Tumor Treating Fields for Glioblastoma Treatment: Patient Satisfaction and Compliance With the Second-Generation Optune® System

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ABSTRACT

BACKGROUND: Tumor treating fields (TTFields) are a non-invasive antimitotic therapy that delivers alternating electric fields via the Optune® system. The Phase III EF-14 trial in newly diagnosed glioblastoma multiforme (GBM) showed significantly improved progression-free, overall and long-term survival when Optune was used together with maintenance temozolomide (TMZ) compared with TMZ alone. Compliance (average monthly use) was associated with better clinical outcome. The first-generation Optune system weighed approximately 6 pounds (~2.7 kg). The second-generation redesigned Optune system weighs 2.7 pounds (~1.2 kg). We tested and compared GBM patient experience with the second-generation system versus the first-generation system.

METHODS: Ten newly diagnosed and recurrent GBM patients in Germany (median age: 52.9 years [31-79]) were prospectively monitored over the first month of transitioning from the first-generation to the second-generation Optune system. Questionnaires using a numerical analog scale assessed feedback at baseline (first generation) and after 1 month of second-generation use.

RESULTS: After transitioning to the second-generation system, compliance improved by more than 10% in four patients, was maintained in five patients and decreased by more than 10% in one patient. Following transition, eight out of nine patients reported a reduction in the triggering of malfunction alarms. Self-reported patient feedback showed improved handling and portability (weight, mobility) of the second- versus the first-generation Optune system.

CONCLUSIONS: This patient user survey suggests that patient satisfaction with the second-generation Optune system is improved versus the first-generation system. Improved features of the new system help patients achieve and maintain a higher rate of treatment compliance.

KEYWORDS: glioblastoma, compliance, optune, tumor treating fields, TTFields, patient satisfaction

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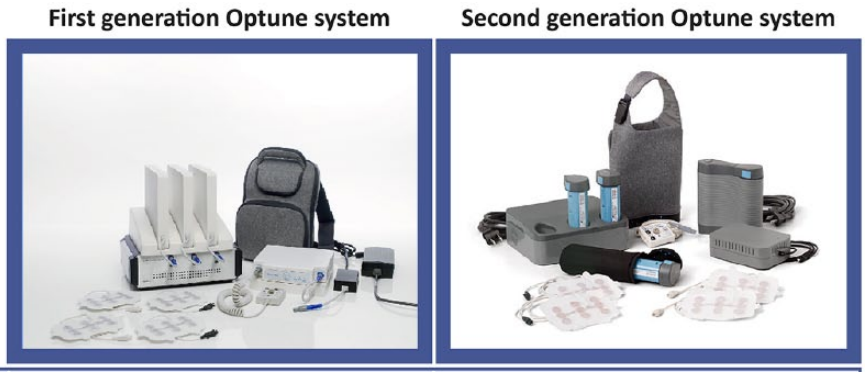
Introduction

Glioblastoma multiforme (GBM) is a highly malignant brain tumor and represents the most common malignant primary tumor of the central nervous system.[1,2] The standard of care since 2005 for patients with newly diagnosed GBM has been maximal surgical resection followed by concomitant radiochemotherapy with temozolomide (TMZ), followed by 6-12-monthly cycles of maintenance TMZ.[3] This treatment regimen results in median overall survival (OS) and progression-free survival (PFS) of 15-17 and 6-8 months, respectively.[3-6] Phase 3 trials with various pharmacologic agents have been conducted with the objective of further improving survival of GBM patients without much success.[4–8] Tumor treating fields (TTFields) (Optune®) are a loco-regional, non-invasive cancer treatment modality that have been shown to significantly improve survival of newly diagnosed GBM patients when added to standard of care[9,10] while maintaining health-related quality of life.[11,12] Following regulatory approval, National Comprehensive Cancer Network (NCCN) Guidelines® now recommend TTFields in combination with TMZ for the treatment of patients with both newly diagnosed (Category 1) and recurrent glioblastoma (Category 2B).[13]

The Optune system delivers TTFields to the region of the GBM tumor via transducer arrays placed on the patient's scalp. TTFields are low-intensity (1-3 V/cm), intermediate-frequency (100-300 kHz), alternating electric fields that disrupt cancer cell division.[9,10,14,15] As TTFields are a loco-regional treatment delivered directly to the brain, systemic toxicities are avoided.[9,10,16]

