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The Case for “Hyperthermia” Thermal Therapy for Cancer

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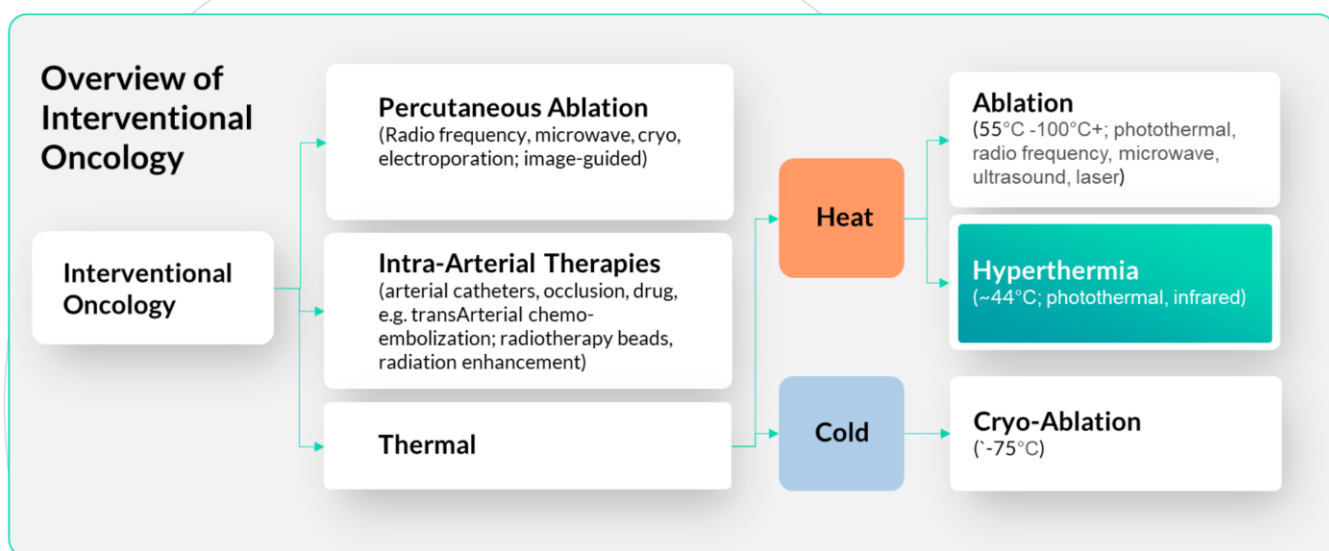


The Case for “Hyperthermia” Thermal Therapy for Cancer

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This white paper provides an overview of the field of thermal therapy for cancer treatment, focusing primarily on heat therapy.

Broadly, thermal therapy can be separated into cooling or heating therapy, both of which are subsets of interventional oncology (see Figure 1 below). Cold therapy, or cryoablation therapy, ablates tissue using extreme cold temperatures. It is effective at ablating tissues, but it is non-selective for tumor tissue, and it does not confer the therapeutic advantages of hyperthermia. The term “hyperthermia” has been used to describe any elevated temperature used to treat disease; here we use the increasingly common practice of referring to gentle heat as “hyperthermia” and high heat as “ablation”. Thus, heat therapy can be divided into **ablation**, which is typically 131°F (55°C) and hotter, and **hyperthermia**, which targets a temperature of about 111°F (44°C).



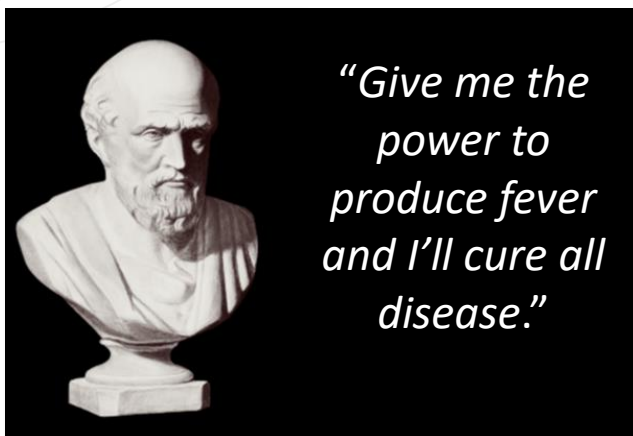
An overview of where hyperthermia (upper right) fits in relation to the broader field of interventional oncology. Hyperthermia is distinguished from ablation by temperature; ablation is 131°F (55°C) and above, while hyperthermia is in a narrow range centering on 111°F (44°C).

