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Research progress in the application of radiotherapy in the treatment of pediatric tumors

Z-H. Wang[1], Y. Liu[2], J-Q. Guo[3], H-L. Liang[2], W-W. Zhi[4*]

[1]Department of Radiation Therapy, Linfen Central Hospital, Linfen, Shanxi, China 041000
[2]Department of Cardiovascular Surgery, Xijing Hospital, Air Force Military Medical University, Xi'an, China
[3]Department of Medical, Xi'an Fourth Hospital, Xi'an, China
[4]Department of Cardiovascular Surgery, Xi'an Fourth Hospital, Xi'an, China

► ***Original article***

***Corresponding author:**
Wei-Wei Zhi, Ph.D.,
***E-mail:** zweiwei0331@sina.com*

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***Keywords:** Children, tumor, radiotherapy, treatment, research progress.*

ABSTRACT

Background: The principle of treatment of pediatric tumors is to kill tumors to the greatest extent and improve long-term quality of life through surgery, radiotherapy, chemotherapy, and other means combined according to the specific disease and pathological type. Radiotherapy is an important means for the treatment of pediatric tumors. With the development of radiotherapy technology, it plays an increasingly important role in clinical work. This paper briefly summarizes the characteristics of radiotherapy in pediatric tumors and introduces the application of radiotherapy in some major pediatric tumors. ***Materials and Methods:*** Relevant articles published in the PubMed database between 2010 and 2022 were searched. The researchers then looked at the data one by one and looked at the citation, which was their reference at the end of each paper. Inclusion criteria were, articles describing radiation therapy for pediatric tumors; experimental and clinical studies of different radioactive means; and standard methods and rigorous thinking. Exclusion criteria were, meta-analysis article; the literature was published before 2010. ***Results:*** In this paper, radiation therapy for acute lymphoblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, neuroblastoma, retinoblastoma, glioma, Wilms's tumor and rhabdomyosarcoma is summarized and their characteristic radiation conditions are analyzed. ***Conclusions:*** Radiotherapy for children with tumors should not blindly pursue high-dose radiotherapy, but the combination of different therapeutic methods should be adopted to achieve the purpose of tumor treatment and minimize the impact on the growth and quality of life of patients.

INTRODUCTION

As the incidence of childhood malignant tumors increases year by year, childhood malignant tumors have become the main cause of disease-related deaths in children, which may be closely related to environmental deterioration and food safety issues [1, 2]. The frequency of this occurrence differs according to factors such as age, gender, tumor classification, and geographical location [3]. For instance, Eduardo pointed out that Asians had the highest incidence in terms of children with pancreatic malignancies [4]. In countries with low- and middle-income levels, patients frequently exhibit late-stage disease symptoms due to restricted availability of early detection facilities and specialized care centers [5, 6]. Malignant tumors are the second leading cause of death among children in developed countries [1, 7]. In accordance with the Shanghai Mortality monitoring report in 2005, malignant tumors were the top four causes of death in children [1, 7], indicating that malignant tumors had become one of the major diseases threatening children's health. In recent years, the diagnosis and treatment of pediatric malignant tumor has two characteristics [8]: One factor is the rising incidence with each passing year. The second is the continuous improvement of treatment methods and efficacy. The event free survival rate (EFS) of patients with acute lymphoblastic leukemia is 50%-70%. EFS of acute lymphoblastic leukemia (ALL) have reached over 80%~90% [2, 9], and EFS of malignant solid tumors such as early nephroblastoma, hepatoblastoma and retinoblastoma (RB) have also reached over 85% ~93% [5, 7, 10].

In the past 30 years, with the development of medical technology and the strengthening of the understanding of the characteristics of pediatric tumors, the combined application of individualized surgery, radiotherapy and chemotherapy has significantly improved the prognosis of pediatric malignant tumors [9, 11]. The mortality rate of childhood malignant tumors in the United States was 49% in the 1970s and decreased to 30% in the 21st century [7, 12]. Radiotherapy (RT) is a crucial element in the multi-disciplinary treatment of the majority of childhood cancers, serving therapeutic or palliative purposes [5, 6, 9-11]. Most adult cancers have

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documented evidence-based estimates of the rate of utilization for radiotherapy (RUR) [5, 6, 9-11]. In contrast, the frequency of reporting pediatric RUR is uncommon. In the United States, there was a gradual reduction in the utilization rate of radiotherapy among children between 1973 and 2008, likely due to advancements in systemic therapy and surgical procedures, as well as efforts to lessen radiation-induced toxicity [12]. Thus, although the global incidence of pediatric cancer increased from 124 cases/million person-years to 140.6 cases/million person-years from 1970 to 2004, the 5-year overall survival rate increased from 58.1% to 79.6% [2, 13]. As we all know, radiation therapy is a critical method for treat pediatric tumors. Due to the advancement of radiotherapy technology, radiotherapy is playing an increasingly important role in clinical work. So far, there is no unified standard for dose index of pediatric tumor radiotherapy. In addition, radiation dose, optimal exposure time and so on are still under discussion.

Therefore, this paper aims to briefly summarize the characteristics of radiotherapy in pediatric tumors and introduces the application of radiotherapy in some major pediatric tumors.

MATERAIALS AND METHODS

Method

Relevant articles published in the PubMed database between 2010 and 2022 were searched. Keywords include Children, Pediatric, tumor, Radiotherapy, Treatment. The researchers then looked at the data one by one and looked at the citation, which was their reference at the end of each paper. We also conducted a search for relevant articles published between 2013 and 2022 in the China National Knowledge Infrastructure (CNKI) database. The next terms were included in the search: Children, Pediatric, tumor, Radiotherapy, Treatment.

Data source

PubMed and CNKI databases were searched for monographs and reviews from December 2022.

Data screening and evaluation

Inclusion criteria included, articles on radiotherapy of childhood tumors; experimental and clinical studies of different radiological methods; large number of research samples, the research methods and content were detailed and the article was easy for readers to understand. Exclusion criteria included, meta-analysis article and the literature was published before 2010.

