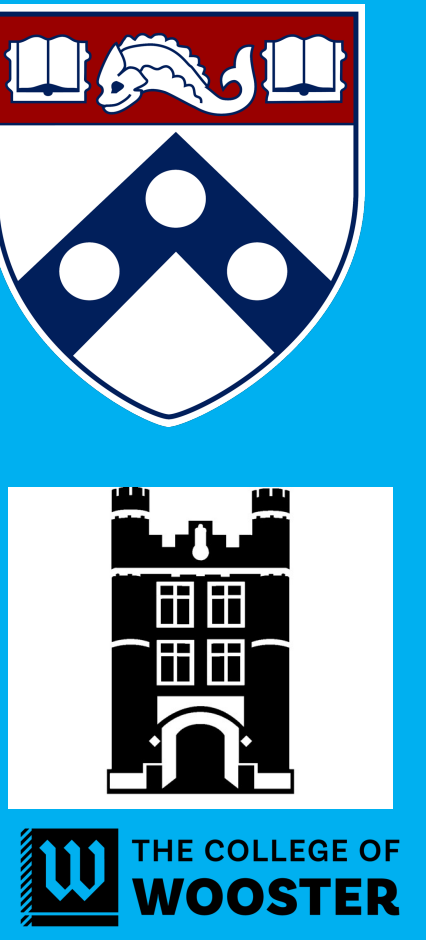




Liver Tumors in Beckwith Wiedemann Syndrome: Can Alpha-Fetoprotein Levels Distinguish Benign From Malignant Tumors?

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Introduction

- Beckwith Wiedemann Syndrome (BWS) is an overgrowth disorder typically brought to the attention of physicians by the recognition of physical features in children, categorized as major and minor features. It is associated with genetic and epigenetic changes on chromosome 11p15 region.

