The impact of incomplete registration on survival rate of children with very rare tumors

Jelena Rascon (jelena.rascon@gmail.com)
Vilnius University Hospital Santaros Klinikos https://orcid.org/0000-0003-4420-6943
Lukas Salasevicius
Vilniaus universitetas Medicinos fakultetas
Giedre Rutkauskiene
Lietuvos sveikatos mokslu universitetas Medicinos fakultetas
Ieva Vincerzevskiene
Nacionalinis vezio institutas

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Abstract

Background. Pediatric very rare tumors (VRTs) represent a heterogeneous subset of childhood cancers, with reliable survival estimates depending dramatically on each (un)registered case. The current study aimed to evaluate the number of VRTs among Lithuanian children, to assess the impact of the registration status on survival rate and to track changes in treatment outcome over the 16-year study period. Methods. We performed a population-based retrospective study across children below 18 years old diagnosed with a VRT in Lithuania between the years 2000 and 2015. The identified cases were cross-checked with the Lithuanian Cancer Registry – a population-based epidemiology cancer registry – for the fact of registration and survival status. The overall survival was calculated according to the registration status and treatment period. Results. Thirty-seven children with VRTs were identified within the defined time frame. Six of them (16.2%) were not reported to the Lithuanian Cancer Registry at diagnosis. The probability of overall survival at 5 years (OS5y) differed significantly between the registered (n = 31) and unregistered (n = 6) cohorts: 51.6% vs 100%, respectively (p = 0.049). A 5-year survival estimate for children diagnosed with a VRT at the age of 0-14 years differed by 10% according to the registration completeness: 52.1% calculated for the entire cohort vs 42.1% for registered patients only. The OS5y did not improve over the analyzed period: 61.1% in 2000-2007 vs 57.9% in 2008-2015 (p = 0.805). The survival continued to decline beyond 5 years due to late cancer-related adverse events: 59.5% of patients were alive at 5 years as compared to 44.3% at 10 years. Conclusions. The OS5y of children affected by VRT was lower than in more common childhood cancers. The survival rate of the unregistered patients was superior that mislead interpretation of treatment outcome. Meticulous registration of VRTs is crucial for correct evaluation of treatment outcome, especially across small countries with few cases.

Introduction

Malignant tumors in children are very rare: a recently calculated incidence of pediatric cancer in childhood was 155.8 cases per million children between the ages of 0 to 19 years (1). Although infrequent, the vast majority of pediatric cancers can be treated in international clinical trials or following treatment guidelines developed by expert groups. Despite the well-elaborated management strategies for the most common childhood malignancies, childhood cancer remains the second leading cause of illness-related mortality among children in developed countries (2).

Pediatric very rare tumors (VRTs) represent a particular subset of childhood cancers, comprising approximately 9 to 11% of all malignancies occurring in children below the age of 20, 75% of them diagnosed between the ages of 15 to 19 years old (3-5). The European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) defined a VRT as any solid malignancy or borderline tumor that has an incidence rate of $\leq$2 per million per year and/or is not considered for treatment in clinical trials (6). This definition was adopted by the EXPeRT members to re-examine a list of malignant entities considered as pediatric VRT under umbrella of the Joint Action in Rare Cancers project (5). In clinical practice, VRTs pose a diagnostic and therapeutic challenge due to their extreme rarity and lack of uniform treatment guidelines and ongoing clinical trials.

The overall survival rates of childhood cancer differ across European countries. Pooled data provided by the European cancer registries for the EUROCARE5 study demonstrated that survival rate of children treated between 2000 and 2007 in Eastern Europe was 20-30% lower than in other European countries (7-9). In particular, cure rates in Lithuania were approximately 10-20% lower as compared to the European average. A quality study evaluating completeness of the registration in Estonian Cancer Registry demonstrated that under-reporting of pediatric malignancies can decrease the incidence of childhood cancer and survival estimates (10). Our previous pilot study focused on the tumors of the central nervous system (CNS) revealed that up to 27% of cases were missing in the Lithuanian Cancer Registry (LCR) (11). Based on this observation, we initiated the current population-based study that aimed to evaluate the number of VRTs in Lithuanian children and to verify their registration status in the LCR as well as its potential impact on survival rate.

