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Local chemotherapy in treatment of brain tumors. Part 2. Efficiency of treatment of patients with neuroepithelial brain tumors secondary to intraoperative local chemotherapy

Summary
According to the results of an open-label, controlled, retro-prospective, comparative, randomized clinical trial, an increased efficacy of combined treatment of malignant brain tumors with intraoperative local chemotherapy (LCT) with Temodex was established. Thus, in particular, the median survival rate of patients with Grade III–IV supratentorial tumors secondary to intraoperative LCT increased with radical resection of the tumor from 44.6 (11.15 months) to 78.6 (19.65 months) weeks (WW = 12.6, p = 0.0001). With subtotal removal, this parameter increased from 36.1 (9.025 months) to 68.92 (17.23 months) weeks (WW = 9.13, p = 0.0001), with convexital localization – from 40.0 (10.0 months) to 78.6 (19.65 months) weeks (WW = 15.4, p = 0.0001), and with paraventricular localization – from 33.4 (8.35 months) to 59.1 (14.775 months) (WW = 5.59, p = 0.015), respectively. It was shown that when comparing patients aged 40 to 60 years with Grade III–IV tumors in the control and treatment groups, the median survival rate increased from 41.8 (10.45 months) to 65.0 (16.25 months) weeks (WW = 11.7, p = 0.0001). The relapse-free period in patients with Grade II–IV tumors of the treatment and control groups equaled 69.0 (17.25 months) and 35.0 (8.75 months) (WW = 22.2, p = 0.0001), respectively. In patients with highly malignant Grade III–IV tumors secondary to LCT, the relapse-free period was 59.0 (14.75 months) weeks, while in the control group – 34.0 (8.5 months) weeks (WW = 26.0, p = 0.0001).

At the same time, the median progression-free survival in patients with the most malignant Grade IV tumors of the treatment group reached 56.0 (14 months) weeks, in the control group – 31.5 (7.875 months) (14.0–100.0) (WW = 26.2, p = 0.0001).
The one-year cumulative proportion of surviving patients with Grade III–IV tumors in the treatment group was 72.7 %, in the control group – 20.8 % (WW = 20.6, p = 0.0001), and with two-year monitoring – 27.7 % secondary to LCT and 1.3 % – secondary to the standard treatment (WW = 26.3, p = 0.0001). The tumor relapse risk (RR) in patients with Grade II–IV tumors in the control group was 4.56 (1.67–12.5) times higher than in patients in the treatment group (χ^2=10.5; p = 0.012). The tumor relapse risk in patients with Grade III–IV tumors in the control group was 1.14 (1.0–1.29) times higher than in patients in the treatment group (F = 0.1; p = 0.007). The tumor relapse risk in patients with Grade IV tumors in the control group was 1.10 (1.0–1.3) times higher than in similar patients in the experimental group (F = 0.01; p = 0.009).

Key words: primary neuroepithelial brain tumors, intraoperative local chemotherapy, temozolomide, Temodex, survival, relapse-free period.

INTRODUCTION

Systemic chemotherapy is the most common therapeutic approach to the combined treatment of cancers [6–8].

In neurosurgical practice, adjuvant chemotherapy in combination with radiation treatment after tumor resection significantly prolongs the life of patients. For comparison, the life expectancy after removal of glioblastoma without chemotherapy and radiation treatment applied is 4.5 months on average, and with their use – 14.6 months [5, 23].

However, there are a number of problems associated with systemic chemotherapy. In the first instance, a significant number of restrictions and contraindications. Secondly, high toxicity to healthy and unaffected tissues. Thirdly, a low medicinal product concentration in the tumor tissues [10].

One of the promising solutions to these problems in brain tumors (BT) is the use of local systems implanted during surgery. They are a combination of a chemotherapeutic agent with a polymer that plays the role of a reservoir, which contributes to the achievement of the active substance prolonged release effect. A high medicinal product concentration accumulates in the tumor and persists for several weeks. Thus, the chemotherapeutic agent affects tumor cells directly, significantly reducing toxicity to normal nerve tissue, thereby reducing the chemotherapy side effects.

OBJECTIVE OF THE STUDY

To increase the efficacy of combined treatment of patients with neuroepithelial supratentorial brain tumors by intraoperative local chemotherapy.

MATERIALS AND METHODS

The trial was carried out on the basis of the Neurosurgical Department of the HI "Minsk City Clinical Emergency Hospital" as part of clinical trials approved by the Ministry of Health of the Republic of Belarus No. 01-03-04/6042 dated July 4, 2012.

Trial design: open-label, controlled, comparative, retro-prospective, randomized trial in parallel groups.

Part 1 of this article renders a detailed description of the medicinal product (MP) Temodex, trial design, criteria for the enrollment of patients in the clinical trial, the technology of intraoperative local chemotherapy and the methodology of statistical processing of the data obtained [3].

Secondary trial endpoints.

The endpoints of the trial: overall survival rate and progression-free survival:

- overall survival rate (OS) was calculated from the date of the treatment initiation to death from any cause or to the date of the patient's last visit. Overall survival rate characterized the entire group of patients who started treatment and showed the actual survival rate for the specified follow-up period;

- – progression-free survival (PFS) was calculated from the date of the treatment initiation to the date of the relapse detection (the date of the last observation in case of no disease progression and the patient continued to be observed, or the date of the patient death if the date of progression could not be accurately established) or until the date of disease progression. Disease progression was verified by magnetic resonance imaging (MRI)/X-ray computed tomography (RCT) of the brain (BM) or by clinical signs of such if the control MRI or RCT was not performed. Progression-free survival characterized the course of the disease in the entire group of patients who started treatment. This parameter was chosen because it was used mainly for those diseases when complete remission was rarely achieved. The progression-free survival determines what proportion of patients who started treatment are able to survive the specified period without signs of disease progression or relapse regardless of whether complete remission has been achieved.

The trial endpoints were tracked in 128 patients with intracerebral tumors: 39 patients in the treatment group and in 89 patients in the control group.

The treatment efficacy was additionally analyzed by randomization of patients into separate comparison groups depending on the pathomorphology of the tumor process, radical nature of surgery, tumor localization and age of the patient.

For the statistical assessment of survival in the groups, a variant of the non-parametric Wilcoxon test, proposed for incomplete observation by Gehan and Peto, was used. Survival rates were assessed using the Kaplan-Meier method with a validity assessment by a logarithmic rank test. The results of the trial were considered reliable if the probability of an error-free forecast was not less than 95.5 % ($p < 0.05$).

RESULTS AND DISCUSSION

By the time of the analysis of the trial results (January 2015), 10 patients (25.6 %) continued to be observed in the treatment group, 29 (74.4 %) died. In the control group, 84 patients (94.4 %) died, 5 (5.6 %) remained alive ($\chi^2 = 10.5$, $p = 0.001$) respectively.