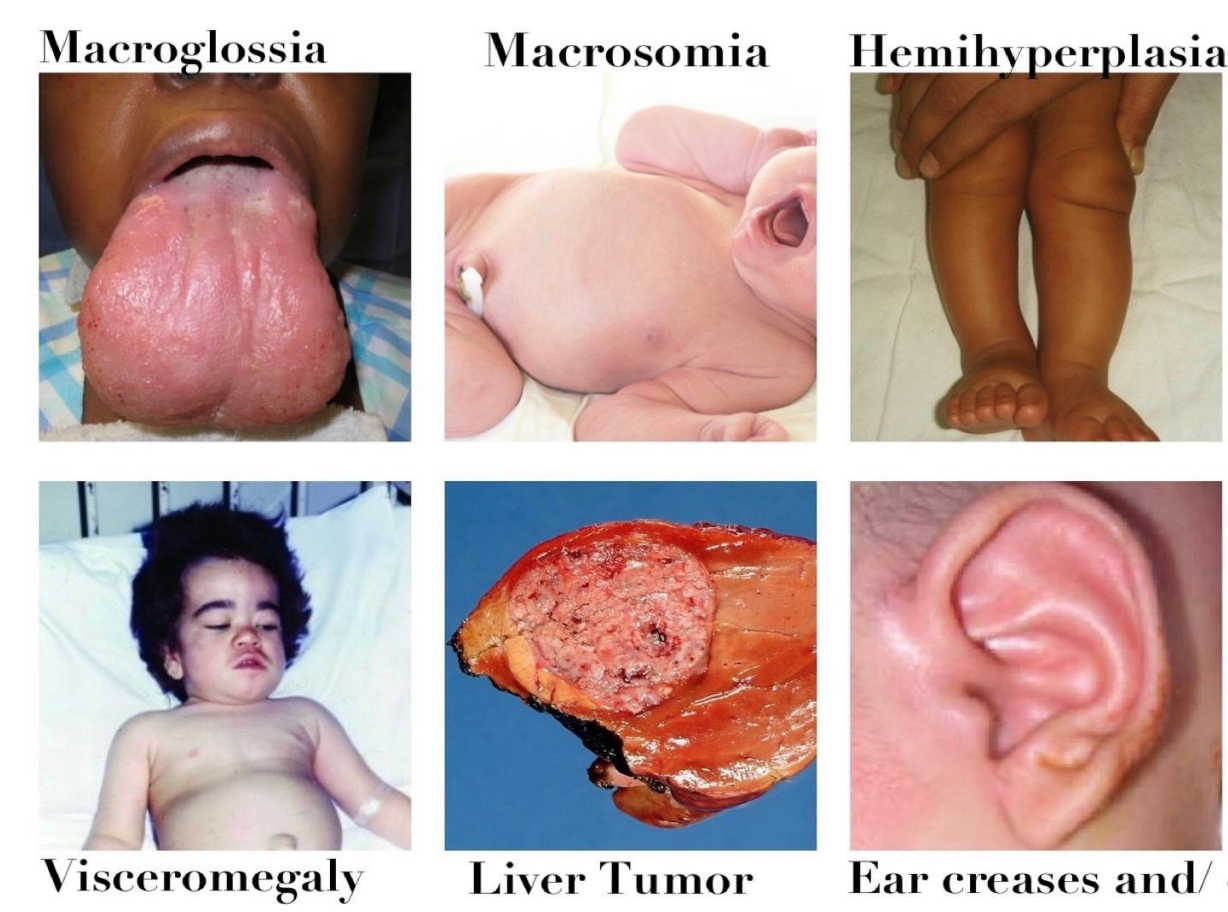


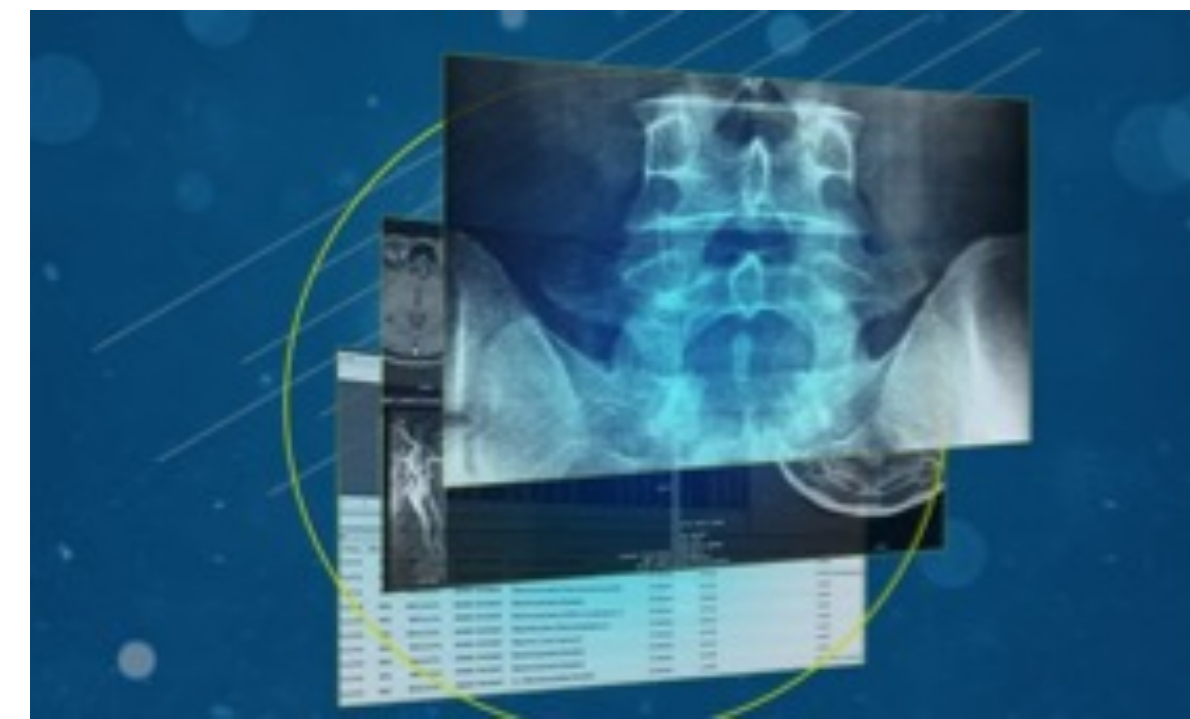
Figure 1. A sample of various Beckwith-Wiedemann syndrome (BWS) major and minor clinical features of characterization

- BWS is associated with the development of liver tumors in children under the age of 4 years. Screening has been implemented for early detection. Screening methods include using a blood sample measuring alpha-fetoprotein (AFP) and direct visualization of the liver using imaging with abdominal US and MRI.
- The necessity of AFP screening has some concerns due to challenges with its interpretation and how invasive a blood draw is causing anxiety to patients. An elevated AFP level is not an absolute indication of a malignant tumor, and various factors, such as prematurity, make interpretation challenging.

