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LETTER TO THE EDITOR

The potential for local ablative therapy of oligometastases in head and neck squamous cell carcinoma: a real-world data analysis

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Background

Patients with head and neck squamous cell carcinoma (HNSCC) who develop post-treatment distant metastases (DM) have a poor prognosis and few treatment options. DMs from HNSCC are rare compared to other solid tumors, occurring in 5%–20% of patients [1,2]. Some patients with DM may have limited metastases in few metastatic sites. This has been coined the 'oligometastatic state' and is most often defined as up to five DMs [3–6]. In HNSCC, 30%–40% of patients with DM have oligometastases at DM diagnosis [3]. Oligometastases may be eligible for surgery, radiotherapy or other local ablative therapies (LAT), and the patients may benefit from an aggressive local strategy with prolonged disease-free survival, deferral of systemic treatment, and sometimes even cure [7–9]. LAT has shown promising results, especially for stereotactic body radiation therapy (SBRT) [8,10]. Prospective SBRT studies in the palliative setting include only a few HNSCC patients [11,12].

Historically, fit patients with oligometastatic HNSCC were offered metastasectomy (most often lung resections) and SBRT was infrequently used. Technical advances in radiotherapy have facilitated improved precision and sparing of normal tissue, making SBRT a favorable option. The proportion of patients with oligometastatic HNSCC was assessed in a complete cohort including the potential for SBRT treatment.

Methods

The study was approved by the Danish Data Protection Agency (#P-2019-765) and the Danish Patient Safety Authority (#31-1521-24).

Study population

Patients were identified in the Danish Head and Neck Cancer (DAHANCA) database. The national database has prospectively recorded treatment and outcome data on close to 100% of Danish HNSCC patients [13]. The inclusion criteria were squamous cell carcinoma of the pharynx or larynx diagnosed from 2008 to 2017 at Rigshospitalet, a large tertiary hospital in Copenhagen.

Data collection

The extent of DM (organs and number of metastases) was recorded from recurrence scans (CT/MRI/^{18}F-FDG-PET). ^{18}F-FDG-PET scans were available for DM work-up in 73% of patients for the whole study period (61% from 2009 to 2013 increasing to 85% from 2014 to 2020). As per current international consensus, oligometastatic disease (OMD) was defined as one-to-five DMs. Polymetastatic disease (PMD) was defined as more than five DMs. Loco- and/or regional recurrences were not considered. According to the DAHANCA database registration guidelines, metachronous recurrences (de novo post-treatment recurrences) occur more than two months after the end of primary treatment. The scan of interest was defined as the first scan with a possible DM. Additional scans were allowed to add information on the DM extent if they were available within one month after the first scan. Scans were reviewed by a radiologist and a radiation oncologist. For six patients, no scans were available and the number of metastases was extracted from the description in the patient medical records. Most DMs were verified histologically (78%). As validation, pathological reports from 457 patients (2008–2011) without DMs were reviewed and no missing DMs were identified.

