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Research Article

Evaluation of Oncological Hyperthermia Centers and Turkey Modeling

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Abstract

Hyperthermia is a complementary treatment method that enhances the effect of radiotherapy (RT) and chemotherapy (CT) by rising the cancer tissue temperature. Several biological bases are included in the utilization of oncological hyperthermia. The hyperthermia-induced cytotoxicity mechanisms are outlined clearly and correlated with irreversible damage to cellular respiration, alterations in nucleic acid and protein synthesis, increased cell membrane permeability, and lysosomes liberation.

Keywords: saliva; peptidomics; type 2 diabetes; AlphaFold; bioprinting; mucosal barrier

1. Introduction

Hyperthermia is a complementary treatment method that enhances the effect of radiotherapy (RT) and chemotherapy (CT) by rising the cancer tissue temperature. Several biological bases are included in the utilization of oncological hyperthermia. The hyperthermia-induced cytotoxicity mechanisms are outlined clearly and correlated with irreversible damage to cellular respiration, alterations in nucleic acid and protein synthesis, increased cell membrane permeability, and lysosomes liberation [1,2].

Furthermore, this treatment method has a remarkable effect when applied simultaneously with RT since the cells in the S phase and hypoxic cells are more sensitive to heat. Furthermore, it leads to radiosensitive outcomes by enhancing the oxygenation due to an increase in the blood flow [3,4]. It is worth mentioning that this therapeutic method may improve the cytotoxic effects when applied simultaneously with CT. This is owing to the increased blood flow and membrane permeability as a result of an increase in the local temperature [5,6]. These alterations in tumor oxygenation and the blood flow make cancer cells more sensitive to RT (7-9). Although the latest technology and current therapies are used in the treatment of cancer in Turkey, oncological hyperthermia equipment is not available in this country. As previously mentioned, oncological hyperthermia is one of the effective parts of cancer treatment. Moreover, it has been widely used at an increasing rate in recent years all over the world.

2. Objectives

This study aimed to demonstrate the necessity of oncological hyperthermia devices in Turkey where cancer treatment is performed effectively. In this direction, some important oncology and oncological hyperthermia centers have been examined, and the obtained information has been investigated as to what kind of planning can be developed in this country.

3. Methods

The data were collected via contacting the relevant reference comprehensive cancer-related centers that use non-invasive oncological hyper- thermia systems. Moreover, the published literature was searched in terms of the use of oncological hyperthermia devices. Following that, vast amounts of data were gathered about the number of patients who underwent hyperthermia during the treatment procedure, varieties in cancer types, and rate of hyperthermia use.

The annual number of patients with cancer and rates of diagnosis were evaluated according to the cancer statistics related to the communicated countries. In these countries, the number and rates of patients requiring oncological hyperthermia treatment were determined according to the number of patients across the country and cancer diagnoses. In addition, the number of devices per person was examined according to the number of oncological hyperthermia centers and devices. Given the aforementioned information, phase III clinical trials investigated the effects of RT and/or CT, as well as simultaneous use of hyperthermia, which were published in the literature. In the next stage, the number of annual diagnosed cancer cases and the diagnosis groups were obtained based on the cancer-related data archived in the Cancer Department in Turkey. In line with the abovementioned data, the information was compared, and modeling was prepared for this country. If the oncological hyperthermia device can be reached, it would be possible to evaluate the number of cancer patients that can be applied to this treatment across the country. Subsequently, the number of oncological hyperthermia devices required throughout the country and the regions (in which these devices should be built) could be determined according to the number of these applications.

4. Results

The data were collected from 23 oncological hyperthermia treatment centers across the world, each of which is considered a reference in cancer treatment and research. After examining the number of devices, it was observed that 12 and 23 superficial and deep regional hyperthermia devices were present in these centers, respectively. In these centers, on average, 8760 and 4380 patients had undergone deep regional and superficial hyperthermia each year, respectively. Regarding the distribution of cancer diagnoses, the results showed that hyperthermia treatment was applied in soft tissue sarcomas (25%), cervical cancer (20%), breast cancer (19%), gastrointestinal system tumors (12%), genitourinary system tumors (8%), head and neck tumors (7%), melanoma (5%), and other cancer types (4%). Considering the population and annually diagnosed cancer cases of these countries, approximately, 200 million cancer cases and 650,000 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 people. In other words, in these countries, there are 0.18 hyperthermia devices per one million population, and an average of 375 patients are treated annually per hyperthermia device. Concerning the annual cancer cases, hyperthermia is applied in superficial and deep solid tumors, which account for approximately 2.2% of all patients treated for malignancy. Therefore, the patient load/year per device is observed as 375 cases (10).