TTFields do not have a systemic half-life like oral or intravenous therapies and exert their therapeutic effect while the electric fields are being applied only on actively dividing cancer cells but not on healthy cells. Thus, compliance with treatment is critical to maximize effectiveness. It was previously established that average monthly compliance rates of 75% improve survival outcomes in recurrent GBM patients compared with lower compliance rates.[17,18] In newly diagnosed GBM, compliance was shown to be an independent predictor of survival and



	First generation Optune system	Second generation Optune system
Total weight (Device and battery)	2.7 kg/6 lb	1.2 kg/2.7 lb
TTFields generator (The device)	0.9 kg/2 lb	0.7 kg/1.5 lb
Battery weight	1.8 kg/4 lb	0.5 kg/1.2 lb
Size	Device: 8.3 x 8.3 x 1.75 in Battery: 8.25 x 8.25 x 1.1 in	Device with incorporated battery: 7.1 x 2.3 x 7.6 in
Features	Portability	Easy-grip texture allows for better handling

Figure 1. Comparison of the first- and second-generation Optune systems for GBM. The redesigned second-generation device weighs less and is reduced in size. The rechargeable battery integrated into the device to improve portability and allow patients to maintain activities of daily living.

the higher the compliance, the better the outcomes. A threshold value of 50% average monthly compliance with TTFields is needed to obtain extension of both PFS and OS.[19] Patients with a compliance rate of over 90% had a median OS of 24.9 months (28.7 months from diagnosis) and a 5-year survival rate of 29.3%.[19] Therefore, it is recommended that patients use the Optune device continuously, to obtain maximal benefit. Patient compliance data stored on the device is available to both physicians and patients for compliance monitoring.

Patient satisfaction with use of the Optune system (eg, general handling, convenience, and portability) might also be a relevant factor affecting patient compliance. Prior to Optune treatment initiation, patients are trained from a technical perspective by a dedicated Device Support Specialist from Novocure to correctly operate the device. This includes specific training regarding battery charging, battery exchange, switching the device on, and handling alarms. Since the device is portable, a reduced size and weight are likely to improve overall patient satisfaction.

The first-generation Optune system (called NovoTTF-100-A System, CE mark 2007) comprises two main components: an electric field generator and insulated transducer arrays with a total weight of approximately 6 pounds (~2.7 kg) (Figure 1). This first-generation Optune system has been redesigned to facilitate the convenience and manageability of TTFields therapy and further improve patient compliance. The second-generation Optune system (called NovoTTF-200-A System, CE mark 2015) (Figure 1) weighs approximately 2.7 pounds (~1.2 kg), less than half the weight of the first-generation Optune system including battery and is therefore expected to be more user-friendly, enhancing the convenience and manageability of TTFields therapy for GBM patients. All design changes have been confined to the system used to deliver TTFields without affecting the patient-applied transducer arrays or the treatment delivered to the patient. The overall safety architecture and treatment monitoring, which are both hardware limitations and software controls built into the device, are functionally the same as that used in the first-generation Optune system. However, a smaller battery is inserted into the second-generation device to form a single package as opposed to the separate components connected by a cable in the first-generation Optune system. Figure 2 shows the system components of the second-generation device including the redesigned electric field generator with the smaller rechargeable battery inserted. The main components to the user interface, that is, the power switch, TTFields button, error indicator, low battery indicator, and array connection, remain unchanged. A new power indicator, which shows a distinction between running on battery or wall power and a battery fuel gauge have been added for patient convenience. The net results of the second-generation Optune design improvements are a greater than 50% reduction in size and weight compared with the first-generation Optune system.

To evaluate the impact of the second-generation Optune system on patient satisfaction and compliance, Novocure identified treating physicians and their patients being treated with the first-generation Optune who were willing and able to switch to the second-generation device, and agreed to participate in a patient satisfaction survey. This report presents the

Figure 2. Components of the second-generation Optune system.

