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Original Research

Ambient air pollution and survival in SCLC/LCNEC: Analysis of a single centre retrospective cohort

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SUMMARY

Background: Small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma of the lung (LCNEC) are the deadliest forms of lung cancer with dismal prognosis. Recent evidence suggests that, beyond cigarette smoke, air pollution can have a role in the pathogenesis of non-small cell lung cancer (NSCLC) and is associated with poorer survival. However, whether air pollutants exposure could affect survival outcomes in SCLC/LCNEC is unknown.
Methods: We retrospectively analysed data from SCLC/LCNEC cases observed in the province of Brescia province Brescia between 2017 and 2021. Air pollutants mean concentrations were calculated during the same timeframe and the Brescia province was divided in six subareas dichotomized into lightly and heavily polluted areas based on the mean $PM_{2.5}$ concentrations. Primary endpoint was to determine the impact of air pollutants exposure on SCLC/LCNEC overall survival (OS). Additionally, we explored the distribution of SCLC/LCNEC across the subareas classified for different air pollutants concentrations.
Findings: We observed 221 cases of SCLC/LCNEC, accounting for about 18 % of new lung cancer cases. Residency in heavily polluted areas (HR 1.51, $p = 0.03$) and extensive stage disease at diagnosis (HR 2.47, $p = 0.0001$) emerged as independent factors for poorer survival. Exploratory analyses showed an association between the distribution of SCLC/LCNEC cases and higher PM_{10} and NO_2 concentrations (OR 1.16, $p < 0.001$ and OR 1.46, $p < 0.001$, respectively).
Interpretation: These results indicate that long-term exposure to high levels of $PM_{2.5}$ represent an independent unfavourable prognostic factor for SCLC/LCNEC. Our data suggest that air pollution may also favour the onset of these malignant diseases. Case-control studies are warranted to confirm these preliminary results.

1. Background

Small Cell Lung Cancer (SCLC) and Large Cell Neuroendocrine Carcinoma of the lung (LCNEC) represent approximately 10–15 % and 1–3 %, respectively, of all lung cancers but they have one of the highest mortality rates among human neoplasms with an expected 5-year survival rate less than 7 % [1,2]. After decades without therapeutic innovations, the pivotal studies IMPOWER-133 and CASPIAN set median survival of extensive stage SCLC at approximately 12–13 months with the addition of immune checkpoint inhibitors (atezolizumab and durvalumab, respectively) to the chemotherapy backbone [3,4]. However, no significant changes have emerged in the treatment of LCNEC, for which platinum-based chemotherapy remains the gold standard [5].

Apart from the disease stage, little is known about what the impact of additional prognostic factors might be, and further research is needed to improve patient's survival.

In Western countries the overall incidence of SCLC/LCNEC is reported to be decreasing in both sexes as a result of policies for

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discouraging tobacco smoking which is the main risk factor for both SCLC and LCNEC [6–8]. After cigarette smoking, air pollution including gaseous pollutants and particulate matter (PM) pollutants is the second leading cause of lung cancer [9]. In particular, PM with an aerodynamic diameter less than 2.5 micrometres ($PM_{2.5}$) is the most harmful PM and it has been classified as a type I carcinogen in humans [10]. A recent study by Swanton and co-researchers provided evidence for a direct link between environmental PM and promotion of lung cancer in cells with pre-existing oncogenic mutations [11]. Smoking and air pollution are synergistic risk factors for lung cancer but, while cigarette smoking is variably decreasing in Western countries, air pollution rates are increasing worldwide [9].

A recent study from the Institute of Global Health in Spain analysed the proportion of annual preventable deaths due to air pollution in approximately 1000 European cities [12]. From the core analysis of air pollution as detected in terms of $PM_{2.5}$ and NO_2 concentration in the index year 2015, the cities of Brescia, Bergamo and other cities of the Po Valley in Northern Italy displayed the highest levels of air pollutants concentrations. However, the degree of air pollution in this area is very diverse, with industrial areas that are heavily polluted and rural areas that are less polluted. To our knowledge, no data exist on whether environmental air pollutants may affect the prognosis of SCLC/LCNEC. In our study we tried to investigate if clinical features or occupational and environmental exposure to toxic agents could affect the prognosis of patients diagnosed with SCLC/LCNEC.

