

Long-term survival in glioblastoma patients after Tumor Treating Fields (TTFields) therapy

Aaron Rulseh, Adam Derner, Jan Sroubek, Jan Klener, Josef Vymazal

Department of Radiology, Department of Neurosurgery, Na Homolce Hospital, Prague, Czech Republic

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Background/Objective

Glioblastoma (GBM) is the most common and malignant primary intracranial tumor, representing as much as 30% of primary brain tumors. Despite the introduction of aggressive treatment with temozolomide (TMZ) the median overall survival of adult patients remains approximately 10 months and as high as 14 months in patients receiving combined treatment with radiotherapy. Only 3–5% of patients survive more than three years, and sporadic reports of survival exceeding five years are rare. Recurrence of GBM is nearly universal, and patients with recurrent glioblastoma (rGBM) fare even worse, with a median survival of only 5–7 months with optimal therapy.

Tumor Treating Fields (TTFields) is an anti-mitotic cancer treatment comprising low-intensity, anti-mitotic at intermediate-frequency electric fields (100–300 kHz), which acts at cell specific frequencies. TTFields disrupt mitotic spindle microtubule assembly and segregation of intracellular organelles during cell division, leading to apoptosis. TTFields has received CE and FDA approval for the treatment of newly-diagnosed and recurrent GBM. Our center was the first in the world to apply TTFields to histologically-proven GBM patients in a small pilot study of 20 individuals in 2004 and 2005.

Methods

Study inclusion criteria included KPS $\geq 70\%$ and age ≥ 18 years; the patients were divided into two groups. The first group was comprised of 10 patients diagnosed with rGBM after failing TMZ treatment, and were treated with TTFields as monotherapy. The second group was comprised of 10 newly-diagnosed GBM (ndGBM) patients at least 4 weeks after combined chemo-radiotherapy (TMZ), and received TTFields combined with maintenance TMZ. Treatment duration varied from 1–1.5 years, and all histological samples were independently examined in two laboratories in two countries. All subjects were followed by magnetic resonance imaging (MRI) as well as neurological evaluation approximately every 2 months throughout the study. Subject baseline characteristics are shown in the table.

Subject	Group	Age (years)	Gender	KPS (%)	Tumor localization
1	RGBM	54	Male	100	R. TP
2	RGBM	59	Male	100	R. T
3*	RGBM	52	Female	70	R. P
4*	RGBM	43	Male	100	L. FP
5	RGBM	69	Male	80	R. TP
6	RGBM	52	Male	70	R. PO
7	RGBM	55	Male	90	R. FT
8	RGBM	39	Male	100	R. TP
9	RGBM	28	Female	90	L. TPO
10	RGBM	57	Female	70	L. T
11	GBM	36	Male	100	L. F
12	GBM	70	Male	90	R. T
13*	GBM	32	Male	100	R. F
14	GBM	58	Male	100	R. T
15	GBM	42	Male	90	R. T
16	GBM	45	Female	100	R. F
17*	GBM	33	Female	90	R. F
18	GBM	55	Male	100	L. O
19	GBM	65	Male	80	L. FT
20	GBM	56	Male	90	R. T

Results

Twenty percent of study participants (4/20) have survived until the time of this report, roughly 15 years (range 14.6–16.8 years). Patients continue to undergo regular neurological and radiological examinations, and do not show any signs of recurrence. Standard MRI data are supported by MR spectroscopy, which does not show any tumor-like patterns in regions with corresponding abnormal signal intensity.

Younger age and a higher KPS are favorable prognostic markers for longer survival, and the surviving patients were relatively younger. The mean age of surviving rGBM patients was 47.5 years compared to 51.5 years for the rest of the rGBM group. In the ndGBM group, the mean age was 32 years for surviving patients, compared to 51 years for the rest of the group. However, these differences do not explain 15 years of disease-free survival.

Our results indicate that TTFields may be remarkably successful in both newly diagnosed and recurrent GBM patients. As all of these 4 surviving patients showed initial radiological progression, we recommend that TTFields be continued for a sufficient time, at least one year in surviving patients, and that initial radiologic progression following treatment initiation should not be considered a reason to discontinue TTFields therapy.