How Is Heat Therapy Beneficial for Cancer Treatment?

Heat has long been known to have beneficial effects for maintaining health. Fever, in response to a bacterial or viral infection, is an important, natural curative response of the body’s immune system. Heat is also known to have important therapeutic effects for cancer.

Before going further, important questions to consider are: “Where did thermal therapy for cancer come from?” and “If cancer thermal therapy works, then why isn’t it used more widely?”

To gain perspective on this, we will look at the story of Bessie Dashiell and William Coley.



The Legacy of Bessie Dashiell – The Advent of Thermal Therapy and Immunotherapy for Cancer

(This section is taken from the [Cancer Research Institute](#) website and 'A Commotion in the Blood'.)

In the summer of 1890, a young woman named Elizabeth (“Bessie”) Dashiell got her hand caught between the seats of a passenger train car while traveling on vacation. Over the next few weeks, she noticed that her hand became increasingly sore at the site of injury. Eventually, when the pain persisted for more than a month, she visited a doctor by the name of William Coley in New York City.



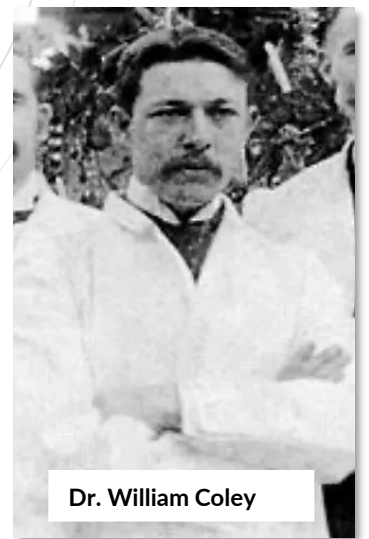
Bessie Dashiell with her close friend John D. Rockefeller Jr. in 1890.

Coley, who was then 28 and a newly practicing surgeon, performed a biopsy expecting to find an infection, but he found no signs of pus or inflammation. Instead, he discovered that his 17-year-old patient had an aggressively growing bone tumor called a sarcoma. The cutting edge of treatment for this type of cancer called for amputation of the limb. Bessie had her arm amputated below the elbow in November 1890. Despite this drastic measure, the cancer continued to spread, eventually riddling her body with painful tumors. Bessie died in January of 1891, at the age of 18.

Bessie Dashiell’s story might have been lost to history, as have the stories of so many cancer victims over the centuries. But Bessie’s tragedy served as the catalyst for the work of two influential individuals without whom we would not have the cancer treatments we have today.

The first person we have already met: William Coley. Coley was trained as a surgeon, but the depressing experience with Bessie Dashiell inspired him to search for a better way to treat this cancer. He was led to hospital records at the New York Hospital where he pored through past case histories until he found something interesting: the case of a patient named Stein; a German immigrant who had been treated with surgery for a cancer very similar to Bessie’s. Instead of succumbing to the disease, however, the man walked out of the hospital disease free.

Coley learned that the patient had come down with a severe post-operative skin infection called erysipelas and developed a very high fever (such infections were common in the days before the advent of antibiotics) which borders on what we now call hyperthermia. The man nearly died from the infection, but eventually his body mustered an immune response to fight it. Coincidentally, the man’s tumor shrank down to nothing, and he left the hospital days later, with no trace of disease.



Dr. William Coley



Zola, Coley's patient, shown here with a tumor in his right tonsil.

He was still alive years later when Coley tracked him down in his neighborhood on the Lower East Side. Coley surmised that the bacterial infection had somehow caused the tumor to regress, perhaps through the release of a “toxin.” He combed through the literature and found other cases of such spontaneous remissions that seemed to coincide with a case of erysipelas. Coley decided to test whether purposely infecting patients with erysipelas could cause their tumors to regress. He performed the first of these inoculations in 1891, on a patient named Zola, an Italian immigrant with a tumor “the size of a hen’s egg” in his right tonsil, who likely had only weeks to live. To Coley’s astonishment, the experiment worked: the man’s cancer regressed completely, and he lived another 8 years. This was the birth of immunotherapy.

Coley continued to experiment with his “toxin” therapy for the next 30 years, achieving lasting remissions in some cases. While Coley was convinced of the value of his toxins, others were more skeptical. In fact, the American Medical Association published an editorial in 1894 discrediting the therapy, and as the years passed, Coley’s toxins largely fell out of use, eclipsed first by radiation and then by chemotherapy.