Data on the overall survival of patients with Grade II–IV tumors in the treatment and control groups, survival rates depending on the radicality of resection of Grade III–IV tumors, survival rates of patients with the most malignant Grade IV tumors depending on the extension of Grade III–IV tumors, the survival rates of patients in different age categories of Grade III–IV tumors are presented by the Kaplan–Meier curves in Fig. 1-9 and Table. 1.
The analysis of the survival rates of patients with BT secondary to LCT, depending on the biological properties of the tumor process, revealed the following. The median survival rate of patients with Grade II–IV tumors was 78.6 (19.1 months) (53.4–119.0) weeks in the treatment group, 42.0 (10.5 months) in the control group (31.0–57.2) weeks (WW = 22.0, $p = 0.0001$) (Fig. 1, Table 1).

A significant increase in the median survival rate was observed in patients with Grade III–IV tumors in the treatment group compared to the control group.

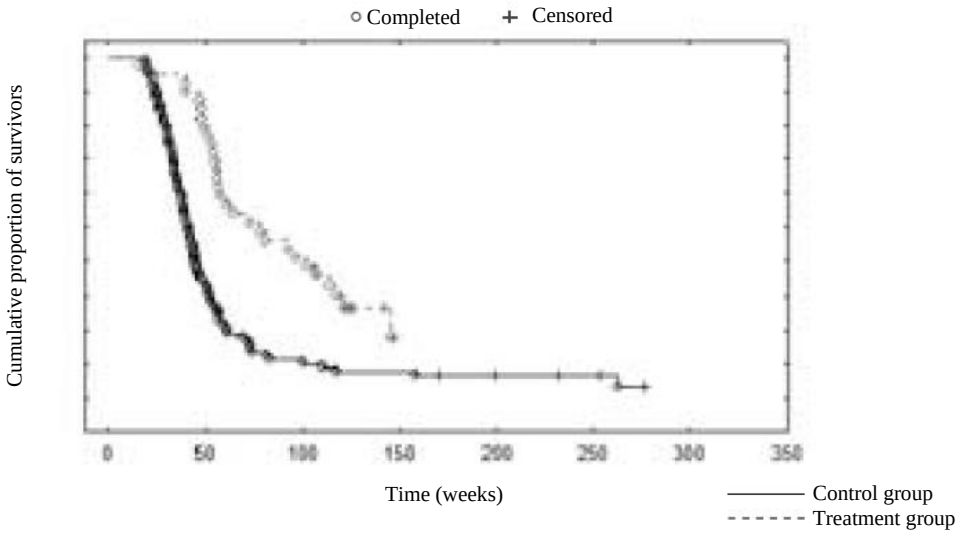

Fig. 1 Overall survival of patients with Grade II–IV brain tumors depending on the treatment technology used

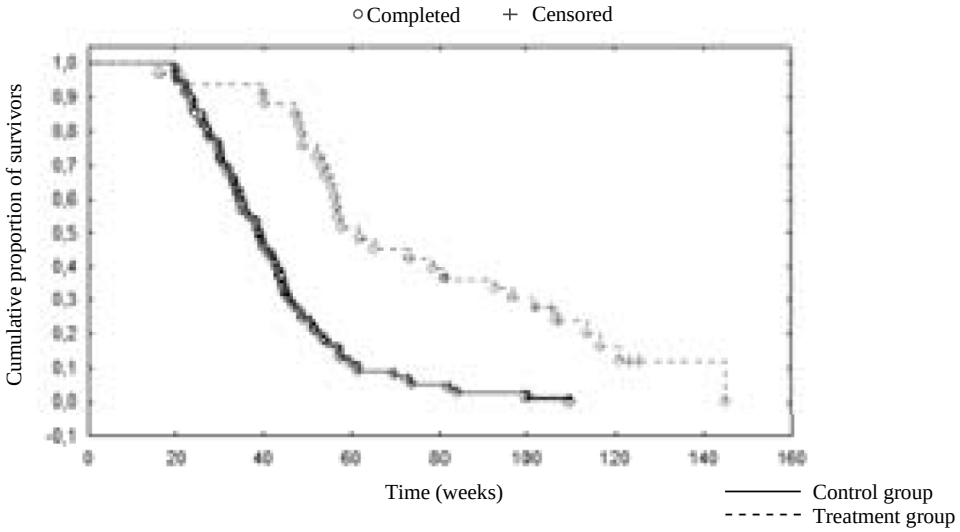

Fig. 2. Overall survival of patients with high-grade Grade III–IV brain tumors depending on the treatment technology used

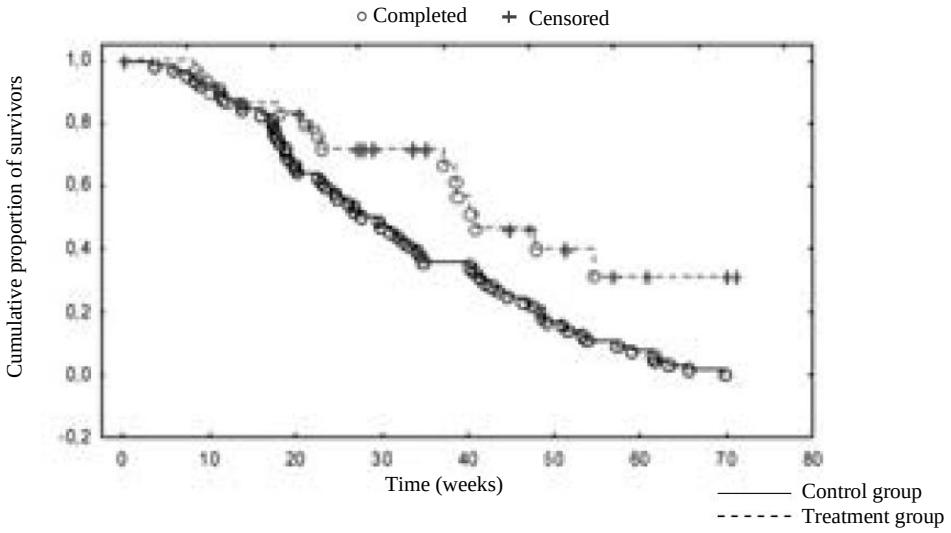

Fig. 3. Overall survival of patients with Grade IV brain tumors depending on the treatment technology used

