

Epidemiology, pathological characteristics and survival of retroperitoneal soft-tissue sarcomas compared with non-retroperitoneal soft tissue sarcomas

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Abstract. Retroperitoneal soft-tissue sarcomas (RPS) are rare forms of mesenchymal tumors that account for ~0.15% of all malignancies. The purpose of the present study was to determine the differences between RPS and non-RPS anatomopathological and clinical features and to analyze whether the hazard ratio for short-term mortality differs between patients with RPS and non-RPS, after adjusting for differences in baseline anatomopathological and clinical features. The Veneto Cancer Registry, a high-resolution population-based dataset spanning the regional population, was used as a data source for the analysis. The current analysis focuses on all incident cases of soft-tissue sarcoma recorded by the Registry from January 1, 2017 to December 31, 2018. A bivariate analysis was carried out to compare demographic and clinical characteristics in RPS and non-RPS. Short-term mortality risk was analyzed by primary tumor site. The significance of variations in survival by site group was determined using Kaplan-Meier curves and the Log-rank test. Finally, Cox regression was used to assess the hazard ratio for survival by sarcoma group. RPS accounted for 22.8% of the total sample (92 out of 404 cases). The mean age at diagnosis was 67.6 years for RPS vs. 63.4 for non-RPS; 41.3% of RPS were >150 mm vs. 5.5% for non-RPS. Stages III and IV were more prevalent in RPS (53.2 vs. 35.6%), despite the fact that, in both groups, advanced stages are the most common onset at diagnosis. Regarding surgical margins, the

present study showed that R0 is the most prevalent in non-RPS (48.7%), while R1-R2 is the most frequent in patients with RPS (39.1%). The 3-year mortality rate for retroperitoneum was 42.9 vs. 25.7%. Comparing RPS and non-RPS, the multivariable Cox model showed a hazard ratio of 1.58 after adjusting for all other prognostic factors. RPS clinical and anatomopathological characteristics differ from those of non-RPS. Overall, despite adjusting for other prognostic factors, the retroperitoneum site was an independent prognostic factor associated with a worse overall survival in sarcoma patients compared with other sites.

Introduction

The incidence of soft tissue sarcoma (STS) is less than 6 cases per 100,000, or 1-2% of all adult cancers (1). Retroperitoneal soft-tissue sarcomas (RPS) are rare forms of mesenchymal tumors that account for approximately 0.15% of all malignancies (1-3). The annual incidence is 0.3-0.4 cases per 100,000 inhabitants, with the most common histological subtypes being liposarcomas (20-25%), leiomyosarcomas (14%), and undifferentiated pleomorphic sarcomas (14%). RPS represent 12-15% of all soft-tissue sarcomas and, due to their location, are frequently incidental findings (4-7). RPS can grow to an extremely large size before signs or symptoms such as abdominal pain, back pain, or bowel dysfunction indicating their presence (2,6).

RPS tend to be more locally aggressive, with high rates of local and metastatic recurrence, and therefore poor overall long-term survival (1). In fact, a study of 2,920 RPS patients using SEER Program data from 2002-2012 revealed overall 5- and 10-year survival rates of 58.4 and 45.3%, respectively (8). Since surgical resection is the only curative therapy for RPS, the grade and extent of surgical resection with a negative margin are the most important prognostic factors (3,5). Nevertheless, other factors, including age and sex, tumor size, grade, and histology, and the presence of multifocality, have also been indicated as predictors of mortality in RPS patients (5,8). Similarly, Tan et al. demonstrated that the most

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significant prognostic markers for overall STS are tumor size, grade, histologic subtype, and surgery for the primary lesion and metastasis (3).

Some of these prognostic factors are incorporated in the staging system. However, the clinical relevance of the AJCC staging system for soft-tissue sarcomas is still under debate (3,9-13). In a performance analysis conducted in 2017 on data from the SEER database, Cates concluded that, when staging retroperitoneal sarcomas, the new 8th edition of the AJCC staging system performed worse than the previous 7th edition (10).

This study aims to verify the differences between RPS and non-RPS anatomopathological and clinical characteristics, determining whether the hazard ratio for short-term mortality differs between RPS and non-RPS patients, after adjusting for these variables.

Materials and methods

The Italian National Health System is a public service grounded in the fundamental values of universality, free access, freedom of choice, pluralism in provision, and equity. Organizationally, it is regionally based and primarily supported by general taxation (14).

