Multicenter Observational Study of Adverse Effects Following GammaTile® Implantation 30-Days Post-Operatively After Resection of Intracranial Brain Neoplasms

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Background

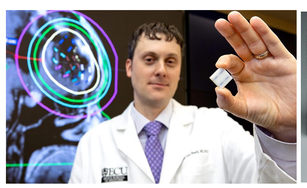
- Placement of a radiation source within a neoplasm, brachytherapy, has been used effectively to treat a variety of neoplasms.
- This localized delivery of radiation therapy has been shown to be effective and avoids external beam radiation and associated morbidities.
- Brain tumors include primary neoplasms, metastatic neoplasms, and hematopoietic neoplasms.
- Traditional and emerging modalities of diagnosis and therapy of brain tumors include:
  - Biopsy or resection
  - Radiation therapy
  - Chemotherapy and immunotherapy
- The Food and Drug Administration cleared the use of an implanted device, GammaTiles® (GT Medical Technologies, Tempe, AZ), consisting of cesium-131 seeds embedded in a collagen carrier, for use after resection of recurrent brain tumors (2018) and subsequently for newly-diagnosed intracranial neoplasms (2018).
- GammaTiles provide a potential additional treatment modality for the treatment of brain neoplasm as "brachytherapy" where radioactive material is implanted along the the cavity following resection of a neoplasm.
- This study:
  - Provides a case summary of a patient with recurrent glioblastoma treated with GamaTiles.
  - Reports findings from a multi-institution consortium of centers deploying GammaTiles as part of treatment of CNS neoplasms to evaluate the patterns of clinical application and evaluate the safety profile through characterization of morbidity, mortality, and readmission within 30 days across institutions and tumor types.

Methods/Materials

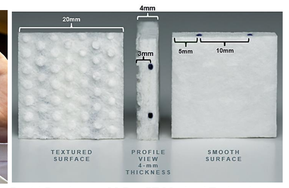
- Illustrative Case: The patient's radiologic images and pathology specimens and electronic medical records were thoroughly reviewed.
- Adverse event data from the GammaTile registry are compiled.

GammaTile Information

- GammaTiles® consist of a bioresorbable collagen carrier.
- Tiles are implanted with cesium-131 seeds.
- There is a structural offset of the radiation sources from the brain tissue to prevent direct seed-to-tissue contact and associated radiation necrosis.
- Tiles are designed to achieve 60 Gy dose of radiation at 5 mm depth when 3+ tiles are implanted
- Cesium Source: 9.7-day half-life with more than 95% of the dose delivered in 6 weeks

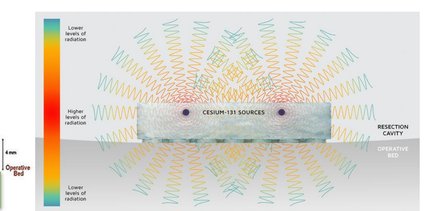


Sean Peach, M.D. Holding Gamma Tile: Non-Radioactive Model



David Brachman, M.D., GT Medical Technologies, Tempe, AZ https://gammatile.com/

Cesium-131 Distribution and Intensity



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Results

ECU Health GammaTile Experience & Case Example of Placement: No Adverse Event

ECU Health GammaTile Data:

- >45 Cases with GammaTile Placement
  - Largest number of patients entered into GammaTile registry of any participating center
- **Case Mix**
  - High-Grade Gliomas
    - High-Grade Astrocytoma
    - Glioblastoma
    - Recurrent Oligodendroglioma
  - Meningiomas, recurrent or primary
  - Metastases, recurrent or primary
  - Hemangioblastoma, recurrent
- **Procedure**
  - Patient with CNS neoplasm needing resection identified
  - Resection undertaken
  - GammaTiles placed

Representative Case History:

- A 59-year-old man with a diagnosis of astrocytoma, World Heath Organization Grade 4; presented with recurrence after two previous resections and treatment with radiation therapy and temozolomide.
- 10/01/2019: 1st Resection
- 01/08/2020: 2nd Resection
- 11/05/2020: 3rd Resection and Gamma Tile Placement
- Complete molecular evaluation revealed IDH-wildtype status (no mutation in IDH1 or IDH2), a TERT promotor mutation (c-124C>T), a FGFR3-TACC3 fusion, and absence of MGMT promoter methylation.
- MRI evaluation in 04/2023 and 03/2024 revealed stable nodular enhancement in the anterolateral margin of surgical cavity.