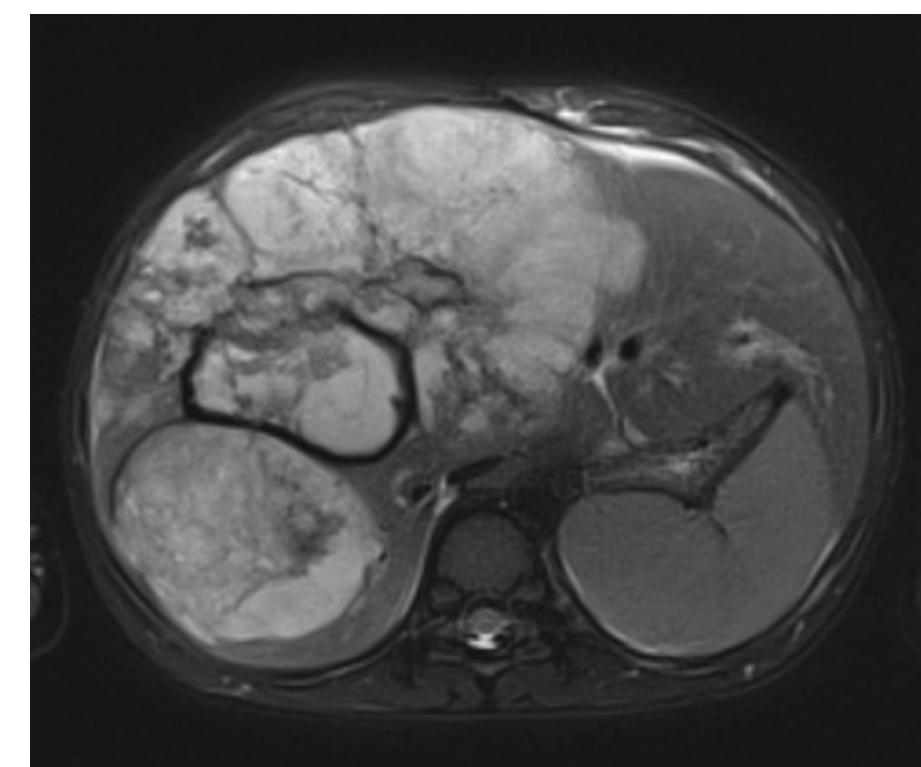
Aims

- To determine if AFP can be used to determine if liver masses are malignant hepatoblastoma (HB) from benign hemangiomas (HM).
- To determine if there is a cutoff AFP value that can be used to distinguish between HB and HM.
- To examine imaging studies to determine if imaging patterns can be used to distinguish between HB and HM.
- To review the literature for information regarding whether AFP is useful in BWS patients with liver masses and compare to our study.

Methods



- Search the radiology database using the Illuminate search engine which is linked to PACS to gather patients.
- Search words: BWS, liver mass, AFP, magnetic resonance imaging (MRI), hemangioma, hepatoblastoma, and contrast enhanced ultrasound.
- Search EPIC (electronic health records) for AFP levels taken up to three months after birth.
- Record the patient's name, gender, date of birth, age, MRN, tumor diagnosis date, type of tumor, BWS or normal, and AFP levels on an Excel spreadsheet.
- After gathering the AFP values perform statistical tests to test for significance. Use the Statistical Package for the Social Sciences (SPSS) for data entry and analysis.



- Imaging review of magnetic resonance imaging's (MRI), ultrasound's (US) to determine the diagnostic accuracy of the imaging study. Create rubric to gather a list of imaging features and create table.

Meta-analysis

- Identify the articles for review.
- Decide the eligibility of the studies.
- Finalize the list of studies to include.
- Fill out data extraction table.

