CLINICAL WHITE PAPER | BY DAVID BRACHMAN, MD

INTRACRANIAL NEOPLASMS: THE EVOLUTION OF RADIOTHERAPIES

CURRENT STANDARD OF CARE FOR BRAIN TUMORS

The current initial standard of care for aggressive brain tumors—whether they are primary brain tumors (ie, tumors that originate in the brain), or metastatic tumors from cancers that started outside of the brain—is resection. After surgery, a follow-up treatment, also referred to as adjuvant treatment, is often recommended to help eliminate any residual traces of the tumor.[1] In the case of brain tumors, more often than not, adjuvant therapy involves using radiation, in part because few chemotherapy agents reliably cross the blood brain barrier.[1]

Adjuvant radiation is used either alone or in combination with chemotherapy, and the most common method of radiation treatment is external beam radiation therapy (EBRT).[1,2] For EBRT, a large machine generates radiation beams and focuses them inward to travel through the skin, then through the skull, and finally, into the brain.[2] Radiation therapy including EBRT works by creating double-strand breaks in cellular DNA, which interferes with the reproductive integrity of the cells.[3] Radiation primarily impacts cells that are rapidly undergoing cellular division, which is why it is useful for arresting aggressive tumor development. However, it can also stop the normal cellular replication that takes place as part of the body's healing and repair process after surgery. For this reason, external beam radiation treatments are often delayed for 2 to 3 weeks or longer after a surgery.

The goal of EBRT, and all radiation therapy, is to deliver the highest-possible safe dose of radiation to achieve maximum efficacy while limiting radiation exposure to the normal tissues.

EBRT FOR BRAIN TUMORS

As noted above, postsurgical wound healing must occur prior to the initiation of EBRT, leaving a large window of time for unchecked tumor cell replication.[4,5] Additionally, EBRT regimens for primary brain tumors (ie, fractionated EBRT) are often time and resource intensive (typically requiring daily visits from Monday through Friday for 4 to 6 weeks), which poses a significant burden on these vulnerable patients and their caregivers.[3] With stereotactic radiosurgery (SRS), a type of EBRT, it is sometimes possible to truncate the treatment period to a total of 1 to 5 treatments. Involving multiple focused radiation beams, SRS is

used for both metastasis and for relatively small primary brain tumors with well-defined borders.[2] As with standard fractionated EBRT postsurgery, these treatments must also be delayed for a few weeks to allow for postsurgery wound healing. For primary brain tumors (gliomas, meningiomas, and similar tumors), adjuvant fractionated EBRT is administered to a limited region of brain; typically, the tumor bed plus a zone around the bed to encompass possible tumor spread (**FIGURE 1**). For the treatment of a single or a limited number of brain metastases (4 or fewer), SRS delivered in 1 to 5 treatments is often used.[3] When more than 4 brain metastases are present, whole-brain radiation therapy (WBRT), given daily over 2 to 4 weeks, is often recommended.[1]

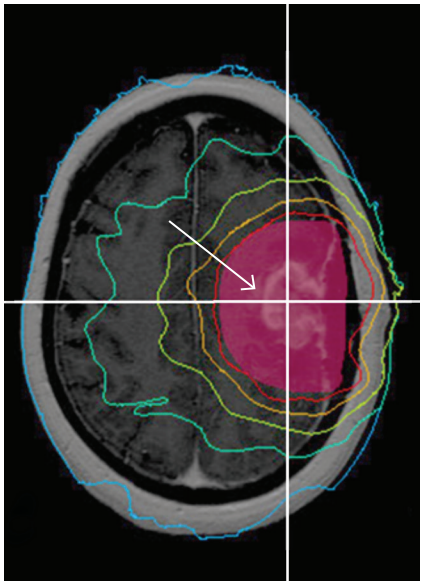

FIGURE 1: *A postoperative adjuvant EBRT treatment plan for a high-grade glioma. Note the surgical treatment bed (white arrow), zone of concern for traces of the residual tumor (red area), and distribution of the actual radiation dose falloff within healthy brain tissue (thin, colored lines).*

KEY TAKEAWAYS

- **The standard of care for aggressive brain tumors is resection.**[1]
- **Adjuvant therapy (chemotherapy or radiation) is recommended when surgery is unable to remove all traces of a tumor.**[1,3]
- **The most common method of adjuvant radiation treatment is fractionated EBRT.**[1,3]
  - **Radiation travels from outside of the body through the skull and into the brain, exposing healthy tissue.**
  - **EBRT typically involves a 2- to 3-week treatment delay to allow for postoperative wound healing, and the treatment regimen is time and resource intensive (typically requiring daily visits from Monday through Friday for 4 to 6 weeks).**[3]