In 2015, the Veneto's Regional Oncology Network produced a comprehensive document on the clinical management of patients with soft-tissue sarcoma (15,16). The network's publication was based on current national and international literature and included a detailed description of the clinical procedures to be applied from initial diagnosis to end-of-life care (4,17-19).

Clinical data source. The Veneto Cancer Registry (RTV), a high-resolution population-based dataset spanning the regional population (approximately 4.9 million residents), and the regional health service records served as data sources for the analysis. The analysis focuses on all adult (>19 years old) incident cases of STS (excluding gastrointestinal stromal tumor, Kaposi's sarcoma, Ewing's sarcoma, uterine and visceral sarcomas) recorded by the Registry in 2017 and 2018 (latest available cohorts).

Cancer registration procedures are based on comprehensive information gathered from various sources (e.g., pathology reports, clinical charts, death certificates, and health service administrative records). The variables recorded for STS include: age and sex; tumor site; the primary tumor's diameter (mm); tumor grade (G1, G2, G3, and GX); combined clinical-pathological TNM stage at diagnosis (I, II, III, and IV, AJCC 7th edition); status of surgical resection margins (R0, R1, and R2); and medical treatment (chemotherapy or radiotherapy, if any). The pathology report was validated by a single histology assessment; A regional centralized formal reference center has been established since January 2020. The vital status was available after 3 years of follow-up.

Ethics. All analyses were conducted on anonymous aggregated data with no possibility of individuals being identified. The study was approved by the Ethics Committee of the Veneto Oncological Institute (No. 0001218/22).

Statistical analysis. Descriptive statistics were first computed; categorical variables were represented as frequencies and percentages, and continuous numerical variables were summarized using means, median, standard deviations (SD), and minimum-maximum intervals.

A bivariate analysis then compared demographic and clinical characteristics in retroperitoneal and non-retroperitoneal soft-tissue sarcomas. The Chi-squared test and Student's t-test were used, respectively, to statistically assess the differences in proportions and means.

The 2017, 2018 STS age-standardized incidence rates in the Veneto region were calculated stratifying by sex and tumor site. The direct standardization method was adopted applying the event rates for each ten-year age and sex group of the study population to sizes of same age and sex standard population. In this study, the world population was considered as the standard reference. The weighted average population sizes for each age group and sex in both 2017 and 2018 were extracted from the World Bank censuses (20).

Short-term mortality risk was analyzed by primary tumor site. The Wilson score method was used to calculate confidence intervals (C.I.) for percentages. Using Kaplan-Meier curves and the Log-rank test, the significance in variations in survival by site group was determined.

Cox regression was used to assess the hazard ratio for survival by sarcoma group. Hazard ratios (HR) were estimated both with univariate (Model 1) and multivariable models by progressively adjusting for TNM stage and variables not included in AJCC staging system which resulted differently distributed by sarcoma subtype in bivariate analysis: sex, age, surgical margins and medical treatments (Models 2, 3, 4).

Sensitivity analysis was also carried out reperforming the Cox models on all patients except stage IV cases.

Results were deemed statistically significant at the $P < 0.05$ level. All data analyses were conducted using R 4.0.4 (RStudio, Inc., Boston, Massachusetts).

Results

The regional population-based cancer registry (censoring the entire Veneto population of nearly 4.9 million people) recorded 190 incident cases of adult STS in 2017 (including 41 RPS) and 214 incident cases of adult STS in 2018 (among them 51 RPS). Retroperitoneal STS accounted for 22.8% of the total sample (92 out of 404 cases).

In 2017, 2018, the world age-standardized incidence rates per 100,000 inhabitants for STS in the Veneto region were 3.4, respectively 3.68, while incidence rates for RPS stood at 0.72 and 0.70. In 2018, world age-standardized incidence rates for STS by sex per 100,000 inhabitants were 4.05 for males and 3.31 for females, respectively, while for RPS, incidence rates by sex per 100,000 inhabitants stood at 0.64 for males and 0.76 for females, respectively.

The main demographic and clinical characteristics of STS patients included in the study are presented in Table I. The age at diagnosis ranges from 20 to 95 years, with a mean age of 64.4 years and a median age of 66 years. The limbs were the most common primary site (41.6%), followed by the retroperitoneum (22.8%) and the trunk (22.5%). Half the STS cases

Table I. Retroperitoneal vs. non-retroperitoneal STS-cohort demographic and clinical characteristics.

