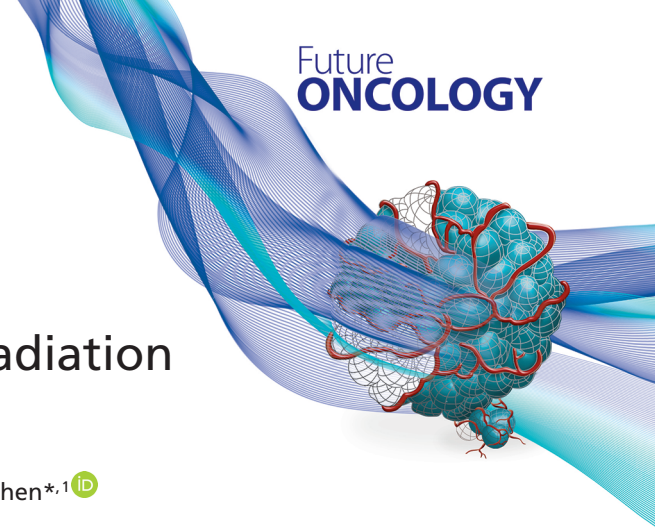
Review

For reprint orders, please contact: reprints@futuremedicine.com



GammaTile®: Surgically targeted radiation therapy for glioblastomas

Dominic J Gessler[1], Clara Ferreira[2], Kathryn Dusenbery[2] & Clark C Chen*[,1]

[1]Department of Neurosurgery, University of Minnesota, Minneapolis, MN 55455, USA

[2]Department of Radiation Oncology, University of Minnesota, MN 55455, USA

*Author for correspondence: Tel.: +1 612 624 1207; Fax: +1 612 624 0644; cchen@umn.edu

Glioblastoma is the most common primary malignant neoplasm of the central nervous system in adults. Standard of care is resection followed by chemo-radiation therapy. Despite this aggressive approach, >80% of glioblastomas recur in proximity to the resection cavity. Brachytherapy is an attractive strategy for improving local control. GammaTile® is a newly US FDA-cleared device which incorporates ^{131}Cs radiation emitting seeds in a resorbable collagen-based carrier tile for surgically targeted radiation therapy to achieve highly conformal radiation at the time of surgery. Embedding encapsulated ^{131}Cs radiation emitter seeds in collagen-based tiles significantly lowers the technical barriers associated with traditional brachytherapy. In this review, we highlight the potential of surgically targeted radiation therapy and the currently available data for this novel approach.

First draft submitted: 29 May 2020; Accepted for publication: 17 June 2020; Published online: 3 July 2020

Keywords: brachytherapy • central nervous system • GammaTile • glioblastoma • radiation therapy • STaRT

Across adult and pediatric populations, malignant neoplasms are associated with substantial morbidity and mortality [1]. Although progress has been made in the treatment of select cancers, glioblastoma remains an exception [2]. Glioblastoma is the most common malignant primary brain tumor in adults, with an incidence rate of 3.2/100,000 [3]. The mainstay of therapy is a multimodal strategy of neurosurgical resection followed by administration of concurrent chemoradiation therapy 4–8 weeks after initial surgery [2,4,5]. More recently, tumor treating fields has emerged as a US FDA-approved treatment option in combination with chemoradiation for newly diagnosed glioblastomas or in the recurrent setting. The expected overall survival has remained 14–21 months over the past several decades [5,6].

Notably, most glioblastoma progression or recurrence occurs locally, in regions immediately adjacent to the resection cavity [7–9]. While glioblastomas often appear as a discrete entity on MRI, surgical and autopsy studies reveal microscopic tumor cells extending at least 2 cm away from the visible tumor [7,9,10]. The density of these microscopic cells is greatest near the resection cavity and 50–70% of glioblastoma patients suffer tumor growth adjacent to the resection cavity during the 4–8-week recovery period [11–13], which prognosticates poor survival [14]. Not unexpectedly, the majority of available studies suggest a delay in initiation of radiation therapy beyond this recovery period is associated with poorer survival outcomes [14,15]. In patients who initiate concurrent chemo- and radiation- therapy within the 4–8-week recovery period, >80% of recurrences occur adjacent to the resection cavity [16,17]. These results suggest that therapeutic platforms that augment local control have the potential to improve clinical outcomes. Recognizing the importance of local control in glioblastoma treatment, NRG-BN001 is a multi-institutional clinical trial that aims to determine whether radiation dose escalation targeting regions surrounding the resection cavity improves survival when combined with temozolomide treatment.

Brachytherapy emerged as an attractive option in this context. Brachytherapy refers to the implantation of interstitial or intracavitary radioactive sources adjacent to the target tissue [18,19]. The notion of brachytherapy was proposed only a few years after the initial discovery of natural radioactivity over 100 years ago [20] and predates other therapeutic radiation techniques. Brachytherapy continues to be a major therapeutic platform for prostate, breast, gynecologic, ocular and other non-CNS neoplasms [21–23]. A key lesson learned during this century of brachytherapy development is an appreciation for the critical importance of the physical properties of the radiation

source. Consequently, radioactivity emitting sources utilized in the past have mainly been replaced by safer and more efficacious isotopes, in other words, capable of delivering a more targeted dose and exhibiting shorter half-lives [24–26].