RECURRENT BRAIN TUMORS AND THE UNMET CLINICAL NEED FOR A NEW POSTOPERATIVE ADJUVANT THERAPY

When an aggressive tumor returns, resection alone is not usually curative, but it can provide symptom relief, and the extent of resection correlates with the likelihood of longer-term control.[6] Thus, whenever feasible, recurrent brain tumors are treated by combining maximum safe surgical resection with an adjuvant therapy.[1] As noted previously, few effective chemotherapies cross the blood brain barrier, and even fewer are available for recurrent tumors.[1] Additionally, for many patients, repeating adjuvant EBRT is often not an option, as they received a maximum safe dose of EBRT during their initial treatment.[7] If EBRT is repeated, the radiation will pass through the same (or nearby) skin, skull, and normal brain tissue that were impacted previously. The risks of injury from radiation to healthy tissues increases with the repeated radiation dose and the total irradiated brain volume treated.[8]

Consequently, to keep the risk of injury from escalating, we must either lower the radiation dose and/or lower the volume of brain treated.[8] The problem is we know that lower treatment doses are potentially less effective, and minimizing the treatment volume can lead to missing tumor cells (**FIGURE 2A–C**). Since EBRT comes from the outside inward, it typically exposes a large volume of normal brain tissue in proportion to the actual area in need of treatment.[9] As volume has 3 dimensions (H x W x L), even a seemingly small increase in

any one of these measurements can lead to a large increase in the end volume. To avoid toxicity with EBRT, clinicians use treatments in the lower dose range of the highest safe doses.[1,8] These lower radiation doses are temporarily helpful in many cases, but rarely enough to produce reliable tumor control. Hence, there is a critical need for a new radiation paradigm for recurrent brain tumors.

Determining the precise treatment zone with postoperative imaging can be an additional challenge, and as mentioned previously, leaving the residual tumor cell replication unchecked for several weeks until the wound from the operation has healed is a suboptimal necessity of EBRT.[4,5,10] Thus, although many recurrent aggressive brain tumors may be technically resectable, surgery is frequently not offered at recurrence because: 1) resection alone is unlikely to remove all tumor cells, and 2) no repeat safe and effective adjuvant therapy has historically been available to prevent any tumor cells missed at surgery from regrowing.[11] For these reasons, effective re-treatment options are extremely limited, and there is no clearly established standard of care.[1,12]

