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ORIGINAL ARTICLE

# Cancer treatment in disabled children

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## Abstract

The incidence of cancer in children with intellectual disability has been poorly documented. We report our experience of treating children and adolescents with cancer and intellectual disability (40 patients), from 2004 to 2018. A treatment-sparing approach was adopted for 6 patients with severe intellectual impairment to minimize toxicity: a child with postpartum asphyxia and medulloblastoma did not receive radiotherapy; 1 patient with mitochondrial encephalopathy and a testicular germ cell tumor did not receive bleomycin and lung metastasectomy; 2 patients (1 with Down + West syndrome + Wilms tumor (WT) and 1 with Denys-Drash syndrome + WT) did not receive vincristine; 1 child with corpus callosum agenesis and anaplastic ependymoma did not receive chemotherapy; 1 child with structural chromosomal aberrations and a primitive neuro-ectodermal tumor received personalized chemotherapy. Heminephrectomy was performed in 4 patients with WT to preserve their kidney function. We found no statistically significant correlation between relapse or mortality rates and the use of a treatment-sparing approach. The 5-year overall survival (OS) and event-free survival (EFS) rates were 84.5% and 66.1% as opposed to 82.5% and 46.9%, respectively, for patients in our usual-treatment and treatment-sparing groups.

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*Conclusion*: We only opted for a treatment-sparing approach for patients with severe disabilities, and their OS was in line with that of children without intellectual disability.

**What is Known:**
- *There are few reports on children/adolescents with cancer and intellectual disability (ID).*
- *It is not clear how to manage them and whether a treatment sparing should be considered, especially in the case of severe disability.*

**What is New:**
- *Most patients received the standard cancer treatment and only in the case of severe disability, a therapeutic saving approach was applied.*
- *No statistically significant correlations between relapse/mortality rates and the use of a treatment-sparing approach were found.*

**Keywords** Intellectual disability · Pediatric tumors · Syndromes · Treatment sparing

**Abbreviations**

| | |
|---|---|
| ASRE | European age-standardized rate |
| EFS | Event-free survival |
| ID | Intellectual disability |
| OS | Overall survival |
| PFS | Progression-free survival |
| WAGR | Wilms tumor, aniridia, genitourinary anomalies, and mental retardation |
| WT | Wilms tumor |

## Introduction

Pediatric tumors account for 1% of all tumors in the general population [1]. Many childhood cancers stem from aberrations in early developmental processes, while the role of environmental factors or other exogenous factors is minimal [2–4]. The European age-standardized rate (ASRE) of pediatric cancer was 164 new cases per million children a year, and neoplasms are the first cause of death due to disease in children aged 1–14 years [5].

Intellectual disability (ID) affects about 1–2% of the population in the developed world and can be defined as a disruption in intellectual functioning and adaptive behavior developing before 18 years of age. ID is rising globally, with the majority of those affected living in less-developed countries, where ID rates ranging from 4 to over 8% have been reported [6–8]. The incidence of cancer among young people with ID has been poorly documented, but is believed to be much the same as in the general population [9, 10]. Children with particular syndromes carry an increased cancer risk during early adulthood, however, especially for hematological cancers (leukemia and non-Hodgkin lymphoma). In particular, some specific conditions are associated with a higher risk of both cancer and ID. People with Down syndrome are at greater risk of leukemia and testicular cancer [11–13]. WAGR syndrome (Wilms tumor (WT), aniridia, genitourinary anomalies, and mental retardation) carries a variable risk of both cancer and ID [14]. Tuberous sclerosis is associated with brain tumors and renal cell carcinomas [15, 16]. In Noonan syndrome, there is a higher likelihood of glioma, neuroblastoma, rhabdomyosarcoma, and leukemia [17–19], while in Costello syndrome, neuroblastoma, rhabdomyosarcoma, and early-onset bladder cancer are reported [17, 20]. Patients with Rubinstein-Taybi syndrome can develop hepatoblastoma, medulloblastoma, rhabdomyosarcoma, leiomyosarcoma, seminoma, and embryonal carcinoma [21]. Brain tumors can also cause ID, especially in children. The proportion of cancer-related deaths due to any cause is reportedly from 5 to 18% in children and adolescents with ID, compared with 20% in the general population [10]. The life expectancy of individuals with ID has been increasing rapidly over the past 30 years, and so has the number of cancers (thyroid carcinoma and tumors of the gallbladder, esophagus, testicle, and nervous system) being diagnosed in this population, especially when they reach adulthood [10].

