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The Diagnostic Accuracy of Serum Alpha-Fetoprotein Levels in Follow-up for Recurrence of Sacrococcygeal Teratoma; a Nationwide Review of SCT Cases in the Netherlands

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ABSTRACT

Background: Serum alpha-fetoprotein (AFP) is often used as tumour marker for recurrent sacrococcygeal teratoma (SCT). We aimed to assess the normal dynamics of serum AFP levels after initial resection and diagnostic accuracy of serum AFP levels the follow-up for recurrence in SCT.
Methods: This retrospective study included 57 patients treated for SCT in the six pediatric surgical centers in the Netherlands from 1980 to 2018.
Main results: 57 patients were included in the study of whom 19 children developed 20 recurrences at a median of 14.0 months after initial resection. No significant difference was found in serum AFP level dynamics between the recurrence and non-recurrence group after initial resection ($p = 0.950$). Serum AFP levels did not significantly increase before recurrence ($p = 0.106$) compared to serum AFP levels of children without recurrence at the same time. However, serum AFP levels did significantly increase in malignant recurrences ($n = 7$) ($p = 0.03$) compared to patients without recurrence. A cut-off value of 55 μg/L was found to be predictive for recurrent SCT with an Area Under the Curve (AUC) of 0.636 with sensitivity of 50% and specificity of 100%.
Conclusion: Dynamics of serum AFP levels are not different between patients with and without recurrence after initial resection of SCT. Serum AFP levels are not predictive for mature or immature recurrent SCT and normal AFP levels do not rule out recurrent SCT. However, serum AFP levels exceeding 55 μg/L can indicate recurrent SCT, especially malignant recurrences.

1. Introduction

Sacrococcygeal teratoma (SCT) is the most common congenital neoplasm with an estimated incidence of 1 per 28,500 newborns in the Netherlands with a male:female ratio of 1:4 [1,2]. Overall prognosis is relatively favourable, and approximately 80% of patients are diagnosed prenatally [3,4].

Surgical resection is the preferred treatment for SCT. Malignant SCTs are treated with chemotherapy in addition to the surgical resection, leading to an overall survival rate of 90% for malignant SCTs twelve years after initial resection [5]. A systematic review of fifteen articles including 613 patients with SCT recurrence post-initial resection found a mean recurrence rate of 18% (range 0–33%) [6]. This review found a shift towards malignancy in recurrence histology, with 56–70% of recurrent SCT cases displaying evidence of malignant yolk sac tumour (YST) upon histological evaluation, whereas only 34% of initial SCTs exhibited malignant histology

Abbreviations: AFP, Alpha-Fetoprotein; AUC, Area under the curve; CI, Confidence interval; SCT, Sacrococcygeal teratoma.

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[1,6–8]. Established risk factors for recurrence are incomplete resection of the SCT or coccyx, tumour spillage during initial resection and microfoci of YST on histological evaluation [9].

Oncological follow-up for at least three years is recommended since most recurrences are found within this time period [10]. This follow-up typically includes physical examination, radiological imaging, and monitoring of serum alpha-fetoprotein (AFP) levels [11].

AFP is a protein synthesized in the fetal liver and yolk sac. Consequently, serum AFP levels usually increase during the neonatal period. Within a few months after birth, serum AFP levels normalize and exist in small amounts in adult serum [12] AFP is used as tumour marker for malignant germ cell tumours [5]. Elevated serum AFP levels, exceeding normal age-related values with a prolonged half-life, can indicate incomplete resection or malignant relapse after surgical resection of SCT [3,13–15].

Serum AFP levels in healthy newborns have been described to decline after birth [12,16]. However, utilizing these normal age-related levels can pose challenges in SCT patients because serum AFP levels may continue to increase until SCT resection. Moreover, it is unknown whether SCT patients have equal serum AFP levels at birth compared to healthy neonates due to possible additional AFP production by the SCT. Moreover, interpreting the dynamics of serum AFP levels in the neonatal period after resection can be challenging, given that AFP levels are naturally elevated in neonates, and an increase does not necessarily indicate SCT recurrence. A recent systematic review found that serum AFP levels to detect recurrent SCT seems promising mainly for malignant recurrences. Furthermore, most studied series focus on absolute serum AFP levels rather than analyzing the dynamics of these levels [6].

