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ORIGINAL ARTICLE

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Long-term follow-up of cancer in neonates and infants: a national survey of 142 patients

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Abstract To determine the mortality and survival rates, side effects of surgery and adjuvant chemo- and radiotherapy, somatic development, and fertility, the data of 142 patients under the age of 1 year operated upon for solid malignant tumors from 1975 through 1983 were analyzed. The follow-up period ranged from 16 to 25 years (mean 20); 79 patients survived. The male/female ratio of the survivors was 51/28. Investigations were based on the Hungarian Tumor Registry, personal interviews with the patients and their parents, and detailed questionnaires. Fifty-one patients died, 44 of them before the age of 3 years; 13 were lost to follow-up. Of the 79 survivors, 48 had abdominal and 31 extra-abdominal tumors (35 neuroblastomas, 21 renal tumors, 15 soft-tissue sarcomas, 5 gonadal tumors, 2 sacrococcygeal carcinomas, 1 hepatic tumor). Side effects of surgical intervention included partial urinary incontinence (2), partial fecal incontinence (1), intestinal obstruction (2), nerve injury (1), thorax deformity (4), and scar formation resulting in psychological problems (12). Chemotherapy alone (41 patients) resulted in side effects in 19 patients, radio- and chemotherapy in combination (23) caused side effects in 20. Fifteen patients did not receive adjuvant therapy. The most serious late side effects were 24 spinal deformities, one-half of them severe, breast underdevelopment, muscular deformity, and renal damage. In 19 patients more then one side effect was detected. Height and weight gain decreased ($P < 0.01$ and < 0.05, respectively) in the first 8–10 years of follow-up and accelerated significantly ($P < 0.05$ and < 0.05, respectively) in the second half of follow-up. The short follow-up time (16–25 years) permitted only limited analysis of infertility. Whenever possible, surgical excision should be the treatment of choice. No routine aggressive chemotherapy is indicated. Radiation therapy, which frequently results in long-term musculoskeletal morbidity, should be avoided. Catch-up somatic development occurred in the second part of the follow-up period.

Keywords Malignant tumors in neonates · Long-term follow-up

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Introduction

Infantile, but mainly neonatal, tumors differ in type, incidence, natural history, and response to therapy from apparently similar tumors in older children [9, 10, 20, 24–26, 28, 33]. Some tumors that by all criteria appear to be malignant can regress spontaneously, e.g., stage IV-S neuroblastoma (NB). Others are clearly benign, but because of their size and localization can be life-threatening, e.g., hemangioendotheliomas of the liver. Other initially benign tumors can undergo malignant transformation, e.g., sacrococcygeal teratomas. An intermediate group has some malignant characteristics, such as infiltrative growth, but do not metastatize, e.g., fibrous tumors or fibromatoses, and are indistinguishable from fibrosarcoma. In several cases there is a clear distinction between histologic malignancy and favorable clinical outcome. The response to therapy of these tumors is often age-related and more favorable than in older children and adults.

Over the last 3 decades there has been a substantial and significant improvement in survival from most forms of childhood cancer, including neonatal and infantile malignancies [4, 9, 10, 20, 25, 29, 31, 34, 35]. However, some types of therapy that contribute to the improved survival can also cause serious late sequelae resulting in unacceptable morbidity and mortality. Therefore, long-term follow-up should be co-ordinated from specialized oncologic centers so that problems can be anticipated and treated.

