THE EFFECTIVENESS OF INTRAOPERATIVE PHOTODYNAMIC THERAPY IN THE COMPLEX TREATMENT OF STAGE III AND IV NEPHROBLASTOMA IN CHILDREN

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Abstract

Nowadays, the problem of malignant neoplasms management remains a priority task. To achieve further progress in cancer treatment, it is necessary to focus on existing but still undervalued methods. One of these approaches is photodynamic therapy (PDT), which can be used in combination with surgery as well as with other antitumor drugs without any risk of inducing cross-resistance. Being miner invasive and selective in tumor targeting, and having no risk of complications, the technique is attractive for application in oncologic pediatrics as an innovation capable of expanding the range of therapeutic techniques. The aim of the study was to investigate the effectiveness of intraoperative photodynamic therapy in children with stage III–IV nephroblastoma. The study included 66 patients aged 0–11 years with stage III and IV nephroblastoma. The patients of the control group (35 children) underwent surgical treatment in combination with chemotherapy and radiation therapy according to the SIOP protocol. The patients of the main group (31 children) underwent therapy according to the SIOP protocol, but in combination with intraoperative PDT. The 5-year survival rate in the main group was 90.3%, in the control group – 71.4% ($p = 0.05$). The recurrence rate in the main group was 9.7%, in the control group – 11.4%. Thus, high therapeutic efficacy of PDT during intraoperative irradiation of the tumor bed after its removal has been demonstrated. The technique contributes to the increased survival rate of patients with retroperitoneal tumors, which is a promising method to be used in pediatric oncological practice.

Key words: pediatric surgery, photodynamic therapy, nephroblastoma, radachlorin.

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For citations: Rostovtsev N.M., Polyakov V.G., Kuzmina N.E., Neizvestnykh E.A., Kuzmina A.V. The effectiveness of intraoperative photodynamic therapy in the complex treatment of stage III and IV nephroblastoma in children, *Biomedical Photonics*, 2025, vol. 14, no. 4, pp. 34–42. doi: 10.24931/2413–9432–2025–14-4-34-42

ЭФФЕКТИВНОСТЬ ИНТРАОПЕРАЦИОННОГО ПРИМЕНЕНИЯ ФОТОДИНАМИЧЕСКОЙ ТЕРАПИИ В КОМПЛЕКСНОМ ЛЕЧЕНИИ НЕФРОБЛАСТОМЫ III, IV СТАДИИ У ДЕТЕЙ

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Резюме

Проблема борьбы со злокачественными новообразованиями остается приоритетной для современного общества. Для достижения дальнейшего прогресса в лечении онкологических заболеваний необходимо акцентировать внимание на существующих, но все еще недооцененных методиках. Одной из таких технологий является фотодинамическая терапия (ФДТ), которая может использоваться в сочетании с хирургическим вмешательством, применяться с другими противоопухолевыми препаратами без риска индукции перекрестной резистентности. Малая инвазивность, избирательность в поражении опухоли, отсутствие риска осложнений делают методику привлекательной для применения в онкопедиатрии как инновации, способной расширить диапазон используемых тера-

певтических методик. Целью исследования стало изучение эффективности ФДТ у детей с нефробластомой III-IV стадии при интраоперационном применении. В исследование включены 66 пациентов в возрасте от 0 до 11 лет с нефробластомой III-IV стадии. Пациентам контрольной группы, включавшей 35 детей, проведено хирургическое лечение в комплексе с химиотерапией и лучевой терапией по протоколу SIOP. Пациентам основной группы, включавшей 31 ребенка, проведена терапия по протоколу SIOP, но в комбинации с интраоперационной ФДТ. 5-летняя общая выживаемость в основной группе составила 90,3%, в контрольной – 71,4% (p = 0,05). Частота рецидивов в основной группе составила 9,7%, в контрольной – 11,4%. Предложенная методика комплексного лечения забрюшинных опухолей по протоколу SIOP в комбинации с интраоперационным фотодинамическим воздействием на ложе удаленной опухоли у детей позволяет улучшить результаты оперативного лечения и увеличивает выживаемость пациентов с забрюшинными опухолями. Полученные данные об эффективности делают методику перспективной для применения в детской онкологической практике.

Ключевые слова: детская хирургия, фотодинамическая терапия, нефробластома, радахлорин.

