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Chapter

Photodynamic Therapy in Complex Therapy of Retroperitoneal Tumors in Children

N.M. Rostovtsev, V.G. Polyakov and N.E. Kuzmina

Abstract

During the period from 2009 to 2021, 93 patients aged 0–11 years (48 boys and 45 girls) with retroperitoneal tumors were treated. There were 66 patients with nephroblastoma and 27 patients with adrenal neuroblastoma among them. As per treatment strategies, the patients were separated into two groups: the control group and the study group. The control group (comparison) received therapy according to the protocols, whereas the study group consisted of patients who received photodynamic therapy (PDT) in addition to the standard treatment. The control group consists of 47 patients with retroperitoneal tumors, including 35 patients with nephroblastoma and 12 patients with adrenal neuroblastoma. The study group included 46 children: 31 patients with nephroblastoma and 15 patients with adrenal neuroblastoma. The 5-year survival rate in the control group was 74.5%, and it was 91.3% in the study group (p = 0.030). Recurrent tumors developed in 14.9% of the patients in the control group, while in the study group, relapse occurred in 8.7% of the patients (p = 0.357). The PDT used in this study for treatment of retroperitoneal tumors improves the results of surgical treatment. It also appreciably increases the survival rate of patients with retroperitoneal tumors. Overall, PDT is a hopeful antitumor approach and can be effectively used in the complex therapy of retroperitoneal tumors in children.

Keywords: children, photodynamic therapy, nephroblastoma, neuroblastoma, radachlorin

1. Introduction

The problems of pediatric oncology are quite urgent, since malignant neoplasms are leading in the structure of child mortality worldwide, second only to external causes. The incidence of cancer cases is estimated by the World Health Organization (WHO) as about 100 per million children. These are rare diseases among the pediatric population, ranging from 0.5 to 4.6% of all cancers [1, 2].

Neuroblastoma (NB) and nephroblastoma, or Wilms' tumor (WT), are the two most common extracranial solid tumors in childhood [3, 4]. Both tumors are most often located in the retroperitoneal space, develop from embryonic cells, and in most cases are diagnosed in children younger than 5 years [4]. NB is an embryonic malignant tumor arising from the ganglia of the borderline sympathetic trunk and chromaffin tissue. The prevalence of NB is estimated as 1 case per 7000–10,000 live births, it accounts for 6–10% of all malignancies in children [5, 6]. The most common localizations of this tumor are adrenal glands (40%) and retroperitoneal space (25%), less often NB develops in the posterior mediastinum (15%), in the neck (5%) and pelvis minor (5%). The prevalence of WT, which is the most common kidney tumor in childhood, is 1 case per 10,000 children under the age of 15 [7]. About 10% of cases of the disease are associated with the presence in patients of such congenital syndromes as WAGR syndrome, Beckwith-Wiedemann syndrome, Denys-Drash syndrome, and hemihypertrophy [8]. From the point of view of embryogenesis, WT is a solid malignant tumor consisting of derivatives of nephrogenic tissue at different degrees of differentiation. These tumors may contain not only a variety of tissue elements present in a normal kidney, but also skeletal muscles, cartilages, mucosal and stratified squamous epithelium. In typical cases, WT is a large solid growth, often with areas of necrosis, hemorrhages, and cysts. However, in about 7% of cases, WT is a multifocal growth. The tumor can spread to the pelvis and ureter, causing obstruction of the urinary tract. In addition, it can invade the intrarenal blood and lymph vessels, penetrate the renal capsule, and grow into the paranephric and other adjacent tissues, spread from the renal vein into the inferior vena cava [4].