Therefore, we aimed to describe the expected dynamics of serum AFP levels after SCT resection and to assess the diagnostic accuracy of serum AFP levels for recurrent SCT.

2. Materials and methods

2.1. Study design and participants

A national, multicenter, retrospective case–control study was conducted of patients treated for sacrococcygeal teratoma in the Netherlands. STARD (Standards for Reporting Diagnostic accuracy studies) 2015 guidelines were followed for this study [17].

The medical records of children treated for SCT between January 1980 and December 2019 at the six pediatric surgical centers in the Netherlands (Sophia Children's Hospital Rotterdam, Radboud University Nijmegen Medical Centre, Wilhelmina Children's Hospital Utrecht, University Medical Centre Groningen, Emma Children's Hospital Amsterdam UMC, and University Hospital Maastricht) were studied retrospectively.

Children who underwent surgical treatment for SCT and had serum AFP levels measurements during follow-up, were eligible for the study. Patients with a presacral teratoma as part of the Currarino triad were excluded because of their different biological behaviour. Patients with incomplete SCT resection defined as macroscopically incomplete SCT resection during initial surgery, were also excluded. Since, in these patients, it is difficult to distinguish residual tumour from recurrence [18]. Only patients with recurrent SCT with serum AFP levels measured within three months before recurrence detection were included in the study. All non-recurrence patients with less than two serum AFP levels measurements during follow-up were excluded from the study. Recurrence patients were matched individually with two patients without recurrence within five years after initial resection. Matching criteria was the age of the individual patient at last serum AFP level measurement prior to recurrence detection. This age was matched with the age of non-recurrence patients during follow-up.

Clinical and outcome data were collected from the original medical records. Medical records contained information retrieved by systematic follow-up.

Patients treated for SCT in the Netherlands are followed after initial resection in the outpatient clinic. Follow-up in the outpatient clinic is scheduled 1–2 weeks after discharge from the hospital, after 6 weeks, three months, six months and one year. The first three years after initial resection oncological follow-up is scheduled every three months. Oncological follow-up consists of physical examination, serum AFP levels and an ultrasound of the abdomen. Physical examination is performed by the pediatric surgeon and usually consists of abdominal examination and examination of the scar tissue. If signs of recurrence are found by physical examination, ultrasound or serum AFP levels are elevated, a MRI is conducted to diagnose a possible recurrent SCT. Furthermore, children receive an additional hip ultrasound at the age of three months to detect possible hip dysplasia. Additional follow-up is scheduled at the age of two years, four years, five years, eight years, twelve years an seventeen year to detect possible difficulties in miction and defecation. Additionally, quality of life, motor development and cognitive development are evaluated during the follow-up moments [19].

According to the Medical Ethical Board of AMC, the Medical Research Involving Human Subjects Act (WMO) does not apply to the study and official approval of the committee was not required (reference number: W20_372 # 20.417).

2.2. Statistical analysis and definitions

SCTs were classified according to the Altman criteria proposed by the Surgical Section of the American Academy of Pediatrics [20]. Serum AFP levels (μg/L) of SCT patients with recurrence were compared with age-matched SCT patients without recurrence.

Data are presented as mean with standard deviation (SD) if normally distributed and median with interquartile range (IQR)/range if skewed; count data are presented as numbers and percentages. Differences in patient demographics between recurrence and non-recurrence were calculated with χ^2 analysis or Fisher's exact test if a group had less than five patients. Absolute AFP dynamics after initial resection were compared with linear regression analysis after initial resection. Diagnostic accuracy of serum AFP levels to detect recurrent SCT, was calculated with receiver operating characteristics (ROC) curve. To compare increase or decrease of serum AFP levels between recurrent and non-recurrent patients, ΔAFP was used. ΔAFP was calculated as the difference in serum AFP levels between serum AFP-level prior to recurrence detection (AFP2) and the serum AFP-level measured at recurrence detection (AFP1). This number was divided by AFP1. Leading to the formula: ΔAFP=(AFP2-AFP1)/AFP1. Absolute serum AFP levels and ΔAFP prior to recurrence were analysed with Mann–Whitney U test. Absolute AFP levels and AFP dynamics prior to recurrence per histology were analysed with linear regression analysis and Kruskal–Wallis test.

