Use of hyperthermal heating and intraoperatively administered applicator for the treatment of local malignant tumors

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SUMMARY

Background: *This article describes a method for non-contact local hyperthermal heating of patient's tissue using inductive electromagnetic radiation.* **Aim:** *The aim of the study was a theoretical and experimental assessment of the thermal and electromagnetic parameters of the proposed method based on heating of intraoperatively administered, personal, tissue-replacing applicator using induction magnetic field.* **Methods:** *Theoretical estimates of the thermal and electromagnetic parameters of this method were performed based on heat conduction equations. An experimental study of the process was carried out using originally designed laboratory inverter and confirmed theoretical calculations.* **Results:** *The performed assessments and calculations confirmed the possibility of creating clinically effective hyperthermia in the removed tumor bed by the method of local non-contact intraoperative hyperthermia.* **Conclusion:** *The proposed method can be used both independently and in combination with chemo- and radiotherapy, thus reducing the risk of recurrence for locally advanced forms of malignant tumors of the oropharyngeal region after surgical treatment.*

Keywords: *laryngeal cancer, intraoperative non-contact hyperthermia, induction heating, polymer matrix, ferromagnetic filler*

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INTRODUCTION

Among malignant neoplasms of the head and neck, cancer of the larynx and laryngopharynx occupy a leading position and account for up to 50% of all cases (1). The main age and sex group affected by this disease is middle-aged and older men (2). The initial development of a tumor of a given localization usually goes unnoticed. Therefore, in most cases, the disease is diagnosed at the late stages of its development (3). At the same time, the effectiveness of treatment for laryngeal cancer directly depends on the period of its detection (4). Although in the last decades significant progress in the treatment of laryngeal cancer has been made, a high probability of five-year survival rate (above 90%) can only be achieved for stages T1 and T2. While, in patients with advanced stages (T3 and T4) statistics of five-year survival are below 60% (5, 6). The most common treatment for patients with advanced-stage III and IV laryngeal tumors is laryngectomy that inevitably leads to loss of organ function and does not exclude relapses.

Research by oncologists is aimed at improving the effectiveness of treatment, reducing the frequency of relapses, and preserving important functions. In order to achive this task complex methods have been developed, usually based on combination of surgical treatment (including partial resection) with pharmacological and radiation therapy (7-9).

One of the promising, complex methods for the treatment of malignant tumors is hyperthermia, when tumor is heated to a temperature of 41-45°C. The effect of hyperthermal heating has a direct and indirect effect on cancer cells - as a result of their increased radio-sensitivity during radiation therapy or chemo-sensitivity during chemotherapy (1, 10).

The main obstacle arising during the implementation of hyperthermal heating is risk of spreading of the tumor to adjacent healthy tissues. Depending on the localization of a particular neoplasm, oncologists have to choose between different methods to create optimal effect of local hyperthermia. In practice, the most widely used are the ones based on the absorption of electromagnetic radiation in the radio frequency range by body tissues (11). Ultra-high-frequency (UHF) radiation has a slightly higher penetrating power. However, this advantage is abrogated by a much lower focusing ability. Beside this a common disadvantage of radiation in the UHF or MMW range is overheating of subcutaneous fat, which is characterized (in contrast to muscles) by a higher electrical resistance (12).

Another well-known method of creating local hyperthermia for cancer treatment is associated with the implantation of ferromagnetic conductors (steel needles) inside the tumor, which are heated by eddy currents of alternating magnetic fields with a frequency below 1 MHz that are known to be poorly absorbed by the body tissues (13). The main problem with this method is the sharp temperature drop near the implant i.e. the tissues closest to implant tend to overheat, while the more remote tissues do not reach the target temperature.

In recent years, another method for hyperthermia has been developed, based on induction heating of fluids containing magnetic nanoparticles injected into the tumor, reaching a Curie temperature close to 43°C (14). The limitations of this method, beside difficulty of creating source of alternating magnetic field with amplitude of about 104 A/m, is also uneven distribution of magnetic nanoparticles due to the specificity of blood flow in the tumor.