2. Clinical manifestations

It should be noted that retroperitoneal tumor in children is primarily not clinically manifested and has no specificity during a long period of time. The primary tumor symptom complex is a variety of pathological manifestations caused by the influence of the tumor process on metabolism, immunity, and functional activity of the regulatory systems of the body. The most common symptoms are physical inactivity, lack of appetite, weight loss, lethargy, asthenia, rapid fatigability, moodiness, anemia, low-grade fever, and abdominal pain. The syndrome of minor signs of a tumor is present in most patients, but usually neither parents nor doctors attach significant importance to it. Usually, the first clinical manifestation is a palpable tumor in the abdomen, which is found accidentally. The tumor is smooth, sometimes coarse-grained, dense, painless, and moderately mobile. Macrohematuria occurs in less than 1/4 of patients and is considered a manifestation of tumor invasion into the renal pelvis system. Arterial hypertension is often observed [9].

Surgical treatment of both tumors is mandatory in antitumor therapy. In accordance with the recommendations of the SIOP (International Society of Pediatric Oncology) protocol used in European countries, chemotherapy is performed within 4 weeks before surgery in order to reduce the risk of intraoperative tumor rupture [10, 11].

Successful treatment of solid tumors involves early diagnosis, radical removal of the tumor with an extensive operative exploration of abdominal organs and regional lymph nodes, as well as neoadjuvant and adjuvant chemotherapy. The use of ablastic methods in the surgical treatment of tumors, which include photodynamic therapy (PDT), is becoming extremely important.

PDT is a treatment method based on the use of photosensitive substances, i.e., photosensitizers (FS) and light of a certain wavelength. FS selectively accumulates in the tumor tissue, then the affected tissues are illuminated with the light generated by special surgical laser units. As a result of subsequent cellular photochemical reactions, reactive oxygen species are released destroying pathological cells, causing nutrition disorders, leading to tumor apoptosis due to the damage to its micro-vessels. The antitumor effects of PDT in vivo result from three interrelated

mechanisms, namely direct cytotoxic effects on tumor cells, damage to the tumor vascular network, and induction of a strong inflammatory reaction that can result in the development of a systemic immune response [12–15]. The established presence of an immunological component of photodynamic effect indicates the prospects of combining PDT and immunotherapy methods to improve the results of cancer treatment [16].

The use of photodynamic therapy in the treatment of oncological diseases has begun relatively recently. To date, the vast majority of works devoted to the use of PDT are studies carried out in the adult population, their purpose is to clarify the therapeutic effectiveness of PDT, identify priority FS and the scope of their application [17, 18].

However, the problem has been little studied in pediatric population, since it is associated with certain difficulties caused by limited technical capabilities and lack of application experience. Despite the great interest of researchers in this method, there are few data on the use of PDT in pediatric patients. There are only some works indicating the high efficiency of PDT application in pediatric dentistry, dermatology, and ophthalmology [19–22].

Nevertheless, the anatomical and physiological features of childhood require the development of specific therapeutic techniques: namely schemes and modes of use, taking into account the age and severity of the disease. We have not found data about the methodology and optimal modes of PDT, as well as the use of Radachlorine as FS for the treatment of solid tumors and the prevention of intraoperative metastasis in children in the literature review. This made it necessary to further study the possibilities of PDT in the treatment of solid tumors in children and determine the purpose and objectives of this study. Taking into account the data obtained during the preclinical study [23], we are to prove the effectiveness of PDT using Radachlorine photosensitizer aiming at increasing the clinical efficiency (5-year survival rate) of treatment of children with solid retroperitoneal tumors.

3. Materials and methods

The study was performed in the surgical department and Oncologic Hematology Center for Children and Adolescents named after Professor V.I. Gerain of the State Budgetary Healthcare Institution "Chelyabinsk Regional Children's Clinical Hospital."

The studied group consisted of 93 patients with retroperitoneal tumors (48 boys and 45 girls), 66 patients with nephroblastoma, 27 patients with adrenal neuroblastoma. Taking into account the performed therapy, the patients were divided into two groups: the comparison group and the study group. The comparison group (control) received therapy according to the protocols SIOP 93, SIOP 2001, NB2004. The study group consisted of patients who received photodynamic therapy in addition to the standard treatment.