Pertaining to brachytherapy for CNS tumors, the first application of brachytherapy dates back to 1936, when radon was used as treatment for an intrasellar tumor [27]. Later, other sources such as iridium-192 (^{192}Ir), gold-198 (^{198}Au) and iodine-125 (^{125}I) were tested, with ^{125}I becoming the most commonly utilized isotope in recent years [28,29]. However, the aggregate of available studies suggests that ^{125}I is associated with increased risk for radiation necrosis, which has been hypothesized to be related to a combination of the long half-life time of ^{125}I and cavity dynamics [9,30–34].

In recent years, cesium-131 (^{131}Cs) has emerged as a promising isotope for brachytherapy for CNS tumors. While ^{131}Cs shares many characteristics with ^{125}I, the half-life of ^{131}Cs is significantly shorter than that of ^{125}I (9.7 vs 59.4 days, respectively). This shortened half-life translates into improved ease of use [34], improved efficacy [35], as well as a superior safety profile [24,36].

There is long-standing interest in brachytherapy as a means of improving local control for patients afflicted with glioblastoma [37]. Despite promising institutional experiences [38], interest in brachytherapy waned after failure of two randomized controlled trials to demonstrate improved survival after ^{125}I brachytherapy [39,40]. While these studies failed to meet primary survival end points, there were nevertheless signals of efficacy. For instance, in the Laperriere study [39], a "tail" of longer-term survivors was noted in the ^{125}I brachytherapy treated arm, a finding reminiscent of the landmark temozolomide trial and recent immunotherapy trials [6,41]; this tail was not observed in the comparative arm. Moreover, improved survival was noted in the Brain Tumor Cooperative Group, with an approximate 1-month survival difference that did not reach statistical significance ($p = 0.101$) [40]. It should be noted that FDA clearances of carmustine wafers and temozolomide were based on survival differences of similar magnitude [42]. Moreover, in a separate study, Laperriere *et al.* examined clinical specimens obtained after ^{125}I brachytherapy and showed decreased cellularity and increased necrosis in these samples relative to samples from the comparative arm [43], suggesting brachytherapy contributed to improved local control.

In addition to these observations, there have been two developments that fueled a resurgence of interest in brachytherapy. First, the efficacy of concurrent temozolomide therapy raises the possibility that the addition of brachytherapy would further amplify efficacy, a possibility supported by two recently published case series [13,44]. Second, the advent of GammaTile® (GT), a device with ^{131}Cs radiation emitting seeds embedded in a resorbable collagen-based carrier tile has significantly lowered the technical barrier to radiation planning and surgical application.

Emerging data continues to demonstrate a favorable efficacy and safety profile of GT, described generically as surgically targeted radiation therapy (STaRT), against a spectrum of CNS tumors, including recurrent meningiomas [45], high grade gliomas [13] and brain metastases (Table 1) [18,46–48]. Here, we review the technical specifications of STaRT, describe our preliminary clinical experiences and discuss opportunities and limitations pertaining to clinical translation of STaRT as a glioblastoma therapy.

GammaTile®

GT is an FDA-cleared brachytherapy platform where titanium encapsulated ^{131}Cs seeds (Model CS-1, Rev. 2, IsoRay Medical Inc., WA, USA) are embedded in a resorbable collagen-based matrix (Saturable DuraGen Matrix, Integra Lifesciences, NJ, USA) tile (described as STaRT), providing a more modular system than previously available (Figure 1). GT is approved as treatment for both newly diagnosed malignant brain tumors and recurrent brain tumors irrespective of histology. A single tile measures 2 cm × 2 cm and contains four radioactive ^{131}Cs seeds with a half-life time of 9.7 days and mean photon energy of 30.4 KeV [50,51]. The modular nature, the pliability and tissue adherent collagen matrix maximizes likelihood of conformal radiation delivery, facilitates dosimetric planning and expedites surgical implantation. The tissue offset of 3 mm provided by the tile dimensions reduces the likelihood of focal necrosis around the sources. The source delivers a low dose rate, which, when combined with the short half-life, affords a favorable safety profile. GT delivers 120–150 Gy at the cavity surface and maintains 60–80 Gy at 5 mm depth, exceeding the standard dose of external beam radiation therapy (EBRT) by 1.5-twofold [45,46].

Table 1. Studies evaluating permanent ^{131}Cs brachytherapy in brain neoplasms.