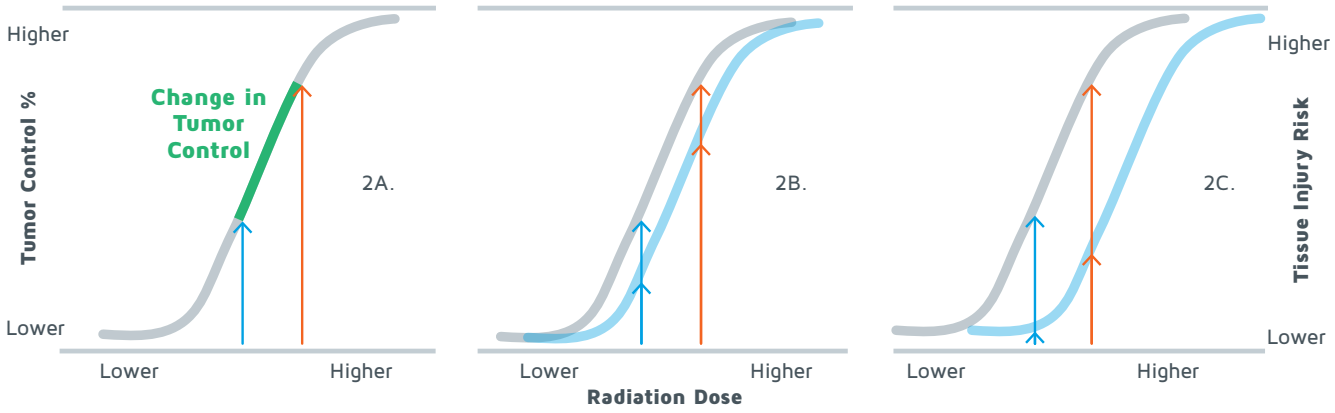

FIGURE 2A–C: ***A.*** *This radiation dose–response curve (gray line) illustrates how a relatively small change in the radiation dose can result in a steep increase or decrease in the percentage of neoplastic cells responding to treatment (blue arrow is lower dose; orange arrow is higher dose). Conversely, even a small decrease in the dose (blue arrow) can potentially lead to a steep decline in tumor control. With EBRT, doses are often decreased to avoid brain injury when repeat treatments are needed.* ***B.*** *When we add a curve (blue line) to gauge the impact on the normal tissue of doses used in repeat adjuvant EBRT, we get a set of curves, which illustrate that the likelihood of tumor control and the likelihood of tissue injury are not too far apart—a relatively unfavorable therapeutic outcome.* ***C.*** *As compared to repeat EBRT, treatment with GammaTile Therapy reduces the volume of tissue receiving potentially harmful doses of radiation, which shifts the tissue injury curve to right, creating the potential for a more favorable therapeutic outcome.*

KEY TAKEAWAYS

- **When possible, recurrent brain tumors are treated combining maximum safe surgical resection with an adjuvant therapy such as chemotherapy or radiation.**[1]
- **For many patients who would otherwise be good candidates, repeat surgery is not offered because repeat adjuvant EBRT is not an option, as they received their maximum safe dose of EBRT during their initial treatment.**[1,7,12]
  - **The risks of injury from radiation to healthy tissues increases with the repeated radiation dose and the total irradiated brain volume treated.**[8]
  - **To avoid toxicity from the interplay of an additional brain radiation dose and additional brain radiation volume, clinicians often need to use a less efficacious, reduced radiation dose in EBRT re-treatment.**[8]
  - **No routinely safe and effective repeat adjuvant therapy has historically been available.**[1,12]

THE UNFULFILLED PROMISE OF BRACHYTHERAPY IN BRAIN TUMOR TREATMENT

The term brachytherapy is derived from the Greek word for 'short,' brachy, which refers to the distance between the radiation source and the target area.[13] Brachytherapy is a specialized type of radiation therapy that involves placing an emitting radiation source, which is commonly a radioactive isotope, very close to either a tumor or adjacent tissue that is likely to harbor neoplastic cells.[14] It is used to deliver the highest-possible safe dose of radiation to the tumor site while minimizing a patient's overall radiation exposure.

Combining resection with adjuvant reirradiation via brachytherapy represents a theoretically attractive therapeutic option for several reasons. Early postresection initiation of radiation—when residual tumor burden is minimal—could produce a higher therapeutic ratio in rapidly proliferating tumors.[4,5] Brachytherapy using a low-energy (ie, short range) isotope exposes less normal tissue to radiation than EBRT techniques, and it may limit neurocognitive deficits.[9,15–17] Importantly, radiation source placement under intraoperative visualization also allows for more precise identification of the area at risk than the postoperative imaging utilized for EBRT treatment.[10]

Compared to EBRT treatments that come from the outside into the body, traveling through different healthy tissues and structures not affected by the tumor, brachytherapy offers distinct treatment advantages. **Brachytherapy enables enhanced dose control, as the dose conforms to the treatment area, and dose intensity, as the highest doses are at the site of the tumor bed**. In many ways, brachytherapy can be considered the ultimate form of conformal radiation therapy, and it functions best when delivered with specialized applicators that are specifically designed for each anatomic site or clinical circumstance.[14]

Brachytherapy employs several different isotopes, and plays a central role in the management of various tumor types, including prostate, skin, gynecologic, and breast cancers.[18,19]

While brachytherapy for the brain has demonstrated considerable efficacy against cancer cells, unfortunately, the isotopes used and the direct seed-to-tissue contact have resulted in severe complications due to the difficulty in avoiding toxicity and necrosis.[20] The clinical gain achieved has been directly offset by the adverse impact to the eloquent brain tissue.[20] Previous brachytherapy devices, in most cases, were not specifically designed for use in the brain.[20] Refinements for intracranial applications would require more precise, uniform radiation-source placement and some type of structural offset that would better protect healthy, eloquent brain tissue while delivering a targeted dose intensity to tumor cells.