The comparison group included 47 patients with retroperitoneal tumors, including 35 patients with nephroblastoma and 12 patients with adrenal neuroblastoma. The study group included 46 children: 31 patients with nephroblastoma and 15 patients with adrenal neuroblastoma. The distribution of patients into treatment groups depending on the type of tumor is shown in **Table 1**.

The patients of the clinical groups were divided into age subgroups according to the age periodization according to A.V. Mazurin, I. M. Vorontsov [24]. **Table 2** shows the distribution of patients by age.

Depending on the gender, the patients of the studied groups were distributed in the following way as presented in **Table 3**.

Clinical groups $(n = 93)$	Tumor		
	nephroblastoma	neuroblastoma	
Comparison group (n = 47)	35	12	
Study group (n = 46)	31	15	

Table 1.

Distribution of patients into clinical groups depending on the type of tumor.

Clinical groups (n = 93)	Age groups		
	0–3 years	4–6 years	7–12 years
Comparison Group (n = 47)	31	14	2
Study group (n = 46)	31	10	5
Total (n = 93)	62	24	7

Table 2.

Distribution of patients in clinical groups by age.

Clinical groups	boys	girls
Comparison Group (n = 47)	25	22
Study group (n = 46)	23	23
Total (n = 93)	48	45

Table 3.

Distribution of patients into clinical groups depending on gender.

As can be seen from **Table 2**, in both clinical groups, the vast majority of patients are children of early age group from 0 to 3 years, that is, 62 children (66.7%). The next group is preschool-age children from 4 to 6 years, that is, 24 children (25.8%). Retroperitoneal tumors are revealed less frequently in older children, there are only seven patients in the age group older than 7 years (7.5%). The number of boys and girls in the clinical groups of patients is almost the same (**Table 3**): 48 boys (51.6%) and 45 girls (48.4%). The findings received by us do not contradict the literature data [10, 11, 25, 26], according to which retroperitoneal tumors develop more often in children aged 1–3 years, and in 90% of cases, the diagnosis is made before the age of 7. Our study also did not establish gender prevalence in the occurrence of tumor in children. The incidence among boys and girls was the same.

Depending on the therapy to be carried out, the patients were divided into two groups. Patients of the comparison group underwent surgical treatment in combination with chemotherapy and radiation therapy according to the protocol. Patients of the study group received therapy according to the SIOP protocol in combination with PDT.

All children with an identified oncological condition underwent a complex of mandatory diagnostic tests, in accordance with the Clinical Recommendations of the Ministry of Health of the Russian Federation. Patients with retroperitoneal tumors necessarily underwent a physical examination to determine density of the tumor surface, mobility, and size of the growth. Palpation of all accessible groups of peripheral lymph nodes was performed. Blood pressure measurement and neurological status assessment were mandatory.

Laboratory tests included clinical blood analysis, common urine analysis, biochemical blood analysis (electrolytes, whole protein, liver samples, creatinine,

urea, lactate dehydrogenase, alkaline phosphatase) and a study for tumor markers of NB catecholamines in urine and serum, NSE (to exclude NB).

Studies of molecular biological markers (N-MYC oncogene amplification and 1p deletion) and histological examination were carried out, and histomorphologic diagnosis in all patients with WT and NB was made. Taking into account the data obtained, the tumor process was staged according to SIOP and NWTS.

Instrumental methods of examination included ultrasound of the abdominal cavity organs and retroperitoneal space with blood flow mapping, CT of the abdominal cavity organs and retroperitoneal space with intravenous contrast, MRI of the abdominal cavity and retroperitoneal space with and without contrast enhancement. If necessary, angiography and a radioisotope study of the kidneys were performed to assess kidney function. Compulsory examinations were electrocardiography and echocardiography.

Special attention was paid to safety and ethical issues of the study.