This study aims to validate theoretically and experimentally original applicator containing ferromagnetic filler that replaces the removed tissue and in order to use local induction heating for the treatment in medical oncology. Developed method using induction heating of a intraoperatively administered, personal, tissue-equivalent applicator could be used in combination with radiation and chemotherapy.

MATERIALS AND METHODS

The basis of the proposed method for creating hyperthermia was the previously developed method of contact intraoperative high-dose radiotherapy (HDR) with the manufacture of an individual tissue-equivalent

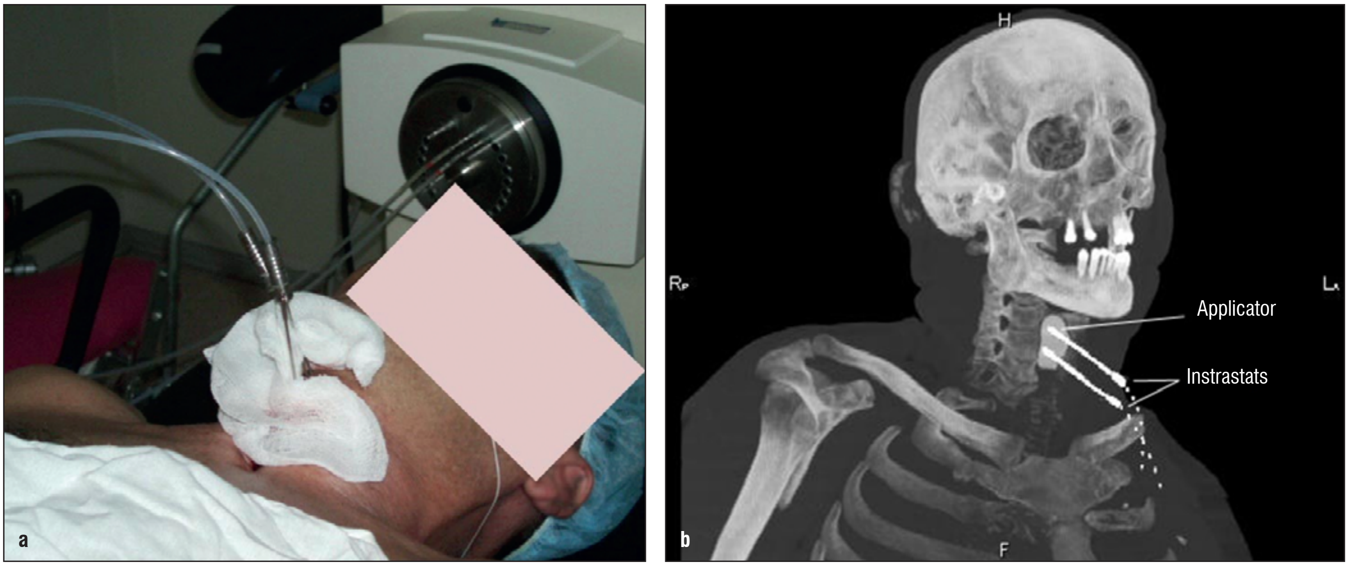

Figure 1. High dose rate contact radiation therapy procedure after resection of a laryngeal tumor and placement of an individual applicator with HDR intrastats (a) and multiplanar reconstruction of the larynx with an applicator and intrastats for HDR procedure (b)

applicator for fixing the intrastats for the radiation therapy application in the removed tumor bed (12). The applicator was heated in an alternating magnetic field of an external inductor with radiation frequency of 100 kHz. This method of radiation therapy allowed for the most accurate calculation of the distribution of the radiation dose over the volume of the tumor removed by surgery (Figure 1).

For a preliminary assessment of the thermal parameters of the developed method, it was necessary to study a simple model of a heated applicator *i. e.* a sphere with a radius R0 made of a polymer material, inside which ferromagnetic spherical particles with a radius r0 were uniformly distributed. When the applicator was in an alternating magnetic field with an amplitude of strength H0 and a cyclic frequency ω, the Foucault currents made each particle a source of thermal energy. Provided r0<<R0 and sufficient density of conductive ferromagnetic particles, in the first approximation, heat sources could be considered uniformly and continuously distributed over the applicator volume.