Data extraction and literature quality evaluation

For literature selection and quality assessment, two authors independently read the abstract in accordance with the inclusion and exclusion criteria given in the paper. If the content of the abstract was clear, it was directly included; if the content of the abstract was unclear, the experimental method was read to see whether it met the inclusion criteria. If two authors have different opinions about the same article, three colleagues check them. The final decision was made after discussion among the three authors. A total of 56 articles were selected, including 45 in English and 11 in Chinese. A total of 40 English experiments and literature reviews were included in this study. The literature retrieval rate was 71.43%. Figure 1 shows the selection of literature retrieval. Finally, we extract relevant information from the following report by reading the whole article in detail.

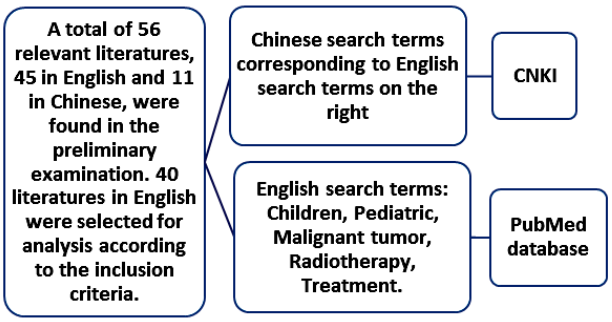

Figure 1. Literature search process.

RESULTS AND DISCUSSION

Radiation therapy for children with tumors

Correct diagnosis and typing

Whether childhood leukemia or malignant solid tumor, standardized treatment is a prerequisite for good prognosis. Accurate classification is the basis of standardized treatment. For example, the international treatment plan design is based on morphology, immunology, cytogenetics, and molecular biology typing (MICM typing). The application of multi-parameter flow cytometry (MP-FCM), high resolution banning technology, fluorescence in situ hybridization (FISH), multiple PCR and other technologies provide guarantee for MICM typing. Non-Hodgkin lymphomas (NHL), neuroblastoma (NB), rhabdomyosarcoma (RMS) and other malignant solid tumor treatment plans are also designed on the basis of preoperative staging and pathological classification, and are gradually developing to molecular classification, such as the classification of NB included N-my c gene. At present, the NHL widely uses the 2008 WHO NHL Pathologic classification and the American Children's Study Center (St. Jude) NHL staging system. NB uses the International NB Staging System (INSS). RB uses the St. Jude staging system. RMS uses the TNM International Classification of Cancer System. Tumors in children mostly originate from mesenchymal tissue, about half of which are accompanied by

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congenital malformations. In the early stage, most of them are treated with fever, headache, or painless mass [14], which is different from tumors in adults. The incidence of tumors in children is related to radiation exposure, drug, virus infection and genetic factors. It has been proved that the occurrence of pediatric tumors can be promoted by gene polymorphism and methylation, and the family history of tumors is also a high-risk factor. The risk of children's illness will also be increased by chemical and physical factors such as automobile exhaust, indoor and outdoor chemicals, cigarettes, and air pollution [15]. There are differences in the incidence of tumors in children of different ages. Children aged 0 to 4 are more likely to get sick. Statistics show that the incidence of tumors in children of this age is twice that in children aged 5 to 14 [16]. In addition, the incidence of male children is significantly higher than that of women, especially acute leukemia, non-Hodgkin's lymphoma, Ewing's sarcoma, osteosarcoma, and other diseases. Most cases come from male children [17].

Characteristics of radiotherapy

Radiotherapy is of special significance in the treatment of childhood malignancies. Oncologists need to weigh the benefits of radiotherapy against the adverse effects associated with radiotherapy to determine the target area and dose. Most pediatric tumors are sensitive to radiotherapy and are classified according to radiotherapy sensitivity into highly sensitive, moderate sensitive and low sensitive. Highly sensitive tumors include Wilms tumor, lymphoma, acute leukemia, etc. Moderately sensitive tumors include retinoblastoma, neuroblastoma, rhabdomyosarcoma, etc. Low-grade sensitive tumors include osteosarcoma, fibrosarcoma, etc. Most children's tumors grow rapidly and have unclear boundaries with surrounding normal tissue, which requires a larger irradiation volume than conventional radiotherapy. In order to protect the surrounding normal tissue, the irradiation field is often reduced in time according to the tumor changes after radiotherapy reaches a certain dose in clinical practice to reduce tissue damage. At present, three-dimensional conformal intensity modulated radiotherapy technology is widely used to make the dose distribution in the target area more uniform, and conformal irradiation is carried out according to the target area design, to obtain better protective effect of surrounding tissues than two-dimensional radiotherapy technology [18]. Cutting-edge radiotherapy technologies, such as proton radiotherapy, due to their special physical properties, have a sharp decline in dose intensity (Bragg peak) after the end of the proposed range, which can further reduce the dose to normal tissues [19]. The effects and individual differences of children's tumors on radiotherapy are more obvious than those of adults, and the tolerance of normal tissues to radiation is also very different from that of adults. In order to avoid radiotherapy injury, lower single dose and total dose are used in clinical work. The value of radiotherapy in the treatment of pediatric tumors is worthy of affirmation. Preoperative radiotherapy can reduce the tumor, increase the radical resection rate, and eliminate invisible subclinical lesions. Radiotherapy is an appropriate remedy for positive postoperative margins. The combination of chemotherapy and radiotherapy can enhance the efficacy of each other and reduce the effective radiotherapy dose.