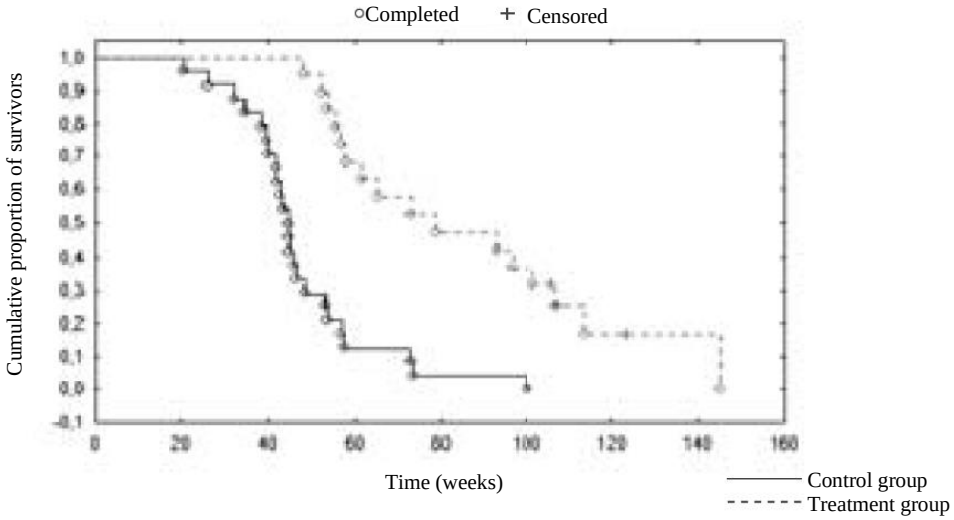

Fig. 4. Overall survival of patients with total removal of Grade II–IV tumors depending on the treatment technology used

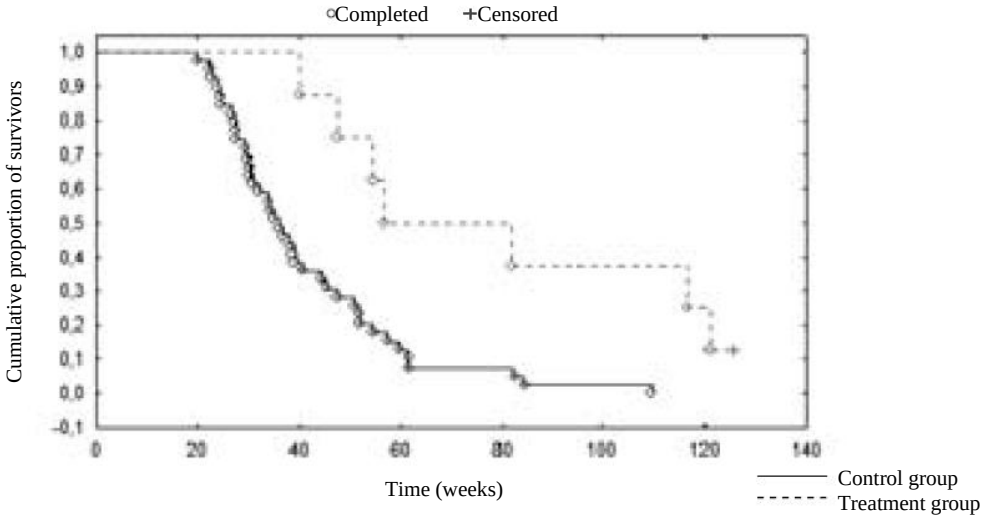

Fig. 5 Overall survival of patients with subtotal resection of Grade III–IV tumors depending on the treatment technology used

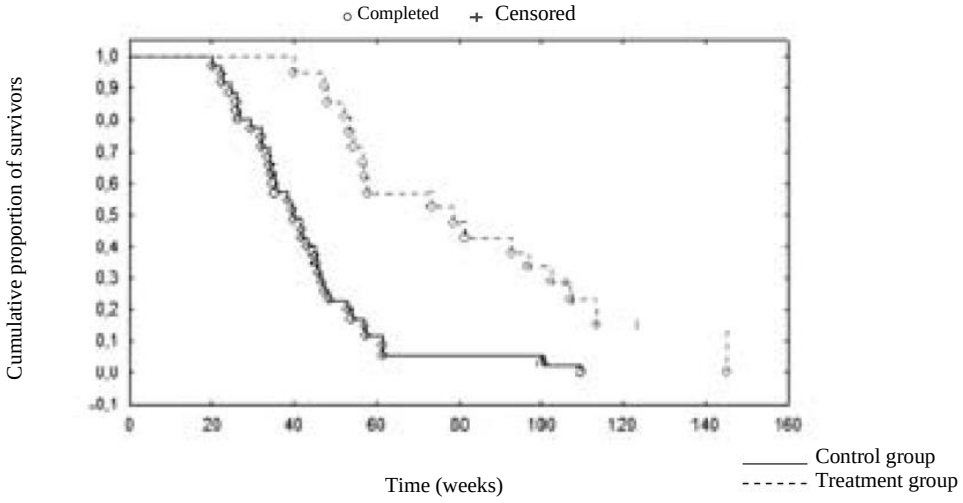

Fig. 6. Overall survival of patients with convexital Grade III–IV tumors depending on the treatment technology used

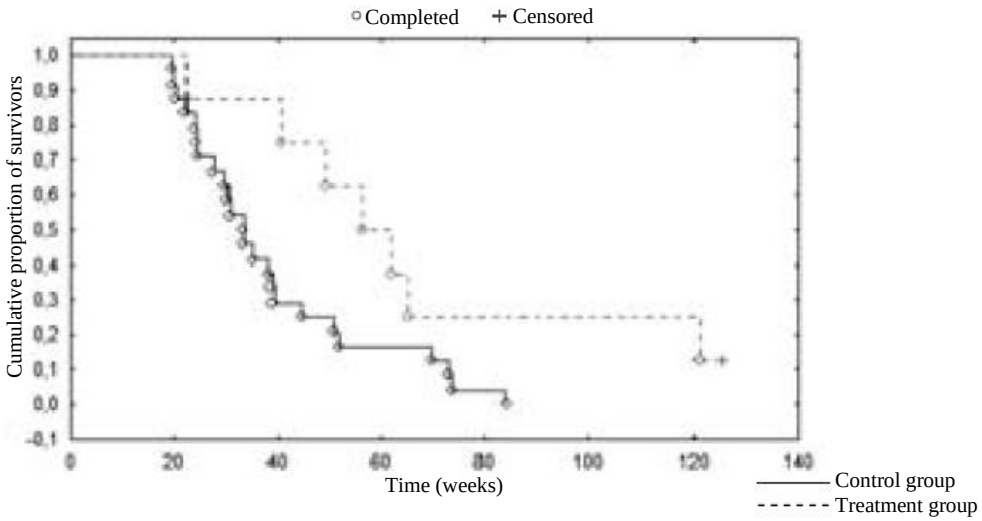

Fig. 7. Overall survival of patients with paraventricular Grade III–IV tumors depending on the treatment technology used

