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Local chemotherapy in treatment of brain tumors. Part 1. Characteristics of neurosurgical intervention and the course of the postoperative period in patients with brain tumors secondary to local chemotherapy

Summary

The assessment of the clinical progression of the postoperative period in patients with neuroepithelial brain tumors when using intraoperative local chemotherapy (iLCT) with Temodex, which is an anticancer medicinal product of the active substance of temozolomide immobilized on highly substituted dextran phosphate.

Clinical manifestations and features of the early postoperative period were analyzed depending on the radicality of tumor resection, its localization and extension. Complications and causes of mortality were studied in patients undergoing standard surgery and iCLT.

It was shown that the frequency and nature of complications when using Temodex did not differ from those in the control group.

In response to iLCT, no significant general toxic, neurotoxic and nephrotoxic effects were observed. The transient increased level of hepatic transaminases did not require medicinal product correction and returned to the reference values after 3–6 months after the intervention.

The general toxic effect of Temodex was not revealed; in response to local chemotherapy, reactive transient activation of hepatic enzyme systems was registered.

It was found that the severity of the patient's condition in the early postoperative period depended on the tumor localization, extension and volume, the radicality of removal of the tumor nidus secondary to local chemotherapy.

It was revealed that the best treatment results in the form of a compensated state were achieved in patients undergoing iLHT after total/subtotal resection of convexital tumors.

Key words: primary neuroepithelial brain tumors, intraoperative local chemotherapy, temozolomide, Temodex, safety, tolerance.

INTRODUCTION

Modern technologies for the treatment of primary (neuroepithelial) brain tumors (BT) are based on the obligatory surgical stage – the maximum possible removal of a mass lesion with minimal damage to the surrounding brain tissue and with subsequent chemo/radiotherapeutic effect on the residual tumor [5].

Despite the constant improvement of surgical removal of BTs, the use of these treatment options, low survival, high mortality and disability of patients remain, especially in high-grade tumors [1, 4], including among the socially active population [8, 11, 12]

The foregoing makes it obvious the need to improve existing and develop new technologies for treating patients in this group [2, 3, 6, 7, 9, 10].

A joint innovative development of Belarusian chemists and neurosurgeons, carried out with the financial support of the State Committee for Science and Technology and the Ministry of Health of the Republic of Belarus started in 2005 and ended in 2013 with randomized clinical trials and registration of the medicinal product Temodex for intraoperative local chemotherapy (State Registration No. 14/12/2324 dd. December 23, 2014).

OBJECTIVE OF THE STUDY

To study the features of the management of patients with neuroepithelial tumors secondary to local chemotherapy with Temodex.

MATERIALS AND METHODS

The trial was carried out within the framework of clinical trials of the medicinal product (MP) Temodex, approved by the order of the Ministry of Health of the Republic of Belarus No. 01-03-04/6042 dd. July 4, 2012.

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

The trial enrolled 136 patients with primary cerebral tumors who were treated at the Neurosurgical Department of the HI "Minsk City Clinical Emergency Hospital" from 2010 to 2013.

Patients in the control group underwent only resection of the tumor mass; patients in the treatment group additionally underwent intraoperative local chemotherapy (iLCT) with Temodex.

Observation of the patients was carried out in a hospital until the moment of their discharge, i.e. 12–14 days after the surgery.

At all stages of their hospitalization at the Neurosurgical Department, patients received complex treatment in accordance with the current protocols.

After discharge, patients of both the control and the treatment groups underwent a course of radiation treatment and chemotherapy at the place of residence in accordance with the protocols of the Ministry of Health of the Republic of Belarus (daily intake of temozolomide 60 Gy at dose of 75 mg/m2 orally; 3–4 weeks after the completion of chemoradiation therapy, individualized cycles of chemotherapy courses were carried out at a dose of temozolomide 150–200 mg/m2 orally for 5 days).

In case of clinical and neuroimaging signs of continued tumor growth observed when monitoring patients, repeated surgical interventions were performed at the Neurosurgical Department of the HI "Minsk City Clinical Emergency Hospital".

