TTF kombiniert mit Stereotaxie: Was ist die Rationale und gibt es Evidenz?

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Interessenkonflikte ?

Reisekostenerstattung durch Novocure

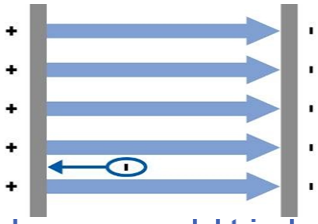
Grundlagen

- Optune ist tragbar, nicht-invasiv und ermöglicht eine lokale Therapie mit TTFields

- TTFields sind elektrische Wechselfelder geringer Intensität (1-3 V/cm) und intermediärer Frequenz (200 kHz beim GBM), die in 2 Richtungen abgegeben werden

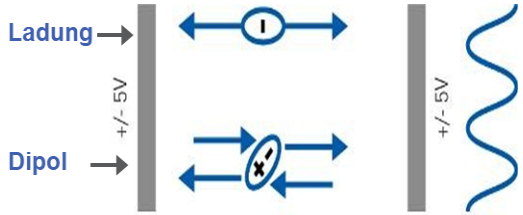
- Die Positionierung der Transducer Arrays auf der Haut wird für alle Patientinnen und Patienten individualisiert

Wirkung elektrischer Felder



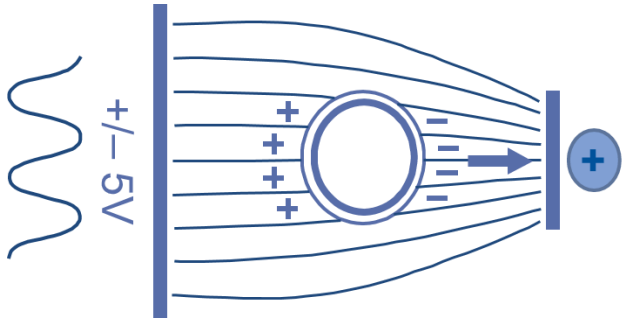
Konstantes, homogenes elektrisches Feld

- Ladungen bewegen sich in Richtung der entgegengesetzten Polarität



Alternierendes elektrisches Feld

- Ladungen bewegen sich hin-und her; Dipole rotieren



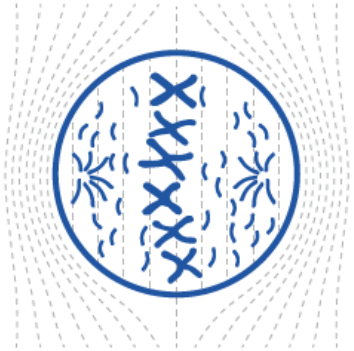
Inhomogenes (konvergierendes) elektrisches Feld

- Konzentrierte elektrische Feldintensität bei der kleineren Elektrode
- Ladungen und Dipole bewegen sich zum Bereich der höchsten Feldintensität (Dielektrophorese)

Gutin PH, et al. Am Soc Clin Oncol Educ Book. 2012;32:126-131.

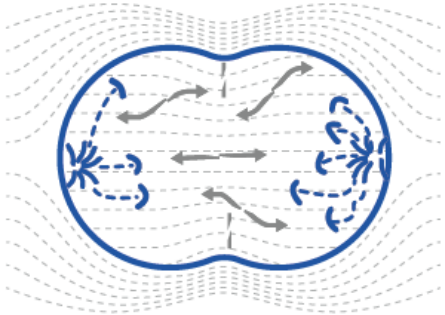
Wirkung auf Zellen (Zellteilung)

METAPHASE



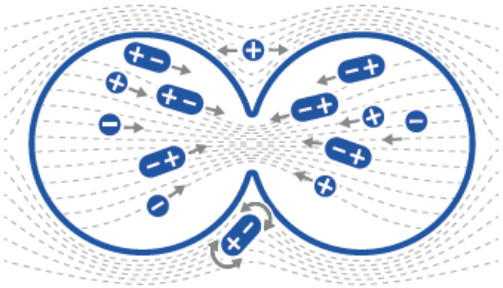
- Aufbau der Mikrotubuli/ des Spindelapparates wird gestört

ANAPHASE

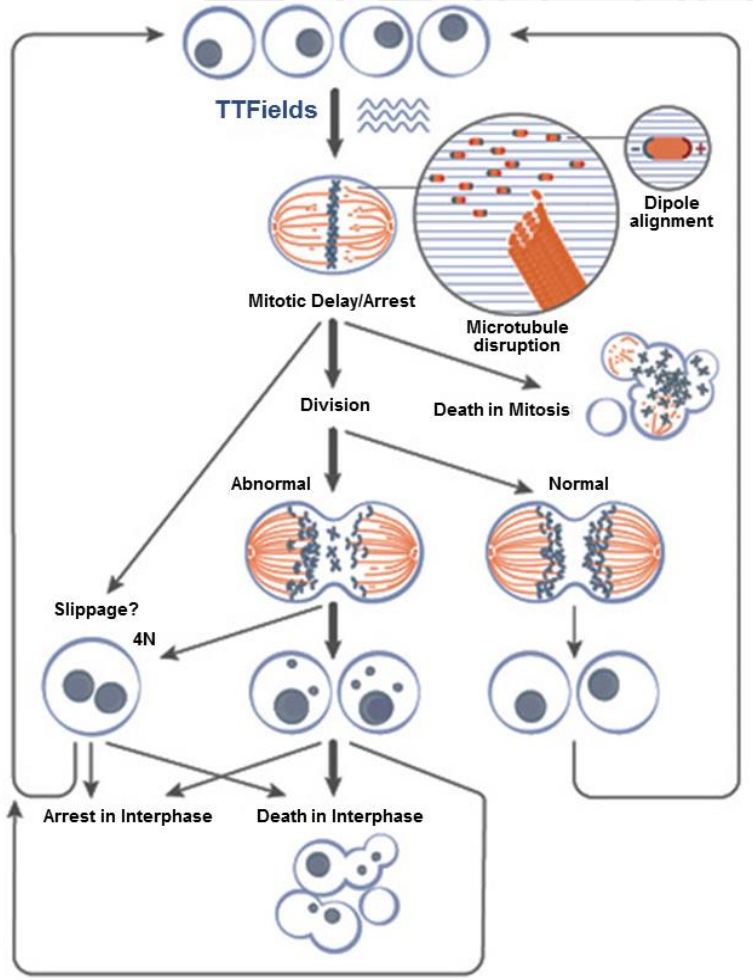


- TTFields stören die Lokalisation von Septin Proteinen
- Bläschenbildung an der Zellmembran (Blebbing)
- Ungleiche Chromosomen-verteilung

TELOPHASE



- Intrazelluläre Dielektrophorese von Makromolekülen und Organellen



Stark vereinfachte Darstellung ohne Anspruch auf Vollständigkeit. Zwischen den einzelnen Phasen gibt es fließende Übergänge.

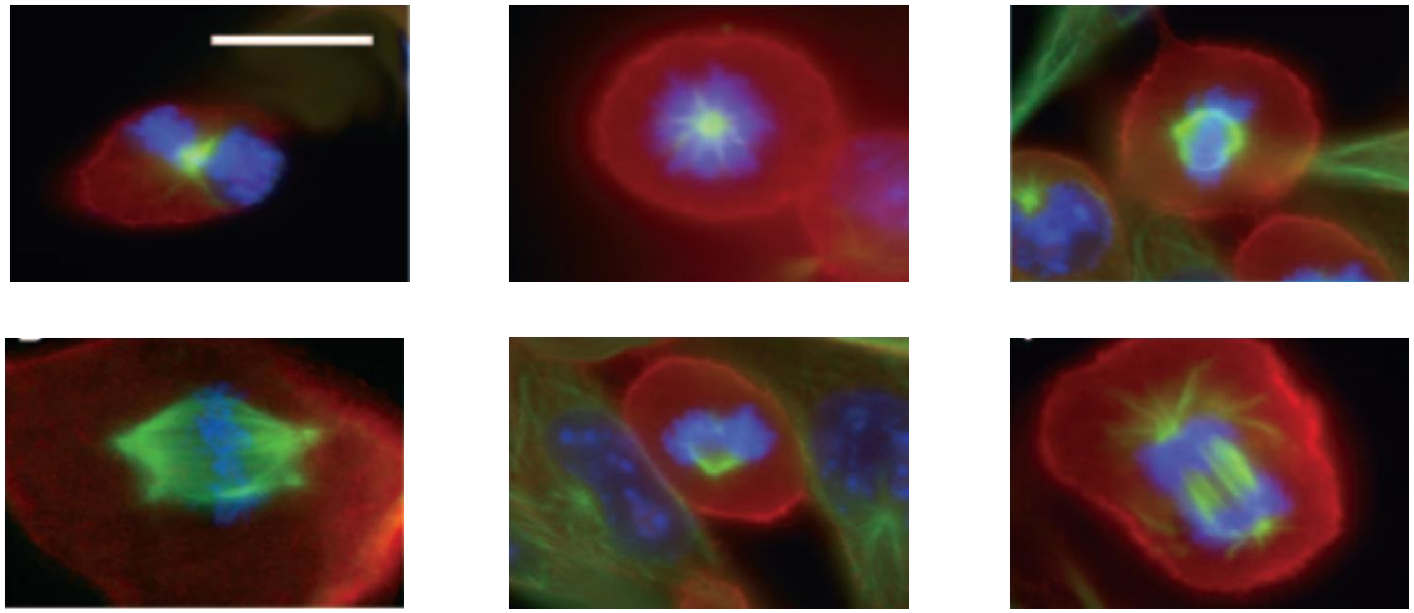
1. Mun EJ et al. Clin Cancer Res 2018, 24:266–275; **2.** Kirson ED et al. Cancer Res. 2004;64(9):3288-3295; **3.** Giladi M et al. Sci Rep. 2015 Dec 11;5:18046. doi: 10.1038/srep18046. **4.** Gutin PH, Wong ET. Am Soc Clin Oncol Educ Book. 2012:126-131; **5.** Gera N et al. PLoS One. 2015 May 26;10(5):e0125269

Wirkung auf Zellen (Zellteilung)

Die Mitosie dauert normalerweise ca. 1 Stunde.