A similar projection has been performed for Turkey, and the national statistics from 2014 were taken into consideration. Based on these data, it can be predicted that approximately 200,000 new cancer patients will be diagnosed annually (11). In this 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 one million population. Considering annual new cancer cases, services can be provided at an approximate rate of 400 patients/year with the same number of hyperthermia devices.

According to the data of 2018 TURKSTAT, approximately 50% of the country's population live in the top 10 cities with the densest population. On the account of the neighboring cities, transportation networks, and planning zones for modern RT centers, most cancer treatments are delivered in these cities. In this regard, when hyperthermia devices are planned in comprehensive oncology centers (regional training and research hospitals specialized in cancer treatment that have sufficient devices, equipment, and doctors) in which the population and the patient density are highest, services can be provided to more than 400 patients annually. After installing hyperthermia devices in these regions and centers, it will become possible to deliver more effective and holistic cancer treatments; moreover, the planning will be more cost-effective.

5. Discussion

Laboratory and clinical studies have shown the multifaceted mechanism of hyperthermia. In addition to cytotoxic (stopping) and apoptotic (killing) effects on cancer cells, hyperthermia stimulates and strengthens the body's immunity cells (1, 2). The activity of the immune cells and the transfer of CD8-T cells to tumor sites are increased by hyperthermia. Normal tissues, such as tumor tissue, are also sensitive to hyperthermia (12). Tumor tissue reproduces rapidly and uses a lot of energy. This makes tumor tissues more hypoxic with a 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 CT and RT, the use of hyperthermia combined with these treatments increases the effectiveness of RT and CT. Hyperthermia increases the oxygenation of the tumor and makes tumor cells radiosensitive by increasing the blood flow to tumor tissue. Furthermore, it affects the repair stage of RT- induced DNA damage. Additionally, it makes the tumor cell more sensitive to RT by preventing the repair of the damage that occurs in the tumor DNA. Although the cytotoxic effect of RT increases when combined with hyperthermia, the radiosensitizing 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 hyperthermia combined with RT have proven the effectiveness of this treatment combination. In these studies, an increase has been observed in the rates of local control and treatment. Effective treatments are also applied in Turkey with the latest technological devices in large RT centers. This study was designed considering that this effect 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 leading to protein folding. As a result, the cell undergoes apoptosis or necrosis depending on the temperature level. Cellular resistance to protein degradation is caused by increased temperature owing to 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. The HSP70-activated NK cells destroy primary and metastatic tumor cells that express HSP70. Following that, the HSP70 proteins released from dead tumor cells increase the T-cell infiltration into the tumor (13,14). The effect of hyperthermia that improves the success of RT is similar to that of CT. Hyperthermia increases the effectiveness of CT using synergistic effects. In line with an 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 conducted by Engelhardt, Dahl, Urano, and Issels have shown that hyperthermia demonstrates synergism in CT as in RT (16-20). Table 1 summarizes the synergism and activity of some chemotherapeutic agents and HT under various microenvironmental conditions.

Although hyperthermia is considered 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). Moreover, the role of hyperthermia in the treatment of cancer has been summarized in a study carried out by Sauer, R et al. and published by the German Cancer Society in Sthrahlenther Oncol in 2012. This study is regarded as an explanatory text in which hyperthermia is recommended, especially in primary tumors and local recurrences (23). Hyperthermia 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, and in the near future, the combined oncological treatments with hyperthermia will be delivered to more patients and the beneficial effects of this should be observed. Hyperthermia also makes cancer cells more sensitive to RT and the effects of certain anti-cancer drugs in a way that could potentially reduce the number of RT treatments required. Today, better outcomes are obtained in terms of treatment results and toxicity due to advanced application techniques (i.e., three-dimensional hyperthermia) and real-time observation (i.e., magnetic resonance imaging monitorization) (9). However, in some countries, various reasons, such as reimbursement problems, technical difficulties, and difficulties in homogenous heating and monitoring temperature.

