

Title:

Tumor Treating Fields Utilization in a Glioblastoma Patient with a Preexisting Cardiac Pacemaker: The First Reported Case

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Abstract

Background: Tumor treating fields (TTF) have become an important, evidence-based modality in the treatment of glioblastoma (GBM). In patients requiring cardiac pacemakers, TTF therapy is complicated by theoretical concerns regarding possible electrical interaction between the devices.

Case Description: A 57-year-old man with past medical history of sick sinus syndrome requiring cardiac pacemaker implantation suffered an acute neurologic change associated with a left parieto-occipital lesion, which was found to be GBM. After completion of guideline-concordant chemoradiation, he chose to undergo TTF therapy. Because of the absence of cardiac symptoms and the theoretical risk of far-field sensing by the pacemaker of the TTF device (potentially resulting in pacemaker inhibition), the pacemaker was turned off prior to receiving TTF. Following TTF implementation, the patient responded well; he remains alive more than 25 months following his GBM diagnosis, exceeding the median 20.9 month survival of the recently completed phase III TTF randomized clinical trial for newly diagnosed GBM. Furthermore, he has exhibited neither cardiac morbidity nor adverse scalp reactions to TTF therapy.

Conclusions: The first reported case of successful TTF administration in a GBM patient with a previously implanted cardiac pacemaker may allay the concerns of neuro-oncologists, cardiologists, radiation oncologists, and all certified TTF prescribers regarding the applicability of TTF in suitable candidates with preexisting cardiac pacemakers. This case indicates that TTF therapy may be efficacious in patients with indwelling MRI-conditional cardiac pacemakers turned to the off position, and that physical removal of the pacemaker is not necessary prior to starting TTF.

Introduction

Conclusion of a recent phase III trial has demonstrated that tumor treating fields (TTF) significantly improve overall survival and progression-free survival in glioblastoma (GBM), which has led to its approval by the Food and Drug Administration (FDA), its adoption in the National Comprehensive Cancer Network Guidelines, and its increasing utilization throughout the United States (1-3). For GBM patients with cardiac comorbidity necessitating pacemaker placement, TTF therapy (Optune; Novocure Ltd., St. Helier, United Kingdom) presents certain considerations which may make practitioners reluctant to recommend its utilization. The first is the theoretical risk of electrical interference between the TTF current and the cardiac pacemaker, as indicated on the Optune website: "Optune has not been tested in people with implanted electronic devices, which may cause the devices not to work properly". The second consideration is the perceived inability to use MRI guidance (secondary to the presence of the pacemaker) for planning of the TTF cranial grid array prior to treatment initiation. We report on a patient with a previously implanted cardiac pacemaker who successfully underwent TTF therapy for GBM.

Illustrative Case

Our patient was a 57-year-old man with a medical history of sick sinus syndrome for which he underwent a dual chamber bipolar pacemaker (Medtronic A2DR01 Advise DR MRI pulse generator with two Medtronic 5076 CapSureFix Novus leads – one atrial and one ventricular; Medtronic, Inc., Minneapolis, MN) implantation in 2015. Unlike older pacemaker models, this model is MRI-conditional, approved by the FDA for 1.5T and 3T full body MRI scan based on the results of a 2015 randomized trial (4).

Shortly afterwards, the patient suffered an acute onset of cognitive changes for which he was brought to the hospital. Although head CT was negative for hemorrhage, brain MRI revealed a left medial temporal lesion and hippocampal cerebritis. Following stabilization, he received operative neurosurgical intervention, which revealed anaplastic astrocytoma. Postoperatively, he declined both radiation therapy (RT) and systemic chemotherapy and decided to pursue alternative treatment. Unfortunately, four months later, he returned to the emergency room with headaches and weakness. Imaging revealed midline shift and a left parieto-occipital recurrent lesion. He underwent a second resection, which revealed GBM (vimentin positive, p53 positive, IDH1 positive, Ki-67 10-20%). Postoperatively, he was referred to radiation oncology and neuro-oncology, and underwent both RT and systemic temozolomide, completing RT two months after surgery. Two months later, he was seen in follow-up in Radiation Oncology clinic and elected to pursue TTF therapy.

Because of the theoretical risk of far-field sensing by the pacemaker of the TTF device, which could potentially have resulted in pacemaker inhibition, the patient underwent a testing session involving cardiologic monitoring, where the pacemaker was confirmed to be turned off (to OOO mode). The patient tolerated this procedure well, as he was in his own native rhythm. He understood that we could

not be certain that there would be no interference between the TTF and pacemaker, and elected to proceed with TTF despite this known risk.

Following TTF implementation, the patient continued primarily with concomitant systemic temozolomide, as he was unable to tolerate bevacizumab. At last follow-up in our multidisciplinary RADIANS (RADiation oncology And NeuroSurgery) multidisciplinary clinic, he remains alive more than 26 months following his GBM diagnosis, exceeding the median 20.9 month survival of the TTF + temozolomide group in the final analysis of the recently completed phase III randomized clinical trial (1, 5). Furthermore, he has exhibited no adverse scalp reactions to TTF therapy nor any cardiac morbidity. Such an excellent response despite receiving no GBM therapy besides temozolomide is indicative that he suffered no defects in the functionality of his TTF device despite the presence of his cardiac pacemaker.