Wirkung auf Zellen (Zellteilung)

Abnorme Mitosefiguren unter TTFields

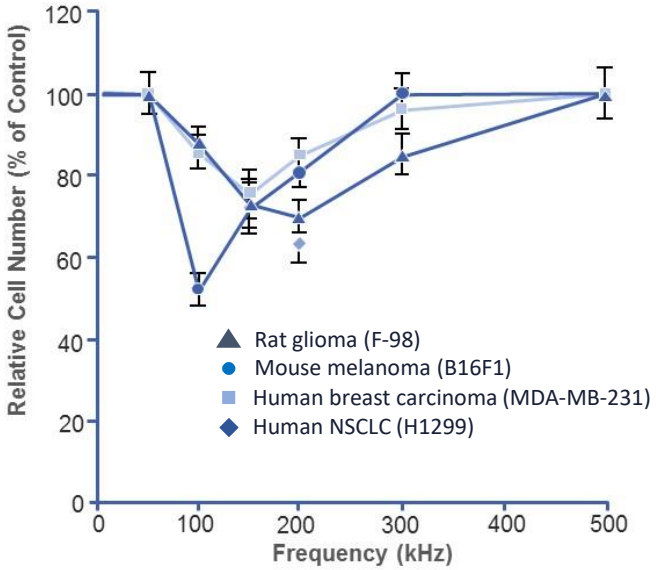


Mikrotubuli (grün), Aktin (rot) and DNA (blau)

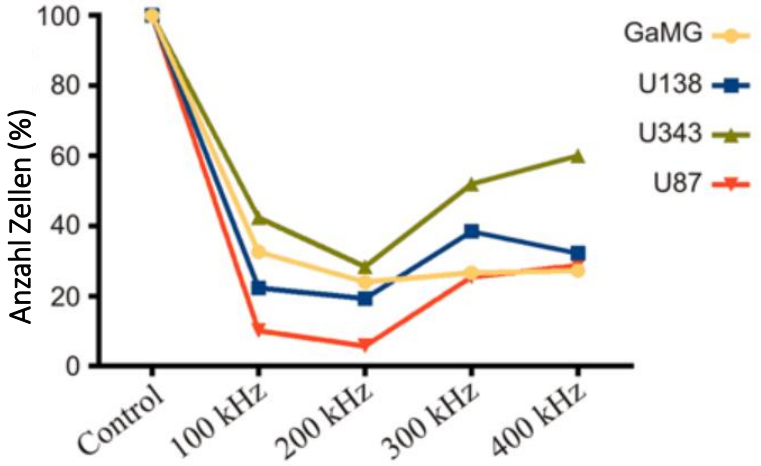
Kirson ED, et al. Disruption of cancer cell replication by alternating electric fields. *Cancer Res*. 2004;64(9):3288-3295.
1. Kirson ED, et al. *Cancer Res.* 2004;64(9):3288-3295.

Effekt unterschiedlicher Frequenzen auf Tumorzelllinien

Relative Änderung der Zellzahl nach 24 Stunden[1]



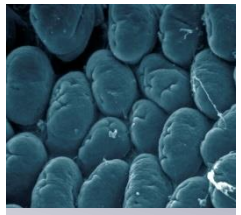
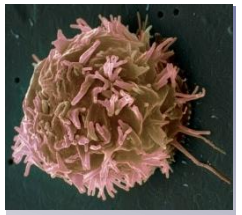
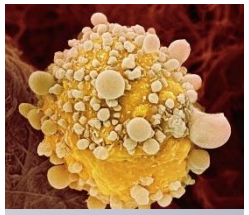
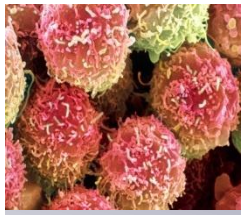
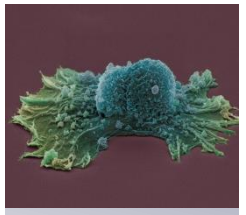
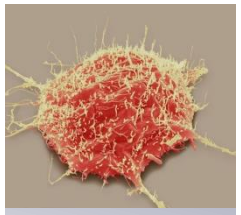
Humane Gliom-Zelllinien (72h)[2]



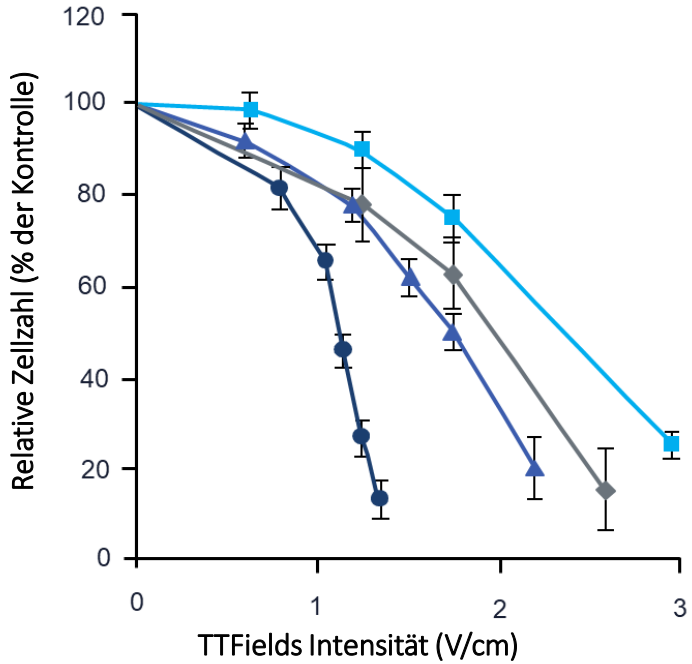
1. Kirson ED, Dbalý V, Tovarys F, et al. Proc Natl Acad Sci U S A. 2007 Jun 12;104(24):10152-7. **2.** Kessler AF et al. Article Cell Death Discovery Volume 4, Article number: 77 (2018)

Überblick: Frequenzspezifität

Die Effekte auf Zellen sind frequenzspezifisch und umgekehrt proportional zur Zellgrösse

					
Normaler Darm[1]	Brustkrebs[2]	Pankreas-krebs[3]	NSCLC[4]	Ovarial-Krebs[5]	GBM[2,6]
~50 kHz	150 kHz	150 kHz	150 kHz	200 kHz	200 kHz

Effekt unterschiedlicher Feldintensität auf Tumorzelllinien



- Inhibierung der Proliferation ist dosisabhängig
- Effektive Inhibierung ab >1,0 V/cm

- Mouse melanoma (B16F1)
- Human breast carcinoma (MDA-MB-231)
- Rat glioma (F-98)
- Human NSCLC (H1299)

Kirson ED, Dbalý V, Tovarys F, et al. Proc Natl Acad Sci U S A. 2007 Jun 12;104(24):10152-7.

Giladi et al. Radiation Oncology (2017) 12:206
DOI 10.1186/s13014-017-0941-6

Radiation Oncology

RESEARCH Open Access

Tumor treating fields (TTFields) delay DNA damage repair following radiation treatment of glioma cells

Moshe Giladi[1*†], Mijal Munster[1†], Rosa S. Schneiderman[1], Tali Voloshin[1], Yaara Porat[1], Roni Blat[1], Katarzyna Zielinska-Chomej[2], Petra Hååg[2], Ze'ev Bomzon[1], Eilon D. Kirson[1], Uri Weinberg[1], Kristina Viktorsson[2], Rolf Lewensohn[2] and Yoram Palti[1]

Abstract

Background: Tumor Treating Fields (TTFields) are an anti-neoplastic treatment modality delivered via application of alternating electric fields using insulated transducer arrays placed directly on the skin in the region surrounding the tumor. A Phase 3 clinical trial has demonstrated the effectiveness of continuous TTFields application in patients with glioblastoma during maintenance treatment with Temozolomide. The goal of this study was to evaluate the efficacy of combining TTFields with radiation treatment (RT) in glioma cells. We also examined the effect of TTFields transducer arrays on RT distribution in a phantom model and the impact on rat skin toxicity.

Methods: The efficacy of TTFields application after induction of DNA damage by RT or bleomycin was tested in U-118 MG and LN-18 glioma cells. The alkaline comet assay was used to measure repair of DNA lesions. Repair of DNA double strand breaks (DSBs) were assessed by analyzing γH2AX or Rad51 foci. DNA damage and repair signaled by the activation pattern of phospho-ATM (pS1981) and phospho-DNA-PKcs (pS2056) was evaluated by immunoblotting. The absorption of the RT energy by transducer arrays was measured by applying RT through arrays placed on a solid-state phantom. Skin toxicities were tested in rats irradiated daily through the arrays with 2Gy (total dose of 20Gy).

Results: TTFields synergistically enhanced the efficacy of RT in glioma cells. Application of TTFields to irradiated cells impaired repair of irradiation- or chemically-induced DNA damage, possibly by blocking homologous recombination repair. Transducer arrays presence caused a minor reduction in RT intensity at 20 mm and 60 mm below the arrays, but led to a significant increase in RT dosage at the phantom surface jeopardizing the "skin sparing effect". Nevertheless, transducer arrays placed on the rat skin during RT did not lead to additional skin reactions.

Conclusions: Administration of TTFields after RT increases glioma cells treatment efficacy possibly by inhibition of DNA damage repair. These preclinical results support the application of TTFields therapy immediately after RT as a viable regimen to enhance RT outcome. Phantom measurements and animal models imply that it may be possible to leave the transducer arrays in place during RT without increasing skin toxicities.

Keywords: TTFields, Radiation treatment, Glioma, Radiosensitization, DNA damage repair

