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Lymphocyte-to-monocyte ratio is an independent prognostic factor in surgically treated small cell lung cancer: An international multicenter analysis

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ABSTRACT

Introduction: The prognostic value of lymphocyte-to-monocyte ratio (LMR) has already been evaluated in a wide range of malignancies including patients with non-surgically managed small cell lung cancer (SCLC). However, the impact of LMR on survival in surgically treated SCLC patients has not yet been assessed. The aim of this study was to determine the clinical role of LMR in patients undergoing surgical resection for SCLC.

Materials and methods: In this retrospective study, individuals receiving radical surgery for SCLC between January 2000 and December 2019 from three participating European institutions were included. LMR was calculated from the most recent blood test prior to surgery. Optimal cut-off values for LMR were determined and correlated with clinical data and survival outcomes.

Results: In total, 101 patients underwent surgical resection for SCLC during the study period. 76 (75.2%) received anatomic lung resection (defined as lobectomy or pneumonectomy), 63 (62.4%) were male and the median age was 63 (range 41–80) years. LMR > 2.50 significantly associated with improved overall survival (OS) (35.3 vs. 20.7 months, p = 0.032) and disease-free survival (DFS) (25.8 vs 18.5 months, p = 0.011). Moreover, multivariate Cox proportional hazard model identified LMR > 2.50 as an independent prognostic factor of longer OS (hazard ratio (HR) 0.617; 95% confidence interval (CI) 0.383–0.993; p = 0.047) and DFS (HR 0.505; 95% CI 0.266–0.959; p = 0.037).

Conclusion: Preoperatively elevated LMR is a robust prognostic factor associated with improved OS and DFS in patients undergoing surgery for SCLC. Further studies are warranted to better understand the overall impact of LMR when applying surgery in these patients.

1. Introduction

Lung cancer (LC) remains the leading cause of cancer-related deaths worldwide[1]. Characterized by rapid growth and early metastasis, small cell lung cancer (SCLC) is an exceptionally aggressive type of LC and a global burden that accounts for 15–20% of all LC cases [2,3]. Since

Abbreviations: LMR, lymphocyte-to-monocyte ratio; SCLC, small cell lung cancer; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

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the majority of patients are diagnosed with advanced stage SCLC, surgical resection of the primary tumor is rarely indicated [4,5]. Despite therapeutic inventions over the last decades, the overall prognosis for SCLC still remains poor with a 5-year survival rate below 10% [6-8].

Importantly, several observational studies and large cancer registries have previously reported promising long-term results in patients undergoing surgical resection for SCLC [9-12]. Moreover, implementation of upcoming national LC screening programs might increase the overall number of SCLC patients eligible for surgery in the next decades [13]. Consequently, the clinical role of surgery might be re-discussed as part of the therapeutic armamentarium against SCLC in the future [14]. SCLC has been recently shown to be a far more heterogeneous disease than previously supposed [15]. Indeed, the research focus has shifted to distinct molecular subtypes with unique therapeutic vulnerabilities [16-18]. Moreover, various prognostic and predictive biomarkers have been evaluated in order to achieve more personalized therapeutic approaches in SCLC [19].

The lymphocyte-to-monocyte ratio (LMR) has already been demonstrated to represent a robust prognostic factor in various hematological and solid malignancies [20-23]. Regarding the role of LMR in LC, elevated pre-treatment LMR has been demonstrated to consistently associate with improved overall survival (OS) and disease-free survival (DFS) both in surgically and non-surgically treated patients [24]. However, only three studies out of 23 investigating LMR in LC included SCLC patients whereas none of these studies evaluated the clinical relevance of LMR in SCLC patients undergoing surgical resection. Here, we aimed to determine the role of LMR in surgically resected SCLC patients.

2. Materials and methods

2.1. Study design and clinical definitions

In this study, patients from three European thoracic surgery centers (Medical University of Vienna / Austria, National Koranyi Institute of Pulmonology / Hungary and National Oncology Institute and Semmelweis University Budapest / Hungary) were retrospectively included. All patients underwent surgical resection for SCLC between January 2000 and December 2019. SCLC was histologically confirmed from resected specimen according to institutional protocols.

Importantly, patients with postoperatively confirmed pathological stage III or IV SCLC or individuals with any evidence for acute or chronic inflammatory diseases (e.g. rheumatoid arthritis) were excluded from the study. Chronic obstructive pulmonary disease (COPD), as a comorbidity constituted an exception since it represents one of the most common persistent conditions in SCLC and therefore exclusion of COPD-patients would have significantly decreased the overall number of assessable patients [25,26]. Notably, however, the presence of COPD did not influence preoperative LMR levels significantly in our cohort (Supplementary Fig. 1).