Study	Year	# patients	Tumor	Local FFP	Distant FFP	Median OS	1-Year OS	Complications (total %)	Ref.
Wernicke *et al.*	2014	24	Brain metastasis	93.8% (1 year)	48.4% (1 year)	9.9 months	50%	CSF leak, infection, seizure (12.5%)	[18]
Pham *et al.*	2015	24	Brain metastasis	†	†	†	†	†	[49]
Wernicke *et al.*	2017	42	Brain metastasis	89% (1 year)	52% (1 year)	15.1 months	58%	Seizure, infection, CSF leak (26%)	[47]
Wernicke *et al.*	2017	13	Brain metastasis	83.3% (1 year)	46.7% (1 year)	7.7 months	24.7%	Infection, pseudomeningocele, seizure, asymptomatic radionecrosis (46%)	[48]
Brachman *et al.*	2019	19	Recurrent meningioma	Not reached‡	n/a	26 months	Not reported	Alopecia, seizure, radionecrosis, hygroma, infection (36%)	[45]
Brachman *et al.*	2019	74	Previously radiated brain tumor	Reported as local control§	Not reported	n/a	n/a	Infection, CSF leak, hematoma, shunt placement, coma, radionecrosis (17%)	[46]

†Reported in Wernicke *et al.* (2017) [47].
‡90% local control with 15.4 months median follow-up.
§Median follow-up of 13.4 months, median local control for high grade glioma (n = 40) was 12 months; median local control for recurrent meningioma (n = 23) was 48.5 months; median local control for brain metastasis (n = 12) was not reached.
CSF: Cerebrospinal fluid; FFP: Freedom from progression; n/a: Not applicable; OS: Overall survival.

10.2217/fon-2020-0558

Figure 1. Shown is a 20 mm × 20 mm × 4 mm GammaTile® with ^{131}Cs seeds (encircled in blue).
GT: GammaTile®.
Image courtesy of GT Medical Technologies (www.gtmedtech.com).

Advantages of GT

The novelty of GT is in its design, which has the following advantages.

- Embedding ^{131}Cs (half-life of 9.7 days) within a bioresorbable collagen matrix tile (described as carrier tile brachytherapy or STaRT) eliminates the need for subsequent surgical removal, which contributes to improved quality of life for the patients [49]. The use of a resorbable matrix ensures minimal intracranial residue after implant.
- ^{131}Cs, which is considered low-dose rate brachytherapy, has a better adverse effect profile than other commonly used isotopes, such as iodine-125 (^{125}I) [52].
- The carrier material functions as a spacer and implanted compensator and avoids direct contact of the ^{131}Cs seeds with the brain parenchyma while the seeds are active, potentially preventing harmful interactions and reducing the risk of necrosis. The 3 mm of tissue offset provides a clinically useful dose attenuation as a direct result of the inverse square law [53].
- From a neurosurgical perspective, implant of STaRT is akin to the use of other resorbable collagen matrices routinely implanted during surgery [54]. As such, GT implant does not require modification of routine surgical maneuvers or lengthen surgical duration.
- The design and the characteristic adherence of the collagen matrix which makes up the carrier tile, minimizes seed migration after implantation to maintain inter-source spacing after closure. As such, the design affords more uniform coverage of the target area [55].
- The collagen carrier tile remains intact for the duration of approximately 6 weeks or more (equal to or greater than 4 half-lives of ^{131}Cs) and holds the resection cavity in a fixed configuration. Resection cavity contraction could lead to overlapping of traditionally used individual or Tyvek suture enclosed radioactive seeds. Such overlap increases the risk for brachytherapy morbidity, including radiation necrosis. The reduced risk for resection cavity contraction minimizes the risk for such consequent dose inhomogeneity [34].
- STaRT circumvents any delay between surgical resection and radiation therapy. Typically, a delay of 4–8 weeks between neurosurgical resection and the initiation of EBRT is anticipated in order to allow for surgical wound healing. There are select centers that initiate therapy prior to 4 weeks postoperatively. However, some delay in

chemoradiation after surgery is universal. Implantation of STaRT bypasses this delay to initiate adjuvant RT at the time of surgery.

- EBRT requires patient immobilization through face mask application. Some patients experience claustrophobia in this context; the use of STaRT eliminates this risk while ensuring 100% patient compliance with their radiation treatments.
- STaRT decreases the burden on the patient and to the healthcare system. Daily visits to the hospital are required for EBRT, which compromises the quality of life for the patient and increases the burden on the healthcare system. STaRT eliminates the need for daily visits. In the face of a pandemic, such as the one currently challenging healthcare delivery, access to cancer surgery is still vital [56]; GT placement eliminates the need for up to 30 or more visits to healthcare facilities for radiation therapy (RT), reducing this exposure risk to a vulnerable population.
- Cost-effective modeling suggests that GT may be more cost effective than EBRT for the healthcare system [57].
- There is no requirement for expensive equipment or lengthy training. Precise targeting is accomplished through visualization of the surgical bed and placing the tiles typically takes a few minutes, so there is no steep learning curve.
- In EBRT, the radiation beam must travel through healthy tissue, which carries the potential to harm non-tumorous tissue. STaRT is localized to limit radiation delivery to the tumor affected parenchyma [53]. This localized delivery reduces possible side effects and neurocognitive decline associated with EBRT [18]. Also, STaRT minimizes the likelihood of treatment related hair loss, which occurs after EBRT.

