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Case report

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Long-term survival of a patient suffering from *glioblastoma multiforme* of the brain as well as kidney cancer diagnosed and treated simultaneously

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Primary tumors of the brain account for up to 2% of all malignant neoplasms. The average life expectancy for patients with malignant gliomas of the brain is 12. 6 months. *Glioblastoma multiforme* is the most common one. Most patients diagnosed with it die within the first two years after the date of diagnosis. Only 2% of all cases survive for more than 36 months.

Renal cell carcinoma (RCC) accounts for 2–3% of all malignant neoplasms in adults. The incidence of RCC, at all levels of advancement, has increased in recent years, resulting in increased mortality. Average survival with this diagnosis is about 50% and depends on the severity of the disease.

We present the case of a 62-year-old patient, who has survived for many years after radical treatment of *glioblastoma multiforme* of the brain. The patient was simultaneously diagnosed with kidney cancer. Before the final diagnosis was given, a detailed diagnostic process had been carried out at several medical institutions. The diagnostics were initiated as a result of an epileptic seizure that had occurred for the first time in the patient's life. Radiological examination led to the suspicion of metastases to the brain as well as a tumor of the right kidney. The treatment started with surgery of the brain tumor. Afterward, radical removal of the right kidney was performed.

After obtaining the final histopathological results from the brain tumor histopathological preparations were consulted in another city and medical center. Next, the patient received complementary radiotherapy to the site of tumor removal, combined with temozolomide and continuation of chemotherapy after irradiation was finished. The treatment of the kidney cancer was finalized with a surgery. To date, the patient has survived for more than six years without relapse or neoplastic dissemination, in very good general and neurological condition.

The case analysis allows for identifying, in the patient, several prognostic factors of long-term survival, such as: the relatively young age of the patient when the disease was diagnosed, good general and neurological condition before treatment, small size of the tumor, radical surgical treatment, location of the tumor outside of the lateral ventricles, no contact of the tumor with the subventricular zone of the brain (SVZ), as well as the low HDL (high-density lipoprotein) and LDL (low-density lipoprotein) levels in biochemical blood tests before surgery of the brain tumor.

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Key words: *glioblastoma multiforme*, prognostic factors of long-term survival of the patient.

Introduction

Primary tumors of the brain account for up to 2% of all malignant neoplasms. The incidence of primary malignant neoplasms of the brain and other neoplasms of the central nervous system in Poland is approx. 3000 cases per year [1]. The probability of developing this neoplasm increases with age and amounts to 60% among brain tumors, and even 80% if the person is 60 years of age or older. The average life expectancy for patients with malignant gliomas of the brain is 12. 6 months [2]. Most patients diagnosed with it die within the first two years after the date of diagnosis [3]. Only 2% of all cases survive for more than 36 months [4].

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Primary renal neoplasms constitute approximately 3% of all malignant neoplasms in adults [5]. The most common histological type is the renal cell carcinoma, which accounts for about 85–90%. It is the most common type of kidney cancer and one with a poor prognosis. Average survival with this diagnosis is about 50% and depends on the severity of the disease [5].

The article presents the case of a patient who has survived for many years in good general condition, without any neurological deficits, after simultaneous treatment for a primary brain tumor in the most malignant form — *glioblastoma multiforme* — and an advanced malignant kidney neoplasm detected locally at the same time.

Case description

The patient, age 56, was admitted to the neurological department as a matter of urgency in February 2012 due to a sudden loss of consciousness, a convulsive seizure with disorders of consciousness, and consequent left-side paresis. These symptoms had occurred for the first time in the patient's life. CT (computed tomography) of the head was performed which showed, in the right temporal lobe, a hypodense area not amplified after administering contrast, with an edema and mass effect, leading to the suspicion of a metastatic lesion. The neurological department applied antiedematous treatment, which resulted in a rapid improvement in the patient's general and neurological condition. The diagnostics were expanded by an MRI (magnetic resonance images) examination of the head. Lumbar puncture was also performed, which ruled out a neuroinfection.

The MRI examination showed, peripherally in the right temporal lobe, a structure of high signal intensity in T2-weighted images, low signal intensity in T1 SE images, amplified heterogeneously and mostly marginally after contrast administration, with a diameter of approx. 13 mm, most probably a metastasis of a neoplastic disease. Around it, there was an extensive edematous area with a width of about 3.5 cm. The ventricular system on the right side was pressured at the level of the anterior horns. Lateral ventricles displaced to the left, by 3–4 mm. Figures 1–3 show images with this study MRI.