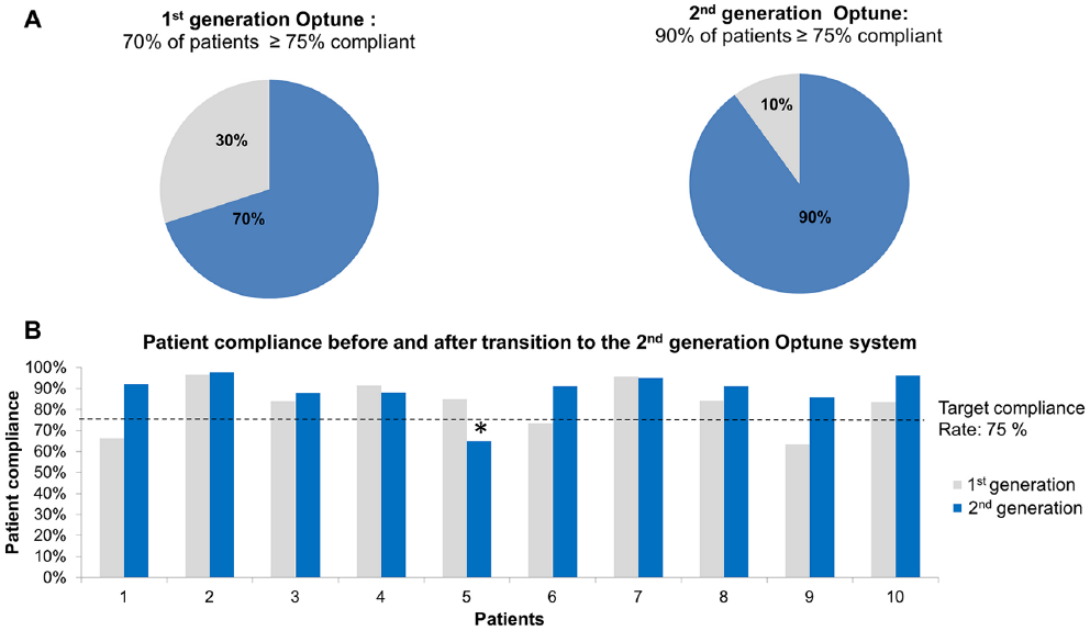


Figure 3. Patient treatment compliance: (A) A greater percentage of patients using the second-generation Optune system achieved target compliance rates of ⩾75%, (B) Compliance was numerically increased or maintained in most patients transitioning from the first- to the second-generation Optune system. The dotted line indicates the target compliance rate of 75% (18 h/day). The symbol "*" denotes patient health decline led to lower compliance.

results of the survey, with a focus on the technical aspects of the second-generation device.

Material and Methods

Ten GBM patients (male = 8, female = 2, median age: 52.9 years [31-79]), who had used the first-generation Optune system for at least 4 weeks, were monitored over the first month of transitioning to the second-generation Optune system. Each patient signed a consent form prior to data collection. Before initiation of this patient survey, treating physicians confirmed patient characteristics relevant to the survey. Patients with newly diagnosed or recurrent GBM with stable disease or no evidence of disease progression were eligible to participate. At least, one full month using the first-generation device was required for participation. Additional inclusion criteria included a Karnofsky performance status score ⩾70, no new seizure activity in the past month prior to enrollment and the ability to operate the device either independently or with the aid of a caregiver. Treating physicians were responsible for medical follow-up, as usual, according to local clinical practice. The frequency of 200 kHz for GBM treatment was preset, so no electrical output adjustments were required by the patient.

Patients completed identical questionnaires at baseline (first-generation Optune system) and after transitioning to the

second-generation Optune system after 4 weeks at scheduled Device Support Specialist visits.

Responses to questions were completed by means of numerical analog scales (Supplementary file). Patient responses in case of a question not answered at baseline or during follow-up, or if the interpretation was unclear, were excluded from calculations of overall mean values for that question.

The Device Support Specialists were responsible for educating both patients and caregivers on the use of the new device and provided technical support to patients as needed. Medical support was only provided by the treating physician who maintained overall responsibility for the treatment and treatment regimen.

In addition to patient reported feedback, the complete compliance report as well as objective recordings of alarm states was downloaded from the device by the Device Support Specialist at baseline and at follow-up visits. Simple descriptive summary statistics were calculated for patient responses to the questionnaire and alarm states.