Disabilities are common: about 1 in every 50 children has a disability. Children with a disability may have special needs and require early intervention, and as much support as possible, to better develop their potential so that every child can be socially competent in adulthood. This means that support must be provided in different fields, ranging from the psychological to the neurocognitive, educational, medical, and social, and including physiotherapy, hearing aids, and speech therapies.

## Materials and methods

The present study concerns children and adolescents with cancer and an intellectual disability, focusing on the type and degree of their disability in the linguistic, cognitive, motor, relational, and autonomy domains. We analyzed the neuropsychiatric reports of each patient and retrospectively scored their disability at the time of their cancer's diagnosis and again a year after completing its treatment. The scores ranged from 0 (no deficit) to 3 (severe deficit) for each of the following domains: speech, cognitive, motor, relational, and autonomy. All patients reported cognitive impairment. Adding up the single domain scores, we defined three levels of patient disability: mild (1–5), moderate (6–10), and severe (11–15). We considered "treatment sparing" any omission of a

specific drug or switch to a different drug or treatment modality vis-à-vis those commonly used to treat the general population. We defined as a diagnostic delay any interval longer than 2 months between the onset of symptoms and the diagnosis of cancer.

We examined (a) whether our patients with cancer and ID received the best possible treatment for their cancer according to specific national or international protocols; (b) in case of treatment sparing, which specific treatment was omitted and how this affected OS, progression-free survival (PFS), and event-free survival (EFS); (c) the impact cancer treatment on the patients' ID at the end of their care program, using ad hoc score; (d) the reason for sparing some patients certain treatments, and particularly whether this was due to the ID severity or to the risk of treatment-related side effects.

### Statistical analysis

OS was defined as the time elapsing from diagnosis to death from any cause. EFS was defined as the time from diagnosis to first event or death. PFS was defined as the time from diagnosis to disease progression/recurrence or death, whichever came first. Time was censored at the latest follow-up for patients still alive and free from eventual other events of interest. The curves were estimated using the Kaplan-Meier model and compared using the log-rank test. The median follow-up was estimated with the reverse Kaplan-Meier method using OS data.

## Results

Between 2004 and 2018, 42 consecutive patients with cancer and ID were treated at the Pediatric Oncology Unit of the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, and 40 were eligible for this analysis.

Demographic, clinical, and pathological characteristics of the selected patients were reported in Table 1. The patient' median age at diagnosis was 4 years (range 0.5–20), and 22 of them were males. The most frequent types of cancer were central nervous system tumors (27.5%), followed by WT (22.5%), hepatoblastoma (10%), and soft tissue sarcomas (10%). Table 1 shows the different types of tumor involved.

Autism (12.5%) and postpartum encephalopathies (7.5%) were the most common disabilities, while a definitive diagnosis of ID was impossible in 20% of cases. Table 2 summarizes the various types of ID.

In 9/40 cases, an early diagnosis of cancer (WT and hepatoblastoma) was obtained during the scheduled follow-up of the patients' ID, particularly in patients with Beckwith-Wiedemann, WAGR, hemihypertrophy, Kabuki, and Rubinstein-Taybi syndromes. There was a diagnostic delay in 10 cases. A treatment-sparing approach was used for 12 patients (median age 3.2 years, as opposed to 5.8 years in the group without treatment sparing).

Thirty-three children (82.5%) underwent surgery, but 5 patients were spared to some degree: 4/5 were children with WT and Down + Denys-Drash or Beckwith-Wiedemann or WAGR, who underwent heminephrectomy instead of nephrectomy to preserve their kidney function, and one patient with severe ID due to mitochondrial encephalopathy and a germ cell tumor had multiple lung metastases but was spared any lung metastasectomy.