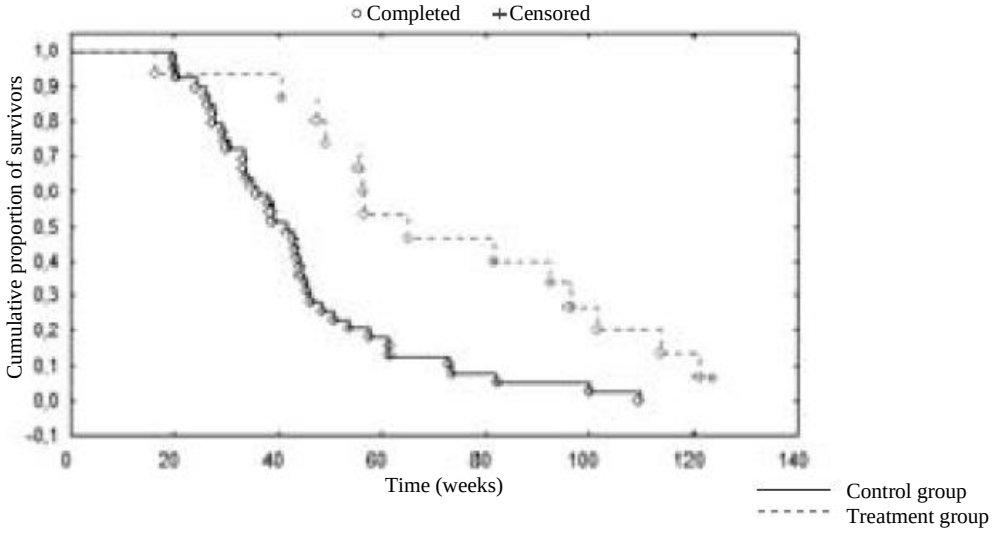

Fig. 8. Overall survival of patients in the age category from 40 to 60 years with Grade III–IV tumors depending on the treatment technology used

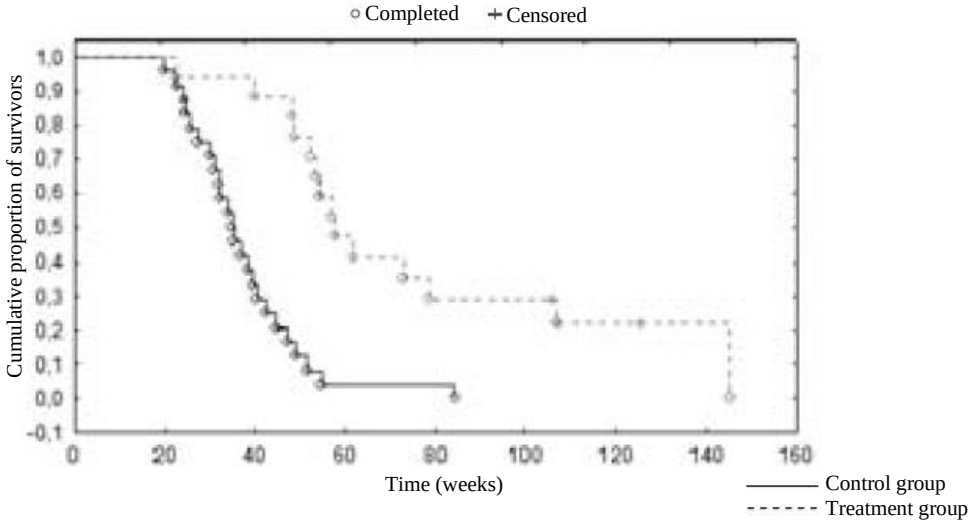

Fig. 9. Overall survival of patients over 60 years of age with Grade III–IV tumors depending on the treatment technology used

Local chemotherapy in treatment of brain tumors.
Part 2. Efficiency of treatment of patients with neuroepithelial brain tumors secondary to intraoperative local chemotherapy

Table 1
The survival rates of patients with neuroepithelial supratentorial tumors, weeks, Me (CI, 25–75%)

Estimated parameter		Treatment group	Control group	Significance of differences
Degree of tumor malignancy	Grade $I_{I–IV}$	78.6 (53.4–19.0)	42.0 (31.0–57.2)	WW=22.0, p=0.0001
	Grade $I_{II–IV}$	61.9 (52.3–105.9)	39.1 (30.1–49.0)	WW=27.0, p=0.0001
	Grade I_V	59.9 (16.0–45.4)	38.4 (19.7–109.8)	WW=25,9, p=0.0001
Tumor resection volume ($G_{III–IV}$)	Total	78.6 (48.3–145.4)	44.6 (20.6–100.1)	WW=12.6, p=0.0001
	Subtotal	68.9 (40.0–125.7)	36.1 (20.1–109.8)	WW=9.13, p=0.0001
Tumor extension ($G_{III–IV}$)	Convexital	78.6 (54.4–105.9)	40.0 (32.1–48.6)	W=15.4, p=0.0001
	Paraventricular	59.1 (44.7–93.1)	33.4 (24.3–47.7)	WW=5.59, p=0.015
Age	40–60	65.0 (16.0–123.4)	41.8 (20.0–109.9)	WW=11.7, p=0.0001
	>60	57.8 (22.4–145.4)	35.4 (19.7–84.0)	WW=11.5, p=0.0001

The median survival rate in patients in the treatment group equaled 61.9 (15.5 months) (52.3–105.9), in the control group – 39.1 (9.8 months) (30.1–49.0) weeks (WW = 27.0, p = 0.0001) (Fig. 2), the median survival rate of patients with high-grade (Grade IV) tumors in the treatment group equaled 59.9 (14.98 months) (16.0–145.4), in the control – 38.4 (9.6 months) (19.7–109.8) weeks (WW = 25.93, p = 0.0001) (Fig. 3).

Significant differences were established in the increase in the median survival rate of patients in the treatment group compared to the control group depending on the radicality of removal of Grade III–IV tumors. After total removal, the median survival rate in the treatment group equaled 78.6 (19.65 months) (48.3–145.4) weeks, in the control group – 44.6 (11.2 months) (20.6-100.1) weeks (WW = 12.6, p = 0.0001); after subtotal removal, the median survival rate in the treatment group equaled 68.9 (17.23 months) (40.0–125.7) weeks, in the control group – 36.1 (9.02 months) (20.1–109.8) weeks (WW = 9.13, p = 0.0001) respectively (Fig. 4–5).

