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Pattern and Outcome of Neurological Complications During the Treatment of Pediatric Acute Leukemias in Upper Egypt

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Abstract

Background: Despite the treatment progress of acute leukemias, neurological complications (NCs) can occur and may have a detrimental impact on the outcome.
Aim: To study the pattern and outcome of NCs occurring during treatment of pediatric acute leukemias in Upper Egypt and to study possible factors influencing their outcomes.
Methods: Children with AL who developed NCs during treatment were included. Patients with central nervous system (CNS) infiltration at diagnosis and those with any neurological insults before diagnosis were excluded. Data were retrospectively collected from patient files and included NCs, their outcome, and possible associated factors.
Results: Neurological complications occurred in 89 out of 537 (16.6%) reviewed patients. Age was ≥ 10 years in 47.2% of patients, acute lymphoblastic leukemia was the most common diagnosis (77.5%) and the majority (77.9%) were classified as high-risk. Almost half of the patients suffered from NCs during the induction phase of treatment. Motor deficits and seizures were the most frequent manifestations. Neurovascular causes and peripheral neuropathy constituted 27% and 21.3% of the etiology. Other causes included CNS relapse (19.1%), seizures due to systemic causes (13.5%), CNS infections (12.4%), and leukoencephalopathy (6.7%). The treatment phase and recovery time differed significantly according to the type of NCs. The outcome of NCs was complete recovery in 67.4% of the patients, incomplete recovery in 7.9%, and no recovery and death in 24.7%. The etiology of NCs was the only factor that had a significant correlation with the outcome of the patients.
Conclusions: Neurological complications during treatment occur in a significant proportion of pediatric patients with acute leukemia in South Egypt. Neurovascular causes and peripheral neuropathy are the most common NCs, and CNS hemorrhage is the most fatal. Supportive measures for these NCs must be optimized to improve outcome.

Keywords: Acute leukemia, Neurological complications, Pediatric, Treatment, Upper Egypt

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Introduction

Acute leukemias in children constitute 97% of all childhood leukemias, of which 75% are acute lymphoblastic leukemia (ALL) and 20% are acute myeloid leukemia (AML). Other rare types of acute leukemia include acute mixed-lineage leukemia (AMLL) and acute undifferentiated leukemia [1]. Acute lymphoblastic leukemia represents the most common cancer in children < 14 years old, accounting for 25.4% of all cancer diagnoses [2]. The treatment progress; through improved diagnostic tools, risk stratification, intensification of treatment, and improved supportive care; has improved the prognosis for children with ALL and AML in recent years [3-5]. Part of the success in the treatment of ALL

is the introduction of the central nervous system (CNS) directed therapy through the systemic application of chemotherapeutic agents with adequate penetration into the CNS (high-dose methotrexate [HDMTX], dexamethasone and high-dose cytarabine), frequent intrathecal chemotherapy administration with methotrexate alone or in combination with other drugs (cytarabine or corticosteroid) with or without cranial irradiation [6]. Despite this progress in treatment, acute complications can occur that affect various systems.

Neurological complications (NCs) during treatment can occur from leukemic involvement of the CNS, treatment (chemotherapy or radiation), coagulation disorders causing cerebrovascular complications, infectious complications as a result of suppressed immunity, and other systemic conditions [7, 8].

Many chemotherapeutic agents commonly used in the treatment of acute leukemia contribute to neurologic toxicity. Vincristine, one of the vinca alkaloids, produces acute peripheral neuropathy through microtubule impairment, through loss of axon transport function, altered ion channels, and neuroinflammation [9]. Asparaginase and steroids are associated with thromboses, including dural sinus thrombosis (DST) [10]. High-dose methotrexate and cytarabine can induce leukoencephalopathy [11].

Neurological complications have a direct detrimental impact on the outcome of pediatric acute leukemias (immediate mortality, neurologic sequelae such as epilepsy or mental / motor retardation that interferes with quality of life) or an indirect impact through the interruption of treatment protocols and dose modification [9, 12, 13]. This study was conducted to find out the pattern and outcome of NCs that occur during treatment of pediatric acute leukemia at South Egypt Cancer Institute with analysis of the factors that may influence their outcome.