Radiotherapy was administered to 16 (40%) children. It was omitted in one patient with medulloblastoma and severe postpartum asphyxia. Three out of 16 patients given radiotherapy (5, 6, and 8 years old) required sedation due to compliance issues related to their ID.

Thirty-seven patients (92.5%) were given chemotherapy, but 6 of them were spared a part of the usual therapy. Vincristine was omitted due to its potential neurotoxicity in 2 patients (1 with Down + West + WT, the other with Denys-Drash + WT). Actinomycin was omitted in one patient with Beckwith-Wiedemann + WT. Ifosfamide and vincristine were omitted, again due to their neurotoxic potential, in one child with Ewing sarcoma and chromosomal aberrations/anomalies (chromosome 13 monosomy and chromosome 10 trisomy). Bleomycin was omitted in a patient with germ cell tumor and numerous lung metastases because of its potential additive pulmonary toxicity. No chemotherapy was administered after radiotherapy in a child with anaplastic ependymoma and corpus callosum agenesis. Seven out of 9 children with WT were spared a part of the usual treatment.

At the time of writing, 31 patients were alive with a median follow-up of 7.8 years (range 4.8–11.1 years). Fourteen out of 40 patients had disease progression or relapse: 9 were given the standard salvage treatment, while 5 were spared to some degree. Figures 1, 2, and 3 show the survival results according to treatment group. The OS (95% CI) at 5 and 10 years was 82.5% (63.1–100%) and 73.3% (51.5–100%) in the treatment-sparing group, and 84.5% (71.6–99.8%) and 70.2% (51.6–95.6%) in the standard treatment group ($p = 0.996$). The PFS (95% CI) at 5 and 10 years was both 51.1% (27.9–93.6%) in the former group, and 74.4% (59.7–92.7%) and 60.6% (42.2–87.1%) in the latter ($p = 0.529$). The EFS (95% CI) at 5 and 10 years was both 46.9% (25.0–87.9%), and 66.1% (50.3–87.0%) and 36.1% (19.7–66.1%), respectively ($p = 0.980$).

The disability score was calculated in 33/40 patients: their median disability score was 9 (range 2–15). More in detail, it was 9 for patients not spared any treatment, and 15 for those who had been managed according to a treatment-sparing approach. Eight out of 33 patients had a disability score of 15. As concerns the disability categories, 8 children had mild ID, 9 had moderate ID, and 16 had severe ID (Table 2). A worse score after being treated for cancer was seen in 2 patients (both