Clinical experience

Candidates for STaRT meet with both the treating radiation oncologist and neurosurgeon. Radiation safety precautions are reviewed by the medical physicist with the patient prior to the surgery. The number of tiles to be implanted is determined based on the anticipated postoperative surface contours of the tumor bed. The number of tiles is then custom-ordered and is available within a week of request. The tiles are received by the radiation oncology department and handled in accordance to institutional policy. On the day of surgery, the tiles are brought to the operating room by the medical physicist, who performs radiation safety checks throughout the implantation process. In our institution, maximum safe resection of tumor is verified through an intra-operative MRI before STaRT. It should be noted that intra-operative MRI is not required for STaRT. After maximal resection, the collaborating radiation oncologist scrubs in to sterilely unpack and prepare the STaRT implant, which is then handed to the surgeon. Tiles are placed into the resection cavity under microscope or loupe magnification. Most implantations take two minutes. Even in large resection cavities requiring a dozen or more tiles the implantation has been completed within five minutes. A thin cut head computerized tomography (CT) and MRI are performed in the postoperative setting to provide the basis for dosimetric calculations (Figure 2). At the completion of the cranial repair, no special precaution is required of nursing staff during the patient's hospitalization since native cranium is able to block the emission of STaRT implant to exposure levels compatible with outpatient discharge (typically considered to be less than 6mRm/h at 1 m [58]). These limited levels of exposure compare favorably to the NCRP dose limit recommendations assuring safe levels of exposure to caregivers and medical personnel. In our practice, STaRT has been well tolerated and patients are discharged home on postoperative day 1 or 2.

Our most common use of STaRT has been in the recurrent glioblastoma setting. Many of these patients had several previous craniotomies and underwent multiple rounds of therapies, including radiation and bevacizumab. A significant portion of our patients was treated with high-dose corticosteroid immediately prior to the resection. Despite the anticipated heightened risk for wound related complications in this population, surgical resections with STaRT implantations have been associated with an excellent safety profile. A dedicated report to describe our experience will be presented elsewhere.

Limitations in clinical translation as a glioblastoma therapeutic

While the rapid dose falloff of ^{131}Cs-based STaRT increases the safety profile in terms of wound healing and radiation induced neurological morbidities, there are limitations in terms of treatment for the microscopic tumor cells that extend beyond 2 cm of the resection cavity where STaRT is implanted. Ultimately, while STaRT affords an increased likelihood of local control, meaningful improvements in clinical outcomes requires synergy with other forms of adjuvant therapy [59,60].

