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The Ongoing History of Thermal Therapy for Cancer

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Abstract

Through 5,000 years of practice, physicians, surgeons, clergy, or lay people have utilized thermal therapy to treat mass lesions now known as cancer. The methods have changed dramatically over this time span and certainly the techniques have improved the efficacy and safety, but fundamentally, hyperthermic therapy is usually a local or regional treatment for most cancer patients. Fortunately, hyperthermia used in combination with chemotherapy or ionizing radiation continues to improve outcomes. We will briefly describe the historic role of hyperthermia in cancer care as well as modern expectations based on technological advancements. In particular, we will focus on the role of hyperthermia for cancers that do not have other, more effective treatments.

Background

Hyperthermia has been used with an “intent to cure ” tumors for at least 4,000 years, and as a tool for the destruction of tumor masses well before that.[1] Tumors refer to any growth or mass that has developed unexpectedly. Well before there was any understanding of the molecular basis for cancer, let alone the ability to diagnose cancer, there was an understanding that cutting or burning of these lesions was an appropriate therapy for some affected individuals. In fact, Hippocrates[1, 2] describes that if a tumor “cannot be cut, it should burned. If it cannot be burned, then it is incurable.” Shockingly, for many cancers this is still the case.

While chemotherapy may “cure ” a few fortunate patients with various types of cancer, malignant diseases such as metastatic hepatocellular carcinoma (HCC) are usually incurable with no meaningful five-year survival probability in the majority of patients. In other patients who have locally advanced unresectable hepatic lesions, radiofrequency thermal ablation is a useful and potentially curative therapy for HCC. Notwithstanding the few patients who have some benefit from transhepatic arterial embolization, there is no curative systemic or regional cytotoxic chemotherapy for HCC. The most recently approved targeted

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therapy for HCC, sorafenib, increases median survival of patients with unresectable HCC by three months.[3] Patients with unresectable metastatic lesions (such as colorectal cancer) to the liver that are amenable to RFA have a median overall survival of 25 to 30 months, in general. 4

There are multiple forms of hyperthermic therapy. The previously described RFA technique is a local therapy involving intratumoral placement of a needle electrode that can produce tissue temperatures as high as 100°C following activation of an electrical current. Alternating electrical current dissipation and ionic stimulation within tissue surrounding the electrode causes hyperthermia. Regional hyperthermia has been used in combination with regional chemotherapy during resection of extremity soft tissue sarcomas or as treatment for in transit limb metastases from melanoma.[5] In these cases, the elevated tissue temperature is maintained for extended periods of time. This takes the form of an isolated limb perfusion of chemotherapy warmed to 42°C-45°C for 60 minutes or longer.[5] Likewise, hyperthermic intraperitoneal chemotherapy is another regional hyperthermic treatment often performed simultaneously with resection of peritoneal malignant disease.[6] Finally, whole body hyperthermic therapy has been utilized by inducing fevers with toxins[7] or externally warming entire patients up to 42°C for extended periods of time.[8, 9]

It is often quoted that Hippocrates “managed” superficial tumors with cautery or direct ablative therapy, but it is not clear if he was actually describing the treatment of cancer.[1] Interestingly, the side effects he mentions include weakness, neurological changes, hemorrhage, and death, which are all adverse events that are similar to what is seen today with whole body hyperthermic treatment.[1, 9, 10] Around the Middle Ages and later, instruments were designed and shaped for direct application of heat to kill tumors or cauterize bleeding, albeit without the benefit of adequate regional or general anesthesia (Figure 1).

Finally, the goal of hyperthermic therapy is to capitalize on the difference in thermotolerance between normal and cancer cells.[11] Mammalian cells die when exposed to temperatures above 55°C for more than a few minutes, however, these normal cells tolerate temperature ranges from 41°C-43°C for hours. Importantly, each half of a degree increase in cellular temperature is associated with increased cell death. Cancer cells in general do not tolerate these temperatures nearly as well or as long. Finding the appropriate balance of temperature and duration is finding the balance between the desired cancer cell death and undesirable normal cell toxicity.

