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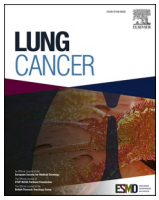

Non-small cell lung cancer with synchronous oligometastatic disease at the time of initial diagnosis. Impact of multimodal treatment on prognosis

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A R T I C L E I N F O

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A B S T R A C T

Background: Synchronous oligometastatic non–small cell lung cancer (sOMD) is a heterogeneous subgroup of stage IV disease in which multimodal treatment may improve outcomes.
Methods: Patients with sOMD (≤5 metastases in ≤ 3 organs) diagnosed between July 2015 and May 2020 at five lung cancer centers were retrospectively analyzed. Patients receiving systemic therapy alone or multimodal therapy consisting of systemic therapy plus local treatment (surgery and/or radiotherapy) were included; those treated with local therapy alone were excluded. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan–Meier method according to treatment modality and treatment sequence. Multivariable Cox regression identified independent prognostic factors.
Results: Among 293 patients (median follow-up, 33.5 months), 74% received multimodal therapy. Median PFS was 9.9 months overall and was significantly longer with multimodal therapy than with systemic therapy alone (10.2 vs. 8.4 months; $p = 0.02$). Median OS was 26.4 months and numerically favored multimodal therapy (31.1 vs. 20.0 months). Among patients receiving local treatment, surgery was associated with longer PFS and OS than radiotherapy. Complete local treatment of all metastatic lesions was associated with improved OS compared with incomplete treatment (31.6 vs. 16.3 months). In multivariable analysis, omission of local therapy independently predicted worse PFS (HR 1.55) and OS (HR 1.52). Older age and poorer ECOG performance status were also independently associated with inferior outcomes.
Conclusions: Multimodal therapy combining systemic and local ablative treatment was associated with improved outcomes compared with systemic therapy alone. A sequential approach, with systemic therapy followed by local ablative treatment, appeared to provide the greatest benefit. Prospective studies are warranted to define the optimal treatment sequence and refine patient selection.

Abbreviations: BZKF, Bavarian Cancer Research Center; CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; NOS, Not otherwise specified; NR, Not reached; NSCLC, Non-small cell lung cancer; OS, Overall survival; PFS, Progression free survival; sOMD, Synchronous oligometastatic non–small cell lung cancer.

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1. Introduction

With an estimated 2.2 million new cancer cases and 1.8 million deaths, lung cancer was the second most frequently diagnosed cancer and the leading cause of cancer-related mortality worldwide in 2020. It accounted for approximately one in ten (11.4%) newly diagnosed cancer cases and one in five (18.0%) cancer-related deaths [1]. More than 40% of affected patients continue to be diagnosed at stage IV, which is associated with a poor prognosis [1,2]. Stage IV disease indicates the presence of systemic disease, and treatment algorithms therefore primarily focus on systemic therapies. However, even at this stage, multimodal treatment concepts may be considered in particular for oligometastatic disease (OMD) [3]. In such cases, the combination of systemic therapy and local ablative treatments may allow for a potentially curative therapeutic approach. To date, treatment guidelines for OMD scenarios have not been harmonized, largely due to inconsistent definitions of the OMD state [4]. Distinct entities are recognized, including de novo OMD, induced oligopersistence, and oligoprogression, each representing heterogeneous baseline conditions. It was not until 2019 that a definition of synchronous OMD (sOMD) was established during a pan-European consensus conference [4]. sOMD is defined by the presence of a maximum of five metastases across no more than three organ systems, without involvement of serous membranes [4].

In the present study the prognostic impact of multimodal treatment strategies as well as the sequencing of systemic and local ablative therapies on survival outcomes was retrospectively investigated in a large cohort of sOMD patients treated within the BZKF lung cancer centers.

2. Method

2.1. Patients

Eligible patients were those meeting the consensus definition of synchronous oligometastatic disease [4]. Tumor staging was performed according to the 8th edition of the lung cancer staging classification [5]. Patients who exclusively received local ablative treatment (surgery or radiotherapy) were excluded.

2.2. Study design and data

This multicenter cohort study included patients with newly diagnosed stage IV NSCLC presenting with sOMD. The study was conducted across five sites of the BZKF. Data were extracted from patients diagnosed with sOMD between July 2015 and May 2020. Candidates meeting the criteria for sOMD were retrospectively identified from institutional clinical databases through full-text searches of electronic health records and thoracic tumor board records. Eligibility for sOMD was subsequently confirmed by manual review of each case. Treatment sequences were reconstructed, and patients were classified into two groups: multimodal therapy, defined as a combination of systemic therapy and local ablative treatment (surgery and/or radiotherapy), or systemic therapy alone. The chronological sequence of treatment modalities was also documented. Clinical, pathological, treatment, and outcome data were extracted retrospectively from the medical records. Progression-free survival and overall survival were assessed from the date of diagnosis until disease progression, death, or last follow-up.