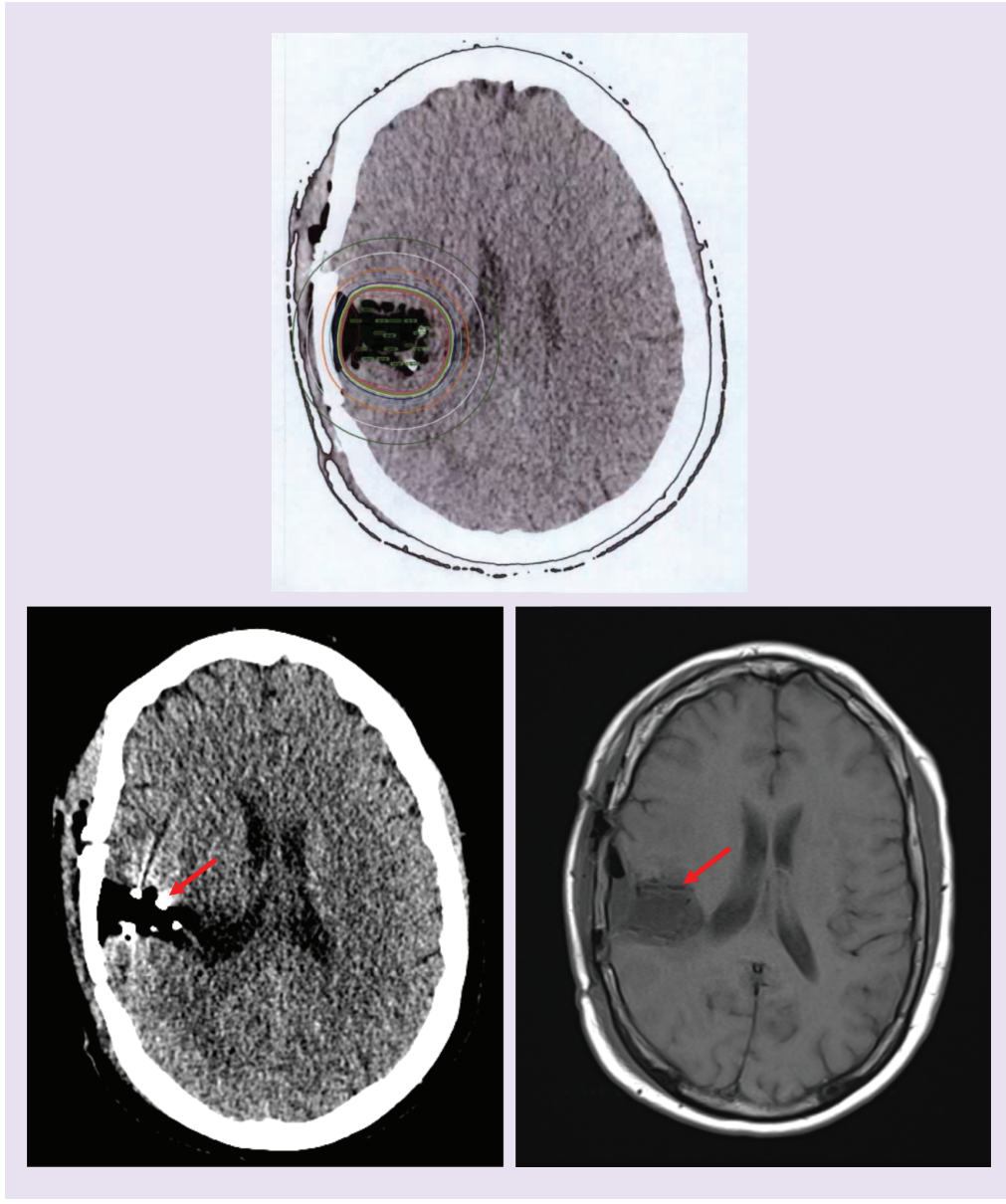


Figure 2. Head CT scan showing radiation dosage plan (top), computed tomography (bottom, left) and MRI (bottom, right) showing GammaTiles® placed after tumor resection. Arrows indicate the encapsulated ^{131}Cs seeds (left) and GT (right).
GT: GammaTile®.

To maximize the probability of efficacy, gross total resection (or near gross total resection) will be required, given tumor cells more than 5–8 mm distant to the resection cavity where STaRT is implanted are unlikely to benefit from this therapy. The availability of intra-operative MRI and 5-aminolevulinic acid may facilitate maximal surgical resection and facilitate STaRT efficacy in this context. Initiation or resumption of postoperative adjuvant systemic treatment can be undertaken as soon as medically cleared.

The available literature suggests that a subset of glioblastoma patients suffered from microscopic tumor infiltration into the brainstem. These patients exhibit poor survival [61] and are unlikely to meaningfully benefit from treatments aimed to boost local control.

When applied in the newly diagnosed setting, the safety of combining STaRT with the standard-of-care temozolomide/EBRT remains an unresolved matter (Tables 2 & 3) [62,63]. Thoughtful safety studies involving dose titration of STaRT are warranted in this regard. One possible approach would be to deliver the typical EBRT

Table 2. GammaTile® clinical trials.

ClinicalTrial.gov	GT Clinical Trial	Status
NCT03088579	Intraoperative brachytherapy for central nervous system lesions: a validation study of a radioactive seed loading device	Unknown
NCT04365374	SRS compared with collagen tile brachytherapy	Ongoing

GT: GammaTile®; SRS: Stereotactic radiosurgery.

Table 3. Studies combining brachytherapy with other standard of care treatment.

Study	Year	# patients	Tumor	Treatment	Median OS	PFS	Complications (total %)	Ref.
Chen *et al.*	2007	18	Newly diagnosed GBM†	Resection, ^{125}I BT and postoperative RT	28.5 months	14.25 months	Study terminated early due to high toxicity, radionecrosis, intracranial hemorrhage, infection, deep vein thrombosis (61%)	[62]
Waters *et al.*	2013	11	Newly diagnosed GBM	Resection, GliaSite (^{125}I) or MammoSite (^{192}Ir), postoperative radiation therapy and temozolomide	15.6 months	10 months	Seizure, reversible hemiparesis (18%)	[13]
Archavlis *et al.*	2014	17	Recurrent GBM	Reresection with 5-ALA, HDR BT (^{192}Ir), temozolomide	9 months	7 months	Thrombocytopenia, leukopenia, increased LFTs, infection, radionecrosis (35%)	[63]

†Formal pre-operative dose planning was not feasible.
BT: Brachytherapy; GBM: Glioblastoma; RT: Radiationtherapy; PFS: Progression-free survival, 5-ALA: 5-aminolevulinic acid; HDR: High-dose rate; LFT: Liver function test; ^{192}Ir: Iridum-192; OS: Overall survival.

'boost' treatment via STaRT immediately at the time of resection such that 90% of the boost dose would be delivered to the area at greatest risk of harboring residual disease, prior to initiation of wider field EBRT treatments. This approach offers the advantages of immediate treatment, a more condensed treatment time frame and fewer clinical visits. Moreover, it allows potential for dose escalation in the treatment of radio-resistant glioblastomas.

