ORIGINAL ARTICLE

Solid Cancers in the Premature and the Newborn: Report of Three National Referral Centers

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Background: Advances in multidisciplinary care for pediatric cancer have resulted in significant improvement in cure rates over the last decades; however, these advances have not been uniform across all age groups. Cancer is an important cause of perinatal mortality, yet the full spectrum of malignant neoplasms in newborns is not well defined.
Methods: The authors have reviewed the clinical features and outcomes of 37 newborns with congenital malignant tumors treated at three referral centers in North, Central, and South Poland between 1980 and 2014. Event-free survival (EFS) and overall survival (OS) rates were estimated by Kaplan—Meier methods and compared using long-rank test and Cox models.
Results: Twenty-two patients were diagnosed prenatally. The most common diagnoses were neuroblastoma (48.7%), followed by malignant germ-cell tumor (16.2%), and Wilms' tumor (8.1%). Neuroblastoma was the most common malignancy among full-term infants, and malignant sacrococcygeal teratoma was the most common malignancy in premature infants. Thirty

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patients (81%) are alive with a median follow-up of 4.8 years from diagnosis. Patients with Wilms' tumor and malignant germ-cell tumors had the best outcomes (5-year OS 100% for both), whereas the worst prognosis was observed for sarcoma patients (5-year OS 72.92%). Premature infants had better outcome than full-term infants (5-year OS 92.8% vs. 72.58%, respectively).

Conclusion: Although rare, neonatal cancers can present with an aggressive clinical behavior, but they have a generally good outcome. Early diagnosis and management by expert multidisciplinary teams that integrate perinatal medicine experts with pediatric and surgical oncologists are critical. Centralized care with clear referral pathways that facilitate early initiation of specialized treatment should be prioritized.

1. Introduction

Cancer in newborns is rare, with an estimated incidence of 3.65/100,000 live births. Although most neonatal neoplasms are considered to have a benign behavior, malignant tumors represent a significant cause of perinatal mortality,[1−3] which may be related to obstetric or postnatal surgical complications, or disease progression.[4] With advances in obstetrical and perinatal care, including fetal imaging, an increasing proportion of these tumors can be identified prenatally, thus allowing for proper planning for delivery and postnatal care.[5] The prognosis is related to the tumor behavior, which may differ significantly between the perinatal period and later ages, suggesting a role for developmental biology factors.[1,6]

The care of newborns with malignant neoplasms requires a state-of-the-art multidisciplinary team that integrates the specialists involved in the care of high-risk pregnancies and newborns with pediatric oncology experts.[5] Herein, we report the experience of three centers providing multidisciplinary care for congenital malignant tumors in premature and neonatal patients in Poland.

2. Materials and methods

2.1. Patients and treatment

This retrospective study included 38 patients with perinatal malignant neoplasms (excluding mature teratomas) treated at three Pediatric Oncology Centers in Poland during the period 1980−2014 (Mother and Child Institute in Warsaw, Central Poland; Wrocław Medical University in Wrocław, South Poland; and Collegium Medicum, Nicolaus Copernicus University, in Bydgoszcz, North Poland). Treatment was conducted according to the existing disease-specific protocols and treatment guidelines, and it included a "watch-and-wait" approach, or different combinations of surgery, chemotherapy, and radiation therapy. All patients had standard imaging and histological procedures for diagnosis, staging, and follow-up. In the case of a prenatal diagnosis, fetal ultrasound (US) and magnetic resonance imaging (MRI) were performed as clinically indicated. "Total resection" was defined as a complete resection of the tumor without

macroscopic or microscopic residue, "gross resection" was defined as resulting in microscopic residue, and "subtotal resection" was defined as resulting in macroscopic residual disease. Approval for this retrospective study was obtained from all the relevant institutions in compliance with international regulations for protection of human research subjects.