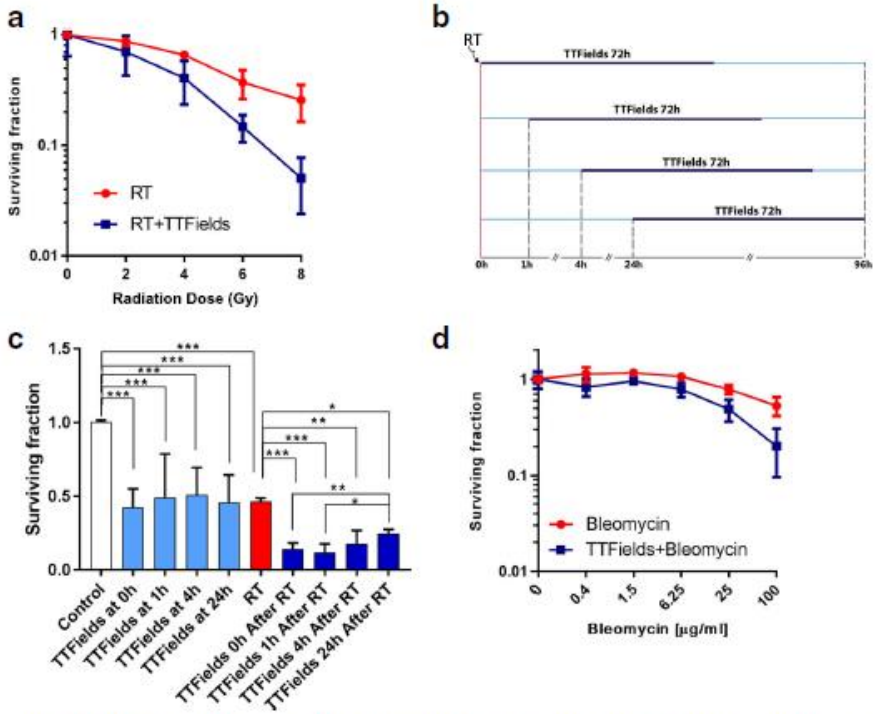


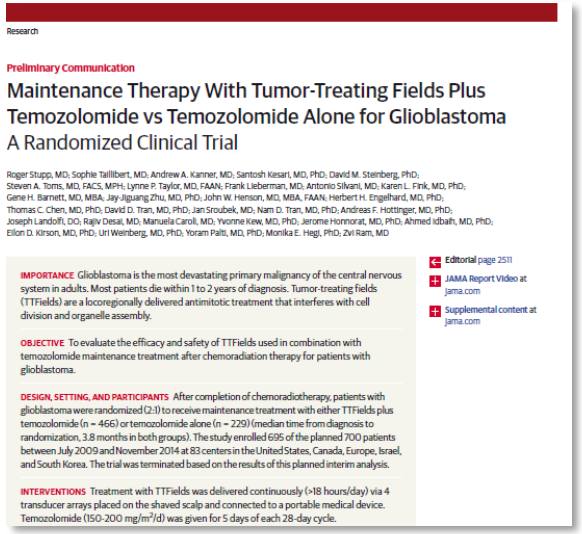
Fig. 1 Surviving fraction of U-118 MG cells treated with 200 kHz TTFields (1.7 V/cm RMS) for 72 h (**a**). The efficacy of the combined treatment of TTFields and irradiation with 4 Gy was tested when 72 h TTFields treatment was applied immediately after RT or 1 h, 4 h, and 24 h after RT in U-118 MG cells (**b**). The efficacy of the combined treatment (**c**) of TTFields and irradiation with 4 Gy in U-118 MG cells RT (red column) and TTFields (pale blue column) treatments alone were compared with untreated cells (white column) – The combination treatment (dark blue column) was compared with RT alone (red column). Surviving fraction of U-118 MG cells treated with bleomycin alone or in combination with 200 kHz TTFields (1.7 V/cm RMS) for 72 h (**d**)

TTFields Gliomzellen

- **TTFields wirken in verschiedenen Phasen der Mitose**
- **TTFields verstärken den Effekt der Bestrahlung in Gliomzellen**
- **Die Zellviabilität wird durch die Kombination von Bestrahlung & TTFields reduziert**
- **TTFields & Bestrahlung reduzieren Invasion und Migration von GBM Zellinien**
- **TTFields inhibieren die Reparatur von strahleninduzierten DNA-Schäden**
- **Untersuchung der Kombination von TTFields und Bestrahlung in klinischen Studien**

Indikation Glioblastom EF-14: JAMA Publikationen

Dezember 2015[1]



Research

Preliminary Communication

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma

A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew A. Kanner, MD; Santosh Kesari, MD, PhD; David M. Steinberg, PhD; Steven A. Toms, MD, FACS, MPH; Lynne P. Taylor, MD, FAAN; Frank Lieberman, MD; Antonio Silvani, MD; Karen L. Fink, MD, PhD; Gene H. Barnett, MD, MBA; Jay-Jiguang Zhu, MD, PhD; John W. Henson, MD, MBA, FAAN; Herbert H. Engelhard, MD, PhD; Thomas C. Chen, MD, PhD; David D. Tran, MD, PhD; Jan Sroubek, MD; Nam D. Tran, MD, PhD; Andreas F. Hottinger, MD, PhD; Joseph Landolfi, DO; Rajiv Desai, MD; Manuela Caroli, MD; Yvonne Kew, MD, PhD; Jerome Honnorat, MD, PhD; Ahmed Idbaih, MD, PhD; Eilon D. Kirson, MD, PhD; Uri Weinberg, MD, PhD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

Editorial page 2511

JAMA Report Video at jama.com

Supplemental content at jama.com

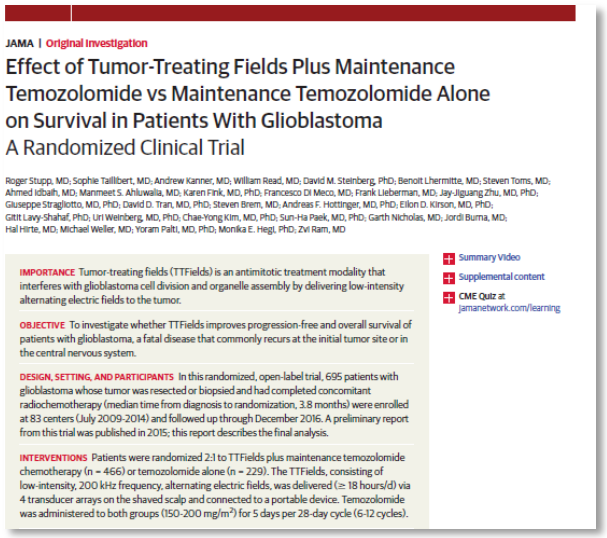
IMPORTANCE Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Most patients die within 1 to 2 years of diagnosis. Tumor-treating fields (TTFields) are a locoregionally delivered antimitotic treatment that interferes with cell division and organelle assembly.

OBJECTIVE To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

INTERVENTIONS Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m^2/d) was given for 5 days of each 28-day cycle.

Dezember 2017[2]



JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma

A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew Kanner, MD; William Read, MD; David M. Steinberg, PhD; Benoit Lhermitte, MD; Steven Toms, MD; Ahmed Idbaih, MD; Manmeet S. Ahluwalia, MD; Karen Fink, MD, PhD; Francesco Di Meco, MD; Frank Lieberman, MD; Jay-Jiguang Zhu, MD, PhD; Giuseppe Stragliotto, MD, PhD; David D. Tran, MD, PhD; Steven Brem, MD; Andreas F. Hottinger, MD, PhD; Eilon D. Kirson, MD, PhD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Chae-Yong Kim, MD, PhD; Sun-Ha Paek, MD, PhD; Garth Nicholas, MD; Jordi Bruna, MD; Hal Hirte, MD; Michael Weller, MD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD

Summary Video

Supplemental content

CME Quiz at jamanetwork.com/learning

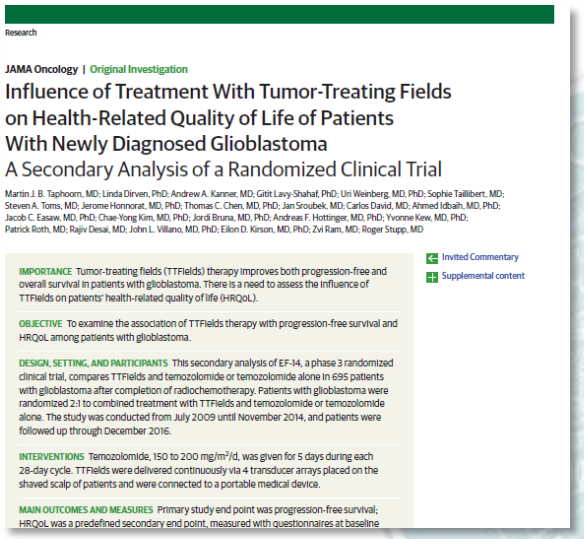
IMPORTANCE Tumor-treating fields (TTFields) is an antimitotic treatment modality that interferes with glioblastoma cell division and organelle assembly by delivering low-intensity alternating electric fields to the tumor.

OBJECTIVE To investigate whether TTFields improves progression-free and overall survival of patients with glioblastoma, a fatal disease that commonly recurs at the initial tumor site or in the central nervous system.

DESIGN, SETTING, AND PARTICIPANTS In this randomized, open-label trial, 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) were enrolled at 83 centers (July 2009-2014) and followed up through December 2016. A preliminary report from this trial was published in 2015; this report describes the final analysis.

INTERVENTIONS Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy (n = 466) or temozolomide alone (n = 229). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered (≥ 18 hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups (150-200 mg/m^2) for 5 days per 28-day cycle (6-12 cycles).

Februar 2018[3]



Research

JAMA Oncology | Original Investigation

Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma

A Secondary Analysis of a Randomized Clinical Trial

Martin J. B. Taphoorn, MD; Linda Dirven, PhD; Andrew A. Kanner, MD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Sophie Taillibert, MD; Steven A. Toms, MD; Jerome Honnorat, MD, PhD; Thomas C. Chen, MD, PhD; Jan Sroubek, MD; Carlos David, MD; Ahmed Idbaih, MD, PhD; Jacob C. Easaw, MD, PhD; Chae-Yong Kim, MD, PhD; Jordi Bruna, MD, PhD; Andreas F. Hottinger, MD, PhD; Yvonne Kew, MD, PhD; Patrick Roth, MD; Rajiv Desai, MD; John L. Villano, MD, PhD; Eilon D. Kirson, MD, PhD; Zvi Ram, MD; Roger Stupp, MD

Invited Commentary

Supplemental content

IMPORTANCE Tumor-treating fields (TTFields) therapy improves both progression-free and overall survival in patients with glioblastoma. There is a need to assess the influence of TTFields on patients' health-related quality of life (HRQoL).

OBJECTIVE To examine the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma.

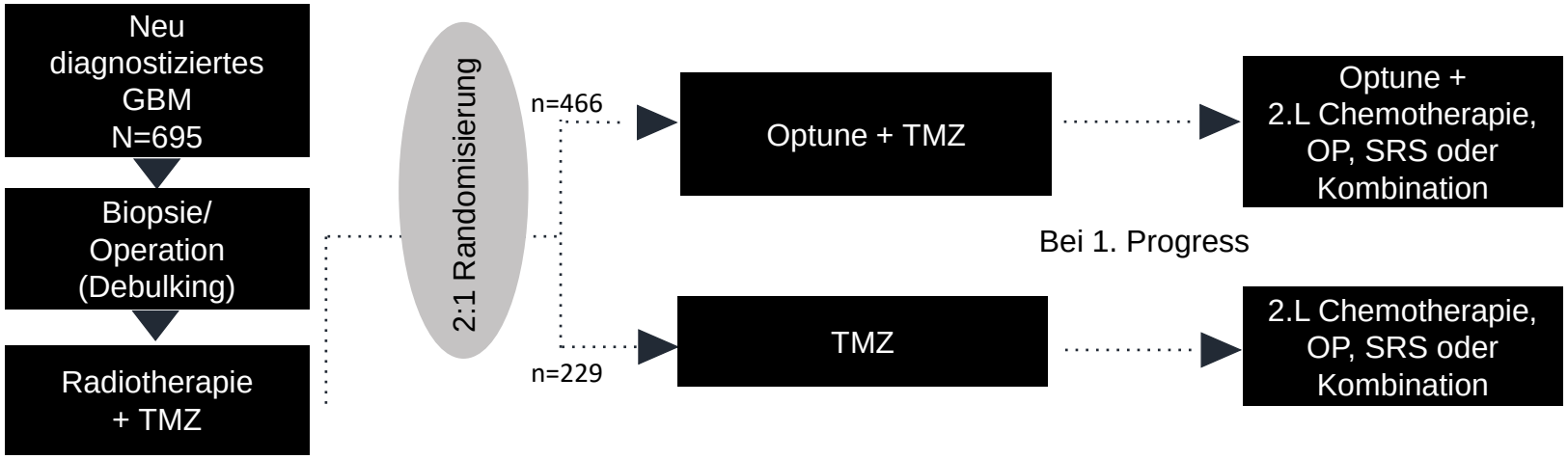
DESIGN, SETTING, AND PARTICIPANTS This secondary analysis of EF-14, a phase 3 randomized clinical trial, compares TTFields and temozolomide or temozolomide alone in 695 patients with glioblastoma after completion of radiochemotherapy. Patients with glioblastoma were randomized 2:1 to combined treatment with TTFields and temozolomide or temozolomide alone. The study was conducted from July 2009 until November 2014, and patients were followed up through December 2016.