Common radiotherapy-related side effects

In children with tumors, the gap between normal tissue tolerance and lethal tumor dose is small, which results in a higher incidence and severity of complications after radiotherapy than in adults. Research data show that two-thirds of children who receive radiation therapy suffer from at least one chronic complication during long-term survival, and some even threaten life [20]. Improving the long-term quality of life of survivors is a major challenge in clinical work. 1) Intellectual influence later intellectual impairment is the most common complication in children receiving whole brain radiotherapy, especially in patients with radiation dose exceeding 36 Gy [21]. This is related to brain tissue atrophy and necrosis caused by brain radiotherapy. 2) Growth retardation is mainly due to irradiation affecting the osteogenic process, irradiation of the metaphysis leads to calcium deficiency, and irradiation of the diaphysis leads to periosteum damage. Together, these factors lead to poor bone growth and development. 3) Endocrine dysfunction insufficient secretion of growth hormone is the most common endocrine disease receiving whole brain radiotherapy [22].

Some studies have confirmed that in brain radiotherapy, the sensitivity of hypothalamus radiation damage is higher than that of pituitary [23], resulting in the most common phenomenon of insufficient growth hormone secretion, which directly affects the height of patients. The average height of tumor survivors who received more than 24 Gy whole brain irradiation is 5-10 cm lower than that of those who did not receive radiotherapy in the same period. 4) Hypothyroidism is most likely to occur in patients receiving neck irradiation, and most patients require lifelong thyroxin replacement therapy [23]. TSH overstimulation caused by hypothyroidism has the risk of promoting thyroid tumorigenesis. 5) Heart injury Children receiving chest irradiation will lead to heart exposure in the irradiation field. Common heart injuries include acute pericarditis, chronic pericarditis, myocarditis and endocarditis. CCSS statistics show that the incidence of heart-related death in patients who received spinal

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cord or chest radiotherapy in childhood is more than twice that of normal people [24]. 6) Radiation-related lung injury Lung injury caused by radiotherapy is caused by the damage of type ii alveolar cells and endothelial cells. The incidence of acute radiation pneumonia is low, while chronic pulmonary fibrosis and restrictive lung disease are more common.

Radiotherapy of some tumors

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia is a prevalent childhood blood cancer, accounting for 75% of leukemias. The clinical manifestations of acute lymphoblastic leukemia are generally anemia, fever and infection, hemorrhage, organ tissue infiltration, and testicular leukemia. Extramedullary leukemia, especially central nervous system leukemia, complicates most patients, resulting in poor prognosis. Chemotherapy is the main treatment method. The application value of radiotherapy in the treatment of leukemia is mainly reflected in the whole-body irradiation before bone marrow transplantation, the management of extramedullary recurrence and the prevention and treatment of central nervous system leukemia. Before bone marrow transplantation, it is necessary to minimize the immune response of the body, which will lead to severe transplantation reaction after surgery. Before bone marrow transplantation, whole body radiotherapy combined with chemotherapy can improve this situation and further kill tumor cells [23]. The survival rate of segmented radiotherapy is better than that of single radiotherapy, and the incidence of complications can be reduced. There is no unified standard for the relationship between dose and time, and the total dose is mostly 1200-1600 cGy, twice a day or three times a day. MSK Cancer Hospital in the United States recommends a single dose of 120 cGy, three times a day, and a total dose of 1320 cGy [25]. Overall, we observed improvements across all subgroups during the evaluated 32-year period in accordance with SCI guidelines. Among the 8201 patients diagnosed with ALL, 92% were of white ethnicity, and 28% were categorized as AYAs (Adolescents and Young Adults). Among the 3958 AML patients, 86% were white, and 77% were AYAs. Among the 15,107 HL patients, 89% were white, and 93% were AYAs (figures 2-8). Overall, we observed improvements across all subgroups during the evaluated 32-year period in accordance with SCI guidelines. Among the 8201 patients diagnosed with ALL, 92% were of white ethnicity, and 28% were categorized as AYAs (Adolescents and Young Adults).

Among the 3958 AML patients, 86% were white, and 77% were AYAs. Among the 15,107 HL patients, 89% were white, and 93% were AYAs. Central nervous system leukemia often occurs in the complete remission period after leukemia treatment. Preventive treatment including radiotherapy can reduce the incidence rate from 60% to 10% and improve the long-term survival rate of patients. In order to avoid side effects such as growth disorders and myelosuppression caused by spinal cord irradiation, the main prophylactic treatment is total cranial irradiation combined with intrathecal injection of methotrexate (MTX). Total cranial radiotherapy should include subarachnoid space and eye protection. It is generally believed that a total dose of 24 Gy can play a therapeutic role, but CCSG found that the efficacy of a total dose of 18 Gy and 24 Gy was comparable for patients at standard risk. MTX intrathecal injection is administered 1 week or 1 day before radiotherapy, with a single dose of 8-12 mg/ m2. Patients under 2 years old were given radiotherapy dose of 20 Gy, and patients over 2 years old were given radiotherapy dose of 18-24 Gy/ 14-15 F. Intrathecal injection of MTX2 was given four to six times a week during radiotherapy [26]. Patients who cannot receive intrathecal injection can receive total cranial plus total spinal cord irradiation, and spinal cord radiotherapy dose of 18-20 Gy is appropriate. Helical tomography radiotherapy technology can enable patients to complete central nerve irradiation therapy at one time, avoiding dose imbalance and cold hot spots caused by radiation field convergence and other reasons caused by traditional technology, and at the same time, it can better protect normal tissues, which has obvious advantages in clinical practice [27]. In the low-risk population, MTX, cytarabine, and prednisone triple intrathecal injection therapy can be used to avoid radiotherapy, but radiotherapy is essential for the high-risk population. For local lesions infiltrated by extramedullary leukemia, 24-30 Gy irradiation can be given to control the progress, during which the field is narrowed according to the tumor volume.