Trial enrollment criteria: age over 18 years, verification of supratentorial tumor mass according to neuroimaging data (magnetic resonance imaging/X-ray computed tomography (MRI/RCT)), no somatic pathology in the stage of decompensation, quality of life according to the Karnofsky PS (KPS) not below 40 % and 3 points per the ECOG-WHO system at the time of the surgery.

At the same time, according to the KPS, the patient's condition was considered compensated when estimated in the range of 100–80 %, ECOG-WHO 0–1, subcompensated – 70–60 %, ECOG-WHO 2; decompensated – KPS 50–40 % and ECOG-WHO 3, respectively.

The trial groups were formed by randomization using random numbers tables.

Table 1 presents the clinical and demographic characteristics of the patients included in the final analysis.

As can be seen, intracerebral tumors typically occurred (up to 80 % in both cohorts) at the age of 41 to 70 years in both men and women of both groups.

In terms of age and sex, the groups were comparable ($c^2 = 6.5$; $p > 0.05$).

Thus, in the treatment group, men accounted for 51.3 % (21 people), women– 48.7 % (20 people), in the control group – 39.0 % (37 people) and 61.0 % (58 people), respectively. The median age of patients in the treatment and control groups was 57 ± 1.69 and 53 ± 1.25, respectively.

Table 1
Randomization of patients in the treatment and control groups by age and sex, % (abs.)

Age, years	Treatment group			Control group		
	Men, n=21	Women, n=20	Total, n=41	Men, n=37	Women, n=58	Total, n=95
21–30	2.4 (1)	0.0 (0)	2.4 (1)	1.1 (1)	3.1 (3)	4.2 (4)
31–40	4.9 (2)	0.0 (0)	4.9 (2)	6.3 (6)	8.4 (8)	14.7 (14)
41–50	12.2 (5)	7.3 (3)	19.5 (8)	10.5 (10)	9.5 (9)	20.0 (19)
51–60	4.9 (2)	19.5 (8)	24.4 (10)	12.6 (12)	19.0 (18)	31.6 (30)
61–70	22.0 (9)	14.6 (6)	36.6 (15)	5.3 (5)	14.7 (14)	20.0 (19)
>70	4.9 (2)	7.3 (3)	12.2 (5)	3.2 (3)	6.3 (6)	9.5 (9)

Table 2 presents randomization of patients depending on the degree of malignancy/morphological structure of the tumor.

Table 2
Randomization of patients depending on the degree of malignancy/morphological structure of the tumor, % (abs.)

Pathomorphology and grade of tumor malignancy (G_I–G_{IV})		Treatment group, n=41	Control group, n=95
Pilocytic astrocytoma	G_I	0.0 (0)	1.0 (1)
Fibrillary astrocytoma	G_{II}	9.8 (4)	7.4 (7)
Oligodendroglioma	G_{II}	7.3 (3)	3.2 (3)
Oligoastrocytoma	G_{II}	0.0 (0)	2.1 (2)
Anaplastic astrocytoma	G_{III}	2.4 (1)	8.4 (8)
Glioblastoma	G_{IV}	80.5 (33)	77.9 (74)

Note: G_n – the degree of malignancy of tumors of the central nervous system (according to the WHO classification, 2007).

In 17.1 % (7 people) of patients in the treatment group and 13.7 % (13 people) in the control group, so-called low-grade and indolent ($G_{I–II}$) tumors, represented by astrocytomas and oligodendrogliomas, were verified.

In 82.9 % (34) of patients in the treatment group and 86.3 % (82) in the control group, the tumor was highly malignant, rapidly growing high-grade tumor ($G_{III–IV}$). As one can see from the Table 2, patients with glioblastomas predominated in both groups.

Table 3 shows the randomization of patients depending on the extent of the tumor in relation to different cerebral compartments.

Table 3
The extension of supratentorial masses, % (abs.)

Prevalence	Treatment group, n=41	Control group, n=95
Subcortical (convexital)	63.4 (26)	48.4 (46)
Paraventricular	22.0 (9)	27.4 (26)
Mediobasal	14.6 (6)	24.2 (23)

Table 3 shows that tumors of sub-cortical (convexital) extension prevailed in both groups with no significant differences in the groups regarding this parameter.

