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Defining an optimal time window to screen for hepatoblastoma in children with Beckwith-Wiedemann syndrome

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Abstract

Patients with Beckwith-Wiedemann spectrum (BWSp) undergo quarterly alpha-fetoprotein measurement for hepatoblastoma (HB) screening up to 4 years of age, paralleling the epidemiology of nonsyndromic HB. However, specific data on the timing of HB development in BWSp are lacking. Here we compare the timing of presentation of HBs in BWSp with a control cohort of consecutive HB cases, demonstrating that halving screening duration of screening procedures in BWSp likely will not impact its effectiveness.

Keywords

alpha-fetoprotein; Beckwith-Wiedemann; cancer screening; hepatoblastoma

1 | INTRODUCTION

Beckwith-Wiedemann spectrum (BWSp) is the most common overgrowth disorder¹ and presents with multiple features of variable severity including macroglossia, abdominal wall defects, macrosomia, hyperinsulinism, ear anomalies, and cancer predisposition.²

Hepatoblastoma (HB) represents the second most common cancer to develop in patients affected by BWSp.³⁻⁵ Patients with BWSp experience an over 2200 times greater HB risk than the general population and up to 1.7% will develop HB.^{3,6} Among BWSp molecular subgroups, the highest HB risk is observed in patients with paternal chromosome 11 uniparental disomy, occurring in 3.5–4.7% of patients^{3,4} and risk appears to be even greater in patients with genome-wide paternal uniparental disomy.^{5,7} In patients with BWSp and

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CONFLICTS OF INTEREST

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KCNQ1OT1:TSS-DMR loss of methylation, HB occurs in 0.7% of cases, representing the most common cancer.⁴

The tumor marker alpha-fetoprotein (α FP) is secreted in more than 95% of HBs starting at very early stages^{8,9} and has been used for cancer screening in this context, using quarterly measurement of its concentration in conjunction with abdominal ultrasound, with the aim of early diagnosis.^{3,5,10,11} As nonsyndromic HB occurs before 5 years of age,⁸ screening in BWSp is adopted during the first 4 years of life.¹² However, specific data on the timing of HB development in the BWSp population are lacking. Here we provide data on HB epidemiology in BWSp, showing differences in the age of presentation compared to sequential cases of children with HB, supporting a reduction in the duration of α FP screening in these patients.

2 | METHODS

A literature search was performed in PubMed from 1980 through 2017 to identify reports of patients with BWSp with HB and data concerning age at the diagnosis. Given the retrospective nature of this investigation, patients were selected notwithstanding molecular diagnosis and the clinical criteria used for the BWS diagnosis, as varying clinical criteria and molecular diagnostic methods were available at the time of these reports. Additional unpublished patients with BWSp and HB were identified through a search of registries at the authors' institutions. Institutional review board approval and patient consent were obtained for personal cases included.

The age at HB tumor development was collected from the patients with BWSp for comparison with 254 sequential patients with HB reported by Litten et al.⁸ Data were analyzed using GraphPad Prism 7.0 (La Jolla, CA, USA).

3 | RESULTS

A total of 76 patients with BWSp and HB were identified (64 from the literature^{4,13–22} and 12 unpublished patients from the authors' cohorts; 10 Kalish/Duffy, 2 Musso/Ferrero).

Mean age at tumor diagnosis in patients with BWSp was 7.1 ± 6.0 months (median 5.0 months). The distribution of age at diagnosis (Figure 1) depicts a left-skewed log-normal distribution (R^2 0.558). Mean age at diagnosis in nonsyndromic HB patients was significantly higher (19.5 ± 14.7 months, median 16.0 months, $P < 0.001$).

The cumulative incidence by age at HB diagnosis in patients with BWSp and nonsyndromic patients is shown in Figure 2. In patients with BWSp, 80% of HB was diagnosed before 12 months of age, 95% before 18 months, 97% before 24 months, and 100% before 30 months, while HB incidence in the control cohort was 39%, 53%, 68% and 79%, respectively. A significant difference in Kaplan-Meier curves of HB incidence of the BWSp cohort and HB cohort was found from the age of 5 months (log-rank Mantel-Cox test $P < 0.001$).

4 | DISCUSSION

HB screening in BWSp is a debated issue and it has been questioned if HB deserves specific screening with α FP measurements.^{23–26} Current recommendations on α FP use differ between health care systems based on the threshold for acceptable risk: a 5% risk threshold has been utilized in Europe compared to a 1% risk threshold adopted in the United States. As a result, α FP screening was not recommended in a recent European Consensus on BWSp due to the challenges in interpreting α FP results,⁵ while α FP screening from birth or BWSp diagnosis until 4 years of age has been recommended by American Association for Cancer Research (AACR) Workshop on Childhood Cancer Predisposition in the United States,¹² keeping with the recommendations employed worldwide for more than a decade.^{11,27}