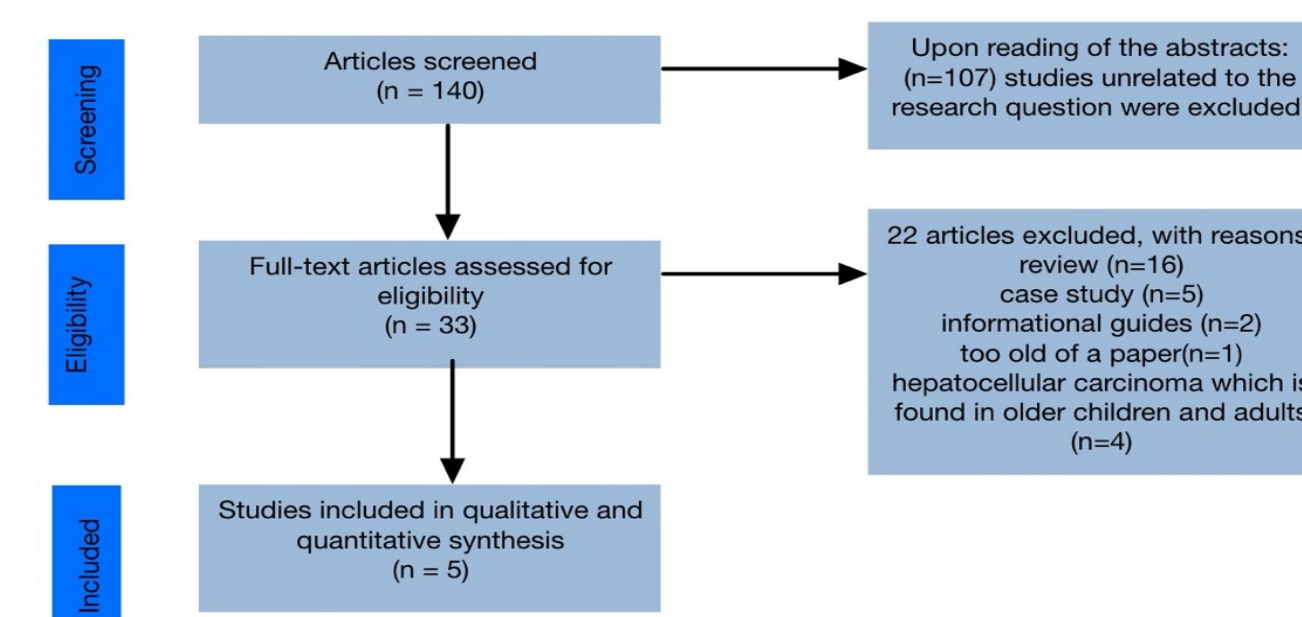


Figure 2. The flow diagram of study selection.

Results

Table 1. BWS hepatoblastoma and BWS hemangioma patients shows no difference in AFP values.

	AFP 1	AFP 2	AFP 3	Just before treatment AFP
Asymp. Sig.	.198	.211	.699	.320

Table 2. Normal hepatoblastoma and normal hemangioma patients shows no difference in AFP values.

	AFP 1	AFP 2	AFP 3	Just before treatment AFP
Asymp. Sig.	.642	.733	.622	.622

Table 3. Pretreatment coordinates of the ROC curve for the BWS hepatoblastoma and hemangioma patients that represent a sensitivity/specificity pair corresponding to a particular threshold (AFP value) shows no good cutoff value.

Positive if AFP value is Greater Than or Equal to	Sensitivity (true positive) for having a hepatoblastoma	1-specificity (false positive) for having a hemangioma	Positive if AFP value is Greater Than or Equal to	Sensitivity for having a hepatoblastoma	1-specificity (false positive) for having a hemangioma
2.600	1.000	1.000	5411.700	.700	.273
3.700	1.000	.909	6089.700	.700	.182
7.850	1.000	.818	24617.500	.600	.182
14.200	1.000	.727	47274.300	.500	.182
97.550	1.000	.636	52762.800	.500	.091
192.300	1.000	.545	55350.750	.500	.000
217.350	1.000	.455	60660.250	.400	.000
384.850	1.000	.364	75700.000	.300	.000
564.500	.900	.364	142650.000	.200	.000
2259.000	.800	.364	644000.000	.100	.000
4652.500	.700	.364	1090001.000	.000	.000

Table 4. AFP values after age correction shows overlap of lesions.