Statistical analyses were performed using SPSS for Windows version 25.0 software (SPSS, Chicago, Illinois, USA) and Graph Pad Prism 8 (GraphPad Sofware, Incl, La Jolla, CA, USA). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

From 1980 to 2018, 310 children were treated for SCT in one of the six Dutch pediatric surgical centers. Thirteen children were lost to follow-up or died immediately after birth and were therefore

excluded. Thirty-seven patients developed recurrence during follow-up. In 25 patients with recurrence, serum AFP levels were available three months prior to recurrence detection. Six recurrence patients were excluded from analysis: five with incomplete SCT resection and one with Currarino syndrome. In total, 19 recurrence patients were included. These patients were matched with 38 non-recurrent patients. In total, 57 children were included; 12 were male (21.1%) and 45 were female (78.9%) with a male: female ratio of 1:3.8.

Patient characteristics are described in Table 1. Mean gestational age (GA) at birth, mean birth weight, Altman classification and age at initial resection was not different between recurrence and non-recurrence group.

At surgery, a sacral approach was used in 37 children, combined with a laparotomy or laparoscopy in eight children. In three children, the teratoma was removed via a laparotomy only. Surgical approach was unknown in nine children. Coccyx was removed in all recurrent patients compared to 27 (71.1%) non-recurrent patients. However, in the remaining 11 (28·9%) non-recurrent patients coccyx removal was unknown.

Histological diagnosis of the initial tumour was different with a mature, immature and malignant percentage of 73.3%, 13.1% and 10.5% in non-recurrence patients, compared to 47.4%, 47.4% and 5.2% in recurrence patients, respectively (p = 0.014). In one (3.1%) non-recurrent patient the histological diagnosis of the initial tumour was unknown. Two children had metastatic disease at time of initial resection. These children did not develop recurrence after initial treatment.

Median age at last follow-up was higher in patients with recurrent SCT: 6.6 years (IQR 3.6–12.3) compared to 4.0 years (IQR 2.0–6.2).

Three children with recurrent SCT died during follow-up at the age of 2.6, 2.9 and 10.6 years. All patients died due to complications of the treatment and of the disease: lung fibrosis due to chemotherapy, ileus to due recurrent SCT in the abdomen and due to recurrent disease with metastasis. All children without recurrent SCT survived.

3.2. Recurrent SCT

Nineteen children developed 20 recurrences at a median of 14.0 months (IQR; 9.0 monts-28.5 months) after initial surgery. One (5.3%) recurrence was found by physical examination during routine follow-up, seven (36.8%) by imaging and ten (52.6%) recurrences were found due to elevated serum AFP levels. Of the seven recurrences found by imaging, three were detected using MRI, two with ultrasound, and the imaging modality for two patients was unknown. In one patient mode of recurrence detection (5.3%) was unknown. Eight (42.1%) recurrences were treated with surgery, nine (47.4%) with a combination of chemotherapy and surgery, one (5.3%) with a combination of radiotherapy and surgery and one (5.3%) with only chemotherapy.

Recurrence histology was mature in ten (52.6%) patients, immature in three (10.5%) and malignant in seven (36.9%). One patient developed two immature recurrences during follow-up.

3.3. Serum AFP levels after initial resection

Of the 505 AFP samples obtained, 427 (84.6%) were analyzed in this study; 78 (15.4%) of the samples were excluded because the sample was taken prior to the initial SCT resection. The number of samples taken per patient ranged from two to 22. The recurrence group contained 168 AFP samples obtained from 19 children. The non-recurrence group contained 226 AFP samples obtained from 38 children.