2.3. Statistical analyses

Data analysis was performed using SPSS Statistics version 29.0.0.0. Descriptive statistics were used to summarize baseline demographic and clinical variables. Categorical data are expressed as counts (n) and percentages (%), and continuous variables are described using median (med), quartiles (IQR), and ranges. Median follow-up time was calculated using the reversed Kaplan-Meier method. OS and PFS were analyzed using the Kaplan–Meier method. Survival outcomes were compared between different treatment modalities using log-rank test.

The main aim of the study was to investigate the benefits of a multimodal treatment approach in patients who met the criteria for a sOMD situation at the time of initial diagnosis. In addition, the sequence of the individual treatment measures and the significance of the type of local ablative procedures in relation to PFS and OS were assessed.

Overall survival (OS) was defined as time from diagnosis to death from any cause, with surviving patients censored at last follow-up. Progression-free survival (PFS) was defined as time from diagnosis to first documented disease progression or death from any cause. Patients without an event were censored at the date of last follow-up. Disease progression was determined based on PFS and OS were defined according to standard clinical criteria.

Treatment modalities were examined according to three predefined binary classification strategies. 1. therapeutic strategy: systemic therapy was compared between patients receiving systemic therapy alone and those receiving combined treatment consisting of systemic and local therapy. 2. chronological sequence of treatments: systemic therapy first vs local therapy. 3. the type of local therapy: surgical vs. radiotherapy. Consequently, Kaplan–Meier analyses were performed accordingly.

In addition, multivariable Cox proportional hazards regression analyses were conducted to assess the influence of various factors on survival outcome. Alongside the primary variable of interest (therapeutic strategy), Variables included in the multivariable Cox proportional hazards regression model were selected a priori based on previously published prognostic factors and clinical relevance The following covariates were included: age at initial diagnosis [6], sex [7] ECOG performance status [8], tumor histology [6], presence of liver metastases [6,9], and number of metastatic sites [6,9,10]. Published evidence has consistently shown that these variables are established prognostic factors and may also affect response to systemic therapy [7]. Patients with missing data for at least one variable were excluded from the analysis. Hazard ratios (HRs) with corresponding 95% confidence interval (CI) were calculated. Kaplan-Meier estimates of survival probabilities at predefined time points and median survival times with corresponding 95%CI were reported.

3. Results

3.1. Patients

A total of 293 patients were identified. The median age at diagnosis was 64.7 years (IQR 14.6). 66% of patients were male, and 76% were current or former smokers. 74% of patients had a good or very good performance status. Adenocarcinoma was the predominant histological subtype, accounting for 65% of cases. Platinum-based chemotherapy or chemo-immunotherapy was administered to 73% of patients, and 74% received multimodal therapy. In 102 patients, a local ablative therapy was initially established and subsequently supplemented with systemic therapy. In 50 patients, systemic therapy was initiated first and was secondarily supplemented with local ablative therapy. In 65 patients, combined radio-chemotherapy was initially started; Of these, 13 patients received immunotherapy as an adjunct treatment (chemo-immunotherapy).. In 95% of patients, one or two organs were affected by metastases, and 82% had three or fewer metastases at baseline. The median number of metastases was 2 [Range 1–5] A total of 631 metastases were diagnosed. Of these, 471 were diagnosed in patients who received multimodal therapy regimens. In 148 patients, local therapy was administered to all metastases. Radiation therapy was administered according to the centers' guidelines, with single fractions ranging from 1.8 to 20.0 Gy and a total dose ranging from 15 to 66 Gy, The patient characteristics, broken down by systemic therapy alone and multimodal therapy, are summarized in Table 1.

Table 1
Demographic and baseline characteristics of the patients.