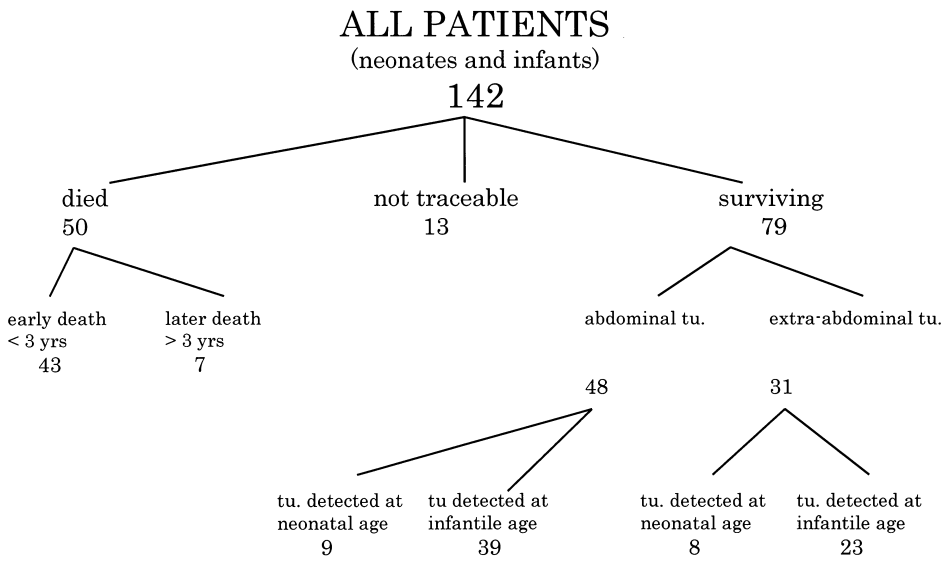

Fig. 1 Clinical data of all patients studied

Awareness of possible long-term complications is not only important in maximizing the eventual health of current survivors, but also for modifying future protocols to avoid late complications and consequences of (multimodal) anticancer therapy such as physical, educational, and psychological disabilities. There have been insufficient followup data to answer important questions regarding the most effective and least toxic forms of treatment in childhood, mainly in the neonatal and infantile age group [7, 19, 20, 23, 25, 29, 32, 33, 35].

This publication will discuss our experience of late sequelae of treatment in patients operated upon for malignancies as neonates or infants during a 9-year period in Hungary. Hungary has a relatively stable population of 10 million, all of whom are covered by the National Health Service. Cancer in Hungary is a notifiable disease, and all children with neoplasms must be referred to one of the tumor centers. Analysis of the mortality and survival, late side effects of surgical interventions and adjuvant chemo- and radiotherapy, somatic development (height and weight), and fertility was carried out.

Materials and methods

During the 9-year period from 1 January 1975 through 31 December 1983, the data of 142 patients operated upon for solid malignant tumors in Hungary under the age of 1 year were studied. Patients younger than 29 days were considered neonates and those younger than 12 months infants. Retinoblastomas and malignancies of the central nervous system were excluded from the study. Mesoblastic nephroma, a congener of Wilms' tumor (WT) (3 patients) was grouped with renal neoplasms. All diagnoses were histologically verified in the tumor centers where autopsies of patients were compulsory. Investigations were based on the Hungarian Tumor Registry, regular personal interviews with the patients and their parents, and detailed questionnaires that were sent to the parents three times during follow-up, which ranged from 16 to 25 years (mean 20). The male/female ratio of the surviving 79 patients was 51/28.

Table 1 Localization of malignancies in surviving patients (n = 79)

Location	No. of patients
Abdominal incl. pelvic	48
Extra-abdominal	31
Head	3
Thoracic	11
Trunk	7
Extremities	4
Genital	6

Growth data (height and weight) were analyzed using standardized growth charts. Statistical analysis was performed with the use of X^2 analysis and Student's t-test for paired groups using two-tailed comparisons, with P-values less than 0.05 considered statistically significant. Fertility was analyzed by asking the patients whether they had children or, if they did not, whether they desired to have them.

The clinical data of all patients are listed in Fig. 1. Of the 79 surviving patients, 17 were diagnosed in the neonatal and 62 in the infantile age group. The localization of the malignancies in the 79 surviving patients is shown in Table 1, the long-term survival according to diagnosis in Table 2.

Results

The mortality according to diagnosis is detailed in Table 3. NB ranked first, followed by renal and soft-tissue tumors. In the 7 patients over 3 years of age (Fig. 1, death was related to the malignancies (2 WT, 2 NB, 1 thoracic germinoma, 2 rhabdomyosarcoma, 1 of whom died of a secondary tumor – leukemia – at age 13 years).

Table 4 shows the modalities of therapy in the 79 surviving patients. Fifteen, 8 of them neonates, had only surgical therapy and did not receive adjuvant therapy (7 NB, 2 renal, 4 soft-tissue, 2 gonadal tumors); 41, 7 of them neonates, received chemotherapy in addition to surgical treatment. In 23 patients (2 neonates), in addition to surgical therapy chemo- and radiotherapy were applied in combination.