Figure 1 shows the mean decline with SD of serum AFP levels after initial SCT resection. No significant difference was found between the decline in serum AFP between recurrence and non-recurrence patients after initial resection (p = 0.950).

Table 1
Patient characteristics.

	Total (n = 57)	Recurrence (n = 19)	Non-recurrence (n = 38)	p-value
Sex				0.187
Female	45 (78·9%)	13 (68·4%)	32 (84·2%)	
Male	12 (21·1%)	6 (31·6%)	6 (15·8%)	
Mean birth weight (SD) (grams)	3123 (705)	2965 (529)	3188 (763)	0.324
Median GA at birth, (IQR) (weeks)	38.1 (36.7–39.5)	38 (33.4–39.2)	38.1 (37–39.9)	0.816
Premature				0.248
Yes	12 (21·1%)	5 (26·3%)	7 (18·4%)	
No	37 (64·9%)	9 (47·4%)	28 (73·7%)	
Missing	8 (14·0%)	5 (26·3%)	3 (7·9%)	
Metastatic disease at initial resection				0.365
Yes	2 (3.5%)	0	2 (5.3%)	
No	51 (89.5%)	15 (78.9%)	36 (94.7%)	
Missing	4 (7.0%)	4 (21.1%)	0	
Resection os coccygis				0.009[a]
Yes	46 (80·7%)	19 (100%)	27 (71·1%)	
No	0	0	0	
Missing	11 (19·3%)	0	11 (28·9%)	
Altman				0.445
I	20 (35·1%)	9 (47·4%)	11 (28·9%)	
II	12 (21·1%)	2 (10·5%)	10 (26·3%)	
III	8 (14·0%)	3 (15·8%)	5 (13·2%)	
IV	11 (19·3%)	4 (21·1%)	7 (18·4%)	
Missing	6 (10·5%)	1 (5·2%)	5 (13·2%)	
Histology of primary SCT				0.014[a]
Mature	37 (64·9%)	9 (47·4%)	28 (73·3%)	
Immature	14 (24·5%)	9 (47·4%)	5 (13·1%)	
Malignant	5 (8·8%)	1 (5·2%)	4 (10·5%)	
Missing	1 (1·8%)	0	1 (3·1%)	
Median age at initial resection (IQR) (days)	10.5 (3–45)	9.5 (2.5–358.8)	10.5 (3–43)	0.635
Median age at last follow-up (IQR) (years)	4.8 (2.1–7.1)	6.6 (3.6–12.3)	4.0 (2.0–6.2)	0.019[a]

[a] Indicates statistical significance. SD = standard deviation. GA = gestational age. IQR = interquartile range.

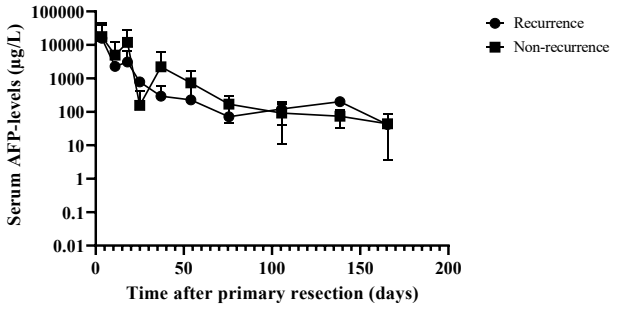

Fig. 1. Dynamics of serum AFP levels after initial SCT resection.

3.4. Elevated serum AFP levels at recurrence

Serum AFP levels prior to recurrence detection were compared with serum AFP levels of age-matched non-recurrent patients. Distribution of serum AFP levels prior to recurrence detection is shown in Fig. 2. Median serum AFP level in recurrence patients prior to recurrence detection was 54 µg/L (IQR 2.75–1074) compared to median of 10 µg/L (IQR 5.1–29.9) ($p = 0.107$). In an attempt to find a cutoff point that indicates possible recurrent SCT, receiver-operating characteristics curves were drawn. In our model, a serum AFP cutoff value with 100% sensitivity of 0.6 µg/L was associated with an Area Under the Curve (AUC) of 0.636 with a 95% confidence interval of 0.41–0.83 ($p = 0.106$) and that should lead to a discrimination between patients with recurrent SCT and patient without recurrent SCT. A cutoff value with 100% specificity and 50% sensitivity of 55 µg/L was found.