Early electrosurgery

Electrosurgical procedures in the first half twentieth century included destruction of cancerous tissues, enlarged lymph nodes, and cauterization of nodules left after enucleation of other masses.[12, 13] Interestingly, these included intraabdominal procedures of the uterus and ovaries[12] as well as intrathoracic procedures for cancers and infections.[13] In 1900, the first modern example of curative electrosurgery for cancer was documented when an artist who had a cutaneous carcinoma accidently touched an electrical wire. The current “treated” his cutaneous carcinoma via hyperthermia and the concept of electrofulguration was born.[14] Soon thereafter, Dr. William T. Bovie and Dr. Harvey Cushing developed and clinically implemented an electrosurgical device for decreasing intraoperative blood loss.[14] Hyperthermic electrothermal ablation can directly trace its history to this moment.

Development of modern techniques

Modern ablative techniques require direct contact between a probe, the target tumor, and surrounding normal tissue. Depending on the modality and intensity of treatment, there is an

immediate zone of intratumoral necrosis, a zone of apoptosis, and a zone of hyperemia without frank cell death.[15] Ideally, there will be a margin of normal tissue death in order to ensure the death of all cancer cells.[4] Although there have been many extremely well done studies and reviews during the 1970's investigating the effects of hyperthermia on normal and cancer cells, a review article by Field and Bleehen described the current understanding of hyperthermia in the treatment of cancer that remains accurate to this day.[16]

Effective local or regional hyperthermic cancer therapy can be induced by either longer heating durations at temperatures of 41-45°C or by short duration treatment of cancer cells with higher temperatures (or both).[17] Likewise, many, but not all, cancer cells respond differently than their normal cell origins to hyperthermic therapy.16 The difference between these two responses permits a general method to treat cancers with hyperthermia. This is not to suggest that all cancers can be treated in the same manner, but this approach has worked well in RF ablation of primary and secondary liver malignancies.18 The approach is to maximize the coagulative necrosis of the malignancy *in situ* while accepting limited necrosis or apoptosis of surrounding normal parenchyma. In this way, excess normal tissue is not needlessly injured while “oncologically” safe margins are maintained. Furthermore, all cancer cells are presumed to be within the area of coagulative necrosis and immediately killed during the procedure. The balance of treatment effectiveness, patient safety, and normal hepatocyte tolerance resulted in a nearly uniform practice of treating properly selected hepatic tumors for ~ 10 minutes with tissue temperatures of at least at 60°C - 65°C.[4]

More recent examples of direct electrosurgery are seen in the practice of endobronchial procedures and cervical lesions. [19-21] While loop electrosurgical procedures are standard therapy for pre-malignant cervical lesions, endobronchial ablative therapy is not standard for cancers of the upper airways currently. However, they provide interesting and effective use of hyperthermic cautery based on the principles previously described. Interestingly, complete excision of pre-malignant or early malignant cervical lesions confers extremely high rates of cure for a disease, much like HCC, that otherwise carries a very poor prognosis when it is found to be advanced.[22-24]

Modern ablative techniques

RF ablation of unresectable metastatic hepatic colorectal malignancies is the prototypical local tumor ablative procedure.[25] Likewise, RF ablation for primary hepatocellular carcinoma, neuroendocrine hepatic metastases, and other unresectable hepatic lesions is very common.[26] Often, RF ablation is performed synchronously with hepatic resection, the gold standard for surgical management of primary and secondary liver malignancies.[25, 27] Finally, management of esophageal dysplastic lesions can often be safely managed with RF ablation.[28]

Microwave ablation is slowly becoming more popular in the USA whereas it has been very useful in Europe and Asia for many years.[29] While monopolar RF ablation works by inducing an alternating electrical current from the probe to the tumor with excess energy dissipated through the patient to large grounding pads, microwave ablation works by exploiting rapid oscillation of water molecules based on the dipole moment of water around a microwave-emitting probe(s). The current in RF ablation passes via the path of least resistance, potentially resulting in asymmetric ablation patterns. Microwave ablation, however, will destroy anything within the confines of the field for a given treatment duration and power, including a potentially higher risk to damage normal tissues such as bile ducts and vascular structures.[29, 30]

Cryoablation is the technique of using extremely cold probes to bring the temperatures of surrounding tumors to below the cytotoxic freezing threshold (less than approximately −20°C to as cold as −130°C) for up to 10 minutes with subsequent active heating for typically 2-3 cycles.[31, 32] While systems vary, most utilize the conversion of high-pressure gas to cold low-pressure liquid to reach these extremely low temperatures. The urologic oncology community utilizes cryoablation more so than RF ablation to treat prostate cancer[33, 34] while there is evidence that in hepatic lesions, RF ablation is more effective than cryoablation.[35-37]

