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Predictors of poor prognosis in prenatally diagnosed sacrococcygeal teratoma: A multiinstitutional review

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ABSTRACT

Introduction: Attempts at defining predictors of poor outcome in fetal sacrococcygeal teratoma (SCT) have been hampered by small patient numbers. We sought to validate the utility of tumor volume to fetal weight ratio (TFR) as a predictor of poor prognosis and to identify other morphological outcome predictors in a multicenter series.
Methods: Records of prenatally diagnosed SCT at three fetal centers from 1986 to 2011 were reviewed. Prenatal imaging characteristics including TFR, morphology, hydrops, and placentomegaly were assessed. Poor prognosis was defined as fetal demise, need for fetal intervention, or perinatal death. Receiver operating characteristic (ROC) analysis was used to select a TFR cutoff value.
Results: Seventy-nine fetuses with SCT were evaluated. Eleven pregnancies ending in elective termination were excluded. ROC analysis revealed that TFR >0.12 prior to 24 weeks gestation was predictive of poor prognosis (AUC=0.913; Sensitivity=91.7%, Specificity=76.2%, PPV=86.8%; NPV=84.2%). Solid tumor morphology and presence of hydrops were found to be predictors of poor prognosis. None of the factors associated with poor prognosis were independent predictors on multivariate analysis.
Conclusion: This study validates TFR >0.12 prior to 24 weeks gestation as an objective predictor of outcomes in fetuses with SCT that can be easily applied in most clinical settings.

Sacrococcygeal teratoma (SCT) is the most common congenital tumor with a reported incidence of 1 in every 35,000 to 40,000 births [1,2] and a 3:1 female preponderance [3]. Although the prognosis of neonatal SCT is usually favorable, the prognosis in prenatally diagnosed SCT tends to be poorer with mortality rates between 30% and 50% [4–6]. The course of fetal SCT can be unpredictable with some tumors remaining stable in size while others grow rapidly. Large, solid, highly vascular SCTs are associated with high mortality and morbidity; usually due fetal anemia and shunting of blood away from the placenta into the tumor leading to the development of high-output cardiac failure followed by polyhydramnios and subsequent premature labor [7,8]. The high-output cardiac failure then leads to placentomegaly or hydrops in the fetus. In severe cases, high-output cardiac failure in the fetus can lead to maternal mirror syndrome, a preeclamptic condition in which the mother develops symptoms of hydrops similar to that of the fetus. In the era of routine prenatal screening and improved fetal imaging using ultrasonography and magnetic resonance imaging (MRI), most SCTs are now diagnosed in utero. Close surveillance with serial ultrasounds and echocardiography is recommended so that fetal intervention or early delivery can be performed when necessary [8,9].

As a result of the advances in fetal imaging and intervention, there is a need for prognostic factors that can guide prenatal counseling and assist in determining the need for higher level of care and fetal intervention versus expectant management. Several factors such as tumor morphology (solid versus cystic), vascularity, tumor growth rate and the presence of polyhydramnios have been found to predict outcomes in prenatally diagnosed SCT [10–12]. In particular large, solid tumors that are highly vascularized with a rapid growth rate have been associated with poor fetal outcomes [3,12,13]. A previous study by Rodriguez et al. identified the tumor volume to fetal weight ratio (TFR) before 24 weeks gestation as being predictive of poor outcomes [14]. The TFR was easy to measure by ultrasound and could be easily adapted for use in routine obstetric evaluation of fetuses with SCT. However, similar

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to previous studies, the study was hampered by small patient numbers at a single institution because of the rarity of SCT.

We therefore sought to validate the utility the TFR as a predictor of poor prognosis and to identify other morphological predictors of poor prognosis in a multicenter series with a large patient cohort.

1. Patients and methods

The multicenter study was approved by the Institutional Review Board of the Baylor College of Medicine, Houston, TX (H-26009) and at each contributing institution.

1.1. Patient population

We performed a retrospective review of the medical records of all patients evaluated for SCT at three large-volume fetal centers (Texas Children's Fetal Center, Fetal Care Center of Cincinnati and University of California, San Francisco Fetal Center) between 1986 and 2011. Pregnancies that ended in elective termination were excluded from final analysis.

1.2. Tumor weight to fetal volume ratio (TFR) calculation

As previously described [14], TFR was calculated by dividing the tumor volume by the estimated fetal weight. Tumor volume was calculated by using the greatest tumor length, breadth and depth to obtain a prolate ellipsoid [15] and the estimated fetal weight was obtained using the Hadlock formula [16].