Intraoperative local chemotherapy technology.

1. The medicinal product Temodex [manufacturer's monograph RB 2028-14, marketing authorization No. 14/12/2324 of December 23, 2014] is a substance of temozolomide (TZ) (manufacturer's monograph RB 1624-11, marketing authorization No. 11/11/1929 of November 2, 2011), immobilized on a matrix, which is highly substituted dextran phosphate (HSDPh) (RB patent No. 15136 and RF patent No. 2455007). TZ and HSDPh are synthesized in the Educational Scientific and Production Republican Unitary Company “Unitechprom BSU” RUE "Belmedpreparaty" provided the finished dosage form for the clinical trials. The pharmacodynamic (cytostatic/cytoreductive) properties of Temodex are based on the immobilization of temodozolamide on the gel-forming highly substituted dextran phosphate and its distribution in the gel spatial lattice due to donor-acceptor interactions. This structure of the medicinal product provides a prolonged effect of the cytostatic agent on the residual tumor tissue.

2. Preoperative planning of the BT resection was carried out according to MRI data with intravenous contrast enhancement with Omniscan at a dose of 20.0 mL. A craniotomy was performed to access the space-occupying lesion. A chemotherapeutic agent was prepared for intraoperative LCT 30 minutes before the end of the main stage (tumor resection) in the operating room (ex tempore). For this purpose, 12 mL of sterile water for injection was added to the contents of the Temodex vial, previously evacuated into a sterile container. As a result, the medicinal product became of gel consistency, the final volume of which equaled 25–30 cm3. After careful hemostasis, a preparation in the form of a gel with a final concentration of the active substance (TZ) of 100 mg was placed into the formed cavity. The dura mater was tightly sutured. In some cases, a rather large defect was formed in it, which was eliminated by plastic repair using the periosteum. After plastic repair of the defect, the bone flap was placed in the proper place. The average total surgery duration secondary to LCT with Temodex was 197.8 ± 5.98 min; in the control group – 183.4 ± 3.85 min ($p < 0.05$).

The degree of radical removal of the BT was assessed by the surgeon visually during the surgery and in the postoperative period according to the data of brain MRI/CT after 48–72 hours. The main criterion for the degree of radicality was the percentage of tumor volumes before and after the surgery. Complete (total) tumor resection means removal of 95–100 % of the space-occupying lesion, subtotal – more than 75–95 %, partial resection – less than 75 %.

Table 4 shows the results of radical removal of brain gliomas depending on the extent of the process.

Table 4
Radicality of removal of supratentorial masses depending on the extension, % (abs.)

Prevalence	Removal radicality					
	Total		Subtotal		Partial	
	TG	CG	TG	CG	TG	CG
Convexital (subcortical)	48.8 (20)	35.8 (34)	14.6 (6)	12.6 (12)	0.0 (0)	0.0 (0)
Mediobasal	2.4 (1)	4.2 (4)	7.3 (3)	7.4 (7)	4.9 (2)	12.6 (12)
Paraventricular	9.8 (4)	13.7 (13)	4.9 (2)	11.6 (11)	7.3 (3)	2.1 (2)
Total	61.0 (25)	53.7 (51)	26.8 (11)	31.6 (30)	12.2 (5)	14.7 (14)

Note: TG – treatment group, CG – control group.

Total tumor resection was performed in case of convexital (subcortical) spread in 48.8 % of cases in the treatment group and in 35.8 % in the control group.
In patients with paraventricular tumors, total resection was performed in 9.8 % and in 13.7 % cases in the treatment and control groups, respectively.
If the tumor extends to the corpus callosum, the subcortical nuclei with mediobasal localization, the tumor was partially removed (Table 5).

Table 5
The radicality degree of removal of supratentorial masses, % (abs.)

Removal radicality	Treatment group, n=41	Control group, n=95
Total	61.0 (25)	53.7 (51)
Subtotal	26.8 (11)	31.6 (30)
Partial	12.2 (5)	14.7 (14)

According to the presented data, the majority of BTs were radically resected in both groups. No differences regarding this parameter were registered.