Patients And Methods

Study population and design

We performed a retrospective population-based study including Lithuanian children below 18 years of age diagnosed with a VRT between the years 2000 and 2015. A VRT was defined as described by the International EXPeRT Cooperative Group (see above) and recently reviewed (5, 6). Only malignant entities (ICD-10-AM codes C00-C96) were selected for evaluation. Pediatric age was defined as less than 18 years at diagnosis.

The institutional databases of both Lithuanian pediatric oncology centers at Vilnius University Hospital Santaros Klinikos (VUHSK) and Lithuanian University of Health Sciences Kaunas Clinics (LUHSKK) were reviewed to identify VRTs as described previously. To verify the fact of registration the retrieved cases were cross-checked with the LCR using personal identification code unique for each individual. Patients' vital status (and the date of death where appropriate) was updated on 31st of December 2019 using a linkage with the national population registry. Patients lost for follow-up were considered alive and censored at the last available contact date.

LCR is a nation-wide population-based cancer registry covering the whole country. Health care providers have a legal obligation to report every new cancer case (ICD-10-AM codes: C00-C96, D00-D09 (in situ), D32-D33, D39.1, D42-D43, D45-D47). LCR collects personal and demographic data as well as disease-related information (cancer site, date of diagnosis, method of cancer verification) and vital status (if appropriate – date and cause of death) of all cancer patients in Lithuania including children.

Baseline characteristics were collected electronically through institutional databases, or, when needed, manually through paper records. To assess treatment outcome a probability of overall survival at five years from diagnosis (OS_{5y}) was considered as a primary endpoint. Survival at 1 and 10 years were assessed as secondary endpoints. For international comparison, survival estimates were additionally calculated for the age group of 0-14 years at diagnosis. The overall survival was compared between the registered and unregistered patients. To evaluate changes in survival rates over the 16-year study period the entire cohort

was split into two groups according to the treatment period: between 2000 and 2007 versus 2008 and 2015.

Statistical analysis

Descriptive statistics methods were used for abnormally distributed continuous and categorical variables. A probability of overall survival at five and ten years were calculated using Kaplan-Meier estimation method. The difference between compared groups was compared using log-rank test. Death of any cause (tumor relapse or progression, treatment-related toxicity and second cancer) was defined as an event. The results were considered statistically significant when p value was <0.05. The statistical analysis was performed using IBM SPSS Statistics 23.0 and STATA 11 softwares.

Results

Patients' characteristics

In total, 37 children were treated for VRTs between the years 2000 and 2015 in Lithuania. Over 16-year study period a median of 1.5 new cases (ranging from 0 to 6) was diagnosed per year. Baseline characteristics of the enrolled patients are listed in Table 1. The median age at diagnosis was 12 (range 0-17, IQR [6.5-15.5]) years with a slight female predominance (n = 21; 57%). Overall, 18 histologic tumor types were identified (Fig.1): adrenocortical carcinoma was the most frequent one (n = 7; 18.9%), followed by hemangioendothelioma (n = 4; 10.8%). Renal and thyroid carcinomas as well as rhabdoid tumors accounted for 3 (8.1%) cases each. There were two cases of pheochromocytoma, gastric adenocarcinoma, salivary gland carcinomas, and ovarian cancers (5.4%) and 9 single cases of various tumor types (Fig. 1).

In five patients (13.5%) an underlying cancer predisposition syndrome was documented (Table 1). Thirty-one VRT (83.8%) presented as a localized tumor, whereas in 6 (16.2%) cases an advanced stage with local or distant metastases was documented at diagnosis. Disease relapse or progression was the main cause that compromised the cure: 17 (45.9%) children died due to resistant malignancy accounting for 85% of all deaths. Two patients (UPN 6 and 25 in the Table 1) developed a second cancer that was the cause of death. Thus, 19 out of 20 (95%) patients succumbed to progression of primary tumor or secondary malignancy. One infant (UPN 31, Table 1) developed a fatal cytomegalovirus-associated pneumonitis. At the time of evaluation, 17 out of 37 children (45.9%) remained in complete remission.