The median survival rate in patients of the treatment group with a convexital tumor was significantly higher than in the control and amounted to 78.6 (19.65 months) (54.4–105.9), while in the control group it was 40.0 (10.0 months) (32.1–48.6) weeks (WW = 15.4, p = 0.0001). In case of paraventricular tumor expansion, the median survival rate in the treatment group was 59.1 (14.78 months) (44.7–93.1), in the control group – 33.4 (8.35 months) (24.3–47.7) (WW = 5.59, p = 0.015) (Fig. 6–7).

Significant differences in the effect of LCT on median survival rate were found in patients depending on age. In particular, the survival rate in patients of the treatment group aged 40 to 60 years is 65.0 (16.25 months) (16.0–123.4), in the control group – 41.8 (10.45 months) (20.0–109.9) weeks (WW = 11.7, p = 0.0001), while at the age of over 60 years, this parameter in the treatment group was 57.8 (14.45 months)

(22.4–145.4), in the control group – 35.4 (8.85 months) (19.7–84.0) (WW = 11.57, p = 0.0001) (Fig. 8–9).

Fig. 10-13 and Table. 2 present the data on the cumulative proportion of surviving patients with one-year and two-year follow-up.

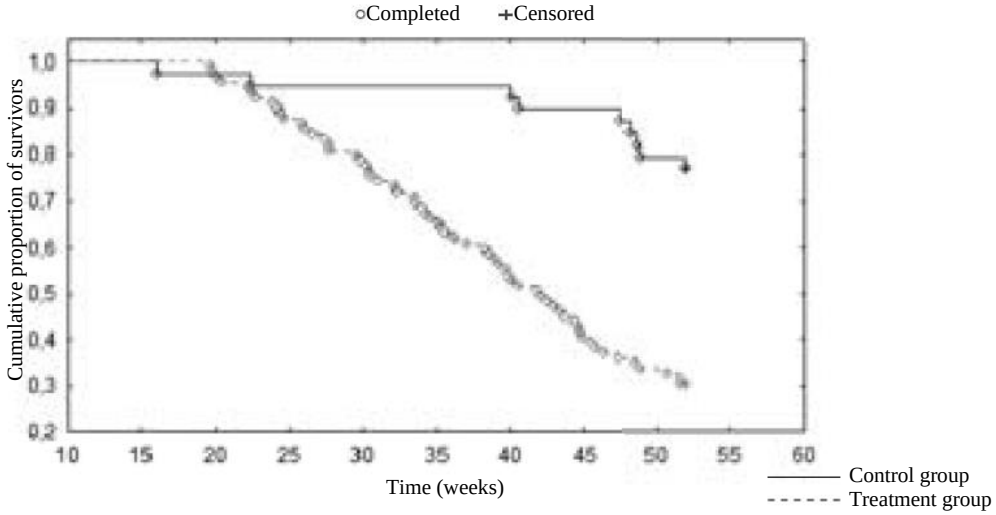

Fig. 10. One-year survival of patients with Grade II–IV tumors depending on the treatment technology used

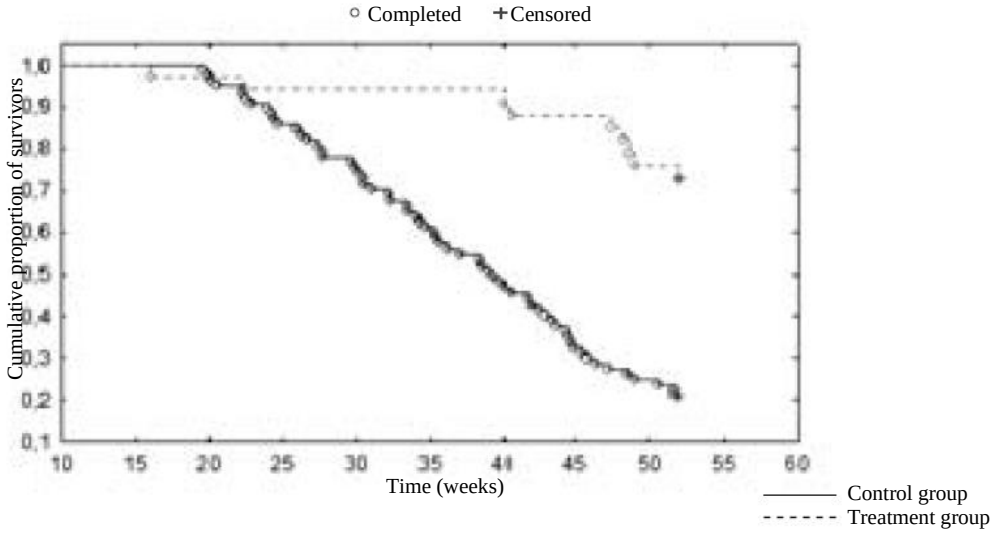

Fig. 11. One-year survival of patients with Grade III–IV tumors depending on the treatment technology used

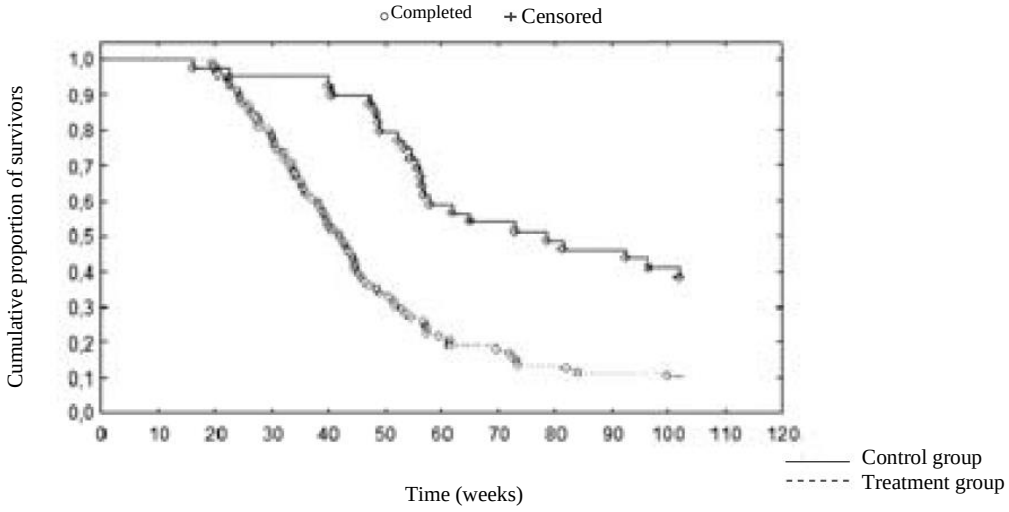

Fig. 12. Two-year survival of patients with Grade II–IV tumors depending on the treatment technology used