Characteristic	All STS cases (n=404)	Retroperitoneal STS (n=92)	Non-retroperitoneal STS (n=312)	P-value
Age (at diagnosis), years				0.026
Mean	64.41	67.61	63.48	
Median	66	75	64	
SD	15.53	15.08	15.56	
Min-Max	20-95	20-92	20-95	
Sex, n (%)				0.029
Male	231 (57.18)	43 (46.74)	188 (60.25)	
Female	173 (42.82)	49 (53.26)	124 (39.74)	
Year of diagnosis, n (%)				0.674
2017	190 (47.03)	41 (44.57)	149 (47.76)	
2018	214 (52.97)	51 (55.43)	163 (52.24)	
Size, n (%)				<0.001
≤100 mm	191 (47.28)	21 (22.83)	170 (54.49)	
101-150	27 (6.68)	5 (5.43)	22 (7.05)	
>150 mm	55 (13.61)	38 (41.30)	17 (5.49)	
Unknown	131 (32.43)	28 (30.43)	103 (33.01)	
TNM stage (AJCC 7th edition), n (%)				0.059
I	105 (25.99)	23 (25)	82 (26.28)	
II	110 (27.23)	19 (20.65)	91 (29.17)	
III resected	98 (24.26)	29 (31.52)	69 (22.12)	
III not resected	4 (0.99)	0 (0)	4 (1.28)	
IV	58 (14.35)	20 (21.74)	38 (12.18)	
Unknown	29 (7.18)	1 (1.09)	28 (8.97)	
Grade, n (%)				0.324
G1	90 (22.28)	16 (17.39)	74 (23.72)	
G2	74 (18.32)	22 (23.91)	52 (16.67)	
G3	187 (46.29)	41 (44.57)	146 (46.79)	
GX	49 (12.13)	12 (13.04)	37 (11.86)	
Unknown	4 (0.99)	1 (1.09)	3 (0.96)	
Surgical margins (first treatment), n (%)				<0.001
R0	177 (43.81)	25 (27.17)	152 (48.72)	
R1-R2	137 (33.91)	36 (39.13)	101 (32.37)	
Unknown	37 (9.16)	15 (16.30)	22 (7.05)	
Not resected	63 (15.59)	16 (17.39)	47 (15.06)	
Medical treatment, n (%)				<0.001
Chemotherapy	59 (14.60)	28 (30.43)	31 (9.94)	
Radiotherapy	55 (13.61)	5	50 (16.03)	
Both	95 (23.51)	16	79 (25.32)	
No	195 (48.27)	43	152 (48.72)	

STS, soft tissue sarcoma; TNM, tumor-node metastasis.

had tumors with a diameter of 100 mm or less, whereas 13.6% had a diameter greater than 150 mm. On average, RPS patients were older (67.6 vs. 63.4 years, $P=0.026$).

In terms of tumor size, the majority of RPS patients (41.3% of the sample) had tumors larger than 150 mm, while the majority of patients in the non-RPS group had tumors of 100 mm or less ($P<0.0001$).

Moreover, in retroperitoneal sarcomas, advanced TNM stages at diagnosis were more common than in the non-RPS group (53.3 vs. 35.6%). No significant differences in grade were found by site group.

With regard to surgical treatments, the percentages of non-resected patients were similar in the two groups (17.4 vs. 15.1%). However, the proportion of R0 patients was significantly

Table II. Overall mortality rates and 95% confidence intervals by STS primary tumor site in all cases, in stages I-II-III resected, III non-resected -IV.