Estimation of intraoperative LCT safety and tolerability. The program for evaluating the treatment safety provided for the study of the nature, frequency and severity of LCT side effects.

The following items were chosen as surrogate (intermediate) observation points in the postoperative period: the dynamics of the patients' status according to the KPS/ECOG-WHO, hematological parameters (complete blood count, biochemical blood test (CBC, BBT)), cerebrospinal fluid analysis, coagulogram, frequency and nature of complications.

All patients have the CBC, BBT, general urine analysis, tested before the surgery, on days 2–3, 10 and 20–25 after the surgery. The patients of the treatment group additionally underwent dynamic monitoring of the parameters of the CBC, BBT, coagulogram, and UA after 3, 6 and 12 months after the surgery.

Statistical processing. The data obtained were processed by methods of descriptive, parametric and non-parametric statistics using the Statistica 10.0 software package. The statistical significance in the data characterizing the qualitative distribution of the features in the study groups was determined on the basis of the value of the eligibility criterion (χ^2). The value of the coefficient was estimated according to the table of χ^2 values. The number of degrees of freedom in determining the significance of the coefficient of eligibility was calculated by the formula:

$$n^1 = (s - 1) \times (r - 1),$$

where s is the number of graphs;
r is the number of rows in the table.

If the distribution data obtained did not meet the conditions for applying the eligibility criterion, Fisher's exact test was used. The results of the trial were considered reliable, the differences between the parameters were significant with the probability of an error-free forecast of at least 95.5 % ($p < 0.05$).

RESULTS AND DISCUSSION

In most patients in both groups, cerebral symptoms (headache, nausea, vomiting, dizziness) regressed on days 2–3 after the surgery. The wound was healed by primary intention. The duration of hospitalization in the treatment group was 22.3 ± 0.91 days, in the control group – 24.5 ± 0.64 ($p < 0.05$).

Table 6 presents data on the dynamics of assessing the status of patients according to the KPS and the ECOG-WHO system. The presented data show no differences in the randomization of patients in the groups according to the general condition before the surgery. So, the overwhelming majority of them met the criteria for a compensated/subcompensated state. On the second day after the surgery, patients in a subcompensated state predominated in both groups, meanwhile, in the treatment group, the proportion of patients in a compensated state was significantly lower, and in a subcompensated state – higher than in the control group. On the 10th day, an increased number of patients in a compensated state was observed in both groups, while their proportion in the treatment group was significantly higher.

Table 6
Dynamics of the clinical status of patients on the second and tenth day after the surgery, % (abs.)

Patient status KPS/ECOG-WHO	Treatment group, n=41			Control group, n=95		
	Before the surgery	2nd day	10th day	Before the surgery	2nd day	10th day
Compensated, 100–80 %/0–1	56.1 (23)	12.2 (5) *	63.4 (26) *	46.3 (44)	29.5 (28)	44.2 (42)
Subcompensated, 70–60 %/2	34.1 (14)	75.6 (31) *	29.3 (12)	43.2 (41)	56.8 (54)	44.2 (42)
Decompensated, 50–40 %/3	9.8 (4)	12.2 (5)	7.3 (3)	10.5 (10)	13.7 (13)	11.6 (11)

Note: * – $p < 0.05$.

Table 7 presents the results of treatment in the postoperative period depending on the radicality of tumor removal and its extension.

According to the data obtained, a decompensated state per KPS/ECOG-WHO scales was observed in patients on the second day after partial resection due to the deep tumor localization.

In most cases, after total and subtotal resection, the patient's condition was subcompensated (in the treatment group – in 75.6 % of cases, in the control group – in 53.6 %) and compensated (12.2 and 29.4 %, respectively).

On the 10th day, the number of decompensated state patients decreased both in the treatment group (from 12.2 to 7.3 %) and in the control group (from 11.6 to 8.4 %).

The compensated state was noted in the treatment group in 63.4 % of cases and significantly more often in the control group after total removal of the neoplasm – 44.2 %. The subcompensated state in the treatment group was observed in 29.3 % of patients, in the control – in 44.2 % of patients.

