamous cell carcinomas, the location of metastases did not differ by p16-status. For p16-positive patients, 21% of DM occurred later than three years of follow-up compared to 7% of p16-negative patients.

Conclusion: Incidence, location of metastases and prognosis of primary metastatic (M1) or post-treatment metastatic (DM) disease in pharyngeal and laryngeal squamous cell carcinoma are similar in this register-based study

Abbreviations: DAHANCA: The Danish Head and Neck Cancer Group; DM: Distant metastases post-treatment; HNSCC: Head and neck squamous cell carcinoma; HPV: human papillomavirus; M1: Distant metastases present at diagnosis; NPC: Nasopharyngeal carcinoma; OPSCC: Oropharyngeal squamous cell carcinoma; RT: Radiotherapy; RTOG: Radiation Therapy Oncology Group; UICC: Union for International Cancer Control

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KEYWORDS
Distant metastases; head and neck cancer; human papillomavirus; radiotherapy; the pattern of failure

Background

The incidence of head and neck squamous cell carcinoma (HNSCC) is changing worldwide due to decreasing smoking rates and increasing rates of human papillomavirus (HPV)-related cancers in high-income countries [1–3]. HNSCC is primarily a locoregional disease and few patients have distant metastases present at diagnosis (M1) [4,5]. HNSCC has therefore traditionally been treated with intensive locoregional therapy. Advances in the treatment of HNSCC have led to the improved locoregional outcome and fewer side effects, but the proportion of patients with distant metastases (DM) remains significant [6–8]. In Denmark, data from a historical cohort of HNSCC patients (1963–1991) [9–13] demonstrated an absolute DM incidence of 6%, however, temporary population-based data on DM across HNSCC subsites are lacking. Development of distant metastases is associated with a dismal prognosis, but it is unclear whether primary metastatic HNSCC (M1) and post-treatment metastatic HNSCC (DM) are the same metastatic disease only dispersed in timing, or if they have unique properties making one more aggressive than the other.

In addition to improvement in locoregional treatment of head and neck cancer, the emergence of human papillomavirus (HPV)-associated oropharyngeal squamous cell carcinomas (OPSCCs) has affected the recurrence pattern in HNSCC. Compared to HPV-negative patients, HPV-positive OPSCC patients are generally characterized by having less comorbidity and superior locoregional control and overall survival rates [14]. Nevertheless, the metastatic potential of HPV-positive OPSCC tumors is comparable to that of HPV-negative tumors, making distant metastases a relatively

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common recurrence in HPV-positive OPSCC [15,16]. Some studies have suggested a more 'disseminated' metastatic pattern in HPV-positive OPSCC with the involvement of unusual anatomical locations of metastases [15,17,18], while other studies do not support this observation [19,20]. Studies generally agree that HPV-positive patients have a unique epidemiologic profile where DMs occur later and a better post-DM survival is observed [6,18,19,21].

Using a complete, population-based cohort of squamous cell carcinoma of the pharynx and larynx over a 10-year period, this study aims to describe the cumulative incidence of M1 and DM and investigate potential differences in M1 and DM, regarding their anatomical location and prognosis (overall survival). For the subgroup of OPSCC, we aim to investigate the hypothesis that the incidence, anatomical location, timing and post-DM survival vary according to p16-status.

Materials and methods

Patient selection

In Denmark, primary radiotherapy (RT) is the most common treatment of pharyngeal and laryngeal carcinoma and is managed in multidisciplinary teams at six head and neck oncology centers. The cohort was retrospectively identified using the Danish Head and Neck Cancer Database (DAHANCA), a population-based clinical database with national coverage of HNSCC patients close to 100% [22]. The data in DAHANCA is prospectively recorded and covers information on the time of diagnosis, primary tumor site, TNM-classification, histology, treatment, follow-up and recurrences. Missing data from DAHANCA was cross-checked with the patients' hospital record, the National Pathology Register (Patobank) and vital status were updated (1st April 2020) using the National Health Database, which is linked to The Danish Civil Registration System. Patients were eligible if they had invasive squamous cell carcinoma of the pharynx or larynx with the first consultation at a head and neck oncology center between 1st January 2008 to 31st December 2017 (Supplementary A). They were excluded if they lived in Greenland or the Faroe Islands, were primarily treated outside of Denmark or had prior or synchronous HNSCC.

Staging, treatment and follow-up

Patients were staged according to UICC 7th edition at diagnosis. HPV-status was determined using p16 as a surrogate marker and p16-positivity defined as >70% of cells stained p16-positive [23].

