Musculoskeletal Misdiagnoses in Pediatric Patients with Spinal Tumors

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Abstract

Objective: Childhood spinal tumors often present with musculoskeletal symptoms, potentially causing a misdiagnosis and delays in diagnosis and treatment. This study aims to identify, characterize, and compare children with spinal tumors who had prior musculoskeletal misdiagnoses to those without, analyzing clinical presentation, diagnostic interval, and outcome. **Study design**: This retrospective cohort study evaluated all children aged 0-14 years diagnosed with a spinal tumor in Denmark from 1996 to 2018. The cohort was identified through the Danish Childhood Cancer Registry, and the registry data were supplemented with data from medical records. The survival was compared using the Kaplan-Meier method. **Results**: Among 58 patients, 57% (33/58) recieved musculoskeletal misdiagnoses before the spinal tumor diagnosis. Misdiagnoses were mostly non-specific (64%, 21/33), involving pain and accidental lesions, while 36% (12/33) were rheumatic diagnoses. The patients with prior misdiagnosis had less aggressive tumors, fewer neurological/general symptoms, and 5.5 months median diagnostic interval versus 3 months for those without a misdiagnosis. Those with prior misdiagnoses tended to have a higher 5-year survival of 83% (95% CI 63-92%) compared to 66% (95% CI 44-82%) for those without (p=0.15) **Conclusion**: Less aggressive spinal tumors may manifest as gradual skeletal abnormalities and musculoskeletal symptoms without neurological/general symptoms, leading to misdiagnoses and delays.

Introduction

Spinal cord tumors are rare tumors in children, with an estimated incidence of 0.27 per 100,000. The most common presenting symptoms are pain of the bony segment directly over the tumor, abnormal gait or coordination difficulties, spinal deformity, focal motor weakness, and sphincter dysfunction. Spinal tumors are one of the childhood tumors most frequently presenting with musculoskeletal symptoms. A recently published nationwide registry-based cohort study by our group, including all children with cancer in Denmark over 23 years, identified a musculoskeletal diagnosis prior to the diagnosis of cancer in one-fifth of the children with spinal tumors. Symptoms among these patients were often nonspecific pain and might mimic rheumatic diseases, which can lead to misdiagnosis and diagnostic delay.

Non-specific musculoskeletal pain is frequent among children and although the percentage of children with cancer among those sent to the rheumatology department is low, up to 60% of children with cancer initially evaluated in the rheumatology department are misdiagnosed. Hematological cancers are predominant in the literature evaluating musculoskeletal misdiagnosis in childhood cancer, including only few cases of spinal tumors.

Misdiagnoses imply a risk of diagnostic delay, and earlier studies have found the diagnostic interval (time from first symptoms until diagnosis) to be twice as long for childhood cancers with a musculoskeletal misdiagnosis. Prompt diagnosis and treatment of pediatric spinal tumors is of special importance, as diagnostic delay can lead to damage to the spinal cord, which may inflict permanent neuronal dysfunction. Survivors of spinal tumors face a high disease burden of long-term effects from tumor and treatment, with substantial morbidity, markedly reducing their quality of life.

The objective of this retrospective cohort study was to identify and characterize the subgroup of children with spinal tumors having a prior musculoskeletal misdiagnosis and evaluate any patterns or red flags. Further, we compared the group with and without musculoskeletal misdiagnosis in terms of clinical presentation, diagnostic interval, and outcome.

Methods

Study design

We performed a nationwide, retrospective study including all consecutive cases of Danish pediatric patients aged 0-14 years diagnosed with a spinal tumor from January 1st, 1996, to December 31st, 2018. The cohort was identified from a nationwide (population of 5.8 million) registry-based cohort study, previously described in detail, using The Danish Childhood Cancer Registry (DCCR). The DCCR includes all cases classified as neoplasms according to the International Classification of Diseases, 10th edition (ICD-10) (diagnoses DC00-DD48). The DCCR is linked to the Danish National Patient Registry (DNPR), the National Pathology Registry, and the Danish Cancer Registry using the unique national identification number assigned to all permanent residents in Denmark at birth or immigration.