2.2. Statistical methods

Overall survival (OS) was defined as the time interval from the date of diagnosis to the date of death or last follow-up. Event-free survival (EFS) was defined as the time interval from the date of diagnosis to the date of disease progression, recurrence, second malignancy, death, or date of last follow-up for patients without events. Results distributions were estimated using the Kaplan−Meier method. Factors were examined as predictors of OS using log-rang test. Values of $p \leq 0.05$ were considered significant. Statistical analysis was performed using STATISTICA 10.0 for Windows (StatSoft Inc., Tulsa, OK, USA).

3. Results

3.1. Patient characteristics and treatment

Between 1980 and 2014, 37 patients with congenital malignant neoplasms (mature and immature teratomas were excluded) were referred for treatment to the three oncology centers. The clinical and treatment characteristics are shown in Tables 1 and 2. The median gestational age at the time of delivery was 38 weeks (range 30−41 weeks); 14 patients (37.8%) were born preterm (<38 weeks). Four children were very low birth weight, born at 30−34 weeks of gestational age; three were low birth weight, born at 34−35 weeks of gestational age, one baby was hypertrophic, born at 35 weeks of gestational age, and the others were eutrophic newborns. All 21 cases diagnosed prenatally through standard screening US imaging were monitored weekly by US or MRI as clinically indicated, and an elective cesarean section was performed in 20 women due to rapid tumor growth (11 of them were premature births). Ten cases (out of 14) of preterm labor

Table 1 Patients' characteristics ($n = 37$).

Characteristics	n (%)
Sex	
Male	20 (54)
Female	19 (46)
Gestational age	
<38 wk	14 (37.8)
≥38 wk	23 (62.2)
Diagnosis	
Neuroblastoma	18 (48.7)
Germ-cell tumor	6 (16.2)
Wilms' tumor	3 (8.1)
Hemangiopericytoma	2 (5.4)
Infantile fibrosarcoma	2 (5.4)
Ewing's sarcoma	2 (5.4)
Brain tumor	1 (2.7)
Hepatoblastoma	1 (2.7)
Malignant mesenchymoma	1 (2.7)
Rhabdoid tumor	1 (2.7)
Stage of disease	
Metastatic	14 (37.8)
Localized	23 (62.2)
Median age at initial treatment (d)	4 (range 1—26)
Treatment	
Watch and wait	1 (2.7)
Surgery alone	13 (35.2)
Surgery + CHT	17 (45.9)
Surgery + CHT + RT	2 (5.4)
Surgery + CHT + RT + HSCT	1 (2.7)
CHT only	2 (5.4)
Refusal	1 (2.7)
Type of surgical procedure	
Biopsy	1 (3)
Gross resection	8 (24.2)
Subtotal resection	8 (24.2)
Total resection	16 (48.6)
Outcome	
Alive	30 (81)
Deceased	7 (29)

CHT = chemotherapy; HSCT = hematopoietic stem cell transplant; RT = radiation therapy.

patients were diagnosed prenatally, 20 of whom were delivered via cesarean section.

All 18 neuroblastoma cases had an abdominal primary tumor. Five patients had International Neuroblastoma Staging System Stages I/II, four patients had Stage IV, and nine patients had Stage IVs (among thirteen metastatic's patients 7 patients had metastases to the liver, 4 to the skin and liver, 1 only to the skin, and 1 to the skin, liver, and bone marrow). *MYCN* status was evaluated in all cases and was found to be amplified in three cases. *MYCN* amplification was defined as more than fourfold increase in signal relative to the number of chromosome 2 by fluorescence *in-situ* hybridization. Initial treatment included observation only for six patients, although chemotherapy was eventually administered to five of them due to progression. Seven patients were treated with surgery only, and eight had surgery and additional therapies (Table 1). Only seven of the 15 patients with neuroblastoma (46.7%) undergoing surgery achieved negative resection margins. Two patients with Stage IV were treated with chemotherapy only and died of disease progression. Three patients (2 Stage IVs and 1 Stage IV) underwent radiation therapy due to progression of liver metastases. The four patients with Stage IV disease were treated with intensive platinum-based regimens, and one patient received consolidation with high-dose chemotherapy and autologous hematopoietic stem cell transplant for *MYCN*-amplified disease. Of the three patients with *MYCN*-amplified disease, two died of disease progression and one is alive after receiving high-dose chemotherapy and autologous transplant. None of the patients received *cis*-retinoic acid or anti-GD2 therapy. Fourteen patients with neonatal neuroblastoma (77.8%) are alive with a median follow-up of 3.8 years from diagnosis (range 0.1—18.8 years). Three patients (2 Stage IV and 1 Stage II) died of disease progression, and one patient with Stage I died from postsurgical complications.