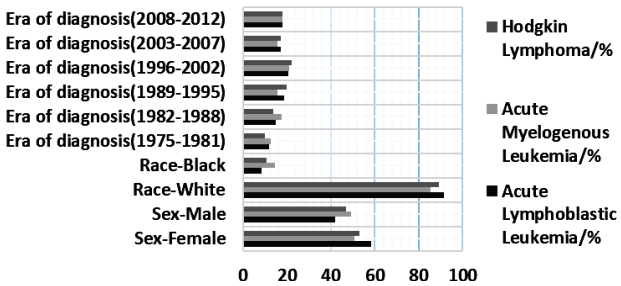

Figure 2. Bar chart of Demographic Distribution of Acute Lymphoblastic Leukemia (ALL), Acute Myelogenous Leukemia (AML), and Hodgkin Lymphoma in Pediatric, Adolescent, and Young Adult Populations: An Analysis Based on Race, Sex, and Era of Diagnosis (Surveillance, Epidemiology, and End Results 9; 1975-2012).

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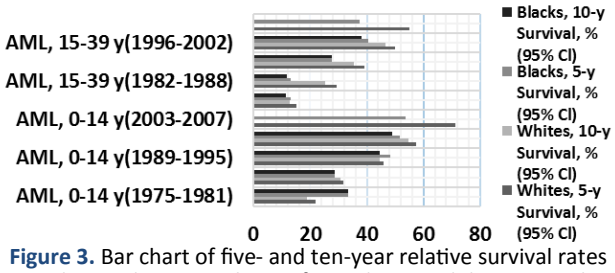

Figure 3. Bar chart of five- and ten-year relative survival rates and annual percent change for pediatric, adolescent, and young adult patients with acute lymphoblastic leukemia (ALL) stratified by race, age, and era of diagnosis.

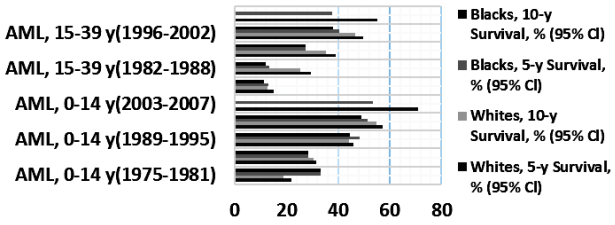

Figure 4. Bar chart of five- and ten-year relative survival rates and annual percent change for pediatric, adolescent, and young adult patients with acute Myelogenous leukemia (AML) stratified by race, age, and era of diagnosis.

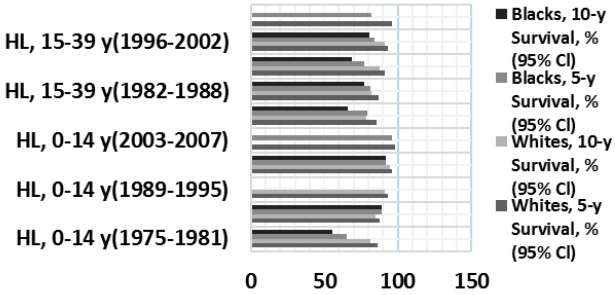

Figure 5. Bar chart of five- and ten-year relative survival rates and annual percent change for pediatric, adolescent, and young adult patients with Hodgkin lymphoma (HL) stratified by race, age, and era of diagnosis.

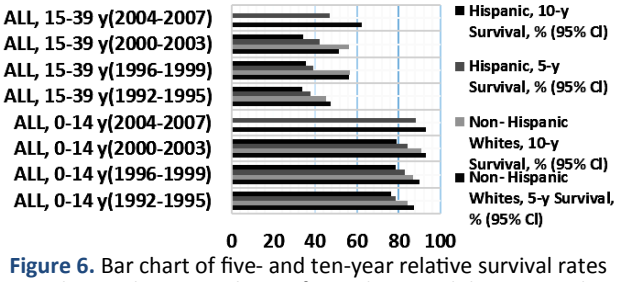

Figure 6. Bar chart of five- and ten-year relative survival rates and annual percent change for pediatric, adolescent, and young adult patients with acute lymphoblastic leukemia (ALL) stratified by race, age, and era of diagnosis.

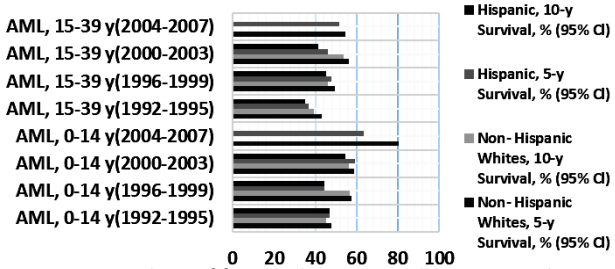

Figure 7. Bar chart of five- and ten-year relative survival rates and annual percent change for pediatric, adolescent, and young adult patients with acute Myelogenous leukemia (AML) stratified by race, age, and era of diagnosis.

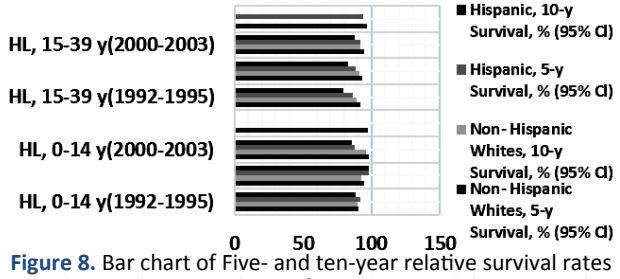

Figure 8. Bar chart of Five- and ten-year relative survival rates and annual percent change for pediatric, adolescent, and young adult patients with Hodgkin lymphoma (HL) stratified by race, age, and era of diagnosis.

Hodgkin's lymphoma

Childhood Hodgkin's lymphoma is considered a curable cancer, and radiation therapy was shown to be effective in treating Hodgkin's lymphoma in the early 1800s. Chemotherapy combined with radiotherapy, currently the standard treatment for this disease, has increased the cure rate of Hodgkin's lymphoma to more than 90% [28]. The biological behavior and outcome of Hodgkin's lymphoma in children are similar to those in adults, and the treatment principles can be referred to conventional methods. However, considering the long-term damage of children to radiation therapy, the dose of radiation needs to be strictly limited. According to the WHO pathological classification criteria, Hodgkin's lymphoma can be divided into classical (cHL) and nodular lymphocytic (NLPHL), of which classical is the most common. For the treatment of cHL, the CCG5942 study showed that among patients with typical Hodgkin's lymphoma who had a complete response after chemotherapy, the 10-year progression-free survival rate in the non-radiotherapy group was 83%, while that in the radiotherapy group was increased to 91%, which confirmed the application value of radiotherapy in the treatment of cHL [29].