The metastatic sites were grouped as (and each counted as one organ): lung (± pleura), bone, liver, lymph nodes, brain, peritoneum, skin, and rarer sites. The following definition of 'symptomatic' was used: If in a patient file, a patient/doctor reported one/more symptoms from an organ where the DM(s) resided. Non-symptomatic patients most often had DMs discovered on scans during control visits. Patients were deemed non-symptomatic if it was symptoms from locoregional recurrences that led to DM discovery.
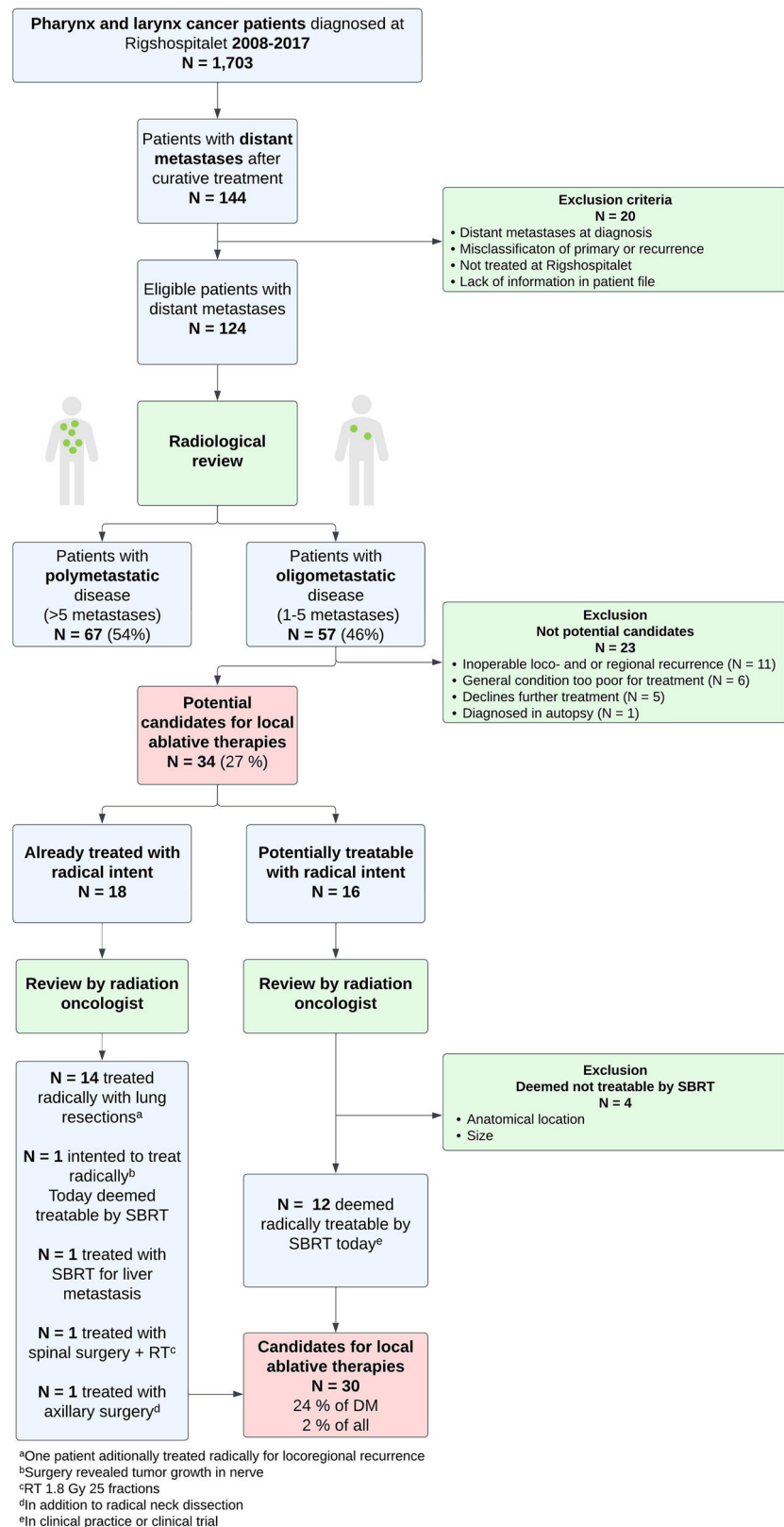
Figure 1. Flowchart showing the selection of candidates for local ablative therapy of pharynx and larynx squamous cell carcinomas. RT; radiotherapy, DM; distant metastases, SBRT; stereotactic body radiation therapy. Created in lucidchart, www.lucidchart.com.

The therapeutic *intent* (radical/palliative) and type of treatment (surgery, radiotherapy, and systemic treatment) were recorded. Patients were considered treated palliatively, either if they received disease-specific treatment with palliative intent or supportive care with no disease-specific treatment.

