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ORIGINAL ARTICLE

PATHWAY EVALUATION OF SYMPTOMS UNTIL DIAGNOSIS IN A COHORT OF PEDIATRIC ONCOLOGY PATIENTS

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ABSTRACT

Introduction: Pediatric cancer, the leading cause of disease-related mortality in children ages 1 to 14, has more promising outcomes with earlier diagnosis. This retrospective study (2011–2023) characterized pediatric oncology patients in Portugal, specifically from the district of Viseu, referred to a tertiary Pediatric Oncology service.

Methods: Data were analysed to assess demographic characteristics, symptom presentation, ED visits before diagnosis, and potential correlations with diagnostic delays.

Results: Among the 104 newly diagnosed pediatric oncology patients, 57 (54.8%) were male. The mean age at diagnosis was 9.6 ± 5.6 years. The most frequent neoplasms were leukemias (group I), lymphomas (group II), and central nervous system (CNS) tumors (group III). The diagnoses occurred at earlier ages in neuroblastoma (group IV) and retinoblastoma (group V), while older patients were more commonly diagnosed with lymphomas, malignant bone tumors and carcinomas. Edema was the most common presenting symptom (24.0%), followed by B symptoms such as night sweats (7.7%) and weight loss (7.7%). Patients had a median of two ED visits before clinical suspicion of cancer. Malignant bone tumors consistentally had more visits to ED before diagnosis suspicion (p=0.025). However within the group of patients with more than 3 ED visits, acute lymphoblastic leukemia cases were predominant. A significant correlation was found for disease progression time over five years of age (r=0.271; p=0.035).

Conclusion: Understanding the diagnostic timeline in pediatric oncology is vital for optimizing early detection. Increased awareness among healthcare professionals can enhance diagnostic strategies, reduce delays and improve patient outcomes.

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Introduction

Pediatric cancer is the second leading cause of death in children between the ages of 1 and 14 in developed countries.[1] Although the survival rate for childhood cancers has increased from less than 50% in 1970 to above 80% today, this pathology is still the leading cause of disease-related mortality in children.[2]

In recent years, there have been significant advances in cancer treatment. Today, several factors contribute to successful treatment, such as disease characteristics, access to healthcare, early suspicion and timely diagnosis. Early diagnosis of paediatric cancer should be a concern for all health professionals who care for children, since paediatric neoplasms are highly curable and, in many cases, early diagnosis is associated with a better prognosis and less intensive therapy. Unfortunately, the diagnosis of these pathologies is usually difficult in the early stages of the disease due to its rarity and the non-specific presentation of symptoms.[2]

This pathology can have a diagnostic delay from the appearance of the first symptoms to diagnosis. From the onset of symptoms to the first doctor's visit, this delay is blamed on the patient (or carers). However, once the patient goes to the doctor, it is up to the professionals to make a timely referral to a pediatric oncologist.[3]

Between 2010 and 2019, 2685 new cases of cancer were diagnosed in children under the age of 15 in Portugal. The overall incidence rate of cancer in children during this period was 180.7/106 child-years. The three main types of tumours were leukaemias (26.7%), central nervous system tumours (23.8%) and lymphomas (15.0%).[4] Overall survival at 5 years was 84.7%, with lymphomas, retinoblastomas, kidney tumours, germ cell tumours and melanomas having a 5-year survival of over 90%.[4]

With the overall increase in survival, we are witnessing a paradigm shift: in addition to treating the disease, it is also crucial to think about the long-term follow-up of patients off treatment. Guidelines on the early diagnosis

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and screening of neoplasms in at-risk populations are available in the literature. This study aims to fill the knowledge gap - how to diagnose children who are not at risk earlier.

The aims of this study were to characterise the sample of patients followed at a Pediatric Oncology Service in Portugal, with particular emphasis on those referred from the Pediatrics Service of a secondary referral site, as well as to characterise the patients who went to the Emergency Department before being diagnosed with cancer.

Methods

A retrospective, observational and analytical study was carried out on a cohort of patients referred to the Pediatric Oncology Department of a level III hospital between 2011 and 2023, from a district with 29,138 inhabitants under the age of 14 and with an average incidence of paediatric cancer of <165/106 (standardised rate between 2010 and 2019 per 106 inhabitants in the European Union).[4,5]

The Pediatric Oncology Service where the study took place provides care for children and adolescents diagnosed with or suspected of having a neoplasm and is a national reference centre for Ophthalmic Neoplasms, serving as a referral hospital for oncological care for patients from the district where it is located and also from 5 adjacent districts, one of which is where the cohort came from.