Future directions

While invasive RF ablation remains the standard of care in the USA, many surgeons expect that intratumoral probe microwave ablation will become a second standard therapy for unresectable cancers. Unfortunately, microwave ablation rapidly produces excessive heat that potentially destroys everything within its field, and as such, is not appropriate for use near vital, critical structures such as the biliary confluence or the ureter. However, as research investigates better ways to protect these important structures, the role of microwave ablation will certainly increase.

Two “futuristic” treatments are noninvasive nanoparticle-mediated intracellular hyperthermic cytotoxicity and irreversible electroporation (IRE). Gold and gold-based nanoparticles are in pre-clinical and early clinical development as a means to induce targeted hyperthermia.[38-40] Through the use of near-infrared lasers or nonionizing radiofrequency fields, multiple groups have demonstrated high specificity for killing targeted cancer cells *in vitro* and *in vivo*.[39, 41-43] While there are some ongoing clinical trials investigating the use of nanoparticle-induced hyperthermia as a targeted cancer treatment, this therapy is still a few years away form being available for clinical trials.

IRE is the technique of placing electrodes on either side of lesion *in situ* and inducing an electric field between them.[36, 44] Appropriately constructed electric fields will permanently create cell membrane defects (i.e., pores) that result in cell death without hyperthermic injury. Similar to microwave ablation, any cell within the electroporation volume will die, but acellular structures (extracellular components of bile ducts) should remain intact as there is not a potential across them. IRE devices are available in the USA, but studies are on-going.

Finally, high intensity focused ultrasound is 10 to 1000 times more intense than diagnostic ultrasound.[45, 46] Targeted tissues (i.e., ultrasound probe is focused on a tumor) absorb high intensity acoustic energy which is converted to heat. Coagulative necrosis is typically achieved within a few seconds.[36] Early phase trials are on going for HCC, prostate, and other cancers.

Conclusion

The history of ablative therapies for cancers has been one of increasing the efficiency and specificity of treatment, not necessarily drastically changing the goals of the treatment *per se*. From the time of antiquity where a heated probe cauterized a skin lesion to today where an intratumoral needle electrode passes electricity to a liver lesion, the challenge has always remained to kill the cancer without harming the patient. New technologies should permit less invasive hyperthermic therapy while non-invasive hyperthermic therapy will be a reality in the near future. While today we treat cancers with invasive local or regional hyperthermia techniques, it is not unreasonable that in the future we will manage cancers with targeted noninvasive hyperthermia.