Table 7
Estimation of the results of treatment of patients on the 2nd and 10th days after the surgery, % (abs.)

Study parameter		The second day after the surgery					
		Treatment group, n=41			Control group, n=95		
		KPS/ECOG-WHO			KPS/ECOG-WHO		
		40–50/3	60–70/2	80–100/1	40–50/3	60–70/2	80–100/1
Radical tumor resection	Total	0.0 (0)	48.8 (20)	12.2 (5)	0.0 (0)	34.7 (33)	18.9 (18)
	Subtotal	0.0 (0)	26.8 (11)	0.0 (0)	2.1 (2)	18.9 (18)	10.5 (10)
	Partial	12.2 (5)	0.0 (0)	0.0 (0)	11.6 (11)	3.2 (3)	0.0 (0)
Expansion	Convexital	0.0 (0)	53.7 (22) *	9.8 (4)	0.0 (0)	29.5 (28)	18.9 (18)
	Paraventricular	0.0 (0)	19.5 (8)	2.4 (1)	2.1 (2)	14.7 (14)	10.5 (10)
	Mediobasal	12.2 (5)	2.4 (1)	0.0 (0)	11.6 (11)	12.6 (12)	0.0 (0)
The 10th day after the surgery							
Radical tumor resection	Total	0.0 (0)	12.2 (5)	48.8 (20)*	0.0 (0)	25.3 (24)	28.4 (27)
	Subtotal	0.0 (0)	12.2 (5)	14.6 (6)	3.2 (3)	12.6 (12)	15.8 (15)
	Partial	7.3 (3)	4.9 (2)	0.0(0)	8.4 (8)	6.3 (6)	0.0 (0)
Expansion	Convexital	0.0(0)	2.4 (1)	70.0 (25)*	0.0 (0)	11.6 (8)	40.0 (38)
	Paraventricular	0.0 (0)	19.5 (8)	2.4 (1)	0.0 (0)	23.2 (22)	4.2 (4)
	Mediobasal	7.3 (3)	7.3 (3)	0.0 (0)	11.6 (11)	12.6 (12)	0.0 (0)

Note: * - $p < 0.05$.

In case of a convexital tumor, the state of patients was significantly more subcompensated in the treatment group on the 2nd day after the surgery, and reliably more often corresponded to the compensated one on the 10th day after the surgery.

Therefore, the analysis of one of the surrogate parameters of the early postoperative period – the dynamics of the patients status according to the KPS –revealed the compensated state after total resection of convexital tumors in the majority of patients, both in the control and in the treatment groups.

In the case of the mediobasal tumor and its associated partial resection, no patients in a compensated state were registered in both trial groups.

No differences in the morphological blood parameters of were observed in the trial groups during the preoperative period. On the 2nd and 10th days after the surgery, a statistically significant transient decrease in the level of hemoglobin and an increase in ESR were noted in patients of the treatment group compared with the control. The specified clinical and laboratory parameters were taken as reference values by the time the patients were discharged from the hospital (20–25 days after the surgery). In the same time interval in both groups, an increase in the number of leukocytes with a shift in the WBC differential to the left and moderate lymphocytopenia was observed in both groups, which also underwent positive dynamics by the 20–25th day after the surgery.

No differences in BBT parameters were registered in the preoperative period between the groups. By the 10th day after the surgery, patients in the treatment group showed a statistically significant increase in the level of ALT compared to the reference values, which returned to normal values by 3–6 months after the surgery.

No significant differences were found in the parameters of the coagulogram between the studied groups as well as their deviations from the reference values.

Complications of the early postoperative period were detected in 9.8 % of patients in the treatment group and in 12.6 % in the control group.

Hemorrhage in the removed tumor bed was observed in 7.6 % of patients in the treatment group and 8.4 % in the control group (Table 8). The volume of hemorrhages (15.0 cm^3 and 27.0 cm^3) and their clinical manifestations in two of the three patients who received LCT did not require revision of the surgical site in two patients. After 3 months, hematomas completely regressed according to control MRI studies. A postoperative cyst was formed in one patient after 2 months with a fluid component of 42.0 cm^3. This required repeated surgical intervention in order to evacuate the contents of the cyst and revise the postoperative cavity. Pathomorphological examination of the neoplasm bed showed no continued tumor growth.