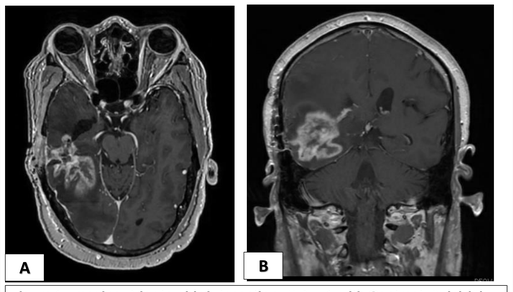


Figure 1. Imaging Prior to Third Resection: MRI, T1 with Contrast, Axial (A) and Coronal (B): Irregular enhancement in area of previous resections in right temporal lobe region, consistent with recurrent neoplasm

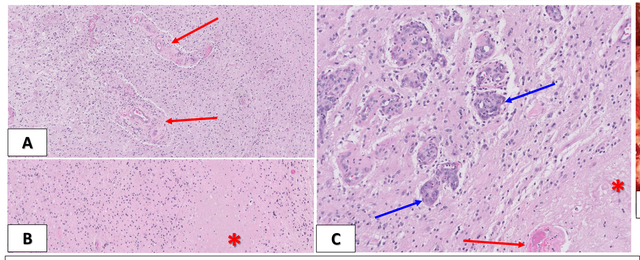


Figure 2. Resection 3: Histology: (A-C) Abundant, viable neoplastic cells were noted, with infiltration around fibrotic blood vessels consistent with previous radiation therapy (→). Patchy tumor necrosis without perinecrotic pseudopalisades was noted (*). Multifocal regions of vascular proliferation were identified (→).
Final Diagnosis: Glioblastoma, IDH-wildtype, WHO grade 4.

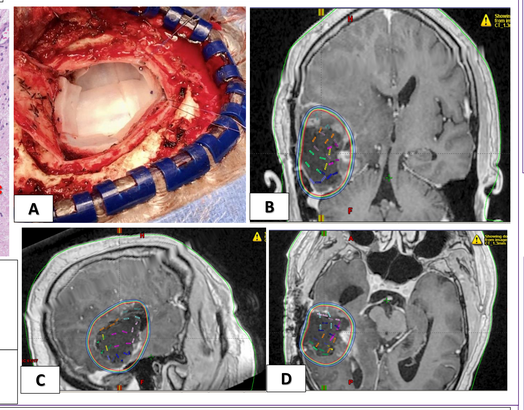


Figure 3. GammaTile Placement and Imaging: (A) Interoperative: Placement of tiles after resection of recurrent neoplasm. (B-C). Postoperative MRI, T1, coronal, sagittal, and axial showing tiles in situ, with color indicating cesium rods, color added after imaging.

Illustrative Case: Clinical Summary

- **10/2019**: 1st Resection, Partial @ UNC Medical Center

53 Months Since First Resection and Original Diagnosis

3 Months

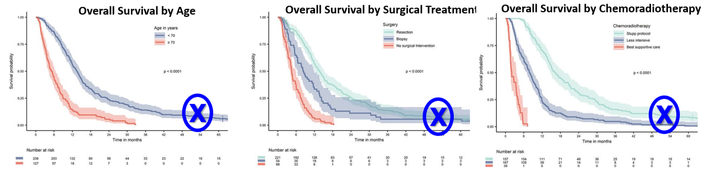
- **01/2020**: 2nd Resection @ UNC Medical Center
  - Radiation therapy (5940 cGy) with temozolomide
  - Temozolomide X 5 cycles

10 Months

- **11/2020**: 3rd Resection with Aminolevulinic Acid Guidance & GammaTile Placement @ ECU Health
  - Bevacizumab X 10 months, discontinued secondary to proteinuria
  - Lomustine (CCNU) X 5 cycles
  - Optune, stopped 09/23 due to scalp irritation

40 Months

- **03/2024** **Stable** post-operative changes on serial imaging



Patient's survival (X) plotted against overall survival data 363 adults diagnosed with glioblastoma between January 2007 and December 2014. Note: Patient failed Stupp protocol chemoradiation after second resection.
Stupp Protocol Definition Used in STudy: Completed radiation therapy, 60 Gy in 2 Gy fractions; concomitant temozolomide during entire radiation therapy period; and completed at least 1 of 6 temozolomide monotherapy courses.

(Bjorland LS, et al. Treatment approach and survival from glioblastoma: results from a population-based retrospective cohort study from Western Norway. BMJ Open. 2021 Mar 12;11(3):e043208.)