All children and adolescents with an initial referral to the Oncology Service were considered eligible, excluding patients with a referral to the service but without a confirmed final diagnosis of neoplasia.

Biopsychosocial data and data on referral and follow-up were obtained by consulting the patient's individual file on the *SClínico* electronic platform, while data on previous emergency admissions and hospitalisations at the cohort's local hospital were obtained from the Alert and *SClínico* digital platforms for diagnoses between 2015 and 2023 and from paper records between 2011 and 2015.

The data was grouped by classification subgroups according to the International Classification for Childhood Cancer 3rd edition for better interpretative accuracy, given the very diverse clinical spectrum of neoplasms in paediatric age. The date of diagnosis, the day the biopsy was taken and the number of days of symptoms, the period between the first day of symptoms and the medical assessment when the clinical hypothesis of a neoplasm was first raised, were considered. In terms of the entity that made the referral, the place of referral was considered to be the one responsible for the first contact with the Paediatric Oncology Service. Primary referrals were considered to be those coming from the paediatric service of the hospital in the district's local referral area; external referrals as those coming from care outside the local paediatric referral network (Health Centres, Private Hospital Units and Hospitals in other parts of the country) and secondary referrals as those coming from other oncology centres (national or international).

When assessing previous admissions to the emergency department, asymptomatic patients were excluded, as their previous admissions were not due to an oncological cause, and patients from secondary referrals were excluded due to the lack of data on admissions to emergency departments in other countries and other referral areas. Only admissions due to symptoms compatible with neoplastic disease were considered.

Data categorised as categorical variables were analysed by frequency, taking into account absolute and relative values, and continuous variables were expressed as measures of central tendency and dispersion, according to their type of distribution (normal or non-normal). The association between categorical variables was studied using the Chi-squared test and differences in the distributions of continuous variables according to subgroups of categorical variables were studied using t-tests for variables with a normal distribution and non-parametric tests for variables with a non-normal distribution. The correlation between two continuous variables was calculated using Spearman's coefficient.

The analysis was carried out using the Statistical Package for Social Sciences version 26.0.

The study was approved by the local Ethics Committee.

Results

During the study period, 104 new patients were diagnosed with neoplastic pathology, 57 (54.8%) of whom were male. The average age at diagnosis was 9.6 ± 5.6 years, with the youngest patient being a 4-day-old newborn with myeloproliferative syndrome associated with Down's Syndrome and the oldest an adolescent aged 17 years and 10 months with myxoid liposarcoma.

Patients with a significant history included 1 patient with a first-degree family history of retinoblastoma, 3 patients with a previous personal history of neoplasia and 13 patients with other personal histories (6 with neurofibromatosis, 4 with immunodeficiency or immunosuppression, 2 with diabetes mellitus and 1 with sarcoglycanopathy).

Forty-two percent of patients were referred from the pediatric emergency department at the study site, and 11.5% were referred from the inpatient department of the same hospital. In this group of patients, they were hospitalised for an average of 5.46 ± 3.33 days before being referred to the oncology service.

Table 1 shows data on the diagnosis and follow-up of patients.

The three most frequent neoplasm groups were I (leukaemias), II (lymphomas) and III (CNS tumours). In terms of age at diagnosis, groups IV (neuroblastoma) and V (retinoblastoma) had the earliest presentation, whereas groups II, VIII (malignant bone tumours) and XI (carcinomas) had on average older patients.

The presence of edema was the most common sign of clinical presentation in the cohort (n=25; 24.0%). The presence of B symptoms included: night sweats (n=8; 7.7%) and weight loss (n=8; 7.7%).

Overall, patients were admitted 2 times [median (Q1; Q3): 2.0 (1.0;2.0)] before clinical suspicion of neoplasia, more frequently in the malignant bone tumour group (p=0.025).

Eight patients had more than three visits to the Emergency Department (ED). The characteristics of these patients are specified in Table 2. Of particular note

Table 1. Diagnosis and patient characteristics according to ICCC Classification subgroup.