Patients can be stratified into low, medium, and high risk according to the assessment of risk factors such as mass size, lymph node involvement and extranodal lesions. Studies have shown that low risk patients with pathological complete response have little benefit from radiotherapy and can be exempted from radiotherapy, while medium and high-risk patients are necessary to consolidate radiotherapy after chemotherapy regardless of whether they achieve complete response [30]. Affected field radiotherapy is currently the standard therapeutic radiation field, and patients cannot benefit from expanding the radiation field and preventing radiation. With the development of precise therapy, further reduction of the radiation field is required to reduce the incidence of related complications. As for the selection of radiotherapy dose, 25 Gy more was given in the past [31]. The GPOH-HD 95 study found that the same effect could be achieved by reducing the dose to 20 Gy. For large residual lesions, the GTV dose should be increased to 35 Gy. NLPHL is less

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common and has a better prognosis than cHL. Mauz-Körholz *et al.* [32] used radiotherapy alone to treat children with NLPHL, and the 5-year event-free survival rate reached 87% and the 10-year overall survival rate reached 100%. At present, the treatment of early and middle NLPHL tends to be a single treatment, and the radiotherapy dose is recommended to be 20-25 Gy.

Non-hodgkin's lymphoma

Non-Hodgkin's lymphoma is the third most common childhood tumor, primarily affecting children between the ages of 7 and 11. The prognosis of different pathological types is quite different. The disseminated type with good cell differentiation has a good prognosis, while the lymphoblastic type has a poor prognosis. All types of non-Hodgkin's lymphoma require high-dose chemotherapy, and the use of radiation has decreased as chemotherapy efficacy has increased. Some studies have confirmed that radiotherapy has no obvious benefit for patients with stage I and II, but local radiotherapy can be used for patients with residual lesions and symptoms of tumor compression after chemotherapy. Radiotherapy can quickly relieve airway compression, superior vena cava syndrome and other symptoms. Generally, the standard treatment regimen typically consists of a single dose of 2~2.5 Gy and a cumulative dose of 6~7.5 Gy [32]. The preventive treatment of the central nervous system is necessary. Mandell *et al.* [35] adopted the preventive method of intrathecal injection of MTX instead of total cranial radiotherapy, and only 1 case of central nervous system metastasis recurrence occurred in 58 patients. This suggests that radiotherapy is not necessary for the prevention of non-Hodgkin's lymphoma. However, for patients who have been diagnosed with CNS lymphoma, radiotherapy is needed to control the tumor and improve the quality of life. Bone marrow transplantation after chemotherapy can improve the prognosis of patients with non-Hodgkin's lymphoma, as can systemic radiotherapy before transplantation.