Treatment was given according to national guidelines (developed by the DAHANCA group). The standard treatment for pharynx and larynx cancer in Denmark is concurrent chemo-radiotherapy with radical intent [24]. Primary radical radiotherapy was given as 6 fractions per week, to a dose of 66–68 Gy in 33–34 fractions. Concurrent chemotherapy was offered to fit patients with stage III–IV disease as weekly cisplatin 40 mg/m^2. Nimorazole (a hypoxic radiosensitizer) was offered to all patients undergoing primary RT [25], except for patients with stage I glottic larynx carcinoma. Patients with M1 were treated either with radical or palliative radiotherapy. Information about the metastatic disease had to be available before treatment, which meant that most M1 patients were treated with a palliative regimen. Treatment with radical radiotherapy may have been initiated to obtain locoregional control or in situations with the oligo-metastatic disease. However, we did not have information on the numbers of metastases and could therefore not identify oligo-metastatic disease in the individual patient.

The patients were evaluated two months after RT and followed every 4 months for 2 years and every 6 months for 3 years, for a total of 5 years. After 2014 this was changed to every 6 months the first 2 years and annually years 3–5 [26]. This evaluation included pharyngo-laryngo-endoscopy and physical examination. Imaging and post-RT neck dissections were only performed upon suspicion of recurrence, not routinely.

Identification of M1 and disease recurrences

A patient was classified as having M1 disease if distant metastases were present at the time of diagnosis (either from biopsies or imaging).

Recurrences after treatment were reported as either local, nodal, distant or combinations thereof. Only data on the first recurrence in patients treated with radical radiotherapy were included in this report. If distant metastases (DM) were observed within 3 months after a locoregional recurrence, they were considered concurrent and combined as the first recurrence. The earliest possible recording of a recurrence was at the clinical assessment two months post-treatment.

DM was defined as tumor growth outside the head and neck region (including the mediastinum), verified with biopsies and/or imaging, and not characterized as a new primary tumor. Location of metastases included lung, pleura, liver, bone, lymph nodes, skin, brain, peritoneum and others. For simplicity, lung and pleura were combined as well as skin, brain, peritoneum as 'other' (except in the analysis of dissemination). For both M1 and DM, more than one anatomical location per patient may be reported.

During the study period 2008–2017 there was no national consensus regarding imaging modalities for treatment planning or recurrence detection and both PET-CT, CT and MRI were used.

Statistics

Incidence of M1 and DM was defined as the absolute, accumulated number of patients who experienced the respective event at the time of analysis. The follow-up time was calculated as the time difference between the date of the first consultation at the head and neck oncology center and the date of either death, recurrence or time of evaluation (1st April 2020).

Overall survival of DM patients was reported from the date of DM recurrence to the date of either death or end of follow-up, whereas overall survival for M1 patients was

reported from the date of the first consultation to death or end of follow-up. The cumulative risk of DM was calculated with the competing risk method, the event of interest was the detection of DM and competing risks were 'locoregional recurrence (T and/or N) without DM' and 'Dead – no evidence of disease'.

All analyses were performed using the statistical software R version 3.6.1. Survival analysis was conducted with the Kaplan Meier method (prodlim package) in R software and log-rank test to compare groups. For categorical variables, Pearson's Chi-square test or Fischer's exact test were used to comparing frequencies. Two-sided p-values <0.05 were deemed significant. Cumulative incidence of DM was calculated with Competing Risk (cmprsk) package in R software and Gray's test was used to compare groups [27,28].

Results

Patient characteristics, treatment and overall survival

The cohort consisted of 7300 patients. For patient characteristics and treatment, see Table 1.

Males constituted 78% and females 22% of the cohort. Pharyngeal cancer was the predominant subsite (67%). Of all patients, 68% presented with stage III or IV. The median age for all patients was 63 years, for DM patients 62 years and M1 patients 65 years. Of oropharyngeal patients ($n = 3765$), 57% were p16-positive and 35% were p16-negative (Supplementary B).

In the cohort, 6352 (87%) patients were treated with radical intended radiotherapy/surgery and 541 (7%) patients were treated with palliative intent, while 236 (3%) patients received no treatment. Of the 353 patients who had radical surgery only, 205 (58%) were T1 glottic laryngeal carcinomas and 130 (37%) were oropharyngeal carcinomas.

At the time of evaluation, 51.5% of the cohort had died. The 2-year and 5-year overall survival rates were 71.2% and 54.9%. The median observation time was 46 months (0–147 months).

Patients with M1 disease

Incidence of M1 and location of metastases

At the time of diagnosis, 197 of 7300 patients (3%) had metastatic disease, ranging from very low proportions in glottic larynx carcinomas (0.3%) to 7% of hypopharyngeal carcinomas (Table 1). M1 disease most often involved lungs

Table 1. Clinical characteristics and treatment of patients[a].