ICCC Classification Groups	n (%)	Age at diagnosis in years Mean (SD)	Most frequent sign or symptom	n (% per subgroup)	Number of days between symptoms and clinical suspicion Median (Q1;Q3)	Number of admissions to the Emergency Department Median (Q1;Q3)	Recurrence n (% per subgroup)	Death during follow-up n (% per subgroup)
I	22 (21,2%)	7,8 ± 6,0	Pallor and fever	50,0%	12,5 (6,25;26,25)	1,00; (1,00;2,5)	6 (27,3%)	5 (22,7%)
II	22 (21,2%)	12,6 ± 4,3	Adenopathy	40,9%	60,0 (30,0;90,0)	2,0 (1,0;2,0)	4 (18,2%)	5 (22,7%)
III	27 (26,0%)	10,3 ± 4,7	Headache and neurological deficits	44,4%	30,0 (4,0;165,0)	1,0 (1,0;1,0)	4 (14,8%)	3 (11,1%)
IV	3 (2,9%)	0,5 ± 0,3	Haematomas, swelling and claudication	33,3%	8,0	1,0	2 (66,7%)	0 (0,0%)
V	2 (1,9%)	1,1 ± 1,4	Leucokoria	50,0%	15,0	1,0	1 (50,0%)	0 (0,0%)
VI	1 (1,0%)	3,2	Oedema and anorexia	100,0%	15,0	1,0	0 (0,0%)	0 (0,0%)
VII	1 (1,0%)	1,4	Fever and swelling	100,0%	15,0	1,0	1 (100,0%)	1 (100,0%)
VIII	7 (6,7%)	13,4 ± 3,7	Bone pain	85,7%	54,5 (39,0;292,0)	3,0 (0,7;3,3)	0 (0,0%)	0 (0,0%)
IX	11 (10,6%)	7,0 ± 5,1	Oedema or swelling	63,3%	85,0 (15,0;150,0)	1,0 (0,0;2,0)	0 (0,0%)	0 (0,0%)
X	5 (4,8%)	10,5 ± 7,0	Oedema or swelling	60,0%	105,0 (24,8;303,8)	1,0 (0,3;1,8)	0 (0,0%)	1 (20,0%)
XI	3 (2,9%)	13,7 ± 3,6	Oedema or swelling	33,3%	30,0	0,0 (0,0;0,0)	0 (0,0%)	0 (0,0%)

Table 2. Patients with more than 3 emergency department visits before suspected diagnosis.

Diagnosis	Cases (n)	Number of admissions (n)	Symptoms
Bladder embryonal rhabdomyosarcoma	1	8	Dysuria, pollakiuria and urinary urgency
Acute lymphoblastic leukaemia	4	7	Bone pain and fever
		6	Asthenia, fever and pallor
		4	Adenopathies, asthenia, fever, anorexia, night sweats and abdominal pain
		4	Pain, fever, pallor and abdominal pain
Langerhans cell histiocytosis	1	6	Oedema or swelling
Myelodysplastic Syndrome	1	4	Recurrent epistaxis
Ewing's sarcoma	1	4	Pelvic pain, weight loss and night sweats

was one case of 8 emergency admissions for dysuria, pollakiuria and urinary urgency, symptoms typically associated with urinary tract infection, before suspicion of a possible bladder neoplasm.

The majority of cases with recurrent ED visits (ranging from 4 to 7) were diagnosed with acute lymphoblastic leukaemia, which is not only the most common neoplasm in children, but also presents with a wide range of non-specific manifestations that can be confused with acute infectious diseases that are common in ED.

There was no significant correlation between the number of admissions to the Emergency Department and patient age (r=-0.076; p=0.483), nor between disease progression time and patient age (r=0.092; p=0.393). However, when the time to progression was divided into age subgroups (>5 years and <5 years), there was a correlation for patients <5 years (r=0.271; p=0.035).

Of the group of 10 patients with a clinical history of more than one year, 2 had more than 3 admissions to the paediatric emergency department (pelvic Ewing sarcoma and MDS, Table 2) and 3 were followed up in hospital for symptoms compatible with their neoplasm (ENT consultation for otalgia and hypoacusis, paediatric rheumatology consultation for pain and general paediatrics consultation for adenopathies).