2. Patients and methods

2.1. Study design and endpoints

This was an observational, retrospective, monocentric study conducted on patients diagnosed with SCLC/LCNEC between 2017 and 2021 at one Italian reference Institution in the north of Italy (Spedali Civili of Brescia). The primary objective of this study was to assess the impact of air pollutants on the survival outcomes of patients with SCLC/LCNEC. An additional exploratory analysis aimed to determine the distribution of SCLC/LCNEC in subareas of the province of Brescia classified for different air pollutants concentrations.

2.2. Subjects and data collection

We retrospectively included patients with histologically or cytologically confirmed diagnosis of SCLC/LCNEC who were consecutively observed between January 01, 2017, and December 31, 2021, at the Medical Oncology and Radiation Oncology Units of the Spedali Civili in Brescia. Inclusion criteria comprised residency in the Brescia province for at least 10 years, availability of demographic data, and a cytologically or histologically confirmed diagnosis of SCLC/LCNEC. Data regarding exposure to potential toxic substances during working life for at least 10 years were also recorded. To assess the impact of air pollutants on patients' outcomes, the province of Brescia was divided into six recognized geographical areas which were dichotomized based on air pollutants mean concentrations (see supplementary material for geographical details of sub-areas of the Brescia province).

2.3. Air pollution ($PM_{2.5}$, PM_{10}, NO_2) assessment

Data on air pollutants were provided from the European Environment Agency (EEA) reports [13], the EUROSTAT datasets [14], the State of Global Air (SOGA) reports [15] and the Regional Agency for the Protection of the Environment (ARPA) reports [16]. Further data were retrieved from the ELAPSE project (Effects of Low-Level Air Pollution: A study in Europe). This study calculated the average concentrations of different air pollutants by means of land use regression (LUR) models and concluded that in 19 European countries in the index year 2010, 89 % and 8 % of people lived in areas with $PM_{2.5}$ and NO_2 concentrations above the European Unit (EU) annual limit of 25 $\mu g/m^3$ and 40 $\mu g/m^3$, respectively [17].

Ambient concentrations of $PM_{2.5}$, PM_{10} and NO_2 were measured in micrograms of particulate matter per cubic meter of air, or $\mu g/m^3$. Air pollutant exposure was calculated as annual mean concentrations of $PM_{2.5}$, PM_{10} and NO_2 in the geographical area of residency of each patient between 2017 and 2021. The annual mean values were calculated from daily average levels measured by the monitoring stations spread throughout the provincial territory. Mean values of annual concentrations (19 $\mu g/m^3$ for $PM_{2.5}$, 26 $\mu g/m^3$ for PM_{10}, 22 $\mu g/m^3$ for NO_2) were used as dichotomized cut-off values to define lightly and heavily polluted areas.

2.4. Statistical analysis

Patients' data were collected from medical records and entered in an anonymized database.

We conducted descriptive analyses with calculation of trend indices. Overall survival (OS) was defined as the time elapsed from diagnosis to death or last follow-up. Uni- and multivariable Cox regression analyses were performed to identify independent prognostic factors of OS. A p value < 0.10 was considered statistically significant for entry level at univariable analysis. Results were expressed as Hazard Ratio (HR) with the relative confidence intervals (95 %CIs). Survival curves were plotted with the Kaplan-Meier method and differences between curves were evaluated with the log-rank test.

We described the distribution of cases among the diverse subareas of the province and conducted additional exploratory subgroup analyses (through Spearman's rank-order correlation, uni- and multivariable logistic regression) to examine the associations between potential risk factors with SCLC/LCNEC geographical distribution. Results were expressed as Odds Ratio (OR) with the relative confidence intervals (95 %CIs). All analyses assumed two-tailed comparisons at a statistical significance level of p 0.05, unless otherwise specified.

The analyses were conducted using STATA (STATACorp LLC, version 14.2) and SPSS (SPSS-IBM Statistics Inc, version 23.0) software packages.

2.5. Ethical considerations

The study was approved by the Institutional Review Board Lombardia 6 (NP 6291) and was conducted in accordance with the Declaration of Helsinki for clinical studies. Due to the retrospective nature of this study, informed consent was signed by all alive patients. Data of patients who died without informed consent have been protected according to the 196/2003 Italian Regulation "Code on the protection of personal data" and in compliance with the European Union no.679/2016. Finally, the study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [18].