INTERVENTIONS Temozolomide, 150 to 200 mg/m^2/d, was given for 5 days during each 28-day cycle. TTFields were delivered continuously via 4 transducer arrays placed on the shaved scalp of patients and were connected to a portable medical device.

MAIN OUTCOMES AND MEASURES Primary study end point was progression-free survival; HRQoL was a predefined secondary end point, measured with questionnaires at baseline

1. Stupp R, et al. JAMA. 2015;314(23):2535-2543. **2.** Stupp R, et al. JAMA. 2017;318(23):2306-2316. **3.** Taphoorn MJB, et al. JAMA Oncol. 2018;4(4):495-504.

EF-14 Studiendesign

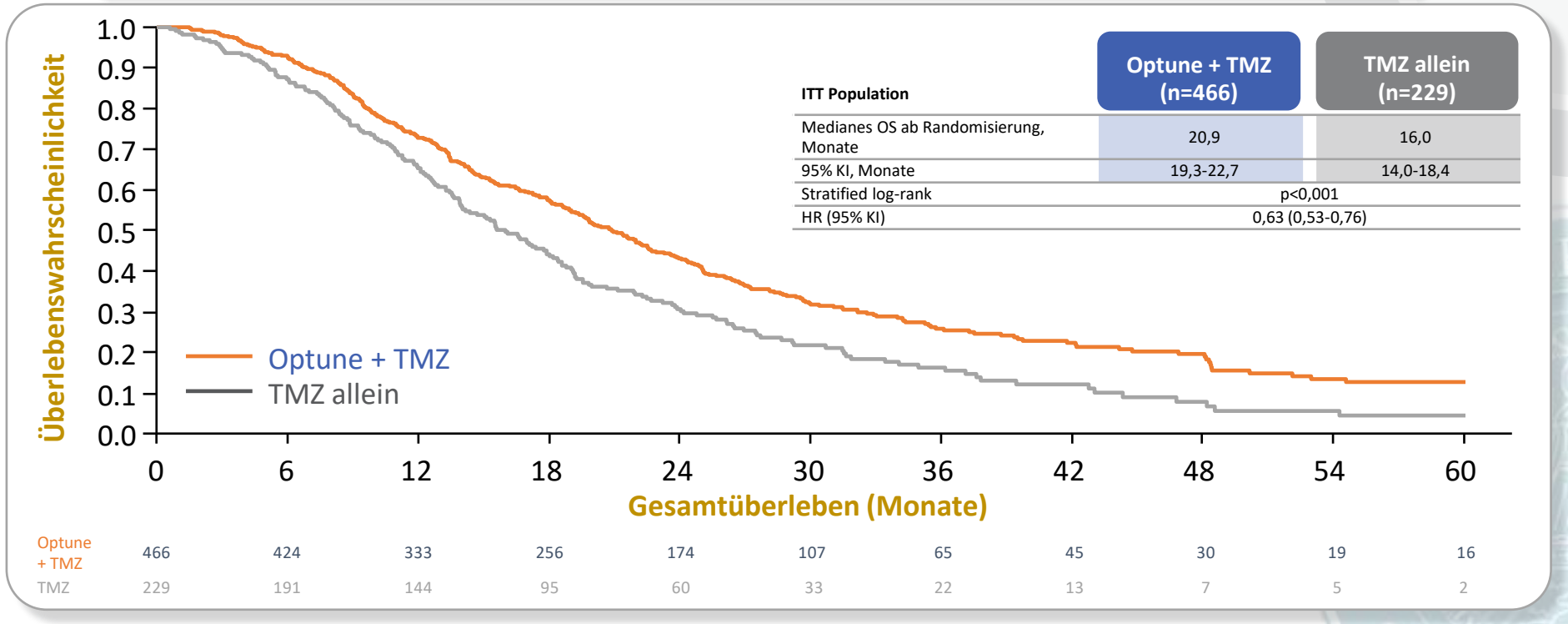


Stratifizierung nach:

1. Resektion (Biopsie vs. partiell vs. Totalresektion)
2. MGMT-Promotor-Methylierungsstatus

EF-14 Gesamtüberleben

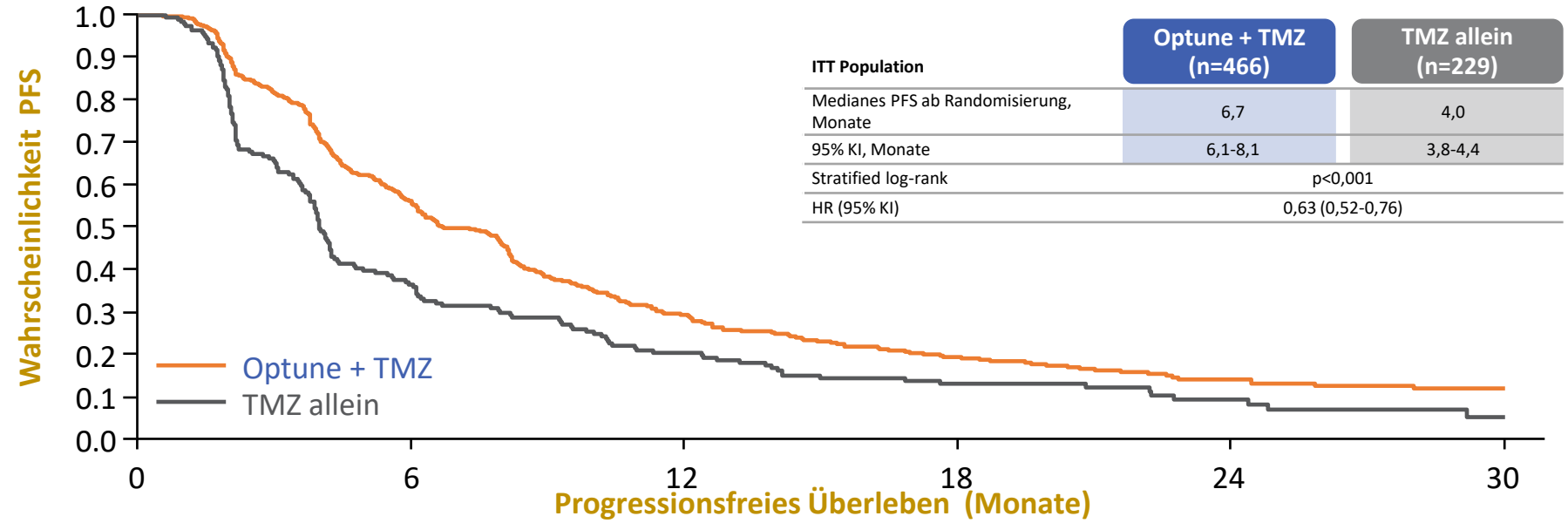
Optune + TMZ verlängerte signifikant das mediane OS um 4,9 Monate



ITT Population	Optune + TMZ (n=466)	TMZ allein (n=229)
Medianes OS ab Randomisierung, Monate	20,9	16,0
95% KI, Monate	19,3-22,7	14,0-18,4
Stratified log-rank	p<0,001	
HR (95% KI)	0,63 (0,53-0,76)	

EF-14 Progressionsfreies Überleben

Optune + TMZ verlängerte signifikant das mediane PFS gegenüber TMZ



ITT Population	Optune + TMZ (n=466)	TMZ allein (n=229)
Medianes PFS ab Randomisierung, Monate	6,7	4,0
95% KI, Monate	6,1-8,1	3,8-4,4
Stratified log-rank	p<0,001	
HR (95% KI)	0,63 (0,52-0,76)	

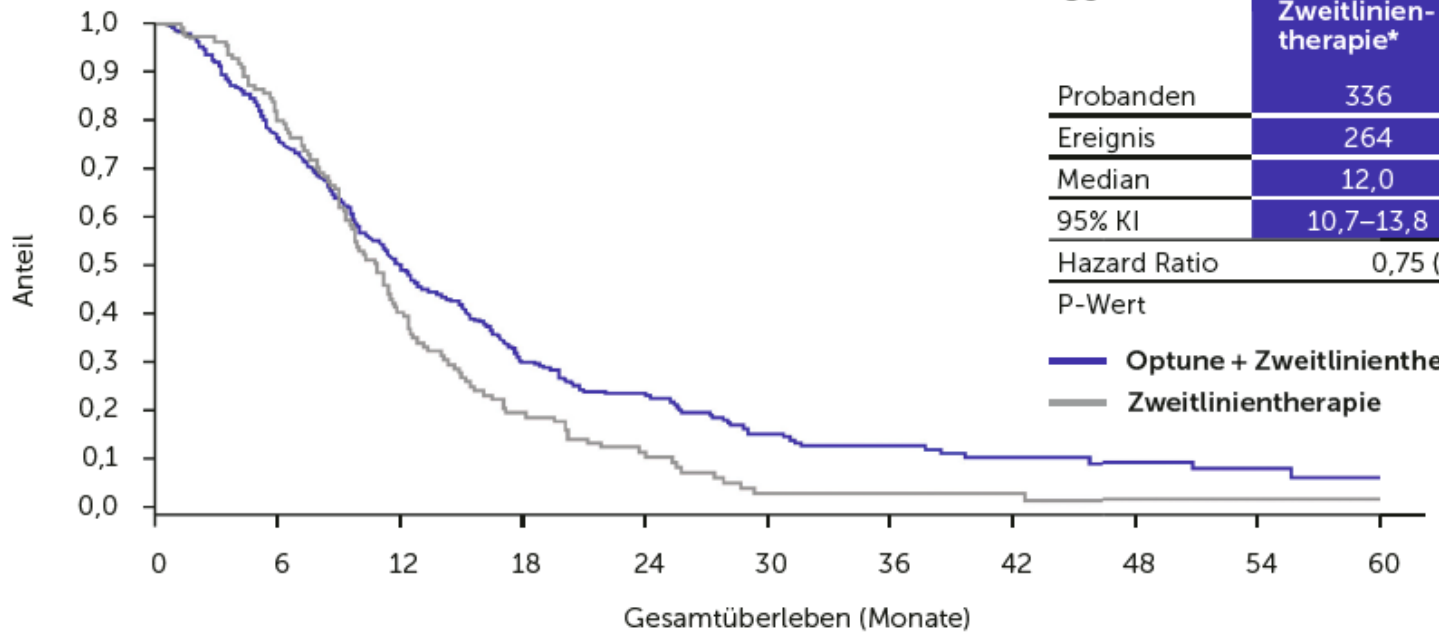
EF-14 Langzeitüberlebensrate

	1 Jahr	2 Jahre	3 Jahre	4 Jahre	5 Jahre
Optune + TMZ (n=466)	73%	43%	26%	20%	13%
TMZ alleine (n=229)	65%	31%	16%	8%	5%
P-Wert	0,029	<0,001	0,009	<0,001	0,004