The study was approved by the local Ethics Committee of GBUZ CHODKB— Protocol No. 17 of 20.03.2015. The sampling of patients was carried out on a voluntary basis. The clinical trial was conducted in accordance with the scientific and moral principles set out in the Helsinki Declaration of the World Medical Association and reflected in OST 42-511-99 "Rules for Conducting Qualitative Clinical Trials in the Russian Federation," ICH GCP rules and current regulatory requirements. All patients were provided with written information about the drug prior to the study. Legal representatives and patients were informed in detail by the doctor who conducted the study about the procedure of introducing a photosensitizer. Before starting the study, the parents signed an informed consent form confirming their voluntary participation.

The inclusion criteria in the study on the effectiveness of PDT in retroperitoneal tumors in children were:

- 1. a diagnosed malignancy of the retroperitoneal space as an initial condition;
- 2. guaranteed voluntary continuous follow-up for 60 months (5 years) after surgical intervention and PDT;
- 3. association between the confirmed tumor and death, as well as the established cause of death;
- 4. availability of complete information in medical documentation, including case history, laboratory data, diagnostic tests.

Based on the results of a comprehensive examination, an "Individual Case Record" was filled in for each patient, including a complete anamnesis, laboratory data, and diagnostic studies.

An assessment was carried out in both groups of patients after PDT and complex treatment within two months. The effectiveness of therapy was evaluated according to standard criteria (WHO), taking into account the dynamics of surgical treatment, tumor recurrence, as well as the patient's condition. Later, postoperative follow-up was carried out on an outpatient basis for 5 years, every 6 months (10 visits). The tumor was monitored, dynamic data control of laboratory findings, ultrasound, and CT were carried out.

To assess the effectiveness of PDT, the operational characteristics of the test were used in accordance with the principles of evidence-based medicine. Criteria for the effectiveness of the conducted PDT:

- full effect—complete disappearance of all manifestations of the disease, the established complete absence of local recurrence of the tumor according to palpation, visual signs, as well as special diagnostic tests;
- local relapse—occurrence of a local relapse within 6 months following surgery;
- without effect—continued tumor growth according to additional research methods;
- partial effect—absence of a tumor, but presence of enlarged lymph nodes, confirmed at two months post-intervention.

The safety of the participants was ensured:

- no unpleasant sensations from PDT, the procedure being performed under anesthesia intraoperatively;
- protective glasses with a light filter used by a doctor and a patient during laser exposure;
- rapid elimination of Radachlorine from the blood and mucous membranes (high contrast index excludes damage to healthy organs and tissues);
- selective accumulation of Radachlorine in the tumor, absence of mutagenic action on the DNA of normal cells.

There were no valid data on adverse medical consequences published. Spectral fluorescence examination of patients was carried out before the injection of Radachlorine, every hour after the injection of Radachlorine and after the end of the PDT procedure. The accumulation of photosensitizer in the tumor was measured using a laser electron spectral device LESA-01-Biospec. During the measurement, the spectrum was determined by analyzing its shape and amplitude of the signal, the integral intensity of Radachlorine fluorescence at various sites of the tumor and adjacent tissues, and the fluorescent boundaries of the tumor. Also, the intensity of fluorescence of the normal skin of the hands and face and oral mucosa of patients was evaluated. The ratio between the values of fluorescence intensity in the tumor and normal tissue, which characterized the selectivity of accumulation in the tumor tissue, was determined.

PDT with Radachlorine was performed intraoperatively after removal of the tumor by means of a high-intensity laser "Lakhta Milon" (Russia), using laser illumination in the range of 0.1–0.8 W/cm². Depending on the depth of infiltrating tumor growth, various doses of light energy were used—from 150 to 400 J/cm², wavelength 650–670 nm, adjusted during an experimental study [23]. The photosensitizer was administered intravenously, at the rate of 0.6–0.8 mg/kg 2–3 hours prior to illumination. The duration of illumination depended on the size of the tumor and averaged 20 minutes.