Of the six patients with a malignant germ-cell tumor, five had a sacrococcygeal primary tumor and one had a head and neck tumor; all had mixed GCT with component of yolk sac tumor histology. A complete resection was achieved in all cases; two of them had positive margins, and one relapsed and subsequently received chemotherapy (Table 1). In all cases, the alpha-fetoprotein levels were elevated for age at the time of diagnosis, but these declined appropriately and normalized after surgery. All six patients are alive with a median follow-up of 4.7 years from diagnosis (range 0.9—11.5 years).

All three patients with Wilms' tumor had localized disease at diagnosis, and one of them presented with hydrops fetalis. All three patients were treated with upfront surgery; two of them received adjuvant chemotherapy (1 for intermediate-risk histology and 1 for positive margins; Table 1). All patients are alive with a median follow-up of 1.3 years from diagnosis (range 0.5—6.8 years).

Eight patients were diagnosed with a congenital sarcoma. This group included two patients with hemangiopericytoma, one in the face and one in a limb; two with infantile fibrosarcoma of the limbs; two with Ewing's sarcoma, one in the face and one in a limb; one with an intra-abdominal malignant mesenchymoma; and one with malignant rhabdoid tumor of the kidney. Seven patients had localized disease at the time of diagnosis, and one patient

were due to obstetrician's choice after assessing risks; six cases were caused by the tumor (3 cases also had polyhydramnios), which implied preterm premature rupture of membranes; and in four cases the reason for preterm labor was not documented. The 16 children diagnosed postnatally were referred after detection of the tumor during standard neonatal evaluations by the primary care providers.

The most common diagnosis was neuroblastoma (48.7%), followed by malignant germ-cell tumor (mature and immature teratomas were excluded; 16.2%) and Wilms' tumor (8.1%). Of the 14 patients with metastatic disease, 13 (92.8%) had neuroblastoma. There were differences in diagnosis between premature and full-term infants; neuroblastoma was the most common malignancy among full-terms, and malignant sacrococcygeal tumors were the most common malignancy in premature infants. Twenty-one

Table 2 Patient characteristics and outcome by diagnosis.

Diagnosis	N	Stage	Median gestational age, wk (range)	Time of tumor detection prenatal/postnatal	Median age at treatment, d (range)	Outcome	Follow up in years (range)
Neuroblastoma	18	I/II (5 pts) IV (4 pts) IVs (9 pts)	38 (36–41)	2 (Stage IVs)/16	6 (1–25)	DOD 3 (Stage IV 2 pts, Stage I/II 1 pts) TRM 1 (Stage I/II 1 pts) NED 14	3.8 (0.01–18.8)
Germ-cell tumor	6	6 L	36 (30–38)	5/1	2.5 (1–5)	NED 6	4.7 (0.9–11.5)
Wilms' tumor	3	3 L	37 (32–40)	2/1	5 (3–26)	NED 3	1.3 (0.5–6.8)
Hemangiopericytoma	2	1 L 1 M	34 (31–37)	2/0	1.5 (1–2)	NED 2	5.9 (0.1–11.7)
Infantile fibrosarcoma	2	2 L	40 (40–40)	0/2	9 (2–16)	NED 2	5.4 (1.4–9.4)
Ewing's sarcoma	2	2 L	38.5 (37–40)	1/1	14.5 (9–20)	DOD 1 NED 1	1.53 (0.1–2.9)
Brain tumor	1	L	34	1/0	Refusal	DOD	0.01
Hepatoblastoma	1	L	37	1/0	5	NED	0.5
Malignant mesenchymoma	1	L	40	0/1	1	NED	8.6
Rhabdoid tumor	1	L	38	0/1	3	DOD	0.5