Coley’s contribution might have been forgotten completely if not for Coley’s daughter, Helen Coley Nauts, who re-discovered her father’s work after his death and founded the Cancer Research Institute to rehabilitate his legacy. As such, immunotherapy owes its existence to the profound effect that Bessie Dashiell had on William Coley and the effect his pioneering research had on his daughter.

Hyperthermia Falls into the Shadows...

Given the unorthodox method Coley used to induce whole-body hyperthermia – intentionally infecting patients with a bacterial disease – it is not surprising that the mainstream medical establishment did not embrace his treatment. However, Coley’s core finding that high fever had beneficial effects for cancer was important, though unrecognized for decades.

Nonetheless, in the decades following Coley’s death in 1936, heat was increasingly used to treat tumors, but it was exclusively very high heat – ablation, which is over 131°F/55°C and typically 212°F/100°C or more – delivered by various means, usually radio frequency (RF) energy. This stemmed from the idea that if heat was beneficial, more would be better.

Ablation was therefore increasingly used for cancer treatment in the 20th century, and it remains in use today. Ablation is delivered by a number of technologies, including RF, ultrasound, microwave, and laser. Ablation is very effective at killing tissue, but it has two large drawbacks:

1. Ablation kills tissue indiscriminately, whether it is healthy tissue or diseased tissue; and
2. Ablation does not yield the host of beneficial biological responses that gentle hyperthermia initiates.

Despite these drawbacks, ablation has been used for decades for cancer and other indications, and there are several reasons why ablation has been used relatively widely. First, ablation is effective, even though it is indiscriminate in terms of the tissue it neutralizes. Second, ablation is well known from a regulatory perspective, and ablation technologies typically receive 510(k) clearance from the FDA, which can provide for a relatively easy route to market. Third, it is easier to deliver unrestrictedly higher temperatures of ablation than it is to establish and maintain gentle hyperthermia's narrow range close to 44°C, since ablation does not require accurate temperature monitoring and heat regulation.

Together, these elements and the fact that the alternative therapy usually involves the more damaging systemic use of chemotherapy, have made ablation a widely used treatment for cancer and other indications, such as cardiac arrhythmias. As our understanding of cancer biology and medical technology has developed over the years, this is changing.

...And Remerges with Renewed Vigor

Hyperthermia has emerged from the shadows over the past decade along with the movement towards more selective, 'precision' therapies, over the 'blunt force' of chemotherapy, radiation, and surgery. Sources such as the National Cancer Institute (NCI) now profile ['Hyperthermia to Treat Cancer'](#) on their website, something that was not there 10 years ago. Notably, the NCI recognizes the important difference between hyperthermia and ablation, and the many benefits of hyperthermia. Additionally, the Cleveland Clinic, a leader in progressive cancer therapy, [identifies gentle hyperthermia](#) as an important emerging treatment for cancer.

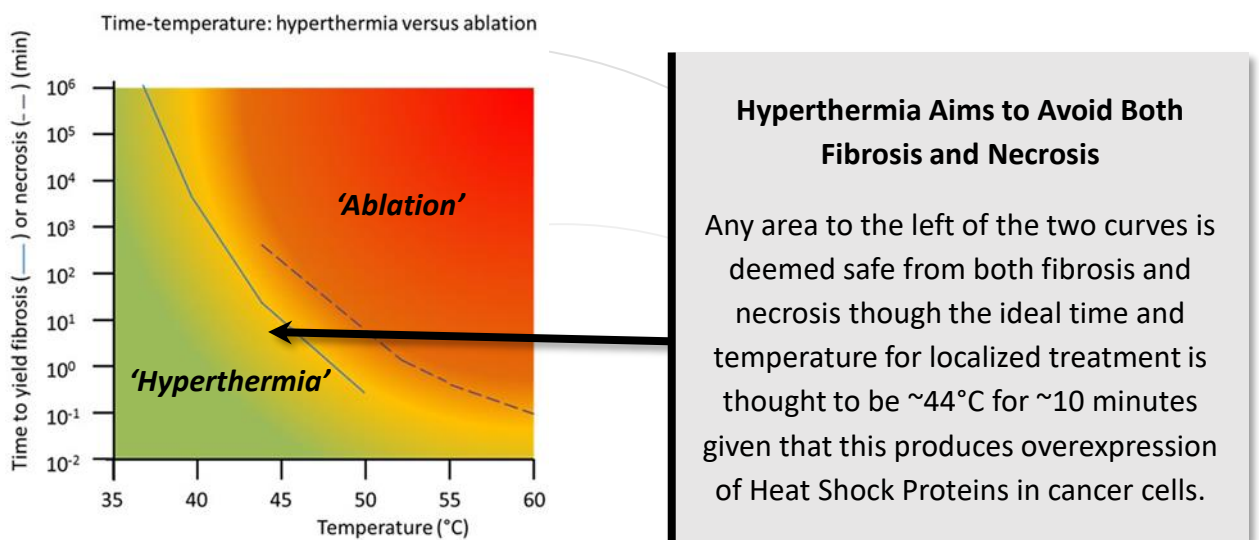
We now know that hyperthermia therapy is a proven treatment modality. Hyperthermia has efficacy on its own, as a monotherapy, and when used in combination with radiation and/or chemotherapy, has been shown to significantly improve tumor response to treatment over those treatments alone. Hyperthermia therapy can be given either locally to a specific body part or can be delivered by perfusing body cavities with heated solutions.