Statistical data processing was carried out using IBM SPSS Statistics 19 package. The analysis of qualitative characteristics in the studied groups was done by means of construction of cross-tabulation tables and calculation of significance by χ^2 -Pirson criterion. The differences were considered statistically significant for p values <0.05, which corresponded to 95% probability of an accurate prediction. To analyze the data of overall 5-year survival and relapse-free survival Kaplan-Meier curves were constructed calculating average survival time, its standard error, and 95% significance interval. A long-range criterion was applied to identify statistical

differences in the survival curves. The differences were considered statistically significant for p values <0.05.

4. Results

We could not find information on the use of photodynamic therapy in children in the treatment of retroperitoneal tumors in the available literature sources. General and relapse-free survival of patients in the studied clinical groups was analyzed by the Kaplan-Meier method to assess the effectiveness of treatment results, regarding the percentage of patients who survived after the use of photodynamic therapy. The duration of observation time was from the intraoperative photodynamic therapy to the end of a 5-year follow-up. Based on the data obtained, the mean values of the survival time before the onset of death and mean values before the onset of relapse in patients of the control and study groups were obtained, as shown in **Tables 4** and **6**. The mean time free from any outcome (death, relapse) is a certain number of months, **Tables 5** and 7. The tables also present standard error (SE) and 95% confidence interval (95% CI) values for the mean time value.

A graphical presentation of the Kaplan-Meier method was the curves of the overall 5-year and relapse-free survival, as shown in **Figures 1** and **2**. The ordinate axis shows the probability of outcome occurrence, and the abscissa axis shows time (months).

Clinical groups (n = 93)	Five-year Survival rate (%)	Mortality rate (cases)	Mortality rate (%)
Comparison Group (n = 46)	74.5	12	25.5
Study group (n = 47)	91.3	4	8.7
<i>P</i> = 0.030.			

Table 4.

Percentage of cases of fatal outcome in patients with tumor, depending on the treatment method.

Clinical groups		Mean values			
Es	Estimate	St.	95% confidence interval		
		error	Lower range limit	Upper range limit	
Comparison group	47.404	3.197	41.138	53.671	
Study group	56.022	1.927	52.257	59.786	

Table 5.

Mean value of survival time before fatal outcome in the studied groups of patients.

Clinical groups (n = 93)	Five-year (%) relapse-free survival rate	Relapses (cases)	Relapses (%)	
Comparison Group (n = 46)	85.1	7	14.9	
Study group (n = 47)	91.3	4	8.7	

Table 6.

Percentage of cases of relapse in patients, depending on the treatment method.

Clinical groups	Mean values ^a			
	Estimate St	St.	95% confidence interval	
		error	Lower range limit	Upper range limit
Comparison group	52.213	2.734	46.855	57.571
Study group	55.477	2.169	51.227	59.728
= 0.357.				

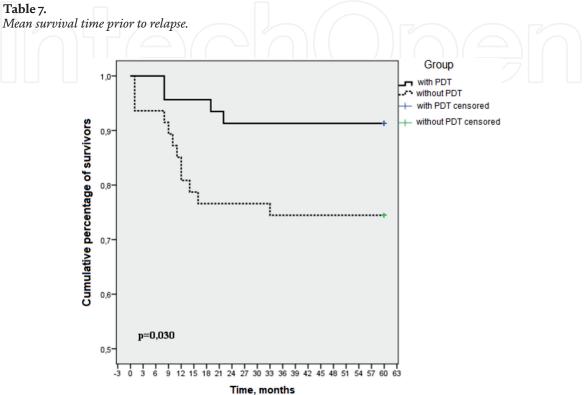


Figure 1. Overall 5-year survival rate of studied patients.