**Table 1** Demographic, clinical, and pathological characteristics

| | Standard treatment | Spared treatment | Overall |
|---|---|---|---|
| Gender, *N* (%) | | | |
| Female | 15 (83.0) | 3 (17.0) | 18 (45) |
| Male | 13 (59.0) | 9 (41.0) | 22 (55) |
| Age (years) | | | |
| Median (1st and 3rd quartile) | 5.8 (3.0–11.1) | 3.2 (1.4–3.8) | 4.9 (2.4–10.2) |
| Delayed diagnosis, *N* (%) | | | |
| Yes | 7 (25.0) | 3 (25.0) | 10 (25.0) |
| No | 21 (75.0) | 9 (75.0) | 30 (75.0) |
| Types of tumor, *N* (%) | | | |
| Central nervous system tumors | 8 (72.0) | 3 (28.0) | 11 (27.5) |
| Hepatoblastoma | 4 (100) | 0 | 4 (10.0) |
| Aggressive fibromatosis | 1 (100) | 0 | 1 (2.5) |
| Langerhans cell histiocytosis | 2 (100) | 0 | 2 (5.0) |
| Hodgkin lymphoma | 2 (100) | 0 | 2 (5.0) |
| T cell non-Hodgkin lymphoma | 1 (100) | 0 | 1 (2.5) |
| Germ cell tumor | 1 (50.0) | 1 (50.0) | 2 (5.0) |
| Neuroblastoma | 2 (100) | 0 | 2 (5.0) |
| Osteosarcoma | 1 (100) | 0 | 1 (2.5) |
| Soft tissue sarcoma | 4 (100) | 0 | 4 (10.0) |
| Ewing sarcoma | 0 | 1 (100) | 1 (2.5) |
| Wilms tumor | 2 (22.0) | 7 (78.0) | 9 (22.5) |
| Intellectual disability, *N* (%) | | | |
| Corpus callosum agenesis | 0 | 1 (100.0) | 1 (2.5) |
| Cerebellar ataxia | 1 (100) | 0 | 1 (2.5) |
| Autism spectrum disorder | 5 (100) | 0 | 5 (12.5) |
| Multiple chromosomal deletions | 1 (100) | 0 | 1 (2.5) |
| Hemihypertrophy | 1 (100) | 0 | 1 (2.5) |
| Mitochondrial encephalopathy | 0 | 1 (100) | 1 (2.5) |
| Postpartum encephalopathy | 2 (67.0) | 1 (33) | 3 (7.5) |
| Neuro-metabolic disorder | 1 (100) | 0 | 1 (2.5) |
| 13 monosomy and 10 trisomy | 0 | 1 (100) | 1 (2.5) |
| Psychosis | 1 (100) | 0 | 1 (2.5) |
| Tuberous sclerosis | 1 (100) | 0 | 1 (2.5) |
| Beckwith-Wiedemann syndrome | 0 | 2 (100) | 2 (5.0) |
| CHARGE syndrome | 1 (100) | 0 | 1 (2.5) |
| Costello syndrome | 2 (100) | 0 | 2 (5.0) |
| Denys-Drash syndrome (DDS) | 0 | 1 (100) | 1 (2.5) |
| DDS + Down syndrome | 0 | 1 (100) | 1 (2.5) |
| Down syndrome + West syndrome | 0 | 1 (100) | 1 (2.5) |
| Kabuki/Hardikar syndrome | 2 (100) | 0 | 2 (5.0) |
| Klinefelter syndrome | 1 (100) | 0 | 1 (2.5) |
| Rubinstein-Taybi syndrome | 1 (100) | 0 | 1 (2.5) |
| WAGR syndrome | 0 | 2 (100) | 2 (5.0) |
| WT1+ | 1 (100) | 0 | 1 (2.5) |
| Cognitive dysfunction of unknown cause | 3 (75.0) | 1 (25.0) | 4 (10.0) |
| Cognitive and somatic dysfunction | 4 (100) | 0 | |
| Of unknown cause | | | 4 (10.0) |
| Surgery, *N* (%) | | | |
| Yes | 28 (85.0) | 5 (15.0) | 33 (82.5) |
| No | 7 | – | 7 (17.5) |
| Chemotherapy, *N* (%) | | | |
| Yes | 32 (86.0) | 5 (14.0) | 37 (92.5) |
| No | 2 | 1 (2.5) | 3 (7.5) |
| Radiotherapy, *N* (%) | | | |
| Yes | 16 (94.0) | | 16 (40.0) |
| No | 23 | 1 (6.0) | 24 (60.0) |

in the group not spared any of the usual treatments). In one of these patients, who had cerebellar ataxia and a germ cell tumor, the score rose from 5 to 8; in the other, who had metabolic encephalopathy and a brain tumor, it increased from 9 to 10. In both cases, their worsening disability scores were due to their progressive neurodegenerative disease.