Registration at the Lithuanian Cancer Registry

All 37 included VRT entities were confirmed by pathology evaluation. The tumors were assigned a specific morphology and behavior code as well as an appropriate ICD-10-AM topography code C00-C96. All patients were eligible for registration at the LCR at diagnosis.

The cross-check of the cases identified in the institutional databases with the LCR data revealed that six out of 37 patients (16.2%) were not reported at the time of diagnosis (Table 1). All of them were diagnosed at LUHSKK and comprised 40% (6/15) of pediatric VRTs treated at the center. The missing cases included salivary gland and thyroid carcinoma (2 cases each), and a single case of adrenocortical carcinoma and uterine adenosarcoma (Fig. 1).

Treatment outcome

The overall survival estimate at 5-years of the entire cohort (including registered and unregistered patients) diagnosed with a VRT at the age of 0-18 years was 59.5% (Table 2). However, the same estimate calculated only for the registered patients was 8% inferior – 51.6%. The difference increased up to 10% calculated only for children aged 0-14 years at diagnosis – 52.2% vs 42.1% (Table 2). The difference between the entire and the registered groups remained at 1-year: 73.0% vs 67.7% for the age group of 0-18 years and 73.9% vs 68.4% for the one of 0-14 years, respectively (Table 2). In long-term perspective cure rates continued to decline beyond 5 years (Fig. 2): survival estimates at 10 years were lower than at 5 years retaining the difference between the entire and the registered cohorts: 44.3% vs 39.7% for the age group of 0-18 years and 46.4% vs 36.1% for the one of 0-14 years, respectively (Table 2).

The probability of OS_{5y} of the unregistered patients was significantly higher than the one of the registered cohort – 100% vs 51.6% ($p = 0.049$, Fig. 2a). However, in a longer follow-up beyond 5 years from diagnosis the difference became insignificant due to late cancer-related deaths in both cohorts – the probability of OS_{10y} was 66.7% for unregistered patients as compared to 39.7% for the registered cohort ($p = 0.230$). The median follow-up time of the respective groups was of 6.6 (range 4.1–9.9 [IQR 4.6–9.2]) and 11.1 (range 5.7–19.3 [IQR 6.0–13.6]) years. We could not document any improvement in cure rate over the analyzed 16-year period. Probability of overall survival for patients treated in 2000-2007 and 2008-2015 did not differ neither at five (61.1% vs 57.9%, respectively), nor at 10 years (44.4% vs 50.7%, respectively, $p = 0.805$, Fig. 2b). The median follow-up time was 13.5 (range 11.1–19.3 [IQR 12.1–18.1]) and 7.0 (range 4.1–10.2 [IQR 5.9–9.4]) years for the first and the second treatment periods, respectively.

Discussion

Our study aimed to evaluate the quality of registration and treatment outcome of pediatric VRTs in Lithuania – a small Eastern European country of 2.92 million inhabitants and 524.5 thousand of children below 18 years of age (as reported in 2015, www.stat.gov). Overall, 37 VRT cases of 18 different histological types were identified over 16 years with the median of 1.5 new cases per year. This means that each Lithuanian pediatric oncology center encountered one-two new VRT cases per year. The small numbers rendered impossible accumulation of sufficient expertise to deal with extremely rare pediatric malignancies. Therefore, close internal and international collaboration e.g. with tumor-specific expert groups and / or the European Reference Network for Paediatric Oncology (ERN PaedCan) is crucial to ensure the best care and cure.

A substantial percentage of unregistered tumors in our study (16.2%) could be partially underpinned by an inconsistency in the national regulatory requirements: there was a formal obligation for health care providers to report every new cancer case to the LCR. However, the legal status of the registry was not appropriately formalized. This resulted in different interpretation of the reporting obligation and restriction in data flow. All unregistered cases came from one of two pediatric oncology centers and reflected institutional policy with regard to data sharing. Most of the missing data identified during this study were recovered retrospectively. Different interpretation of regulatory requirements for data reporting contributed to the data incompleteness also in the Estonian Cancer Registry (10).