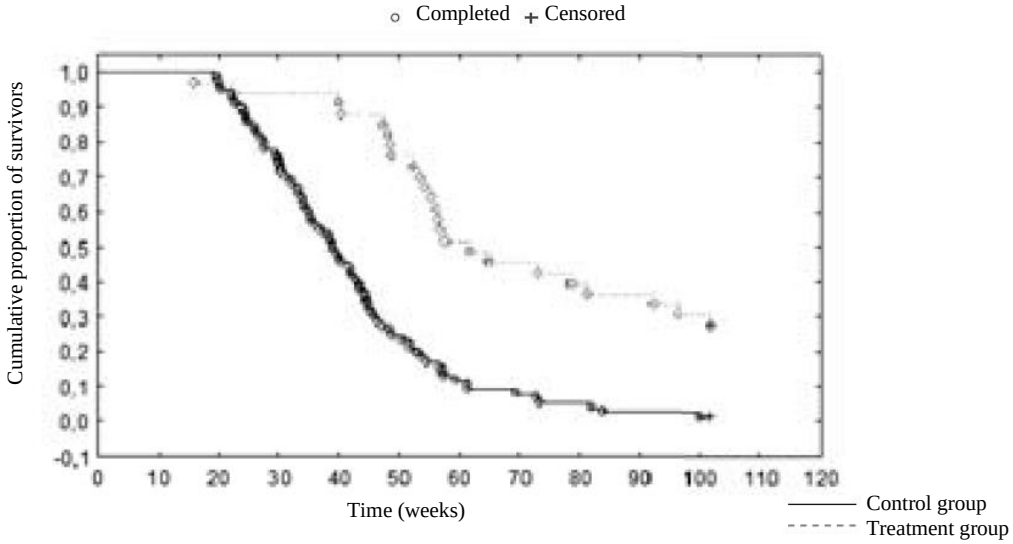

Fig. 13. Two-year survival of patients with Grade III–IV tumors depending on the treatment technology used

Table 2
One- and two-year survival of patients with neuroepithelial supratentorial tumors, % (abs.)

Estimated parameter		Treatment group	Control group	Significance of differences
One-year survival rate	Grade $I_{I–IV}$	76.9 (30)	33.3 (27)	WW=19.6, p=0.0001
	Grade $I_{II–IV}$	72.7 (24)	20.8 (16)	WW=20.6, p=0.0001
Two-year survival rate	Grade $I_{I–IV}$	38.5 (15)	10.1 (9)	WW=23.2, p=0.000
	Grade $I_{II–IV}$	27.3 (9)	1.3 (1)	WW=26.3, p=0.0001

The cumulative proportion of surviving patients in the treatment group with one-year follow-up was 61.5 %, in the control – 15.1 % respectively (Fig. 10). At the same time, the median duration of the cumulative survival period in the study group was 37.1 (9.275 months) (CI 21.6 ÷ 51.3), in the control group – 27.2 (6.8 months) (CI 17.4 ÷ 44.0) (WW = 1002, p = 001) weeks.

As seen from Fig. 10-13 and Table 2, the cumulative proportion of surviving patients with Grade II–IV tumors in the treatment group with one-year follow-up was 76.9 %, in the control – 33.3 % (WW = 19.6, p = 0.0001).

The proportion of surviving patients with Grade III–IV tumors in the treatment group with one-year follow-up was 72.7 %, in the control group – 20.8 % (WW = 20.6, p = 0.0001).

The cumulative proportion of surviving patients with Grade II–IV tumors in the treatment group at two-year follow-up was 38.5%, in the control – 10.1 % (WW = 23.2, p = 0.0001).

The proportion of surviving patients with Grade III–IV tumors in the treatment group at two-year follow-up was 27.7 %, in the control group – 1.3 % (WW = 26.3, p = 0.0001).

Figure 14-16 and Table 3 present data on the duration of the relapse-free period in patients with Grade II–IV neuroepithelial supratentorial tumors in the treatment and control groups.

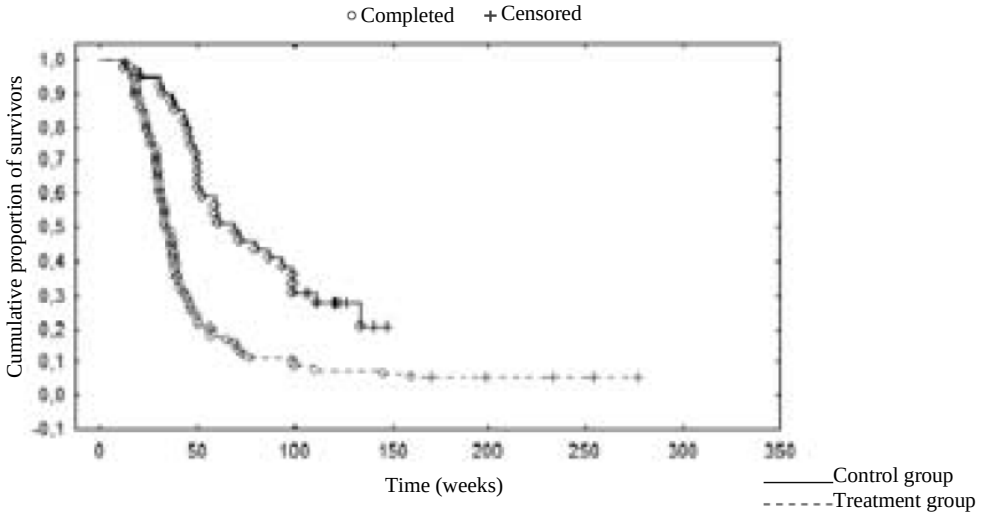

Fig. 14. Duration of relapse-free period in patients with Grade II–IV tumors depending on the treatment technology used

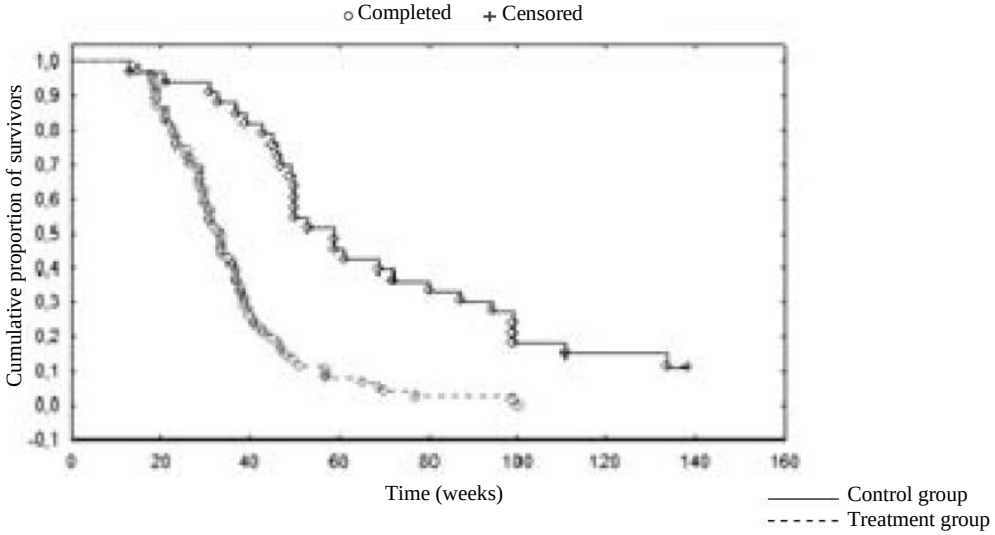

Fig. 15. Duration of the relapse-free period in patients with Grade III–IV tumors depending on the treatment technology used