Methods

This retrospective observational study included children treated for acute leukemia at the Department of Pediatric Oncology, South Egypt Cancer Institute (SECI), Assiut University in the period from May 2011 to June 2018.

Patients

The study included pediatric patients (≤18 years) with acute leukemia who developed any neurological insult during their treatment. Patients with leukemic infiltration at diagnosis of acute leukemia, neurological insults before diagnosis (e.g., Down syndrome or epilepsy), or late-onset encephalopathy were excluded.

The diagnosis of acute leukemia was based on morphological, cytochemical, and immunophenotypic (IPT) analysis of bone marrow aspiration from patients according to WHO 2008 classification [14]. Patients with ALL were stratified according to National Cancer Institute (NCI)/ Rome criteria into standard risk and high risk [15]. Patients with AML or AMLL were considered high-risk patients and were exposed to intensive treatment.

Patients with ALL were treated according to modified Total Therapy study XIIIB adopted from St. Jude Children's Research hospital (SJCRH) for higher risk that included prophase of four days steroid then induction phase with six drug regimens (vincristine, prednisone or dexamethasone, asparaginase, daunorubicin, cytarabine, and etoposide) for 29 days [16]. Patients who achieved complete remission progressed to the consolidation phase with two doses of HDMTX (2gm / m^2 / 2hs infusion), then to the continuation phase (120 weeks) for higher risk consisted of drug pairs administered in weekly rotation with repetition of the chemotherapeutic agent s (vincristine / dexamethasone were received monthly, HDMTX was received every two months). The reinduction phase was started at week 16 with the same regimen as in induction of remission.

Patients with AML were treated according to a protocol modified from MRC12 [17]. Two cycles of ADE consisted of a three-drug regimen (daunorubicin, cytarabine, and etoposide) were received in the induction phase. This was followed by two to three cycles of consolidation with the following drugs; cytarabine, etoposide, mitoxantrone, and asparaginase.

Patients with AMLL leukemia were treated with combinations of the previous two protocols, started by induction and consolidation as AML, and continue with the maintenance treatment of ALL. Intrathecal injection of methotrexate, corticosteroids, and cytarabine wasdded to all patients as a CNS preventive therapy according to their risk.

Data collection

Data collected from patients' files included age, sex, diagnosis of leukemic type, treatment phase, neurological manifestations, and investigations

done for defining the etiology of each neurologic insult.

Definition of neurologic insults

Motor deficits are referred to as one or more limb weakness due to upper motor neuron lesion (UMNL) and / or lower motor neuron lesion (LMNL). Motor deficits due to UMNL were paraplegia, quadriplegia, and hemiplegia. The motor deficits due to LMNL were peripheral neuropathy and radiculopathy. The weakness of the muscles supplied by the cranial nerves was classified as cranial nerve palsy. Patients with mixed deficits presented with two or more of the following neurologic manifestations: seizures, altered consciousness, headache, motor deficit, and affection for the cranial nerve.

The diagnosis of intracranial hemorrhage (ICH), DST and posterior reversible ischemic encephalopathy (PRES) depended on imaging findings and symptoms and is defined here as neurovascular complications.

Seizures associated with systemic or undefined neurologic etiology were collectively defined as 'seizure due to systemic causes'. These conditions included metabolic / electrolyte disturbance, sepsis, or multifactorial etiology.

Neurological manifestations due to CNS leukemic infiltration were included in the analysis.

Outcome of the neurological complications

Reviewing of the patients' files for the outcome of the neurologic insults during the study period within a minimum duration of one year after the NC occurrence was also done. The outcome was determined by the clinical, laboratory, and imaging findings during the follow-up of the patients. Patients were categorized according to the outcome of the NCs into three groups; group 1 included patients who achieved complete clinical, laboratory, and radiological recovery and still alive, group 2 included those with incomplete or stationary manifestations and still living. Patients who didn't achieve complete recovery and died of their NCs represented in group 3.

A study of the factors that may affect the outcome of patients (age, sex, diagnosis, IPT, risk stratification and timing of the insult) was performed. In addition, we analyze the possible relationship between the outcome and the etiology of neurological insult.