Video-assisted thoracoscopic surgery (VATS) was performed with radical intent if the surgeons had intended to remove all metastatic lesions by either wedge resection or lobectomy. VATS was considered diagnostic if it was for histological verification only. Patient recurrence scans were

assessed retrospectively by a radiation oncologist for potential eligibility for SBRT. The eligibility criteria were: Size < 5 cm, no pleural or peritoneal metastases and no involvement of critical structures (e.g., neuroforamina, bronchi).

Statistics

All analyses were performed in R (version 4.1.0). Two-sided p-values below .05 were considered statistically significant. Differences in proportions were assessed with chi-square or Fisher's test. Time to DM was reported as the time from date of entry at the oncological department (primary diagnosis) to the date of DM. Survival was reported as the time from date of DM to date of death or end of follow-up (Dec 1st, 2022). Kaplan Meier and log-rank tests were used to assess the overall survival (OS) of three groups: patients with PMD (all treated non-radically), non-radically treated patients with OMD and radically treated patients with OMD.

Results

From 1,703 patients identified (2008–2017), patient files were reviewed in case of first-recurrence DM (with/without synchronous locoregional failure) ($N = 144$). After review, 124 patients were eligible for this study, with DM occurring from 2009 to 2020 (OMD, $N = 57$ (46%); PMD, $N = 67$ (54%), Figure 1).

Characteristics of primary tumor and treatment

The majority in both groups were male and the median age at DM diagnosis was 61 years (patients with OMD) and 63 years (patients with PMD). The majority had oropharyngeal cancer (OPSCC), and HPV/p16-positive OPSCC tumors were the case for 19% of patients with OMD and 34% of patients with PMD (Table 1). Initial stage III/IV included 97% of patients with PMD and 88% of patients with OMD. The proportion of patients with a smoking history (current or former) was similar (86% OMD and 88% PMD). Prior to the recurrence, all patients were treated with curative intent, >95% were treated with primary radiotherapy, one patient with OMD and two patients with PMD were treated with postoperative radiotherapy and one patient with PMD had surgery alone. Primary concurrent chemotherapy was administered to 54% of patients with OMD and 58% of patients with PMD.

Characteristics of distant metastases and treatment

The median time to DM was 10 months (OMD, range 2–80) and 11 months (PMD, range 3–60 months). For patients with OMD, 35/57 (61%) were asymptomatic while this was the case for 15/67 (22%) of patients with PMD ($p < .001$), see Table 1. Reported symptoms were most often pain, weight loss and lung-related symptoms. No patients with OMD had involvement of more than two organs, and solitary metastases constituted 30/57 (53%). Six patients with OMD (11%) had more than three DMs. All patients with PMD were

treated with palliative intent, 27/67 (40%) had no disease-specific treatment for their DM while the rest had systemic treatment and/or radiotherapy (most often 2–10 fractions, non-SBRT). In the group of patients with OMD ($N = 57$, Figure 1), 23 patients were not potential candidates for LAT due to inoperable loco- and/or regional recurrences (with no possibility of re-irradiation) or patient-related factors. Eighteen patients were already treated with LAT with radical intent at the time (14/18 were lung resections). Finally, 16 patients were potentially treatable with radical intent.

Candidates for local ablative therapy

The 16 patients, who had OMD but were not treated with radical intent, were reviewed by a radiation oncologist. Four patients were not suitable for SBRT due to the anatomical location or size of the metastases. Twelve were deemed radically treatable by SBRT today either by clinical standard or within clinical trials. In addition to the 18 patients with OMD treated radically at the time, 30/124 (24%) was the final

Table 1. Patient and characteristics of distant metastases.