Future perspective

In many non-CNS tumors, brachytherapy has improved disease control and improved clinical outcomes. Thoughtful application of brachytherapy to CNS tumors is likely to produce similar results. The new GT platform which utilizes modular collagen-based carrier tiles to maintain spacing and provide a tissue offset of ^{131}Cs brachytherapy seeds, holds great potential in this regard. The modulatory properties lower technical barriers for clinical application and allow for more accurate coverage. The ^{131}Cs source and the offset affords a favorable safety profile and rapid dose tapering, minimizing risk for adverse events such as radiation necrosis and wound compromise. At the same time, cancers with tumor cells beyond the range of STaRT delivery will require integration of supplementary therapy. Safety of STaRT in the context of standard EBRT warrants consideration as an upfront treatment.

Acknowledgments

GT Medical Technologies (AZ, USA) provided technical details included in this article.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Background

- Most glioblastoma progression or recurrence occurs locally, in regions immediately adjacent to the resection cavity.
- CNS brachytherapy holds promise for minimizing the risk of local recurrence.
- ^{131}Cs is superior to ^{125}I in biological efficacy and side effect profile.

GammaTile®

- GammaTile® consists of ^{131}Cs seeds embedded in a resorbable collagen-based matrix tile. This device is US FDA approved for newly diagnosed malignant brain tumors and recurrent brain tumors. It is described generically as surgically targeted radiation therapy (STaRT).
- STaRT improves radiation dose delivery and safety due to its modular design.

Clinical experience

- STaRT leverages current surgical techniques and surgeon familiarity with the use of resorbable collagen matrix.

Limitations

- Tumor cells more than 5–8 mm distant to the resection cavity where STaRT is implanted are unlikely to benefit from this therapy.

Future perspective

- Meaningful future advances in therapeutic efficacy against glioblastoma will require the understanding of STaRT safety in combination with EBRT and other forms of adjuvant therapy.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Heron M. Deaths: leading causes for 2017. *Natl Vital Stat. Rep.* 66(5), 1–76 (2019).
2. Stupp R, Mason WP, van den Bent MJ *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* 352(10), 987–996 (2005).
3. Ostrom QT, Gittleman H, Xu J *et al.* CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2009–2013. *Neuro-oncology* 18(Suppl. 5), v1–v75 (2016).
4. Stupp R, Hegi ME, Mason WP *et al.* Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 10(5), 459–466 (2009).
5. 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* 318(23), 2306–2316 (2017).

•• **Demonstrates extension of overall survival with the use of tumor treating fields.**

6. Stupp R, Mason WP, van den Bent MJ *et al.* Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N. Engl. J. Med.* 352(10), 987–996 (2005).
7. Ogura K, Mizowaki T, Arakawa Y *et al.* Initial and cumulative recurrence patterns of glioblastoma after temozolomide-based chemoradiotherapy and salvage treatment: a retrospective cohort study in a single institution. *Radiat. Oncol.* 8(1), 97 (2013).
8. Gaspar LE, Fisher BJ, Macdonald DR *et al.* Supratentorial malignant glioma: patterns of recurrence and implications for external beam local treatment. *Int. J. Radiat. Oncol. Biology Phys.* 24(1), 55–57 (1992).
9. Petrecca K, Guiot M-C, Panet-Raymond V, Souhami L. Failure pattern following complete resection plus radiotherapy and temozolomide is at the resection margin in patients with glioblastoma. *J. Neurooncol.* 111(1), 19–23 (2012).
10. Nagashima G, Suzuki R, Hokaku H *et al.* Graphic analysis of microscopic tumor cell infiltration, proliferative potential and vascular endothelial growth factor expression in an autopsy brain with glioblastoma. *Surg. Neurol.* 51(3), 292–299 (1999).
11. Pirzkall A, McGue C, Saraswathy S *et al.* Tumor regrowth between surgery and initiation of adjuvant therapy in patients with newly diagnosed glioblastoma. *Neuro-oncology* 11(6), 842–852 (2009).
12. Pennington C, Kilbride L, Grant R, Wardlaw JM. A pilot study of brain tumour growth between radiotherapy planning and delivery. *Clin. Oncol.* 18(2), 104–108 (2006).
13. Waters JD, Rose B, Gonda DD *et al.* Immediate postoperative brachytherapy prior to irradiation and temozolomide for newly diagnosed glioblastoma. *J. Neurooncol.* 113(3), 467–477 (2013).

•• **Demonstrates safety of radioactive seed implantation in combination with adjuvant chemoradiation therapy as an outlook for possible future combination of different therapies.**

14. Buszek SM, Feghali KAA, Elhalawani H, Chevli N, Allen PK, Chung C. Optimal timing of radiotherapy following gross total or subtotal resection of glioblastoma: a real-world assessment using the National Cancer Database. *Sci. Rep.* 10(1), 4926 (2020).