Statistical analysis

IBM SPSS Statistics for Windows, Version 20.0. (Armonk, NY: IBM Corp.) was used for data management. Numerical data were described with median and range and categorical with number and percentage. A Chi-square or Fisher's exact test was used for testing proportion independence and nominal data of different groups in the study, while t-test was used in case of continuous data. The *p*-value was always two-tailed and significant at the 0.05 level.

Results

Eighty-nine out of 537 total pediatric patients with acute leukemia (16.6%) developed NCs during their treatment. The complications of the CNS constituted 70 (13%) while peripheral neuropathy (PN) constituted 19 (3.6%).

The median age of the studied group was 9 years (range: 1 to 18), with a male to female ratio of 1.3:1. Nearly half of patients were more than 10 years old (47.2%). Most patients (77.5%) had ALL a minority were diagnosed with AML and AMLL (18% and 4.5% respectively). Patients stratified as high risk constituted 77.9%. Almost half of the patients suffered a NC during the induction phase of treatment and 32.6% during the maintenance phase. Motor deficits and seizures were the most frequent neurological manifestations, reported in 27% and 25.8% of the patients, respectively, followed by altered consciousness and headache in 22.5% and 21.4%, respectively. The other demographic data and clinical characteristics are shown in Table 1.

Neurovascular complications constituted 27% of the etiology mainly ICH in 12.4%, followed by PN in 21.3% of patients (17 toxic and 2 infectious and post-infectious). Other causes included CNS relapse (19.1%), seizures due to systemic causes (13.5%), CNS infections (12.4%), and leukoencephalopathy (6.7%). The relationship between NCs and patient characteristics is shown in Table 2.

Regarding seizures due to systemic causes, the seizures occurred during induction and reinduction therapy and were associated with sepsis and electrolyte disturbance mainly hypocalcemia, and only one patient developed seizures after AML consolidation due to hyponatremia and hypocalcemia. The treatment phase was significantly associated with the cause of NCs (P= 0.013). CNS relapse was reported primarily during the maintenance phase of treatment, while seizures due to systemic causes (13.5%), PN (21.3%), and ICH (12.4%) were reported mainly in the remission induction phase (P=0.013). Furthermore, recovery time was significantly different according to the type

of NC (P = 0.001), with a shorter time of recovery was reported for patients with seizures due to systemic causes (1.5 weeks), and CNS relapse (2 weeks) while the longest recovery duration to recovery was reported among patients with PN and PRES (8 and 6 weeks, respectively).

Regarding the imaging done for the diagnosis; when PRES or leukoencephalopathy was suspected, it was found that the computerized tomography (CT) scan was not helpful for diagnosis. Both CT and magnetic resonance imaging (MRI) were performed on four patients with PRES in our study and showed abnormal findings on MRI only while CTs showed no abnormalities. The same for leukoencephalopathy, where both CT and MRI were done for 3 patients and abnormality was detected by MRI only. On the contrary, CNS relapse and ICH were recognized easily by CT scan. Both types of images were performed for two patients with CNS relapse and showed abnormalities in both. In ICH, baseline CT was performed for 8 patients and showed abnormalities in all of them.

Associated symptoms were fever (40.4%) mainly with ICH, systemic causes and CNS infections, hypertension (42.7%) with all CNS complications except systemic causes, tachypnea (15.7%) and tachycardia (29.2%) with ICH and systemic causes, and hypernatremia (12.4%), hypokalemia (27%) and hypocalcemia (24.7%) represented 91.7% of systemic causes. Visual disturbances were found in 13 patients; 6 of them were diagnosed as PRES.

Regarding laboratory findings, elevated liver enzymes (25.8%) and kidney function tests (9%) were reported mainly in patients with ICH. A coagulation profile was available in 46 patients, and abnormalities were detected in 21.4% of the patients, mainly with ICH, PRES, and systemic causes. Hyperleukocytosis (≥100,000) was reported at the time of presentation with the neurologic complication in four patients, three of them had ICH. Leukopenia was found in 51.7% of patients, neutropenia (count <500 cell/ ul) in 30.3%, anemia (hemoglobin <8g/dl) in 3.4% and thrombocytopenia (platelets <100000 cells / ul) in 35.9%, mainly in patients with ICH. Hyper- or hypoglycaemia was not reported in any patient during the study period.