Adverse Events: Compiled Data from GammaTile Registry To 05/27/2023

- A phase 4 observational study opened on 11/14/2020 (NCT04427384) to prospectively enroll 600 subjects at 50 sites capturing demographics, pathology, survival, local control, adverse events (AE), and quality of life.
- Objective: Evaluate the patterns of clinical application and evaluate the safety profile through characterization of morbidity, mortality, and readmission within 30 days across institutions and tumor types.
- Through 5/27/2023:
  - 198 patients from 25 enrolling institutions consented: 26 failed screening and did not receive GammaTiles.
  - 133 completed 30-day postoperative evaluation.
- Data was abstracted from study registry: patients with possible, probable, or definitive attributable surgical- or radiation-related grade ≥3 AE were compiled.
- **Study Registry: Summary of Patients to Date**
  - 188 treated tumors in 174 patients:
  - Neoplasm Types
    - Glioblastoma 81
    - Metastatic Neoplasm 61
    - Meningioma 20
    - Miscellaneous Tumors 12
  - Setting of Placement of Tiles:
    - 136/174 cases: GT after resection of recurrent disease
    - 38/174: GT placed at time of initial resection.
- **Adverse Events (AE) in 133 Patients with 30-Day Postoperative Evaluation**
  - 11 Attributed Grade ≥3 AE in 9 Patients (6.8%):
    - Cerebral Edema (Day 2) 1
    - Intracranial Hemorrhage (Day 5) 1
    - Left Hemiparesis (Day 0) 1
    - Transient Expressive Aphasia (Day 0) 1
    - Seizure Disorder, New-Onset (Day 25) 1
    - MRSA Wound Infection (Day 26) 1
    - Muscle weakness-Right Sided (Day 1) 1
    - Dysphagia (Day 1) 1
    - Nausea (Day 22) 1
    - Thromboembolic Event (Day 15) 1
    - Arterial Thromboembolism (Day 26) 1

Case Distribution

	Glioblastoma		Metastasis		Meningioma			Other	Not Identified	Total
					Recurrent					
	Recurrent	Newly Diagnosed	Recurrent	Newly Diagnosed	WHO Grade 1	WHO Grade 2	WHO Grade 3			
Number Consented	78	14	46	20	5	9	5	10	11	198
Number Completing 30-Day Follow Up	57	14	28	12	4	7	3	8*	-	125

*7 Recurrent: (2) oligodendroglioma grade 2; (2) Hemangiopericytoma, grade 3; Atypical melanocytic neoplasm; Gliosarcoma, grade 4; Hemangioblastoma; 1 Newly Diagnosed: Oligodendroglioma, grade unknown

Summary of Adverse Events ≥ Grade 3 Organized by Tumor Type

Case #	Tumor Type	Days Post-Op	AE Term	AE Grade	Related to Surgery	Related to Radiation	Care Needed
146	Recurrent Astrocytoma Grade 3	22	Nausea	3	Possible	Possible	Medication
71	Recurrent GBM	0	Hemiparesis, Left	3	Possible	Possible	Non-Medication Therapy
84	Recurrent GBM	25	Seizure	3	Possible	Possible	Hospitalization
94	Recurrent GBM	15	Thromboembolic Event	3	Possible	-	Surgical Intervention
110	Recurrent GBM	1	Dysphagia	3	Definite	-	None
111	Recurrent GBM	1	Weakness, Right	3	Definite	-	None
184	Recurrent Oligodendroglioma	0	Transient Expressive Aphasia	3	Definite	-	Medication
35	Meningioma Grade 1	5	Intracranial Hemorrhage	4	Probable	-	Medical Intervention
311	Meningioma Grade 1	2	Cerebral Edema	3	Definite	Possible	Medication
101	Newly Diagnosed Metastasis	26	MRSA wound Infection	3	Definite	Possible	Surgical Intervention
151	Recurrent Hemangiopericytoma	26	Arterial Thromboembolism	3	Possible	Possible	Non-Medication Therapy

Conclusions

- GammaTile brachytherapy is emerging as an important radiation therapy option for primary and metastatic CNS neoplasms with placement of tiles after re-resection of a neoplasm or after initial resection as surgically-targeted radiation therapy (STaRT).
- The 30-day morbidity and readmission rates following tumor resection and GammaTile placement are similar to those previously reported for patients undergoing conventional craniotomy for resection of a neoplasm.
- The low 30-day adverse event rate (6.8%) and low readmission rate (1.4%) to date across 25 enrolling institutions support a highly favorable safety profile for GammaTile therapy.
- Study accrual is on-going.
- Future reports will help benchmark clinical outcomes of GammaTile therapy, provide comparisons to existing treatments, and facilitate future clinical trial design.

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