Evaluation of Oncological Hyperthermia Centers and Turkey Modeling Oncological Hyperthermia Centers and Turkey Modeling

Fatih Goksel
Dr Abdurrahman Yurtaslan Onkoloji Egitim ve Arastirma Hastanesi
Fatih Demircioglu (fthdemircioglu@yahoo.com)
Kartal Dr Lutfi Kirdar Education and Research Hospital https://orcid.org/0000-0001-7926-5973

Research

Keywords: Hyperthermia, cancer, radiotherapy, treatment methods, clinical applications

Posted Date: May 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-27512/v1

Abstract

Background Hyperthermia is a radio/chemo sensitizing method effectively used in oncological treatments. These devices, which have been used effectively in many centers around the world in the treatment of cancer, are currently unavailable in our country. In this study, hyperthermia treatments that could be applied, the number of hyperthermia devices required and the potential effects in our country have been investigated in line with the applications of hyperthermia worldwide.

Methods Based on the data obtained from certain reference centers the number and ratios of hyperthermia applications were determined and the data obtained was modeled according to the number of cancer cases in our country.

Results According to the data obtained, an average of 375 patients are treated annually per hyperthermia device in relevant centers. When a similar projection is applied for our country, hyperthermia treatment can be applied to an average of 400 patients annually with 0,18 hyperthermia devices per one million population. According to this, considering the population and the annual cancer diagnosis rates, it is predicted that 13 deep regional hyperthermia devices are required across the country.

Conclusion The presence of deep regional hyperthermia devices in comprehensive oncology centers that play an effective role in oncological treatment with modern radiotherapy devices and have enough radiation oncologists will significantly benefit the capacity to provide oncological treatment options holistically.

Background:

Hyperthermia is one of the oldest cancer treatments. In Egyptian papyrus, it is depicted that breast cancer in women was treated using hot bricks. Keeping the body temperature stable is very important and many complex cellular and physiological processes play a role in its control. Events such as cellular damage, necrosis, apoptosis that occur when the body temperature rises due to various causes (such as infections) can be life threatening. Cellular death caused by increased temperature also occurs in tumor cells and many researchers and scientists have investigated the therapeutic effect of artificial regional temperature increases on cancerous cells for many years. Heating methods used in the past not have been very effective. Today, modern electromagnetic multi-antenna heating systems have advanced hyperthermia methods and controlled heating of the body as a whole or partially, has become one of the methods used in oncotherapy.

Hyperthermia is an adjunctive therapy method that increases the effect of radiotherapy (RT) and chemotherapy (CT) by increasing the temperature of the cancer tissue.

There are many biological bases for the use of hyperthermia in oncology. Curves similar to cellular survival curves obtained for ionizing radiation have been obtained after exposing mammalian cells to different temperatures over different time periods using cell culture techniques (1, 2). The mechanisms of the cytotoxicity caused by hyperthermia are well defined and associated with the following factors (1, 2):

1. Irreversible damage to cellular respiration,
2.

Changes in nucleic acid and protein synthesis,
3.
Increased cell membrane permeability
4.
Liberation of lysosomes.

Although there are objective tumor responses to hyperthermia alone, most of them are only partial and short-term (3). The synergistic interaction between radiotherapy and hyperthermia can be demonstrated before or after heating irradiation (2). It is believed that this effect is due to inhibition of cellular recovery as a result of sublethal radiation damage caused by hyperthermia. Another rationale in combining the two modalities is that the radioresistant hypoxic component of some tumors is poorly vascularized in acidic pH. These factors bring these cells closer to thermal death. At the same time, cells in the radioresistant S phase are very sensitive to heat. Clinically, hyperthermia is applied locally, regionally and systematically (3, 4). In oncology, "hyperthermia treatment" is the controlled heating process of tumor tissue to 40–45 °C over certain periods of time (usually a maximum of 60 minutes). Depending on the target tumor site, this procedure can be applied superficially or deep regionally.