In the cohort, 11 (10.6%) of the patients were asymptomatic on admission, and the diagnosis was made in 6 cases during routine examinations in at-risk individuals, in 4 cases incidentally during examinations requested for other pathologies (cranioencephalic CT scan in a victim of traumatic brain injury, blood count to control jaundice, extralongitudinal x-ray for suspected scoliosisand preoperative MRI for refractory epilepsy surgery), and in 1 case during prenatal morphological ultrasound.

During follow-up there were 18 relapses (17.3%): 6 in group I and 4 in groups II and III.

There were 15 deaths (14.4%) during follow-up: 5 in group I and 5 in group II. In the only case diagnosed in our sample in group VII (liver tumours), the same patient relapsed and died.

In terms of prognosis, recurrence during follow-up was associated with ICCC neoplasm type (p=0.044), and there was no association with age at diagnosis, time from symptoms to diagnosis, or number of previous emergency admissions. Death was also not associated with age at diagnosis or time from symptoms to diagnosis, and in this cohort was only associated with patients who had a recurrence during follow-up (p<0,001).

Discussion

Available data on the pathway between the beginning of symptoms and a final diagnosis of cancer is limited in the paediatric population. This data is of utmost importance to improve and reduce the time, but also to optimize medical resources, aiming for a more efficient and timely diagnosis, hopefully impacting staging at diagnosis and mortality.

In our study, the 3 most common ICCC groups are consistent with the literature, as the higher frequency in men. However, we have a higher relative frequency of lymphomas than expected, as leukaemias and CNS tumours are usually the most common subgroups.[6]

Regarding age at diagnosis by subgroup, our data are in line with the literature, with leukaemias typically presenting at an earlier age (pre-school age) compared to lymphomas, which are more common in adolescence. However, the mean age of leukaemia in our cohort (7.8 years) was slightly higher than in similar studies.[6]

Overall, there was no association between time of disease progression and patient age, but in specific analysis by age subgroups, there was an association for patients >5 years, i.e. the older the patients, the more days they had symptoms before diagnosis. Other authors have reported similar results, showing a positive association between age and delay in diagnosis, even after controlling for cancer type.[7,8] As well as being more dependent on their parents and carers, which allows for closer observation and contact, younger children also receive more regular health monitoring, with appointments scheduled through the National Child Health Programme, with shorter intervals between appointments. Therefore, younger children often have more frequent contact and monitoring by both their caregivers and health professionals, which may lead to earlier detection compared to older children and adolescents.

Forty two percent of patients were referred from the paediatric emergency department at the study site, unlike other studies in the literature with fewer patients coming from acute care, although in both studies, cases with an emergency diagnosis were younger compared with those who were diagnosed electively.[9,10] Patients with higher number of emergency department admissions presented with non-specific signs like swelling and pain. Trauma remains the leading cause of pain in these age groups. However, unlike pain caused by injury, pain in these cases is not proportional to any identifiable trauma and does not improve over time. Therefore, children experiencing persistent, unexplained bone pain, particularly non-mechanical pain, should be evaluated for potential underlying neoplastic disease.[11,12]

Low urinary tract symptoms were the reason for admission in the case with the most hospital contacts before diagnosis. These symptoms are often present in children with urinary tract infection, vulvovaginitis or functional alterations during potty-training. Multiple episodes with normal screenings in urinalysis should prompt investigation through imaging methods.[13]

Patients with leukemia experienced the shortest interval between symptom onset and diagnosis, averaging 12,5 days. A study by Rodrigues KE et al., which analyzed 419 newly diagnosed cases of Acute Lymphoblastic Leukaemia, identified fever, adenopathy, ecchymosis, and pallor as the most common presenting symptoms. Fever and pallor were the only symptoms shared between their findings and our study.[14]

Comparatively, a longer duration of symptoms was observed in CNS disease and lymphomas. The MOBI-Kids study examined 722 cases of brain tumors in children and young individuals aged 10 to 24 years, reporting that most diagnoses occurred approximately two months after symptom onset.[11] In our case series,

the median time from symptom onset to diagnosis was 30 days.