Table 8
The frequency and nature of complications in the early postoperative period, % (abs.)

Complication	Treatment group, n=41	Control group, n=95
Hemorrhage in the tumor bed	7.6 (3)	8.4 (8)
Meningitis	2.4 (1)	3.2 (3)
Abscess	-	1.1 (1)

Postoperative meningitis was verified in 2.4 % of patients in the treatment group and 3.2 % in the control group, respectively. As a result of the treatment, the meningeal symptom complex regressed by the 5–7th day from the disease onset.

Table 9 shows the causes of death of patients in the treatment and control groups.

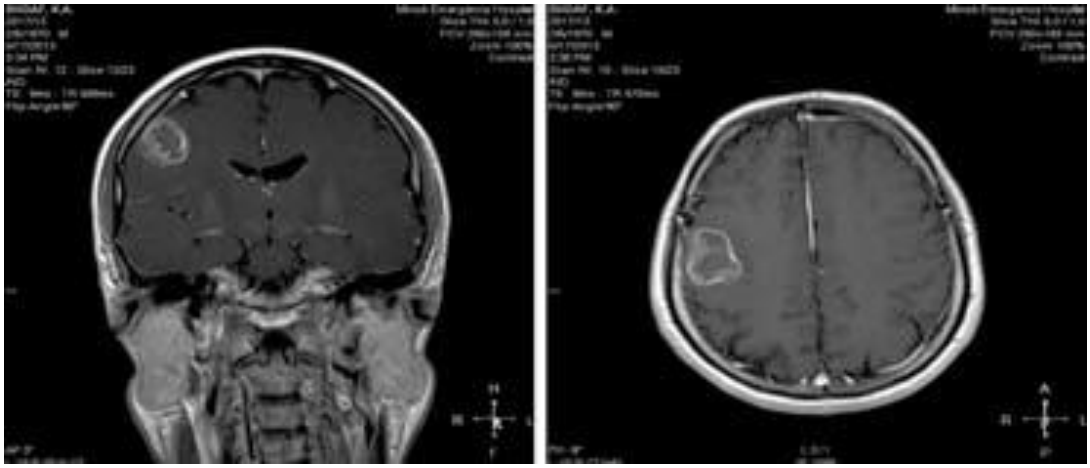
Table 9
Causes and frequency of deaths in patients of the study groups in the early postoperative period, % (abs.)

Cause of death	Treatment group, n=41	Control group, n=95
Brain edema and dislocation	-	3.2 (3)
Pulmonary embolism	4.9 (2)	2.1 (2)

In the control group, brain edema and dislocation, complicating the course of hemorrhages in the removed tumor bed and purulent meningitis, were fatal in 3.2 % of patients.

Pulmonary embolism caused death in 4.9 % of patients in the treatment group and 2.1 % in the control group.

As an illustration of the complication that a patient developed during LCT with Temodex, we present neuroimaging data from one of three patients. Figure 1 shows MRI with contrast enhancement of the brain of patient B. Conclusion: space-occupying lesion of the right parietal lobe with a volume of 24.0 cm3 (probably glioblastoma). On May 24, 2013, surgical intervention was performed: craniotomy in the fronto-parietal-temporal region, total removal of the mass, local chemotherapy with Temodex. X-ray computer tomography on the 3rd day after the surgery revealed hemorrhage in the removed tumor bed with a volume of 24.0 cm3 (Fig. 2). Considering no significant clinical manifestations of the formed intracerebral hematoma and its insignificant volume, it was decided to refrain from surgical intervention; clinical neuroimaging monitoring was continued. MRI with contrast enhancement on the 10th day of the early postoperative period demonstrated a postoperative cavity with a volume of 43.0 cm3, filled with heterogeneous contents with moderate perifocal edema and mass effect. Intensive accumulation of contrast agent along the contour of the cavity remained (Fig. 3). Pathological conclusion: glioblastoma multiforme, Gr4. MRI after 2 months after the surgery demonstrated signs of a cystic mass with a volume of 42 cm3 remaining in the region of the surgery. Based on these data, a re-surgery was undertaken: revision of the removed tumor bed, emptying of the postoperative cyst, as well biopsy of the cyst wall. No events were registered during the postoperative period. Conclusion following brain MRI with contrast enhancement at the 3rd month of the observations: the postoperative cavity has been determined in the parietal lobe on the right, filled with heterogeneous contents. A decrease has been observed in the volume of the cavity up to 26.0 cm3, as well as the decreased accumulation of contrast agent along the contour and regression of the perifocal edema zone (Fig. 4). Brain MRI with contrast enhancement performed 6 months after re-surgery demonstrated postoperative changes in the parietal lobe on the right without signs of tumor progression, the cyst was not detected (Fig. 5).