Clinical and follow-up data of included patients were collected from the available medical records and/or records from the Central Statistical Office. For LMR calculation, the most recent preoperative blood cell count was used. LMR was then calculated by dividing the absolute count of lymphocytes by the absolute count of monocytes.

Similar to their preoperative values, the LMR levels after the surgery might also be of prognostic relevance. Nevertheless, it is well-established that surgical stress could remarkably change the peripheral lymphocyte and monocyte counts, especially in case of lung resection surgery [27,28]. Therefore, the postoperative levels of LMR might vary on a much larger scale than the preoperative values and could primarily mirror the effects of the surgery rather than the pathophysiological changes caused by the tumor itself. Consequently, postoperative LMR was not evaluated in this study.

As per hospital protocol, routine oncological follow-up was carried out for all included patients. Notably, these follow-ups comprised of regular (i.e. every 3 months in the first postoperative year and then every 6–12 months) blood tests, X-rays and / or computed tomography (CT) scans of the chest. If recurrence or metastasis was suspected, further relevant tests (e.g. PET-CT, magnetic resonance imaging (MRI) of the brain, biopsy for histological verification, etc.) were performed according to the individual clinical scenario. Recurrent disease was termed as evidence of recurrence in either mediastinal or hilar lymph nodes or in the ipsilateral lung. Evidence of any other recurrences was considered to be metastases. In distinct cases, patients received tumor-specific adjuvant treatment based on the decision of a multidisciplinary tumor-board consisting of board-certified medical-, radiation- and surgical oncologists. Adjuvant chemotherapy consisted of a platinum agent (cisplatin or carboplatin) combined with etoposide. In rare cases, radiotherapy was also applied. Notably, all diagnostic and therapeutic approaches were conducted in accordance the contemporary National Comprehensive Cancer Network (NCCN) guidelines with no major differences across the three host institutions [29]. Overall survival (OS) was defined as the time of surgery until the date of the last follow-up or death in months. Disease-free survival (DFS) was calculated as the time of surgery until the evidence of metastases or recurrent disease in months. The study has been approved by the respective institutional (Medical University of Vienna, EK 2196/2019) or national (Hungarian Scientific and Research Ethics Committee of the Medical Research Council, ETT-TUKEB 23636–2/2018, 23 636/https://doi.org/10/2018/EÜIG) ethic committees.

2.2. Statistical analysis

Statistical calculations and corresponding illustrations were performed by using GraphPad Prism 8 (GraphPad Software, Inc., USA), Microsoft Excel Version 16.48 (Microsoft Corporation, USA) and SPSS Statistics Version 27.0 (IBM Corp., USA). Kaplan-Meier method was applied for survival curve estimation and the log-rank test was used to compare differences in OS and DFS. Chi-square test, Fisher's exact and independent Student's *t*-test test were used for comparison of qualitative and quantitative variables between two groups. To evaluate independent risk factors for OS and DFS, univariate analysis was performed for all available clinicopathological variables by using the Cox regression model and presented as hazard ratios (HRs) including corresponding 95% confidence intervals (CIs). Variables showing significant prognostic value for OS and / or DFS on univariate analysis were further analyzed by multivariate Cox regression hazard model. All statistical tests were two-sided and $p < 0.05$ was considered statistically significant. X-tile software (Yale University, USA) was used to estimate the optimal cut-off values of preoperative LMR for OS and DFS according to the minimal p-value approach [30]. Briefly, the algorithm behind the optimal cut-off determination of the X-tile software is based on the following consecutive steps: first, the operator has the option to choose a specific LMR-value (=cut-off) that divides the study cohort into two groups: one group above and one group below this LMR cut-off-value. Next, Kaplan-Meier survival curves are visualized from both patient groups and at the same time, the Chi-square test and the log-rank test are calculated to estimate significant differences between the diverging survival curves. Ultimately, according to the commonly practiced "minimal p-value approach", optimal cut-off value is defined as the LMR level that leads to divergent Kaplan Meier survival curves with the lowest p-value in the log-rank test, thus indicating the greatest significant difference in terms of clinical outcome.