During the stay at the ward, an ultrasound examination was also performed of the abdominal organs, and then a CT of the abdominal cavity. These showed, in the upper-external part of the right kidney, a heterogeneous hypodense area strongly amplified by the contrast medium, with the dimensions of 61 × 43 × 81 mm. In addition, a complete blood count and biochemical blood tests were performed for, among others, the level of total cholesterol, as well as its HDL and LDL fractions. A dissemination to the lungs was ruled out in the CT of the chest. Then, the patient was transferred to the Department of Neurosurgery where, in March 2012, a right-side temporal craniotomy was performed. After the surgery, no neurological deficits occurred in the patient. During the patient's stay at the neurosurgical department, an urological consultation took place, after which he was qualified for surgical treatment of the right kidney tumor. In April 2012, right-side nephrectomy was performed without complications. The diagnosis obtained in the histopathological results of the radically removed kidney was *carcinoma clarocellulare* which superficially infiltrated the fibrous capsule of the organ. The level of advancement was determined at pT2N0M1 (metastasis to the brain). However, the histopathological results from the operated brain

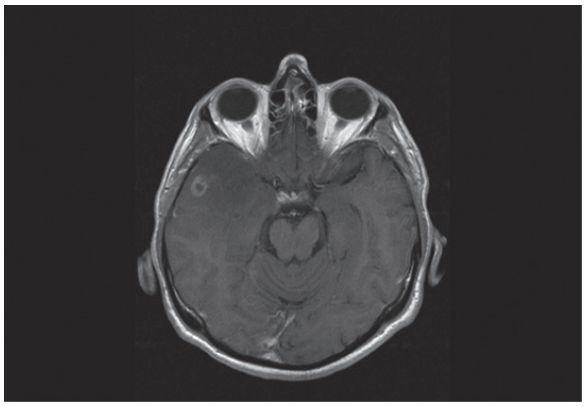


Figure 1. MRI before surgery. Axial T1-weighted image: tumor in the right temporal lobe mostly marginally after administering contrast

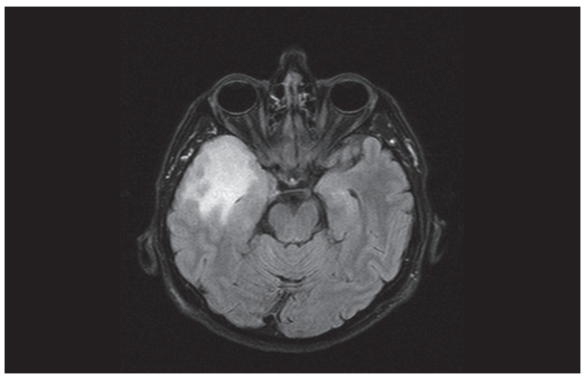


Figure 2. MRI before surgery. Axial T2-weighted FLAIR image show an extensive edematous area around the tumor in right temporal lobe

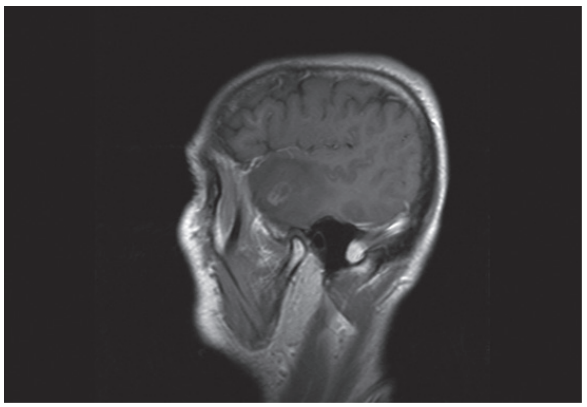
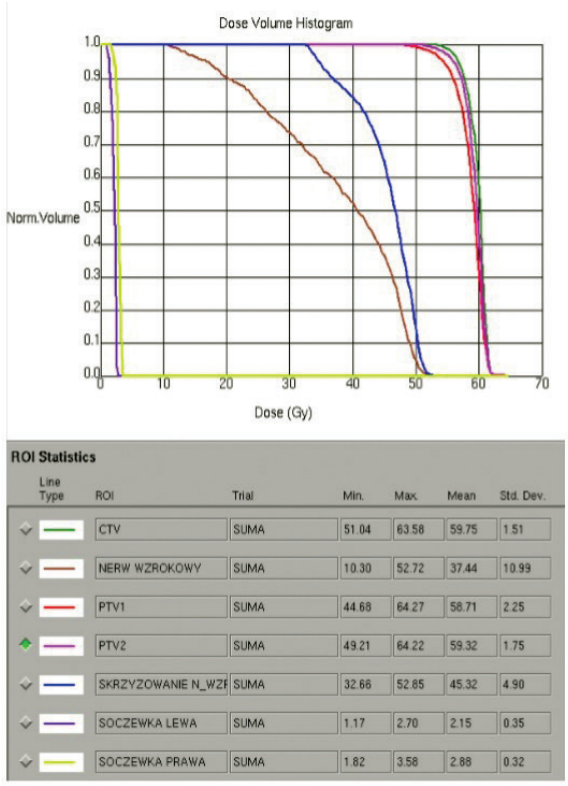