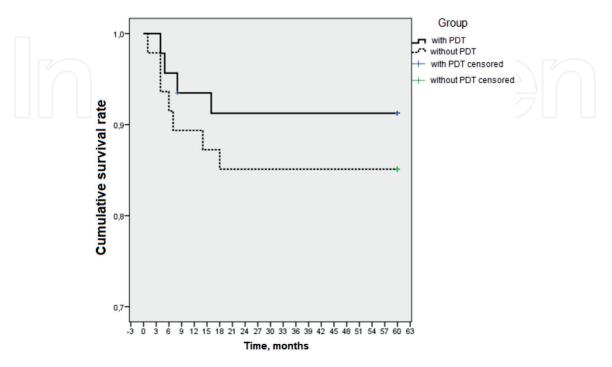


Figure 2. *Comparison of relapse-free survival in studied patients.*

5. Discussion

As previously reported, we were able to find only a few studies on the use of PDT in children in dental, dermatological, and ophthalmological practice in literature [19, 20, 21, 22]. Reports on the use of PDT in the treatment of retroperitoneal tumors in children could not be found. In our study, we relied on the results of a preliminary trial, during which the scheme and mode of PDT were developed [23]. Radachlorine (FS of the second generation) was used as FS, which has a greater selectivity of accumulation (in comparison with FS of the first generation), which provides a greater depth of damage to tumor tissue due to shifts of absorption maxima to a longer wavelength spectrum (650–670 nm), intact surrounding tissues during illumination and low skin phototoxicity. A good clinical efficacy of PDT with Radachlorine as FS in the treatment of tumors of different localization has been demonstrated in the publications of a number of authors. Moreover, different forms of drug formulation make it possible for both local, including intra-focal, and systemic administration of Radachlorine.

In the work of Sukhova T.E. [27], the response of basal cell skin cancer in its various clinical forms, stages, histological types, course of the disease, and tumor localization to PDT with intra-focal administration of Radachlorine and Photoditazine was studied. The study included 74 patients with primary and recurrent basal cell carcinoma of the skin of stage I–II. The patients of group I (n = 45) were injected with Radachlorine (0.5–1 ml / 1 cm² of the tumor surface), patients in group II (n = 34) had Photoditazine (0.3–0.5 ml/1 cm² of the tumor surface). The light dose was 300 J/cm², the illumination wavelength was 662 ± 3 nm for all patients. As a result of the therapy, a complete regression of basal cell skin cancer was established in 43 patients from group I (95.5%) and in 31 from group II (91.2%). At the same time, PDT with Radachlorine FS significantly improved the results of treatment of the ulcerative form of tumor compared with PDT using Photoditazine FS (92.8% vs. 77.8%, respectively, p < 0.05).

Filonenko E.V. et al. [28] used Radachlorine in the treatment of precancerous and tumor diseases of the cervix in 30 patients. Radachlorine was administered once by a 30-minute intravenous infusion at a dose of 1.0 mg/kg body weight 3 hours before illumination (wavelength 662 nm, energy density 300–350 J/cm²). A good clinical result was achieved in 26 patients (86.7%), it was assessed as complete regression of the tumor, in 4 (13.3%)—as partial regression. It is important that during and after the treatment, there were no adverse reactions to the administration of Radachlorine and PDT.

Vashakmadze L.A. et al. [29] reported on the intraoperative use of Radachlorine in patients with a high risk of local tumor recurrence after surgical treatment. The study included 17 patients with morphologically confirmed operable primary or recurrent retroperitoneal tumor. Intraoperative photodynamic therapy was performed with Photogem (five patients), Radachlorine (seven patients), and Photoditazine (five patients). In nine cases, the tumors had the structure of liposarcoma, in 4—leiomyosarcoma, in 2—gastrointestinal stromal tumor, in 1—neurogenic tumor, in 1-hemangiopericytoma. Photosensitizers were administered intravenously: Photohem 48 hours before surgery at a dose of 2.5–3.0 mg/kg, Radachlorine and Photoditazine—at doses of 0.7 and 0.7–1.0 mg/kg, respectively 2–3 hours before the resection stage of the operation. The tumor bed was illuminated after a complete tumor removal within intact tissues from one or more positions, depending on the location of tumor foci. The illumination energy density was 30 J/cm², the duration of the exposure session depended on the illumination area. The accumulation of photosensitizer in the tumor tissue was assessed after removal of the neoplasm using local fluorescence spectroscopy by means of the diagnostic