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Для цитирования: Ростовцев Н.М., Поляков В.Г., Кузьмина Н.Е., Неизвестных Е.А., Кузьмина А.В. Эффективность интраоперационного применения фотодинамической терапии в комплексном лечении нефробластомы III, IV стадии у детей // Biomedical Photonics. – 2025. – Т. 14, № 4. – С. 34–42. doi: 10.24931/2413–9432–2025–14-4-34-42

Introduction

Even with all the latest technological advances, childhood cancer remains a major global problem: malignant neoplasms remain the leading cause of childhood mortality, second only to external causes. Approximately 3,500 children in Russia are diagnosed with malignant neoplasms annually, which is approximately 14–15 per 100,000 children [1,2]. Of particular importance in solving the problems of pediatric oncology is the search for ways to improve specialized medical care for children with malignant neoplasms. The development and implementation of high–tech innovations for the diagnosis and treatment of cancer is a key task of modern medical research.

Wilms' tumor (nephroblastoma), a well-studied and treatable childhood tumor, is a malignant embryonic neoplasm of the kidney and the second most common malignant tumor of the retroperitoneum [3]. Nephroblastoma accounts for 6% of all childhood cancers and is the most common kidney cancer in the pediatric age group, occurring in 1 in 10,000 children under 15 years of age [4–6].

Nephroblastoma can often remain asymptomatic for a long time, with no specific symptoms. Nonspecific symptoms such as loss of appetite, weight loss, lethargy, weakness, fatigue, and abdominal pain are frequently observed. Parents may not attach significant importance to these symptoms, and the first clinical manifestation is usually a palpable abdominal mass, which is discovered incidentally [7]. With prolonged tumor development, the tumor can reach large sizes, which can include invasion of intrarenal blood and lymphatic vessels, penetration of the renal capsule, and invasion of the perirenal tissue, and can also lead to tumor rupture [8,9]. These factors significantly worsen the prognosis and reduce patient survival. In this regard, the search for methods that increase the radicalism of surgical intervention and reduce the frequency of relapses and metastatic lesions remains relevant.

One such method is photodynamic therapy (PDT), which involves the administration of photosensitizers (PS) capable of selectively accumulating in tumor tissue. With specific laser exposure, PDT exerts its antitumor effects, which are associated with a direct cytotoxic effect on tumor cells, destruction of the tumor's vascular stroma, and tumor elimination under the influence of immune cells due to the induction of an inflammatory reaction and the development of a systemic immune response [10–12]. Numerous studies have demonstrated that PDT can be used both before and after chemotherapy, radiation therapy, or surgery without compromising these treatment modalities. None of the clinically approved PS accumulates in cell nuclei (which could cause DNA damage and, therefore, lead to carcinogenic effects), and they have no serious side effects [13–15].

Most of the studies analyzing the therapeutic efficacy and scope of PDT have been conducted in adult oncological practice. Studies of domestic PS devoted to the study of the kinetics of their interstitial distribution have been performed to identify optimal treatment regimens that allowed optimizing techniques and setting PDT targets [16-19]. A significant advantage of PDT as an adjuvant therapy and for intraoperative intervention is its effective use in patients with a high risk of local tumor recurrence after surgery [14].

However, despite the interest of researchers in PDT and the active introduction of the method in adult patients, data on the use of PDT in pediatric practice are sparse. There are only isolated studies indicating the high effectiveness of PDT use in pediatric oncology, dentistry, ophthalmology, and dermatology [20-24].

Clearly, the anatomical and physiological characteristics of children require the development of

unique therapeutic methods, regimens, and schedules tailored to their age and disease severity. We found no literature on the use of PDT with radachlorin in the combination therapy of retroperitoneal tumors in children. Therefore, the aim of our study was to evaluate the clinical efficacy of intraoperative PDT with radachlorin in the treatment of nephroblastoma, addressing the challenges of preventing metastasis and improving survival in children with solid retroperitoneal tumors.

Materials and Methods

The study was conducted at the Surgical Department and the V.I. Gerain Regional Oncohematology Center for Children and Adolescents of the State Autonomous Healthcare Institution "Chelyabinsk Regional Children's Clinical Hospital."

The study was approved by the local Ethics Committee of the Chelyabinsk Regional Children's Clinical Hospital (Protocol No. 17 dated March 20, 2015) and the Ethics Committee of the South Ural State Medical University (Protocol No. 6 dated September 9, 2024). Patient participation in the study was voluntary. The clinical study was conducted in accordance with the scientific and ethical principles set out in the Helsinki Declaration of the World Medical Association and reflected in OST 42-511-99 "Rules for Conducting Quality Clinical Trials in the Russian Federation", ICH GCP guidelines, and current regulatory documents. All patients and their legal representatives were provided with written information about the PDT technique prior to the study. The physician conducting the study provided detailed information on the PS administration procedure to patients and their legal representatives. Before the study, the legal representatives signed an informed consent form confirming the patient's voluntary participation in the study.