Figure 3. MRI before surgery. Sagital T1-weighted image. Tumor with an extensive edematous area around it in the right temporal lobe

tissue demonstrated a neoplasm of glial origin IHC: CK1(–), GFAP(+). Therefore, the preparations were sent for consultation to another oncology center. The consultation confirmed the second independent neoplastic process: *glioblastoma multiforme* G IV. A follow-up MRI of the brain, performed in May 2012, showed the condition after surgery of the right temporal lobe's tumor. Peripherally, in the right temporal lobe, there was a visible postoperative area, most likely a hematoma sized 24 × 12 mm. The following conditions still persisted: the edema of the entire lobe, a slight mass effect, and displacement of medial structures to the left side by approx. 4 mm. Also visible was the post-operative amplification of the pachymeninx in the temporal region. Apart from this, hemispheres of the brain and cerebellum had no pathological foci. The brainstem was normal. The ventricular system was of the correct width, not displaced, and it was symmetrical. The pericerebral spaces were normal. In May 2012, the patient was admitted to the Radiotherapy Clinic, where he was qualified for complementary treatment of the site of brain tumor removal, combined with temozolomide. The areas to be irradiated were determined in scans from the CT examination carried out in order to plan the treatment, as well as MRI images from before the surgery. The patient received a total dose of 50 Gy in 25 fractions of 2 Gy to the area of the contrasting tumor with edema (hyperintensive area in T2-weighted images in the MRI from before the treatment) with a two-centimeter margin PTV1 (Planning Target Volume), using the X 6 MeV photon beam according to the computer plan for IMRT treatment. Next, due to the need to exclude critical structures from the area covered by the full dose, the irradiation field was reduced to include the tumor (T1 amplification area in the MRI) with a one-centimeter margin-PTV2. The total dose received by the patient was 60 Gy in 30 fractions of 2 Gy in six weeks of treatment, Monday through Friday, once a day, using a linear accelerator. Figure 4 and Figure 5 show paramount parts of treatment plan.

During radiotherapy, the patient received 75 mg/m^2 of temozolomide for 42 days, seven days a week, starting from the first day of irradiation. 28 days after the end of radiotherapy, the patient continued treatment with temozolomide at a dose of 150 mg/m^2, i.e., for 5 days during the first treatment course. Next, he received five 5-day treatment courses with temozolomide at a dose of 200 mg/m^2 with breaks of 28 days in-between (starting from the second course). The follow-up complete blood counts and biochemical blood tests during and after the therapy were normal. Afterward, follow-up brain imaging examinations were regularly performed. Follow-up MRIs, during the use of temozolomide as well as after the treatment had finished, showed a normal image of the brain with demyelination changes in the region of the right temporal lobe (in the area operated and then irradiated). Follow-up imaging examinations also exclude a relapse of



Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.
	CTV	SUMA	51.04	63.58	59.75	1.51
	NERW WZROKOWY	SUMA	10.30	52.72	37.44	10.99
	PTV1	SUMA	44.68	64.27	58.71	2.25
	PTV2	SUMA	49.21	64.22	59.32	1.75
	SKRZYZOWANIE N_WZF	SUMA	32.66	52.85	45.32	4.90
	SOCZEWKA LEWA	SUMA	1.17	2.70	2.15	0.35
	SOCZEWKA PRAWA	SUMA	1.82	3.58	2.88	0.32

Figure 4. Treatment plan. In the top: dose-volume histogram analysis. Below: the table with maximum and medium doses in Planing Target Volume: PTV1 PTV2 and critical organs such as lens or chiasm