It is thought that it provides an additive effect when applied simultaneously with radiotherapy, because hypoxic cells and cells in the S phase are more sensitive to heat. In addition, since it increases the blood flow it demonstrates radiosensitive effects also by increasing oxygenation (3, 4). When applied simultaneously with chemotherapy, it may increase cytotoxic effects as a result of increased blood flow and membrane permeability caused by the local temperature increase (5, 6).

High temperature selectively destroys hypoxic and low pH cells. Low pH and hypoxic states make tumor cells resistant to treatment. Therefore, hyperthermia and radiotherapy, chemoradiotherapy and chemotherapy are complementary treatment methods (7, 8). It has been shown that hyperthermia increases the oxygen concentration by increasing the blood flow significantly in solid tumors and moderately in normal tissues surrounding the tumor. These changes in the blood flow and tumor oxygenation make cancer cells more sensitive to radiotherapy (7–9). The latest technology and current treatments are used in the treatment of cancer in our country; however, hyperthermia devices are currently unavailable. This study investigates the potential benefit of incorporating hyperthermia devices into specialized oncology centers for oncological treatment and the number of devices that would be required.

Methods:

In this study, reference comprehensive oncology centers that use non-invasive hyperthermia systems were contacted, the published literature was followed, the data were shared with relevant centers and data about the number of patients who had undergone hyperthermia during the treatment steps, the distribution of oncological diagnoses and the rate of use of hyperthermia was obtained. According to the cancer statistics of these countries the annual patient numbers and diagnosis rates were evaluated. Based on the number of patients and their diagnoses the nationwide usage ratio of oncologic hyperthermia and the number of oncologic hyperthermia devices per population were evaluated. In the light of this information, the effects of radiotherapy and/or chemotherapy and simultaneous hyperthermia applications were evaluated in phase 3 clinical trials published in the literature.

Later, based on the cancer data of our country's Cancer Department, the number of cancer cases diagnosed each year and the diagnosis groups were obtained. In line with the data above, the information was compared and a model was prepared for our country. It was attempted to evaluate the number of hyperthermia treatments that could be performed if hyperthermia devices were available based on the number of patients receiving cancer treatment across the country and also the number devices that would be required depending on the number of treatments.

Results:

The data were collected from 23 hyperthermia treatment centers across the world, each of which is considered a reference in cancer treatment and research. When we examined the number of devices in these centers, it was seen that 12 superficial and 23 deep regional hyperthermia devices were present. In the centers, an average of 8760 patients had undergone deep regional hyperthermia and 4380 had undergone superficial hyperthermia annually. The review of the distribution of cancer diagnoses showed that hyperthermia treatment was applied for soft tissue sarcomas in 25%, cervical cancer in 20%, breast cancer in 19%, gastrointestinal system tumors in 12%, genitourinary system tumors in 8%, head and neck tumors in 7%, melanoma in 5%, and other cancer types in 4%.

Considering the population and annually diagnosed cancer cases of the countries, an approximate 200 million population and 650 thousand new cases are observed annually (10). The ratio of the population to the device numbers shows that there is one hyperthermia device for approximately 5.7 million of population. In other words, in these countries, there are 0.18 hyperthermia devices per one million of population and an average of 375 patients are treated annually per hyperthermia device. With regard to annual cancer cases, hyperthermia is applied to superficial and deep solid tumors, which account for approximately 2.2% of all patients treated for malignancy. Thus, the patient load/year per device is observed as 375 (10).

A similar projection has been performed for our country and our national statistics from 2014 were taken into consideration. Based on these data, it can be predicted that approximately 200 thousand new cancer patients will be diagnosed annually (11). In the projection based on the country population, it is predicted that 13 deep regional hyperthermia devices will be required nationwide according to a design of 0.18 hyperthermia devices per 1 million of population. Taking annual new cancer cases into consideration, services can be provided at an approximate rate of 400 patient/year with the same number of hyperthermia devices. According to the data of 2018 TURKSTAT, approximately 50% of the country's population lives in the top 10 cities with the densest population. Considering the neighboring cities, the transportation networks and the planning zones for modern radiotherapy centers, most cancer treatments are delivered in these cities. In this regard, with hyperthermia devices planned in comprehensive oncology centers, namely the regional training and research hospitals specialized in cancer treatment that have sufficient devices, the equipment and doctors where the population and the patient density are highest, services can be provided to more than 400 patients annually. By installing hyperthermia devices in these regions and centers, it will become possible to deliver more effective and holistic cancer treatments and planning will be more cost-effective.