As listed in Table 1, all unregistered tumors were localized at diagnosis. One could speculate that a potential contributing factor to the under-reporting of local malignancies could be insufficient awareness of surgeons (who used to be the first to encounter a VRT in children and adolescents) about the importance of meticulous registration of every pediatric cancer case. Presumably, pediatric oncologists were not involved in the patient care of at the initial stage. Several studies have shown that multidisciplinary teamwork affects the diagnosis, management and quality of care in cancer patients (12, 13). Thus regular tumor boards, including virtual tumor boards as well as international collaborations, should be regarded as a standard of care in the management of childhood cancers (14, 15). Improvement in multidisciplinary collaboration between pediatric oncologist, surgeons, and cancer registry could ensure completeness of registration and data reliability.

As expected, the 5-year survival rate of the unregistered patients was significantly higher than the one of the registered cohort – 100% vs 51.6%. The 5-year survival rate calculated for the registered patients at the age of 0-14 years – a common parameter used across studies to compare treatment outcome and cancer incidence (1, 7-10) – increased up to 10% when missing cases were included: 42.1% vs 52.2%. Given the extreme rarity of VRTs, accurate reporting to cancer registries is crucial for reliable calculation of treatment outcome. Insufficient registration of pediatric cancers was reported for more common childhood cancers, e. g. for CNS tumors – the study that analyzed survival of European children based on the national population-based cancer registry data highlighted incomplete registration of non-malignant entities in many countries and, as a consequence, a lower overall survival (8). The recent survey focused on the rate of pleuropulmonary blastoma in Europe also demonstrated lower than estimated number of reported cases in Eastern / Central European countries (16). A population-based quality study carried out in Estonia figured out a significant number of under-reported childhood cancer cases that increased 5-year survival from 70 to 76% for children treated in 2010-2014 (10). Thus, completeness of the registration should be improved across Europe.

The main limitation of our population-based study was its retrospective design that did not allow us to verify relevant parameters (e.g. details on adverse events, treatment etc.) due to limited data availability. The overall survival rate in our VRT cohort was inferior (the total OS_{5y} was 59.5%) as compared to the average 80% cure rate of more common childhood cancers. Similar outcomes were reported for adults in a population-based Surveillance of Rare Cancers in Europe (EUROCARE) project (17) – rare cancers displayed lower survival rate (47%) than the common cancers (65%). A scarce expertise due to the rarity of

cases and absence of clinical trials were main contributors to the inferior survival. Pediatric tumor-specific studies likewise reported lower survival rate, e.g. 55% for adrenocortical carcinoma (18), 60% for rhabdoid tumor (19), although some local pediatric VRTs (e.g. thyroid and salivary gland carcinoma) can achieve a decent survival over 90% (20, 21).

The lack of improvement in cure rate over time (the OS_{5y} was 61.1% in 2000-2007 vs 57.9% in 2008-2015) was rather unexpected. National population-based studies on leukemia (22, 23) and single-center reports on solid tumors (24-26) demonstrated significant improvement in overall survival over the last two decades. Disease recurrence or development of a second malignancy was responsible for 95% of deaths (in 19 out of 20 cases) in our VRT cohort. Drug-resistant cancer remains the main challenge for pediatric oncology community: a recent review of the Surveillance, Epidemiology, and End Results (SEER) database demonstrated little improvement in treatment outcome for specific cancer types, mostly considered as VRT, diagnosed in adolescents or young adults during 1975-2011 (27). Of note, in our study a cancer predisposition syndrome was documented in five patients (Table 1). Impaired somatic host genome could be implicated in development of drug-resistance or secondary malignancy (28, 29). We could suggest that the diagnosis of a VRT in a child should prompt a search for possible hereditary genetic susceptibility syndrome.