Data collection

The registry data from DCCR were supplemented with data from medical records from all pediatric departments in Denmark. To assess the impact of a misdiagnosis on patient outcomes, we identified patients with a prior musculoskeletal misdiagnosis and compared their characteristics to the remaining patients without any musculoskeletal misdiagnosis. The following data were collected: demographic information such as age and gender, the clinical presentation (symptom, objective signs), the diagnostic intervals, tumor type and grade, metastases, treatment, comorbidities. We also collected data of cause and date of death, last day of follow-up, and presence of sequelae from tumor or treatment. Sequelae was categorized according to organ and severity, severe sequelae included plegia, incontinens or neurocognitive defects.

The musculoskeletal diagnosis was recorded as a misdiagnosis if the symptoms were later found to be due to the tumor. It was recorded as musculoskeletal comorbidity if it was a coexisting musculoskeletal diagnosis and the symptoms were not later explained by the tumor. The diagnoses included were from hospitalizations, emergency room, and outpatient visits but not from general practitioners.

We used a standardized definition of the diagnostic intervals, including the period from the first symptom until the start of treatment. Further, three additional time intervals were added: 1) a pre-diagnostic symptomatic interval, i.e., the time from the first symptom until diagnosis. 2) a first hospital doctor interval, i.e., the time from the first hospital contact until a specialist was involved; and 3) a specialist interval, i.e., the time from a specialist was involved until the final diagnosis was made. The specialist was defined as either a pediatric oncologist or neurosurgeon, (Fig. 1).

Statistical analysis

Categorical data were tabulated by prevalence, and Fisher's exact test was used for comparisons. All continuous data were non-normally distributed (evaluated by histograms and QQ-plots), and comparisons were made by Mann-Whitney U-test and tabulated with median, interquartile range (IQR) with lower quartiles as 25th percentile and upper quartiles as 75th percentile and range. For mortality analysis, we followed patients from the date of tumor diagnosis until death, emigration, or the end of follow-up (October 1st, 2022). The Kaplan-Meier method was used to compare the one- and five-year survival for the children

with versus without a prior musculoskeletal misdiagnosis. All statistical tests were performed under a two-sided significance level of 0.05. STATA/MP 17.0 was used for the statistical analysis.

The study was approved by the Danish Data Protection Agency (record number 1-16-02-214-16). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (reporting) guidelines.

Results

According to the original cohort based on registry data, 87 patients below 15 years were diagnosed with a spinal tumor in Denmark from January 1st, 1996 to December 31st, 2018.

17 patients were excluded due to misclassification, as they were not classified as classical spinal tumors, being brain tumors, Langerhans cell histiocytosis, lymphoma, hemangioma, hamartoma, sarcoma, and bone sarcomas with location in the spinal cord. Further, 12 patients were excluded due to missing records or insufficient data, (Fig. 2).

The final cohort of the present study included 58 patients aged 0-14 years diagnosed with a spinal tumor. 64% (37/58) had a prior musculoskeletal diagnosis, and 89% (33) of these were a misdiagnosis. Thereby a total of 57% (33/58) had a musculoskeletal misdiagnosis. The majority (64%, 21/33) of the misdiagnoses were non-specific including musculoskeletal pain (46%, 16/33), and accidental musculoskeletal lesions, often evaluated at the emergency room (15%, 5/33) such as torticollis, muscle strains, and sprains. A specific rheumatic misdiagnosis occurred in 36% (12/33) and included arthritis, arthropathy, osteomyelitis, discitis, inflammatory spondylopathy, reactive arthritis, and scoliosis.