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

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

Abbreviations: NYD: not yet determined; ↑: strong interaction, BCNU / TMZ: Carmustine (bischloroethylnitrosourea) / Temozolomide 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 hyperthermia 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. The development of strategic plans, as well as implementation and monitoring techniques, lead to the enhancement of the hyperthermia even further. The mathematical modeling of the effects of hyperthermia on cell biology mentioned previously has led to true thermo-radiotherapy planning (9). The present study evaluated the microwave and radiative multi-antenna systems for superficial and deep regional hyperthermia in oncological treatments, respectively. These systems are among those devices that are currently utilized in reference centers. Several studies show that microwave and radiative multi-antenna systems provide more homogeneous heat distribution which is 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. In addition to training with the goal of cancer treatment 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 CT 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 amount of energy 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 Turkey by radiation oncologists as an adjunct treatment method in cancer treatment. Furthermore, hyperthermia is charged under the heading Radiation Oncology in Annex-8 of the Health Practice Communiqué. To our knowledge, except for conventional RT, a lower number of patients require specific treatments or hyperthermia treatments that may be delivered in combination with CT/RT in this context. Some private hospitals have invested in this area; however, the number does not seem sufficient 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 RT device and high patient admission rates in central areas require specific devices for hyperthermia procedures.

The development of plans for hyperthermia takes longer than conventional treatments, and 4-5 patients can be treated in daily practice only. There are 183 microwave and radiative multi-antenna system hyperthermia devices in use in reference centers worldwide for oncological treatments that are included in double-blind randomized clinical trials (Table 2).

After the evaluation of the number of devices by year, there were 42, 94, and 126 devices in 2005, 2010, and 2015, respectively. These data also demonstrate the increasing number and rate of hyperthermia devices worldwide; moreover, they are becoming increasingly effective in the treatment of cancers that require a multimodal approach. In addition, the presence of a hyperthermia device in an oncology center contributes to patients feeling psychologically better with the idea that they will receive complete treatment. A superficial hyperthermia device was used in our clinic for a short period between 2013 and 2015. It initially served only for palliative purposes; however, it caused a significant increase in the number of patients admitted to the clinic. This supports the requirement that hyperthermia devices be included in the inventory as a complementary treatment at a comprehensive oncology center.

Several studies are being conducted towards making hyperthermia a standard treatment. In clinical studies, objective response rates, such as local tumor control and survival, have been demonstrated depending on temperature by adding regional hyperthermia to RT and/or CT (6,8,12,14,17,21). Therefore, it is necessary to conduct more detailed randomized clinical trials in this regard. Regarding the simultaneous applications with RT 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.

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

Table 2. Number of hyperthermia devices by country.

6. Conclusion

Hyperthermia is an effective radio-chemo- sensitizer for certain indications in the treatment of cancer. Furthermore, superficial hyperthermia is beneficial, especially for advanced breast cancer, malignant melanoma, soft tissue sarcomas, as well as head and neck cancers. Following that, deep regional hyperthermia is utilized, especially for cervical cancer, rectal cancer, anal carcinomas, soft tissue sarcomas, as well as bladder and prostate cancers. In the European Union countries such as Germany, Holland, Sweden, and the USA, hyperthermia is used effectively as an oncological treatment option that is reimbursed within the scope of health insurance. In Turkey, current cancer treatment systems are being implemented with advanced devices and methods at a high number of centers. The presence of hyperthermia devices in comprehensive oncology centers that carry the weight of the treatment numbers and possess extensive device park spaces and sufficient radiation oncologists will provide a significant benefit to oncologists concerning treatment availability and effectiveness. Moreover, they provide patients with higher quality as well as more effective and holistic treatments.

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Footnotes

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