A T1WI B T1WI

Fig. 1 Pre-surgery MRI of patient B., 43 years old. Diagnosis: glioblastoma of the right parietal lobe. A – T1WI mode in frontal projection, B – T1WI-mode in axial projection

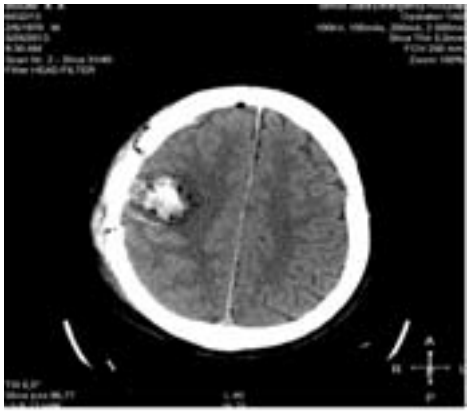
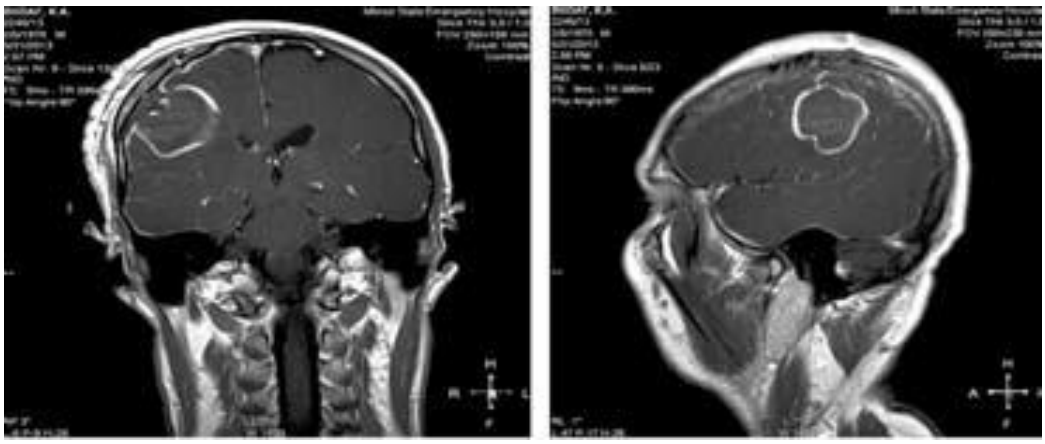


Fig. 2. X-ray computer tomography of patient B, 43 years old. Diagnosis: glioblastoma of the right parietal lobe. Hemorrhage in the removed tumor bed in 3 days after the surgery, axial projection