3. Results

3.1. Characteristics of the study cohort

Between 2000 and 2019, 151 surgically resected and histologically confirmed Caucasian SCLC patients were identified at the three participating institutions. Subsequently, 50 advanced disease stage

(pathologically confirmed stage III or IV SCLC) were excluded from the study cohort (Fig. 1). Of the remaining 101 surgically resected early stage (stage I or stage II) patients, 63 (62.4%) were male and the median age at the time of surgery was 63 (range 41–80) years (Table 1). 76 (75.2%) received anatomic lung resection (defined as lobectomy or pneumonectomy) and 25 (24.8%) underwent sublobar (defined as segmentectomy or wedge resection) lung resection. Most common comorbidities in the study cohort were arterial hypertension, chronic-obstructive pulmonary disease (COPD) and diabetes accounting for 45.5%, 39.6% and 10.9%, respectively. Subsequent analyses showed that the presence of COPD did not influence the preoperative LMR levels significantly (median LMR of COPD vs. non-COPD patients: 2.7 vs. 3.2, p = 0.362, **Supplementary** Fig. 1). Regarding smoking history, 80 (79.2%) patients were current or former smokers at the time of surgery. Notably, 59 (58.4%) patients received adjuvant chemotherapy during the follow-up. The preoperative median LMR of all included patients was 2.75 (interquartile range (IQR) 1.65).

3.2. Prognostic significance of preoperative LMR on overall survival

Regarding OS, X-tile software calculation identified 2.50 as the optimal cut-off value for preoperative LMR. Subsequently, patients were divided into two different groups according to their LMR either above or below this cut-off value. Notably, patients with a preoperative LMR > 2.50 had significantly longer OS than those with LMR ≤ 2.50 (median 35.3 vs 20.7 months, respectively; p = 0.032, Fig. 2).

3.3. Identification of robust prognostic factors of overall survival

In order to identify independent risk factors of OS, several clinic-pathological variables were included for univariate analysis (Table 2). Thereby, adjuvant chemotherapy (HR = 0.351; 95% CI 0.215–0.573; p = 0.001) and LMR > 2.50 (HR = 0.599; 95% CI 0.376–0.955; p = 0.031) were significantly prognostic for OS. Importantly, both variables remained robustly prognostic for OS after including in multivariate analysis (adjuvant chemotherapy p = 0.001 and LMR > 2.50p = 0.047).

3.4. Prognostic significance of preoperative LMR on disease-free survival

Similarly to OS, X-tile software calculation defined 2.50 as the optimal cut-off value for preoperative LMR on DFS. Subsequently, patients were again divided into two different groups according to their LMR either above or below this cut-off value. Of note, patients with a preoperative LMR > 2.50 had significantly longer DFS when compared to patients with an LMR ≤ 2.50 (median 25.8 vs 18.5 months, respectively; p = 0.011, Fig. 3).

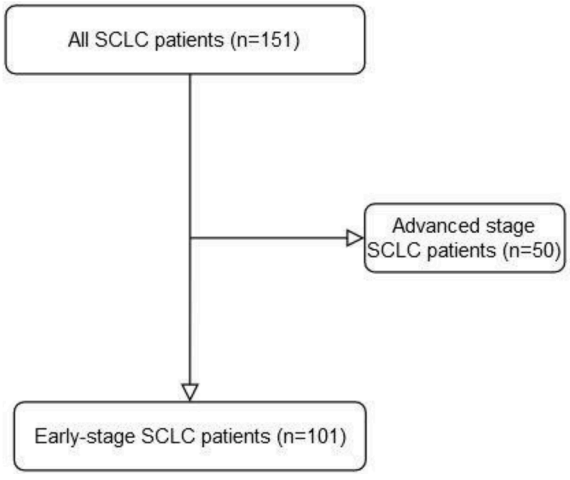

Fig. 1. Between 2000 and 2019, a total of 151 patients underwent surgical resection for SCLC. Of these, 50 patients were pathologically defined advanced stage SCLC (stage III or stage IV) and excluded from the study. (SCLC = small cell lung cancer).

Table 1
Main clinicopathological characteristics of the study population. In total, 101 surgically resected early stage (pathologically confirmed stage I or II SCLC) patients were included in the study.