DOD = dead of disease; L = localized; M = metastatic; NED = no evidence of disease; pts = patients; TRM = treatment-related mortality.

with hemangiopericytoma had lung metastases. A watch-and-wait approach was adopted for two patients (1 infantile fibrosarcoma and 1 hemangiopericytoma), although both progressed and required surgery and chemotherapy. Only two of the eight patients with sarcoma (25%) undergoing surgery achieved negative resection margins. Six patients (75%) are alive with a median follow-up of 2.1 years from diagnosis (range 0.1–11.7 years). Two patients (1 patient with rhabdoid tumor and 1 patient with Ewing's sarcoma) died of disease progression.

One patient with hepatoblastoma was successfully treated with upfront chemotherapy, followed by complete resection, and for a primary brain tumor patient with radiological characteristics of supratentorial primitive neuroectodermal tumor (PNET), treatment was refused by the parents. This patient died within 1 week.

Overall, local control was performed in 33 patients (89.1%); in 13 patients (35.1%) as the only treatment, in 17 patients (45.9%) in combination with chemotherapy, in two patients in combination with chemotherapy and radiation therapy (5.4%), and in one patient in combination with chemotherapy, radiation therapy, and hematopoietic stem cell transplant (2.7%). Only 16 of the 33 patients (48.5%) undergoing surgery achieved negative resection margins. Only one patient with neonatal neuroblastoma had a spontaneous regression.

Complications in the premature babies can been divided into those resulting from preterm delivery and those caused by the tumor. Complications during delivery and postnatal period included respiratory insufficiency requiring oxygen supplementation for a group of infants, and administration of surfactant in two cases. Thirteen critically ill children (prematurity, upper and lower airway obstruction, and tract and abdominal compartment syndrome) required intubation and mechanical ventilation. One patient had hemodynamic instability caused by a highly vascularized large tumor (hemangiopericytoma), another patient had disruption of vascular flow to the lower extremities due to abnormal fetal placement (germ-cell tumor), and one patient presented hydrops fetalis (Wilms' tumor). Only one patient died due to multiple organ failure after surgery (neuroblastoma). Complications among term babies included one occurrence of pneumothorax (neuroblastoma), and three cases of secondary infections (2 neuroblastomas and 1 PNET).