Disease recurrence compromised the cure beyond 5 years – a conventional cut-off for long-term remission. The survival estimates at 10 years were lower as those at 5 years calculated with regard to various aspects: for different age groups, completeness of the registration, comparing registered and unregistered cohorts as well as two treatment periods. Late events were related exclusively to disease progression or second malignancy. The above mentioned analysis of SEER database reported a substantial number of the disease-related adverse events occurring between 5 and 10 year in patients diagnosed with rare cancers at the age of 15-39 years (27). Given the fact that 75% of VRTs develop between the ages of 15 to 19 years old (3-5) a longer follow-up for potential disease recurrence beyond 5 years from diagnosis is warranted.

Our results clearly demonstrated that timely and complete registration must be ensured for accurate statistical analysis and data evaluation. In addition to mandatory national reporting regulations, an ongoing European PARTNER (Pediatric Rare Tumor Network – European Registry) project supported by the European Reference Network for Paediatric Cancer aims to create a pan-European system that should enhance international communications between members of the European Union by combining national registries focused on VRTs and creating registries for countries that do not have one, as well as linking these registries with virtual consultation systems (https://webgate.ec.europa.eu). The undertaken action will certainly strengthen registration at the national level.

Conclusions

Incomplete registration of VRTs in cancer registry is an important issue and can significantly affect epidemiologic and outcome data. Regular verification of the pediatric cancer cases could ensure data quality and completeness of registration. Based on our results we would strongly advocate for an active

collaboration between pediatric oncology centers and national cancer registries to prevent important deviation in statistical analysis and calculation of survival data.

Abbreviations

CNS: Central nervous system; ExPeRT: European Cooperative Study Group for Pediatric Rare Tumours; IQR: Interquartile Range; LCR: Lithuanian Cancer Registry; LUHSKK: Lithuanian University of Health Sciences Kaunas Klinikos; OS_{5y}: Overall Survival at 5 years; OS_{10y}: Overall Survival at 10 years; VRT: Very Rare Tumor; VUHSK: Vilnius University Hospital Santaros Klinikos

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Vilnius Regional Committee of Biomedical Research (Approval No. 2019/10-1155-646) and Kaunas Regional Biomedical Research Ethics Committee (Approval No. BE-2-86). An informed consent was obtained from individual participants subject they are alive and followed up. A waiver of informed consent was granted for patients deceased or lost for follow-up

Consent for publication

Not applicable

Availability of data

The datasets generated and analyzed during the current study are not publicly available due to data protection and privacy but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The study did no dedicated funding,

Authors' contributions

JR and LS wrote the manuscript, GR, IV and JR retrieved, complied and analyzed the data, JR conceptualized and supervised the study. All authors contributed to the study conception, critically revised the manuscript, agreed and approved the final version for submission.

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Tables

Table 1 Baseline characteristics of the study patients (n = 37)