In Table 1 we compare the clinical characteristics: age, gender, tumor type, metastases, treatment, and comorbidities of the group with versus without a musculoskeletal misdiagnosis. There was no difference in gender distribution between the two groups. Patients with a prior misdiagnosis were older (median age 10.5 vs. 5.9, p=0.04). Most of the tumors were low-grade tumors, present in 82% vs 68% (p=0.35). Ependymoma was the most common type of tumor in both groups (found in 27% vs. 20%, p=0.56). Low-grade astrocytoma was slightly more prevalent in the group with a misdiagnosis (24% versus 16%, p = 0.53), whereas high-grade astrocytoma, glioblastoma, medulloblastoma and primitive neuroectodermal tumor (PNET) occurred more often in patients without a misdiagnosis (32% vs. 9%, p=0.002), Table 1. Metastases to the brain were less frequent in the group with a misdiagnosis (9 % vs. 24%, p=0.15). Additional treatment was less prevalent in patients with a misdiagnosis: 21% received steroids or pressure relieving operations compared to 40% of patients without a misdiagnosis (p=0.15), and only 15% received chemotherapy compared to 40% of the patients without misdiagnosis, (p=0.04). Comorbidity occurred less frequent in patients with a misdiagnosis compared to those without (39% versus 60%, p=0.18), mainly due to a lower frequency of CNS comorbidity, including epilepsy and mental retardation, present in 6% with misdiagnosis and 24% without (p=0.15), Table 1.

In Table 2, we present a comparison of the clinical presentation for the group with versus without a misdiagnosis, with pain and paresis as the most common presentation in both groups. Musculoskeletal symptoms were present in 100% of patients with a misdiagnosis versus 56% of patients without (p= < 0.001). In the patients with a misdiagnosis the most common presenting symptom was localized pain in the lower limb, neck, and/or back, occurring in 81% compared to 28% of the patients without a misdiagnosis ($p < 0.001$), Table 2.

Neurological symptoms were less common in patients with a misdiagnosis (63%) compared to those without (96%; p=0.004), (Table 2). Furthermore, general symptoms such as fatigue, fever, and weight loss were less frequent in patients with a misdiagnosis (21% vs. 52%, p=0.02). Physical findings were highly prevalent and did not differ between the two groups, with abnormal neurological findings, particularly paresis, sensory deprivation, and disordered reflexes, being the most frequent (Table 2).

Mistreatment in the form of physiotherapy, chiropractor or painkiller occurred only among the patients with a misdiagnosis (36%, $p < 0.001$). Almost a third (27%) of the misdiagnosed children had received

prior physiotherapy treatment. The time from first symptom until evaluated at the hospital (parental and primary care interval) did not differ compared to the cases not receiving physiotherapy, being respectively 60 days (IQR 22; 540, range 0;788), compared to 59 days (IQR 13; 100, range 3;730), p=0.34. Though, when comparing to the patients without a misdiagnosis they have a shorter interval with 27 days (IQR 4;91, range 0-880), p=0.10.

Table 2 and Fig. 3, provide a comparison of diagnostic intervals for patients with and without a misdiagnosis. Patients with a misdiagnosis experienced a longer total interval (time from onset of symptoms until treatment) with a median time of 165 days (IQR 35;318), compared to 97 days (IQR 28; 176) for those without a misdiagnosis (p=0.07), mainly due to longer parental and primary care intervals. Half of the patients (52%) with a misdiagnosis had a total interval exceeding six months, compared to one third (32%) of patients without a misdiagnosis (p=0.18).

The first hospital doctor was a pediatrician in 60% of all cases. However, for patients with a misdiagnosis, orthopedic doctors or general doctors in the emergency room were the first hospital doctor in 21% of cases, compared to zero cases for patients without a misdiagnosis (p=0.02). A referral to a specialist occurred after the tumor diagnosis was established in 79% of cases, resulting in a median specialist interval of 0 days (IQR 0;1).