1.3. Data collection

Prenatal data were collected including the gestational age at diagnosis and imaging characteristics such as tumor morphology, TFR, presence of hydrops or placentomegaly. Fetal outcomes including termination of pregnancy, intrauterine fetal demise, need for fetal intervention, live birth and survival until discharge were collected. Tumor morphology was graded as less than or greater than 50% solid. Hydrops was defined as the presence of effusion in two or more body cavities with evidence of cardiac dysfunction and/or skin edema. Placentomegaly was defined as placental thickness >5 cm. Patients were stratified by overall prognosis. A good prognosis was defined as survival until hospital discharge. A poor prognosis was defined as intrauterine fetal demise (IUFD), perinatal death or need for fetal intervention. Since some of those that had fetal intervention survived to discharge, we used the terminology – poor prognosis – to identify this high-risk group that either died or required fetal intervention to survive.

1.4. Data analysis

Statistical analyses were performed using IBM SPSS statistical software package version 21 (IBM Corporation, Armonk, NY). Receiver operating characteristic (ROC) curve analysis was used to select a cutoff value for TFR based on optimum sensitivity and specificity. Patients were then stratified by TFR, tumor morphology greater than 50% solid, and presence of placentomegaly and presence of hydrops. The relative risks for poor prognosis based on the aforementioned parameters were calculated. Patient outcomes were then analyzed using Fischer's Exact test. Multivariate regression analysis was performed to identify independent risk factors for the development of poor prognosis. A p-value <0.05 was considered to be statistically significant.

2. Results

2.1. Demographics

A total of 79 fetuses with SCT from all three participating institutions had adequate imaging for analysis. Of these, 11 (13.9%) underwent elective termination of pregnancy and were excluded from the remainder of the analysis. Another patient was excluded for an associated congenital lung malformation and another was excluded because the outcome of the pregnancy was unknown. Of the 66 fetuses that were included in the final analysis, 32 (48.5%) had a poor prognosis of which 18 needed fetal intervention and 14 had perinatal demise (Fig. 1). Of the fetuses that required fetal intervention, 3 pregnancies resulted in IUFD, 6 in postnatal death and 9 survived past the perinatal period. Neonates with poor prognosis were diagnosed with SCT at an earlier median gestational age than those with good prognosis [21.1 weeks (18.50–29.86) vs. 23.9 weeks (16.60–34.14) weeks; p=0.030]

2.2. Validation of TFR

Prior studies had shown that TFR prior to 24 weeks was predictive of outcome. Furthermore, this time line allows for counseling about pregnancy options. In this cohort, 50 patients had imaging prior to 24 weeks from which the TFR could be calculated. ROC curve analysis revealed that TFR greater than 0.12 prior to 24 weeks gestation was predictive of poor prognosis with a sensitivity of 91.7%, specificity of 76.2%, positive predictive value of 86.8% and negative predictive value of 84.2% (Fig. 2). Fetuses were stratified into those with TFR less than or equal to 0.12 (n=21) and TFR greater than 0.12 (n=29) prior to 24 weeks gestation. Of the fetuses with TFR >0.12, 82.8% (24/29) had poor prognosis compared to 19% of fetuses with TFR≤0.12 (4/21) ($p<0.0001$).

2.3. Outcomes of fetuses on morphological predictors

Table 1 illustrates outcomes of fetuses with SCT based on morphological predictors. Of the 66 patients, 41 (62.1%) had tumors that were ≥50% solid and were more likely to have a poor prognosis compared to patients with tumors that were <50% solid (70.7% vs. 9.1%, $p<0.001$). Fetuses with tumors that were ≥50% solid had over a seven-fold risk of poor prognosis compared to those with tumors that were <50% solid (Table 1). Fetuses with hydrops had 3.5-fold greater risk of a poor prognosis compared to those without hydrops ($p<0.001$). Although 71.4% (n=10) of patients with placentomegaly had poor prognosis compared to 40.7% of patients without placentomegaly, this difference was not statistically significant. We did not observe a difference in the incidence of poor prognosis between patients who had polyhydramnios and those who did not have polyhydramnios (Table 1).

2.4. Multivariate analysis

Of the 66 fetuses included in the final analysis, 26 had complete data elements which included the TFR, tumor morphology, presence of hydrops, placentomegaly and polyhydramnios. A multivariate analysis was performed on this cohort and none of the factors associated with poor prognosis were found to be an independent predictors. The accuracy of our multivariate analysis was limited by several missing data points, a consequence of the retrospective nature of the study.

3. Discussion

This current study validates the utility of TFR >0.12 prior to 24 weeks gestation as a predictor of poor prognosis in fetal SCT. In this large, multicenter series we found that TFR ≤0.12 prior to 24 weeks gestational age was associated with good prognosis in 91% of patients. This simple tool will aid in the triage of fetuses with SCT because TFR can be calculated using measures from fetal ultrasonography in most clinical settings. The TFR is therefore applicable for use not only predicting fetal outcomes in SCT but to help triage those with poor prognosis to fetal centers for fetal interventions that can be life saving. The results of our study demonstrate the importance of fetal intervention as half of the fetuses who had fetal intervention survived in the neonatal period thus highlighting the importance of these interventions. Interestingly, the