KEY TAKEAWAYS

- **Brachytherapy is a specialized type of internal radiation therapy that plays a central role in the management of various tumor types, including prostate, skin, gynecologic, and breast cancers.**[18,19]
- **Historically, brachytherapy has not had significant success in the brain due to the eloquent nature of the tissue and the difficulty in avoiding toxicity and necrosis.**[20]
- **The dose control and dose intensity of brachytherapy are promising, but refinements for intracranial applications are needed.**

THE DRAWBACKS OF TRADITIONAL INTRACRANIAL BRACHYTHERAPY

Used primarily to treat high-grade gliomas, brachytherapy with iodine-125 (I-125) has historically demonstrated less than optimal outcomes due to its high complication rate, which is a result of seed placement variability, direct seed-to-tissue contact, and lack of dose control (**FIGURE 3**).[20] Intracranial seeds are most commonly used in high-grade gliomas, with studies frequently finding high rates of brain necrosis and reoperation, although poor outcomes have not been universal.[20–22] Consequently, intracranial brachytherapy with I-125 has mostly been relegated to salvage therapy for patients with highly aggressive brain tumors who are willing to risk the complications.[20]

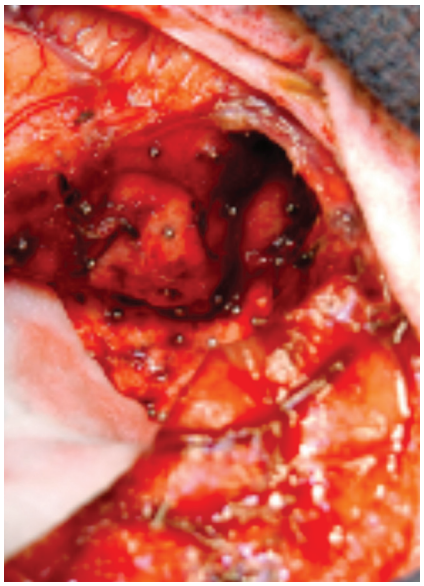

FIGURE 3: *This image depicts the traditional brachytherapy approach with seeds implanted directly into the brain tissue.[22] The variable seed spacing, and direct seed-to-brain contact, lead to inherently variable doses, which both underdose the tumor, and overdose the brain.[22]*

CS-131, A MORE IDEAL INTRACRANIAL ISOTOPE

In the early 2000s, a new seed isotope source, Cesium-131 (Cs-131), became commercially available. Cs-131 is a low-energy source of x-radiation with a markedly shorter half-life compared to I-125—9.7 days vs 60 days (**TABLE 1**). Initially utilized in prostate cancer, Cs-131 has now been investigated for intracranial use. It has a low energy that is similar to that of I-125 (30 keV for Cs-131 vs 28 keV for I-125), with a depth of penetration that matches up well with the requirement for a useful intracranial isotope. Notably, its shorter half-life is thought to offer significant advantages in treating tumors that have relatively short doubling times, such as recurrent intracranial neoplasms.[23] Another advantage is that it lessens the duration of exposure to family caregivers as compared to iodine.[24]

Cs-131 delivers a greater dose immediately after resection, when the tumor burden is at a minimum.[23] Specifically, the short half-life of Cs-131 means 88% of the therapeutic dose can be delivered within 30 days (vs approximately 200 with I-125).[23] In fact, more than half of the therapeutic dose of Cs-131 is delivered within the first 10 days after surgery, which helps prevent residual tumor cells from replicating.

TABLE 1: COMPARING CS-131 AND I-125[23]

	Half-life (days)	Time to deliver 88% of radiation dose (days)
Cs-131	**9.7**	**30**
I-125	**59.4**	**~200**

Only the tissue closest to the radiation source receives the highest levels of radiation, sparing nearby brain and other tissues.[9,16,22] It is postulated that the rapid, intense, intracranial dose delivery of Cs-131 enhances local control and improves efficacy.[22,23]

Cs-131 offers a high dose of radiation that is delivered to a localized area with a very steep dose fall-off that spares adjacent normal brain tissue. Cs-131 seeds have been used with traditional brachytherapy techniques in patients with both initial and recurrent brain metastases by the Cornell group.[25,26]

It is postulated that the rapid, intense, intracranial dose delivery of Cs-131 enhances local control and improves efficacy.[22,23]