3. Results

3.1. Patients' characteristics

Two hundred twenty-one patients were included, and their characteristics are outlined in Table 1. Median age at diagnosis was 68 years (range 41–90) and 60 % were males. Twenty-one % of patients had a family history of lung cancer, while 58 % had a family history of non-pulmonary malignancies. Thirty-three % of patients were active smokers, 63 % were former-smokers and 4 % were never-smokers. Forty % of smokers were females, with an average of 41 p/y (vs 56 p/y for men). Seventy-eight % of patients reported exposure to potentially toxic agents during their working life. The most frequently found at-risk work activities in our series included heavy metalworking and foundry (24 %), plastic (18 %) and textiles (14 %) activities, agricultural

Table 1
Patients' characteristics.

Patients number (221)	Characteristics	Number (%)
Gender	Male	134 (60 %)
	Female	87 (40 %)
Age at diagnosis	< 68 years	96 (43 %)
	≥ 68 years	125 (57 %)
Family history of oncological diseases	Yes	109 (73 %)
	No	63 (37 %)
	Missing	49
Family history of chest tumours	Yes	39 (23 %)
	No	131 (77 %)
	Missing	51
Smoking status	Active smoker	59 (33 %)
	Former smoker	114 (63 %)
	Non-smoker	8 (4 %)
	Missing	40
Professional exposure	Yes	132 (78 %)
	No	38 (22 %)
	Missing	51
Charlson Comorbidity Index (CCI)	> 5	173 (93 %)
	≤ 5	12 (7 %)
	Missing	36
Histology	SCLC	183 (83 %)
	LCNEC	38 (17 %)
Stage according to VALGS	limited	54 (24.5 %)
	extensive	167 (75.5 %)
Exposure to $PM_{2.5}$	$Pm_{2.5} < 19\ \mu g/m^3$	50 (23 %)
	$Pm_{2.5} \geq 19\ \mu g/m^3$	171 (77 %)
Exposure to PM_{10}	$Pm_{10} < 26\ \mu g/m^3$	115 (52 %)
	$Pm_{10} \geq 26\ \mu g/m^3$	106 (48 %)
Exposure to NO_2	$No_2 < 22\ \mu g/m^3$	88 (40 %)
	$No_2 \geq 22\ \mu g/m^3$	133 (60 %)

herbicides and pesticides exposure (12 %), oil and chemistry industry (7 %). Noteworthy 47 % of them were exposed to either smoke or professional exposure, while all patients were exposed to at least one of them. Chronic respiratory or cardiovascular diseases were found in 67 % of patients resulting in a mean Charlson's comorbidity index (CCI) of 8.38 (range 2–12). The predominant histology was SCLC (83 % of patients) while 17 % of patients were diagnosed with LCNEC. At diagnosis, 75.5 % and 24.5 % of patients had advanced and limited stage disease, respectively.

3.2. SCLC/LCNEC geographical distribution

The 221 new cases of SCLC/LCNEC observed at our Institution from 2017 to 2021 represented approximately 18 % of all new lung cancer diagnoses. The distribution by year showed 43 new cases in 2017, 42 in 2018, 40 in 2019, 56 in 2020 and 40 in 2021. Different geographical patterns of case distribution were recorded: 75 (34 % of patients) were living in the city of Brescia, 41 (19 %) were from both the Bassa Bresciana and Franciacorta areas, 33 (15 %) from Val Trompia, 17 (8 %) from Val Sabbia and 14 (6 %) from the West Garda Lake area (supplementary items Table 1).

3.3. Survival outcomes

In the entire study population, the median OS was 8.6 months. The univariable analysis for OS revealed that male sex (HR 1.34 [0.97–1.85], p = 0.07), pulmonary comorbidities (HR 1.46 [1.01–2.11], p = 0.46), occupational exposure to toxic agents (HR 1.45 [0.98–2.14], p = 0.06), extensive-disease stage (HR 2.47 [1.53–3.98], p = 0.0001) and residency in heavily polluted areas according to $PM_{2.5}$ levels (HR 1.51 [1.03–2.21], p = 0.03) were significantly associated with a higher risk of death (Fig. 1 and supplementary materials Figure 1), while no significant differences were observed based on histology, smoking habit or PM_{10} and NO_2 exposure (Fig. 1 and supplementary items Figure 1). At multivariable analysis, extensive-stage disease (HR=3.92 [0.88–17.45], p = 0.04) and residency in heavily polluted area according to $PM_{2.5}$ levels (HR=4.98 [1.08–22.94], p = 0.02) maintained a significant association with a higher risk of death (Table 2).