In order to further investigate any patterns or red flags in the group with a musculoskeletal misdiagnosis we performed an analysis comparing the 12 patients with a specific "rheumatic" misdiagnosis (including arthritis, arthropathy, osteomyelitis, discitis, inflammatory spondylopathy, reactive arthritis, and scoliosis) to the 21 patients with a non-specific musculoskeletal misdiagnosis (including musculoskeletal pain and accidental musculoskeletal lesions). Further the 12 patients with specific "rheumatic" misdiagnosis were compared to the 25 patients without a misdiagnosis, Supplemental Table S1. The patients with a specific rheumatic misdiagnosis predominantly had low-grade tumors (83%), and metastasis did not occur in this group. High-grade tumors occurred in respectively 17% and 19% of the children with misdiagnoses and in 32% of the children without musculoskeletal misdiagnoses (p = 0.45). Pain as the first presenting symptom occurred in 95% of the patients with non-specific misdiagnoses compared to 42% in the group with specific rheumatic misdiagnoses (p<0.001). The frequency of other symptoms and findings did not differ for the children with specific versus non-specific misdiagnoses. When comparing the diagnostic interval for these three subgroups we found an even longer secondary care interval in the subgroup with a specific misdiagnosis, including a long first hospital doctor interval of 128 days (IQR 13; 153), compared to 10 days (IQR 1; 74) for the subgroup with non-specific misdiagnoses (p=0.10), and 7 days (IQR 1; 45) for the group without a misdiagnosis (p=0.01).

The impact of a musculoskeletal misdiagnosis on overall survival is illustrated in a Kaplan-Meier curve (Fig. 4). The group with a prior misdiagnosis tended to have a higher 5-year survival of 83% (95% CI 63-92%), compared to 66% (95% CI 44-82%) for the patients without musculoskeletal misdiagnoses (p=0.15). For the total cohort, 55% achieved complete remission and 25% (15/58) died due to tumor or treatment. The median duration of follow-up was 10.6 years (IQR 5.2; 14.7), being 8.8 years (IQR 7.1; 21.1) for children with misdiagnoses and 11.3 (IQR 8.6; 12.6) years for the children without, p=0.45.

Sequelae were highly prevalent among all patients, reported in 63% with a misdiagnosis and 76% of patients without a misdiagnosis (p=0.37). Severe sequelae occurred in 42% of patients with a misdiagnosis and 56% of patients without (p=0.43). There was no significant difference in the frequency of musculoskeletal sequelae when comparing the two groups (24% vs. 20%, p=0.76). Similarly, there was no significant difference in the frequency of central nervous system (CNS) sequelae between the two groups (52% vs. 60%, p=0.60). The most frequent CNS sequelae were paraplegia, paresis, sensory impairment, incontinence, and decreased cognitive function.

Discussion

This study highlights a high prevalence of musculoskeletal misdiagnoses among Danish children who were diagnosed with spinal tumors. In two-thirds of children with spinal tumors, musculoskeletal misdiagnoses

were identified, resulting in a longer diagnostic interval compared to children without musculoskeletal misdiagnoses. This subgroup of patients frequently exhibited less aggressive tumors, rarely developed metastases or required additional therapy beyond surgery and tended to have a higher 5-year survival. These findings suggest that less aggressive tumors can gradually manifest as skeletal abnormalities and musculoskeletal symptoms without concurrent neurological or general symptoms, thereby leading to misdiagnosis.

Physicians who evaluate children with musculoskeletal pain must always consider the potential presence of an underlying tumor. Although it is widely acknowledged that pediatric cancers are frequently misdiagnosed, with rates ranging from 52-60%, musculoskeletal misdiagnoses have previously mainly been studied in children with hematological cancers.

Patients who were misdiagnosed with musculoskeletal conditions often presented with localized pain in the lower limb, back, or neck, accompanied by gait abnormalities and nocturnal pain. The literature states pain as the most prevalent symptom of spinal tumors, followed by motor weakness, sciatica, and sensory deficits. It is imperative to approach any occurrence of new-onset, persistent, localized, and severe pain in a previously asymptomatic child with utmost seriousness, warranting thorough consideration of an underlying pathological condition.