Discussion:

Laboratory and clinical studies have shown that the mechanism of action of hyperthermia is multifaceted. While hyperthermia has cytotoxic (stopping) and apoptotic (killing) effects on cancer cells, it stimulates and strengthens the body's immunity cells (1, 2). The activity of immunity cells and the transfer of CD8-T cells to tumor sites increases with hyperthermia. Normal tissues like tumor tissue, are also sensitive to hyperthermia (12). Tumor tissue reproduces rapidly and uses a lot of energy; this makes tumor tissue a more hypoxic and lower pH environment compared to normal tissues. High temperature selectively destroys hypoxic and low pH cancer cells; therefore, hyperthermia has treatment characteristics specific to tumors rather than normal tissues (5, 12). Since hypoxia and low pH make cancer cells resistant to chemotherapy and radiotherapy, applying hyperthermia together with these treatments increases the effectiveness of radiotherapy and chemotherapy. By increasing the blood flow to tumor tissue, hyperthermia increases the oxygenation of the tumor and makes tumor cells radiosensitive. Hyperthermia also affects the repair stage of radiotherapy-induced DNA damage and by preventing the repair of the damage that occurs in the tumor DNA makes the tumor cell more sensitive to radiotherapy. While the cytotoxic effect of radiotherapy increases when combined with hyperthermia, the radio-sensitizing effect of hyperthermia on tumors is not observed in normal tissues and the combination of these two treatments does not lead to an increase in early or late side effects.

Randomized studies performed on the combination of hyperthermia and radiotherapy have proven the effectiveness of this treatment combination. In these studies, an increase in local control rates and cure rates has been observed. Effective treatments are also applied in our country with the latest technological devices in large radiotherapy centers. This study was designed considering that this effectiveness can be increased further by incorporating hyperthermia into these treatment combinations particularly in relapsing and metastatic diseases in which planning treatment can be challenging.

At high temperatures, the structure of cellular proteins undergoes degradation, and protein folding occurs. As a result of this event, the cell undergoes apoptosis or necrosis depending on the temperature level. Cells resist protein degradation caused by increased temperature by activating Heat Shock Factors. Among these proteins, HSP70 is an important immune stimulant and its expression on the surface of the malignant cell after hyperthermia allows the tumor cells to be destroyed by Natural Killer (NK) cells. HSP70-activated NK cells destroy primary and metastatic tumor cells that express HSP70. HSP70 proteins released from dead tumor cells also increase the T-cell infiltration into the tumor (13, 14).

The effect of hyperthermia that improves the success of radiotherapy is similar for chemotherapy. Hyperthermia increases the effectiveness of chemotherapy by means of synergistic effects. In line with the increase in temperature, the cytotoxic effect of the chemotherapeutic agent increases. Hyperthermia increases the permeability of chemotherapeutic agents into the tumor by causing vasodilation in tumor vascularization (14, 15).

The preliminary studies of Engelhardt, Dahl, Urano and Issels have shown that hyperthermia demonstrates synergism in chemotherapy, as in radiotherapy (16–20). Table 1 summarizes the synergism and activity of some chemotherapeutic agents and HT under various microenvironmental conditions.

Table 1
Synergism of chemotherapeutic drugs and hyperthermia under various microenvironment conditions.