Optune + TMZ verbesserte signifikant die Überlebensrate über 5 Jahre[1,2]

1. Stupp R.,Taillibert S., Kanner A., et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial, JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718; clinicaltrials.gov Identifier: NCT00916409. **2.** Stupp R, et al; on behalf of EF-14 trial investigators. Slides presented at: AACR 2017

Glioblastomrezidiv



OS	Optune + Zweitlinien-therapie*	Zweitlinien-therapie
Probanden	336	112
Ereignis	264	107
Median	12,0	10,8
95% KI	10,7–13,8	9,4–11,9
Hazard Ratio	0,75 (0,59–0,94)	
P-Wert	0,038	

Optune + Zweitlinientherapie

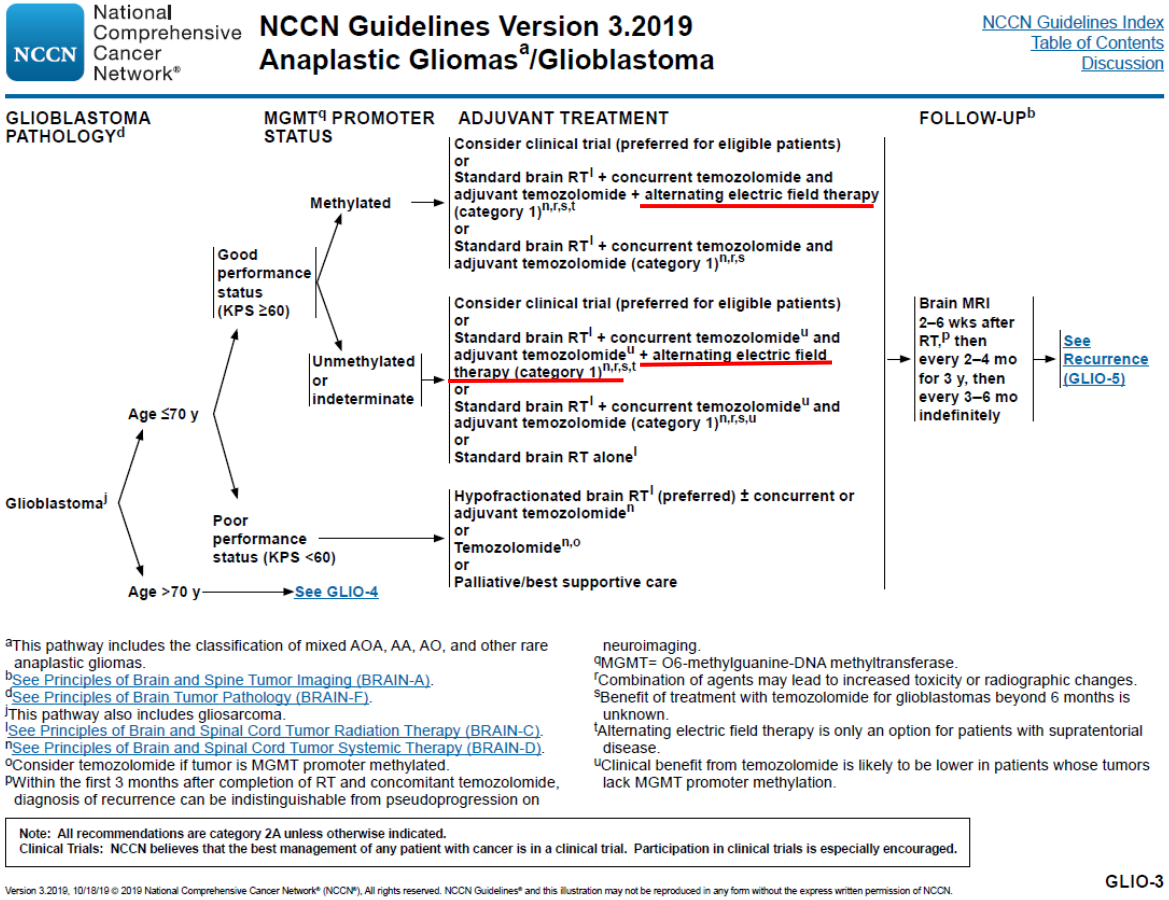
Zweitlinientherapie

* 28 % der Patienten/-innen in der Gruppe Optune + Zweitlinientherapie erhielten eine alleinige Optune-Therapie.

Das Gesamtüberleben (OS) ist signifikant länger unter Optune + Zweitlinientherapie verglichen mit alleiniger Zweitlinientherapie

Kesari S. et al. Tumor Treating Fields with second-line treatment compared to second-line treatment alone in patients at first recurrence of glioblastoma: a post-hoc analysis of the EF-14 phase 3 clinical trial. Poster ACTR-55 presented at SNO meeting 2017

Indikation Glioblastom



[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[d]See Principles of Brain Tumor Pathology (BRAIN-F).
[j]This pathway also includes gliosarcoma.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[o]Consider temozolomide if tumor is MGMT promoter methylated.
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[q]MGMT= O6-methylguanine-DNA methyltransferase.
[r]Combination of agents may lead to increased toxicity or radiographic changes.
[s]Benefit of treatment with temozolomide for glioblastomas beyond 6 months is unknown.
[t]Alternating electric field therapy is only an option for patients with supratentorial disease.
[u]Clinical benefit from temozolomide is likely to be lower in patients whose tumors lack MGMT promoter methylation.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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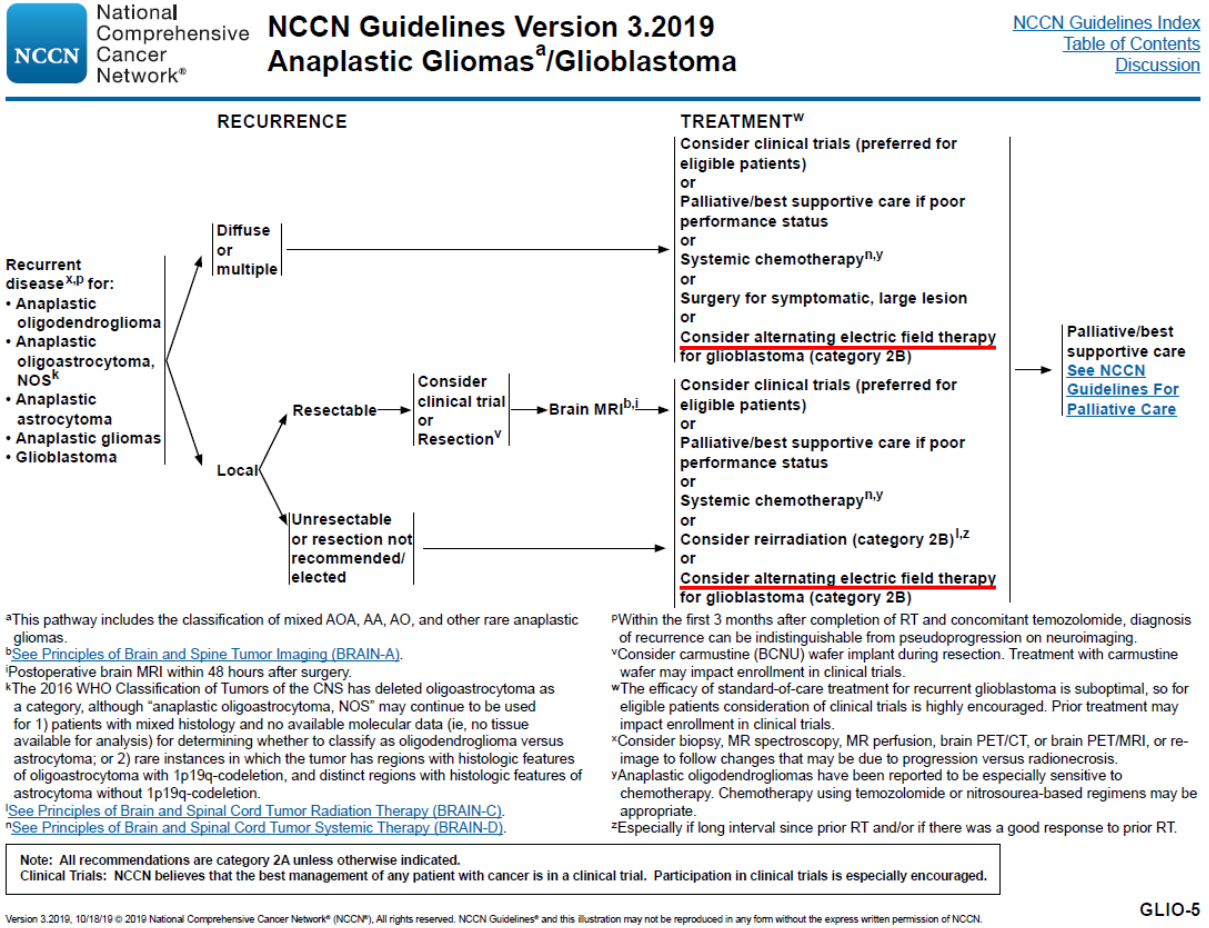
GLIO-3