At the time of analysis, 60 (67.4%) of patients achieved complete recovery and were alive (group 1) ,7 (7.9%) achieved incomplete recovery (groups 2) and 22 (24.7%) patients died (group 3). The relationship between the outcome of NCs and their etiology and the other characteristics is shown in Table 3. Only the etiology of NCs was significantly associated with the outcome of NCs. All patients with PRES and DST achieved complete recovery, while one third of patients with seizures, CNS infections, and ICH collectively did not achieve recovery and died.

Table 1: Demographic and clinical characteristics of 89 children with acute leukemia

Characteristic	*n* (%)
Age (years)	
<10	47 (52.8)
≥ 10	42 (47.2)
Sex	
Male	50 (56.2)
Female	39 (43.8)
Diagnosis	
Acute lymphoblastic leukemia	69 (77.5)
Acute myeloid leukemia	16 (18)
Acute mixed lineage leukemia	4 (4.5)
Immunophenotyping	
B-cell acute lymphoblastic leukemia	46 (51.7)
T-cell acute lymphoblastic leukemia	23 (25.8)
Acute myeloid leukemia / Acute mixed lineage leukemia	20 (22.5)
Risk group	
Standard risk	20 (22.5)
High risk	69 (77.6)
Treatment phase	
Induction	46 (51.7)
Consolidation	5 (5.6)
Maintenance	29 (32.6)
Re-induction	9 (10.1)
Neurological manifestations	
Seizures	23 (25.8)
Headache	19 (21.4)
Altered consciousness	20 (22.5)
Motor deficits	24 (27)
Upper motor neuron lesion	2 (2.25)
Lower motor neuron lesion	19 (21.35)
Mixed motor deficits	3 (3.37)
Cranial nerve affection*	1 (1.1)
Mixed deficits*	18 (20.2)
	Median (range)
Time to recovery (weeks)	4 (1-24)

*Facial nerve paresis was the cranial nerve among our studied cases, alone or in mixed deficits.

Discussion

Neurological complications are relatively common adverse events during the treatment of cancer. Nearly 17% of pediatric patients with acute leukemia in this study suffered from NCs during their treatment, mainly in the form of neurovascular complications and peripheral neuropathies. Most NCs occurred during the remission induction phase. Acute lymphoblastic leukemia constituted 77.5% of our studied patients. Also, among different studies that reported NCs among patients with acute leukemia, patients with ALL were the major contributor [13, 18]. The prevalence of NCs in pediatric patients with hematologic malignancies varied markedly between studies and ranged from 3% to 26.6% [8, 12, 13, 19, 20]. This wide range of difference is attributed to the inclusion criteria, treatment protocols, and diagnostic criteria or definition / identifications of such insults that makes the comparison difficult.

We noticed that most of the patients included in the study were stratified as high risk (77.2%). In addition, almost half of the patients studied were older age. The response to treatment of these

Table 2: The relationship between neurological complications and characteristics of 89 children with acute leukemia