Characteristic	Systemic therapy only (N = 76)	Multimodal therapy (n = 217)
Age: Median yr [min–max]	66.7 [40–89]	63.6 [42–86]
Female /male (%)	36/64	39/61
Non-smoker/Ex-smoker/ smoker (%)	8 / 44 / 47	14 / 40 /46
ECOG performance-status 0/1/ 2/3/4 (%)	53 / 30 / 14 / 3	46 / 35 / 15 / 4
Metastatic sites: 1 / 2 / 3 (%)	63 / 29 / 8	68 / 29 / 3
Number of metastases, 1 / 2 /3 / 4 / 5 (%)	39 / 28 / 15 / 11/ 7	37 / 30 / 15 / 12 / 6
Histology		
Squamous-cell carcinoma (%)	37	25
Non-squamous-cell carcinoma (%)	63	75
Systemic Therapy:		
Platinum-based chemotherapy (%)	41	50
Platinum-based chemo-immunotherapy (%)	24	25
Platinum-free chemotherapy (%)	3	1
Immuno-monotherapy (%)	21	13
Targeted therapy (%)	11	11

3.2. Progression free survial results

The median follow-up time was 33.5 months (95% CI, 28.8–42.4). The median PFS in the entire cohort was 9.9 months (95% CI, 8.5–11.3). Patients who received combined systemic and local therapy experienced a significant improvement in median PFS compared with those treated with systemic therapy alone (10.2 months [95% CI, 1.0–12.2] vs. 8.4 months [95% CI, 5.2–11.5]), p = 0.02). When systemic therapy was administered first and subsequently supplemented with local ablative treatment, a numerical increase in median PFS of 2.6 months was observed; however, this difference did not reach statistical significance (p = 0.27). In patients who received combined radio-chemotherapy as first line treatment, the PFS was 7.8 months [95% CI, 6.4–9.3]. Patients who underwent surgical resection as part of local ablative therapy had a significantly longer median PFS than those treated with radiotherapy (21.0 [95% CI 11.5–30.4] vs. 9.1 [95% CI 7.4–10.8] months, p < 0.001). The results systemic and multimodal treatments are summarized in Table 2 and shown in Fig. 1.

3.3. Overall survival results

The median OS for the entire cohort was 26.4 months (95% CI, 18.1–34.7). A trend toward improved survival was observed in patients receiving combined systemic and local therapy compared with systemic therapy alone (31.1 months [95% CI, 17.2–45.1] vs. 20.0 months [95% CI, 7.7–32.2], p = 0.09] In patients who received combined radio-chemotherapy as first line therapy, the median OS 15.4 [95% CI, 91–21.8]. Results for systemic and multimodal treatment are shown in Fig. 2. Furthermore, there was a strong trend toward improved median OS (p = 0.05) in patients who initially received systemic therapy followed by local ablative treatment compared with those who received local therapy first (median OS: not reached vs. 36.5 [95% CI 23.3–59.7] months). Consistent with this finding, at 36 months of follow-up, 59% of patients in the "systemic therapy first" group were still alive, compared with 50% in the cohort initially treated with local therapy As shown in Table 3.

Patients who underwent surgery as part of local therapy demonstrated a highly significant survival benefit compared with those treated with radiotherapy (median OS not reached vs. 18.2 [95% CI 10.4–26.0] months, p < 0.001). At 36 months of follow-up, 68% of surgically treated patients were alive, compared with 36% of patients who received radiotherapy. These results are summarized in Table 3.

Table 2
Progression-free survival rates from Kaplan-Meier analyses.

	N	12 months	24 months	36 months	Median months [95% CI]	*P*
Therapeutic Strategy						
Systemic Therapy only	76	0.37	0.21	0.35	8.4 [5.2–11.5]	
Multimodal Therapy	217	0.45	0.28	0.46	10,2 [1.0–12.2]	0,02
Sequence of measures						
Local therapy first	102	0.47	0.31	0.19	10.8 [6.6–15,1]	
Systemic therapy first	50	0.56	0.32	0.21	13.4 [10.2–16,7]	0,27
Local Therapy						
Surgery	62	0.6	0.46	0.35	21.0 [11.5–30,4]	
Radiotherapy	155	0.4	0.21	0.12	9.1 [7.4–10.8]	<0,001

The figures show the progression free survival rate at the defined time points, as well as the median PFS, including the 95 per cent confidence interval.