Table 2 Long-term survival of neonates and infants with malignancies (n = 79)

Tumor	No. of patients
Neuroblastomas	35 (8)[a]
Thoracic	9 (2)[a]
Abdominal	24 (6)[a]
Renal tumors	21 (1)[a]
Soft tissue sarcomas incl. rhabdomyosarcoma	15 (7)[a]
Gonadal tumors	5 (0)[a]
Testicular	4 (0)[a]
Ovarian	1 (0)[a]
Sacrococcygeal teratocarcinomas	2 (1)[a]
Hepatic	1 (0)[a]

[a]Malignancy diagnosed at neonatal age

Table 3 Mortality of patients with malignancies diagnosed at neonatal or infantile age

Tumor	No. of Patients
Neuroblastoma	23 (7)[a]
Thoracic	3 (1)[a]
Abdominal	20 (6)[a]
Renal tumors	8 (2)[a]
Soft-tissue sarcomas incl. rhabdomyosarcoma	8 (1)[a]
Teratocarcinoma	4 (0)[a]
Hepatic tumor	6 (1)[a]
Pancreatic tumor	1 (0)[a]

[a]Malignancy was diagnosed at neonatal age

Table 4 Modalities of therapy used in 79 surviving patients

Therapy	No. of patients
Surgery alone	15 8 neonates 7 infants
Surgery + chemotherapy	41 7 neonates 34 infants
Surgery + chemo- and radiotherapy	23 2 neonates 21 infants

Table 5 Side effects of multimodal therapy (surgical, chemo- and radiotherapy) in surviving patients[a]

Side effects	No. of patients
Skin lesion following radiotherapy	2
Muscular deformity	7
Renal calculus[b]	1
Bone morbidity (underdevelopment)	5
Infertility[b]	4
Decreased physical ability to work	3
Irradiation cardiac myopathy and nephritis	1
Irradiation nephritis	2
Goiter	2
Impaired hearing	1
Genital-pelvic underdevelopment	1
Thoracic deformity	4
Breast underdevelopment	7
Spinal deformity	22
Partial urinary incontinence	2
Partial fecal incontinence	1
Nerve injury	1
Intestinal obstruction	2
Psychological problems resulting from scar formation	12
Impaired vision (glasses, contact lenses)[b]	23
Pulmonary or skin allergy[b]	18
Hypertension[b]	1

[a]In 19 patients more than one side effects detected
[b]Side effects might be independent of treatment

Table 6 Side effects of surgical interventions

Side effects/tumor	No. of patients
Partial urinary incontinence/pelvic neuroblastoma	2
Partial fecal incontinence/pelvic neuroblastoma	1
Nerve injury/abdominal neuroblastoma	1
Intestinal obstruction, requiring partial large-bowel resection/Wilms' tumor	2
Thoracic deformity, asymmetry/neuroblastoma	4
Psychological problems resulting from scar formation	12

All late side effects of therapy (surgical, chemotherapy, and chemo- + radiotherapy) in the surviving patients are listed in Table 5. The relationship between some pathological conditions (question marks) and treatment of the malignancy is questionable. In 12 patients scar formation following surgical or radiotherapy resulted in psychological problems. Of the 79 surviving patients, 4 (3 female and 1 male) had one child each; another 4 (2 female and 2 male) complained of infertility; 71 did not yet want children.

In 22 patients side effects of surgical therapy were found (Table 6). Interventions carried out for pelvic or abdominal NB resulted in permanent functional damage in 4 (partial urinary or fecal incontinence or nerve injury). Twenty-three survivors (29.1%) required either corrective glasses or contact lenses. In 5 of these no adjuvant therapy, in 10 chemotherapy, and in 8 chemo- and radiotherapy were used in addition to surgical therapy. Eighteen survivors had pulmonary or skin allergies (22.8%). In 4 of these patients no adjuvant therapy, in 8 chemotherapy, and in 6 chemo- and radiotherapy were used in addition to surgical therapy.