The inclusion criteria for the study evaluating the efficacy of PDT for retroperitoneal tumors in children were:

1) a diagnosed retroperitoneal tumor as an initial condition;

2) a guaranteed voluntary, uninterrupted follow-up period of 60 months (5 years) after surgery and PDT;

3) the presence of complete medical documentation, including medical history, laboratory, and diagnostic data.

The complete medical history, laboratory, and diagnostic data were recorded in the patient's individual medical record.

In order to ensure safety, the participants (doctors and patients) used safety glasses with a light filter during laser exposure. The procedure was performed intraoperatively under anesthesia.

Statistical data processing was performed using IBM SPSS Statistics 19. Qualitative analysis of the study groups was performed using cross-tabulation tables and Pearson's χ^2 test for significance. Differences were considered statistically significant at $p < 0.05$, which corresponds to a 95% probability of an accurate prediction.

To analyze 5-year overall and relapse-free survival data, Kaplan-Meier curves were constructed, calculating the mean survival time, its standard error, and the 95% confidence interval. The log-rank test was used to identify statistical differences in the survival curves; differences were considered statistically significant at $p < 0.05$.

The study involved 66 patients with nephroblastoma: 35 boys and 31 girls. The control group, which included 35 children, underwent surgery in combination with chemotherapy and radiation therapy according to the SIOP protocol. The study group, which included 31 children with stage III and IV disease, regional lymph node metastases, and tumor pseudocapsule invasion, received therapy according to the SIOP protocol in combination with photodynamic therapy. The distribution of patients into groups based on gender and age is presented in Table 1.

The vast majority of patients in the study group were young children, aged 0 to 3 years: 43 children (65.2%). The proportion of preschool-age children, aged 4 to 6 years, was 18 people (27.3%). Only 5 cases (7.6%) of nephroblastoma were noted in patients aged 7 years and older. The ratio of boys to girls in the study group of patients was 1.1: 1 – 35 boys (53.0%) and 31 girls (47.0%). Our data are consistent with the literature [26–28], according to which retroperitoneal tumors develop more often in children aged 1 to 3 years, and in 90% of cases the diagnosis is established before the age of 7; without gender predominance.

As noted above, retroperitoneal tumors can be hidden for a long time, during this period there is a slow increase in the tumor. The primary tumor

Таблица 1
Характеристики пациентов, включенных в исследование

Table 1
Characteristics of the patients included in the study

Характеристики пациентов Characteristics of the patients	Контрольная группа (n = 35) Control group (n = 35)	Основная группа (n = 31) Main group (n = 31)
Пол, n: Gender, n:		
мужской/male	20	15
женский/female	15	16
Возраст, n: Age, n:		
0-3 года/years	24	19
4-6 лет/years	10	8
7-12 лет/years	1	4

symptom complex is diverse in its manifestations, associated with the influence of the tumor process on the metabolism and immunity of the child. Often, in patients with nephroblastoma, the only symptom is the presence of a palpable tumor in the abdomen, which is detected by chance. The neoplasm was palpable in the abdominal cavity, causing an increase in abdominal size and its asymmetry in the majority of children - 59 (89.4%). Intoxication syndrome was also noted in patients: weakness, lethargy, decreased appetite were experienced by 50 children (75.8% of the entire analyzed group). Blood changes (hypochromic anemia, leukocytosis, neutrophilia) were noted in 47 patients (71.2%). Complaints of abdominal pain were presented by more than half of the children - 37 (56.1%). Subfebrile temperature was recorded in 21 children, which amounted to 31.8%, and weight loss - in 9 children (13.6%). Urine analysis changes, such as hematuria, associated with tumor invasion into the renal pelvis and subcapsular rupture of nephroblastoma, were detected in 29 children (43.9%). Half of these children were considered critically ill upon admission. Developmental delays were observed in 16 patients (24.2%). Table 2 presents the pattern of primary clinical symptoms in the study group.

All children included in the study group underwent a series of mandatory diagnostic tests in accordance with the clinical guidelines of the Russian Ministry of Health.