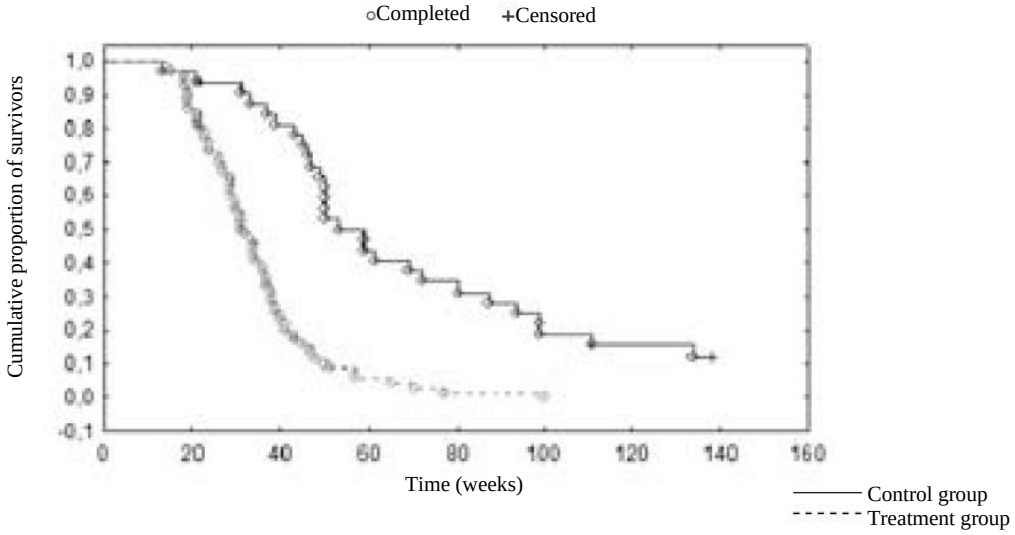

Fig. 16. Duration of relapse-free period in patients with Grade IV tumors depending on the treatment technology used

Table 3
Progression-free survival among patients with Grade II–IV brain tumors depending on the treatment technology used, weeks, Me (25–75%)

Characteristic		Treatment group	Control group	Significance of differences
Degree of tumor malignancy	Grade $I_{I–IV}$	69.0 (47.0–111.0)	35.0 (27.0–48.0)	WW=22.2, p=0.0001
	Grade $I_{II–IV}$	59.0 (46.0–51.0)	34.0 (26.0–41.0)	WW=26.0, p=0.0001
	Grade I_{V}	56.0 (13.0–138.0)	31.5 (14.0–100.0)	WW=26.2, p=0.0001

These data show that LCT resulted in the increased duration of the relapse-free period compared to the standard technology for treating patients with Grade II–IV tumors: the relapse-free period in the treatment group was 69.0 (17.25 months) (47.0–111.0), in the control – 35.0 (8.75 months) (27.0–48.0) (WW = 22.2, p = 0.0001). In patients with Grade III–IV tumors, the relapse-free period in the treatment group reached 59.0 (14.75 months) (46.0–51.0) weeks, in the control group – 34.0 (8.5 months) (26.0–41.0) weeks (WW = 26.0, p = 0.0001).
In patients with the most malignant Grade IV tumors, the relapse-free period in the treatment group was 56.0 (14 months) (13.0–138.0) weeks, in the control group –31.5 (7.875 months) (14.0–100.0) (WW = 26.2, p = 0.0001).

To assess the efficiency of intraoperative LCT with Temodex, the relative relapse risk in patients in the control group in relation to the treatment one was also calculated depending on the degree of malignancy of the tumor process (Grade II–IV, Grade III–IV and Grade IV tumors). The data are presented in Table 4-7.

Table 4
Randomization of patients with Grade II–IV tumors by relapse, % (abs.)

Tumor relapse	Group	
	Treatment	Control
Yes	74.4 (29)	94.4 (84)
No	25.6 (10)	5.6 (5)

Table 5
Randomization of patients with Grade III–IV tumors by relapse, % (abs.)

Tumor relapse	Group	
	Treatment	Control
Yes	87.8 (29)	100 (77)
No	17.1 (4)	0.0 (0)

Table 6
Randomization of patients with Grade IV tumors by relapse, % (abs.)

Tumor relapse	Group	
	Treatment	Control
Yes	28 (87.5)	100 (70)
No	4 (12.5)	0.0 (0)

Calculations of this parameter showed that the tumor relapse risk (RR) in patients with Grade II–IV tumors in the control group was 4.56 (1.67–12.5) times higher than in patients in the treatment group (χ^2 = 10.5; p = 0.012).
The tumor relapse risk in patients with Grade III–IV tumors in the control group was 1.14 (1.0–1.29) times higher compared to patients in the treatment group (F = 0.1; p = 0.007).

The tumor relapse risk in patients with Grade IV tumors in the control group was 1.10 (1.0–1.3) times higher than in similar patients in the treatment group (F = 0.01; p = 0.009).

Two medicinal products are currently used for clinical local chemotherapy, namely bioresorbable plates of Polypheprosane 20 with implantation of Carmustine and Cisplatin immobilized on oxidized cellulose [2, 24]. The first one is the medicinal product developed by an American pharmaceutical company, the second – by a Belarusian company.

Both medicinal products consist of an active substance (chemotherapeutic agent) placed on a polymer carrier (reservoir). Their method of application and mode of action are similar. During the surgery, the medicinal product is placed in the bed of the removed BT, where it is resorbed for several weeks, delivering high doses of cytostatic agent to the residual tumor. It creates an active substance zone, which is adjacent to the circumference of the tumor bed and is about 5 cm. As a result, they possess a cytostatic effect of the chemotherapeutic agent on tumor cells that were not removed during the surgery due to the impossibility of their visualization. In the future, the patient does not need re-surgery to evacuate the implants since they are biodegradable. Medicinal products contraindications are also common: pregnancy, individual intolerance, intraoperative complications that do not allow the system implantation. However, there are a number of differences between the medicinal products.