The late sequelae of chemotherapy and chemo- and radiotherapy in combination in the surviving patients are listed separately for the three most frequent malignancies (NB, renal tumor, soft-tissue sarcoma) (Tables 7–9). Psychological problems resulting from scar formation, impaired vision, and pulmonary and skin allergies are not included in these tables. In the tables "severe spinal deformity" indicates that spinal surgery had already been performed or was being considered. The 2 severe spinal deformities in the patients with thoracic NB following cytostatic treatment might have partially been a result of surgery; 1 patient had a dumbbell tumor. All patients who developed severe spinal deformities (Tables 7–9) had received two or

Table 7 Side effects of adjuvant therapy in patients with neuroblastoma

Modality	Location	No side effects	Side effects	Type of side effects
Chemotherapy: 9 patients	Thoracic	5	5	Spinal deformity 3 (1 severe)
	Abdominal	7	6	Spinal deformity 2; muscular deformity 2
Chemo- andradiotherapy: 9 patients	Thoracic	0	2	Spinal deformity 1; goiter 1; breast underdevelopment 1
	Abdominal	1	6	Spinal deformity 6 (3 severe); irradiation cardiac myopathy and nephritis 1; impaired hearing 1; irradiation nephritis 2; breast underdevelopment 1; muscular deformity 2; skin lesion 1; bone morbidity 2; decreased physical ability to work 1

Table 8 Side effects of adjuvant therapy in patients with Wilms' tumor

Modality	No side effects	Side effects	Type of side effects
Chemotherapy: 10 patients	6	4	Renal calculus 1; breast underdevelopment 1
Chemo- and radiotherapy: 9 patients	1	8	Spinal deformity 5 (2 severe); infertility 2; muscular deformity 1; breast underdevelopment 2; decreased physical ability to work 2; bone morbidity 2

Table 9 Side effects of adjuvant therapy in patients with soft-tissue tumors

Modality	No side effects	Side effects	Type of side effects
Chemotherapy: 5 patients	2	3	Spinal deformity 2; muscular deformity 1
Chemo- and radiotherapy: 6 patients	1	5	Goiter 1; spinal deformity 2 (1 severe); breast underdevelopment 1; infertility 1; muscular deformity 2; skin lesion 1; bone morbidity 1; pelvic and genital underdevelopment 1

more chemotherapeutic agents in large doses (in 1 patient 11 times) or the radiotherapy in combination with the chemotherapy was aggressive (2,000–7,000 rad).

Investigation of somatic development showed an interesting pattern: in comparison with normal values, height and weight decreased significantly in the first half of the follow-up period, the decrease being greater in height than weight ($P < 0.01$ and < 0.05, respectively). However, both height and weight accelerated significantly in the second half of the follow-up period ($P < 0.05$ and < 0.05, respectively).

Discussion

The problems of long-term sequelae of anticancer therapy were of little concern when only a few patients lived long enough to experience them. The impressive advances made in the treatment of childhood cancer, however, have resulted in a growing population of patients who are apparently cured of their disease. This success has directed increasing attention to the quality of life of the survivors. Only a few studies have assessed the survival and functional outcome of infants treated for solid malignant tumors [20, 23, 29, 33, 35]. This publication deals with late sequelae of anticancer treatment in patients in whom malignancies were detected under the age of 12 months in Hungary in a 9-year period.

It is essential to realize that the first 12 months of life is the period of rapid growth, development, and maturation of organs and tissues, which are therefore especially vulnerable to antimitotic therapies. The brain, bones, liver, kidneys, gonads, and pulmonary parenchyma are especially vulnerable, and the ability to grow and mature can be curtailed when (multimodal) anticancer therapy is administered. The infant's ability to absorb, distribute, biotransform, and excrete chemotherapeutic agents is different from that of adults and even older children

[21, 32]. The immature status of the kidney may alter the usual renal route of elimination of some chemotherapeutic drugs such as methotrexate and cisplatinum [21], and damage may occur to glomerular and proximal and distal tubular function or to the bladder. The alkylating agents are particularly dangerous.

Many chemotherapeutic agents are metabolized in the functionally immature liver of the infant [26]. The relatively increased volume of extracellular fluid and paucity of fat in the newborn and young infant results in increased bioavailability of many chemotherapeutic drugs. In addition, the infant's immune system is not as well-developed as that of older children. Therefore, chemotherapy is associated with a higher incidence of infection, leading to serious complications [32]. Higher mortality related to chemotherapy has been reported in infancy [26].

Drug treatment of malignancy will probably not spare the epiphyseal plate, which raises the possibility of growth retardation during treatment and the question of whether subsequent compensation is possible. The impact of chemotherapy on gonadal function is known and dependent on the type and dosage of the drugs. A number of drugs are known to have cardiotoxic effects (vinblastine, adriamycin, anthracycline, alkylating agents).