Discussion

The clinical application of an electrical device to a patient with a preexisting cardiac pacemaker is not a novel concept, as it has successfully been achieved safely and efficaciously in patients requiring deep brain stimulation (DBS) electrode implantation for treatment of medically refractory Parkinson's disease since 2004 (6-7). The greatest theoretical risk is inappropriate shock due to electrical interference (8). This has been seen in reports of cardiac pacemaker discharge at the time of implantation in a patient with preexisting DBS leads, most frighteningly manifesting as microwave diathermy along the path of the DBS lead in a patient, resulting in permanent diencephalic and brainstem lesions concomitant with a vegetative state (9). Another report detailed a patient who underwent a radiofrequency-coupled thalamic stimulator system with an external pulse generator and transmitter; unfortunately, the subcutaneous receiver transmitted the external cardioversion current, resulting in a thalamotomy and the spread of the current to the ventrocaudal nucleus resulting in a central pain syndrome (10). Given such cautionary tales, it is understandable for practitioners to be reluctant to recommend patients with preexisting pacemakers and newly diagnosed GBM having completed concomitant chemoradiation for TTF therapy.

In our patient, open communication between the radiation oncology and cardiology teams regarding TTF in the setting of his pacemaker allowed for a smooth execution of treatment planning where the pacemaker was turned off prior to TTF initiation. Given our patient's underlying cardiac disease (sick sinus syndrome), cardiology believed there was no significant risk of turning his pacemaker off; this estimation has been proven correct by the fact that the patient has demonstrated no cardiac events in the nearly two years since his pacemaker was turned off and has responded very well to TTF. No additions to our patient's baseline cardiology follow-up were recommended by the cardiology team during TTF therapy.

This case brings to mind the obvious question regarding the applicability of TTF therapy for GBM patients with pacemakers that cannot be turned off and the optimal strategy in these situations. Similarly complex scenarios have been published previously involving interactions between DBS electrodes and cardiac pacemakers (6-7). In the seminal report, a preoperative testing session was performed where programming of a test DBS model was performed in the proximity of the patient to evaluate any interaction with their pacemakers utilizing EKG monitoring (6). As in that report, the pacemaker in this patient was a “demand” pacemaker, typical of the vast majority of modern-day implanted pacemakers, which are bipolar in configuration (6). Bipolar devices involve the dipole used for sensing to be located within the heart; this is in contrast to unipolar devices in which the dipole is located between the heart and the pacemaker generator in the chest. For a unipolar device, the metal encapsulating the pacemaker in the chest is electrically active (participating in the sensing circuit), while for a bipolar device metal in the chest is excluded from the sensing circuit because that circuit is composed of the dipole in each lead in the heart, as the anode and cathode are on the lead itself (6). Because the bipolar configuration is less susceptible to oversensing, we believe that bipolar leads are preferable in all cases. Since the bipolar configuration senses within the heart rather than between the heart and the chest wall, the bipolar configuration is less likely to sense extraneous signals. In this patient population, we would recommend that the treating cardiologist maintain bipolar programming; if the cardiologist believes that unipolar programming is required, testing should be performed to rule out TTF device-induced oversensing. Noteworthy is that for patients with pacemakers not compatible with MRI, the cranial grid array mapping for TTF can be performed using CT imaging. Additionally, many centers will perform clinically indicated MRIs on patients with “legacy” i.e. non-MRI conditional pacemakers (11). We would recommend that for patients with more severe cardiac pathology than our patient that cardiology document the cardiac risk per year of turning the pacemaker off, which could

then be compared to the survival benefit of TTF for GBM; depending on the results, cardiology follow-up during TTF therapy may need to be intensified.

In conclusion, our experience with the first manuscript reporting successful TTF administration in a GBM patient with a previously implanted MRI-conditional cardiac pacemaker may allay the concerns of neuro-oncologists, cardiologists, radiation oncologists, and all certified TTF prescribers regarding the applicability of TTF in suitable candidates with preexisting cardiac pacemakers; noteworthy is a previous abstract which described TTF for GBM in three unspecified patients with indwelling pacemakers of unclear specifications and follow-up of unspecified duration (12). This case indicates that TTF therapy may be efficacious in patients with indwelling cardiac pacemakers turned to the off position, and that physical removal of the pacemaker is not necessary prior to starting TTF.

Compliance with Ethical Standards

Funding: This study received no funding

Ethical approval: All studies involving human participants were in accordance with the ethical standards of the institutional research committee.

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Highlights:

1. MRI-conditional cardiac pacemakers do not preclude tumor treating fields (TTF)
2. TTF is efficacious for glioblastoma patients with indwelling pacemakers turned off
3. Physical removal of an indwelling pacemaker is not necessary prior to starting TTF

TTF = Tumor Treating Fields

RADIANS = RADiation oncology And NeuroSurgery

GBM = glioblastoma

FDA = Food and Drug Administration

RT = Radiation Therapy