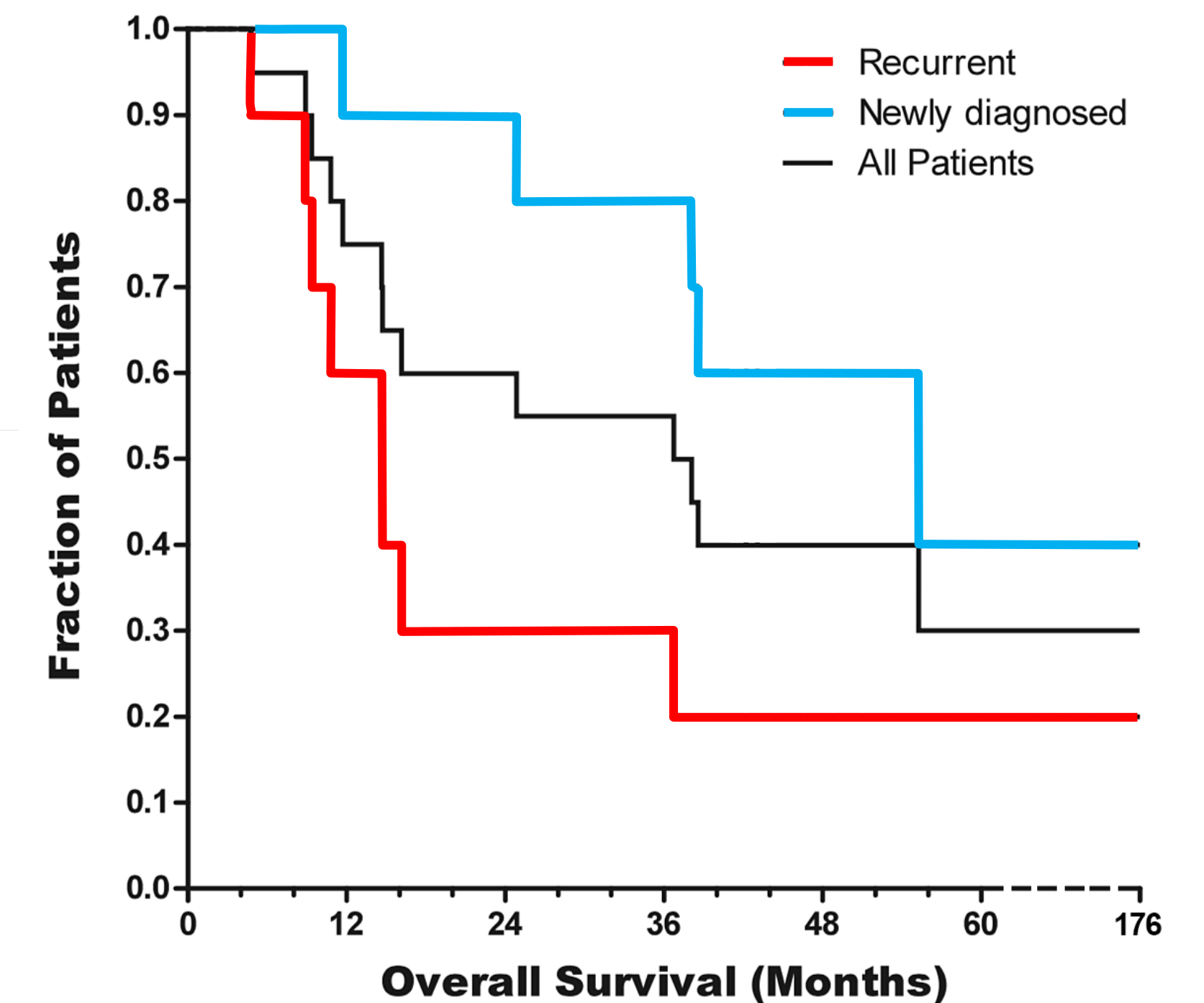


Figure 1. Kaplan-Meier plot showing overall survival in ndGBM and rGBM groups

Conclusions

We report two cases of ndGBM and two cases of rGBM treated with TTFields, all in good health and no longer receiving any treatment approximately 15 years after initiating TTFields treatment, with no clinical or radiological evidence of recurrence.

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