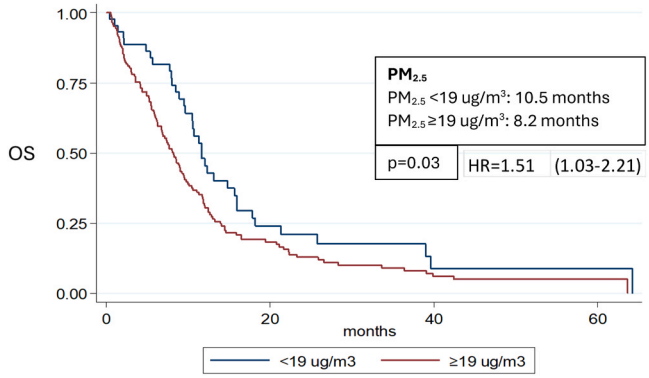

Fig. 1. Overall survival (OS) according to exposure to $PM_{2.5}$ (lightly vs heavily polluted areas).

3.4. Analysis of air pollutants

3.4.1. $PM_{2.5}$

Between 2016 and 2023 the average concentration of $PM_{2.5}$ in the entire province of Brescia was 19 $\mu g/m^3$, in a range between 15.37 $\mu g/m^3$ (2023) and 21.18 $\mu g/m^3$ (2016). The highest average concentration throughout the whole period was recorded in the Bassa Bresciana area (21.24 $\mu g/m^3$), the lowest in the Val Trompia area (13.41 $\mu g/m^3$). The highest average annual levels were found in Franciacorta in 2016 and Garda Lake in 2017 (23.65 $\mu g/m^3$), the lowest in Val Trompia in 2023 (9.32 $\mu g/m^3$) (supplementary items figure 2).

3.4.2. PM_{10}

Between 2011 and 2023 the average concentration of PM_{10} in the entire province of Brescia was 26 $\mu g/m^3$, in a range between 21.40 $\mu g/m^3$ (2020) and 35.10 $\mu g/m^3$ (2011). The highest average concentration throughout the whole period was recorded in the city of Brescia (33.64 $\mu g/m^3$), the lowest in Val Trompia (18.44 $\mu g/m^3$). The highest average annual levels were found in Brescia in 2011 (44.11 $\mu g/m^3$), the lowest in Val Trompia in 2023 (9.52 $\mu g/m^3$) (supplementary items figure 3).

3.4.3. NO_2

Between 2011 and 2023 the average concentration of NO_2 in the entire province of Brescia was 22 $\mu g/m^3$, in a range between 16.54 $\mu g/m^3$ (2023) and 26.07 $\mu g/m^3$ (2016). The highest average concentration throughout the whole period was recorded in the city of Brescia (32.32 $\mu g/m^3$), the lowest in Val Trompia (16.44 $\mu g/m^3$). The highest average annual levels were found in the city of Brescia in 2015 (39.18 $\mu g/m^3$), the lowest in Val Trompia in 2023 (7.25 $\mu g/m^3$) (supplementary items figure 4).

3.5. Exploratory analyses: association between air pollution and SCLC/LCNEC geographical distribution

SCLC/LCNEC cases were differently distributed in areas with different concentrations of air pollutants. Specifically, 33 of them (15 %) were observed in areas with none of the 3 air pollutants above the mean annual value of the province, 72 (33 %) in areas with one or two pollutants above the mean annual value and 116 (52 %) in areas with all the three pollutants above the mean annual value, respectively (supplementary items figure 5). Performing Spearman's rank correlation, we found a correlation between PM_{10} and NO_2 exposure and geographical distribution of SCLC/LCNEC, which was observed regardless of smoking status or professional exposure (supplementary

Table 2
Prognostic factors for overall survival according to univariable and multivariable analyses.