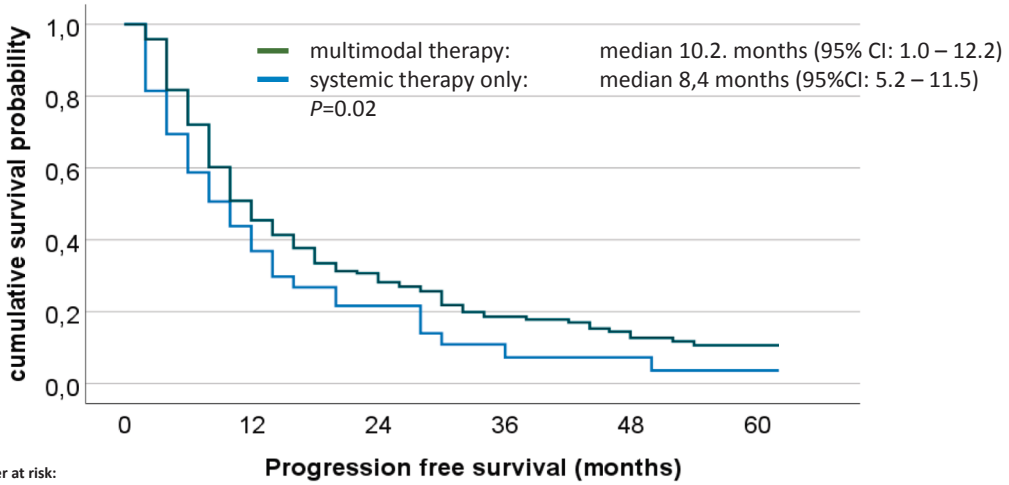
The exploratory analysis of survival in patients in whom all metastases were treated showed an almost doubling of median survival from 16.3 [95% CI 0,0–47.4] to 31.6 [95% CI 18.9–45.0] months compared with patients in whom some, but not all, metastases were treated.

3.4. Multivariable Cox regression analysis of progression-free and overall survival

Adjusting for age, sex, ECOG performance status, number of metastases, liver metastases, and histology, the Cox regression analyses showed that systemic therapy alone was associated with worse outcomes compared to systemic plus additional local ablative treatment, corresponding to a 55% increased hazard of disease progression (p = 0.008) and a 52% increased hazard of death (p = 0.04). Each additional year of age was associated with a 3% increase in the hazard of disease progression (p = 0.001) and death (p = 0.003). Moreover, each one-category deterioration in performance status was associated with a 23% higher hazard of progression (p = 0.017) and a 46% higher hazard of death (p < 0.001). Furthermore, squamous cell carcinoma histology showed a trend with a 46% increased hazard of death compared with adenocarcinoma (p = 0.05). The results are summarized in Table 4.

4. Discussion

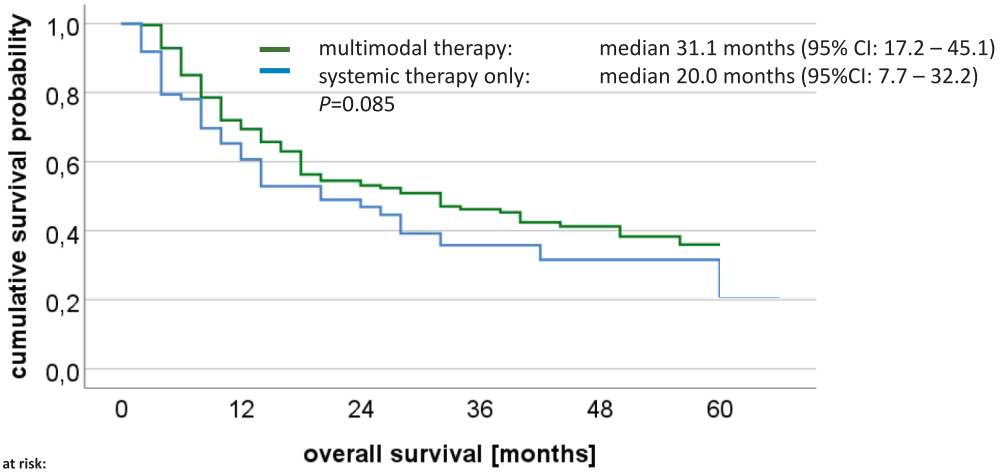
Hellmann and Weichselbaum described in 1995 that tumor development comprises a biological spectrum ranging from a purely local manifestation to a systemic manifestation of disease [3]. This spectrum allows for the definition of intermediate stages along the transition from local to systemic disease, among which the intermediate state of oligometastatic disease (OMD) was proposed. This conceptual framework potentially influences therapeutic decision-making as well as patient prognosis. Subsequently, various definitions of OMD were applied in order to substantiate this hypothesis through clinical evidence novo OMD, oligopersistent disease, and oligoprogressive disease were examined [11–18]. Particularly in the setting of oligopersistence, several studies have demonstrated that, in the context of established systemic tumor control, the addition of local ablative treatments can confer a survival benefit [12,19].