15. Han SJ, Rutledge WC, Molinaro AM *et al.* The effect of timing of concurrent chemoradiation in patients with newly diagnosed glioblastoma. *Neurosurgery* 77(2), 248–53 (2015).
16. Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. *Int. J. Radiat. Oncol. Biology Phys.* 16(6), 1405–1409 (1989).
17. Sneed PK, Gutin PH, Larson DA *et al.* Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. *Int. J. Radiat. Oncol. Biology Phys.* 29(4), 719–727 (1994).
18. 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.* 121(2), 338–348 (2014).
19. Wernicke AG, Taube S, Smith AW, Parashar B. Central nervous system brachytherapy. In: *Handbook of Image-Guided Brachytherapy.* Mayadev J, Benedict S, Kamrava M (Eds). Springer, Cham, Switzerland, 539–556 (2017).
20. Gupta VK. Brachytherapy – past, present and future. *J. Med. Phys.* 20, 31–38 (1995).
21. Jiang P, Geenen M, Siebert F-A *et al.* Efficacy and the toxicity of the interstitial high-dose-rate brachytherapy in the management of recurrent keloids: 5-year outcomes. *Brachytherapy* 17(3), 597–600 (2018).
22. Langley SEM, Laing RW. Iodine seed prostate brachytherapy: an alternative first-line choice for early prostate cancer. *Prostate Cancer Prostatic Dis.* 7(3), 201–207 (2004).
23. Diener-West M, Earle JD, Fine SL *et al.* The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. *Arch. Ophthalmol.* 119(7), 969 (2001).
24. Henschke UK, Lawrence DC. Cesium-131 seeds for permanent implants. *Radiology* 85(6), 1117–1119 (1965).
25. Chiu-Tsao S-T, Napoli JJ, Davis SD, Hanley J, Rivard MJ. Dosimetry for ^{131}Cs and ^{125}I seeds in solid water phantom using radiochromic EBT film. *Appl. Radiat. Isotopes* 92, 102–114 (2014).
26. Shrieve DC, Loeffler JS. Advances in radiation therapy for brain tumors. *Neurol. Clin.* 13(4), 773–793 (1995).
27. Lodge WO. Treatment of intrasellar tumours by radon. *BMJ* 2(3963), 1257–1258 (1936).
28. Gutin PH, Phillips TL, Hosobuchi Y *et al.* Permanent and removable implants for the brachytherapy of brain tumors. *Int. J. Radiat. Oncol. Biology Phys.* 7(10), 1371–1381 (1981).
29. Prados M, Leibel S, Barnett CM, Gutin P. Interstitial brachytherapy for metastatic brain tumors. *Cancer* 63(4), 657–660 (1989).
30. 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.* 187(1), 7–14 (2010).
31. Petr MJ, McPherson CM, Breneman JC, Warnick RE. Management of newly diagnosed single brain metastasis with surgical resection and permanent I-125 seeds without upfront whole brain radiotherapy. *J. Neurooncol.* 92(3), 393–400 (2009).
32. Ruge MI, Suchorska B, Maarouf M *et al.* Stereotactic ^{125}iodine brachytherapy for the treatment of singular brain metastases: closing a gap? *Neurosurgery* 68(5), 1209–18 (2011).
33. Wernicke AG, Lazow SP, Taube S *et al.* Surgical technique and clinically relevant resection cavity dynamics following implantation of cesium-131 brachytherapy in patients with brain metastases. *Oper. Neurosurg.* 12(1), 49–60 (2015).
34. Han DY, Ma L, Braunstein S, Raleigh D, Sneed PK, McDermott M. Resection cavity contraction effects in the use of radioactive sources (I–25 versus Cs-131) for intra-operative brain implants. *Cureus* 10(1), e2079 (2018).
35. 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. Biology Phys.* 55(2), 378–385 (2003).
36. Murphy MK, Piper RK, Greenwood LR *et al.* Evaluation of the new cesium-131 seed for use in low-energy x-ray brachytherapy. *Med. Phys.* 31(6), 1529–1538 (2004).
37. Bashir R, Hochberg F, Oot R. Regrowth patterns of glioblastoma multiforme related to planning of interstitial brachytherapy radiation fields. *Neurosurgery* 23(1), 27–30 (1988).
38. Gutin PH, Leibel SA, Wara WM *et al.* Recurrent malignant gliomas: survival following interstitial brachytherapy with high-activity iodine-125 sources. *J. Neurosurg.* 67(6), 864–873 (1987).
39. Laperriere NJ, Leung PMK, McKenzie S *et al.* Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma. *Int. J. Radiat. Oncol. Biology Phys.* 41(5), 1005–1011 (1998).
40. Selker RG, Shapiro WR, Burger P *et al.* The brain tumor cooperative group NIH trial 87-01: a randomized comparison of surgery, external radiotherapy and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy and carmustine. *Neurosurgery* 51(2), 343 (2002).
41. Ribas A, Hamid O, Daud A *et al.* Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. *JAMA* 315(15), 1600 (2016).
42. Westphal M, Hilt DC, Bortey E *et al.* A Phase III trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro-oncology* 5(2), 79–88 (2003).