Gender	Age at diagnosis (years)	Year of diagnosis	Cancer type	Cancer predisposition syndrome	Event	Outcome	Follow-up (years)	Registration at (L)CR	Treating center
F	14	2000	Hemangioendothelioma of atrium (L)	NS	Progress	Died	1.1	Registered	VUHSK
M	10	2000	Pheochromocytoma (L)	VHL	CR	Alive	19.3	Registered	VUHSK
F	11	2001	Lung cancer (L)	NS	CR	Alive	18.1	Registered	VUHSK
F	2	2002	Liver angiosarcoma (L)	NS	Progress	Died	1.3	Registered	VUHSK
M	16	2005	Adrenocortical carcinoma (A)	NS	Progress	Died	0.6	Registered	VUHSK
F	17	2005	Uterine adenosarcoma (L)	NS	2ndCa	Died	9.6	Unregistered	LUHSKK
F	16	2005	Renal carcinoma (L)	NS	CR	Alive	11.1	Registered	VUHSK
F	7	2005	Adrenocortical carcinoma (L)	NS	Progress	Died	2.2	Registered	VUHSK
M	4	2005	Intestinal hemangioendotelioma (L)	NS	Progress	Died	0.6	Registered	VUHSK
F	8	2005	Carcinoma of thyroid gland (L)	MEN2	Relapse	Died	11.8	Unregistered	LUHSKK
F	17	2006	Renal carcinoma (L)	NS	CR	Alive	13.6	Registered	LUHSKK
F	17	2006	Carcinoma of thyroid gland (L)	NS	Progress	Died	7.0	Registered	LUHSKK
F	17	2006	Pancreatic papillary carcinoma	NS	CR	Alive	13.5	Registered	VUHSK
M	11	2006	Neuroendocrine tumor (L)	NS	Progress	Died	0.7	Registered	VUHSK
F	15	2006	Renal carcinoma (L)	NS	CR	Alive	13.1	Registered	LUHSKK
F	0	2006	Adrenocortical carcinoma (A)	NS	Progress	Died	0.1	Registered	LUHSKK
F	17	2007	Adrenocortical carcinoma (L)	NS	Relapse	Died	8.9	Registered	LUHSKK
F	1	2007	Kaposi-like hemangioendothelioma (L)	NS	CR	Alive	12.1	Registered	VUHSK
F	15	2009	Ovarian carcinoma (L)	NS	CR	Alive	10.2	Registered	LUHSKK
M	6	2010	Renal carcinoma (L)	NS	CR	Alive	9.9	Unregistered	LUHSKK
M	15	2010	Follicular dendritic sarcoma (L)	NS	Progress	Died	0.4	Registered	VUHSK
F	16	2010	Ovarian carcinoma (A)	NS	Progress	Died	0.1	Registered	LUHSKK
F	10	2010	Carcinoma of upper lip (L)	NS	Relapse	Alive	7.0	Registered	VUHSK
M	14	2010	Adenocarcinoma of stomach (L)	NS	CR	Alive	9.2	Registered	VUHSK
F	0	2010	Adrenocortical carcinoma (L)	Li Fraumeni	2ndCa	Died	6.2	Registered	VUHSK
F	14	2011	Adrenocortical carcinoma (A)	NS	Relapse	Died	2.6	Registered	VUHSK
M	15	2012	Colorectal adenocarcinoma (L)	NS	Progress	Died	0.3	Registered	LUHSKK
M	12	2012	Adenocarcinoma of stomach (L)	NS	Progress	Died	0.1	Registered	LUHSKK
F	15	2012	Salivary gland	NS	CR	Alive	7.2	Unregistered	LUHSKK

			carcinoma (L)						
M	17	2013	Pheochromocytoma (L)	VHL	CR	Alive	6.9	Registered	LUHSKK
M	0	2013	Rhabdoid tumor (L)	NS	TRM	Died	0.3	Registered	VUHSK
M	8	2013	Desmoplastic tumor (A)	NS	Relapse	Died	2.1	Registered	VUHSK
M	14	2013	Skin melanoma (L)	NS	CR	Alive	6.7	Registered	VUHSK
F	9	2014	Carcinoma of thyroid gland (L)	MEN2	CR	Alive	5.9	Unregistered	LUHSKK
M	3	2014	Rhabdoid tumor (A)	NS	CR	Alive	5.7	Registered	VUHSK
M	0	2014	Rhabdoid tumor (L)	NS	Progress	Died	0.6	Registered	VUHSK
M	12	2015	Salivary gland carcinoma (L)	NS	CR	Alive	4.1	Unregistered	LUHSKK

Abbreviations: 2ndCa – the second cancer; A – advanced stage at diagnosis; CR – complete remission; F – female; L – local disease at diagnosis; M – male; MEN2 – multiple endocrine neoplasia type 2; NS – not specified; TRM – treatment related mortality; UPN – unique patient number in the study; VHL – von Hippel Lindau syndrome.

Table 2 Survival estimates at 1-year, 5-years and 10-years for children diagnosed with a VRT at the age of 0-14 and 0-18 years: the impact of the registration completeness on the calculated rates.