Despite medical advances, the diagnostic intervals are still very long for spinal tumors. Multiple studies have revealed a median diagnostic interval ranging from 2-8 months. In the presence of a misdiagnosis the diagnostic interval for pediatric cancers is twice as long. To the best of our knowledge, the present study is the first to investigate the impact of a musculoskeletal misdiagnosis on the time intervals of pediatric spinal tumors. Our results indicate that patients with a musculoskeletal misdiagnosis have a significantly longer median total interval of 5.5 months compared to 3 months for patients without a misdiagnosis, primarily due to a longer parental and primary care interval. In addition, the subgroup with a specific rheumatic misdiagnosis had an even longer first hospital doctor interval, often due to a delay after a visit to the emergency room. The median duration was four months for this subgroup compared to one week for the children without a musculoskeletal misdiagnosis (p=0.01).

Multiple studies have previously revealed associations that extend the diagnostic interval (age, symptoms, and tumor grade, among others). Koshimizu et al., conducted a study evaluating factors contributing to a delay in the diagnosis of pediatric spinal tumors. They discovered neurological symptoms as the presenting symptom was associated with early diagnosis, and the symptom of pain in the lower limb or back was associated with a longer duration of symptoms until diagnosis. They recommended that children experiencing pain lasting more than one month should undergo an MRI to exclude serious spinal disorders.

The present study found no association between longer time intervals and decreased survival. Patients with a musculoskeletal misdiagnosis had the highest 5-year survival rate. This is in accordance with most literature. Bouffet et al., found that patients with a shorter symptom duration (<2 months) had a poorer outcome than those with longer symptom duration (>2 months).

Previous investigations of pediatric CNS tumors have identified tumor type and grade as key factors influencing survival, rather than the diagnostic interval. Crawford et al., found that patients with high-grade malignant spinal tumors had a shorter duration of symptoms and significantly poorer survival compared to patients with low-grade tumors. In the present study, patients with a musculoskeletal misdiagnosis frequently had less aggressive tumors, rarely developed metastases or required additional therapy beyond surgery. Furthermore, these patients demonstrated a tendency towards higher 5-year survival rates. This may indicate that less aggressive tumors can provoke slowly developing skeletal abnormalities and musculoskeletal symptoms without neurological or general symptoms, causing misdiagnoses and diagnostic delays.

Survivors of spinal tumors experience a considerable disease burden due to long-term complications from both the tumor and it's treatment, which markedly reduce their quality of life. In this study, sequelae were highly prevalent in all patients, occurring in two-thirds of the cases, consistent with literature, underscoring the significant impact spinal tumors implicate on patients. Notably, the patients with a musculoskeletal misdiagnosis did not demonstrate a higher prevalence or severity of sequelae compared to those without a

misdiagnosis. This is consistent with some studies, while others have suggested that delayed diagnosis leads to decreased long-term quality of life.

The strengths of this study include the population-based setting including a non-selected cohort of all pediatric spinal tumor cases diagnosed in Denmark over a long period of 23 years. The study's broad representation of tumor morphologies reflects the general population. The comprehensive data collection enabled a detailed analysis of the clinical course of pediatric spinal tumors, providing valuable insights into potential areas for improving the diagnostic process. Further, the evaluation of the diagnostic intervals was strengthened by using a standardized model with several subintervals, which increases the generalizability of the results.

This study has some limitations that require cautious interpretation. Firstly, pediatric spinal tumors are rare, leading to few cases and small subgroups, which may limit the statistical precision. Secondly, retrospective evaluation of the clinical presentation based on doctors' notes from medical charts may introduce recall bias, particularly for time intervals and symptoms. Thirdly, a potential methodological limitation is the fact that the data does not include primary care and presumably underestimates the number of preliminary musculoskeletal misdiagnoses. Fourthly, the study did not record where in the health system misdiagnoses occurred, which precludes a definitive determination of a correlation between misdiagnosis and diagnostic delay. Lastly, 12 out of 70 (17%) patients were excluded due to insufficient or missing medical charts, which could affect our findings.