Patient and DM characteristics[a]	OMD ($N = 57$) No. patients	%	PMD ($N = 67$) No. patients	%
Subsite				
Oropharynx	27	47	38	57
p16/HPV+	11	19	23	34
p16/HPV−	15	26	12	18
Hypopharynx	18	32	17	25
Nasopharynx	4	7	3	4
Larynx	8	14	9	13
Stage[b]				
I-II	7	12	2	3
III-IV	50	88	65	97
Smoking				
Never	7	12	6	9
Current/former	49	86	59	88
Symptomatic DM				
Yes	21	37	49	73
No	35	61	15	22
Number of organs with DM				
1	49	86	16	24
2	8	14	27	40
3	0	0	16	24
≥4	0	0	8	12
Localization of DM[c]				
Lung (±pleura)	41	72	56	84
Bone	10	18	25	37
Liver	4	7	18	27
Lymph nodes	11	19	28	42
Other (brain, peritoneum, and skin)	0	0	22	33
Number of metastases				
1	30	53	0	0
2	11	19	0	0
3	10	18	0	0
4	5	9	0	0
5	1	2	0	0
Multiple (>5)	0	0	67	100
DM treatment intent[d]				
Palliative intent	39	68	67	100
Radical intent	18	32	0	0

[a]Missing values are not depicted if less than 5% of total.
[b]American Joint Comitee on Cancer 7th edition.
[c]More than one organ can be involved in the DM, so the sum of proportions exceeds 100.
[d]Palliative intent includes patients treated with disease-specific treatment or patients treated with supportive care.
OMD: oligometastatic disease, PMD: polymetastatic disease.

proportion of HNSCC DM patients assessed as eligible for LAT (Figure 1).

Temporal trends and survival

There were an equal number of DM patients in 2009–2013 ($N = 62$, 37% with OMD) vs. 2014–2020 ($N = 62$, 55% with OMD). The 1- and 3-year OS were calculated (Figure 2): 15% and 0% for patients with non-radically treated PMD, 41% and 15% for non-radically treated patients with OMD and 67% and 49% for radically treated patients with OMD ($p < .001$).

Discussion

In this cohort of HNSCC patients from 2008 to 2017, approximately 7% of HNSCC patients developed DM. Of these, 46% were found to have OMD, whereas half of these appeared to be potential candidates for radical treatment with LAT. Although the absolute numbers are small, LAT could confer long-term survival in selected HNSCC patients otherwise treated with palliative care [9,14].

The time to DM was similar in patients with OMD (10 months) and patients with PMD (11 months). Most patients with OMD were non-symptomatic compared to patients with PMD (61% vs. 22%). OMD could be a window of treatment, where OS could be prolonged by treating OMD before it becomes PMD. Intuitively, this would suggest that the frequency of follow-up imaging could improve clinical outcomes. However, clinical evidence on the value of DM screening post-treatment is lacking [15,16]. Currently, no recommendations on this exist in our national guidelines. The proportion of patients with OMD increased from 37% to 55% in 2009–2013 and 2014–2020, respectively. This might be explained by improved imaging techniques as more patients had ^{18}F-FDG-PET scans in their DM work-up in recent times. DM screening post-treatment becomes more relevant if the proportion of patients with OMD increases and LAT in HNSCC is shown to prolong OS. However, the concept of DM screening should be balanced with the low absolute number of LAT candidates (30/1703). The key could be a priori selection of patients at high risk of DM.

Our study showed increased long-term survival in patients with OMD treated with radical intent compared to patients with OMD treated with non-radical intent (3-year OS 49% vs. 15%). This difference may represent the advantage of LAT but is heavily influenced by selection bias, with differences in performance status, comorbidities and age. Lung resections were the most prevalent LAT in this cohort. This is supported by single-arm studies that favor a pulmonary metastasectomy approach in HNSCC in terms of survival [7]. As a less invasive alternative to surgery, SBRT might increase the likelihood of LAT in elderly or fragile patients. This is especially relevant for HNSCC patients, as comorbidities are highly prevalent [17]. Results indicate that SBRT is comparable to surgery in terms of overall survival for operable stage IA non-small cell lung cancer and may have a favorable toxicity profile in some patients [18,19].