To determine subsequent treatment strategies, risk groups and disease stage were taken into account, classifying tumors from stages I to V in accordance with the recommendations of the International Society of Pediatric Oncology (SIOP, 2001) [4]. The study group included patients with stages III and IV, while the control group included patients with stages III, IV, and V. PDT was performed in patients with stage III and IV nephroblastoma (unilateral tumor, with metastases in regional lymph nodes, and with tumor pseudocapsule invasion).

Focal lung lesions, rounded solid lesions measuring 3–5 mm in size, classified as metastases, were detected in 7 patients in the study and control groups (22.6% and 20.0%, respectively). Table 3 presents the distribution of patients by disease stage according to the TNM classification.

The treatment sequence for all patients was as follows: neoadjuvant chemotherapy – surgery – adjuvant chemotherapy. Patients were divided into two groups based on the surgical treatment regimen. Patients in the control group underwent surgery in combination with chemotherapy and radiation therapy according to the SIOP protocol. Patients in the study group received therapy according to the SIOP protocol, but in combination with PDT. This was modified by adding postoperative photodynamic therapy to the standard therapy, targeting residual tumor and metastatic regional lymph nodes, as confirmed by intraoperative imaging.

Thirty minutes before surgery, the patient, who was in a darkened room, received an intravenous injection of a chlorin e6-based PS solution (radachlorin) at a dose of 1 mg/kg of body weight. The accumulation of chlorin e6 in the patient's tissues was monitored using the LESA-01-Biospec laser electron-spectral system. Intraoperative PDT was performed using a Lakhta-Milon high-intensity laser (Russia): laser radiation in the range of 0.1 to 0.8 W/cm^2, light energy dose of 400 J/cm^2, wavelength of 662 nm. The irradiation duration depended on the tumor size and averaged 20 minutes. A midline laparotomy was used as the

Таблица 2
Структура основных клинических симптомов у пациентов исследуемой группы

Table 2
The structure of the main clinical symptoms in patients of the study group

Клинические симптомы Clinical symptoms	Частота встречаемости, n (%)
Пальпируемая опухоль в животе Palpable abdominal mass	59 (89,4)
Интоксикационный синдром Intoxication syndrome	50 (75,8)
Болевой синдром Pain syndrome	37 (56,1)
Изменения в анализах крови Changes in blood tests	47 (71,2)
Повышение температуры тела Increased body temperature	21 (31,8)
Изменения в анализах мочи (гематурия) Changes in urine tests (hematuria)	29 (43,9)
Снижение веса Weight loss	9 (13,6)

Таблица 3
Распределение пациентов по стадиям TNM

Table 3
Distribution of patients by TNM stage

Параметр	Контрольная группа (n = 35) Control group (n = 35)	Основная группа (n = 31) Main group (n = 31)
T3N1M0, n (%)	28 (80,0)	24 (77,4)
T4N1M1, n (%)	6 (17,1)	7 (22,6)
T5N1M1, n (%)	1 (2,9)	-

surgical approach. Following abdominal exploration, a tumor nephroureterectomy was performed, and the renal and inferior vena cava were examined for tumor thrombosis. For disease staging, regional lymph nodes were removed and sent for pathological examination. After tumor removal, patients in the main group underwent PDT on the resected tumor bed. Postoperative 24-hour monitoring was conducted in the oncology intensive care unit. Further treatment of nephroblastoma depended on the stage, histological type, and tumor volume, based on SIOP guidelines. The individual stages of treatment are presented in Fig. 1–4.

Results

To evaluate the effectiveness of PDT, a Kaplan-Meier analysis of patient survival in the study groups was conducted based on the proportion of surviving patients. The follow-up period was 5 years, during which time examinations by a pediatric oncologist were performed, laboratory parameters were monitored, and imaging data were analyzed to rule out continued growth and metastatic lesions, according to the clinical guidelines of the Russian Ministry of Health. Based on the data obtained, the mean survival times to death and relapse were determined for patients in the control and study groups (Table 4).

The graphical representation of the Kaplan-Meier method were the overall 5-year and relapse-free survival curves shown in Fig. 5-6.

A comparison of the study and control groups revealed a significant difference in overall patient survival. In the group receiving protocol-based therapy without additional PDT, the number of deaths over 5 years of follow-up was 10, with a 5-year overall survival rate of 71.4%. In the group of patients who received PDT in addition to the main therapy, the number of deaths over the 5-year follow-up period was lower (3 cases), with an overall survival rate of 90.3% ($p = 0.05$).

No significant differences were found in relapse-free survival of patients with nephroblastoma depending on the use of PDT: relapse was diagnosed in 3 children (9.7%) in the study group and 4 children (11.4%) in the control group ($p = 0.82$).