Figure 3 shows the differences of serum AFP levels prior to recurrence detection with ΔAFP for recurrence and non-recurrence patients. Median time between samples was 157 days (IQR 91.5–209.3). No significant difference was shown in ΔAFP between recurrent and non-recurrent SCT ($p = 0.174$).

3.5. Serum AFP levels per recurrence histology

Serum AFP levels for recurrent patients were analyzed in subgroups per histology of the recurrent SCT: mature, immature and malignant. Figure 4 shows dynamics of serum AFP levels prior to recurrence detection. Especially in malignant recurrent SCT, an increase in serum AFP levels was shown prior to recurrence detection. However, linear regression analysis showed no significant difference in the dynamics of AFP levels between mature, immature and malignant histology ($p = 0.807$) prior to recurrence detection.

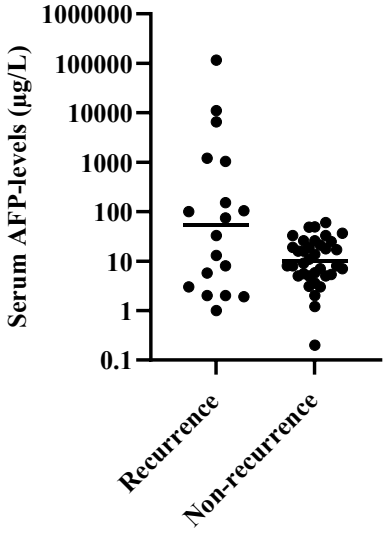

Fig. 2. Distribution of serum AFP levels prior to recurrence.

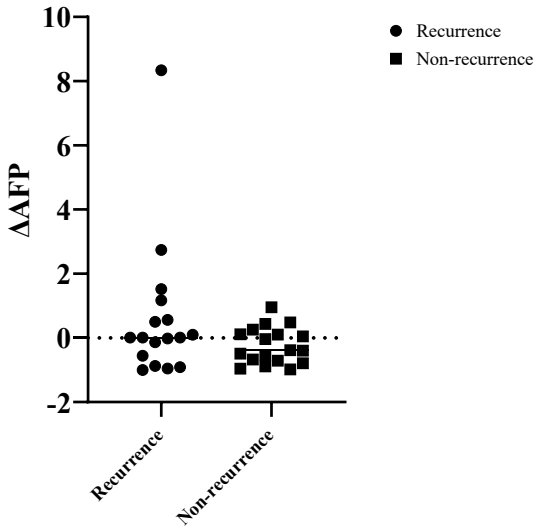

Fig. 3. ΔAFP prior to recurrence detection.

Median serum AFP levels prior to mature (5.7, IQR 1.9–23.9) and immature (38.5, IQR 2.0–75.0) recurrences were not increased compared to median serum AFP levels of patients without recurrence (10.0, IQR 5.1–23.9) at the same age ($p > 0.999$). However, median serum AFP levels prior to malignant recurrence (1032, IQR 100–6500) were higher compared to patients without recurrence ($p < 0.0001$). Furthermore, the median increase of serum AFP levels, measured in ΔAFP, between non-recurrence patients, mature recurrence, immature recurrence and malignant recurrence was significantly different ($p = 0.008$) (Fig. 5).

Seven malignant recurrences were included in this study. In all seven patients, an increase of serum AFP levels prior to recurrence was found. The increase of serum AFP levels in patients with malignant recurrent SCT prior to recurrence detection ranged from 11 µg/L to 7940 µg/L.