The active substance of the American analogue is carmustine (each plate contains 7.7 mg of carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea) – an alkylating type of chemotherapeutic agent from the group of nitrosourea derivatives, homogeneously distributed in the copolymer matrix – Polypheprosane 20. After resection of the brain tumor, up to 8 plates are placed in the formed cavity. Implants dissolve slowly, i.e. within 2–3 weeks [9, 18].

The medicinal product is approved by the Food and Drug Administration (FDA) and is approved as a treatment option for all initially diagnosed malignant glial tumors, including glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma, as well as for the treatment of the recurrent tumors of these types. It is considered as the accepted treatment option of initially diagnosed and recurrent malignant glial tumors in the most recent National Comprehensive Cancer Network (NCCN Guidelines) Guidelines for central nervous system tumors [19].

The results of the clinical use of cisplatin immobilized on oxidized cellulose in the treatment of BT have been published in several scientific works [1, 4]. The basis of the medicinal product is cellulose oxidized by nitric oxide, which also possesses a hemostatic effect. The cellulose is used as a polymer carrier for the active substance cisplatin (cis-diamminedichloroplatin). The concentration of the chemotherapeutic agent in the polymer is 1 ± 0.15 mg per 1 cm2 of the pad. The permissible amount for implantation of cisplatin pads immobilized on oxidized cellulose in the removed tumor bed equals 15–20 pieces. Body resorption occurs within 20–30 days. E.A. Korotkevich et al. [4] studied the effect of the medicinal product in 40 patients. The control group consisted of 155 patients who received only postoperative external beam radiation treatment.

Significant differences ($p < 0.05$) were obtained between the mean values of the duration of the relapse-free period in the treatment (50.8 ± 3.2 weeks) and control groups (31.9 ± 2.8 weeks). Life expectancy in patients of the treatment group under the age of 40 was 159.3 ± 6.3 weeks, in the control group – 124.7 ± 5.2 weeks. The calculation of survival rates using the Life table method showed that the cumulative survival rate in the treatment group was higher than in the control group.

According to literary sources over the past 10 years, most of the reports on intraoperative LCT consider the American analogue, to a lesser extent – to the Belarusian one [11, 12]. Since February 2003 in the USA (USA FDA approved) and since 2004 in Europe, the medicinal product Carmustine, immobilized on bioresorbable plates, has been used as a local medicinal product to treat Grade II–IV neuroepithelial supratentorial BT.

During this time, sufficient experience has been accumulated in the use of this medicinal product; its efficiency and side effects have been studied. Researchers, analyzing the antineoplastic effect of the American medicinal product, showed a significant increase in the survival rates. So, in Germany in 2003, using data from 38 centers in 14 countries of the world with the participation of 240 patients with high-grade gliomas, tumor resection secondary to LCT with this medicinal product and subsequent radiation treatment has been shown to result in a median survival rate of 13.9 months, in the control group – 11.6 months [14]. A 10-year US trial of the antineoplastic efficacy of Carmustine immobilized on bioresorbable plates in 1013 patients showed that those who received the medicinal product experienced more radical tumor removal. In patients with glioblastoma multiforme, the median survival rate was 13.5 months after primary resection and 11.3 months after re-surgery associated with the continued tumor growth. In patients with anaplastic astrocytoma and anaplastic oligoastrocytoma, the median survival rate was 57 months (66% of patients are alive for 2 years) and 23.6 months after repeated tumor resection (47% of patients are alive for 2 years) [15]. Not all researches share the opinion that the American analogue contributes to a significant increased survival. For example, R. Soffietti and L. Dörner argue that a positive effect is possible only when this medicinal product is used either with radiation treatment or in combination with radiation treatment and temozolomide [21].

The great advantage of the American medicinal product is its huge evidence base, based on many clinical trial data [16, 17, 20]. Chowdhary S.A. et al. [16] presented an indicative literature review based on a selection of 62 trial on medicinal product action and summarized the results. Regarding the initially diagnosed malignant glial tumors, the one-year survival rate was 67 % with Carmustine used immobilized on bioresorbable plates, and 48 % without its administration; the two-year survival rate was 26 and 15 % respectively; the median survival rate was 16.4 ± 21.6 months and 13.1 ± 29.9 months respectively. For recurrent malignant gliomas, the one-year survival rate was 37 % with the American medicinal product and 34 % without it. Thus, a clear statistical dependence of the increased life expectancy is traced in case of local chemotherapy with this medicinal product.

Postoperative mortality among patients receiving the medicinal product was 0.9 %. Less than 1 % of patients required removal of the plates, and approximately 3 % required re-surgery.

The most common causes of re-surgeries were infectious complications, hydrocephalus, hematoma or cyst formation in the removed tumor bed, delayed postoperative wound healing, which was sometimes accompanied by wound cerebrospinal fluid leakage [22].

The official website of the medicinal product of the American pharmaceutical company [13] presents the information on possible complications, side effects, as well as prevention and precautions when using the medicinal product. Based on the information provided, the most common complication was seizures. Fifty-four percent (54 %) of patients experienced the occurrence or intensification of seizures during the first 5 postoperative days. Intracranial hypertension (cerebral edema) in the early postoperative period occurred in 23 % of patients. Impaired healing of postoperative wounds was observed in 16 % of patients and it was complicated by wound cerebrospinal fluid leakage in 5 % of patients. Infectious complications (meningitis) were observed in 4 % of patients. Elimination of the above complications is achieved by postoperative monitoring of patients and, if necessary, by re-surgery and medicinal product withdrawal.

CONCLUSION

The trial of the antineoplastic activity of Temodex as a medicinal product for local chemotherapy of Grade II–IV tumors in combination with adjuvant chemotherapy indicates the achievement of results that are quite comparable with those for the medicinal product of the American and Belarusian origin in terms of increasing overall survival and the duration of the relapse-free period. It should be noted that the medicinal product did not show any significant general toxicity and neurotoxicity. The data on complications of the early postoperative period were also comparable with the control group. Moreover, given the fact that Temodex matrix consists of hydrophilic highly substituted dextran phosphate, it can be assumed that this will also have an additional anti-edematous effect of the medicinal product in the region of neurosurgical intervention.

The development and introduction of new domestic medicinal products for local prolonged chemotherapy, the study of their mechanisms of its action and efficiency will expand the range of medicinal products available for the treatment of malignant tumors, which will provide a neurosurgeon with a choice and create conditions for economic efficiency and import substitution.

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