Targeting is more localized with Cs-131 than it is with EBRT. EBRT affects a larger volume of the brain, increasing the risk for high toxicity rates and brain necrosis.[9,27] The dose necessary to control aggressive brain tumors is typically a minimum of 60 Gy, with the dual goals of fully treating the areas of concern and minimizing radiation exposure to adjacent healthy tissues. It is believed that with aggressive brain tumors, doses higher than 60 Gy may enable more reliable tumor control.[28] However, doses above 60 Gy have been shown to increase the risk of brain toxicity when combined with the volume of brain tissue treated, particularly with EBRT techniques.[26]

Brachytherapy with an internally placed, low-energy isotope like Cs-131 has been shown to expose a smaller volume of brain tissue to radiation than EBRT (**FIGURE 5**), and is able to achieve an increased local dose of 80 to 120 Gy.[25] As potentially useful as brachytherapy with Cs-131 seems, it is still necessary to overcome several of the current shortcomings of traditional brain brachytherapy techniques including issues of: 1) direct seed-to-brain contact, which can result in extremely high doses at the sites of contact, 2) the undesirable spacing variability inherent with the placement of individual seeds (**FIGURE 3**), and 3) the time-consuming nature of the traditional placement methods, often adding 30 minutes or more per case.[22,29,30] Thus, to safely take full advantage of the potential therapeutic benefits of brain brachytherapy, advances beyond just a better isotope are needed.

KEY TAKEAWAYS

- **Cs-131 is a low-energy source of x-radiation with a markedly shorter half-life than I-125.**[23]
  - **This shorter half-life is thought to offer significant advantages in treating tumors that have relatively short doubling times, such as recurrent intracranial neoplasms.**[23]
- **Brachytherapy with Cs-131 has been shown to expose a smaller volume of brain tissue to radiation than EBRT, *and* is able to achieve an increased local dose of 80 to 120 Gy compared to approximately 60 Gy with EBRT.**[9,25]

THE GENESIS OF GammaTile™ STaRT™: A NEW TREATMENT OPTION FOR PATIENTS WITH RECURRENT BRAIN TUMORS

A group of brain tumor specialists in Phoenix, Arizona, joined forces to create a new treatment option to address the critical, unmet need for a postsurgical adjuvant therapy for patients with recurrent gliomas, meningiomas, and metastasis. To overcome the drawbacks of previous adjuvant brain radiation treatment paradigms, the group developed a modular, permanently implanted collagen-based device. This device, the GammaTile, functions as a 3D spacer that optimizes interseed spacing while simultaneously preventing harmful direct seed contact with the brain. The collagen carrier is easily handled, and it facilitates rapid completion of the implant by allowing simultaneous placement of multiple seeds.

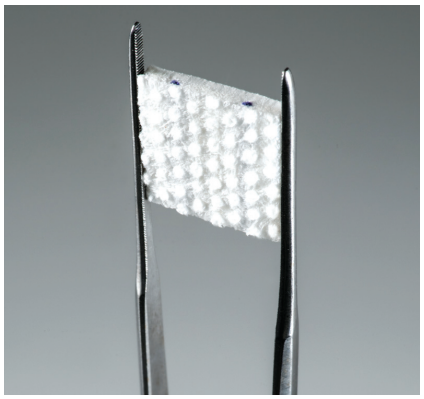

FIGURE 4: *Surgically targeted radiation therapy (STaRT) with GammaTile Therapy.*

THE RIGHT TIME

Fundamentally different from EBRT and traditional brain brachytherapy, GammaTile Therapy is a surgically targeted radiation therapy (STaRT) (**FIGURE 4**) that provides immediate, dose-intense treatment at the completion of resection. By getting a head STaRT on fighting the tumor, resection plus GammaTile Therapy extends recurrence-free survival with minimal complications, reduced patient burden, and assured compliance.[31,32]

THE RIGHT TREATMENT AND DOSE INTENSITY

GammaTile Therapy uses Cs-131 to deliver the maximum dose at the treatment site while minimizing exposure to healthy tissue. With the GammaTile carrier design and seed strength, the radiation dose in the first few millimeters of the operative bed (the site of greatest concern for tumor residual) is 80 to 120 Gy. This dose is 1.3 to 2 times greater than the 60 Gy typically achieved by fractionated EBRT. The shorter range afforded by this low-energy brachytherapy isotope limits high-dose radiation to uninvolved tissues to a greater extent than possible with intraoperative x-ray treatments or EBRT.[9,15,29,33]