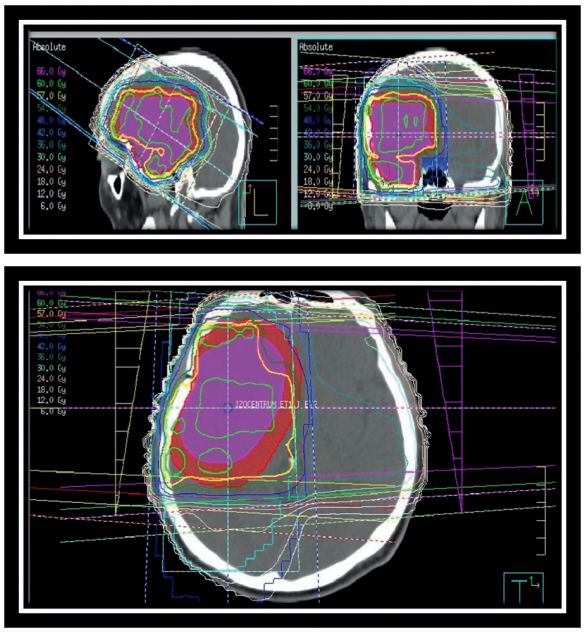


Figure 5. Treatment Plan-DRR (digital reconstruction) with virtual simulation

kidney cancer or dissemination of the neoplastic disease. The last follow-up examination of the head, performed in July 2018, showed a normal brain image with "a visible post-operative fluid-filled site over an area of 37 × 23 mm, with

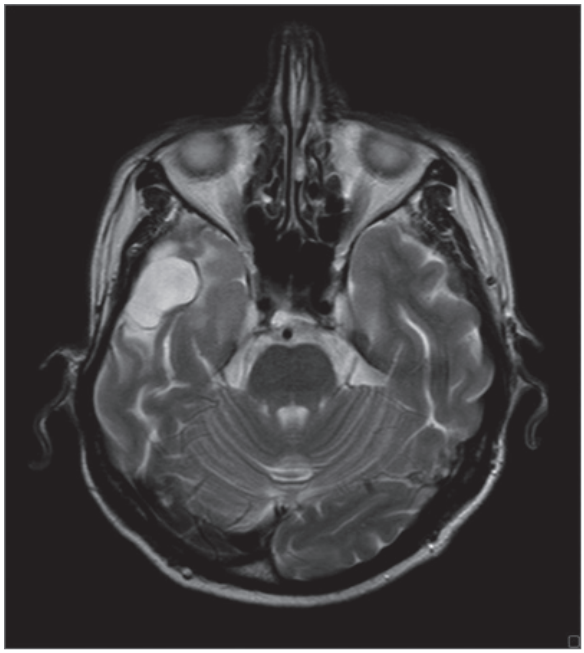


Figure 6. Last follow-up MRI — seven years after treatment. Axial T2-weighted image. Postoperative fluid-filled site with surrounding area of gliosis in the right temporal lobe

a surrounding area of gliosis, without the effect of contrast amplification, and without traits of local relapse". Figure 6 and Figure 7 show images with the last follow-up MRI study.

The patient is still in very good general condition, WHO-0, in full verbal-logical contact, without any neurological deficits, no late manifestations related to the brain after the treatment. No signs of a postradiation reaction in the irradiated area of the scalp were detected.

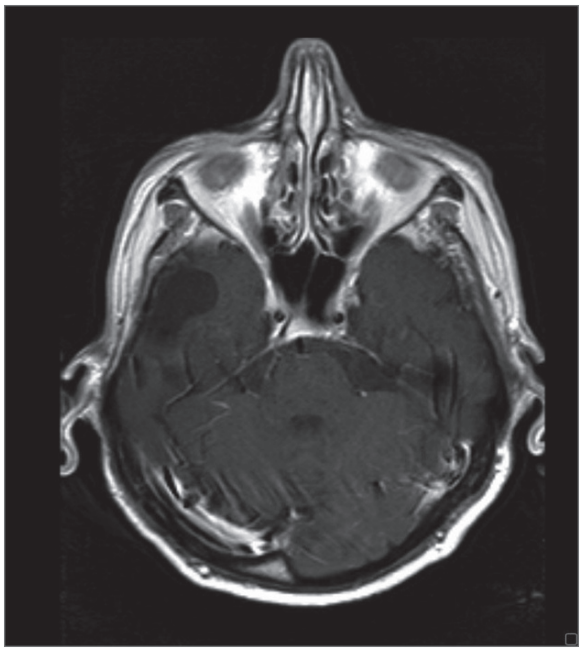


Figure 7. Last follow-up MRI — seven years after treatment. Axial T1-weighted image. Postoperative fluid-filled site in the right temporal lobe