unit "Spectrum." The researchers observed a relapse of the disease after surgical treatment with intraoperative PDT sessions in six (out of 17) patients within a period of 2–6 months. Three patients (out of six) developed local relapses of the disease 2, 4, and 6 months after the treatment (surgery accompanied by intraoperative PDT). The authors remarked that PDT was performed in patients who developed local relapses of the disease at the stage of testing the technique, choosing the modes and radiation dose. The researchers made conclusions about the safety of photodynamic therapy and the precision of the photosensitizer accumulation used to retroperitoneal sarcoma tissue, which was confirmed by local fluorescence spectroscopy data.

The work of this research group was the most interesting and similar in structure to our study. Like other research groups, we expected a good clinical response associated with the high selectivity of Radachlorine and, consequently, with the high photodynamic activity of the drug. Modern fiber-optic technology facilitates the delivery of light of the desired wavelength and energy flux density to tumors located almost anywhere in the body. Local illumination, together with the protection of sensitive tissues at the edge of the area, allows for specific treatment of the tumor without destroying normal tissues outside the treated area. The combination of surgical treatment with intraoperative PDT was used to increase the efficacy of surgical interventions and reduce the number of local relapses.

Analysis of the data of our study showed that in the group of patients receiving therapy according to the protocol, without the additional use of photodynamic therapy, the number of deaths was 12, therefore the survival rate was 74.5%. In patients of the study group who received photodynamic therapy in addition to the standard therapy, the number of fatal outcomes during the 5-year follow-up period was less and amounted to four cases. The survival rate, respectively, was higher—91.3%. Comparison of 5-year survival curves in the control and study groups according to the nonparametric log-rank criterion showed a significant difference in the groups (p = 0.030). At the same time, the average survival time before the onset of death in patients who received photodynamic therapy significantly exceeded the mean survival time in patients who received therapy according to the protocol, without additional use of PDT, i.e., 56 months vs. 47 months, respectively (p < 0.050).

There was no statistically significant difference in the analysis of relapse-free survival in patients of clinical groups: in the study group, relapse occurred in 8.7% of patients, in the comparison group—in 14.9% of patients (p = 0.357). The mean survival time to relapse in both groups had no significant difference and made up 55 months in patients receiving photodynamic therapy versus 52 months in patients not receiving photodynamic therapy (p = 0.357).

Nevertheless, the obtained data regarding relapse-free survival are optimistic. Firstly, preclinical studies have shown the possibility of combining PDT regimens that inhibit primary tumor growth and stimulate antitumor immunity [30, 31, 32]. In this case, PDT is a potential method that is due to its immunological mechanisms, can strengthen the control of primary and metastatic tumors, and consequently, facilitate recovery and improve the quality of life in cancer patients. Secondly, the selectivity of photosensitizer accumulation in the tumor can be artificially increased by targeted delivery of the drug to tumor cells. Currently, several techniques to selectively target photosensitizer to the tumor are being developed. Search for transport systems that provide even higher selectivity and precision is described in the world literature [33]. We believe that the method is promising in terms of further research and the accumulation of clinical experience, and the development of exposure modes will allow assessing its effectiveness and impact on the recurrence rate in extra-organ retroperitoneal tumors.

6. Conclusions

The proposed method of complex treatment of retroperitoneal tumors using PDT allows improvement of the results of surgical treatment; it significantly increases the survival rate of patients with retroperitoneal tumors (91.3% vs. 74.5%) (p < 0.050). Thus, PDT is a promising antitumor strategy, technically possible, and can be successfully used in the complex therapy of retroperitoneal tumors in children.

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