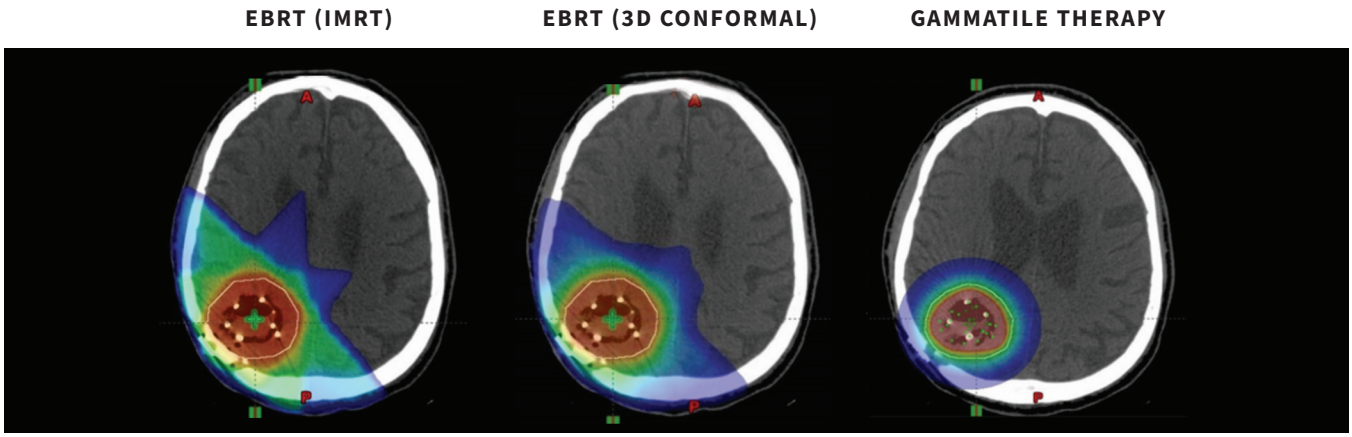

FIGURE 5: *Representative distribution and intensity of radiation doses with 3 different radiation modalities: EBRT with intensity-modulated radiation therapy (IMRT) treatment, EBRT with 3D conformal treatment, and GammaTile Therapy. Note that GammaTile Therapy delivers more localized radiation, both in overall extent (blue-green is lower radiation doses) and in the areas exposed to higher dose radiation (red-orange).*

Placement by the surgeon under direct operative visualization virtually ensures treatment to the area(s) that is at the highest risk for recurrence.

THE RIGHT PLACE

Keeping the radiation dose in the right place is as critical as keeping the radiation source from direct contact with the brain tissue. Both of these objectives are achieved with the tissue-sparing, patented, bioresorbable, conformable, 3D collagen tile that comprises GammaTile Therapy. Placement by the surgeon under direct operative visualization virtually ensures treatment to the area(s) that is at the highest risk for recurrence.

GammaTile Therapy enforces uniform radiation-source spacing, both within a single tile of 14 U (2 cm x 2 cm x 4 mm in thickness) and between multiple tiles. This enables rapid, accurate placement of the tile(s) and a predictable radiation dose in the therapeutic range while reducing local hot and cold spots. With the GammaTile collagen carrier, source migration postimplant is minimal.[34] In addition, because of the shorter half-life of Cs-131, any dose differences observed from source movement should have a clinically insignificant impact compared to the dosimetric impact seen with I-125.[35]

KEY TAKEAWAYS

- **Fundamentally different from EBRT and traditional brain brachytherapy, GammaTile Therapy is a surgically targeted radiation therapy (STaRT) that provides immediate, dose-intense treatment at the completion of resection.**
  - **The 3D spacer optimizes interseed spacing while simultaneously preventing harmful direct seed contact with the brain.**
  - **Cs-131 delivers the maximum dose at the treatment site while minimizing exposure to healthy tissue.**[36]
  - **Uniform radiation-source spacing enables rapid, accurate placement, delivering a predictable radiation dose in the therapeutic range while reducing local hot and cold spots.**
- **By getting a head STaRT on fighting the tumor, resection plus GammaTile Therapy extends recurrence-free survival with minimal complications, reduced patient burden, and assured compliance.**[31,32]

CONCLUSION

GammaTile Therapy fulfills the promise of brachytherapy for treatment of recurrent brain tumors in a whole new way, offering significant advantages to patients, clinicians, and hospitals. In addition to its excellent efficacy and safety profile, GammaTile Therapy advances the current standard of care for these vulnerable patients by extending their recurrence-free survival and helping preserve their quality of life.[33,34] GammaTile Therapy is a viable, effective treatment option for individuals with recurrent brain tumors, especially those who have failed treatment with EBRT or for whom further EBRT is contraindicated.