4. Discussion

In this nationwide study, our aim was to evaluate the normal dynamics of serum AFP levels after the initial SCT resection and to assess the diagnostic accuracy of serum AFP levels in detecting recurrent SCT during follow-up. Therefore, nineteen patients with recurrent SCT were matched with 38 non-recurrence patients. After initial SCT resection, no difference was found in the rate of

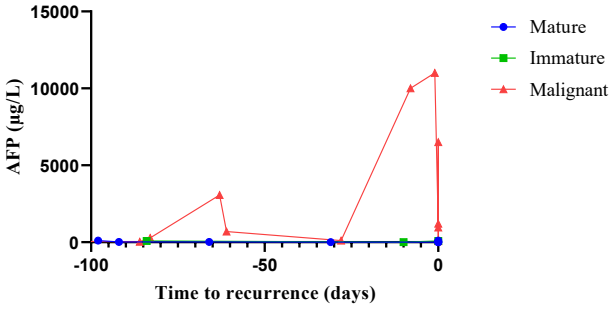

Fig. 4. Serum AFP levels per histology of the recurrent SCT.

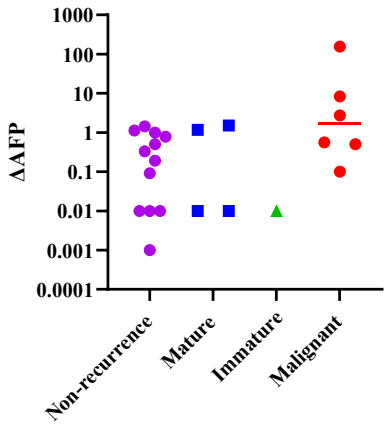

Fig. 5. Distribution of serum AFP levels per recurrent histology prior to recurrence.

decline of serum AFP levels between recurrence and non-recurrence patients. Others have compared the half-life of AFP between recurrent and non-recurrent SCT after the initial resection, finding a prolonged half-life of serum AFP levels in recurrent SCT patients [3]. This could be explained by a possible incomplete resection, leading to continued AFP secretion by the residual tumour rather than SCT recurrence. In this study, patients with macroscopically incomplete initial resections were excluded due to the difficulty in distinguishing residual tumour from recurrent SCT.

Furthermore, reference values for AFP have been described, and serum AFP levels start to decline immediately after birth in healthy infants [12,16]. However, interpreting these values in SCT patients poses challenges as AFP levels might continue to rise until SCT resection due to additional production by the tumour. In this study, analysis of reference values for AFP after initial resection was not performed due to the small patient group, resulting in an extremely broad 95% confidence intervals. Tables containing reference values for serum AFP levels have been published by others [12,16]. Additionally, it was found that children had not reached adult serum AFP levels by the age of two years [16]. Serum AFP levels may potentially remain higher throughout the period of liver and gut cell growth. Therefore, we recommend utilizing these tables with specific serum AFP levels for infants and young children even after SCT resection. Moreover, factors other than recurrent SCT can also cause elevated AFP levels, such as hepatic disorders and neonatal hyperbilirubinemia [3,16].

We found that serum AFP levels in children with recurrence were not increased prior to recurrence detection compared to patients without recurrence with serum AFP level measurements around the same age. Additionally, the increase measured as ΔAFP in serum AFP levels was not significantly different between recurrent and non-recurrent patients.

An ideal marker should possess high sensitivity to effectively rule out the disease. However, in our study, high sensitivity resulted in a cutoff value of 0.6 μg/L. This would yield a high rate of false positive results, implying that nearly all children would be suspected of having recurrent SCT during follow-up, necessitating additional imaging. Conversely, we established a cutoff value of 55 μg/L for serum AFP levels to detect recurrent SCT with a specificity of 100%. Thus, serum AFP levels exceeding 55 μg/L indicate recurrent SCT. However, low serum AFP levels can generate false negatives and do not entirely rule out recurrent SCT.

Furthermore, serum AFP levels were analyzed based on recurrence histology. However, no difference was found between the median serum AFP levels in mature and immature recurrences compared to the serum AFP levels of non-recurrent patients. The increase, measured as ΔAFP, in serum AFP levels before detecting recurrence was higher in patients with malignant recurrent SCT in comparison to children with mature and immature recurrence and those without recurrent SCT. Others also described elevated AFP levels in YST and immature teratomas with microscopic foci of YST [21–23]. These findings align with a recent systematic review, demonstrating a 96% sensitivity of serum AFP levels in detecting malignant recurrent SCT% [6].