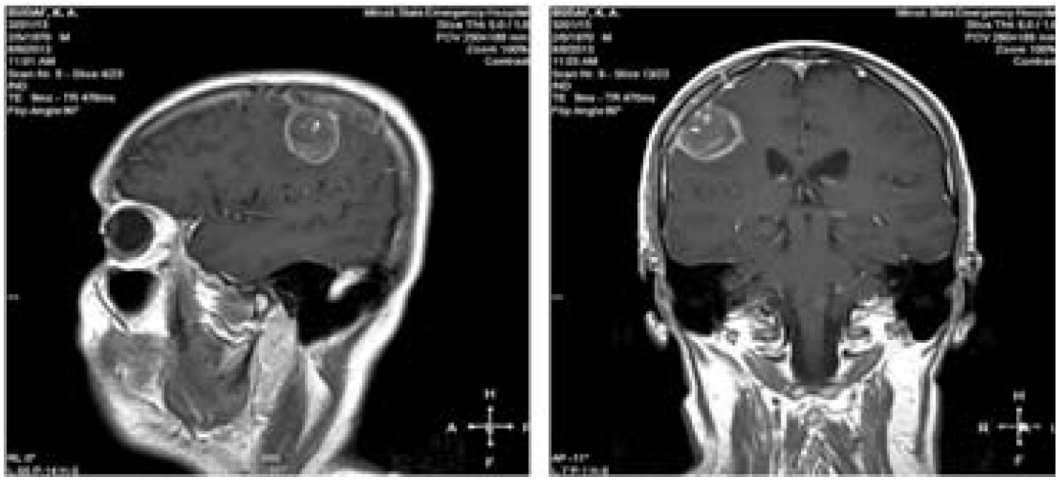


A T1WI B T1WI

Fig. 3. MRI of patient B., 43 years old. Diagnosis: glioblastoma of the right parietal lobe. Postoperative cyst with a fluid component. A – T1WI mode in frontal projection. B – T1WI mode in sagittal projection on the10th day after the surgery

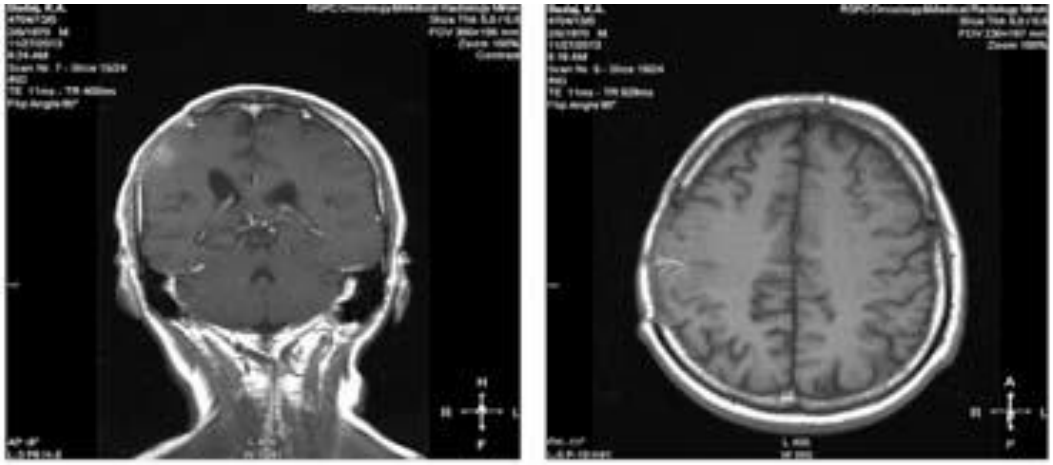
As the analysis of this clinical observation shows, LCT did not significantly affect the clinical and neuroimaging manifestations of one of the most frequent complications of the early postoperative period – hemorrhage in the bed of the removed mass.

Therefore, local chemotherapy with Temodex is technically simple to perform and does not affect the duration of surgery. The technology of intraoperative local chemotherapy does not significantly affect the number and severity of complications in the early postoperative period. Local chemotherapy with Temodex is not accompanied by significant and persistent toxic manifestations.



A T1WI B T1WI

Fig. 4. MRI of patient B., 43 years old. Diagnosis: glioblastoma of the parietal lobe on the right. Postoperative cyst with a fluid component. A – T1WI, sagittal projection mode. B – T1WI, frontal projection mode 3 months after the surgery



A T1WI B T1WI

Fig. 5 MRI of patient B., 43 years old. A – T1WI, frontal projection mode. B – T1WI, axial projection 6 months after the surgery

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