AFP Range (before treatment/ at diagnosis)	BELOW RANGE	IN RANGE	ABOVE RANGE
BWS Hepatoblastoma (10 patients before treatment)	2	0	8
Normal Hepatoblastoma (14 patients before treatment)	0	0	14
BWS Hemangioma (12 patients at diagnosis)	2	3	7
Normal Hemangioma (16 patients at diagnosis)	8	2	6

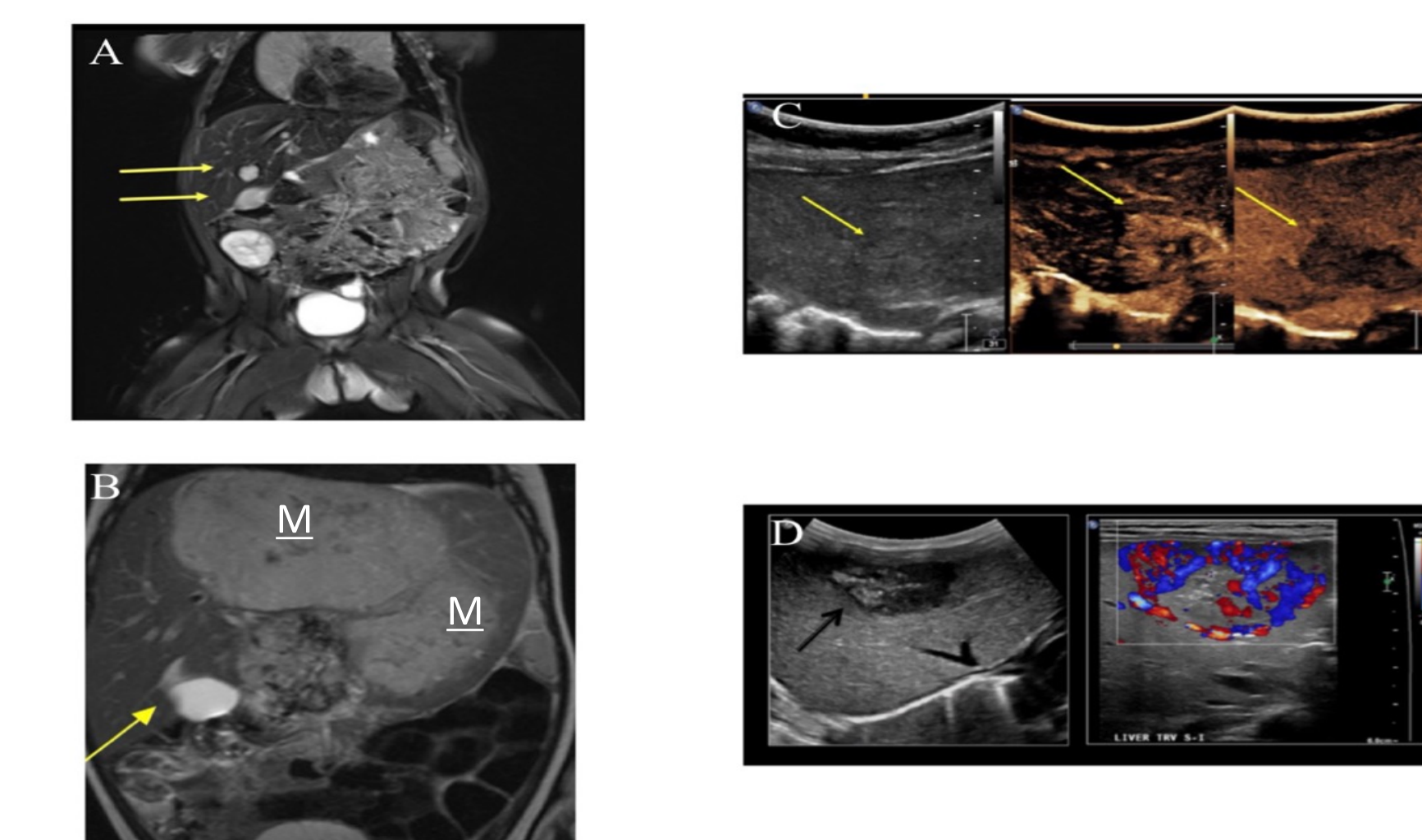


Figure 3. Imaging techniques (MRI, US, and CEUS) utilized throughout this study. Images shown depict BWS patients.

- (A) MRI of hemangiomas (yellow arrows)
- (B) MRI of hepatoblastoma (M). Yellow arrow points to gallbladder.
- (C) CEUS of hepatoblastoma, note enhancement and washout.
- (D) US with color doppler of hemangioma.