Stage	Years from diagnosis	Retroperitoneal STS	Non-Retroperitoneal STS				Total
			All	Limbs	Trunk	Head-Neck	
TNM stage I	1	26.09 (8.14, 44.03)	8.54 (2.49, 14.58)	6.82 (0, 14.27)	12.5 (1.04, 23.96)	0 (0, 0)	12.38 (6.08, 18.68)
	2	34.78 (15.32, 54.25)	15.85 (7.95, 23.76)	13.64 (3.5, 23.78)	21.88 (7.55, 36.2)	0 (0, 0)	20 (12.35, 27.65)
	3	40.91 (20.36, 61.45)	19.51 (10.93, 28.09)	15.91 (5.1, 26.72)	28.13 (12.55, 43.7)	0 (0, 0)	24.04 (15.83, 32.25)
TNM stage II	1	21.05 (2.72, 39.38)	9.89 (3.76, 16.02)	6.38 (0, 13.37)	20 (2.47, 37.53)	8.33 (0, 19.39)	11.82 (5.79, 17.85)
	2	26.32 (6.52, 46.12)	14.29 (7.1, 21.48)	8.51 (0.53, 16.49)	25 (6.02, 43.98)	16.67 (1.76, 31.58)	16.36 (9.45, 23.28)
	3	42.11 (19.9, 64.31)	20 (11.74, 28.26)	15.22 (4.84, 25.6)	35 (14.1, 55.9)	16.67 (1.76, 31.58)	23.85 (15.85, 31.85)
TNM stage III resected	1	20.69 (5.95, 35.43)	5.8 (0.28, 11.31)	4.26 (0, 10.03)	5.56 (0, 16.14)	25 (0, 67.43)	10.2 (4.21, 16.2)
	2	20.69 (5.95, 35.43)	11.59 (4.04, 19.15)	10.64 (1.82, 19.45)	11.11 (0, 25.63)	25 (0, 67.43)	14.29 (7.36, 21.21)
	3	24.14 (8.56, 39.71)	16.18 (7.42, 24.93)	17.39 (6.44, 28.34)	11.11 (0, 25.63)	25 (0, 67.43)	18.56 (10.82, 26.29)
TNM stages III not resected-IV	1	40 (18.53, 61.47)	28.13 (12.55, 43.7)	15.38 (0, 35)	46.67 (21.42, 71.91)	0 (0, 0)	35.48 (23.57, 47.39)
	2	70 (49.92, 90.08)	50 (32.68, 67.32)	23.08 (0.17, 45.98)	73.33 (50.95, 95.71)	50 (1, 99)	61.29 (49.17, 73.41)
	3	75 (56.02, 93.98)	56.25 (39.06, 73.44)	30.77 (5.68, 55.86)	73.33 (50.95, 95.71)	75 (32.57, 117.43)	67.21 (55.43, 78.99)
TNM stage IV	1	40 (18.53, 61.47)	25 (8.96, 41.04)	16.67 (0, 37.75)	41.67 (13.77, 69.56)	0 (0, 0)	34.48 (22.25, 46.72)
	2	70 (49.92, 90.08)	46.43 (27.96, 64.9)	25 (0.5, 49.5)	66.67 (39.99, 93.34)	50 (1, 99)	60.34 (47.76, 72.93)
	3	75 (56.02, 93.98)	53.57 (35.1, 72.04)	33.33 (6.66, 60.01)	66.67 (39.99, 93.34)	75 (32.57, 117.43)	66.67 (54.43, 78.9)
All cases	1	26.09 (17.11, 35.06)	11.92 (8.27, 15.58)	8.93 (4.62, 13.24)	19.78 (11.6, 27.96)	6.98 (0, 14.59)	16.09 (12.51, 19.67)
	2	35.87 (26.07, 45.67)	20.53 (15.97, 25.09)	14.29 (8.99, 19.58)	32.97 (23.31, 42.63)	18.6 (6.97, 30.24)	25.5 (21.25, 29.74)
	3	42.86 (32.69, 53.02)	25.67 (20.72, 30.61)	20.48 (14.34, 26.62)	37.36 (27.42, 47.3)	20.93 (8.77, 33.09)	31 (26.47, 35.53)

STS, soft tissue sarcoma; TNM, tumor-node metastasis.

Table III. Cox regression models adjusted for different sets of covariates.

A, Model 1 (unadjusted)			
Parameter	HR	95% CI	P-value
Retroperitoneal STS ^a	1.75	1.20-2.56	0.004
B, Model 2 ^b			
Parameter	HR	95% CI	P-value
Retroperitoneal STS ^a	1.51	1.02-2.24	0.040
C, Model 3 ^c			
Parameter	HR	95% CI	P-value
Retroperitoneal STS ^a	1.63	1.08-2.46	0.019
D, Model 4 ^d			
Parameter	HR	95% CI	P-value
Retroperitoneal STS ^a	1.58	1.04-2.42	0.034

^aReference non-retroperitoneal STS. ^bAdjusted by sex and age. ^cAdjusted by sex, age, and TNM stage. ^dAdjusted by sex, age, TNM stage, surgical margins, and medical treatment.

lower in RPS than in non-RPS (27.2 vs. 48.7%, $P=0.0008$). The percentage of subjects receiving any type of medical therapy is similar between RPS and non-RPS (46.74 vs. 48.72%), but there are significant differences in the percentages of specific treatments: chemotherapy (47.82 vs. 35.26% respectively) and radiotherapy (22.82% vs. 41.35%).