Results

Patient compliance

Seven out of 10 patients (70%) using the first-generation Optune device achieved compliance values of ⩾75% (Figure 3A). In contrast, 9 out of 10 patients (90%) exceeded the target compliance rate of 75% during their first month of transitioning to the second-generation Optune device. In most patients, compliance was numerically increased or maintained (where compliance was at a high level at baseline) after transitioning to the new device (Figure 3B). An absolute increase in compliance of more than 10% was reported in four patients and compliance was maintained (increase or decrease by less than 10%) in five patients. Compliance decreased by more than 10% in one patient and this was most likely attributed to a decline in the patient's health. Of note, 3 out of 10 patients who had not reached 75% at baseline with the first-generation system achieved ⩾75% compliance after their transition to the second-generation Optune system. These data suggest that the new designed device may enhance patient compliance to therapy.

Patient satisfaction (handling, portability)

Numerical analog scales were used to assess patient feedback at baseline (first-generation Optune system) and at approximately Day 28 of transitioning to the second-generation Optune system. Evaluation of patient feedback revealed improved handling of the second-generation device. On average, patients reported that the new device was easier to use (Figure 4A, left). In addition, patients reported improved mobility with the new device due to the reduced weight (Figure 4A, right). In general, the data show that in most cases, patients reported improved or maintained handling and portability of the second-generation Optune system.

Compared with the first-generation Optune system, the internal fan in the second-generation Optune device generates significantly less noise, and this was reflected in patient feedback. At baseline, 10 out of 10 patients reported hearing the fan whereas only 4 out of 10 patients did so after their transition to the second-generation system. In total, 9 out of 10 patients reported reduced fan noise after switching to the second-generation device (Figure 4B). In summary, patients reported improved handling and portability as well as quieter operation with the second-generation device.

Number of alarms

The Optune device digitally records a wide range of technical as well as handling errors, which ensure optimal TTFields delivery, maximal therapeutic efficiency, and patient safety. After transitioning to the second-generation Optune device, eight out of nine patients experienced a numerical reduction in the number of daily alarms (Figure 5A, left). The average daily alarm rate for all patients reduced from 3.5 when using the first-generation Optune system to 2.6 with the second-generation (Figure 5A, right). An unusually high number of alarms was reported by one patient indicative of an operating problem that was not related to the new design and this patient was excluded from the analysis on this parameter. This objective evaluation of a reduction in average alarm rates is supported by self-reported patient feedback through numerical analog scales (Figure 5B). The patient feedback also showed that patients tended to find it easier to identify the cause for an alarm when using the second-generation Optune.

Discussion

This prospective survey design allowed us to compare subjective patient feedback between the first- and second-generation Optune systems, and the impact of the redesign on patient satisfaction and treatment compliance.

The first phase 3 clinical trial of TTFields in patients with recurrent GBM (EF-11) demonstrated that a ⩾75% average monthly compliance rate was associated with improved survival outcomes.[17] Following further analyses of patient compliance in the EF-14 study in patients with newly diagnosed GBM, clinical benefit was observed with compliance rates of ⩾50% and high compliance rates (>90%) resulted in further improvements in survival outcomes.[19] Therefore, it was of interest to evaluate whether compliance rates are improved after patients switched to the second-generation Optune system. The data from this survey indicate that compliance was maintained or increased after the transition from the first- to the second-generation Optune system, with 90% of patients achieving compliance rate of >75% per months during the first month on therapy. This suggests that a greater proportion of patients using the second-generation Optune system achieved recommended target compliance rates required for optimal therapeutic efficiency.