	All patients ($n = 7300$) Number	M1 patients ($n = 197$)[b] Number	%[c]	Radical treatment intent ($n = 6352$)[d] Number	DM patients ($n = 498$)[e] Number	%
Gender						
Male	5678	159	2.8	4958	411	8.3
Female	1622	38	2.3	1394	87	6.2
Subsite						
Oropharynx	3765	95	2.5	3315	248	7.5
p16/HPV+	2133	31	1.5	2032	132	6.5
p16/HPV-	1319	49	3.7	1047	100	9.6
p16/HPVunknown	313	15	4.8	236	16	6.8
Hypopharynx	872	61	7.0	660	122	18.5
Nasopharynx	256	14	5.5	211	32	15.2
Supraglottic[f]	835	21	2.5	699	54	7.7
Glottic	1516	5	0.3	1422	40	2.8
Subglottic	55	0	0.0	45	2	4.4
T-classification						
T1	2066	21	1.0	1970	47	2.4
T2	2738	47	1.7	2498	198	7.9
T3	1409	50	3.5	1155	143	12.4
T4	868	60	6.9	599	98	16.4
N-classification						
N0	2749	18	0.7	2508	79	3.1
N1	1060	19	1.8	944	57	6.0
N2	3077	114	3.7	2662	320	12.0
N3	293	36	12.3	199	40	20.1
Stage						
I	1150	0	0.0	1112	10	0.9
II	1049	0	0.0	967	32	3.3
III	1311	0	0.0	1188	79	6.6
IV	3662	197	5.4	3034	375	12.4
Primary treatment intent						
Radical radiotherapy	5891	40	0.7	5851	486	8.3
Radical radiotherapy + surgery	150	2	1.3	148	7	4.7
Radical surgery alone	353	0	0.0	353	5	1.4
Palliative treatment	541	107	19.8	0	0	0.0
No treatment	236	43	18.2	0	0	0.0

[a]Missing values are omitted from the table if ≤5% of total.
[b]M1: Patients with distant metastases at time of diagnosis.
[c]Row percentage: The proportion of patients in this category out of total patients, for example, 2.8% of all male patients have M1 disease.
[d]Primary treatment intent either radiotherapy or surgery, excluding M1 patients.
[e]Distant metastases in patients treated with either radical radiotherapy or surgery.
[f]Laryngeal cancer will be referred to as glottic and non-glottic (supraglottic + subglottic) in the text.