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References

1. Hornback NB. Historical aspects of hyperthermia in cancer therapy. Radiol Clin North Am. May; 1989 27(3):481–488. [PubMed: 2648453]
2. Hippocrates. On the articulations. The genuine works of Hippocrates. Clin Orthop Relat Res. Jul. 2002 (400):19–25. [PubMed: 12072741]
3. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. Jul 24; 2008 359(4):378–390. [PubMed: 18650514]
4. Curley SA, Izzo F. Radiofrequency ablation of primary and metastatic hepatic malignancies. Int J Clin Oncol. Apr; 2002 7(2):72–81. [PubMed: 12018113]
5. Issels RD, Lindner LH, Verweij J, et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol. Jun; 2010 11(6):561–570. [PubMed: 20434400]
6. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. Oct 15; 2003 21(20):3737–3743. [PubMed: 14551293]
7. Meyer JL. Hyperthermia as an anticancer modality--a historical perspective. Front Radiat Ther Oncol. 1984; 18:1–22. [PubMed: 6368320]
8. Robins HI, Cohen JD, Schmitt CL, et al. Phase I clinical trial of carboplatin and 41.8 degrees C whole-body hyperthermia in cancer patients. J Clin Oncol. Sep; 1993 11(9):1787–1794. [PubMed: 8355046]
9. Bull JM, Scott GL, Strebel FR, et al. Fever-range whole-body thermal therapy combined with cisplatin, gemcitabine, and daily interferon-alpha: a description of a phase I-II protocol. Int J Hyperthermia. Dec; 2008 24(8):649–662. [PubMed: 18608594]
10. Atmaca A, Al-Batran SE, Neumann A, et al. Whole-body hyperthermia (WBH) in combination with carboplatin in patients with recurrent ovarian cancer - a phase II study. Gynecol Oncol. Feb; 2009 112(2):384–388. [PubMed: 19059635]
11. Wust P, Nadobny J, Szimtenings M, Stetter E, Gellermann J. Implications of clinical RF hyperthermia on protection limits in the RF range. Health Phys. Jun; 2007 92(6):565–573. [PubMed: 17495657]
12. Kelly HA. Electrosurgery in Gynaecology. Ann Surg. Jan; 1931 93(1):323–325. [PubMed: 17866478]
13. Lilienthal H. Electrosurgery: A Clinical Report on 118 Operations. Ann Surg. Jun; 1933 97(6): 801–807. [PubMed: 17866981]
14. O'Connor JL, Bloom DA, William T. Bovie and electrosurgery. Surgery. Apr; 1996 119(4):390–396. [PubMed: 8644002]
15. Curley SA. Radiofrequency ablation of malignant liver tumors. Oncologist. 2001; 6(1):14–23. [PubMed: 11161225]
16. Field SB, Bleehen NM. Hyperthermia in the treatment of cancer. Cancer Treat Rev. Jun; 1979 6(2):63–94. [PubMed: 39673]
17. Westra A, Dewey WC. Variation in sensitivity to heat shock during the cell-cycle of Chinese hamster cells in vitro. Int J Radiat Biol Relat Stud Phys Chem Med. 1971; 19(5):467–477. [PubMed: 5314347]
18. Curley SA. Radiofrequency ablation of malignant liver tumors. Ann Surg Oncol. May; 2003 10(4): 338–347. [PubMed: 12734080]

19. Emam M, Elnashar A, Shalan H, Barakat R. Evaluation of a single-step diagnosis and treatment of premalignant cervical lesion by LEEP. Int J Gynaecol Obstet. Dec; 2009 107(3):224–227. [PubMed: 19732893]
20. Kietpeerakool C, Suprasert P, Khunamornpong S, Sukpan K, Settakorn J, Srisomboon J. “Top hat” versus conventional loop electrosurgical excision procedure in women with a type 3 transformation zone. Int J Gynaecol Obstet. Apr; 2009 109(1):59–62. [PubMed: 20022598]
21. Duhamel DR, Harrell JH 2nd. Laser bronchoscopy. Chest Surg Clin N Am. Nov; 2001 11(4):769–789. [PubMed: 11780295]
22. Sankaranarayanan R, Keshkar V, Kothari A, Kane S, Fayette JM, Shastri S. Effectiveness and safety of loop electrosurgical excision procedure for cervical neoplasia in rural India. Int J Gynaecol Obstet. Feb; 2009 104(2):95–99. [PubMed: 18962583]
23. Rema P, Suchetha S, Thara S, Fayette JM, Wesley R, Sankaranarayanan R. Effectiveness and safety of loop electrosurgical excision procedure in a low-resource setting. Int J Gynaecol Obstet. Nov; 2008 103(2):105–110. [PubMed: 18760779]
24. Chirenje ZM, Rusakaniko S, Akino V, Mlingo M. A randomised clinical trial of loop electrosurgical excision procedure (LEEP) versus cryotherapy in the treatment of cervical intraepithelial neoplasia. J Obstet Gynaecol. Nov; 2001 21(6):617–621. [PubMed: 12521783]
25. Pawlik TM, Izzo F, Cohen DS, Morris JS, Curley SA. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol. Nov; 2003 10(9):1059–1069. [PubMed: 14597445]
26. Mayo SC, Pawlik TM. Thermal ablative therapies for secondary hepatic malignancies. Cancer J. Mar-Apr; 2010 16(2):111–117. [PubMed: 20404607]
27. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. Jun; 2004 239(6):818–827. [PubMed: 15166961]
28. Shaheen NJ, Frantz DJ. When to consider endoscopic ablation therapy for Barrett's esophagus. Curr Opin Gastroenterol. Jun 4.2010
29. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: a prospective review of a 5-year experience. Ann Surg Oncol. Jan; 2009 17(1):171–178. [PubMed: 19707829]
30. Bhardwaj N, Strickland AD, Ahmad F, et al. Microwave ablation for unresectable hepatic tumours: clinical results using a novel microwave probe and generator. Eur J Surg Oncol. Mar; 2009 36(3): 264–268. [PubMed: 19880269]
31. DeCastro GJ, Gupta M, Badani K, Hruby G, Landman J. Synchronous cryoablation of multiple renal lesions: short-term follow-up of patient outcomes. Urology. Feb; 2009 75(2):303–306. [PubMed: 19931123]
32. Saksena M, Gervais D. Percutaneous renal tumor ablation. Abdom Imaging. Sep-Oct; 2009 34(5): 582–587. [PubMed: 19089491]
33. Gontero P, Joniau S, Zitella A, et al. Ablative therapies in the treatment of small renal tumors: how far from standard of care? Urol Oncol. May-Jun; 2009 28(3):251–259. [PubMed: 19897385]
34. Mouraviev V, Joniau S, Van Poppel H, Polascik TJ. Current status of minimally invasive ablative techniques in the treatment of small renal tumours. Eur Urol. Feb; 2007 51(2):328–336. [PubMed: 17069964]
35. Jansen MC, van Hillegersberg R, Schoots IG, et al. Cryoablation induces greater inflammatory and coagulative responses than radiofrequency ablation or laser induced thermotherapy in a rat liver model. Surgery. May; 2010 147(5):686–695. [PubMed: 20042207]
36. Padma S, Martinie JB, Iannitti DA. Liver tumor ablation: percutaneous and open approaches. J Surg Oncol. Dec 15; 2009 100(8):619–634. [PubMed: 20017157]
37. Khan NA, Baerlocher MO, Owen RJ, et al. Ablative Technologies in the Management of Patients with Primary and Secondary Liver Cancer: An Overview. Can Assoc Radiol J. Feb 24.2010
38. Cobley CM, Au L, Chen J, Xia Y. Targeting gold nanocages to cancer cells for photothermal destruction and drug delivery. Expert Opin Drug Deliv. May; 2010 7(5):577–587. [PubMed: 20345327]