3.2. Follow-up and outcome

Twelve patients (32.4%) had disease progression or relapse. Thirty patients (81%) are alive with a median follow-up of 4.8 years from diagnosis (range 0.1–18.8 years). The 5-year EFS and OS estimates were 61% and 80.38%, respectively (Figure 1). Patients with Wilms' tumor and germ-cell tumors had the best outcome, and the worst prognosis was observed in patients with sarcoma. The outcome for patients with neuroblastoma was not significantly different from all other patients (data not shown). Premature infants did better than full-term babies, although differences were not statistically significant. The 5-year EFS and OS estimates for premature infants were 77.9% and 92.8%, respectively, compared with 50.72% and 72.58% for full-terms, respectively. On univariate analysis, neither
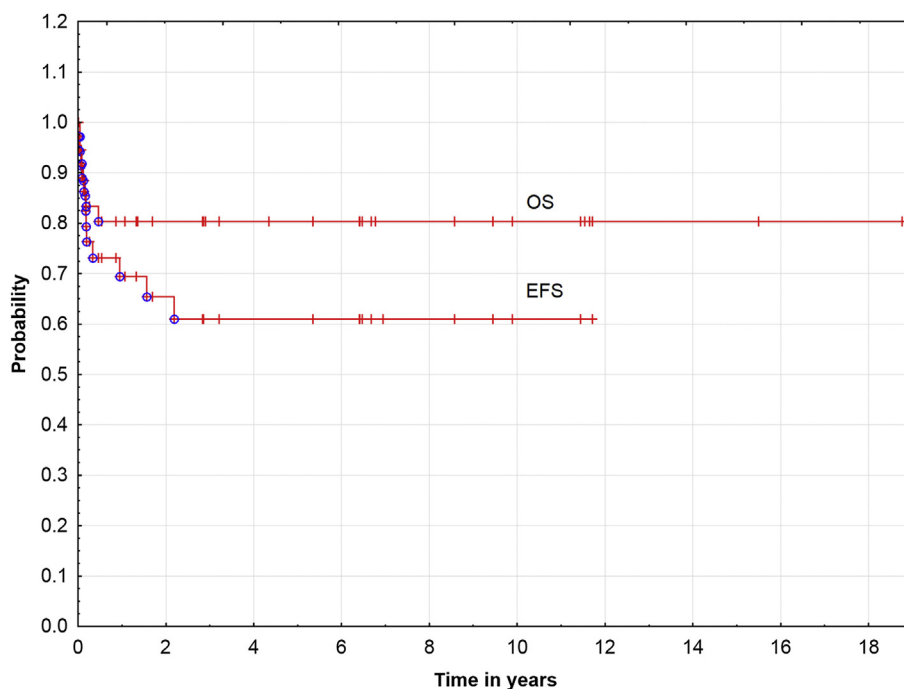
Figure 1 Kaplan—Meier curve of overall survival (OS) and event-free survival (EFS) for the study group.

gestational age nor surgical margins nor diagnosis was found to have prognostic significance (Table 3).

4. Discussion

Neonatal cancers are defined by their occurrence in an infant in the first 28 days after birth, or up to 44 weeks of gestational age in the case of preterm babies.[3] Our series confirms the previously published data, highlighting the fact that neonatal tumors differ in distribution from those occurring later in life. Solid malignancies account for approximately 75% of neonatal cancers, and given their rarity, their incidence patterns and outcomes are not well described.[1—5] For many of these tumors, such as low-risk

neuroblastoma or sacrococcygeal teratomas, outcomes have been described to be excellent; however, neonatal neoplasms often have a very aggressive clinical presentation that may precipitate rapid clinical deterioration of these vulnerable infants.[1,2,7—15] Complications during delivery or in the immediate newborn period due to the involvement of critical organs may result in significant morbidity and mortality unless a rapid diagnosis and plan of care is established. It is for this reason that it is of extreme importance to centralize care in experienced centers where multidisciplinary treatment is available. In our series, the patients seen at three referral centers represent half of the expected cases in Poland, highlighting the success in implementing this referral model. Furthermore, the low incidence of postnatal complications in our series further supports the need to implement referral networks.

Complications during delivery and the immediate postnatal period were relatively low; only two patients required administration of surfactant due to respiratory distress, a complication that needs to be anticipated in these infants.[14] Some children had oxygen administered because of prematurity and it was not conditioned by the tumor. In addition, caution should be exercised with regard to prenatal occurrence of Wilms' tumor, as infants may present with hydrops fetalis as did one of our cases.[2,11] It should be emphasized that a large-size tumor can disturb circulation and may also be the cause of local ischemia or as well as general circulatory disturbances, as was the case in two of our patients. Other complications reported in newborns with cancer include polyhydramnios, hypertension, or hypercalcemia.[11,16,17] In our series, polyhydramnios was the cause of cesarean section in three cases.

While our series is consistent with other published data, we contribute valuable information about the importance of dedicated multidisciplinary care for this vulnerable

Table 3 Univariate analysis of prognostic factors using log-rank test (n = 37).