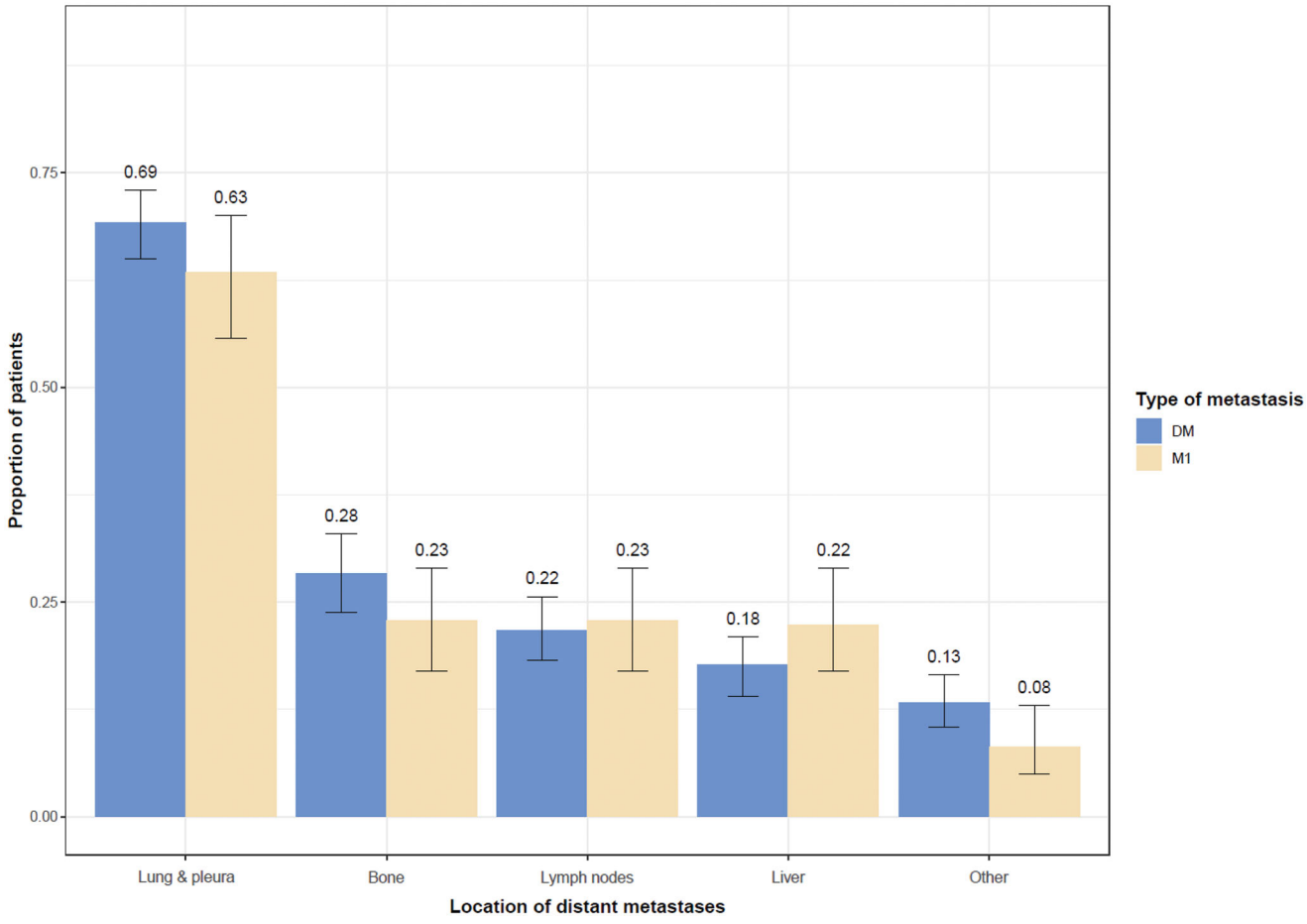

Figure 1. The figure shows the proportion of pharynx or larynx SCC patients with distant metastases in a specific anatomical location. The analysis is based on 197 M1 patients and 498 DM patients. As several anatomical locations may be involved at the same time, the sum of proportions is > 1. Error bars represent 95% CI.

and less likely liver, bones and lymph nodes outside the neck with similar frequencies (Figure 1 **(pale bars)**). No brain metastases were observed for M1 disease. Two M1 patients (1%) were excluded from the analysis due to missing information on the involved metastatic location. There was no temporal development in the proportion of M1 disease during the period 2008–2017.

Overall survival for M1 patients

At the time of evaluation, 194 of 197 (98%) M1 patients had died. One- and two-year overall survival for M1 patients were 28% and 9%, respectively (Figure 2), with a median of 5.9 [95% CI 5.0; 7.9] months.

The primary treatment of 197 M1 patients was radical RT in 42 (21%) patients, palliative treatment in 107 (54%) patients while 43 (22%) patients received no treatment. Median overall survival based on primary treatment was 11.6 [6.0; 14.6] months (radical treatment), 6.9 [5.1; 8.7] months (palliative treatment) and 1.5 [1.1; 3.2] months (no treatment).

Patients with DM disease

Incidence of DM and pattern of recurrences

Looking at first recurrence only for patients treated with radical RT, 1642 of 6352 (26%) patients experienced a recurrence of any kind. DM occurred in 498 of 6352 (8%) patients, 287 of 498 (58%) patients had isolated DM. Local recurrence occurred in 947 of 6352 (15%) and regional recurrence occurred in 614 of 6352 (10%) patients. The incidence of DM ranged from very low proportions in glottic larynx carcinomas (2.8%) to 18.5% in hypopharyngeal carcinomas (Table 1).

In OPSCC patients treated with radical RT, 344 of 2032 (17%) p16-positive patients and 390 of 1047 (37%) p16-negative patients experienced a recurrence of any kind. Loco- and/or regional recurrence occurred in 333/1047 (32%) of p16-negative patients compared to 247/2032 (12%) in p16-positive patients. DM occurred in 6% (p16-positive) and 10% (p16-negative), respectively. Of p16-positive OPSCC patients with any recurrence, 132 of 344 (38%) were DM compared to 100 of 390 (26%) in p16-negative patients ($p < 0.001$).

In decreasing order, DM most often involved lungs, liver, bones and lymph nodes outside the neck (Figure 1 **(blue bars)**). The anatomical distribution of metastatic locations in DM and M1 was similar ($p = 0.2$). Eleven DM patients (2%) were excluded from analysis due to missing information on the involved location. We observed 8 patients with brain metastases in the DM group.