Characteristic	CNS relapse *n*=17 (19.1%)	Posterior reversible encephalopathy syndrome *n*=7 (7.9%)	Intracranial hemorrhage *n*=11 (12.4%)	Dural sinus thrombosis *n*=6 (6.7%)	Leukoencephalopathy *n*=6 (6.7%)	Peripheral neuropathy *n*=19 (21.3%)	CNS infection *n*=11 (12.4%)	Seizures due to systemic causes *n*=12 (13.5%)	*p* value
	n (%)								
Age (years)									
<10 years	6 (12.8)	5 (10.6)	5 (10.6)	3 (6.4)	4 (8.4)	11 (23.4)	6 (12.8)	7 (14.9)	0.194
≥10 years	11 (26.2)	2 (4.8)	6 (14.3)	3 (7.1)	2 (4.8)	8 (19)	5 (11.9)	5 (11.9)	
Sex									
Male	14 (28)	4 (8)	3 (6)	4 (8)	3 (6)	12 (24)	4 (8)	6 (12)	0.132
Female	3 (7.7)	3 (7.7)	8 (20.5)	2 (5.1)	3 (7.7)	7 (17.9)	7 (17.9)	6 (15.4)	
Diagnosis									
ALL	17 (24.6)	6 (8.7)	4 (5.8)	4 (5.8)	6 (8.7)	18 (26.1)	9 (13)	5 (7.2)	0.718
AML	0	1 (6.3)	6 (37.5)	1 (6.3)	0	1 (6.3)	2 (12.5)	5 (31.3)	
AMLL	0	0	1 (25)	1 (25)	0	0		2 (50)	
Immuno-phenotyping									
B-cell ALL	10 (21.7)	5 (10.9)	3 (6.5)	1 (2.2)	4 (8.7)	13 (28.3)	7 (15.2)	3 (6.5)	0.4
T-cell ALL	7 (30.4)	1 (4.3)	1 (4.3)	3 (13)	2 (8.7)	5 (21.7)	2 (8.7)	2 (8.7)	
AML / AMLL	0	1 (5)	7 (35)	2 (10)	0	1 (5)	2 (10)	7 (35)	
Risk group									
Standard	4 (20)	3 (15)	0	1 (5)	1 (5)	5 (25)	5 (25)	1 (5)	0.272
High	13 (26.5)	4 (11.1)	11 (43.2)	5 (16.1)	5 (10.2)	14 (31.5)	6 (18.2)	11 (43.2)	
Treatment phase									
Induction	0	5 (71.4)	8 (72.7)	6 (100)	3 (50)	9 (47.4)	5 (45.5)	9 (75)	0.013
Consolidation	1 (5.9)	0	1 (9.1)	0	0	1 (5.3)	1 (9.1)	1 (8.3)	
Maintenance	15 (88.2)	2 (28.6)	1 (9.1)	0	2 (33.3)	6 (31.6)	4 (36.4)	0	
Re-induction	1 (5.9)	0	1 (9.1)	0	1 (16.7)	3 (15.7)	1 (9.1)	2 (16.7)	
	Median (range)								
Time to recovery (weeks)	2 (1-4)	6 (1-8)	5 (1-8)	5 (4-24)	2.8 (0.5-12)	8 (1-24)	3 (1-12)	1.5 (1-4)	0.001

CNS: Central nervous system, **ALL**: Acute lymphoblastic leukemia, **AML**: Acute myeloid leukemia, **AMLL:** Acute mixed lineage leukemia

Table 3: The relationship between the outcome of neurological complications and the studied variables

Variable	Outcome			*p* value
	Group 1 (Complete recovery)	**Group 2** (Incomplete recovery)	**Group 3** (No recovery / death)	
Age (years)				
<10	35 (74.5)	4 (8.5)	8 (17)	0.1
≥ 10	25 (59.5)	3 (7.1)	14 (33.3)	
Sex				
Male	33 (66)	3 (6)	14 (28)	0.595
Female	27 (69.2)	4 (10.3)	8 (20.5)	
Diagnosis				
Acute lymphoblastic leukemia	46 (66.7)	6 (8.7)	17 (24.6)	0.814
Acute myeloid leukemia	11 (68.8)	1 (6.3)	4 (25)	
Acute mixed lineage leukemia	3 (75)	0	1 (25)	
Immunophenotyping				
B-cell acute lymphoblastic leukemia	35 (76.1)	2 (4.3)	9 (19.6)	0.354
T-cell acute lymphoblastic leukemia	11 (47.8)	4 (17.4)	8 (34)	
Acute myeloid leukemia / Acute mixed lineage leukemia	14 (70)	1 (5)	5 (25)	
Risk group				
Standard risk	16 (80)	0	4 (20)	0.251
High risk	44 (63.8)	7 (10.1)	18 (26.1)	
Etiology				
Peripheral neuropathy	14 (73.7)	5 (26.3)	0	0.022
Central nervous system relapse	7 (41.2)	0	10 (58.8)	
Seizures due to systemic causes	8 (66.7)	0	4 (33.3)	
Central nervous system infections	8 (72.7)	1 (9.1)	2 (18.2)	
Intra-cranial hemorrhage	6 (54.5)	0	5 (45.5)	
Posterior reversible encephalopathy syndrome	7 (100)	0	0	
Dural sinus thrombosis	6 (100)	0	0	
Leukoencephalopathy	4 (66.3)	1 (16.7)	1 (16.7)	
Treatment phase				
Induction	34 (73.9)	2 (4.3)	10 (21.7)	0.683
Consolidation	3 (60)	0	2 (40)	
Maintenance	17 (58.6)	4 (13.8)	8 (27.6)	
Re-induction	6 (66.7)	1 (11.1)	2 (22.2)	

receive more intensified treatment including additional asparaginase, intrathecal, or radiotherapy. Several studies on CNS complications revealed that these complications are more common in older patients with T-cell ALL who received intensified treatment [7, 19, 21].