Chemotherapy	HT	Oxygenated cell	Hypoxic Cell	pH ≤ 7
Adriamycin	↑↑	↑↑	NYD	NYD
Cyclophosphamide	↑↑	↑↑	NYD	NYD
Bleomycin	↑↑↑	↑↑	↑↑↑	↑↑↑
Mitomycin –C	↑↑	↑↑↑	↑↑↑	↑↑↑
BCNU/TMZ	↑↑	↑	↑↑	↑↑
Carboplatin	↑↑	↑	↑↑↑	↑
Vincristine	↑	↑	NYD	NYD
Methotrexate	↑	↑	NYD	NYD
5FU	↑	↑	NYD	NYD
Abbreviations: NYD: not yet determined; ↑: strong interaction, BCNU / TMZ: Carmustine (bischloroethylnitrosourea) / Temozolomide				

Although hyperthermia is considered as an alternative treatment, it has deserved to become a standard treatment modality today based on phase III randomized studies published in important journals specified as group A and its positive outcomes (8, 12, 13, 15, 21, 22). Hyperthermia is included as a standard treatment method in the treatment algorithms of certain cancer treatment organizations (NCNN, German Cancer Society, EORTC). The role of hyperthermia in the treatment of cancer has been summarized in the article published by The German Cancer Society in 2012 in Sthrahlenther Oncol by Sauer, R et al. and this publication is an explanatory text about the subject. HT is recommended especially in primary tumors and local recurrences (23). HT is more than likely the most powerful radio- and chemo-sensitizer to date. However, it is not yet suitable for inclusion in the treatment of all tumor sites, and there are still problems in routine clinical applications. The technology is still being developed. No doubt, in the near future, combined oncological treatments with HT will be delivered to more patients and the beneficial effects of this should be observed.

Hyperthermia also makes cancer cells more sensitive to radiotherapy and the effects of certain anti-cancer drugs in a way that could potentially reduce the number of radiotherapy treatments required.

Today, better outcomes are obtained in terms of treatment results and toxicity due to advanced application techniques (three-dimensional hyperthermia) and real time observation (MRI monitorization) (9). However, in some countries, various reasons such as reimbursement problems, technical difficulties and difficulties in homogenous heating and monitoring temperature may prevent the widespread use of hyperthermia. On the other hand, technological advancements and the results of clinical studies published in recent years are increasing the willingness and consensus to make effort to install HT in an increasing number of institutions.

The development of new techniques with more sensitive heat conduction and heat monitoring capacity has rendered a higher acceptance among doctors. With better planning, implementation and monitoring techniques, HT can be developed even further. The mathematical modeling of the effects of HT on cell biology mentioned previously has led to true thermo-radiotherapy planning (9).

Our study evaluates microwave systems for superficial hyperthermia treatments and radiative multi-antenna systems for deep regional hyperthermia treatments for oncological treatments. All devices in use in reference centers are these systems. There are many studies that show that microwave and radiative multi-antenna systems provide more homogeneous heat distribution and are more effective in deep and superficial tumors compared to capacitive systems (24–26). Therefore, it is predicted that the hyperthermia devices to be planned in our country for oncological treatment should be microwave and radiative multi-antenna system hyperthermia devices.

Besides training with the goal of treating cancer using ionizing radiation and understanding the effects of radiation and tumor behavior, radiation oncologists also undergo theoretical and practical training about the role and principles of chemotherapy in cancer treatment, its preparation, delivery, potential side effects and interactions with methods such as hyperthermia (radiosensitizer) within the scope of their specialization training. In local-regional hyperthermia procedures, the energy amount determined by the radiation oncology specialist is directed to the device through a network and the output levels are monitored throughout treatment to deliver hyperthermia safely.

Hyperthermia treatment is also performed in our country by radiation oncologists as an adjunct treatment method in cancer treatment. Hyperthermia is charged under the heading Radiation Oncology in Annex-8 of the Health Practice Communiqué. According to this information, except for conventional radiotherapy, a lower number of patients require specific treatments or hyperthermia treatments that may be delivered in combination with chemo/radiotherapy in this context. Some private hospitals have invested in this area, but the number does not seem sufficient and not enough for oncological treatment. These devices should also be available in the Ministry of Health Training and Research Hospitals where cancer treatments are performed at much higher rates. Reference hospitals that have more than one radiotherapy device and high patient admission rates in central areas require specific devices for hyperthermia procedures. The planning of hyperthermia takes longer than conventional treatments and in daily practice only 4–5 patients can be treated.