## Discussion

The reported incidence of cancer in children with ID is poorly documented; anywhere, it is rising as the lifespan of this population does. The genetic alterations underlying some syndromes associated with ID are also risk factors for the

**Table 2** Overall and domain disability scores at diagnosis

| ID | Treatment group | Speech imp. | Motor imp. | Relational imp. | Autonomy imp. | Cognitive imp. | Total score | Disability level group |
|---|---|---|---|---|---|---|---|---|
| 25 | Spared | 0 | 1 | 0 | 0 | 1 | 2 | Mild |
| 27 | Spared | 0 | 1 | 0 | 0 | 1 | 2 | Mild |
| 40 | Standard | 1 | 0 | 1 | 1 | 1 | 4 | Mild |
| 3 | Standard | 1 | 2 | 0 | 1 | 1 | 5 | Mild |
| 24 | Standard | 1 | 0 | 1 | 1 | 2 | 5 | Mild |
| 28 | Standard | 1 | 1 | 1 | 1 | 1 | 5 | Mild |
| 12 | Spared | 1 | 1 | 1 | 1 | 1 | 5 | Mild |
| 39 | Spared | 1 | 1 | 1 | 1 | 1 | 5 | Mild |
| 23 | Standard | 1 | 1 | 2 | 1 | 1 | 6 | Moderate |
| 31 | Standard | 2 | 0 | 1 | 1 | 2 | 6 | Moderate |
| 17 | Standard | 1 | 1 | 1 | 2 | 2 | 7 | Moderate |
| 7 | Standard | 2 | 0 | 2 | 2 | 2 | 8 | Moderate |
| 26 | Spared | 2 | 0 | 3 | 2 | 1 | 8 | Moderate |
| 2 | Standard | 3 | 0 | 3 | 2 | 1 | 9 | Moderate |
| 29 | Standard | 2 | 1 | 2 | 2 | 2 | 9 | Moderate |
| 30 | Standard | 1 | 3 | 1 | 3 | 1 | 9 | Moderate |
| 21 | Spared | 1 | 2 | 2 | 2 | 2 | 9 | Moderate |
| 13 | Standard | 2 | 2 | 2 | 2 | 3 | 11 | Severe |
| 20 | Standard | 2 | 1 | 2 | 3 | 3 | 11 | Severe |
| 6 | Spared | 3 | 1 | 3 | 2 | 2 | 11 | Severe |
| 5 | Standard | 3 | 1 | 3 | 2 | 3 | 12 | Severe |
| 10 | Standard | 3 | 1 | 2 | 3 | 3 | 12 | Severe |
| 4 | Standard | 3 | 1 | 3 | 3 | 3 | 13 | Severe |
| 36 | Spared | 2 | 3 | 2 | 3 | 3 | 13 | Severe |
| 33 | Standard | 3 | 3 | 2 | 3 | 3 | 14 | Severe |
| 34 | Standard | 3 | 3 | 3 | 3 | 3 | 15 | Severe |
| 35 | Standard | 3 | 3 | 3 | 3 | 3 | 15 | Severe |
| 37 | Standard | 3 | 3 | 3 | 3 | 3 | 15 | Severe |
| 1 | Spared | 3 | 3 | 3 | 3 | 3 | 15 | Severe |
| 14 | Spared | 3 | 3 | 3 | 3 | 3 | 15 | Severe |
| 15 | Spared | 3 | 3 | 3 | 3 | 3 | 15 | Severe |
| 16 | Spared | 3 | 3 | 3 | 3 | 3 | 15 | Severe |
| 22 | Spared | 3 | 3 | 3 | 3 | 3 | 15 | Severe |

development of tumors [11–21]. The risk of a diagnostic delay in such cases may be high, because of patients' difficulties in reporting their symptoms, but this greater risk may be balanced by the screening routinely done in such cases. In our sample, 22.5% of the tumors diagnosed came to light during patients' follow-up for their ID, and there was a