Number at risk:

multimodal therapy	217	92	45	24	5	1
systemic therapy only	76	26	11	2	2	1

Fig. 1. Kaplan–Meier curves of progression free survival comparing systemic therapy with systemic therapy plus local therapy. CI = confidence interval.



Number at risk:

multimodal therapy	215	134	74	51	31	11
systemic therapy only	74	39	22	9	5	2

Fig. 2. Kaplan–Meier curves of overall survival comparing systemic therapy with systemic therapy plus local therapy. CI = confidence interval.

In 2019, a definition of synchronous OMD was published for the first time as part of a pan-European consensus conference. According to this definition, synchronous OMD is characterized by a maximum of five metastases involving no more than three organ systems, with exclusion of serosal involvement and bone marrow carcinomatosis [4]. This definition was applied in the present study, in which patients with de novo synchronous OMD (sOMD) were identified in a retrospective multicenter cohort. The prognostic relevance of a multimodal treatment approach combining systemic therapy and local therapy was evaluated in comparison with systemic therapy alone. In addition, the prognostic significance of the sequence of individual measures was analyzed in detail.

The results of the present study demonstrate that, in the context of sOMD, multimodal treatment strategies contribute to a significant improvement in prognosis. On the one hand, these data confirm the feasibility of multimodal treatment approaches, as already demonstrated in a Phase 2 study in 2012 [16], and, furthermore, provide evidence of the associated improvement in prognosis since both progression-free survival and overall survival were significantly and clinically meaningfully improved in a cohort with de novo OMD and potential involvement of multiple organ systems as well as varying tumor biology This complements the clinical indications for which the efficacy of multimodal treatment approaches has already been demonstrated in both single-organ oligometastatic settings and in cases of synchronous oligometastatic EGFR-mutated non-small cell lung cancer. since the analysis included both patients with and without molecular alterations [20–22].

Furthermore, the data suggest that patients may derive greater benefit from the preferential initiation of systemic therapy compared with a treatment strategy primarily focused on local therapy. This observation may be subject to selection bias, as local ablative therapies were presumably administered only in patients with disease control under systemic therapy, corresponding to stable disease, whereas patients with primary progressive disease were no longer offered a

Table 3
Overall survival rates from Kaplan-Meier analyses.

	N	12 months	24 months	36 months	Median months [95% CI]	*P*
Therapeutic Strategy						
Systemic Therapy only	76	0.61	0.47	0.35	20,0 [7.7–32.2]	
Multimodal Therapy	217	0.69	0.53	0.46	31.1 [17.2–45.1]	0.085
Sequence of measures						
Local therapy first	102	0.71	0.53	0.50	36.5 [23.3–59.7]	
Systemic therapy first	50	0.85	0.73	0.59	NE	0.053
Local Therapy						
Surgery	62	0,80	0.68	0.68	NE	
Radiotherapy	155	0,65	0.46	0.36	18.2 [10.4–26.0]	<0,001

The figures show the survival rate at the defined time points, as well as the median OS, including the 95 per cent confidence interval.

multimodal treatment approach. However, our data are also consistent with the work of Gomez et al., who were able to show that local consolidative therapy, with or without maintenance therapy, for patients with three or fewer metastases from NSCLC that did not progress after initial systemic therapy improved progression-free survival compared with maintenance therapy alone [12]. This suggests that multimodal treatment approaches provide clinical benefit, particularly when systemic tumor control is already in place.

The applied Cox regression model, using the reference criteria (male sex, adenocarcinoma histology, absence of liver metastases, combined chemo-immunotherapy, and multimodal treatment concept), additionally proves that omission of local therapeutic measures was associated with a 55% increase in the risk of progression and a 52% increase in the risk of death. As systemic treatment modalities included chemo-immunotherapy, platinum-based combination chemotherapy, immunotherapy monotherapy, and targeted therapies, the therapeutic strategies discussed here are likely transferable across different systemic treatment regimens, as has been documented in previous studies [23–25]. At least for systemic immuno-oncology therapies, this statement is supported by the recently published work of Wiesweg et al. [26] which demonstrated that 2-year recurrence-free survival was significantly improved from 15.1% to 51.4% by adding checkpoint inhibitors to chemotherapy.