Although no specific studies have evaluated the yield of this screening strategy and its impact on survival, several data indicate that quarterly α FP measurement can result in a downgrade shift of tumor stage at diagnosis,^{10,21} potentially reducing mortality and treatment complications. This practice seems also to allow an earlier recognition with respect to liver ultrasound, as α FP rise usually anticipates imaging diagnosis.^{10,22,27} The importance of an early detection lies in prognosis implications. The overall 5-year survival rate of HB based on current treatment regimens is 70%,²⁸ ranging from 92% to 31% based on stage at diagnosis and age, with children diagnosed <1 year of age having a better prognosis.²⁹

Despite this evidence, drawbacks to this screening strategy include difficulties in interpreting α FP values in the first 2 years of life and absence of standardized protocols for managing α FP increases. Repeated blood draws in early infancy may create a burden for patients and their families, representing an indirect cost and factor affecting compliance. However, a recent survey among parents of patients with BWSp found that parents are often comforted by screening³⁰ and less invasive methods have been proposed, such as α FP measurement on capillary blood.³¹

The duration of α FP screening up to the fourth year of age in BWSp has been chosen to parallel the epidemiology of nonsyndromic HB, where most tumors develop before the fifth year of age.⁸ However, it has been suggested that HB in BWSp has different characteristics compared to the nonsyndromic HB.²¹ In this study, we provide the first data on HB epidemiology in BWSp, demonstrating that age at tumor diagnosis in patients with BWSp is lower than that observed in a cohort of HB cases. Cumulative HB incidence diagnosed by age in patients with BWSp reaches a plateau well before that observed in the control HB patients cohort, with all HB diagnosed before the age of 30 months in BWSp, suggesting that screening up to 24–30 months may be sufficient to detect nearly all tumors in this population. Although the value of this observation is somewhat limited due to the retrospective nature of this study, the differences in the HB diagnosis trend across early infancy are clear. Actually, it should be noted that the 254 cases by Litten et al used as comparator cohort are consecutive and were not examined with respect to potential syndromic diagnoses: therefore, it is possible that some of them had BWSp or other tumor predisposing diagnoses. Moreover, this review did not evaluate the molecular diagnosis or

clinical features present in patients and further investigation including these data may be beneficial to identify patients with BWSp most at risk for developing HB.

These data imply that it is approximately possible to halve the duration and number of blood draws in patients with BWSp: 10 blood draws may be sufficient to allow the detection of most HBs. The present data also highlight the importance of an early diagnosis of BWSp and immediate initiation of screening protocol in patients with a suspected diagnosis, as more than 80% of the HB cases occurred in the first year of life.

In conclusion, these retrospective data suggest that a reduction of duration of HB screening from 4 years to 30 months in BWSp can be considered, allowing reduction of direct and indirect costs and patients' burden with likely no impact on effectiveness of screening with respect to current practice.

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Abbreviations:

αFP	alpha-fetoprotein
BWSp	Beckwith-Wiedemann spectrum
HB	hepatoblastoma

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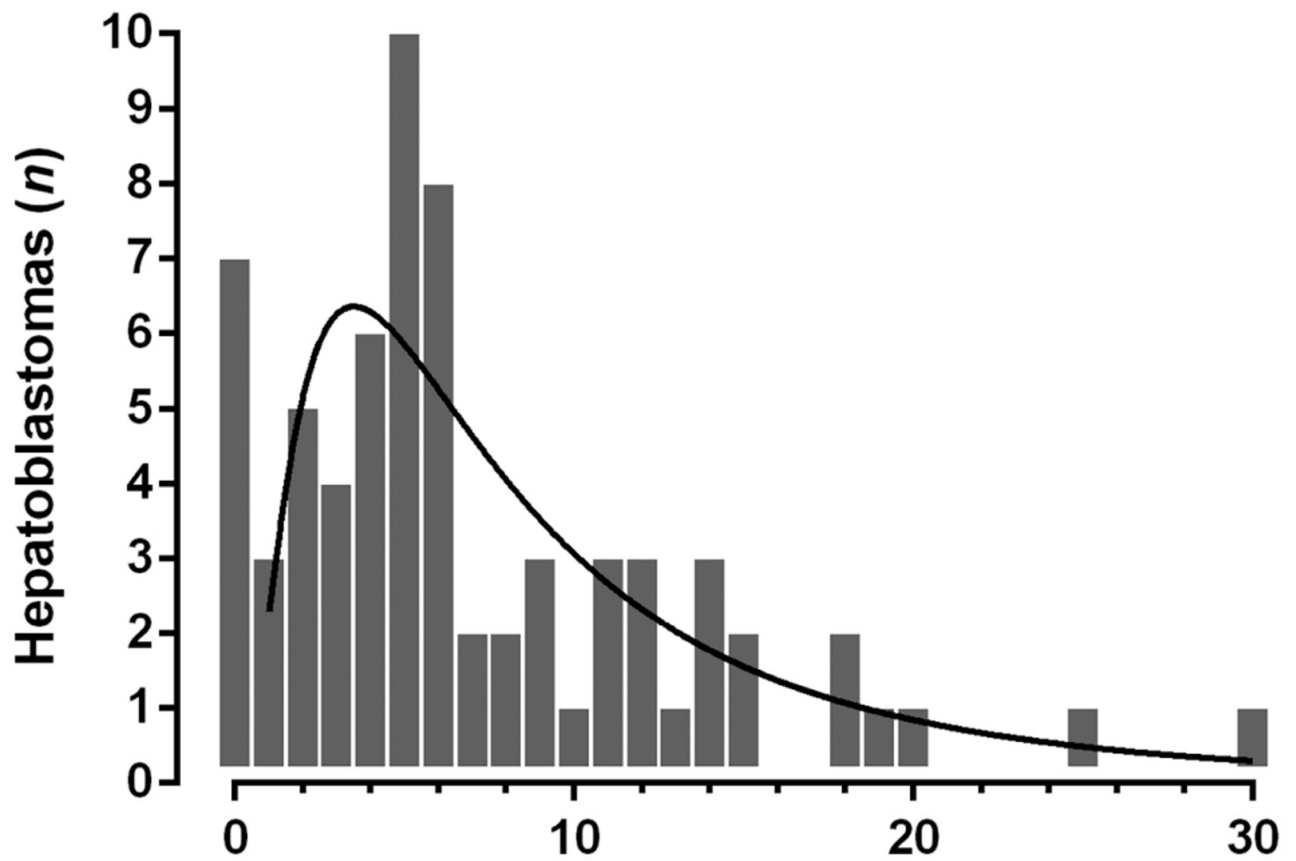