[a]This pathway includes the classification of mixed AOA, AA, AO, and other rare anaplastic gliomas.
[b]See Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[i]Postoperative brain MRI within 48 hours after surgery.
[k]The 2016 WHO Classification of Tumors of the CNS has deleted oligoastrocytoma as a category, although "anaplastic oligoastrocytoma, NOS" may continue to be used for 1) patients with mixed histology and no available molecular data (ie, no tissue available for analysis) for determining whether to classify as oligodendroglioma versus astrocytoma; or 2) rare instances in which the tumor has regions with histologic features of oligoastrocytoma with 1p19q-codeletion, and distinct regions with histologic features of astrocytoma without 1p19q-codeletion.
[l]See Principles of Brain and Spinal Cord Tumor Radiation Therapy (BRAIN-C).
[n]See Principles of Brain and Spinal Cord Tumor Systemic Therapy (BRAIN-D).
[p]Within the first 3 months after completion of RT and concomitant temozolomide, diagnosis of recurrence can be indistinguishable from pseudoprogression on neuroimaging.
[v]Consider carmustine (BCNU) wafer implant during resection. Treatment with carmustine wafer may impact enrollment in clinical trials.
[w]The efficacy of standard-of-care treatment for recurrent glioblastoma is suboptimal, so for eligible patients consideration of clinical trials is highly encouraged. Prior treatment may impact enrollment in clinical trials.
[x]Consider biopsy, MR spectroscopy, MR perfusion, brain PET/CT, or brain PET/MRI, or re-image to follow changes that may be due to progression versus radionecrosis.
[y]Anaplastic oligodendrogliomas have been reported to be especially sensitive to chemotherapy. Chemotherapy using temozolomide or nitrosourea-based regimens may be appropriate.
[z]Especially if long interval since prior RT and/or if there was a good response to prior RT.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GLIO-5

Indikation Glioblastom

Erstmalig diagnostiziertes Glioblastom (GBM)

Optune ist nach einer Operation und Strahlentherapie mit adjuvantem Temozolomid für die Behandlung von Patienten mit einem erstmalig diagnostizierten GBM indiziert, die gleichzeitig eine Temozolomid-Erhaltungstherapie erhalten. Die Behandlung ist für erwachsene Patienten im Alter ab 18 Jahren vorgesehen und sollte nach der aktuellsten Operation und Strahlentherapie mit adjuvantem Temozolomid beginnen. Die Behandlung kann gleichzeitig zur einer Temozolomid-Erhaltungstherapie (gemäß Fachinformation auf der Packungsbeilage von Temodal) oder nach Abschluss einer Temozolomid-Erhaltungstherapie erfolgen.

Rezidivierendes Glioblastom (GBM)

Optune ist für Patienten vorgesehen, die nach einer Operation, Strahlentherapie und Chemotherapie gegen die primäre Erkrankung, anschließend an einem rezidivierenden GBM leiden. Die Behandlung ist für erwachsene Patienten im Alter ab 18 Jahren vorgesehen und sollte frühestens 4 Wochen nach der aktuellsten Operation, Strahlen-/Chemotherapie beginnen

TTF Dosimetry

Int J Radiat Oncol Biol Phys. 2019 Aug 1;104(5):1106-1113. doi: 10.1016/j.ijrobp.2019.04.008. Epub 2019 Apr 23.

Correlation of Tumor Treating Fields Dosimetry to Survival Outcomes in Newly Diagnosed Glioblastoma: A Large-Scale Numerical Simulation-Based Analysis of Data from the Phase 3 EF-14 Randomized Trial.

Ballo MT[1], Urman N[2], Lavy-Shahaf G[2], Grewal J[3], Bomzon Z[2], Toms S[4].

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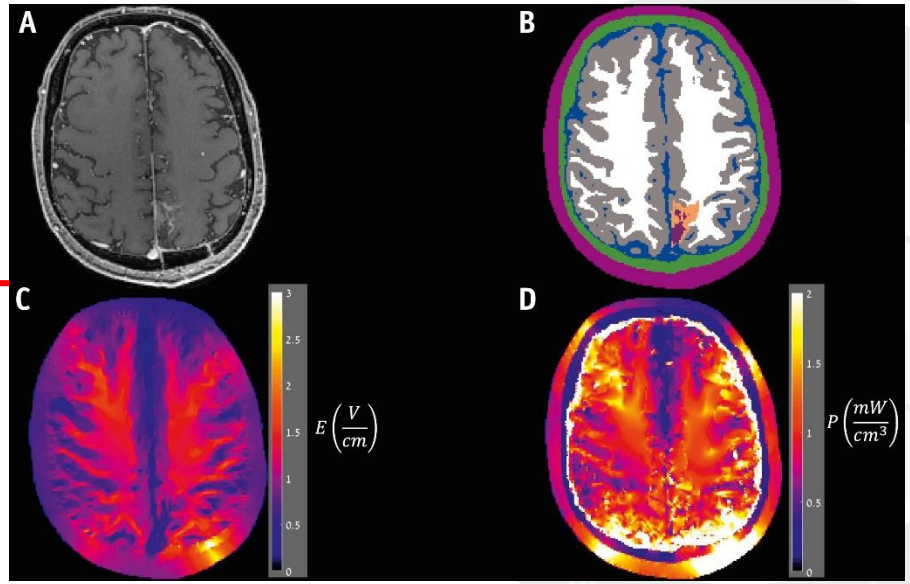
Abstract

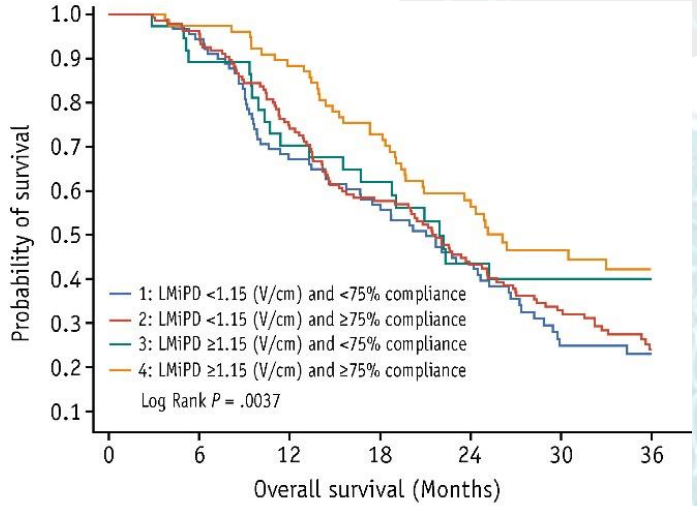
INTRODUCTION: Tumor Treating Fields (TTFields) are approved for glioblastoma based on improved overall survival (OS) and progression-free survival (PFS) in the phase 3 EF-14 trial of newly diagnosed glioblastoma. To test the hypothesis that increasing TTFields dose at the tumor site improves patient outcomes, we performed a simulation-based study investigating the association between TTFields dose and survival (OS and PFS) in patients treated with TTFields in EF-14.

METHODS AND MATERIALS: EF-14 patient cases (N = 340) were included. Realistic head models were derived from T1-contrast images captured at baseline. The transducer array layout on each patient was obtained from EF-14 records; average compliance (fraction of time patient was on active treatment) and average electrical current delivered to the patient were derived from log files of the TTFields devices used by patients. TTFields intensity distributions and power densities were calculated using the finite element method. Local minimum dose density (LMiDD) was defined as the product of TTFields intensity, tissue-specific conductivities, and patient compliance. The average LMiDD within a tumor bed comprising the gross tumor volume and the 3-mm-wide peritumoral boundary zone was calculated.

RESULTS: The median OS and PFS were significantly longer when the average LMiDD in the tumor bed was ≥0.77 mW/cm^3: OS was 25.2 versus 20.4 months (P = .003, hazard ratio [HR] = 0.611) and PFS was 8.5 versus 6.7 months (P = .02, HR = 0.699). The median OS and PFS were longer when the average TTFields intensity was >1.06 V/cm: OS was 24.3 versus 21.6 months (P = .03, HR = 0.705) and PFS was 8.1 versus 7.9 months (P = .03, HR = 0.721).

CONCLUSIONS: In this study we present the first reported analysis demonstrating patient-level dose responses to TTFields. We provide a rigorous definition for TTFields dose and set a conceptual framework for future work on TTFields dosimetry and treatment planning.





1:	90	84	59	48	34	16	12
2:	135	130	101	77	56	38	21
3:	37	33	26	22	13	9	5
4:	78	75	68	55	37	21	16

	Patients	Event	Censored	Median OS	95% CI
1:	90	69	21	21	15.70, 24.60
2:	135	105	30	21.70	16.23, 25.07
3:	37	22	15	21.93	15.53,
4:	78	50	28	25.13	20.80, 39.43

TTFields + Strahlentherapie

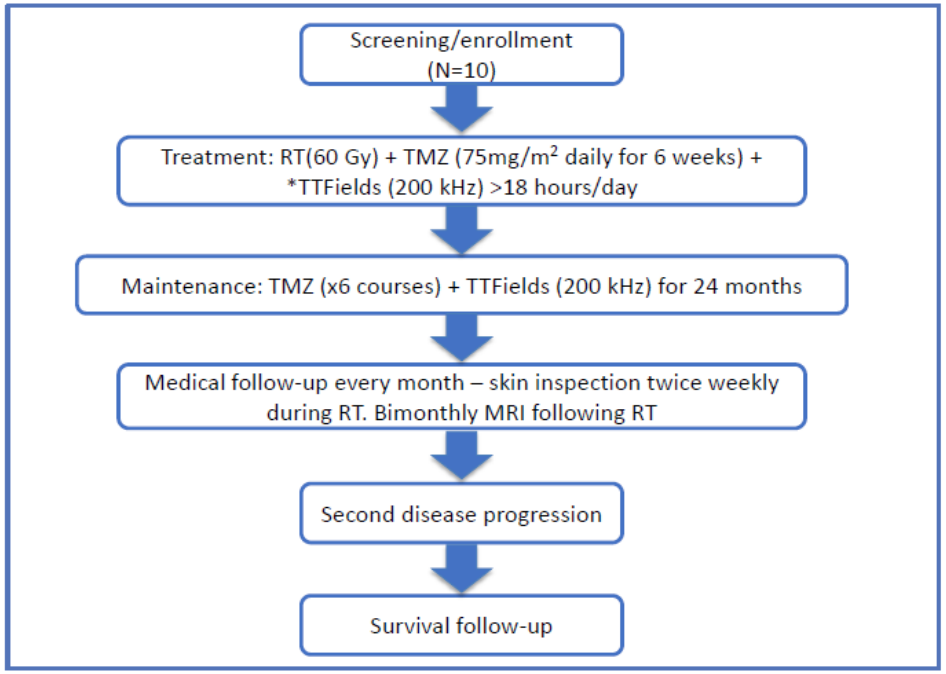
Pilot study: Tumor Treating Fields combined with radiotherapy and temozolomide (Rachel Grossman et al.)