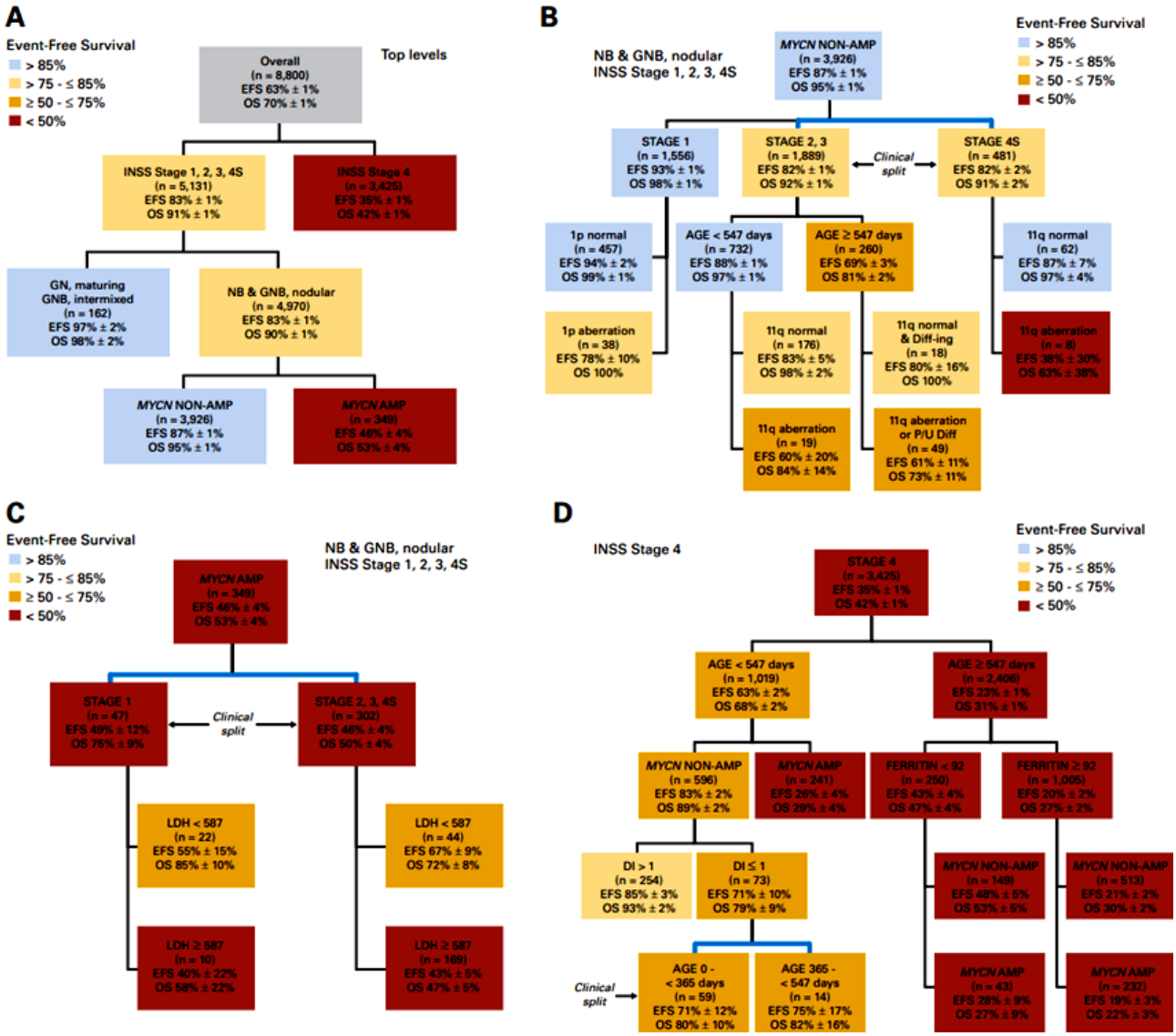

Figure 9. EFS tree regression analysis of the International Neuroblastoma Risk Group (INRG) analysis queue.

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Neuroblastoma

Neuroblastoma (NB) is the most prevalent extracranial solid tumor in childhood, accounting for approximately 8%-10% of all childhood malignant tumors and contributing to 15% of childhood cancer-related mortality [33]. The prognosis for high-risk children is generally poor, with a 5-year survival rate of less than 40% under conventional treatment [34]. Neuroblastoma originated from the medulla of sympathetic ganglia or adrenal gland, accounting for the first incidence of solid tumors in children. The biological behavior of this kind of tumor varies greatly from individual to individual. Patients less than 1 year old have the possibility of cure, and comprehensive treatment is needed for advanced patients. The incidence of neuroblastoma in China has been increasing year by year, and most of them are diagnosed as stage iii or iv, with a highly invasive and poor prognosis [35]. According to the clinical stage of INSS, DNA ploidy, MYCN gene, onset age and tumor cell differentiation degree, neuroblastoma is divided into four groups: very low risk, low risk, medium risk, and high risk [36]. Figure 9 shows the EFS tree regression analysis of the International Neuroblastoma Risk Group (INRG) analysis queue. (A) is the top layer of the whole tree. Classical metastasis is a critical prognostic factor identified through EFS tree regression analysis EFS and OS were 83%±1% and 91%±1%, respectively, in patients with INSS not in stage 4 (including stage 4S), and 35%±1% and 42%±1%, respectively (figure 9A). (B) is the subtree of NB and gnb nodular, non-stage 4 MYCN non-AMP tumor patients.

The separation of stage 2 and 3 patients from stage 4S patients was a clinical decision and was not statistically significant. EFS of MYCN non-AMP tumor patients were 87%±1%, OS 95%±1%, EFS of MYCN AMP tumor patients 46%±4%, OS 53%±4%. In the MYCN non-AMP cohort, the prognosis of stage 1 patients was significantly better than that of stage 2, 3 and 4S patients (EFS: 93%±1% vs 82%±1%; OS 98%±1% v92%±1%; figure 9B). (C) The analysis further reveals a noteworthy subtree consisting of NB and gnb nodular, non-stage 4 MYCN AMP patients. The distinction of stage 1 from stage 2, 3, and 4S patients is based on clinical judgment and lacks statistical significance. Although the incidence of EFS in stage 1 patients does not differ significantly from that in stage 2, 3, and 4S patients, stage 1 tumor patients with MYCN AMP typically receive less intensive treatment.

Due to differences in treatment strategies, further survival tree analysis was carried out in stage 1 patients and stage 2, 3 and 4S patients respectively. LDH has the greatest effect on the prognosis of stage 1 tumor patients with MYCN AMP (figure 9C). (D) is the subtree of patients with stage 4 INSS. The rates of EFS and OS in children under 18 months were 63% ±2% and 68%±2%, respectively. The rates of EFS and OS in children over 18 months were 23%±1% and 31%±1%, respectively. Although EFS tree regression showed that serum ferritin (<*v*≥92 ng/mL) was a prognostic factor for patients aged 18 months and older, but the results were poor in both cohorts, with EFS rates of 43%±4% and 20%±2%, respectively (figure 9D) [37]. Very low-risk and low-risk patients, especially those with no N-MYC expansion and negative lymph nodes, can be treated with surgery alone, middle-risk patients can be treated with neoadjuvant chemotherapy before surgery, and radiation therapy can be used for children older than 1 year.

The POG study showed that patients who received surgery combined with chemoradiotherapy had a tumor-free survival rate of 58%, which was significantly higher than patients who received surgery combined with chemotherapy alone (31%). The treatment of high-risk group is relatively complex, and the efficacy is not good. It is generally recommended to actively carry out high-dose chemotherapy and bone marrow transplantation after operation, and the failure mode is mostly the recurrence of primary lesion. In clinical practice, there is also a treatment method of internal radiotherapy with meiodaforman radionuclide. Studies have confirmed that this therapy combined with chemotherapy is safe, and the remission rate of refractory tumors can reach 25% [36], which can be used as an alternative treatment plan for high-risk neuroblastoma. In addition to conventional indications, radiation therapy has a good effect on soft tissue and bone-related pain symptoms.

The irradiation field of the limited stage is limited according to the tumor area of CT and MRI. If lymph node metastasis and surrounding infiltration occur, the irradiation scope needs to be expanded, but whether the lymph node area of the next station needs to be irradiated is controversial. In terms of radiotherapy dose, it is recommended that children aged less than 18 months receive local irradiation of 15 Gy, and add 5-10 Gy after field shrinkage. Children over 18 months old were given 15~20 Gy in local field, and 5~10 Gy was added after field shrinkage. For children with liver enlargement, attention should be paid to kidney protection during liver irradiation, and the total dose of 4.5~6 Gy is appropriate. For patients with systemic metastasis, autologous or homogenous myelosuppression is used as salvage treatment, and whole-body irradiation is required before suppression, with a dose of 7.5-12 Gy [37]. At present, there have been some large-scale clinical studies on the treatment of I^{131} radioisotope in neuroblastoma, and it has been found that neuroblastoma has a sensitive response to I^{131} [37].