Radiation therapy in infants (which can not be avoided in some patients with WT, NB, etc.) is more dangerous than in children [35]. Progressive renal damage (chronic nephritis, hypertension) appears to be inevitable and progressive when doses greater than 2,000 rad are administered. A number of chemotherapeutic agents (methotrexate, cisplatinium, and alkylating agents) appear to increase the risk of radiation damage to the kidneys [6].

Radiotherapy causes fibrotic changes and damage to the musculoskeletal system, growth plates, and growth potential of the bones. Spinal growth, which contributes significantly to the final height, is especially sensitive to radiation [35]. This is exemplified in a study of 81 children who received abdominal radiation (mean dose 3380 rad) for WT: 57 (70%) had roentgenographic evidence of structural scoliosis and 21 developed structural kyphosis associated with scoliosis; 8 required spinal surgery [27]. Radiation therapy has also produced deformities of the chest, including hypoplasia, asymmetry, and pectus excavatum [14, 34]. The younger the child is at the time of spinal irradiation and the higher the radiation dose, the greater the damage to the skeletal system and the compromise to final height, and the more obvious the disproportion between leg length and spinal length [30]. In addition to the direct effects, irradiation can also impair growth by damaging the endocrine glands (pituitary or thyroid) [8].

Decreased fertility and sterility may result from gonadal irradiation. The intrapelvic ovaries are likely to receive more direct or scattered radiation than the small, extra-abdominal testes [8].

In experience with 266 cases of NB treated at the James Whitcomb Riley Hospital for Children, survival in infants under 1year of age was 76% while it was 32% for children older than 1 year [10]. This favored outlook in the 1st year of life extends across all stages, including stage IV metastatic disease, in which almost one-half of all infants survive despite having bone-cortex metastases [22]. The operative complication rate is higher in patients undergoing primary tumor resection at the time of diagnosis [15, 31]. This optimism is supported by the observation of Castel Sanchez et al., who found that unfavorable biological factors are less frequent under the age of 1 year, except in stage IV patients [3]. Only those patients with IV-S NB will require radiation and chemotherapy whose survival is threatened by complications secondary to hepatomegaly [15]. Resection of the primary tumor does not seem to influence survival, however, good supportive care is essential [11].

For congenital mesoblastic nephroma, surgery is currently the only therapy, and chemotherapy should be reserved for the rare recurrence. The treatment of WT in infancy will be dictated by the nature of the tumor and its stage as outlined in the NWTS or SIOP protocol.

On the basis of the Intergroup Rhabdomyosarcoma Study (IRS), Ragab et al. found that infants younger than 1 year of age had a significantly greater frequency of undifferentiated and botryoid sarcoma (18% in infants vs 7% in older children) and a higher rate of bladder-prostate-vagina primary tumor sites than older children (24% vs 10%) [26]. Infants with soft-tissue tumors appeared to tolerate chemotherapy more poorly than older children. Life-threatening and fatal toxicities were more common in infants younger than 1 year of age. Because of the increased toxicity in infants, the IRS protocol was amended so that infants would initially receive only 50% of the recommended dose for older children [26]. This modification has resulted in decreased morbidity; the survival curves were similar for both age groups. However, in contrast to WT and NB, in which age (< 1 year) is a favorable prognostic factor, age does not appear to be an important prognostic factor in rhabdomyosarcoma [26].

The generally suggested treatment of fibrosarcoma in neonates and infants is early radical excision well within healthy tissue in the hope of preventing local recurrence, which is reported to occur in 16%–47% of cases [1, 5]. In biologic behavior, sacrococcygeal teratomas (SCT) range from benign neoplasia to potential and actual malignancies. The advocated treatment is early and complete surgical excision, including resection of the coccyx [17, 29]. A benign SCT removed in the first days of life can recur 21–43 years following the original operation. Patients with intrapelvic extension of teratoma seem to be particularly at risk for recurrence [17, 29].

Long-term studies on the subsequent growth of survivors of childhood solid malignancies are few [13, 27], and we were not able to find any dealing exclusively with somatic development in long-term survivors treated for cancer before the age of 1 year. Herbert et al. documented that children reached statistically significant

improvement following chemotherapy alone 3 years after diagnosis [13]. Chemotherapy in neonates and infants with NB is associated with compromised somatic development [10], however, in a recent study rapid somatic growth from birth through diagnosis in patients with NB diagnosed before 1 year of age suggests possible involvement of certain growth factors [33]. Children treated with chemotherapy and abdominal irradiation showed no overall height loss, but manifested significant reductions in sitting height [13].