Hyperthermia has many benefits over ablation and other forms of interventional oncology. Importantly, it can be used together with other forms of cancer treatment, including drugs and radiation, and it can be used as a neoadjuvant for (prior to) surgery, to reduce the size of tumors and better define their margins.

Evidence for the beneficial effects of hyperthermia continues to grow. These effects include dramatic shrinkage of tumors, stimulation of the immune system, neutralization of cancer stem cells, and increased perfusion of tumors, which can help drugs better access all tumor compartments.

Hyperthermia therapy has been found to be effective for the treatment of numerous human cancers including colorectal cancer, head and neck cancer, breast cancer, esophageal cancer, and pancreatic cancer. During hyperthermia therapy, the tumor is heated to approximately 44°C (111.2 °F). At this temperature, normal tissue is not harmed, and, unlike ablation, tumors are found to have increased blood perfusion and oxygenation, an increase in apoptosis (programmed cell death), inhibition of DNA repair, and increased responsiveness of the immune system to the tumor.

A field of thermal dosimetry, as outlined in the figure below, has developed. The interplay of temperature and time at that temperature has been studied in detail, notably by Mark Dewhirst and colleagues (Dewhirst *et al.*, 2003). A variety of temperatures for thermal therapy has been investigated, with research showing that 111°F (44°C) is the optimal temperature to maximize the benefits of hyperthermia, while minimizing collateral damage.



A plot of time to yield muscle fibrosis (solid line) or necrosis (dashed line) at specific temperatures for hyperthermia and ablation (from Kok *et al.* and based on work by Dewhirst *et al.*).

Also, studies have found that gentle hyperthermia, *i.e.*, 44°C/111°F, for 10 minutes has several important biological effects on tumors: It induces tumor shrinkage due to death of cancer cells; tumors have different metabolism from healthy tissue and they are more heat-sensitive;