Retinoblastoma

Retinoblastoma is the most common orbital tumor in children, which originates from

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neuroepithelial cells and seriously threatens children's vision and even life [38]. The occurrence of this tumor may be related to the inactivation of RB gene and the damage of many other genes. The treatment of retinoblastoma should preserve vision as much as possible on the premise of improving survival and prognosis, which is related to the quality of life of long-term survival. When the lesion is limited, local treatment can be selected. At present, the commonly used methods include transpupillary thermotherapy, photocoagulation therapy, cryotherapy, and selective arterial focus chemotherapy and radionuclide method [39]. Enucleation, as a radical treatment, is suitable for patients whose vision cannot be preserved after local treatment. External radiation therapy is suitable for incomplete local treatment, multiple tumors, tumor invasion into the vitreous, tumor progression, etc. When the tumor appears intracranial infiltration or metastasis, whole cranial radiotherapy is required.

Retinoblastoma is prone to subretinal spread and metastasis and vitreous implantation is common. In clinical practice, the extended irradiation field is used to cover the entire retina [39]. The traditional radiotherapy technology adopts the two-field irradiation method of anterior field and lateral field, and the lead plate is added to protect the lens. In recent years, the new radiotherapy technology such as intensity modulated radiotherapy and proton radiotherapy is more and more widely used, which can be conformally illuminated along the height of the eyeball to better protect the surrounding tissues [39]. The dose of local radiotherapy is 35-50 Gy, and studies have shown that the incidence of retinal degeneration is significantly increased when the single irradiation dose exceeds 2.5 Gy [39]. Therefore, a single dose of 1.8-2 Gy is more appropriate, and the total dose of radiotherapy can be appropriately reduced when combined with other local treatment methods.

Gliomas

Gliomas in children tend to occur in the cerebral hemispheres and are more common in the sub tentorium. They are typically characterized by increased intracranial pressure and neurological symptoms caused by tumor compression. According to the WHO grade of glioma, grade I and II are more common in children, while grades III and IV are relatively rare. For low-grade gliomas, surgical treatment is preferred, and radiotherapy is not required if complete resection is achieved. Local radiotherapy can be given to those with incomplete surgical resection, and temporary observation can be carried out for children less than 3 years old, and radiotherapy can be given after 3 years old. Chemotherapy is used for patients who have not been completely resected, are less than 3 years old, and have high risk factors for recurrence. The main chemotherapy drugs include temozolomide, lomustine, procarazid, etc. All patients with high-grade glioma need radiotherapy and chemotherapy after surgery.

There is no standard regimen for chemotherapy, but lomustine + vincristine + prednisone combined regimen or oral temozolomide alone is used. GTV in the target area of radiotherapy should include the whole tumor bed or residual lesion, and CTV should be expanded by 1.5~2 cm based on GTV. Whether to completely surround the edema area around the lesion is controversial at present. Regarding irradiation segmentation methods, a recent study compared the prognosis of conventional radiotherapy (6-week course) with hyperfractionated radiotherapy (6-week course, 117 cGy twice daily, total dose of 7020 cGy). After follow-up, the median time overall survival (OS) was 8.5 months in the conventional group and 8.0 months in the hyperfractionated group. Compared with conventional radiotherapy, OS or event-free survival (EFS) has not been found to be significantly better in patients receiving hyperfractible radiotherapy, so conventional segmentation is still recommended [40]. The irradiation dose was 50-54 Gy, and the GTV was increased to 60 Gy after field shrinkage. In recent years, some researchers have applied proton radiotherapy technology in the treatment of glioma. Hug *et al.* [41] performed proton radiotherapy on 27 children with low-grade glioma. After 39 months of follow-up, the local control rate reached 78% and the survival rate reached 85%, reflecting the advantages of proton radiotherapy. The prognosis of pediatric high-grade glioma is poor, with a 5-year survival rate of less than 19%. The improvement of prognosis depends on early detection and timely treatment of the disease.

Wilms tumor

Wilms tumor, also known as Wilms tumor, originates from the embryo base of the metanephric kidney and can grow anywhere in the kidney. It is one of the most common tumors in children. According to the tumor morphology, the tumor can be divided into good prognosis type (FH) and poor prognosis type (UH), and the prognosis difference between the two types is obvious. Radiotherapy was early applied in the treatment of Wilms tumor, and the survival rate increased from 30% in the 1930s to 80% in the 21st century [42]. The result of Singh *et al.* [43] showed that most patients present at an advanced stage, and therefore most cases are difficult to perform surgery when present. They suggest that neoadjuvant chemotherapy after surgery may be considered a balanced approach with comparable response and survival outcomes [43]. Surgery is the first choice for early patients with limited stage. When the tumor is huge and difficult to operate, preoperative radiotherapy can be performed, and

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surgery can be performed when the tumor shrinks to be surgically respectable, with an irradiation dose of 15-20 Gy. For postoperative patients in FH group, radiotherapy should not be given to children less than 1 year old in principle to avoid later radiotherapy reactions. Radiotherapy is not required after stage I and II, but peritoneal metastasis and liver invasion are common in stage iii patients, requiring total abdominal irradiation at a dose of 10.8 Gy/6F. For patients with incomplete surgical resection, 10.8 Gy/6 F is recommended.