There are 183 microwave and radiative multi-antenna system hyperthermia devices in use in reference centers worldwide for oncological treatments and included in double-blind randomized clinical trials (Table 2). Reviewing the number of devices by year showed that there were 42 devices in 2005, 94 in 2010, and 126 in 2015. As these data also demonstrate, the number and the rate of hyperthermia devices are also increasing worldwide, and they are becoming increasingly effective in the treatment of cancers that require a multimodal approach.

Table 2
Number of hyperthermia devices by country

Devices	USA	EU	Belgium	Germany	Italy	Netherlands	Poland	Spain	Switzerland
500	52	21	1	4	5	2	7	2	2
2000/2000 3D	8	21	0	15	3	2	1	1	1
2000-3D-MRI	0	5	0	4	0	1	0	0	0

Studies towards making hyperthermia standard treatment are continuing. In clinical studies, by adding regional hyperthermia to RT and/or CT, objective response rates such as local tumor control and survival have been demonstrated depending on temperature (6, 8, 12, 14, 17, 21). In this context, more detailed randomized clinical trials are required. For simultaneous applications with radiotherapy for primary and locally recurring tumors, in line with the current studies and future data, the most appropriate approach will be to deliver hyperthermia to patients deemed appropriate by relevant oncology councils and for the indications to be specified clearly by scientific councils.

Conclusions:

Finally, hyperthermia is an effective radio-chemo-sensitizer for certain indications in the treatment of cancer; superficial hyperthermia especially for advanced breast cancer, malignant melanoma, soft tissue sarcomas and head and neck cancers and deep regional hyperthermia, especially for cervical cancer, rectal cancer, anal carcinomas, soft tissue sarcomas, bladder and prostate cancers. In EU countries such as Germany, Holland, Sweden and the USA, HT is used effectively as an oncological treatment option that is reimbursed within the scope of health insurance. In our country, in a high number of centers, current cancer treatment systems are being implemented with advanced devices and methods. The presence of hyperthermia devices in comprehensive oncology centers that carry the weight of the treatment numbers and that possess extensive device park space and enough radiation oncologists, will provide a significant benefit to oncologists with respect to treatment availability and effectiveness and in providing patients with higher quality and more effective and holistic treatments.

Abbreviations

- RT: Radiotherapy

- CT: Chemotherapy

- NK: Natural Killer

- MRI: Magnetic Resonance Imaging

Declarations

- Hospital TUEK approval was received for this retrospective article.

- The authors give consent for publication.

- The data and materials were available and they can be shared.

- There were no conflict of interest between the authors.

- There were no funding for this manuscript.

- Both authors contributed to all stages of the article.

- We would like to thank all hyperthermia centers and hospital administrations that we share information with.

- Authors' information (Not applicable)

References

1. G Bruggmoser, S Bauchowitz, R Canters, et al. Guideline for the clinical application, documentation and analysis of clinical studies for regional deep hyperthermia. Strhlenther Oncol suppl 2; 198-211, 2012.
2. Datta NR , Bodis S. Hyperthermia with radiotherapy reduces tumour alpha/beta: Insights from trials of thermoradiotherapy vs radiotherapy alone. Radiother Oncol. 2019 Sep;138:1-8. doi: 10.1016/j.radonc.2019.05.002. Epub 2019 May 24.
3. Hermisson M et al. Hyperthermia enhanced chemosensitivity of human malignant glioma cells. Anticancer Research, 2000.
4. Kroesen M, Mulder HT, van Holthe JML, et al. The Effect of the Time Interval Between Radiation and Hyperthermia on Clinical Outcome in 400 Locally Advanced Cervical Carcinoma Patients. Front Oncol. 2019 Mar 8;9:134. doi: 10.3389/fonc.2019.00134. eCollection 2019.
5. Istomin YP, Zhavrid EA, Alexandrova EN, et al. Dose enhancement effect of anticancer drugs associated with increased temperature in vitro. Exp Oncol 2008.
6. Issels RD. Hyperthermia adds to chemotherapy. Europen Journal of Cancer 2008.
7. Gerweck LE. Hyperthermia in cancer therapy: The biological basis and unresolved questions. Cancer Research 1985.
8. Wust P, Hildebrandt B, Sreenivasa G, et al. Hyperthermia in combined treatment of cancer. Lancet Oncol 2002.
9. Crezee H, van Leeuwen CM, Oei AL, Stalpers LJ, Bel A, Franken NA, et al. Thermoradiotherapy planning: integration in routine clinical practice. Int J Hyperthermia (2016) 32(1):41–9.10.3109/02656736.2015.1110757
10. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015 Mar;65(2):87-108. doi: 10.3322/caac.21262. Epub 2015 Feb 4.
11. Turkey Cancer Statistics, RT Ministry of Health Turkish Public Health Institution, Ankara, 2017