In terms of presenting symptoms, the most frequent symptom in the lymphoma, bone tumor, and CNS tumor groups is similar, whereas in leukaemia cases, organomegaly and hemorrhagic diathesis were more commonly observed.[15]

Attention should be closely paid to the subgroup of patients with a higher risk for malignancy. Screening in children with conditions that carry a higher risk of neoplasia, such as neurofibromatosis, is crucial for early detection and timely intervention. In the cohort, of the 11 asymptomatic patients, the diagnosis was made in 6 cases during routine examinations in at-risk individuals. Regular surveillance through clinical evaluations and appropriate imaging can help identify tumours at an early stage, improving treatment outcomes and reducing complications. Additionally, consistent follow-up in specialized consultations allows healthcare professionals to monitor disease progression, recognize subtle warning signs, and initiate further investigations when necessary.[16] Early diagnosis improves treatment success and quality of life by reducing disease severity, making screening and follow-up essential for high-risk children. Neurofibromatosis was the most frequent risk factor; hence, neurofibromatosis (NF) type 1 is the most prevalent form of NF, with an estimated prevalence of 1 in 3000. Children with neurofibromatosis have a higher risk of developing tumors, including optic pathway gliomas, malignant peripheral nerve sheath tumours, and juvenile myelomonocytic leukaemia in NF1. Regular screening and follow-up are essential for early detection, allowing timely intervention and improving outcomes.[17] Concerning other types of personal history, a first-degree family history of retinoblastoma requires early evaluation of the offspring if familial forms are suspected, as transmission is autosomal dominant (50% risk of transmission). Immunosuppression is a recognised risk factor for neoplastic disease. In such cases, the threshold for diagnostic suspicion should be lower. Type 1 diabetes has been associated with an elevated risk of certain types of cancer, although the majority of the observed risk appears to be concentrated in patients with type 2 diabetes and those undergoing kidney transplantation.[18]

Particular attention should be paid to Neuroblastoma as even tough diagnosis seems fast in our cohort (8 days between symptoms and diagnosis), literature reports that nearly half of neuroblastoma cases have already metastasized by the time they are detected, highlighting the aggressive nature of the disease and the urgent need for increased awareness and vigilance. Surprisingly, this neoplasm can also present in asymptomatic patients, where it shows a benign behaviour, particularly in the neonatal period, being diagnosed in utero through morphologic scans and regressing in the post-natal period, without the need for treatment. While there are no specific early symptoms, neuroblastoma should always be considered when a child exhibits clinical signs that do not align with a typical acute illness or follow an unusual course for their age, such as persistent or hard-to-manage pain, unexplained weight loss, claudication or a decline in overall health.[19]

The prognosis in our cohort meets some data from the literature. Our findings highlight important factors in prognosis, particularly the role of recurrence in outcomes. The lack of association between prognosis and factors such as age at diagnosis, symptom duration before diagnosis, or the number of emergency visits contrasts with some literature suggesting that diagnostic delays can impact outcomes in specific cancers. However, the strong correlation between recurrence and mortality ($p < 0.001$) underscores the aggressive nature of relapsed disease, aligning with existing research that recurrent pediatric malignancies often carry a worse prognosis. Additionally, the finding that prognosis was influenced by the ICCC neoplasm type ($p=0.044$) suggests that intrinsic tumor biology plays a critical role in outcomes, reinforcing the need for risk-adapted treatment strategies.[6,11,20]

Conclusion

Understanding the mechanisms that govern the period between the onset of symptoms and the diagnosis of cancer in pediatric patients is crucial for improving early detection and outcomes. By studying this critical time frame, we can identify patterns that influence when and how pediatric cancer is suspected, ensuring that both subtle and concerning symptoms are recognized earlier. This research is essential for optimizing diagnostic strategies and ensuring that potential warning signs are not overlooked, particularly in children without known risk factors.

Health professionals play a key role in this process, particularly in how they approach screening and early evaluation. While certain high-risk groups benefit from targeted surveillance, most pediatric cancer cases arise in children with no identifiable risk factors. Therefore, it is essential to refine the clinical approach for these patients, improving healthcare providers' ability to distinguish between common illnesses and potential malignancies. Enhancing the level of suspicion in primary and emergency care settings can reduce unnecessary emergency department visits and streamline referrals, ultimately shortening the time to a definitive diagnosis.

These studies not only improve diagnostic efficiency but also provide valuable insights into healthcare practices, leading to more effective and evidence-based pathways for early cancer detection. A more structured approach to early cancer recognition has the potential to reduce delays, improve resource utilization, and ultimately increase survival rates.

Compliance with Ethical Standards
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