	N	5-yr OS (%)	p	5-yr EFS (%)	p
Gestational age					
<38 wk	13	92.8	0.171	77.9	0.061
≥38 wk	23	72.58		50.72	
Surgical margins					
Positive	17	94.11	0.263	55.21	0.263
Negative	16	80.3		76.98	
Histology					
Neuroblastoma	18	76.76	NS	55.11	NS
Germ-cell tumor	6	100		60	
Sarcoma	8	72.92		58.34	
Wilms' tumor	3	100		100	

EFS = event-free survival; NS = not significant; OS = overall survival.

population. Between 1980 and 1999, only four newborn infants were referred to the three tertiary centers, whereas after 2000, thanks to the cooperation of gynecologists, obstetricians, surgeons, and oncologists, we implemented a referral system and more than 30 children were referred, with a significantly improved outcome.

Germ-cell tumors and neuroblastoma are the most common malignant solid neoplasms in the newborn period, followed by soft-tissue sarcoma, renal tumors, brain tumors, and leukemia.[3,13,16,18] This distribution was confirmed in our series, although we had a higher proportion of neuroblastomas, probably resulting from the exclusion of mature and immature teratomas. Brain and hematologic malignancies are also underrepresented in our series, owing to the established referral patterns in Poland.

Importantly, our series shows that although neonatal tumors present as rapidly growing neoplasms, their ultimate behavior differs from their older counterparts, accounted by differences in biology. This is exemplified by the distinct clinical course of neuroblastoma during infancy; more than 70% of our cases had metastatic disease, and yet their outcome was excellent. This is a well-known phenomenon for Stage IVs neuroblastoma; however, expert management of those patients is critical because rapidly enlarging liver metastases may result in significant respiratory and hemodynamic compromise.[8,10] A similar phenomenon is seen in infantile sarcomas, such as hemangiopericytoma and fibrosarcoma; these high-grade sarcomas are known to present with very aggressive and rapidly growing soft-tissue masses that have often been treated with radical, mutilating surgeries.[6,7,9] However, infantile hemangiopericytoma, like infantile fibrosarcoma, is characterized by better clinical behavior, with documented chemoresponsiveness and spontaneous regression, and it requires a more conservative surgical approach.[6,7,19] This was confirmed in our series, where three of four children were successfully treated with subtotal surgery and chemotherapy. Again, early recognition and rapid referral to an expert center is necessary to provide risk-adapted therapies and minimize long-term, irreversible organ damage. By contrast, other sarcomas such as Ewing's sarcoma and rhabdoid tumors do have a more aggressive behavior necessitating intensive multidisciplinary sarcoma treatments.[6,20]

Our report also underlines the importance of selecting a conservative surgical approach. While complete surgical resection of these tumors is the mainstay of treatment, efforts must be made to avoid the use of radical and mutilating procedures. In our series, more than half of the patients undergoing surgery had positive resection margins; this is commonly associated with a very high risk of relapse in solid tumor oncology, yet only two patients in this group died of disease. This highlights the importance of selecting the most appropriate surgical approach based on the knowledge of the natural history of each malignancy; a conservative, nonradical approach is appropriate for infantile fibrosarcoma, infantile hemangiopericytoma, and neuroblastoma,[6,7,9,10] whereas a more radical procedure is required for most renal, brain, and liver tumors, as well as other sarcomas.[11,12,21,22]

In summary, neonatal solid tumors represent a small group of malignancies that typically present with an aggressive clinical behavior; however, their outcome is generally favorable, owing to their unique biological features. Early diagnosis and management by expert multidisciplinary teams that integrate perinatal medicine experts with pediatric and surgical oncologists with knowledge of the natural history of each disease are critical for the outcome of these patients. Centralized care with clear referral pathways that facilitate early initiation of specialized care should be implemented.

Conflicts of interest

Nothing to declare.

Acknowledgments

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