FIGURE 1. Hepatoblastoma (HB) diagnosed by month of age in patients with Beckwith-Wiedemann spectrum (BWSp) *Note:* The distribution of age at diagnosis depicts a left-skewed log-normal distribution (R^2 0.558).

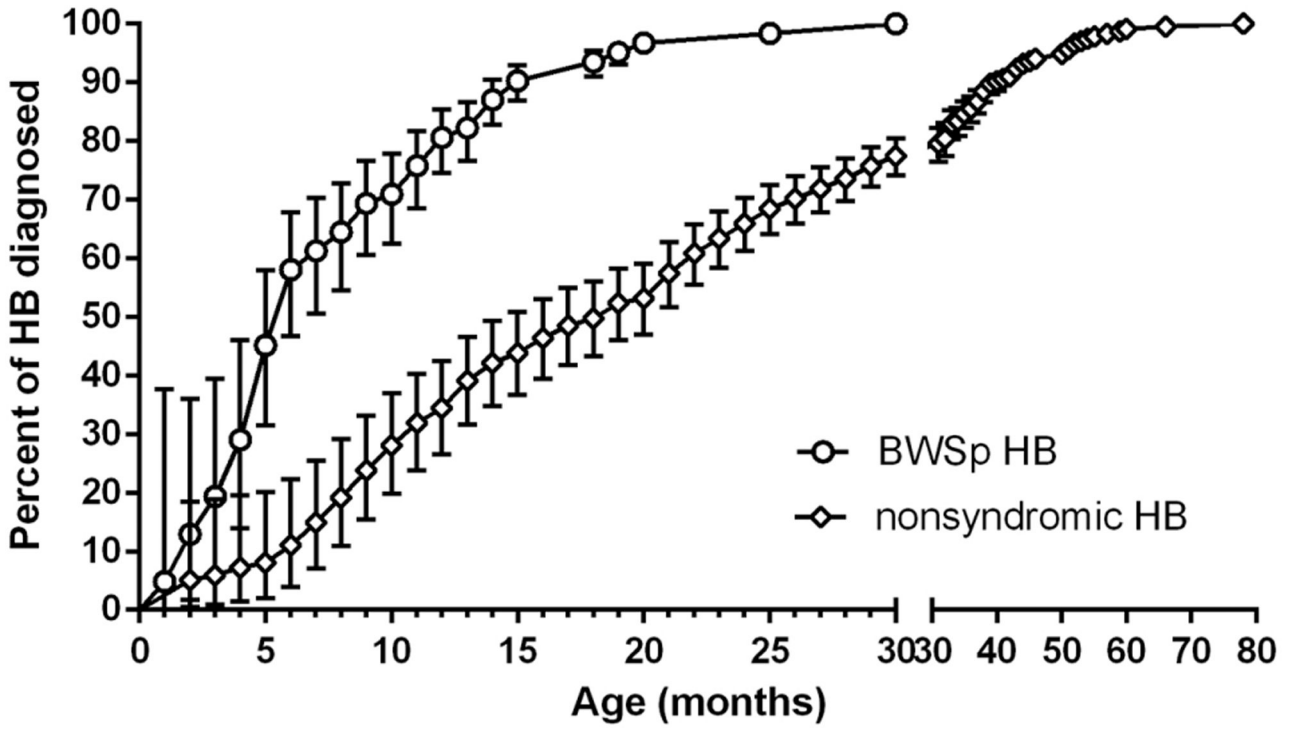


FIGURE 2. Cumulative incidence of hepatoblastomas (HBs) diagnosed by month of age in patients with Beckwith-Wiedemann spectrum (BWSp; empty circles) and in the comparator historical cohort of HB patients published by Litten et al⁸ (empty diamonds) with respective 95% confidence interval (vertical bars) Note: Kaplan-Meier curves were significantly different from the age of 5 months (log-rank Mantel-Cox test $P < 0.001$).

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