Stratification factors		Univariate analysis			Multivariate analysis		
		HR	95 %CI	P	HR	95 %CI	P
Age	< 68 years ≥ 68 years	1.20	0.68–1.64	0.26			
Sex	Male Female	1.34	0.97–1.85	**0.07**	1.34	0.88–2.05	0.17
Chronic cardiovascular Diseases	No Yes	0.86	0.62–1.19	0.36			
Chronic respiratory Diseases	Yes No	1.46	1.01–2.11	**0.046**	1.23	0.77–1.98	0.38
Histology	SCLC LCNEC	1.07	0.69–1.67	0.75			
Disease stage	Extensive Limited	2.47	1.53–3.98	**0.0001**	3.92	0.88–17.45	**0.04**
Smoking habit	≥ 20 p/y < 20 p/y	1.66	0.73–3.77	0.22			
Occupational exposure	Yes No	1.45	0.98–2.14	**0.06**	1.24	0.78–1.98	0.37
Area of residency according to $PM_{2.5}$ exposure	Heavily polluted Lightly polluted	1.51	1.03–2.21	**0.03**	4.98	1.08–22.94	**0.02**
Area of residency according to PM_{10} exposure	Heavily polluted Lightly polluted	0.94	0.69–1.3	0.72			
Area of residency according to NO_2 exposure	Heavily polluted Lightly polluted	1.03	0.75–1.42	0.85			

items Table 2). Univariable logistic regression highlighted a significant association between air pollutants concentrations and geographical distribution of SCLC/LCNEC, both for PM_{10} (OR 1.16 [1.07–1.25], p = <0.001) and NO_2 (OR 1.46 [1.27–1.68], p = <0.001), which was confirmed for NO_2 at multivariable analyses (OR 3.07 [1.90–4.94], p = <0.001) as detailed in supplementary items table 3.

4. Discussion

In line with published evidence, the median survival of the whole series of our study was 8.5 months [19]. This is even more significant considering that most patients had been treated in the pre-immunotherapy era. Female sex, absence of chronic respiratory diseases and occupational exposure to toxic agents emerged as favourable prognostic factors. Conversely, residency in heavily polluted areas (defined by $PM_{2.5}$ levels) and extensive stage disease were correlated with significantly shorter survival. Both these associations were maintained at multivariable analysis regardless of sex, comorbidities, smoking habit and professional exposure. To our knowledge, this is the first evidence suggesting that chronic environmental exposure to high levels of $PM_{2.5}$ represents an independent, unfavourable risk factor for SCLC/LCNEC patients' survival. Indeed, previous studies showing that air pollutants have an adverse impact on lung cancer specific mortality and overall mortality, have only enrolled patients with adenocarcinoma or squamous cell histologies [12,20].

As expected, our case series confirms the primary association between smoking and SCLC/LCNEC, since 96 % of patients were current or former smokers. Moreover, the average consumption of 50 pack/years highlights that our SCLC/LCNEC patients were also heavy smokers. 40 % of smokers were females, reflecting the increasing tobacco exposure in females in more recent years.

Intriguingly, occupational exposure to potentially toxic substances involved more than 75 % of patients during their working life and all patients were exposed to either smoke or occupational toxic agents. These working activities reflected known occupational risk factors such as metalworking, chemical and dust exposure. This data is consistent with the findings of recent studies that have documented a strong interaction between smoke and occupational exposures in increasing the risk of SCLC/LCNEC onset [21–23]. A recent paper by Curiel Garcia et al found that subjects exposed to either smoke or potentially toxic substances increased the risk of developing SCLC/LCNEC compared to unexposed controls. Moreover, the combination of the two risk factors more than doubled the disease incidence [23].

The close association between cigarette smoking and SCLC/LCNEC (less the 5 % occurs in never-smokers) suggests that other carcinogens may have a limited impact on the onset of this extremely aggressive and deadly tumour. While the causal relationship with cigarette smoking is widely known, no evidence exists about the role of air pollutants in SCLC/LCNEC pathogenesis. Indeed, even though particulate matter have been proven to be the second leading cause of lung cancer and its interaction with cigarette smoke has been demonstrated [9], the role of fine particles as an independent risk factor for lung cancer has been shown only for adenocarcinoma and squamous cell carcinoma histotypes [20].