All patients	101 (100%)
Male	63 (62.4%)
Age (years, median, range)	63 (41–80)
Smoking status	
Current smoker	51 (50.5%)
Former smoker	29 (28.7%)
Non-smoker	10 (9.9%)
Unknown	11 (10.9%)
COPD	40 (39.6%)
Hypertension	46 (45.5%)
Diabetes	11 (10.9%)
Sublobar resection	25 (24.8%)
Wedge resection	22 (21.8%)
Segmentectomy	3 (3.0%)
Anatomic lung resection	76 (75.2%)
Lobectomy	69 (68.3%)
Pneumonectomy	7 (6.9%)
Adjuvant chemotherapy	59 (58.4%)
Lesion preoperatively visible during BSC	
Yes	16 (15.8%)
No	41 (40.6%)
Not performed	44 (43.6%)
Lymphocytes (x10^9/L, median, IQR)	1.88 (1.14)
Monocytes (x10^9/L, median, IQR)	0.70 (0.46)
LMR (median, IQR)	2.75 (1.63)

(BSC = bronchoscopy; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; LMR = lymphocyte-to-monocyte ratio).

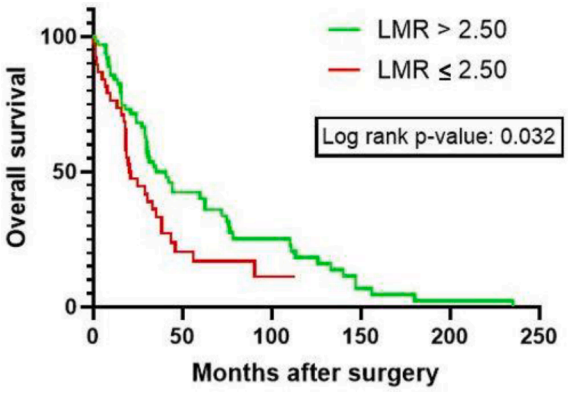

Fig. 2. Kaplan-Meier survival analysis for OS in patients with surgically resected early-stage (stage I + II) SCLC based on the preoperative LMR. Patients with a preoperative LMR > 2.50 (n = 63) show significantly longer OS (median 35.3 vs 20.7 months, p = 0.032) compared to patients with a preoperative LMR ≤ 2.50 (n = 38). (OS = overall survival; LMR = lymphocyte-to-monocyte ratio; SCLC = small cell lung cancer.).

3.5. Identification of robust prognostic factors of disease-free survival

Similarly to OS, all available clinic-pathological variables were included in univariate analysis to be tested for their prognostic potency. Subsequently, univariate analysis revealed that adjuvant chemotherapy (HR = 0.446; 95% CI 0.238–0.837; p = 0.012) and LMR > 2.50 (HR = 0.457; 95% CI 0.245–0.851; p = 0.014) were the only significant factors that associated with favorable DFS (Table 3). Furthermore, adjuvant chemotherapy (HR = 0.478; 95% CI 0.252–0.905; p = 0.023) and LMR > 2.50 (HR = 0.505; 95% CI 0.266–0.959; p = 0.037) remained the only significant prognostic factors for improved DFS after multivariate

Table 2
Univariate and multivariate analysis of clinical variables as prognostic factors for overall survival in surgically resected early-stage (stage I + II) SCLC patients.

Overall survival	Covariables	HR	95% CI	p-value
Univariate analysis	Sex (male)	1.441	0.904–2.297	0.125
	Age (>63 years)	1.113	0.715–1.733	0.636
	Smoking status →Smoker vs. non-smoker	1.456	0.652–3.250	0.359
	COPD	1.092	0.695–1.716	0.703
	Hypertension	1.131	0.724–1.769	0.588
	Diabetes	0.767	0.352–1.672	0.505
	Surgery type (lobar resection)	0.616	0.370–1.026	0.063
	Adjuvant chemotherapy	0.351	0.215–0.573	0.001*
	Lesion pre-OP visible on BSC	0.663	0.320–1.375	0.270
	LMR > 2.50	0.599	0.376–0.955	0.031*
Multivariate analysis	Adjuvant chemotherapy	0.357	0.218–0.585	0.001*
	LMR > 2.50	0.617	0.383–0.993	0.047*

(COPD = chronic obstructive pulmonary disease; OP = operative; BSC = bronchoscopy; LMR = lymphocyte-to-monocyte ratio).