The exploratory analysis conducted here as a supplement to the study on complete versus incomplete local therapy suggests that treating all metastatic sites may potentially of greater survival benefit since themedian survival increased from 16.3 months to 31.6 months. This statement is also supported by the work of Wiesweg et al. demonstrating an median OS of 34.4 months for patients with complete local ablative treatment. [26].

Furthermore, the data suggest that patients may derive greater benefit from the preferential initiation of systemic therapy compared with a treatment strategy primarily focused on local therapy. This observation may be subject to selection bias, as local ablative therapies were presumably administered only in patients with disease control under systemic therapy, corresponding to stable disease, whereas patients with primary progressive disease were no longer offered a multimodal treatment approach.

In this context, the highly significant prognostic improvement observed in patients who underwent surgical intervention rather than radiotherapy is notable. This effect is likely attributable to patient-specific factors that could not be fully captured in the present analysis. Beyond providing local tumor control surgery may have positive effects on future treatment by allowing a pathological assessment of response to previous systemic therapy and providing tumor material for molecular testing. It is conceivable that concomitant systematic lymphadenectomy contributed to further prognostic benefit.

The retrospective nature of data collection represents an inherent limitation of these findings. The sOMD concept was not evaluated prospectively. Treatment decisions were made on an individual patient basis at the center level by the multidisciplinary team and radiotherapy approaches varied widely in terms of stereotactic radiosurgery / stereotactic body radiotherapy, fractionation, palliative or curative radiotherapy. and did not necessarily follow a standardized therapeutic algorithm. Consequently, the conclusions should be regarded as hypothesis generating and require prospective validation.

In summary, robust evidence suggests that the incorporation of multimodal treatment strategies in patients with sOMD at baseline leads to a significant and clinically meaningful improvement in prognosis. Preferably, effective systemic therapy should be initiated first to achieve disease control, followed by the addition of local ablative approaches which, ideally, should include treatment of all metastases in order to achieve maximum therapeutic benefit.. Surgical and radiotherapeutic strategies should be considered equivalent options in this setting.

Institutional review board information

The study was approved by the Ethics Committee of the University of

Table 4
COX regression analysis comparing systemic therapy with systemic therapy plus local therapy.

Reference Category	Comparison	PFS HR (95% CI)	*P*	OS HR (95% CI)	*P*
Treatment					
Multimodal therapy	Systemic therapy only vs. multimodal therapy	1.55 (1.12–2.15)	0.008	1.52 (1.02–2.27)	0.040
Demographics					
Age	Per 1-year increase	1.03 (1.01–1.04)	0.001	1.03 (1.01–1.05)	0.003
Sex	Male vs. female	0.91 (0.68–1.22)	0.524	1.09 (0.76–1.56)	0.636
Performance status	Per 1-point ECOG increase	1.23 (1.04–1.45)	0.017	1.46 (1.29–1.78)	<0.001
Disease characteristics					
Number of metastases	Per additional metastasis	1.08 (0.96–1.21)	0.225	1.12 (0.97–1.29)	0.120
Liver metastases	Present vs. absent	1.01 (0.58–1.77)	0.960	1.05 (0.53–2.07)	0.888
Histology					
Adenocarcinoma	Squamous cell carcinoma vs. adenocarcinoma	1.12 (0.82–1.54)	0.473	1.46 (1.00–2.13)	0.051
Adenocarcinoma	Mixed/NOS vs. adenocarcinoma	1.58 (0.91–2.74)	0.103	2.04 (1.06–3.96)	0.034
		n = 260; n = 210 progress, n = 50 censored		n = 260; n = 136 death, n = 124 censored	

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified.

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CRediT authorship contribution statement

Christian Schulz: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Sarah Swart:** Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Karolina Müller:** Methodology, Formal analysis, Data curation. **Denise Bernhardt:** Writing – review & editing, Data curation. **Seyer Safi:** Writing – review & editing, Data curation. **Amanda Tufman:** Writing – review & editing, Data curation, Conceptualization. **Niels Reinmuth:** Writing – review & editing, Data curation. **Björn Hackanson:** Writing – review & editing, Data curation. **Stephan Raab:** Writing – review & editing, Data curation. **Florian Fuchs:** Writing – review & editing, Data curation. **Kai Hildner:** Writing – review & editing, Data curation. **Daniel Heudobler:** Writing – review & editing, Conceptualization.

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.

Acknowledgments

CS and SS conceived the study and wrote the manuscript. KM carried out the statistical analysis, supervised the project and provided critical feedback. All other authors (DB, SeS, AT, NR, BH, SR FF, KH, DH) supervised the project, added data and provided critical feedback.

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