We investigated the metastatic location of DM according to the HNSCC subsite (Figure 3**)**. The proportions are similar across subsites, the confidence intervals overlap and there

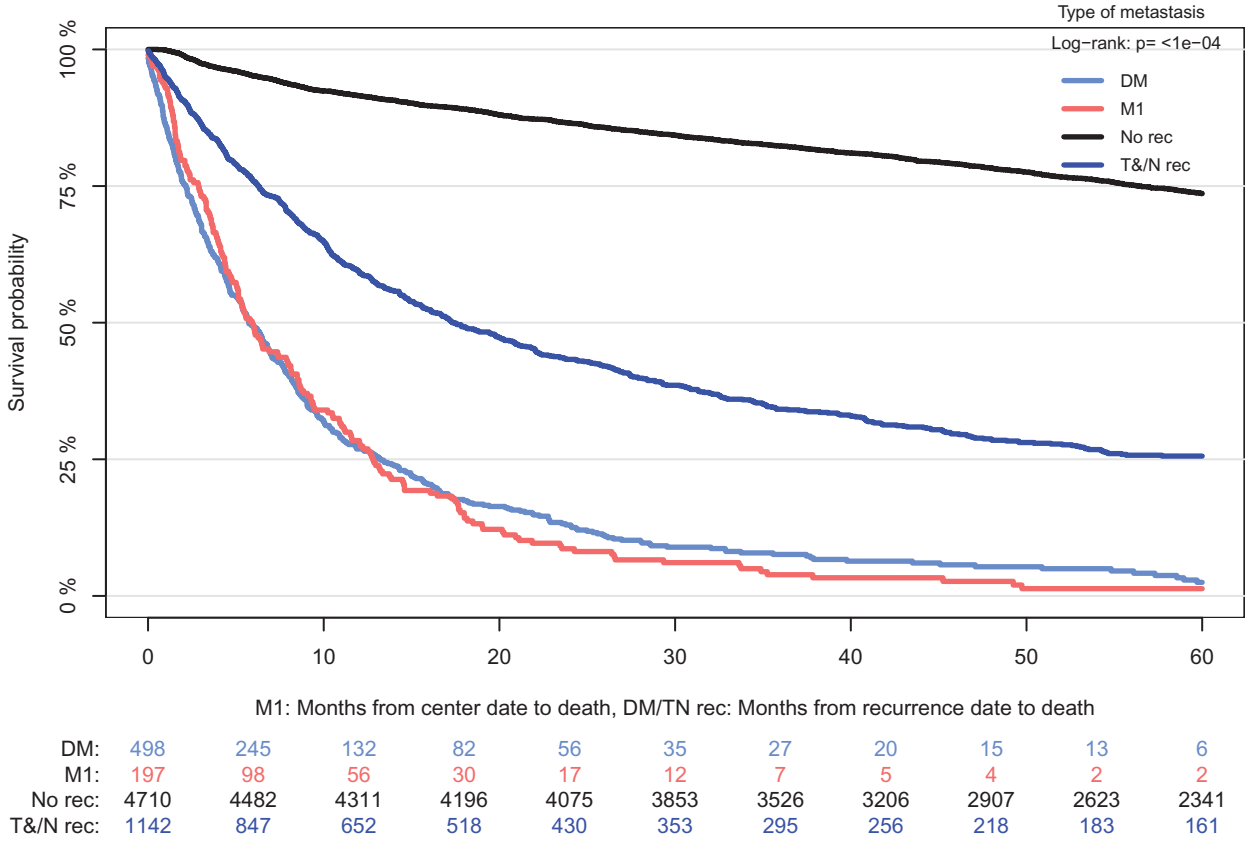

Figure 2. Kaplan–Meier curves displaying the overall survival of patients treated with radical intent with no recurrence ($n = 4710$), patients treated with radical intent with locoregional recurrence (T&/N, $n = 1144$), patients with distant recurrence with/without concurrent locoregional recurrence (DM, $n = 498$) and patients primarily diagnosed with distant metastases (M1, $n = 197$).

was no significant difference in a chi-squared test for p16-positive and p16-negative OPSCC ($p = 0.9$, data in Supplementary C). 27 patients (5%) were excluded from the analysis due to missing information. The pattern of involved metastatic locations for patients with 'p16 unknown' was similar to the included groups (data not shown). When divided into the following groups: Lung and pleura, bone, lymph nodes outside the neck, liver, brain, peritoneum, skin, other, we found that 81 of 132 (61%) patients with p16-positive OPSCC and DM had involvement of one location, 38 (29%) of two locations and 13 (10%) of $\geq$3 locations. P16-negative patients had involvement of one location in 64 of 100 (64%), 19 (19%) of two locations and 14 (14%) of $\geq$3 locations. This distribution was not significantly different ($p = 0.2$).