12. Ott OJ, Schmidt M, Semrau S, et al. Chemoradiotherapy with and without deep regional hyperthermia for squamous cell carcinoma of the anus. Strahlenther Onkol. 2019 Jul;195(7):607-614. doi: 10.1007/s00066-018-1396-x. Epub 2018 Nov 2.
13. De-Colle C, Weidner N, Heinrich V, et al. Hyperthermic chest wall re irradiation in recurrent breast cancer: a prospective observational study. Strahlenther Onkol. 2019 Apr;195(4):318-326. doi: 10.1007/s00066-018-1414-z. Epub 2019 Jan 3.
14. Merten R, Ott O, Haderlein M, et al. Long-Term Experience of Chemoradiotherapy Combined with Deep Regional Hyperthermia for Organ Preservation in High-Risk Bladder Cancer (Ta, Tis, T1, T2). Oncologist. 2019 Jul 10. pii: the oncologist.2018-0280. doi: 10.1634/theoncologist.2018-0280.
15. He M, Sun J, Zhao D, et al. Modified-FOLFIRINOX combined with deep regional hyperthermia in pancreatic cancer: a retrospective study in Chinese patients. Int J Hyperthermia. 2019;36(1):394-402. doi: 10.1080/02656736.2019.1579371. Epub 2019 Mar 27.
16. Engelhardt R (1987) Hyperthermia and drugs. Recent Results Cancer Res 104: 136-203.
17. Dahl O (1988) Interaction of hyperthermia and chemotherapy. Recent Results Cancer Res 107: 157-169.
18. Hahn GM (1979) Potential for therapy of drugs and hyperthermia. Cancer Res 39: 2264-2268.
19. Urano M, Kuroda M, Nishimura Y (1999) For the clinical application of thermochemotherapy given at mild temperatures. Int J Hyperthermia 15: 79-107.
20. Issels RD (1993) Hyperthermia and thermochemotherapy. Cancer Treat Res 67: 143-160.
21. Issels RD et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high risk soft-tissue sarcoma; a randomised phase III multicenter study. Lancet Oncol, 2010.
22. Wendtner CM et al. Response to neoadjuvant chemotherapy combined with regional hyperthermia predicts long-term survival for adult patients with retroperitoneal and visceral high-risk soft tissue sarcomas. J Clin Oncol, 2002.
23. Sauer R, Creeze H, Hulshof M, et al. Concerning the final report "Hyperthermia: a systematic review" of the Ludwig Boltzmann Institute for Health Technology Assessment, Vienna, March 2010. Strahlenther Onkol. 2012 Mar;188(3):209-13. doi: 10.1007/s00066-012-0072-9.
24. Kok HP, Crezee J. A comparison of the heating characteristics of capacitive and radiative superficial hyperthermia. Int J Hyperthermia. 2017 Jun;33(4):378-386. doi: 10.1080/02656736.2016.1268726. Epub 2017 Jan 8.
25. Kok HP, Navarro F, Strigari L, Cavagnaro M, Crezee J. Locoregional hyperthermia of deep-seated tumours applied with capacitive and radiative systems: a simulation study. Int J Hyperthermia. 2018 Sep;34(6):714-730. doi: 10.1080/02656736.2018.1448119. Epub 2018 Apr 18.
26. Kurpeshev O.K., Van der Zee J., Cavagnaro M. Hyperthermia for Deep Seated Tumours-Possibilities of Heating with Capacitive Devices. Медицинская радиология и радиационная безопасность. 2019; 64(4): 64–75.