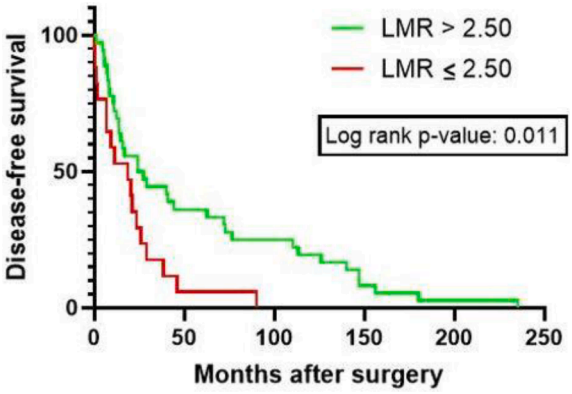

Fig. 3. Kaplan-Meier survival analysis for DFS in patients with surgically resected early-stage (stage I + II) SCLC based on the preoperative LMR. Patients with a preoperative LMR > 2.50 (n = 36) show significantly longer DFS (median 25.8 vs 18.5 months, p = 0.011) compared to patients with a preoperative LMR ≤ 2.50 (n = 17). (DFS = disease free survival; LMR = lymphocyte-to-monocyte ratio; SCLC = small cell lung cancer.).

analysis.

4. Discussion

To the best of our knowledge, this is the first study investigating the prognostic value of LMR in patients undergoing surgery for SCLC. Our study demonstrated that preoperatively elevated LMR is a robust prognostic factor of longer OS and DFS in surgically resected SCLC patients.

Clearly, SCLC is regarded as one of the most aggressive malignancies characterized by rapid growth and early metastatic spread. Although several studies reported encouraging long-term results in patients who underwent surgical resection for stage III SCLC, current clinical practice guidelines recommend surgical resection (supplemented with chemo- or chemo-radiotherapy) only in individuals with localized limited stage disease (i.e. cT1-2N0M0) [31-33]. In addition, early- and advanced stage SCLCs show considerable differences in pathological and clinical features, and are associated with widely divergent survival outcomes [15]. Consequently, in order to investigate the prognostic relevance of

Table 3
Univariate and multivariate analysis of clinical variables as prognostic factors for disease free survival in surgically resected early-stage (stage I + II) SCLC patients.

Disease free survival	Covariables	HR	95% CI	p-value
Univariate analysis	Sex (male)	1.109	0.729–1.993	0.729
	Age (>65.2 years)	1.323	0.743–2.354	0.342
	Smoking status →Smoker vs. non-smoker	1.675	0.702–3.997	0.245
	COPD	1.370	0.777–2.416	0.277
	Hypertension	1.464	0.814–2.632	0.203
	Diabetes	1.003	0.395–2.546	0.996
	Surgery type (lobar resection)	0.591	0.318–1.099	0.097
	Adjuvant chemotherapy	0.446	0.238–0.837	0.012*
	Lesion pre-OP visible on BSC	0.647	0.232–1.801	0.404
	LMR > 2.50	0.457	0.245–0.851	0.014*
Multivariate analysis	Adjuvant chemotherapy	0.478	0.252–0.905	0.023*
	LMR > 2.50	0.505	0.266–0.959	0.037*

(COPD = chronic obstructive pulmonary disease; OP = operative; BSC = bronchoscopy; LMR = lymphocyte-to-monocyte ratio).

preoperative LMR in a fairly homogenous patient cohort where surgical resection is indeed feasible according to the contemporary guidelines, we excluded all post-operatively confirmed pathological stage III or IV SCLC patients.

Median 5-years survival rates up to 50 % have been reported in stage I and II SCLC patients receiving surgery and adjuvant therapy [9,34]. Despite complete R0 resection, the application of adjuvant treatment has been reported to represent one of the key-factors for optimal long-term results [35]. This is in line with the findings in our surgical study cohort, where adjuvant chemotherapy was a clear independent prognostic factor of improved OS and DFS. Up to 40% of the patients in our study cohort did not receive adjuvant chemotherapy during the follow up, which is consistent with previously reported findings in large-scale cancer data bases [12,36]. Changes or differences in the treatment protocols concerning adjuvant therapy might influence the clinical outcomes and might as well affect the validity of LMR in predicting the prognosis. Of note, in our study, all included patients were treated according to the same contemporary guidelines and the adjuvant treatment algorithms for stage I-II SCLC patients did not undergo fundamental changes in the study period [37]. Moreover, according to the results of our multivariate Cox regression model, preoperatively elevated LMR was associated with improved OS and DFS regardless of the presence or absence of adjuvant chemotherapy.