- **Suggests benefit of locally applied chemotherapy as a potential option.**

43. Siddiqi SN, Provias J, Laperriere N, Bernstein M. Effects of iodine-125 brachytherapy on the proliferative capacity and histopathological features of glioblastoma recurring after initial therapy. *Neurosurgery* 40(5), 910–918 (1997).
44. Welsh J, Sanan A, Gabayan AJ *et al.* GliaSite brachytherapy boost as part of initial treatment of glioblastoma multiforme: a retrospective multi-institutional pilot study. *Int. J. Radiat. Oncol. Biology Phys.* 68(1), 159–165 (2007).
45. Brachman DG, Youssef E, Dardis CJ *et al.* Resection and permanent intracranial brachytherapy using modular, biocompatible cesium-131 implants: results in 20 recurrent, previously irradiated meningiomas. *J. Neurosurg.* 131(6), 1819–1828 (2019).
46. Brachman D, Youssef E, Dardis C, Smith K, Pinnaduwage D, Nakaji P. Surgically targeted radiation therapy: safety profile of collagen tile brachytherapy in 79 recurrent, previously irradiated intracranial neoplasms on a prospective clinical trial. *Brachytherapy* 18(3), S35–S36 (2019).

•• **Study suggests potential benefit of GammaTile® for the treatment of several brain neoplasms.**

47. Wernicke AG, Hirschfeld CB, Smith AW *et al.* Clinical outcomes of large brain metastases treated with neurosurgical resection and intraoperative cesium-131 brachytherapy: results of a prospective trial. *Int. J. Radiat. Oncol. Biology Phys.* 98(5), 1059–1068 (2017).
48. 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.* 126(4), 1212–1219 (2017).
49. 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.* 127(1), 63–71 (2015).
50. Youssef E, Nakaji P, Thomas T, McBride H, Fram E, Brachman D. SCDT-36. Novel modular, permanently implanted collagen-based device for intraoperative brachytherapy in patients with central nervous system tumors. *Neuro-oncology* 19(Suppl. 6), vi272–vi272 (2017).
51. Rivard MJ. Brachytherapy dosimetry parameters calculated for a ^{131}Cs source. *Med. Phys.* 34(2), 754–762 (2007).
52. Chitti B, Goyal S, Sherman JH *et al.* The role of brachytherapy in the management of brain metastases: a systematic review. *J. Contemp. Brachyther.* 12(1), 67–83 (2020).
53. Vitaz TW, Warnke PC, Tabar V, Gutin PH. Brachytherapy for brain tumors. *J. Neurooncol.* 73(1), 71–86 (2005).
54. Ferreira C, Alaei P, Chen C, Reynolds M, Sterling D, Dusenbery K. RTHP-32. First experience with gammatile permanent implants for recurrent brain tumors. *Neuro-oncology* 21(Suppl. 6), vi216–vi216 (2019).
55. D P, S S, E Y *et al.* "Dosimetric impact of source migration and decay based on radioisotope type in collagen carrier brain brachytherapy implants". *Med. Phys.* e244(45), (2018).
56. Ardizzone L, Barber T, Drebin J *et al.* Cancer surgery and COVID19. *Ann. Surg. Oncol.* 27(6), 1713–1716 (2020).
57. Raizer JJ, Fitzner KA, Jacobs DI *et al.* Economics of malignant gliomas: a critical review. *J. Oncol. Pract. Am. Soc. Clin. Oncol.* 11(1), e59–e65 (2014).
58. Yondorf MZ, Parashar B, Sabbas A *et al.* Radiation exposure after neurosurgical resection and permanent intraoperative cesium-131 radio-isotope brachytherapy in patients with brain tumors. *Brachytherapy* 13, S109–S110 (2014).
59. Champeaux C, Weller J. Implantation of carmustine wafers (Gliadel®) for high-grade glioma treatment. A 9-year nationwide retrospective study. *J. Neurooncol.* 147(1), 159–169 (2020).
60. Ko A, Fink K, Stelzer K, Silbergeld D. Safety and efficacy of concomitant chemotherapeutic wafers and iodine-125 seeds for recurrent glioblastoma. *Surg. Neurology Int.* 3(1), 137 (2012).
61. Drumm MR, Dixit KS, Grimm S *et al.* Extensive brainstem infiltration, not mass effect, is a common feature of end-stage cerebral glioblastomas. *Neuro-oncology* 22(4), 470–479 (2020).

• **Highlights glioblastoma invasion of brain stem.**

62. Chen AM, Chang S, Pouliot J *et al.* Phase I trial of gross total resection, permanent iodine-125 brachytherapy and hyperfractionated radiotherapy for newly diagnosed glioblastoma multiforme. *Int. J. Radiat. Oncol. Biology Phys.* 69(3), 825–830 (2007).
63. Archavlis E, Tselis N, Birn G, Ulrich P, Zamboglou N. Salvage therapy for recurrent glioblastoma multiforme: a multimodal approach combining fluorescence-guided resurgery, interstitial irradiation and chemotherapy. *Neurol. Res.* 36(12), 1047–1055 (2014).