39. Goodrich GP, Bao L, Gill-Sharp K, Sang KL, Wang J, Payne JD. Photothermal therapy in a murine colon cancer model using near-infrared absorbing gold nanorods. J Biomed Opt. Jan-Feb.2010 15(1):018001. [PubMed: 20210487]

40. Cherukuri P, Glazer ES, Curley SA. Targeted hyperthermia using metal nanoparticles. Adv Drug Deliv Rev. Mar 8; 2010 62(3):339–345. [PubMed: 19909777]

41. Curley SA, Cherukuri P, Briggs K, et al. Noninvasive radiofrequency field-induced hyperthermic cytotoxicity in human cancer cells using cetuximab-targeted gold nanoparticles. J Exp Ther Oncol. 2008; 7(4):313–326. [PubMed: 19227011]

42. Glazer ES, Curley SA. Radiofrequency field-induced thermal cytotoxicity in cancer cells treated with fluorescent nanoparticles. Cancer. 2010; 116(3):3285–3293. (3). [PubMed: 20564640]

43. El-Sayed IH. Nanotechnology in head and neck cancer: the race is on. Curr Oncol Rep. Mar; 2010 12(2):121–128. [PubMed: 20425597]

44. Al-Sakere B, Andre F, Bernat C, et al. Tumor ablation with irreversible electroporation. PLoS One. 2007; 2(11):e1135. [PubMed: 17989772]

45. Fischer K, Gedroyc W, Jolesz FA. Focused ultrasound as a local therapy for liver cancer. Cancer J. Apr; 2010 16(2):118–124. [PubMed: 20404608]

46. Margreiter M, Marberger M. Focal therapy and imaging in prostate and kidney cancer: high-intensity focused ultrasound ablation of small renal tumors. J Endourol. May; 2010 24(5):745–748. [PubMed: 20380511]

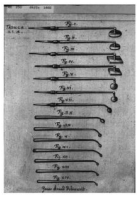

Figure 1.
Fourteen different instruments utilized for cautery as engraved by Jonas Arnold Deliveavit (ca. 1666). Image was acquired from The National Library of Medicine's *Images from the History of Medicine* collection in the public domain.