Overall survival and cumulative incidence of DM

At the time of evaluation, 467 of 498 (94%) DM patients had died. The median overall survival time after recurrence for DM patients was 5.7 [95% CI 5.1; 6.8] months (see Figure 2), which was inferior compared to patients with locoregional recurrence (median 17.4 [15.6; 20.1] months). One- and two-year overall survival for DM patients were 27% and 13%, respectively. Four long-term survivors (>60 months) were observed in the DM group.

The 5-year cumulative risk of DM among patients treated with radical intent was 7.9% (Data in Supplementary D). 78% (6.2 of 7.9) of DMs occurred within the first two years after treatment. The cumulative incidence of DM reached a plateau after the first three years and 11% (0.9 of 7.9) of DM occurred later than three years after treatment across all subsites of HNSCC. Hypopharyngeal and nasopharyngeal carcinomas had a significantly higher cumulative incidence of DM ($p < 0.001$), leading to a two- to three-fold higher risk of DM at two years compared to oropharyngeal or laryngeal carcinomas.

For p16-positive OPSCC patients, the 2-year and 5-year cumulative incidence of DM was significantly lower (4.3% and 6.6%) than for p16-negative OPSCC patients (8.6% and 9.6%) ($p = 0.002$). For p16-positive patients, 21% (1.4 of 6.6) of DM occurred later than three years of follow-up compared to 7% (0.7 of 9.6) of p16-negative patients.

Overall survival in patients with DM according to HNSCC subsite

Survival analysis was performed on DM stratified for the anatomical subsite of the primary tumor (Supplementary E). The post-DM survival of nasopharyngeal carcinoma and p16-positive OPSCC patients were similar and significantly better (log-rank $p < 0.001$), than other subsites. One-year post-DM survival was 43% (p16-positive OPSCC), 40% (Nasopharynx), 16% (Glottic Larynx), 13% (Hypopharynx), 13% (Non-glottic Larynx) and 10% (p16-negative OPSCC).