In the study group, relapse was detected in 3 patients, requiring repeat surgeries. Relapses were associated with unfavorable tumor histology, severe disease stage, and parental noncompliance with the treatment regimen due to social problems. Analysis of

Рис. 1. Мультиспиральная компьютерная томография органов брюшной полости и забрюшинного пространства, нефробластома левой почки.
Fig. 1. Multislice computed tomography of the abdominal organs and retroperitoneal space, nephroblastoma of the left kidney.

Рис. 2. Внешний вид ребенка с нефробластомой: асимметрия живота в связи с наличием крупной опухоли.
Fig. 2. The appearance of a child with nephroblastoma: abdominal asymmetry due to the presence of a large tumor.

Рис. 3. Ревизия брюшной полости с опухолью во фланке.
Fig. 3. Revision of the abdominal cavity with a tumor in the flank.

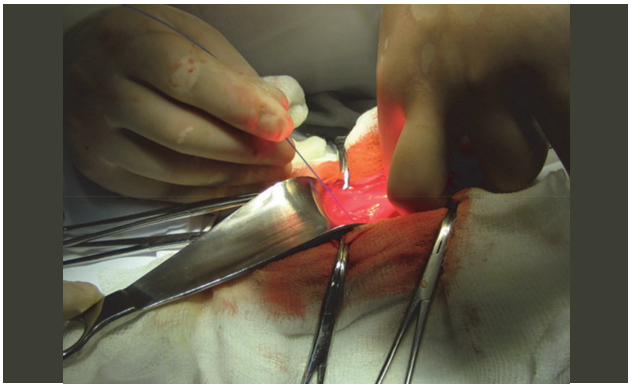

Рис. 4. Фотодинамическая терапия ложа опухоли.
Fig. 4. Photodynamic therapy of the tumor bed.

Таблица 4
Эффективность терапии в основной и контрольной группах (5-летнее наблюдение)

Table 4
Therapy effectiveness in the main and control groups (5-year follow-up)

Показатели эффективности Efficacy indicators	Контрольная группа (n = 35) Control group (n = 35)	Основная группа (n = 31) Main group (n = 31)
5-летняя общая выживаемость, % 5-year overall survival, %	71,4	90,3
Число летальных случаев, n (%) Number of deaths, n (%)	10 (28,3)	3 (9,7)
Среднее время дожития до летального исхода (m±SD), мес Mean survival time to death (m±SD), months 95% ДИ 95% CI	54,7±2,9 49,1-60,4	57,1±2,9 53,0-61,2
5-летняя безрецидивная выживаемость, % 5-year relapse-free survival, %	88,6	90,3
Среднее время дожития до рецидива (m±SD), мес Mean survival time to relapse (m±SD), months 95% ДИ 95% CI	54,1±2,8 48,6-59,6	54,7±2,9 49,1-60,4

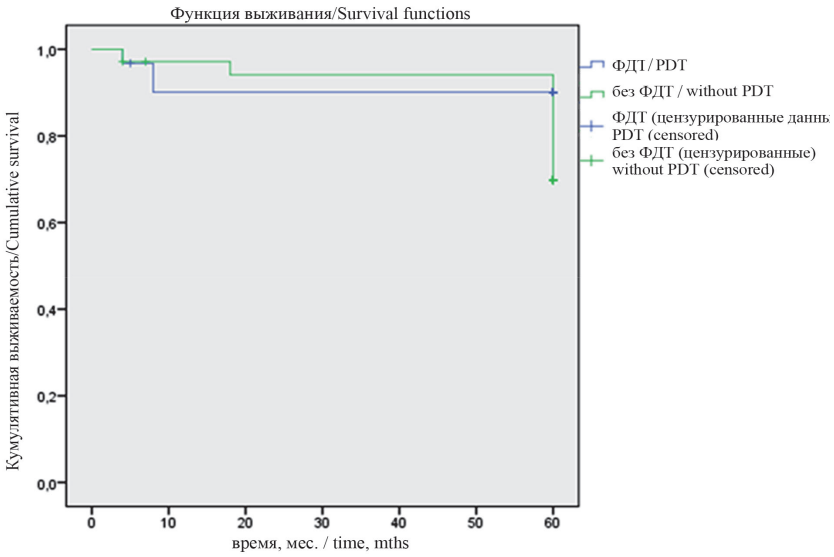

Рис. 5. Общая 5-летняя выживаемость пациентов исследуемых групп с нефробластомой (мес)
Fig. 5. Overall 5-year survival of patients in the study groups with nephroblastoma (months)