The NCs occurred more often during the induction phase in most studies and ranged from 29% to 57% [8, 12, 19]. Many factors contribute to the higher incidence of NCs during remission induction; the disease effect, the use of intensive combined neurotoxic chemotherapy (vincristine, L-asparaginase, steroids, and intrathecal injections), and the use of other intensive chemotherapeutic agents that cause severe leucopenia / thrombocytopenia. Therefore, NCs may be multifactorial with difficulty differentiating chemotherapy-induced NCs from other causes [22].

Peripheral neuropathies are frequent adverse events. They represent the most frequent cause of interruption of treatment protocols and dose modification that led to worsening treatment outcome [9]. In spite of nearly similar chemotherapeutic regimens, the prevalence of PN varies widely among studies. Peripheral neuropathy represented 21.3% of NCs in this study, which is close to the 30% and 41.2% prevalence in other studies [20, 23]. On the other hand, PN was an infrequent complication (5% and 10%) in other studies [13, 22]. This wide variation in the prevalence of PN may be due to the existence of risk factors for the development of PN in patients receiving chemotherapy such as increased body mass index,

uncontrolled diabetes, vitamin B deficiencies, preexisting infections (Epstein-Barr virus, hepatitis B/C, HIV), autoimmune diseases (rheumatoid arthritis, lupus), kidney, liver, or thyroid disorders and family history of neuropathy [9, 24]. Five patients out of the 19 patients with PN showed a stationary course and recovery of the other patients occurred within a median of 8 weeks (1- 24) which differs from what Rahman et al, that all patients with PN recovered within 10 days [23]. We did not find a significant difference in clinical criteria between patients who recovered and those who did not show recovery. This can be explained by the presence of the risk factors mentioned above. Being a retrospective study, we couldn't identify these risk factors.

Intracranial hemorrhage was the most frequent neurovascular complication in our study and constituted 12.4% of all NCs. Verma et al, reported a high frequency of ICH (24.4%) among children with hematological malignancies [13]. One of the mechanisms of occurrence of neurovascular events in children with malignancy is the presence of hyperleukocytosis due to hyperviscosity and leukostasis. The occurrence increased if it's associated with a platelet count <20,000/mm^3. Consequently, platelet transfusion is mandatory in this situation to prevent cerebral hemorrhage [25]. Kong et al, reported that ICH occurred significantly more often in patients with extreme hyperleukocytosis [26]. In addition, Intusoma et al. concluded that hyperleukocytosis is associated with a high risk of early ICH [21]. In the current study, hyperleukocytosis and thrombocytopenia were found in 4 patients at the time of neurologic insult, 3 of them were ICH.

Central nervous system relapse and ICH were the most fatal complications in our study, contributing to 45.5% and 22.7% of mortality. Verma et al. reported a very high mortality rate among children with ICH, thrombosis, or CNS involvement with 24% and 7.3% of their mortality being related to neurovascular complications and CNS leukemia, respectively [13].

In conclusion, neurovascular complications and peripheral neuropathy are the most common NCs. Significant risk factors for the occurrence of these NCs couldn't be assessed as comparison with patients with no NCs is needed. Intracranial hemorrhage was more common among patients with AML and those with hyperleukocytosis especially if it was associated with thrombocytopenia. More studies are needed to confirm the significant association. Central nervous system relapse and ICH were the most fatal complications in our study.

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Authors' contribution

Conception or design: HAS, RMH & AS; Acquisition, analysis or interpretation of data: All authors; Drafting or revising the manuscript: All authors; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

The deidentified datasets used and/or analyzed during the current study are available from the corresponding author (AS) on reasonable request.

Ethical considerations

This study was approved by the Institutional Review Board of South Egypt Cancer Institute, Assiut University, Assiut, Egypt (approval No.: 224).

An informed written consent was taken from patients' parents or guardians.

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Study registration

Not applicable.

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