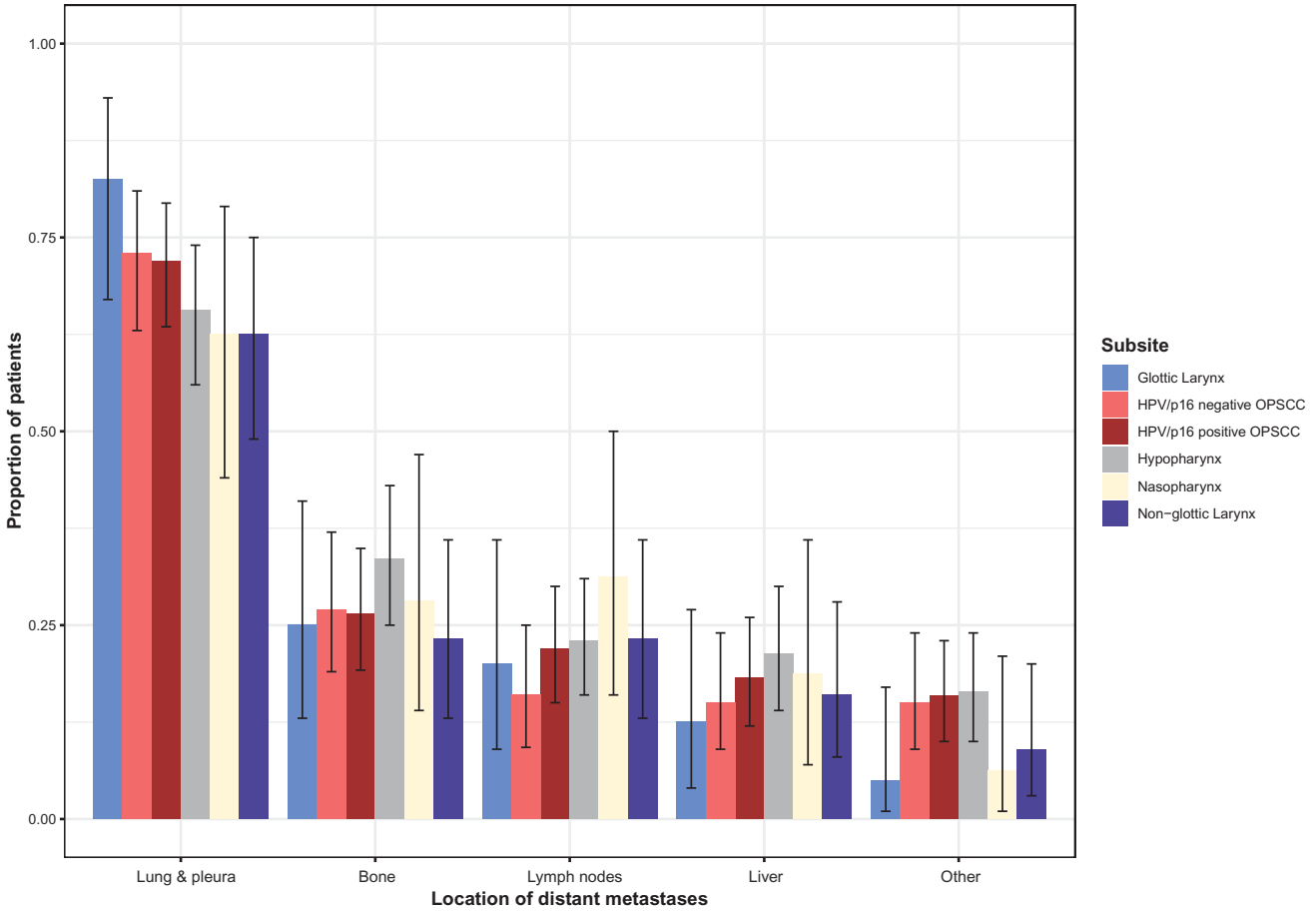

Figure 3. The figure shows the proportion of patients with distant metastases according to anatomical location of metastases by HNSCC subsite. The analysis is based on the following groups who experienced distant metastasis after treatment with radical intent: Glottic larynx ($n = 40$), HPV/p16-positive OPSCC ($n = 132$), HPV/p16-negative OPSCC ($n = 100$), Hypopharynx ($n = 122$), Nasopharynx (32) and Non-glottic Larynx ($n = 56$). As several anatomical locations may be involved at the same time, the sum of proportions is >1. Error bars represent 95% CI.

Discussion

This is the largest study to directly compare distant metastases present at diagnosis (M1) and developed after primary treatment (DM) in the same population of pharynx and larynx squamous cell carcinoma patients. We found that the location of metastases and prognosis of M1 and DM were similar.

The incidence of M1 (3%) is comparable to other population-based head and neck cancer studies [4,5]. This proportion may be dependent on the imaging modalities used in the diagnostic work-up. An incidence of up to 6% has been reported with the systematic use of whole-body PET-CT at diagnosis, while others have found 3% using a similar systematic approach [29,30].

There was no difference in overall survival or patterns of metastatic locations in M1 and DM patients, indicating that the metastatic process and prognosis are similar. Our observation of metastatic locations for M1 and DM is consistent with what has been reported in studies looking at M1 and DM individually [4,8,31]. No brain metastases were observed for any patient with M1 disease. The organ preference for metastasis is likely determined on a cellular level including the interaction of tumor cells and the microenvironmental differences in tissues [32].

Studies on M1 and DM in HNSCC tend to compare overall survival from the primary diagnosis to death, in which case survival of M1 patients is obviously worse than DM. In one study [33], comparing overall survival from the time of detection of metastases to death, there was no difference between M1 and DM. The poor survival of M1 and DM patients compared to patients with locoregional recurrence can in part be explained by the more frequent possibility of salvage surgery in patients with locoregional recurrence [34]. The overall survival for patients with M1 disease was improved if the patient received radical therapy (median: 11.6 months) compared to palliative treatment (median: 6.9 months)). This is not surprising since patients selected for intensive treatment generally are more fit. However, our data support recent evidence pointing to the benefit of radical radiotherapy added to palliative chemotherapy in patients with primary metastatic nasopharyngeal carcinoma [35]. Whether this holds across HNSCC subsites remains to be confirmed in clinical trials.

We found a DM incidence of 8%, which is comparable to other studies, ranging from 1.5% to 26% [7], with a higher incidence in studies that have higher autopsy rates. Most DMs are diagnosed within the first two years after treatment [31], and our 5-year cumulative risk of DM was 7.9%. The incidence of DM in national historical cohort data from 1963

to 1991 [9–13] was 6% compared to 8% in our study, a small increase. However, when looking at the overall group of recurrences, the proportion of DM increased from 12% to 30% compared to the historical data, which means that a considerably larger part of the recurrence treatment today is directed toward metastatic recurrences. This may be the result of several factors: improvements in treatment leading to higher locoregional control and the rise of p16-positive OPSCC. Patients with p16-positive OPSCC are typically healthier at baseline and with a biological advantage of the HPV association in their prognosis.

The most common location of distant metastases was lung, bone, lymph nodes, and liver which is in agreement with previous studies [6,8,31,36]. We were not able to confirm the occasional finding that hypopharyngeal and nasopharyngeal carcinomas have a higher metastatic affinity for liver and bone [4].