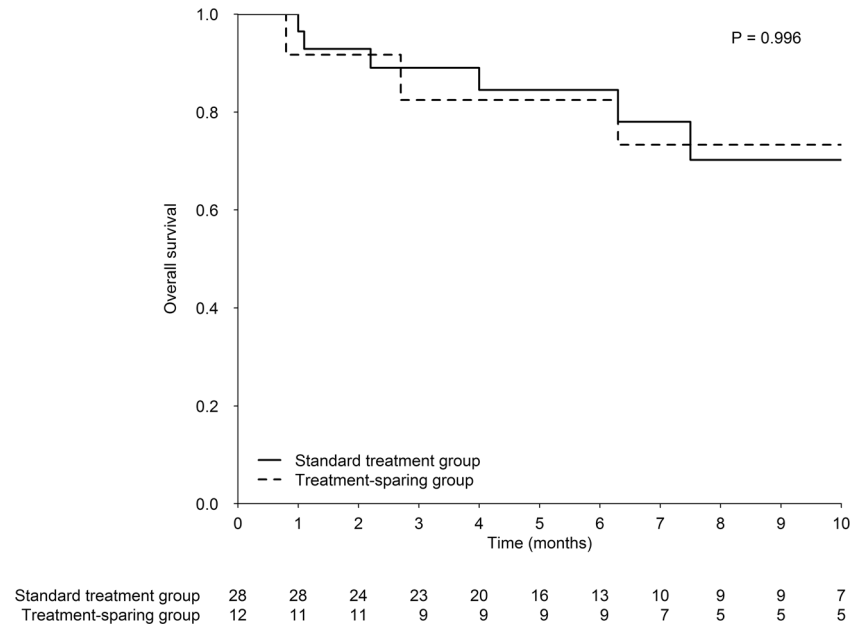


**Fig. 1** Overall survival: Kaplan-Meier curves according to treatment group

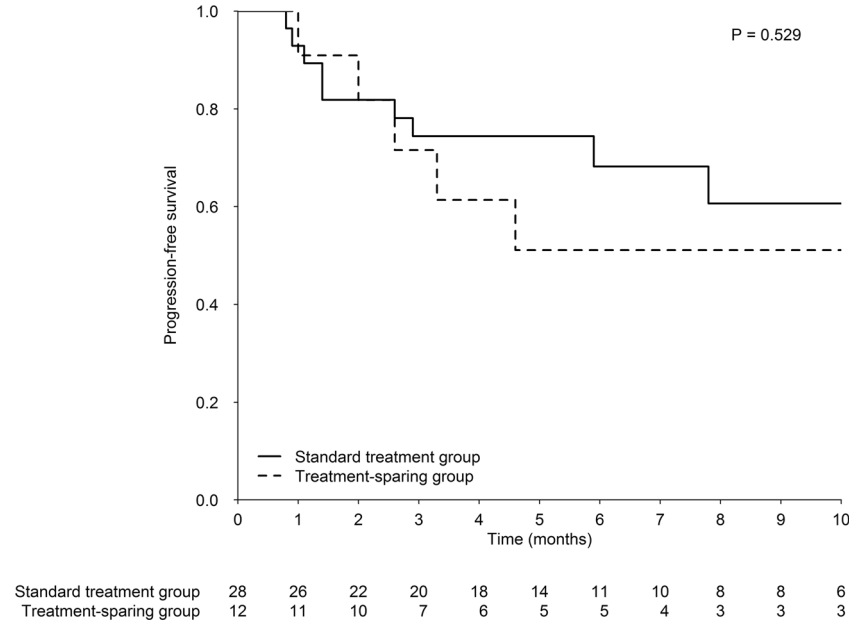


**Fig. 2** Progression-free survival: Kaplan-Meier curves according to treatment group

diagnostic delay in 25% of patients. This means that pediatricians should be involved in the accurate scheduled assessment of children with ID, and a good alliance between parents and pediatricians is crucial.

In our study, we examined the oncological treatment of patients with both cancer and ID in an effort to elucidate whether it was useful to spare such patients' certain cancer treatments, whether the degree of their disability influenced this decision, and what impact any treatment sparing had on their prognosis.

We found that 92.5% of our patients received chemotherapy. Basically, only 3 patients were spared most of the usual treatment, and they all had a disability score of 15/15. We judged that there was a considerable risk of the treatments making their ID worse, or of their disability posing a high risk of the cancer treatment having severe consequences (for example, the patient with mitochondrial encephalopathy was not in a condition to tolerate major surgery).

The OS, PFS, and EFS of the patients in our sample were similar, regardless of whether a treatment-sparing approach was used (as shown in Figs. 1, 2, and 3), but it is important to bear in mind that only 3/40 patients were spared a major part of the usual treatments, and 9/40 patients had a WT (which typically carries a good prognosis).