All patients in the UH group needed total abdominal irradiation with a dose of 10.8 Gy/6 F and a local dose of 10.8 Gy/6 F after field contraction. The dose of local exposure is proportional to the age of the child, as recommended by NWTS-4 (National Wilms Tumor Investigator). Children under 12 months were given 12-18 Gy, and children over 41 months were given 38 Gy. SIOP2017 found that irradiation of infiltrating lymph nodes in stage III patients did not benefit significantly [44]. NWTS-4 studies have shown that the prognosis of postoperative patients is significantly correlated with the timing of radiotherapy intervention [45]. Radiotherapy is recommended to be given within 10 days after surgery and no more than 14 days after surgery. For stage IV patients with lung metastases, whole-lung radiotherapy can benefit from increasing the irradiation of the whole lung by 12 Gy on the basis of abdominal radiotherapy and increasing the number of local metastases to 16-18 Gy.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common malignant soft tissue sarcoma in children and adolescents, accounting for 3% to 7% of childhood malignancies, and about 350 new cases are diagnosed in the United States each year [46]. Missaoui *et al.* [47] reported on rhabdomyosarcoma in Tunisia, showing that rhabdomyosarcoma accounted for 53.6% of soft tissue sarcomas and 3.8% of all childhood cancer cases registered during the same period, with a male to female ratio of 2.7 and a mean age of diagnosis of 5.9 years. RMS occurs in the head and neck, bladder, extremities, and trunk. Embryonal rhabdomyosarcoma (ERMS) and alveolar rhabdomyosarcoma (ARMS) are mainly divided into two subtypes according to different histological types. In the past few years, the treatment of RMS has entered a bottleneck period. Even after high-intensity and multi-mode comprehensive treatment, high-risk children still benefit little, and the 5-year survival rate is no more than 50% [48]. In the past 30 years, the prognosis of the disease has been significantly improved, and the 5-year survival rate has reached more than 70% [49].

The treatment principle of pediatric rhabdomyosarcoma is like that of other solid tumors, mainly surgery and chemotherapy to control the local primary lesion, and chemotherapy to eliminate the minor lesion to prevent hematogenous metastasis. Rhabdomyosarcoma is sensitive to radiotherapy and can be used in various stages of treatment [50]. These include primary irradiation, metastatic lymph node area irradiation, and postoperative irradiation. The dose of primary lesions and invaded lymph nodes should be 66 Gy, and the dose of subclinical lesions under microscope should be 45-50 Gy. In the advanced stage, 18 Gy of whole lung irradiation should be performed for lung metastases, 18 Gy of whole abdomen irradiation should be performed for abdominal metastases, and 30.8 Gy of local dose should be performed for retroperitoneal metastases [49, 50]. Whole cranial + spinal cord irradiation is performed when central nervous system invasion occurs. At present, there are also some clinical trials on rhabdomyosarcoma. For example, the randomized phase III trial studied the efficacy of combination chemotherapy (vincristine sulfate, penicillin, and cyclophosphamide alternately used vincristine sulfate and irinotecan hydrochloride) and combination chemotherapy plus temiolimus in the treatment of rhabdomyosarcoma (cancer formed in soft tissues such as muscle) [51].

After treatment, there is an intermediate chance of recovery (medium risk). The drugs used in chemotherapy prevent the growth of tumor cells in different ways, either by killing cells, preventing cell division, or by preventing cell proliferation. Combined chemotherapy and temiolimus may prevent the growth of tumor cells by blocking some enzymes needed for cell growth. However, it is still unclear whether combination chemotherapy or combination chemotherapy plus temiolimus is more effective in treating patients with moderate risk rhabdomyosarcoma. In recent years, brachytherapy has been used and accepted. The application of particle implantation therapy in adult solid tumors has achieved good results, but its application in pediatric tumors is limited due to the uncertainty of dose and number for children. With the development and improvement of physics and dosimetry, brachytherapy is expected to become a new option for the treatment of solid tumors in children.

Problems and challenges of radiotherapy in children

More and more patients will benefit from radiotherapy with the further study of biological behavior of children's tumors and the improvement of radiotherapy technology. However, there are still many practical problems and technical difficulties in clinical work. It is necessary to explore the optimal radiation dose and combination chemotherapy scheme for different types of tumors. The protection of normal tissues plays a vital role in radiotherapy technology, and even relates to the long-term survival time and quality of life of patients. More safe

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and reliable treatment methods, including proton therapy, heavy ion therapy and other high-tech radiation technologies, provide patients with more safe and reliable treatment methods, which can further reduce the dose of organs at risk, thus avoiding and reducing related complications. Due to the immaturity of children's mental development, the compliance to treatment is significantly lower than that of adults.

The accuracy of positioning during radiotherapy will be directly affected by the patient's degree of cooperation, specifically affecting the therapeutic effect. For patients who cannot cooperate with treatment, sedatives and anesthetics are often used in clinical practice, which requires consideration of the selection and dosage of such drugs. The safety and long-term side effects of repeated use need to be measured and discussed, and it is critical to do a good job of parent communication. In line with the current medical situation in China, there is a lack of bulk data analysis on the incidence of children's tumors, and most data sources are limited in regions. Therefore, the epidemiological statistics of big data is necessary, which is the basis for the research on etiology and prognosis, to fully understand the characteristics of pediatric tumors in China and help to take preventive measures and early detection of diseases. In addition, due to the relative shortage of human resources and equipment resources for radiotherapy in China, and the development of radiotherapy discipline is weaker than that of surgery and chemotherapy, a large part of patients misses the best time for radiotherapy intervention, and further whole course treatment effect will also be affected.

CONCLUSION

In conclusion, children are a special group of people, and the target area needs to be more precise, and the dose control is stricter in radiotherapy. Tumor is a kind of disease that needs comprehensive treatment. During treatment, the pursuit of single high-dose radiotherapy should be avoided as far as possible. Instead, the most reasonable treatment plan for children should be made by combining the comprehensive consideration of surgery and chemotherapy departments, that is, to control the growth of the tumor and minimize the impact on its growth and development.

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Declarations

***Consent for publication*:** The patients have given their consent for publication. Written informed consent was obtained from the patients for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

***Competing interests*:** The authors declare that they have no competing interests.

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