The presence of HPV in OPSCC is one of the strongest prognostic factors in head and neck cancer, reflected in the new TNM classification where HPV status is included [37]. We found the absolute number of DMs to be lower for p16-positive OPSCC tumors vs. p16-negative OPSCC tumors (6% vs. 10%), but DM is more likely in recurrent p16-positive disease (38% vs. 26%, $p < 0.001$). Given the increasing incidence and high locoregional cure rate of HPV-positive OPSCC, a rise in the absolute number of DMs may be expected in the future.

A conflicting finding in the literature concerns whether HPV-positive OPSCCs have a more disseminated – or explosive – spread of DM and/or recurrences in rare or unusual locations. In a systematic review by Tiedemann *et al.* [38], HPV-positive OPSCCs were five times more likely to develop DM in non-regional lymph nodes and much more likely to disseminate to multiple locations (>two locations) (HPV-positive: 36%, HPV-negative: 2%) [15,18,39]. In a study of 36 OPSCCs with DM, Huang *et al.* [18] observed that metastatic locations for HPV-positive patients involved unusual locations (brain, skin, intraabdominal lymph nodes). In our cohort, p16-positive and p16-negative OPSCCs developed DM in similar locations (including non-regional lymph nodes), and there was no indication of p16-positive OPSCC being more widespread, as only 10% of p16-positive patients had more than 2 locations involved compared to 14% of p16-negative patients.

With the inclusion of more OPSCC DM patients than any previous studies, we find no indications that p16-status affects organ preferences. Studies from P. Sinha *et al.* [20] and C. Fahkry *et al.* [19] reached the same conclusion. Notably, other dominantly HPV-negative HNSCC, like hypopharyngeal carcinoma and oral cavity carcinoma, have also been found to metastasize to unusual locations (brain, skin, muscles, abdominal organs) [21]. These conflicting findings probably arise from 'metastatic location' and 'degree of spread' being time- and survival-dependent variables. It may be that we observe a pattern of DM in HPV-positive OPSCC patients which would have been observed for HPV-negative patients, had they lived long enough [21]. This is also likely the explanation for reports [15,38,40] that HPV-positive OPSCC could bypass regional nodes and spread hematogenous to, for example, the brain to a higher degree than HPV-negative OPSCC. However, looking at first recurrence only, we found no difference between p16-positive and p16-negative OPSCC.

Post-DM survival was superior for p16-positive OPSCC and nasopharyngeal carcinoma (NPC) patients. DM patients with p16-positive OPSCC and NPC were slightly younger than the rest of our DM study cohort (median age DM overall 62 years, nasopharyngeal patients 61 years and p16-positive OPSCC patients 59 years). But more importantly, both p16-positive OPSCC and NPC are virally driven diseases, the latter associated with Epstein–Barr–Virus. This means a lower frequency of risk factors normally associated with HNSCC and a corresponding lower risk of co-morbidities, which may affect survival. The viral association may also influence the outcome of treatment, and a recent study [41] found that in HPV-positive tumors, HPV infection promoted T-cell infiltration and immune recognition. This is hypothesized to elevate the immune response in the tumor leading to a better outcome. HPV-positive OPSCC may also have a higher response rate to both palliative chemotherapy and immunotherapy as indicated in the EXTREME trial (p16-pos 34%/p16-neg 27%) [42] and the Checkmate 141 trial (HPV-positive 17.4%/HPV-negative 14.3%) [43].

DM is rarely a primary endpoint in clinical trials and the literature is characterized by retrospective, hospital-based studies with a limited number of DM patients. The strength of our study is that the data comes from a uniformly treated, population-based cohort and that recurrences have been registered prospectively. The inclusion of M1 patients provides us with a more nuanced history of distant metastasis.

A limitation is the lack of information on the degree of dissemination in an organ (number of metastases or volume) and the nature of oligometastatic disease could therefore not be addressed. The lack of detailed information on the treatment of recurrences is also a limitation and a confounder for survival rates. Some new primary cancers may have been misclassified as DMs (and vice versa), but in the case of new primary cancers, patients continued in the head and neck cancer follow-up program. Finally, the inclusion of more than the first recurrence would be optimal to circumvent the difference in risk of locoregional recurrences across HNSCC subsites, but these data were not registered consistently.

Conclusion

M1 and DM head and neck patients share the same poor prognosis and anatomical location of distant metastases, pointing to the same mechanisms being responsible for the dissemination. Although distant metastases occur later for p16-positive OPSCC, they involve the same metastatic locations as their p16-negative counterparts.

Disclosure statement

No potential conflict of interest was reported by the author(s). The results presented in this study are not associated with the funding sources.

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Data availability statement

The data that supports the findings of this study are available in the supplementary material of this article. Other data can be made available upon request.

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