Interestingly, the 221 cases of our cohort, accounting for about 18 % of all new lung cancer diagnoses, were mainly concentrated in areas with high pollution levels. In details, 52 % of SCLC/LCNEC cases occurred in areas with all three pollutants (PM_{10}, $PM_{2.5}$, NO_2) exceeding the median annual value, while 33 % of them occurred in areas with one or two pollutants above the median and only 15 % occurred in areas with all the 3 air pollutants below the median. However, it should be noted that the mean levels of air pollutants in the region with zero pollutants over the threshold is actually just below the mean annual value in the Po Valley, but it remains well above the current WHO recommendation.

An exploratory analysis from our study revealed a potential association for both PM_{10} and NO_2 exposure and SCLC/LCNEC distribution at univariable analysis, which was maintained for NO_2 also at multivariable analysis. The absence of a clear relationship with $PM_{2.5}$ instead of NO_2 is consistent with the results from a recent study by Wenjie Li and Wei Wang, which showed a stronger relationship between NO_2 exposure and lung cancer, rather than particulate matters [24]. These findings generate the hypothesis that beyond smoking and toxic working exposure, nitrogen oxides and particulate matters in outdoor air pollution could be involved in the SCLC/LCNEC pathogenesis. Given that the cumulative oncogenic effect of exposures has a minimum latency of 6–8 years in non-smoker individuals, the recent improvements in air quality will likely yield beneficial effects in the coming decades [25].

A sub-analysis from the Global Burden of Disease (GBD) study conducted in 2019 showed that the burden of air pollution in terms of $PM_{2.5}$ concentration has significantly declined from 1990 to 2019 in Italy [26]. Accordingly, tracheal, bronchus and lung (TBL) cancer resulted in lower

mortality and disability-adjusted life years (DALYs) by 43.7 %/100.000 inhabitants. Between 2016 and 2023 the annual mean concentration of $PM_{2.5}$ in the province of Brescia has dropped from 21.18 μg/m^3 to 15.37 μg/m^3, in compliance with the threshold established by the Italian law (25 μg/m^3) but not with the threshold recommended by WHO (5 μg/m^3). Similarly, atmospheric levels of PM_{10} and NO_2 have also shown a declining trend over the years. However, it is important to note that among the patients enrolled in this study, the exposures to smoke and toxic agents began even decades prior to the onset of their neoplasms, when air pollutant concentrations were well above the recommended thresholds and smoking was a prevalent habit. Given that the cumulative oncogenic effect of exposures has a minimum latency of 6–8 years in non-smoker individuals [27], the recent improvements in air quality will likely yield beneficial effects in the coming decades.

The present study certainly has several limitations. First, it was not possible to investigate the role of additional risk factors, such as exposure to radon or indoor water pollutants, due to lack of data. Second, only patients observed at the main Institution of the province were included. While we are confident that they represent the vast majority of SCLC/LCNEC cases in this area, we cannot rule out that missing patients could exist. Thus, the present study does not qualify as a true epidemiological case-control study. Third, this study does not consider the potential patients who have moved out of the Brescia province after living there for a long time. Additionally, the study design did not permit to draw any definitive conclusion about the association between environmental exposure and development of SCLC/LCNEC. Nevertheless, the present study's findings indicate that air pollutants should be a major issue in policies to improve air quality and reduce morbidity and mortality. Given the results of the present study, a future direction would be to start a larger multicentre case-control study of SCLC/LCNEC in areas using the new air pollutants thresholds established by the WHO.

In conclusion, to our knowledge, this study represents the first to demonstrate a significant independent adverse impact of $PM_{2.5}$ exposure on SCLC/LCNEC patients' survival. The present study lays the foundation for future multicentric prospective studies aiming to confirm detrimental effects of air pollutants and to promote further appropriate air quality improvement measures.

CRediT authorship contribution statement

Deborah Cosentini: Writing – review & editing, Conceptualization. **Daniela Nonnis:** Data curation. **Luca Carlofrancesco Ammoni:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Stefano Maria Magrini:** Data curation. **Valentina Cortesi:** Resources, Methodology, Formal analysis, Data curation. **Paolo Borghetti:** Data curation. **Alfredo Berruti:** Writing – review & editing, Validation, Methodology, Conceptualization. **Salvatore Grisanti:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Alice Baggi:** Data curation. **Camilla Vultaggio:** Data curation. **Vito Amoroso:** Data curation. **Giorgio Facheris:** Data curation. **Mattia Facchetti:** Data curation. **Susanna Bianchi:** Data curation. **Marta Laganà:** Data curation.

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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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116190.

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