Conclusion

Misdiagnosis frequently occurs in children with spinal tumors who exhibit musculoskeletal symptoms, leading to delayed diagnosis. This subgroup of patients frequently exhibited less aggressive tumors, rarely developed metastases or required additional therapy beyond surgery and tended to have a higher 5-year survival. These findings suggest that less aggressive tumors can give rise to gradually developing skeletal abnormalities and musculoskeletal symptoms, without accompanying neurological or general symptoms, thereby leading to misdiagnosis.

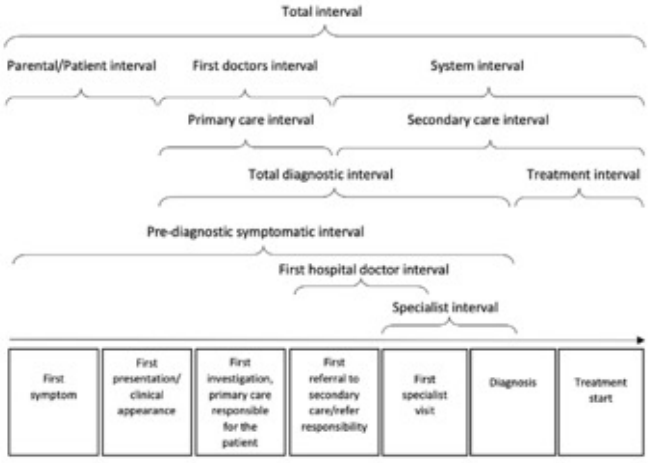
Figure Legends

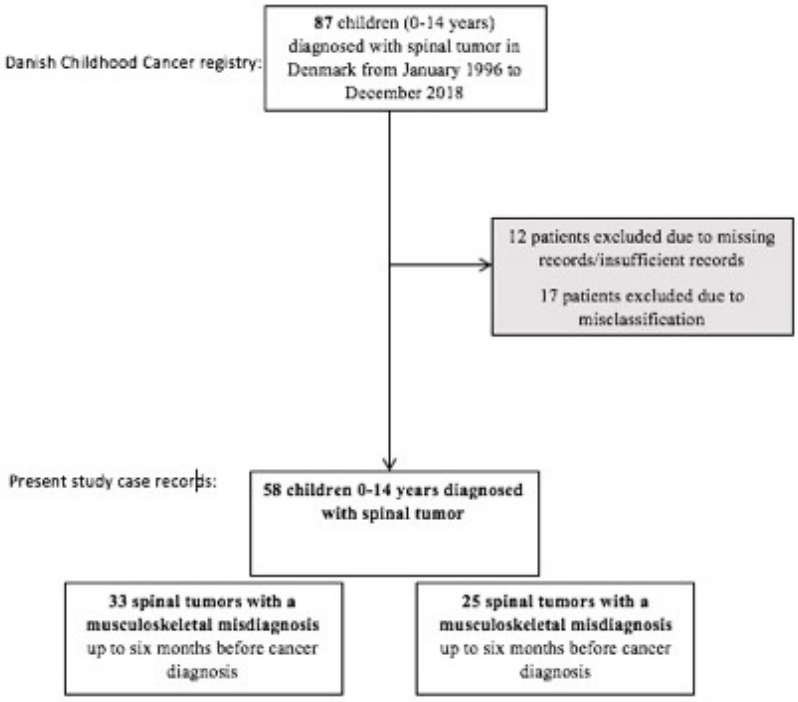
Figure 1. An illustration of the time intervals from first presenting symptom until the start of treatment.