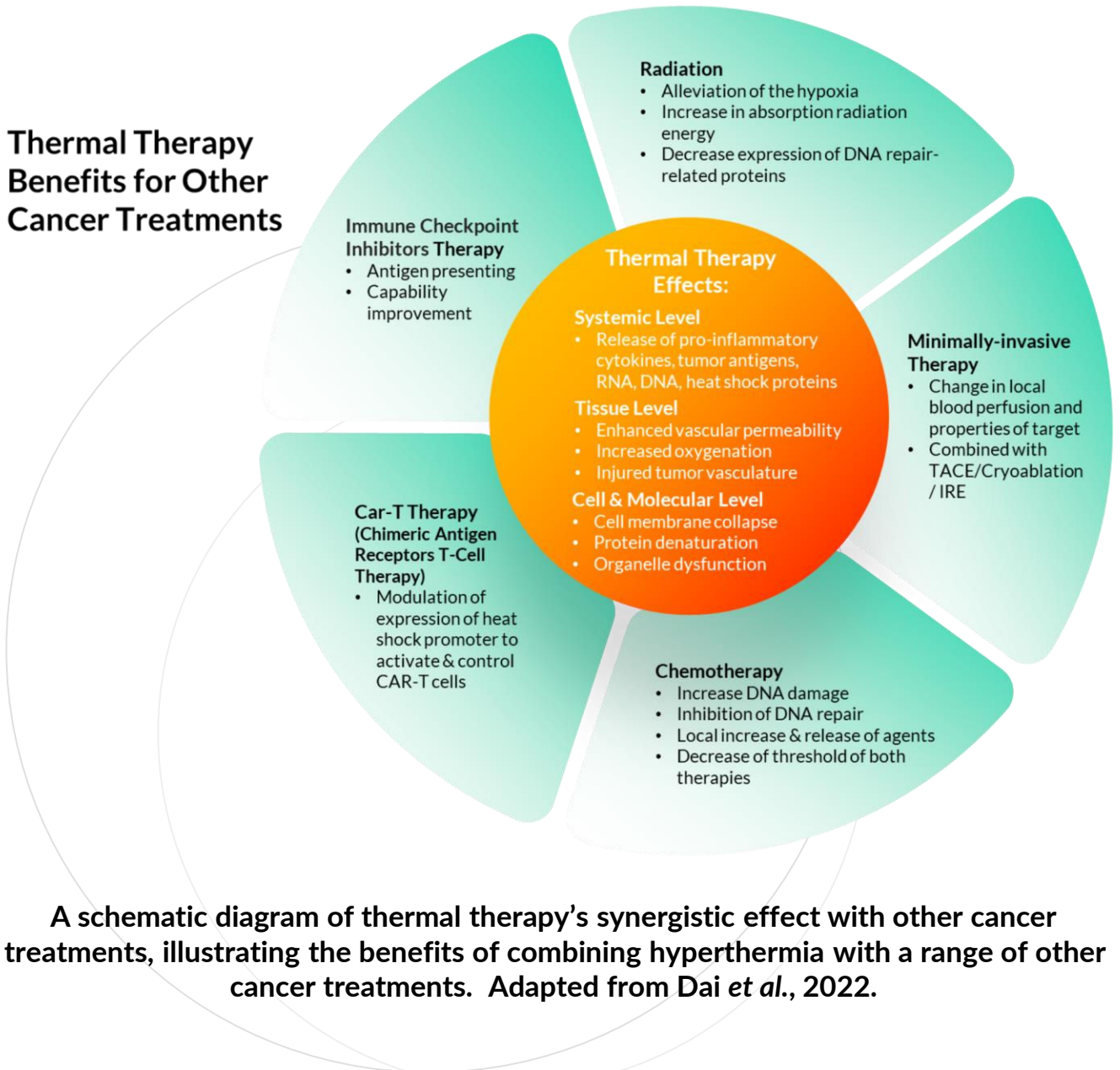
There is a degree of immune system stimulation due to release of partially denatured antigens and cytokines into circulation; It helps to neutralize cancer stem cells, which are generally quite drug-resistant;

It increases perfusion of the tumor, thus enabling better access all tumor compartments for anti-cancer drugs.

As detailed in the above graph, it is important to point out that this temperature does not cause rapid tissue fibrosis, coagulation, or necrosis. Instead, it induces production of high levels of heat shock proteins in cancer cells, and these heat shock proteins lead to the biological effects listed above.

These effects are due to biological responses at the cell and molecular level, at the tissue level, and at the systemic level, all of which make hyperthermia a powerful tool for fighting cancer. The potential synergistic effects of combining thermal therapy and other cancer treatments, including radiation, chemotherapy, immune checkpoint inhibitors (ICIs), CAR-T therapy, and other minimally invasive therapies are illustrated in the figure below.

Thermal Therapy Benefits for Other Cancer Treatments



Despite the proven clinical benefits of hyperthermia therapy, it has not been widely adopted, primarily because most of the techniques for delivering therapy are either quite invasive, the equipment required for the less invasive techniques is prohibitively expensive, or the systems have not been optimized for gentle hyperthermia.

Fortunately, however, this is changing, and hyperthermia is increasingly used as part of cancer treatments today. Hyperthermia is now recognized by leading institutions, including the National Cancer Institute and the Federal Drug Administration, as an effective, safe treatment for many types of solid tumors. The time for developing a next-generation safe, minimally invasive, effective, and affordable technology for delivering hyperthermia is now.

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Some Good On-line Resources

From the NIH:

<https://www.cancer.gov/about-cancer/treatment/types/hyperthermia>

From The Cleveland Clinic, a leading clinical organization that uses cutting edge treatments:

<https://my.clevelandclinic.org/health/treatments/17114-hyperthermia-therapy>

From the Cancer Research Institute – The Legacy of Bessie Dashiell:

<https://www.cancerresearch.org/blog/december-2013/the-legacy-of-bessie-dashiell>