AUTHOR | DAVID BRACHMAN, MD, FACRO

David G. Brachman, MD, is a nationally recognized radiation oncologist, researcher, and author with more than 50 peer-reviewed publications and extensive neurooncology clinical expertise. Dr Brachman recently retired from practice after more than 15 years as the chairman and medical director of the Radiation Oncology department and codirector of the GammaKnife program at St. Joseph's Hospital and Medical Center and Barrow Neurological Institute in Phoenix, Arizona. His considerable radiation oncology background includes being named a professor of Radiation Oncology at the University of Arizona College of Medicine-Phoenix and more than 15 years serving on the NCI-sponsored Radiation Therapy Oncology Group CNS Tumor Steering Committee. Dr. Brachman was instrumental in the development of GammaTile Therapy and is cofounder and chief technology officer of GT Medical Technologies.

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers. Version 1.2018.
2. External beam radiation therapy for cancer. National Cancer Institute Web site. https://www.cancer.gov/about-cancer/treatment/types/radiation-therapy/external-beam. Published May 1, 2018. Accessed July 9, 2018.
3. Radiation therapy basics. American Cancer Society Web site. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/radiation/basics.html. Updated July 2, 2018. Accessed August 25, 2018.
4. Burnet NG, Jena R, Jefferies SJ, et al. Mathematical modelling of survival of glioblastoma patients suggests a role for radiotherapy dose escalation and predicts poorer outcome after delay to start treatment. *Clin Oncol (R Coll Radiol)*. 2006;18:93-103.
5. Iorio-Morin C, Masson-Cote L, Ezahr Y, et al. Early Gamma Knife stereotactic radiosurgery to the tumor bed of resected brain metastasis for improved local control. *J Neurosurg*. 2014;121 Suppl:69-74.
6. Aizer AA, Bi WL, Kandola MS, et al. Extent of resection and overall survival for patients with atypical and malignant meningioma. *Cancer*. 2015;121:4376-4381.
7. Shi W, Scannell Bryan M, Gilbert MR, et al. Investigating the effect of reirradiation or systemic therapy in patients with glioblastoma after tumor progression: a secondary analysis of NRG Oncology/Radiation Therapy Oncology Group Trial 0525. *Int J Radiat Oncol Biol Phys.* 2018;100(1):38-44.
8. Stewart FA. Re-treatment after full-course radiotherapy: is it a viable option? *Acta Oncol*. 1999;38:855-862.
9. Purdy JA. Dose to normal tissues outside the radiation therapy patient's treated volume: a review of different radiation therapy techniques. *Health Phys*. 2008;95:666-676.
10. Lecchi M, Fossati P, Elisei F, et al. Current concepts on imaging in radiotherapy. *Eur J Nucl Med Mol Imaging*. 2008;35:821-837.
11. Lu VM, Jue TR, McDonald KL, Rovin RA. The survival effect of repeat surgery at glioblastoma recurrence and its trend: a systematic review and meta-analysis. *World Neurosurg*. 2018;115:453-459.e3.
12. Ammirati M, Cobbs CS, Linskey ME, et al. The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2010;96(1):85-96.
13. A brief essay on the introduction of brachytherapy. American Brachytherapy Society Web site. https://www.americanbrachytherapy.org/aboutbrachytherapy/history.cfm. Accessed July 9, 2018.
14. Petereit DG, Frank SJ, Viswanathan AN, et al. Brachytherapy: where has it gone? *J Clin Oncol*. 2015;33(9):980-982.
15. Ruge MI, Kocher M, Maarouf M, et al. Comparison of stereotactic brachytherapy (125 iodine seeds) with stereotactic radiosurgery (LINAC) for the treatment of singular cerebral metastases. *Strahlenther Onkol*. 2011;187:7-14.
16. Pham A, Yondorf MZ, Parashar B, et al. Neurocognitive function and quality of life in patients with newly diagnosed brain metastasis after treatment with intra-operative cesium-131 brachytherapy: a prospective trial. *J Neurooncol*. 2016;127:63-71.
17. Rogers LR, Rock JP, Sills AK, et al. Results of a phase II trial of the GliaSite radiation therapy system for the treatment of newly diagnosed, resected single brain metastases. *J Neurosurg*. 2006;105:375-384.
18. Skowronek J. Current status of brachytherapy in cancer treatment - short overview. *J Contemp Brachytherapy.* 2017;9(6):581-589.