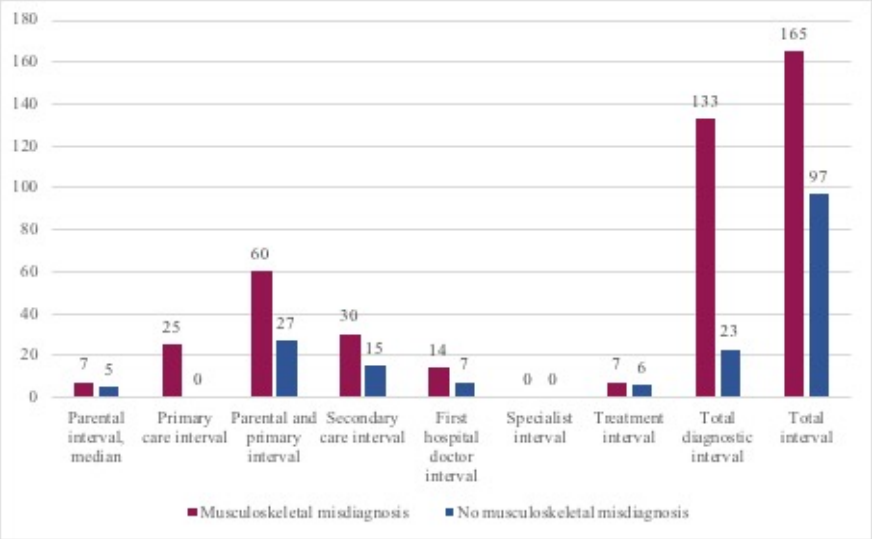
Figure 2. Flow chart of the study population.

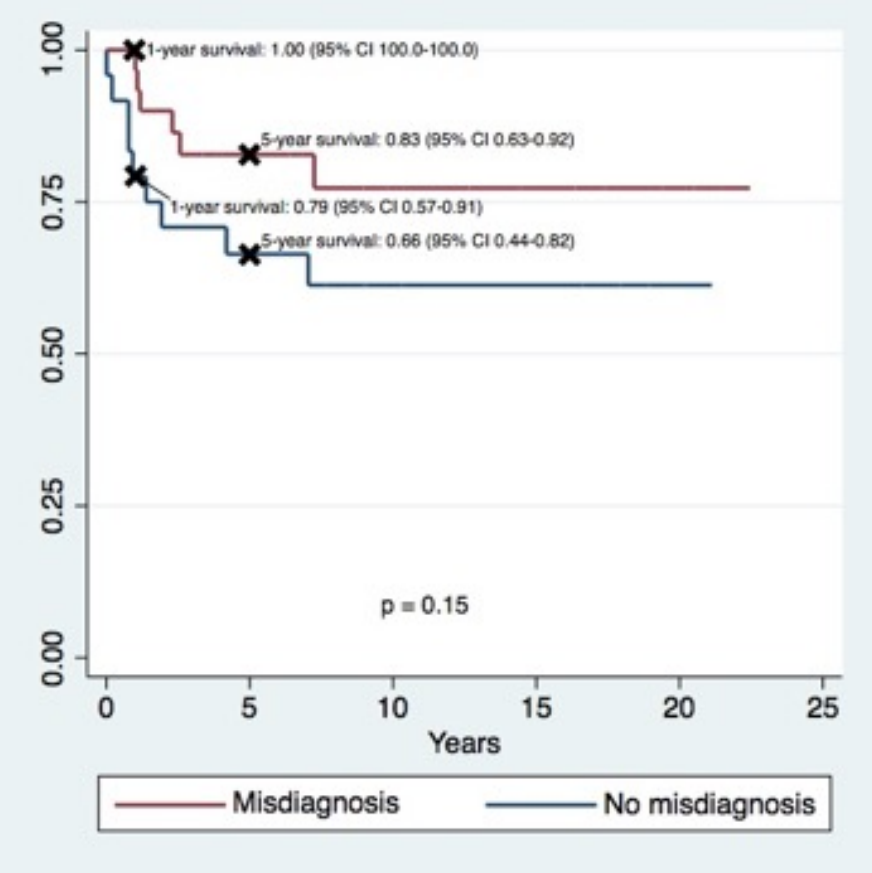
Figure 3. Diagnostic intervals (days) in the group with versus without a musculoskeletal misdiagnosis.

Figure 4: Kaplan-Meier overall survival curves for the patients with versus without a musculoskeletal misdiagnosis.









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`Table 2.docx` available at https://authorea.com/users/695159/articles/683970-musculoskeletal-misdiagnoses-in-pediatric-patients-with-spinal-tumors