Analyzing STS survival by primary tumor site, Table II highlights that the retroperitoneum site has the overall highest short-term mortality compared to non-RPS sarcoma: 42.9 vs. 25.7% after 3 years from diagnosis. The difference in mortality is even more pronounced in the less advanced stages (40.9 vs. 19.5%, 42.1 vs. 20.0%, respectively in stage I, II) and in unresected or metastatic (III non resected and IV staged) subjects (75.0 vs. 56.3%).

The Kaplan-Meier curves in Fig. 1 clearly illustrate the differences in survival rates by STS site in all cases and stratified for stages I-II-III resected and III unresected-IV subgroups.

The results of the Cox regressions are presented in Table III. Comparing RPS and non-RPS groups, the unadjusted model estimated a statistically significant hazard ratio of 1.75 (95% C.I.: 1.20, 2.56) ($P=0.004$), indicating that RPS patients had an overall worse prognosis. Also, the higher mortality hazard ratio remained statistically significant in the full multivariable model, confirming that RPS patients had a lower survival rate than non-RPS patients, even after adjusting for other prognostic factors.

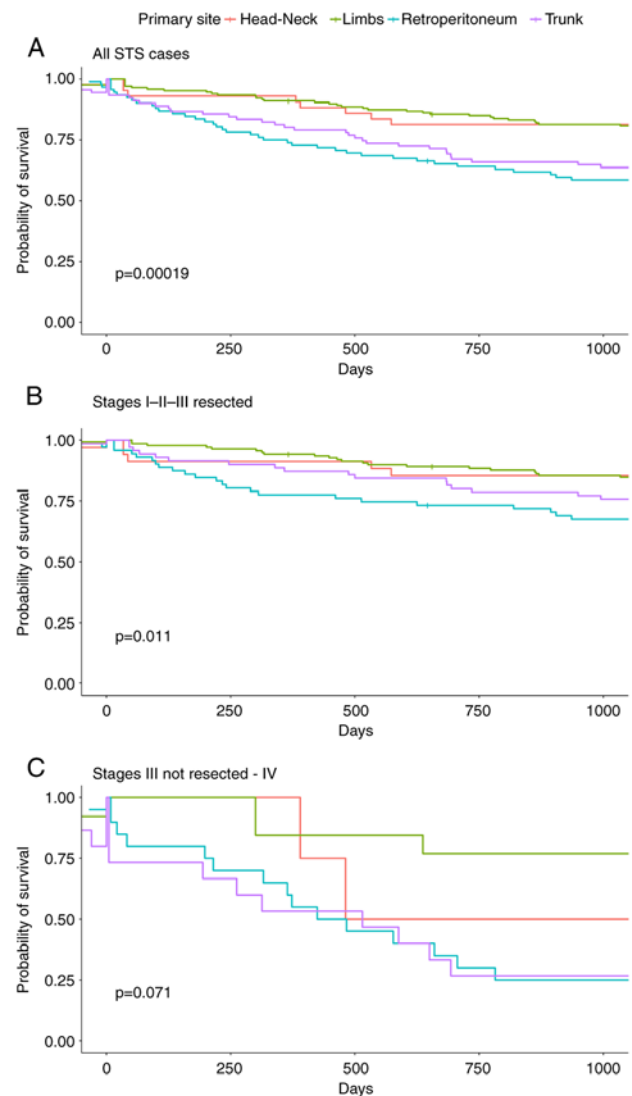


Figure 1. Kaplan-Meier survival curves by STS primary tumor site in (A) all STS cases, (B) stages I-II-III resected and (C) in stages III not resected-IV. STS, soft tissue sarcoma.

Finally, the results of sensitivity analysis, excluding stage IV cases, confirmed previous findings, an HR 1.94 (95% C.I.: 1.91, 3.18) ($P=0.008$) was estimated in the univariate model, significant excesses of mortality were found in all multivariate models except when adjusting by surgical margins and medical treatments.

Discussion

This study evidenced that retroperitoneal soft-tissue sarcomas differ from non-retroperitoneal STS in both demographic (sex and age) and clinical-anatomopathological characteristics (TNM stage and surgical margins). Short-term survival was lower for RPS subjects. In addition, even correcting by other prognostic characteristics such as age, sex, TNM stage, and surgical margins, the multivariable analysis demonstrated that RPS patients have a higher hazard ratio compared to non-RPS.

RPS comprised nearly twenty percent of all incident population cases, a higher proportion than other comparable

population studies have shown. In 2014, Brennan *et al* enrolled 10,000 soft-tissue sarcoma cases diagnosed in the USA between 1982 and 2013 and found that 16% were RPS (21). However, Gutierrez *et al.*, who studied 8,249 STS incident population cases, found that only 12% of them were RPS (947 out of 8,249) (22).