Patients must be selected to offer the right treatment to the right patient, and studies suggest that patients with a maximum of three metastases are more likely to benefit [11]. As of now, OMD is a radiological diagnosis [20]. Occult metastases exist and the true number of metastases is not known. Biological measures, such as liquid biomarkers, are needed to support patient selection to determine the presence of true oligometastatic disease [3].

Limitations include changes in imaging techniques over the study period. As more ^{18}F-FDG-PET scans were available
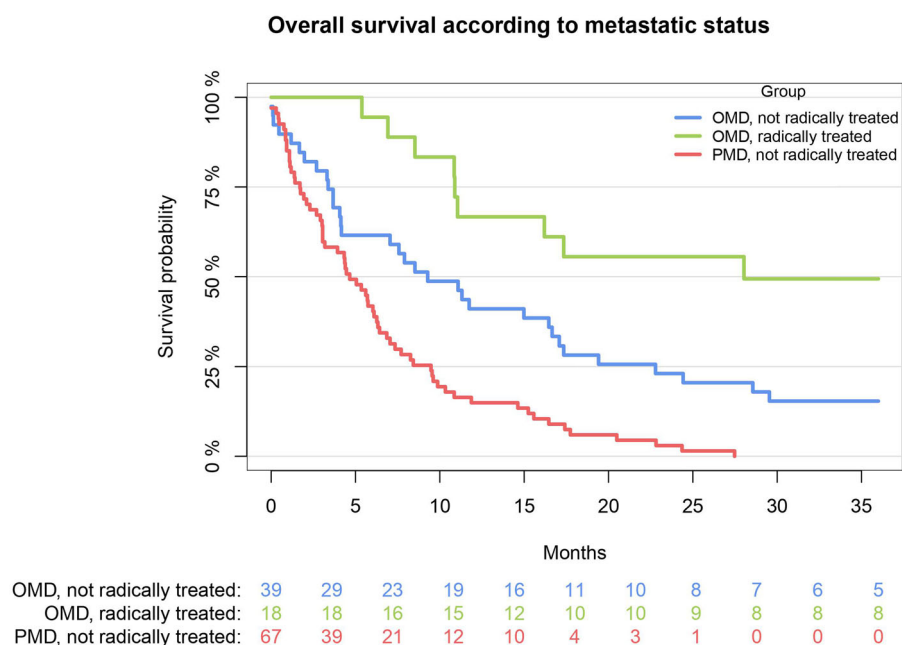
Overall survival according to metastatic status

Figure 2. Kaplan-Meier Curves displaying the overall survival of patients with polymetastatic disease, non-radically treated (PMD, $N = 67$), and patients with oligometastatic disease (OMD, $N = 39$, non-radically treated, $N = 18$, radically treated), respectively. The observed time is from date of distant metastasis diagnosis (after definitive, primary treatment) to death or end of follow-up.

in recent times, the proportion of patients with OMD was affected by the defined time period and is likely to increase in the future with higher image resolutions. A potential source of misclassification is the high prevalence of new primary lung cancers in HNSCC patients. This could overestimate the cohort size and the proportion of patients with solitary oligometastasis, especially. Patients were assessed at tumor board meetings reviewing pathology reports, imaging and disease trajectory, and for all included patients, their metastases were very or most likely from their primary HNSCC. The strengths include the prospective collection of data in DAHANCA. The data presented are from real-world treatment at our institution. It thereby represents a realistic proportion of HNSCC patients eligible for LAT or enrollment in clinical trials. This should be explored prospectively in a multicenter setting.

Conclusion

Overall, DMs in patients with HNSCC are rare (7%). About half of patients with DM from HNSCC have OMD and half of these appeared eligible for treatment.

Disclosure statement

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