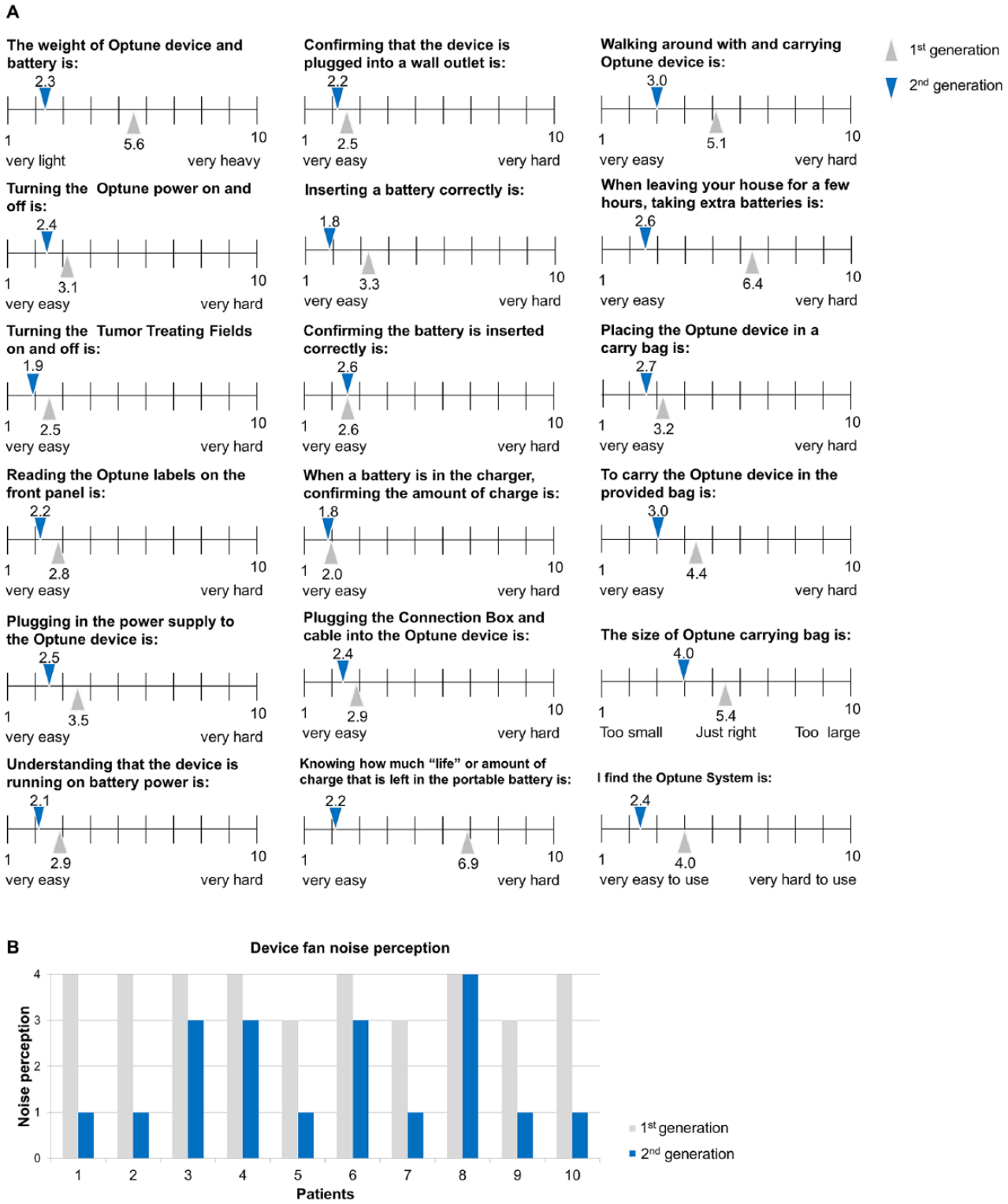


Figure 4. (A) Optune patient feedback for handling and portability: Shown is feedback of patients (mean values) before and after transition to the second-generation Optune system as assessed by numerical analog scales, (B) Optune device fan noise perception: Patients were asked before and after transition to the second-generation Optune system if they (1) never hear the device fan running; (2) hear the device fan running only during daytime; (3) hear the device fan running only during nighttime; (4) hear the device fan running during day and night.

It is likely that compliance rates achieved with the second-generation device are related to some of its new features. These results, together with the finding that nine out of 10 patients reported reduced fan noise after switching to the second-generation device, indicate that handling and mobility has improved with use of second- generation Optune