	0-18 years		0-14 years	
Overall survival, alive % (95% CI)	All patients (n = 37)	Registered only (n = 31)	All patients (n = 23)	Registered only (n = 19)
At 1 year	73.0 (55.6-84.4)	67.7 (48.3-81.2)	73.9 (50.9-87.4)	68.4 (42.8-84.4)
At 5 years	59.5 (42.0-73.2)	51.6 (33.0-67.4)	52.2 (30.5-70.0)	42.1 (20.4-62.5)
At 10 years	44.3 (26.6-60.7)	39.7 (22.1-56.8)	46.4 (25.0-65.4)	36.1 (15.7-57.1)

CI – confidence interval.

Figures

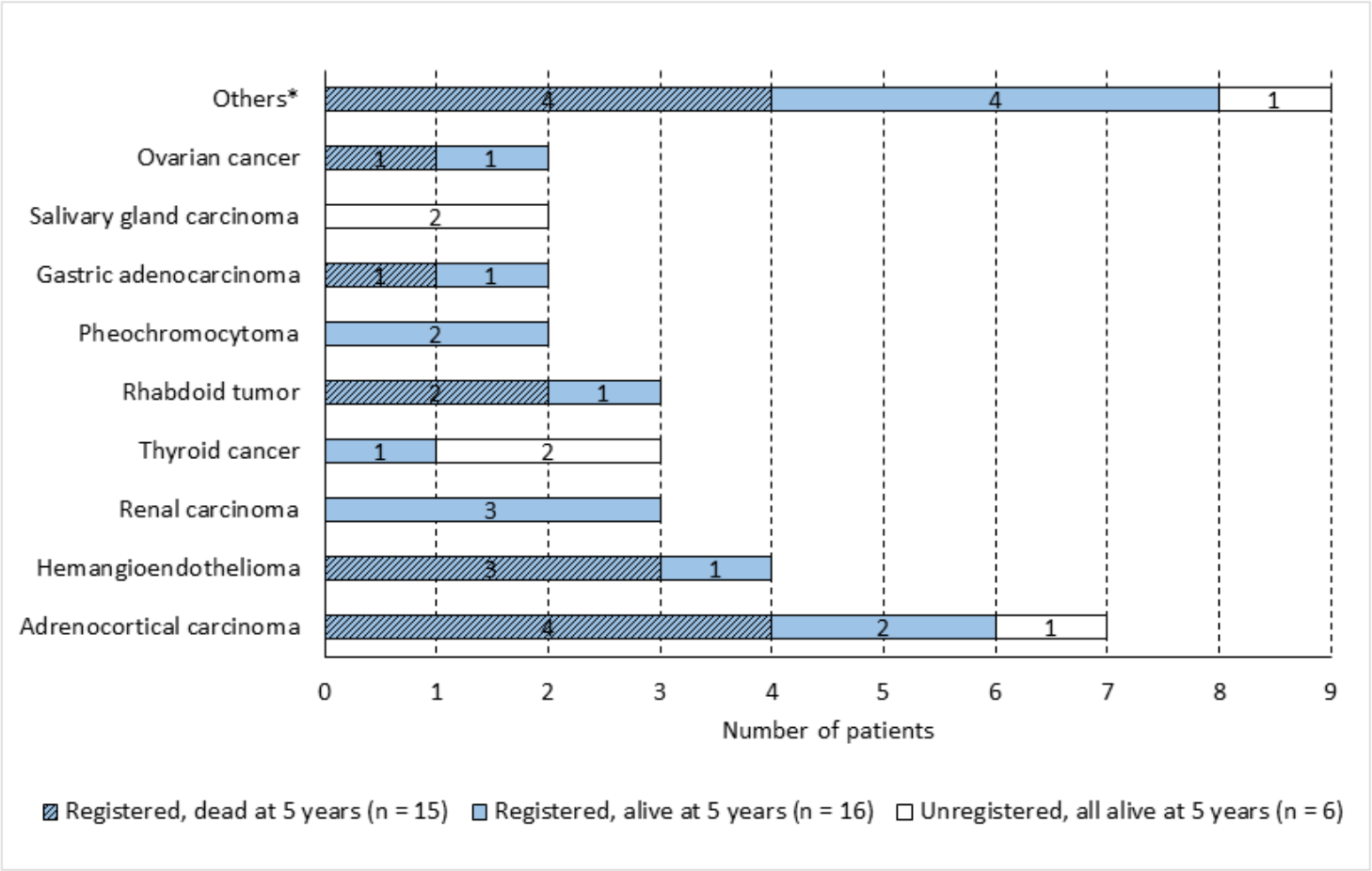

Figure 1

Distribution of the analyzed VRTs and survival status at 5 years across tumor types with regard to registration status. *The group “Others” comprised 9 single VRT types. Eight cases were registered: 4 patients (colorectal carcinoma, desmoplastic tumor, neuroendocrine carcinoma, dendritic cell sarcoma) did not survive by 5 years, the other 4 (lip carcinoma, melanoma, pancreatic carcinoma, lung carcinoma) remained alive. One unregistered patient (uterine adenosarcoma) was alive at the same time point.

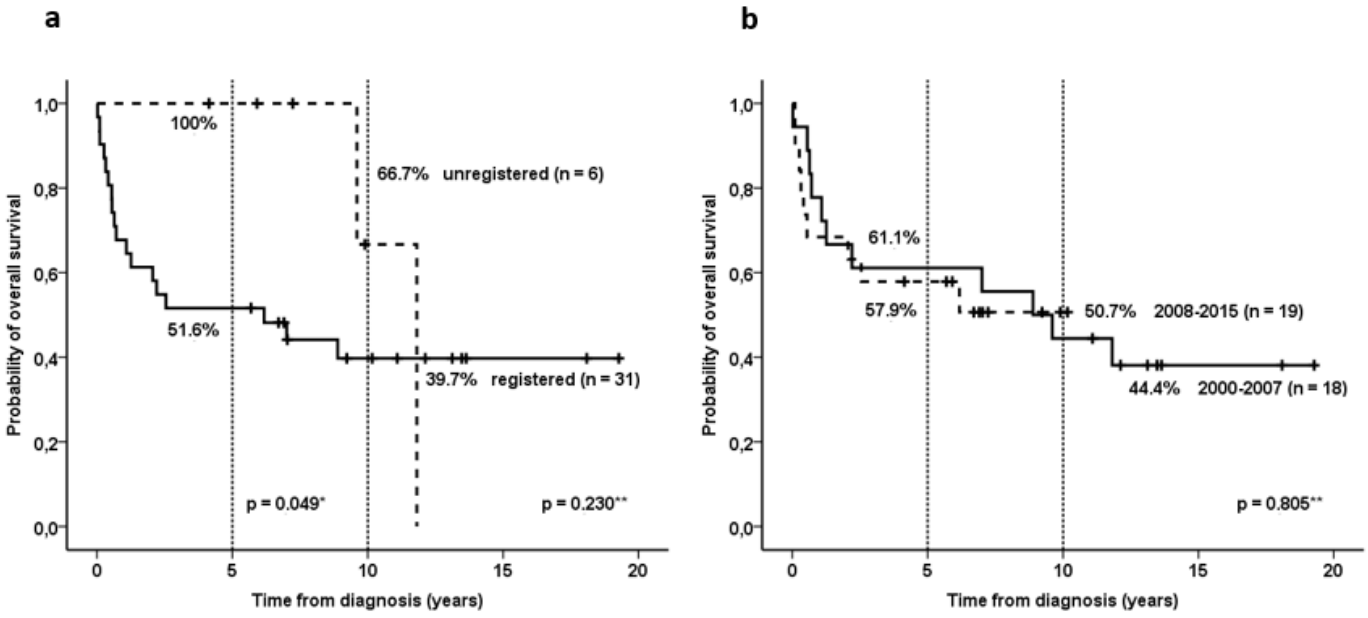

Figure 2

Probability of overall survival according to registration status (a) and treatment period (b). *Log-rank test for data censored at 5 years; **Log-rank test for data censored at the last follow-up.