19. Lukens JN, Gamez M, Hu K, Harrison LB. Modern brachytherapy. *Semin Oncol*. 2014;41(6):831-847.

20. Combs SE, Debus J, Schulz-Ertner D. Radiotherapeutic alternatives for previously irradiated recurrent gliomas. *BMC Cancer*. 2007;(7)167.

21. Magill ST, Lau D, Raleigh DR, Sneed PK, Fogh SE, McDermott MW. Surgical resection and interstitial iodine-125 brachytherapy for high-grade meningiomas: a 25-year series. *Neurosurgery*. 2017;80(3):409-416.

22. Dagnew E, Kanski J, McDermott MW, et al. Management of newly diagnosed single brain metastasis using resection and permanent iodine-125 seeds without initial whole-brain radiotherapy: a two institution experience. *Neurosurg Focus*. 2007;22(3):E3

23. Armpilia CI, Dale RG, Coles IP, Jones B, Antipas V. The determination of radiobiologically optimized half-lives for radionuclides used in permanent brachytherapy implants. *Int J Radiat Oncol Biol Phys*. 2003;55(2):378-385.

24. Parashar B, Wernicke AG, Pavese A, et al. Cesium-131 permanent seed brachytherapy: dosimetric evaluation and radiation exposure to surgeons, radiation oncologists, and staff. *Brachytherapy*. 2011;10:508-513.

25. Wernicke AG, Yondorf MZ, Peng L, et al. Phase I/II study of resection and intraoperative cesium-131 radioisotope brachytherapy in patients with newly diagnosed brain metastases. *J Neurosurg*. 2014;121(2):338-348.

26. Wernicke AG, Smith AW, Taube S, et al. Cesium-131 brachytherapy for recurrent brain metastases: durable salvage treatment for previously irradiated metastatic disease. *J Neurosurg*. 2017;126(4):1212-1219.

27. Pinnaduwage D., Youssef E., Sorensen S., Srivastava S., Yan X., Brachman D. Dosimetric impact of radioisotope type on permanent brain seed implants. *Medical Physics*. 2017;44(6):3146.

28. Nguyen D, Rwigema JC, Victoria Y, et al. Feasibility of extreme dose escalation for glioblastoma multiforme using 4π radiotherapy. *Radiat Oncol*. 2014; 9:239.

29. Chiu-Tsao ST, Napoli JJ, Davis SD, et al. Dosimetry for 131Cs and 125I seeds in solid water phantom using radiochromic EBT film. *Appl Radiat Isot*. 2014;92:102-114.

30. Ware ML, Larson DA, Sneed PK, et al. Surgical resection and permanent brachytherapy for recurrent atypical and malignant meningioma. *Neurosurgery*. 2004;54:55-63.

31. Brachman DG, Youssef EY, Dardis CJ, et al. Resection and permanent intracranial brachytherapy using modular, biocompatible cesium-131 implants: results in 20 recurrent previously irradiated meningiomas. *J Neurosurg*. In press.

32. Data on file, GT Medical Technologies, Inc.

33. Schueller P, Palkovic S, Moustakis C, et al. Clinical results and isodose planning of neuronavigation-guided intraoperative radiotherapy (IORT) in 77 brain tumor patients: adequate target volume coverage improves results. *Rev Cancer (Madrid)*. 22(extra):58.

34. Pinnaduwage D. Dosimetric impact of Cesium 131 seed migration in collagen carrier brain brachytherapy implants. Paper to be presented at: 2018 ASTRO Annual Meeting; October 21-24, 2018; San Antonio, TX.

35. Pinnaduwage D, Sorensen S, Youssef E, et al. Dosimetric impact of source migration and decay based on radioisotope type in collagen carrier brain brachytherapy implants. *Medical Physics*. 2018;45(6):e244.

36. Nedialkova L, Sabbas A, Trichter S, et al. Dosimetric comparison of Cs-131 versus I-125 intraoperative brachytherapy for patients with resected brain metastasis renders Cs-131 more sparing of normal brain tissue: clinical relevance for prevention of radiation necrosis from a prospective trial. *Int J Radiat Oncol Biol Phys*. 2013;87:S755-S756.

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