Studiendesign

- **Prospektiv, einarmig, open-label**
- **Patienten behandelt mit RT/TMZ/TTFields gefolgt von TMZ/TTFields bis zu 24 Monaten**
- **Primärer Endpunkt: Sicherheit von konkomitant RT/TMZ mit TTFields, inkl. RT Behandlungsverzögerungen**
- **Sekundäre Endpunkte: progression-free survival (PFS), overall survival (OS).**

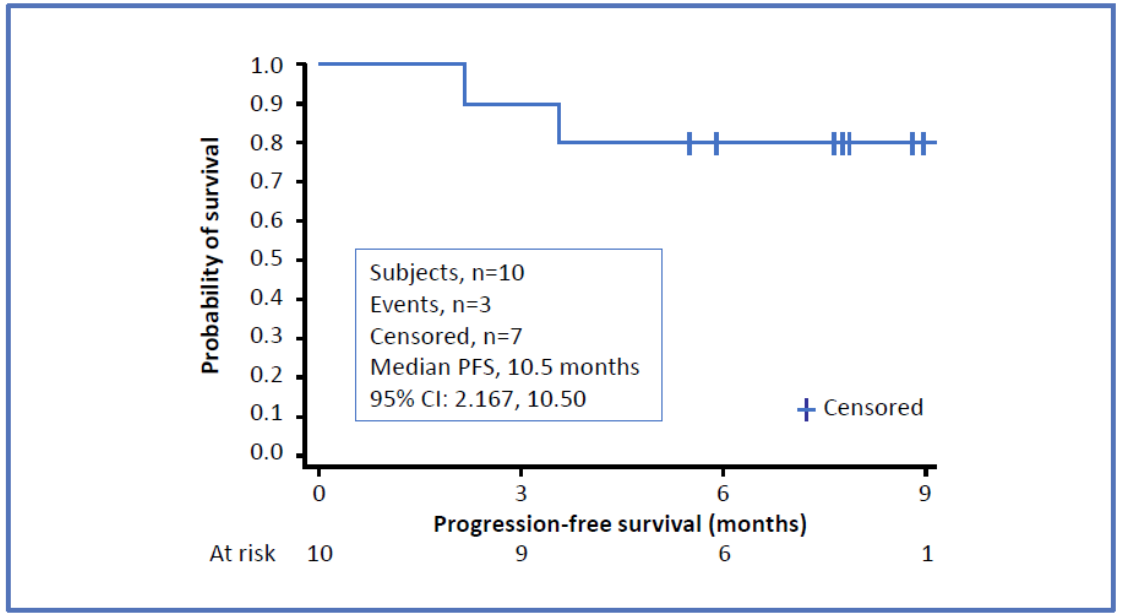
Studienpopulation

- **10 neu diagnostizierte GBM Patientinnen und Patienten (supratentoriell)**
- **Vorherige maximale Operation oder Biopsie; angemessene Erholung des Patienten**
- **Karnofsky Performance Status ≥70.**
- **Ausgeschlossen: Patienten mit implantieren Schrittmachern oder elektronischen Geräten im Gehirn**



Grossman R, Limon D, Bokstein F, Ram Z. Tumor Treating Fields combined with radiotherapy and temzolomide for newly diagnosed glioblastoma: Final results from a pilot study. In: Proceedings of the 110th Annual Meeting of the American Association for Cancer Research; 2019 March 29 - April 3; Atlanta, GA. Philadelphia (PA): AACR; 2019. Abstract nr CT008.

TTFields + Strahlentherapie

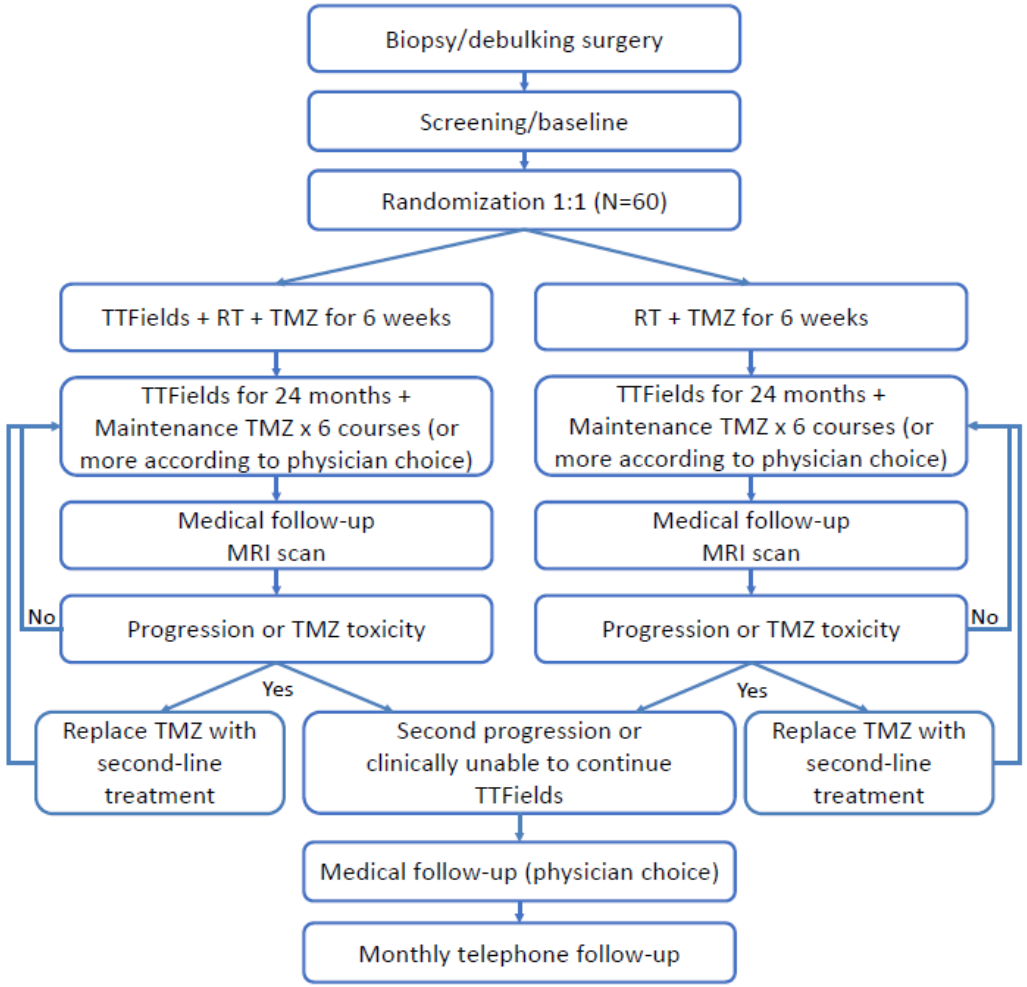


- **Medianes PFS unter RT/TMZ/TTFields: 10.5 Monate**
- **Medianes OS: noch nicht erreicht**

- **Das einzige TTFields-bezogene AE war Hauttoxizität**
- **Es gab keinen Anstieg der RT- oder TMZ-bezogenen Toxizität in Folge der TTFields Therapie**
- **RT Verzögerungen wurden nicht durch Hauttoxizität verursacht**
- **Basierend auf diesen Ergebnissen wurde eine randomisierte Phase 2 Studie (n=60, nGBM) initiiert**

Grossman R, Limon D, Bokstein F, Ram Z. Tumor Treating Fields combined with radiotherapy and temzolomide for newly diagnosed glioblastoma: Final results from a pilot study. In: Proceedings of the 110th Annual Meeting of the American Association for Cancer Research; 2019 March 29 - April 3; Atlanta, GA. Philadelphia (PA): AACR; 2019. Abstract nr CT008.

TTFields + Strahlentherapie



- Randomized phase 2 trial of Tumor Treating Fields plus radiation therapy plus temozolomide compared to radiation therapy plus temozolomide in patients with newly diagnosed glioblastoma (Rachel Grossman et al.)

TTFields + Strahlentherapie

Straube *et al. Radiation Oncology* (2018) 13:31
https://doi.org/10.1186/s13014-018-0976-3

Radiation Oncology

RESEARCH Open Access

Dosimetric impact of tumor treating field (TTField) transducer arrays onto treatment plans for glioblastomas – a planning study

Christoph Straube[1,2*], Markus Oechsner[1], Severin Kampfer[1], Sophia Scharl[1], Friederike Schmidt-Graf[3], Jan J. Wilkens[1,4] and Stephanie E. Combs[1,2,4]

Abstract

Background: Tumor-Treating Fields (TTFields) are a novel treatment strategy for glioblastoma (GBM) that is approved for the use concomitantly to adjuvant chemotherapy. Preclinical data suggest a synergistic interaction of TTFields and radiotherapy (RT). However, the dosimetric uncertainties caused by the highly dense arrays have led to caution of applying the TTF setup during RT.

Methods: In a RW3 slab phantom we compared the MV- and kV-CT based planned dose with the measured dose. VMAT-plans were optimized on MV-CTs of an Alderson head phantom without TTF arrays and then re-calculated on the same phantom equipped with TTF arrays. Dose at organs at risk (OAR) and target volumes (PTVs) were compared.

Results: Measurements at a depth of 2, 3 and 4 cm of a RW 3 slab phantom show an attenuation due to TTField arrays of 3.4, 3.7 and 2.7% respectively. This was in-line with calculated attenuations based on MV-CT (1.2, 2.5 and 2.5%) but not with the attenuation expected from kV-CT based calculations (7.1, 8.2 and 8.6%). Consecutive MV-CT based VMAT planning and re-calculation reveals, that the conformity and homogeneity are not affected by the presence of TTField arrays. The dose at organs at risk (OAR) can show increases or decreases by < 0.5 Gy, which should be considered especially in cases next to the scull base.

Conclusion: MV-CT based dose calculation results in reliable dose distributions also in the presence of TTField arrays. There is a small but clinically not relevant interaction between the TTField arrays and VMAT dose application. Thus, daily replacement of TTField arrays is not necessary in regard to deeply located OARs. RT is feasible, when a VMAT treatment plan is optimized to an array free planning CT. As the biologic effect of a concomitant treatment especially on OARs is currently unknown, a concomitant treatment should be performed only within clinical trials.