We were able to calculate a disability score for 33 patients (some children were too young to evaluate certain

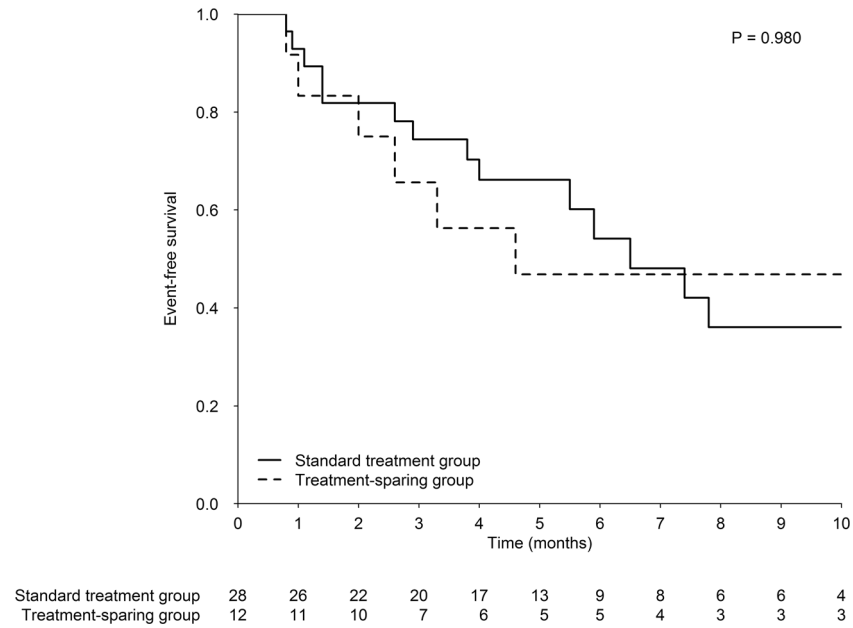


**Fig. 3** Event-free survival: Kaplan-Meier curves according to treatment group

parameters): 16 of them had a severe disability, and 8 scored 15 (the maximum score), including all three patients managed with a major treatment-sparing approach. When we compared the disability scores between the baseline, before any tumor treatment, and 1 year after the treatment's completion, we found a worsening score in 2 cases: both of these patients had received standard treatment, but their clinical deterioration was caused by a worsening of their degenerative disease, not by the cancer treatments.

Children with ID and cancer pose a challenge for pediatric oncologists, who have to balance their oncological treatment with the risk of worsening their ID. Early diagnosis is crucial, but the presence of ID can make it difficult to assess the signs and symptoms in such patients.

In reporting our experience, we would like to emphasize that most patients received the standard antineoplastic treatment without any negative impact on their ID, and that it was only in a few, severe cases that patients were spared a part of the usual treatment. Of course, it is very important to discuss any proposed therapies with parents, radiotherapists, surgeons, psychologists, anesthetists, geneticists, neurologist, rehabilitation physicians, and all the other specialists involved in care both of ID and cancer, always paying attention to the patient's disability and quality of life, as well as their oncological disease. We need to consider the feasibility of customizing the treatments for some patients because it does not seem to have a negative impact on their prognosis, since the OS of our patients was similar to that of the general pediatric cancer population.

**Authors' contributions** All authors contributed to the study conception and design. Data collection was performed by Chiara Barteselli and Cristina Meazza; methodology by Cristina Meazza; formal analysis by Francesco Barretta; writing - original draft preparation by Cristina Meazza, Elisabetta Schiavello, Veronica Biassoni, Marta Podda, Giovanna Gattuso; writing - review and editing by Giovanna gattuso, Monica Terenziani, Andrea Ferrari, Filippo Spreafico, Roberto Luksch, Michela Casanova, Stefano Chiaravalli, Nadia Puma, Luca Bergamaschi; supervision by Maura Massimino. All authors read and approved the final manuscript.

## Compliance with ethical statements

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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