The majority of SCLC patients are diagnosed with surgically not treatable advanced-stage disease [15]. Despite the recent introduction of immune-checkpoint blockade therapy and trials with novel chemotherapeutic agents, the overall prognosis in advanced SCLC remains dismal with median OSs ranging between 10 and 14 months [38-40]. However, several retrospective observational studies and cancer registries have demonstrated encouraging long-term results in SCLC patients undergoing surgical resection even in more advanced stages [12,41]. Simultaneously, recent randomized trials with computed-tomography (CT) based screening programs for current or former smokers have shown an impressive increase in detection of LC at curable stages [42]. Koning et al. showed that the proportion of stage IA to IIB LC cases increased from 20% to 70% between non-screening detected and screening-detected patient cohorts, respectively [43]. As SCLC is the LC type with the strongest link to tobacco exposure, it is possible that the

total number of early-stage SCLC patients might slightly increase in the near future due to enrollment in national LC screening programs. Therefore, the therapeutic relevance of surgery may significantly gain in importance and thus inevitably opening the door for a re-discussion of current guidelines on treatment strategies in SCLC [32,44].

In times of increasing tendency towards more personalized and targeted approaches in medicine, identification of patient subgroups most likely to benefit from distinct therapeutic interventions has become pivotal in SCLC research [19]. Consequently, several prognostic and predictive biomarkers have been already evaluated in SCLC [24]. In accordance with our findings, an elevated LMR was shown to correlate with improved clinical outcome in cohorts comprising non-surgical SCLC patients [45,46]. Although the exact biological mechanism concerning the LMR results is still not clear, it might be arguable to explain these findings in light of the well-known functions of lymphocytes and monocytes in cancer. Lymphocytes are crucial in the anti-tumor immune response as they suppress malignant cell proliferation and migration [47]. Indeed, tumor-infiltrating and cytotoxic lymphocytes in the tumor microenvironment have been shown to sufficiently eliminate malignant cells, resulting in longer OS and DFS in a wide range of various malignancies [48-50]. This is precisely why recently invented immune-checkpoint inhibitors in cancer are therapeutically successful and have also provided promising results in SCLC patients [51-53]. In contrast to lymphocytes, monocytes are thought to be involved in tumorigenesis through differentiation to tumor-associated macrophages (TAMs) [54]. TAMs have been found to directly promote tumor invasion and progression in various solid cancers including SCLC [55-57]. Therefore, LMR might represent a biological balance between cancer-suppressing lymphocytes and tumor-promoting monocytes.

Notably, this present study has several limitations that must be acknowledged. First of all, given its retrospective design, clinical and follow-up data were limited. Moreover, despite the participation of three high-volume thoracic surgical departments, the overall number of included patients with $n = 101$ remained low to conclude robust clinical findings. In contrast, the multicenter and international character strengthens the findings of the study, which represents the first comprehensive investigation on the prognostic role of LMR in a surgical SCLC cohort to date.

5. Conclusion

To conclude, our study suggests that preoperatively elevated LMR is associated with longer OS and DFS in surgically treated early-stage SCLC patients. Indeed, LMR > 2.50 was identified as a novel independent prognostic factor of improved OS and DFS after surgery for SCLC. Consequently, LMR might have the potential to be applied as a prognostic biomarker when selecting SCLC patients for surgical resection in the future. Ultimately, further studies are warranted to confirm our findings.

CRediT authorship contribution statement

Christian Lang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Felix Egger:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Mir Alireza Hoda:** Conceptualization, Resources, Supervision, Writing – review & editing. **Alessandro Saeed Querner:** Data curation, Investigation, Methodology, Software, Writing – review & editing. **Bence Ferencz:** Data curation, Writing – review & editing. **Victor Lungu:** Data curation, Writing – review & editing. **Robert Szegedi:** Data curation, Writing – review & editing. **Levente Bogyo:** Data curation, Writing – review & editing. **Klara Torok:** Data curation, Writing – review & editing. **Felicitas Oberndorfer:** Data curation, Resources, Writing – review & editing. **Thomas Klikovits:** Data curation, Resources, Writing – review & editing. **Anna Schwendenwein:** Formal analysis, Validation, Writing – review & editing. **Kristiina Boettiger:** Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Ferenc Renyi-Vamos:** Data curation, Resources, Writing – review & editing. **Konrad Hoetzenecker:** Data curation, Funding acquisition, Writing – review & editing.**Karin Schelch:** Funding acquisition, Supervision, Validation, Writing – review & editing. **Zsolt Megyesfalvi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Balazs Dome:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.05.010.

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