Table 5. Imaging with regards to tumor diagnosis shows a range of protocols.

First imaging occurrence?	BEFORE DIAGNOSIS	AFTER DIAGNOSIS	SAME DAY
BWS Hepatoblastoma (n=10)	7	2	1
Normal Hepatoblastoma (n=14)	11	2	1
BWS Hemangioma (n=12)	11	0	1
Normal Hemangioma (n=16)	9	4	3

Table 6. AFP under various circumstances can't distinguish benign vs malignant liver tumors in BWS patients.

	Survey Cohort (Our data)	Wong et al.	Duffy et al.	Kang et al.	Zarate et al.	Everman et al.
Patients	52	130	147	60	63	23
BWS patients	22/52 (42%)	0/130(0%)	147/147 (100%)	0/60 (0%)	29/63 (46%)	23/23 (100%)
Normal patients	30/52 (57.6%)	130/130(100%)	0/147 (0%)	60/60 (100%)	34/63(54%)	0/23 (0%)
AFPs in patients with BWS	22/52 (42%)	0/130(0%)	147/147 (100%)	0/60 (0%)	29/63 (46%)	23/23 (100%)
AFPs in normal patients	30/52(57.6%)	130/130(100%)	0/147(0%)	60/60 (100%)	34/63 (54%)	0/23 (0%)
AFPs in patients with Hepatoblastoma	24/52(46%)	147/130(43.1%)	0/147(0%)	20/60 (33%)	1/63 (1.6%)	0/23 (0%)
AFPs in patients with Hemangioma	28/52(53.8%)	24/130(18.5%)	0/147(0%)	40/60 (66%)	2/63 (3.2%)	0/23(0%)
Prenatal Patients	34/52 (65.4%)	Not reported	48/147 (32.6%)	Not reported	15/63(24%)	7/23(30%)
Age corrected patients	52/52 (100%)	Not reported	147/147(100%)	0/60 (0%)	63/63 (100%)	0/23 (0%)
Earliest age of AFP	1 day	0-13 weeks	1 day	0 years	1 day	1 month
Latest age of AFP	8 years	17 years	4 years	18 years	8 years	9 years
Imaging	CEUS, US, MRIs	CEUS	Not reported	CEUS, US, MRIs	US	Not reported
Patients with elevated AFP	35/52 (67%)	Not reported	Not reported	14/60	4/63(6.3%)	Not reported
Conclusion	AFP cannot distinguish benign vs malignant tumors in BWS patients.	CEUS criterion is useful in distinguishing hepatoblastoma from hemangioma. It was also noted in the results that AFP levels of normal patients with hepatoblastoma was significantly higher than that of normal patients with hemangioma.	Predictive AFP values for BWS premature & non premature were created. More analysis is needed to determine if AFP values differ within the less common molecular subtypes of patient with BWS.	Using CEUS, US, MRIs with AFP could be a powerful diagnostic tool in pediatric patients with distinguishing benign from malignant tumors.	No difference in AFP levels between BWS patients without liver lesions and control patients. No difference in the decline of AFP between the BWS and normal populations.	AFP levels within BWS patients decline slower than a normal range of AFP levels at given ages. AFP levels should be compared to a normal BWS curve as opposed to healthy children. Elevated AFP levels can raise concern for hepatoblastoma but another less serious lesion is also possible.

Conclusion

- AFP is not able to distinguish benign versus malignant tumors in patients with BWS or in the normal population.
- There was no good cutoff value that would correctly identify our patients with no misclassifications due to a lot of overlap of the AFP values between the BWS hepatoblastoma and hemangioma groups.
- No publications showed a clear use of AFP alone to help distinguish benign versus malignant tumors within the BWS population which is the conclusion of our study.

Limitations & Future Works

Limitations

- Small sample size
- AFP values were not truly matched for age
- Small pool of studies and not many imaging articles with regards to AFP
- All these patients in this study did not have the same type of ultrasound or MRI imaging

Future

- Larger sample size
- Age matching using gestational age and age matched AFP data.
- Perform study reviewing latest imaging techniques of contrast enhanced ultrasound and hepatobiliary MRI contrast agents.
- Look at whether the presence of multiple lesions has an effect on the AFP level.