Clinical Policy Title: Tumor treatment fields for glioblastoma

Clinical Policy Number: 05.02.05

Effective Date: July 1, 2015
Initial Review Date: March 18, 2015
Most Recent Review Date: April 19, 2017
Next Review Date: April 2018

Policy contains:
- Alternating electric fields (AEF).
- Tumor treatment fields (TTF).
- Electric tumor treatment fields (ETTF).
- Optune.
- Glioblastoma multiforme.

Related policies:

CP# 05.02.01 Proton beam therapy
CP# 05.02.02 Brachytherapy
CP# 05.02.03 Intensity modulated radiotherapy IMRT

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of tumor treatment fields (TTFs) for the management of patients with glioblastoma multiform (GBM) to be investigational and, therefore, not medically necessary.

Limitations:

There is insufficient evidence to demonstrate the use of cranial electrical stimulation for depression. All other uses of tumor treatment fields are not medically necessary.

E0766 - Electrical stimulation device used for cancer treatment, includes all accessories, any type.

Alternative covered services:
Chemotherapy and radiotherapy.

**Background**

GBM is the most frequently occurring primary brain tumor in the United States, affecting some 17,000 patients each year. The median survival rate for GBM is 14 – 16 months. A few patients may survive five years, representing <3 percent of all GBM patients.

Because of the discouraging prognosis for those suffering from GBM when treated with traditional therapies, there has been a search for alternative treatment modalities that can provide localized treatment without adversely impacting normal brain tissue.

TTFs are low-intensity (1 – 2 volts/CM), intermediate frequency (100 – 200 KHz) alternating electrical fields (AEFs) established through insulated electrodes on the skin around the region of a malignant tumor. Tumor cells undergoing mitosis may be destroyed, leaving nondividing cells unaffected.

The use of TTF has had modest success in the reduction of growth of GBM in limited series of trials in several single-institution programs.

On September 24, 2014, the U.S. Food and Drug Administration (FDA) cleared Optune® as a class III device, a category of intervention generally reserved for the highest-risk devices and therefore subject to the highest level of regulatory control.

The use of AEF has also been utilized for treatment of depression. While there have been a few papers describing successful therapy of this condition, they have generally not been controlled studies, and have been characterized as suboptimal in design and fraught with inconsistent outcomes.

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on March 6, 2017. Search terms were “tumor treatment fields” and “alternating electric fields.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes
and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

The National Comprehensive Cancer Network (NCCN) guidelines of 2014 include alternating electric field therapy for local recurrence of GBM as a category 3 recommendation, after palliative supportive care, systemic chemotherapy, or reirradiation therapy have been offered to the patient.

The American Academy of Neurological Sciences (AANS, 2014) guidelines recommend treatment of GBM with chemotherapy (i.e., bevacizumab) as it provides improved disease control, as measured by best imaging response and progression-free survival at six months. The AANS also recommends that, for progression of disease despite treatment, the patient be enrolled in a clinical trial.

Rulseh published a study in 2012 of 20 GBM patients treated with TTF, of whom only five were long-term survivors (of at least five years).

Hayes Inc.’s review of the literature found very few well-designed studies to weigh as evidence of efficacy of therapy.

In sum, the findings of medical evidence for tumor treatment fields for therapy of GBM are insufficient to confidently support their use.

**Policy updates:**

During the past 18 months, there has been further information published regarding TTF for glioblastoma.

In a phase III clinical trial for recurrent glioblastoma (Wong, 2015), TTF was shown to have equivalent efficacy when compared to conventional chemotherapies, while lacking the typical side effects associated with chemotherapies. Furthermore, an interim analysis of a recent clinical trial in the upfront setting demonstrated superiority to standard of care cytotoxic chemotherapy, most likely because the subjects’ tumors were at an earlier stage of clonal evolution, possessed less tumor-induced immunosuppression, or both. The authors concluded that the efficacy of TTF can be increased by combining it with other anti-cancer treatment modalities.

**Summary of clinical evidence:**
### Key points:

- Phase III clinical trial for recurrent glioblastoma.
- TTF showed equivalent efficacy when compared to conventional chemotherapies.
- In one trial, TTF demonstrated superiority to standard of care cytotoxic chemotherapy.
- The authors concluded that the efficacy of TTF can be increased by combining it with other anti-cancer treatment modalities.

### Key points:

- Thirty-seven patients in treatment with TTF and standard chemotherapy, but two different regimens.
- This is a descriptive study without good randomization.

### Key points:

- Analysis from PRIDe registry data from patients treated with NovoTTF therapy from October 2011 to November 2013.
- Four-hundred-and-fifty-seven patients with recurrent GBM, not randomized and included a mix of chemotherapy only, TTF only, and both chemotherapy and TTF.
- Groups with TTF had higher response rates than chemotherapy alone with lower side effects.
- This is a descriptive study from a registry and not a controlled trial.

- Phase III clinical trial comparing TTF (n = 120) to standard chemotherapy (n = 117).
- Median survival was 6.6 months versus 6 months for standard treatment.
- No improvement in overall survival was demonstrated; however, efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens commonly used for recurrent GBM. Toxicity and quality of life clearly favored TTF.

### References

#### Professional society guidelines/other:


#### Peer-reviewed references:


**CMS National Coverage Determination (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

L34823 TUMOR TREATMENT FIELD Therapy (TTFT). CMS Medicare Coverage Database website. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ver=10&articleId=52711&CoverageSelection=Both&ArticleType=All&PolicyType=Final&b=All&KeyWord=tumor+treatment+field&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAABAAA%3d%3d&. Accessed March 6, 2017.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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