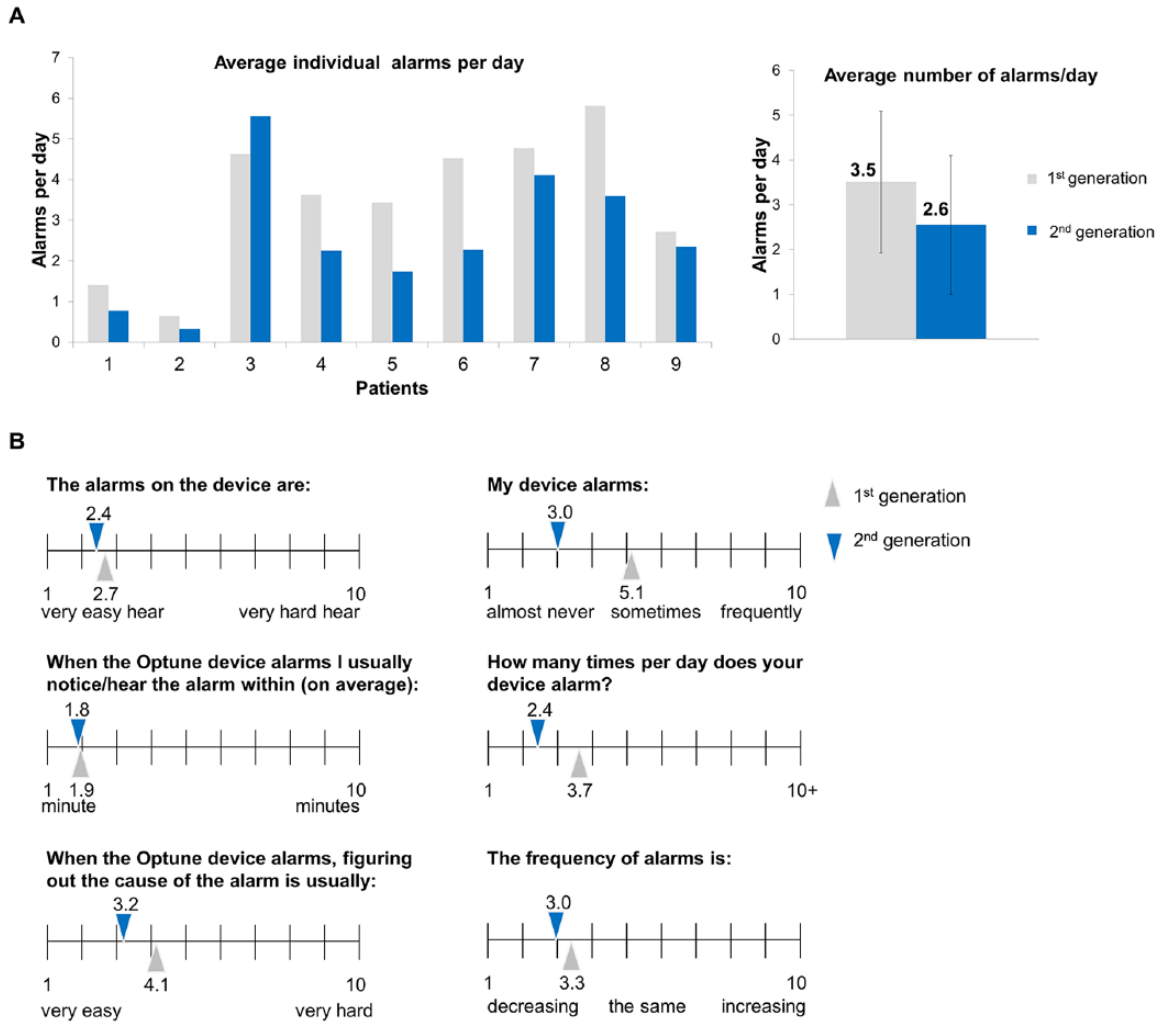


Figure 5. Number of alarms per day: (A) Left: shown are the average daily alarms of patients transitioning from the first- to the second-generation Optune system (n=9). Right: Number of alarms per day for all patients (mean ± standard deviation) (n=9). (B) Optune patient feedback for alarm functions: Shown is feedback of patients (mean values) before and after transition to the second-generation Optune system as assessed by numerical analog scales.

system. With respect to fan noise, patients reported verbally that the reduced level of noise from the second-generation device greatly improved sleep patterns.

In addition, the data suggest that use of the second-generation Optune device results in fewer alarms being triggered, a fact also observed and reported by the patients and possibly a contributing factor to the numerically improved compliance among some second-generation Optune users.

The key limitation of this study is the small sample size, which was mainly related to logistical reasons as we only wanted to involve a small number of Device Support Specialists and a limited number of treatment sites in this study. Despite the small sample size, the results of this prospective patient survey in 10 GBM patients indicate that the improved handling and portability and overall design modifications of the second-generation Optune system help patients comply with daily treatment duration goals.

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Author Contributions

All authors participated in designing the survey, writing, reviewing and approving the manuscript. MA and MV engineered the second-generation device.

Supplemental material

Supplemental material for this article is available online.

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