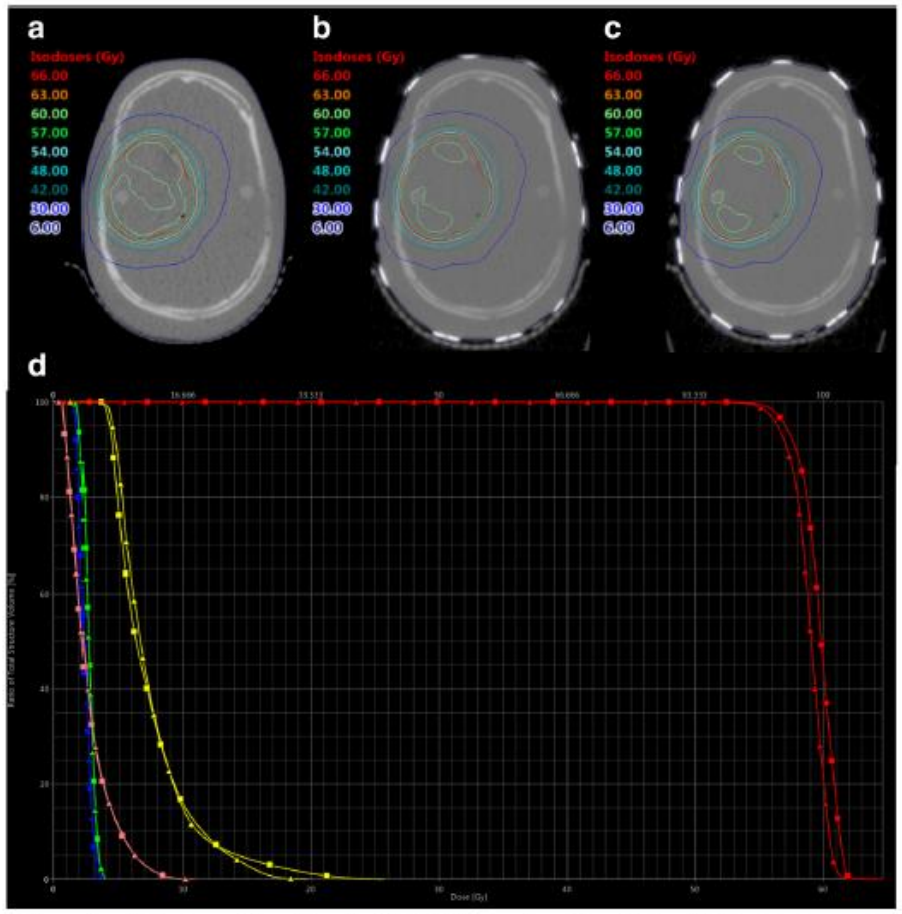
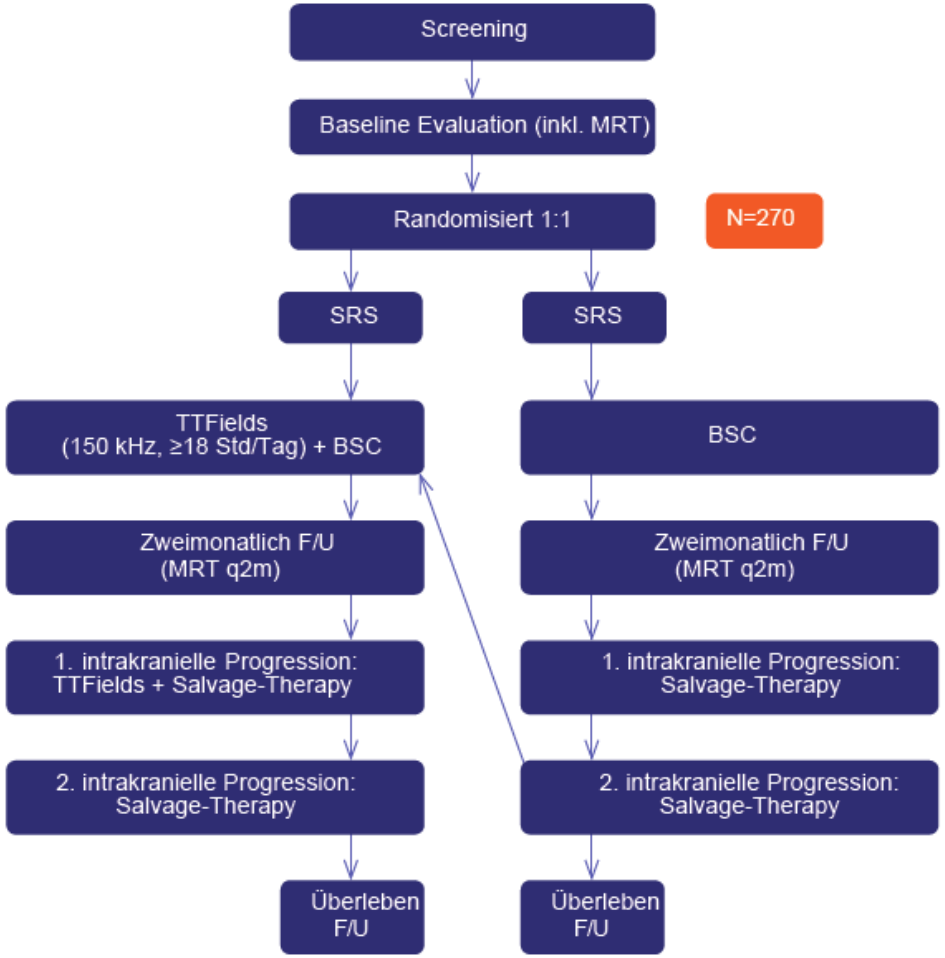


Fig. 3 MV-CTs of an Alderson head phantom without (**a**) and with TTField arrays in position A (**b**) and B (**c**). A treatment volume resembling the PTV for a parietal glioblastoma was optimized to the MV-CT in (**a**) and re-calculated to MV-CT (**b**) and (**c**). (**d**) shows a DVH-comparison between the plan for (**a**) (squares) and (**b**) (triangles). Red: PTV, yellow: chiasm, blue: left optical nerve, green: right optical nerve, pink: brainstem

Klinische Studien TTF

- TTFields sind zur Therapie des Glioblastoma multiforme zugelassen
- TTFields sind durch die FDA zur Behandlung des malignen Pleuramesothelioms zugelassen

Klinische Studien TTF METIS



Open-label, randomisierte Studie zu Radiochirurgie mit oder ohne Tumortherapiefelder (150 kHz) für 1-10 Hirnmetastasen von nicht-kleinzelligem Lungenkarzinom (NSCLC)

Klinische Studien TTF METIS

Wesentliche Einschlusskriterien*

- Neudiagnose von 1-10 Hirnmetastasen von histologisch/zytologisch bestätigtem NSCLC
- Hirnmetastasen zugänglich für SRS
- ≥18 Jahre alt
- Min. 3 Monate Lebenserwartung
- KPS ≥70
- Erhalt optimaler Therapie gegen extrakranielle Erkrankung

Wesentliche Ausschlusskriterien*

- Leptomeningeale Metastasen
- Einzelne, resezierbare Metastase
- Simultane auf das Gehirn abzielende Therapien
- Signifikante Komorbidität, die sich auf den Erhalt einer optimalen systemischen Therapie auswirkt
- Implantierbare elektronische medizinische Geräte im Gehirn
- Schwanger oder stillend

Primärer Endpunkt

- Zeit bis zur intrakraniellen Progression

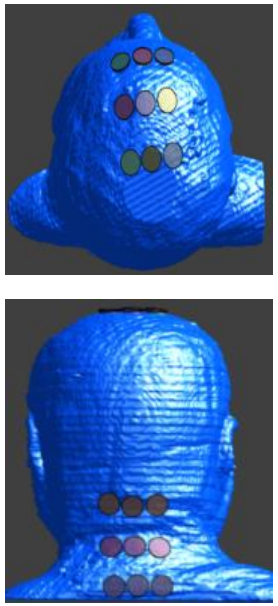
Sekundäre Endpunkte*

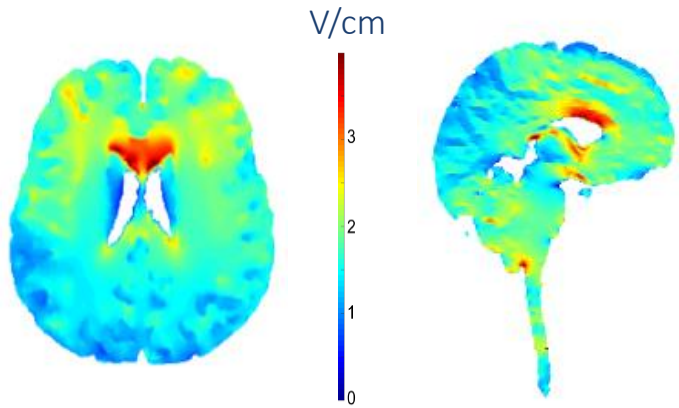
- Zeit bis zur 1. und 2. intrakraniellen Progression in zwei Kohorten: 1-4 und 5-10 Hirnmetastasen
- Raten für intrakranielle Progression nach 2-, 4-, 6-, 8-, 10-, 12 Monaten
- OS (Gesamtüberleben)
- Zeit bis neurokognitivem Versagen
- Radiologische Ansprechraten nach Studienbehandlungen
- UE Frequenz und Schwere

Klinische Studien TTF METIS

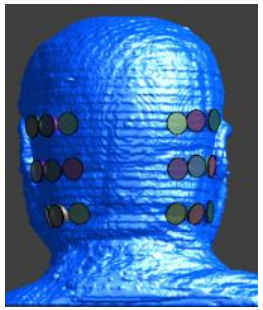
Array Layout Simulation zur Behandlung von infratentoriellen und supratentoriellen Hirnregionen

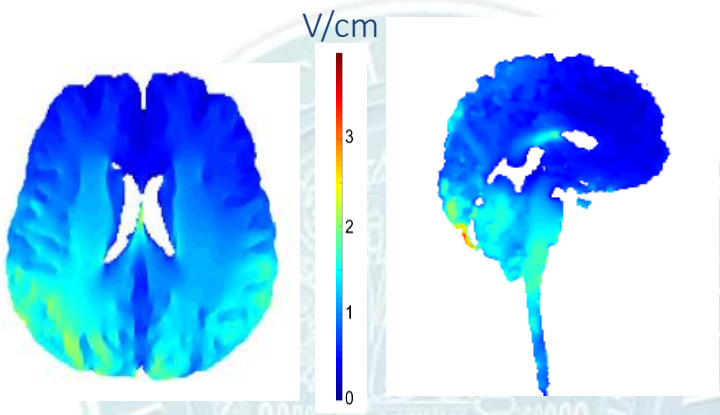
Supratentorielle Abgabe von TTFields





Infratentorielle Abgabe von TTFields





1. Bomzon Z, et al. Poster presented at the 7th Annual Brain Metastases Research and Emerging Therapy Conference, October 6–7, 2017, Marseille, France. Poster #4

Danke

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