Discussion

The etiology of malignant neoplasms of the central nervous system has not been fully understood yet. Hereditary diseases, such as type I and II neurofibromatosis, the Von Hippel-Lindau and the Li-Fraumeni diseases are deemed to be contributory to the predisposition to developing brain tumors [6]. Occupational exposure and environmental impact are also factors increasing the risk of disease. *Glioblastoma multiforme* is a brain tumor with the worst prognosis. Five-year mortality is greater than 90%. The average total survival does not exceed 15 months [7]. It is a hypercellular neoplasm formed by astrocytes of poor diversification. The characteristic features of this neoplasm are: variable histological pattern, high proliferative activity, cellular atypy, proliferation of vessels creating glomerular structures, and presence of necrotic areas within the tumor. It is the most common form of gliomas, which usually develops in adults over 50 years of age. Typically, it is located supratentorially in the frontal-temporal area. It occurs particularly often in the white matter in the vicinity of the centrum semiovale and corpus callosum [6]. There are several histological subtypes of *glioblastoma multiforme* (GBM): giant cell, small cell, pleomorphic, gemistocytic, with an oligodendroglioma component, gliosarcoma, and the mixed variant [2, 3]. The 'classical' form of GBM and its variants are deemed to have the highest degree of histological malignancy (grade IV according to WHO). It is also one of the best known tumors in molecular terms. Due to the genetic mechanism, there is a division into the primary GBM, which can grow *de novo* and most often concerns older people, with a short history and usually a sudden course of the disease, and the secondary GBM, which can develop from a glioma with a low degree of malignancy, usually in younger people — under 45 years of age. The first type of tumor is associated with excessive expression, mutations and multiplications in the EGFR (endothelial growth factor receptor), *MDM2* genes, loss of heterozygosity (LOH) of *10p* and *10q*, as well as mutation of *PTEN* (suppressor gene) and deletion of p16. The second type is associated with a mutation in the *p53*, LOH of the *17p*, *10q* and *19q* genes [7]. A characteristic feature of GBM is the specific, infiltrating nature of growth, associated with the spreading of neoplastic cells in the immediate vicinity of the primary, solid mass of the tumor. This feature largely determines the poor response to both surgical and radiotherapy treatment. Chemoradiotherapy allows to prolong the survival time, especially in patients with methylation of the gene promoter responsible for the synthesis of the MGMT repair enzyme (06-methylguanine-DNA-methyltransferase). The presence of methylation is the best known beneficial predictive factor [8]. Diagnostic tests performed on the patient: CT and MRI of the brain confirmed a single, small change in the brain, located outside the ventricular system. According to Adenberg et al., we may assume that

the tumor is not in contact with the lateral ventricles if its shortest distance from the ventricles is greater than 10 mm [9]. The above imaging examinations show that GBM did not infiltrate the subventricular zone (SVZ), which is a very positive prognostic factor [9–11], because tumors which occupy this area grow the fastest, have a higher tendency to locally relapse and disseminate [11].

More and more studies report that the prognosis in some cancers is closely related to the metabolism of fats, e.g., in the renal cell carcinoma and the squamous cell esophageal carcinoma [12]. Preoperative levels of total cholesterol and its individual HDL and LDL fractions in peripheral blood serum may be a prognostic factor also in patients suffering from *glioblastoma multiforme* [13]. In the blood tests performed before the operation, the patient had a total cholesterol level of 6.61 mmol/l, HDL of 1.78 mmol/l, and LDL of 4.65 mmol/l. According to a study by R. Liang et al. [13], patients with this diagnosis, who had a total cholesterol level of > 3.91, LDL of > 1.84 mmol/l, and HDL of > 1.32 mmol/l, had significantly longer total survival. This is probably due to the fact that cholesterol is the main component of cell membranes and, therefore, has a significant effect on proliferation and increase in tumor mass, which results in the increased trapping of these substances from the blood and, ultimately, decreasing their level in the tested serum. Patients with results lower than the aforementioned values had significantly shorter total survivals [13].

Conclusion

On the basis of the presented case, we can see that it is possible for a patient suffering from *glioblastoma multiforme* of the brain, simultaneously combined with renal cell carcinoma of a kidney, to survive for many years.

We think that this was due to the occurrence of many positive prognostic factors in the patient. These included: age below 60 (at the time of diagnosis, the patient was 55 years old), small size of the tumor, radical surgery, location of the lesion outside of the ventricular system of the brain, lack of infiltration to the subventricular zone of the brain (SVZ) as well as, according to recent studies, the relatively high levels of total cholesterol and its HDL and LDL fractions in blood serum from before the surgery. What is also important is that the patient, seven years after the treatment, is in very good physical and mental condition, without any neurological deficits, without local relapse or neoplastic dissemination of any of the diseases.

Conflict of interest: none declared

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