4.1. Limitations

Several limitations need to be acknowledged. Firstly, serum AFP levels were not routinely measured in all patients during follow-up, leading to the exclusion of some patients from further analysis and missing additional information of AFP dynamics during follow-up. Given the extensive duration of the study, guidelines might have evolved over time. However, presently, in the Netherlands, most centers routinely conduct serum AFP level assessments in patients treated for SCT. These checks occur every six months during the initial three years post-resection, followed by checks up until seventeen years post-resection [19]. In a prior systematic review we conducted, we recommended monitoring serum AFP levels every six months for at least three years to detect (malignant) recurrent SCT [6]. Secondly, we did not conduct subgroup analysis for preterm and term infants due to the limited number of patients in this study. Other studies have identified higher serum AFP levels in preterm infants, attributable to placental clearance of AFP from the fetal to maternal side, resulting in a slower decrease in serum AFP levels in preterm infants compared to term infants [12,24]. Nevertheless, the impact of differential serum AFP dynamics between term and preterm infants in this study is likely minimal, as the percentage of preterm and term infants did not significantly differ between the recurrence and non-recurrence groups. Furthermore, only serum AFP levels of SCT patients were analyzed; there was no comparison to healthy infants since serum AFP levels are not part of routine neonatal intensive care check-ups.

Additionally, patients in this study were matched solely based on the age of serum AFP level measurement during follow-up. Due to the small patient population, matching based on more factors was not feasible. Nonetheless, patient groups exhibited relatively similar baseline characteristics. Lastly, we were unable to calculate a cutoff point with AUC for malignant recurrent SCT due to the limited number of patients included in our study with malignant recurrent SCT.

4.2. Recommendations

We recommend to use appropriate reference tables for AFP levels after SCT resection [12,16]. For premature infants, we recommend using tables by Blohm et al. with specific tables for premature infants since serum AFP levels in premature infants are higher compared to term infants [16]. Furthermore, the decline of serum AFP levels in premature infants slower due the fact that the liver in these children is not fully developed yet. The diagnostic value of serum AFP levels remains limited in the first year of life due to the wide reference range and the fact that these values are often established on small patient series especially in patients treated for SCT. More research with serum AFP levels routinely measured during follow-up is necessary to determine AFP dynamics after SCT resection more accurately and to provide serum AFP levels references tables for patients treated for SCT. Furthermore, a delayed decline after initial resection is more likely to be caused by incomplete SCT resection or other SCT independent factors than recurrent disease since no delayed decline in our study was found

in recurrence patients compared to non-recurrent patients. This study found that low serum AFP-levels do not rule out recurrent SCT during follow-up, especially mature and immature recurrences. In these patients, we advise regular physical examination and imaging modalities to detect possible recurrent SCT. However, imaging can be challenging to interpret in abdominal pelvic regions after SCT resection and diagnostic accuracy of imaging modalities is relatively unknown. Further research could be helpful in filling these knowledge gaps. Serum AFP levels exceeding 55 μg/L during follow-up are an indication SCT recurrence, especially malignant recurrences. Dynamics of serum AFP levels during follow-up are useful in particular to predict malignant recurrent SCT and imaging modalities should be considered in patients with an increase in serum AFP levels during follow-up to detect possible malignant recurrence.

5. Conclusion

The majority of studies describe absolute serum AFP levels rather than the dynamics of these levels after the initial resection of SCT for detecting recurrent disease. This study is among the first to analyze the dynamics of serum AFP levels in diagnosing recurrent SCT [6]. We found that the decline in serum AFP levels after the initial SCT resection is similar for both recurrence and non-recurrence patients, hence not serving as a predictive marker for recurrent SCT. However, the dynamics in serum AFP levels, measured as ΔAFP, prove useful in detecting recurrences. A cut-off value of 55 μg/L could potentially indicate recurrent SCT. Serum AFP levels during follow-up can be especially useful in detecting malignant recurrent SCT.

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Conflicts of interest

The authors declare no conflict of interest.

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