Analyses revealed that RPS are larger in size than non-RPS (42 vs. 5% ≥ 150 mm). Previous studies have demonstrated similar findings (22,23). A study reported that the mean tumor size for head and neck STS was 31, 94 mm for the trunk and extremities, and 151 mm for RPS. In addition, Anaya *et al* (23) demonstrated that almost half of RPS (46% or 157 out of 343) were larger than 150 mm. This may be due to the fact that RPS is frequently found incidentally, hence it is diagnosed at a later stage, letting the tumor to grow to a large size before being detected (23-25). In our work we found that stages III and IV are consistently more frequent in RPS than in non-RPS (53.2 vs. 35.6%), but the advanced stages are the most common stage for both groups at diagnosis. This can be explained by their heterogeneous clinical behavior and presentation, which can sometimes be misinterpreted, resulting in a late diagnosis and poorer prognosis. On analyzing the STS SEER database, Giuliano *et al.*, found that 40% of patients were in stages III and IV (1,189 out of 2,920) (8).

Regarding surgical margins, our study showed that R0 is the most common status in non-RPS, while R1-R2 is approximately forty percent more frequent in RPS. Consistently, a study of surgically-treated RPS patients revealed that more than 43.5% belonged to the R1 and R2 groups (26). This higher frequency of RPS with non-negative margins is largely attributable to the difficulties that surgeons face in achieving wide resection margins, which correlate to the tumor's location within the retroperitoneum, resulting in complex anatomical critical vasculature and viscera relationships at presentation (5,8).

RPS had a statistically lower survival than non-RPS, even after adjusting for other prognostic factors. This could be related to the generally quite inferior results of surgery in retroperitoneum rather than other sites because of the large size at presentation and difficulty in resecting the tumour due to its anatomical location (27). Another study revealed a 3-year mortality rate of approximately 40%, but other sites had a better survival rate overall (21). Also, Gutierrez *et al* observed a lower overall median survival for the retroperitoneum compared to other primary sites (median survival for RPS was 21 vs. 38, 34 months for head-neck, and extremities, respectively) (22).

This work has its strengths, primarily it was a population-based and not center-specific study, thus minimizing the risk of selection bias. Nevertheless, the study has several weaknesses. First of all, the small sample size and short follow-up duration of this cohort. Moreover, no oncological therapies were registered under this study, which is only based on the population-based regional registry. However, the Regional Oncology Network for the Veneto Region produced a comprehensive clinical pathway detailing the clinical procedures to be applied in each step of the clinical management of STS patients, standardizing the therapy of patients across the territory according to the best clinical evidence (28).

In conclusion, there were demographic, clinical and anatomopathological differences between RPS and non-RPS cases. Despite adjusting for all other prognostic factors, the retroperitoneum site remained an independent prognostic factor associated with a lower overall survival compared to the other sites.

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Availability of data and materials

The data that support the findings of this study are available from Veneto Epidemiological Registry but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of from the Veneto Epidemiological Registry (Veneto Regional Authority).

Authors' contributions

ABu, SM, MR, AM, MB and CRR conceived the study. CC, ST, MZ, PDF, ABr, AV and SM collected and curated the clinical data. ABu and VB developed the methodology and CC performed the formal data analysis and visualizations. MR, AM and MB performed the literature search. ABu, AM, MB and CC interpreted the data and wrote the draft. MR, ST, PDF, ABr, AV and SM revised the draft before the submission. ABu, MR, CRR and SM supervised the project. SM and CRR acquired the funding. ABu, SM, MZ and MR confirm the authenticity of all the raw data. All authors have read and agreed to the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the Veneto Oncological Institute's Ethics Committee (n. 0001218/22). The study complied with the resolution No. 9/2016 of the Italian Guarantor for the Protection of Personal Data, which also confirmed the permission of processing personal data for medical, biomedical and epidemiological research, and that data concerning people's health status can be used in aggregate form in scientific studies. To ensure confidentiality and anonymity, the Veneto Regional Authority removes all direct identifiers and replaces them with a code number in all datasets to retain the opportunity to link data from different administrative databases. The data analysis was performed on anonymous aggregated data with no chance of individuals being identifiable. In this case, according to No. 9/2016 of the Italian Guarantor for the Protection of Personal Data, it is possible to not collect written consent from patients.

Patient consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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