Decreased somatic development in the first years of follow-up can be explained by postulating that the untreated malignancy caused a period of growth retardation prior to diagnosis and a catabolic state accompanying chemo- and radiotherapy. This retardation became at least partially reversible only when the (multimodal) anticancer therapy had finished. When comparing infants with solid malignant tumors treated only surgically with those treated with chemotherapy or chemo- and radiotherapy in combination, we found a higher incidence of delayed growth in the latter group. This developmental delay is sometimes carried on to adolescence.

Patients cured of one malignancy are at higher risk for developing a second neoplasm than the general population. Li found in a retrospective analysis that the frequency of second malignant tumors in children was approximately 20 times higher than the expected rate [18]. Blatt et al. documented that the cumulative incidence of a second cancer appearing was approximately 1% within 10 years, and at 20 years from diagnosis the actuarial risk was 3% [2]. There is evidence that patients treated with both radiation and chemotherapy have a greater risk of developing a second malignancy than those with either modality alone. We found one second neoplasm in a female who received chemotherapy and irradiation because of a rhabdomyosarcoma of the genitourinary tract and died of leukemia at the age of 13 years.

Because few neonates and infants have metastatic disease at the time of diagnosis, total excision of the malignancy alone is often curative. Neither routine adjuvant chemotherapy nor radiation therapy would appear to be indicated in low-risk patients (neonates and infants in the first 3 months of life) because of the favorable prognosis of cancer after complete removal of the tumor and the known and anticipated long-term morbidity associated with those treatments. Chemotherapy is primarly indicated in infants who have either metastatic disease or a non-resectable tumor. The choice of agents is determined by the histologic type. Dose reduction and careful monitoring of toxicities are needed when anticancer drugs are used, especially those that are dependent on the liver or kidney for processing and excretion. Radiation therapy should be used selectively; when indicated, meticulous technique is employed to minimize the potentially serious damage to normal tissue. Aggressive multimodal therapy might be more dangerous than the underlying disease.

Currently, not enough is known about the sexual function and fertility potential of these patients. Our patients were too young to evaluate fertility; another 10 years are necessary to answer this important question.

The increasing knowledge of the long-term morbidity and mortality related to treatment should be used not only to further refine present-day treatment, but should also encourage the search for alternative means of therapy in the future. More knowledge of the biological behavior and prognosis of solid malignant tumors in neonates and infants will help us to reduce unnecessary treatments (surgery, chemotherapy, or chemo- and radiotherapy in combination) with particularly deleterious late side effects [19, 23, 32, 33] and to eliminate unnecessary components of treatment and substitute them with less damaging alternatives.

The high death rate (38.7%) of our traceable 129 patients and the large number of late sequelae, mainly spinal deformities, are probably related to the aggressive chemotherapy [32] and radiotherapy [19] in combination and ineffective supportive therapy. The high number of (late) side effects in our patients and in the literature [9, 16, 26, 28] indicates that dose-reduced chemotherapy is not associated with life-threatening side effects and, more importantly, has not negatively affected the survival of patients with NB [26].

In our material, the high number of complications attributed to surgery, chemotherapy, or radiotherapy and 2 deaths without evidence of progression of the neoplasm in the early postoperative period indicate that these patients should be managed with more conservatism and optimism. Avoidance of preventable comorbid conditions may allow an improved long-term outcome with better survival and growth potential.

In addition to normal (or nearly normal) somatic development, mental development is also essential. Hays et al. reported that childhood cancer survivors, with the exception of Central-nervous-system cancers, experienced few educational and occupational sequelae of their diseases in their 4th and 5th decades of life [12]. Everything possible should be done to support these young adults, because there are some concerns on the part of the lay public when it becomes known that a person previously had a malignant tumor.

The aim of the present generation of pediatric oncologists is to sustain the improvement in survival while minimizing treatment-induced late effects at the least, rather than any cost. The pace of further improvement in anticancer therapy for neonates and infants with solid malignant tumors depends on those talented people who can apply and refine leads from progress in cancer therapy and basic research and to modify them.

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