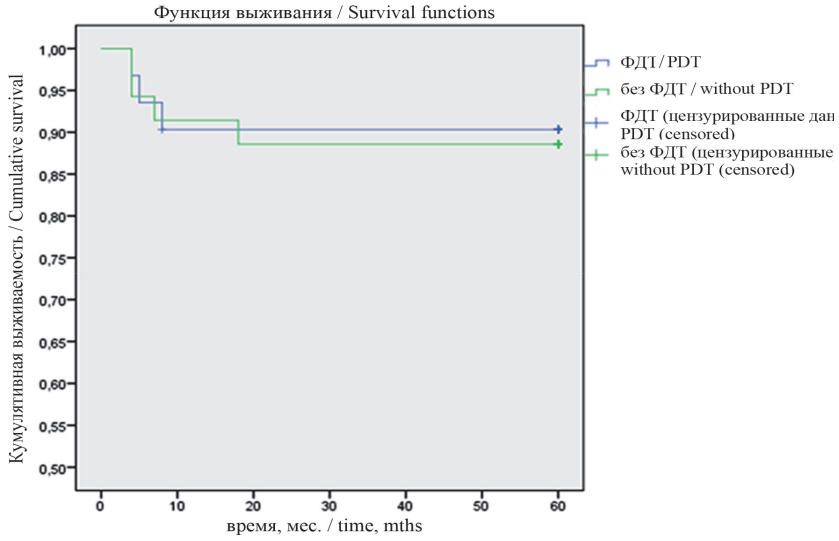

Рис. 6. Безрецидивная выживаемость пациентов с нефробластомой (мес)
Fig. 6. Recurrence-free survival of patients with nephroblastoma (months)

relapse rates prompted a more thorough assessment and monitoring of the child's outpatient care.

Discussion

As previously reported, there are isolated studies on the use of PDT in pediatric practice [20–24]. No reports on the use of PDT in the treatment of retroperitoneal tumors in children were found. In our study, we relied on the results of a preliminary experiment, during which a PDT regimen and protocol were developed [29]. Radachlorin, a second-generation chlorin e6-based photosynthesis agent, was used as the photosynthesis agent. This agent exhibits greater selectivity for accumulation (compared to first-generation photosynthesis agents), resulting in greater tumor penetration depth, preservation of surrounding tissue during irradiation, and low cutaneous phototoxicity. Publications by a number of authors demonstrate good clinical efficacy of PDT using chlorin e6-based PS in the treatment of tumors of various localizations. Thus, in the work of T.E. Sukhova [30], the response of basal cell skin cancer in its various clinical forms, stages, histological types, course and localization to PDT with intralesional administration of radachlorin and photoditazine was studied. At the same time, PDT with radachlorin allowed to significantly improve the results of treatment of the ulcerative form of the tumor compared to PDT carried out using photoditazine (92.8% and 77.8%, respectively, $p < 0.05$). Another research group: E.V. Filonenko et al. [31] used radachlorin in the treatment of precancerous and tumor diseases of the cervix with good clinical results: complete tumor regression was achieved in 86.7% of patients. It is important that no adverse reactions to the administration of the drug radachlorin and PDT were detected during or after treatment.

L.A. Vashakmadze *et al.* reported the intraoperative use of radachlorin in patients with a high risk of local tumor recurrence after surgical treatment [32]. Intraoperative photodynamic therapy with photohem, radachlorin, and photoditazine was performed in 17 patients with morphologically confirmed resectable primary or recurrent retroperitoneal tumors. The tumor bed was irradiated after its complete removal within the healthy tissues from one or more positions, depending on the location of the tumor foci. The researchers noted a relapse of the disease after intraoperative PDT in 6 of 17 patients within 2 to 6 months. Importantly, the authors noted the development of local relapses in patients who received intraoperative PDT at the stage of practicing the technique, selecting modes, and the radiation dose. The researchers drew conclusions about the safety of PDT and the affinity of the used PS for the tissue of retroperitoneal sarcomas. The work of this research group was the most interesting and similar in structure to our study.

Conclusion

The proposed method of comprehensive treatment of retroperitoneal tumors using the SIOP protocol in combination with intraoperative photodynamic therapy at the tumor bed in children improves surgical outcomes and increases survival in patients with retroperitoneal tumors. The obtained efficacy data make this method promising for use in pediatric oncology.

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