The experimental verification of the theoretically derived results was carried out using a originaly designed laboratory inductor with a 60 mm long air coil consisting of 10 turns with a diameter of 45 mm. Induction heating occurred in the frequency range of 100 ± 20 kHz. The function of the ferromagnetic filler was performed using steel spheres with a diameter of 1 mm.

The high-frequency current required for induction heating of the applicator was obtained in the course of experiments using a laboratory inverter, schematically shown in Figure 2. Its principle of operation was as follows: Two powerful field-effect transistors, which were the keys of two arms of the power half-bridge, received a rectified stabilized voltage from a powerful regulated mains electrical supply (laboratory autotransformer). The transistors opened and closed alternately by a signal applied to their gates from the driver. The switching frequency, and hence the current frequency, was determined by the driver pulse generator (PG). The inductor (air coil 60 mm long with 10 turns with a diameter of 45 mm and a compensating capacitor connected in parallel) was connected to the bridge through a matching transformer (not shown). The resonant frequency of the inductor corresponded to the frequency of the PG due to the selection of the capacitance of the capacitor.

The electronic part of the unit allowed switching currents up to 1 kW. However, with an increase in power consumption (starting from 100 W), the need for additional forced cooling of the heating coil of the inductor was evident. Further experiments (described below) were carried out at two different powers (20 W and 40 W) that did not require cooling of the coil.

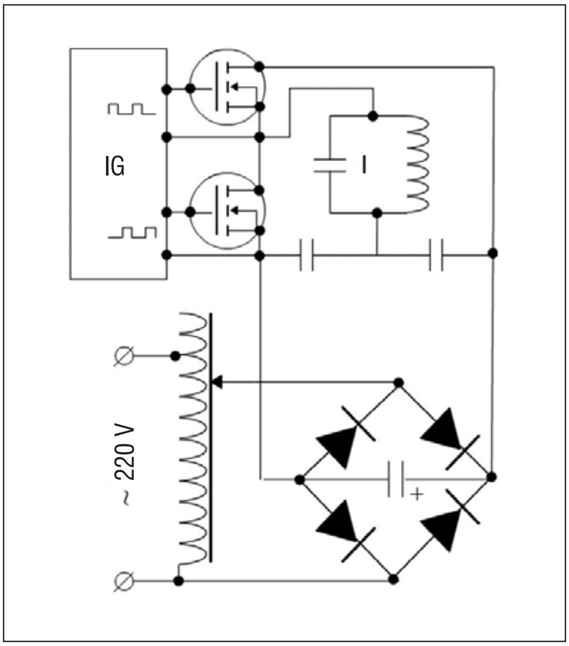

Figure 2. Schematic diagram of the used laboratory unit

To test the possibility of induction heating, different samples of a polymer applicator of the approximately spherical shape of the same size (20 mm in diameter) were made. The function of ferromagnetic fillers was performed by a mixture of ultrafine powders of nickel (80%) and aluminum (20%) with a particle size of 10-100 nm, steel spheres with a diameter of

0.5-1 mm, as well as direct reduced iron (DRI) in the form of small turnings with a size of about 0.1 × 1 × 3 mm. The filler mass fractions varied in the range of 10-60%. The composition of different applicator samples with different filler mass fractions was presented in Table 1.

RESULTS AND DISCUSSION

To obtain the desired hyperthermic effect in living tissues, the surface of the applicator must have a temperature of at least 45°C. Then at $T_0 = 37°C$, it follows that:

$$w = \frac{24\kappa_2}{R_0^2}$$

Assuming that the thermal conductivity of body tissues is equal to the thermal conductivity of water $\kappa_2 = 0.6$ W/(m·K) and if the the size of the applicator is $R_0 = 0.01$ m, we obtained the specific thermal power released in the applicator for assessment: $w \approx 0.1$ W/cm^3. In this case, the temperature gradient was 0.5°C/mm. For example, at an applicator temperature of 45°C, the border of effective hyperthermal heating (41°C) will be at a distance of 8 mm from the applicator surface, insuring that tissues in the potential risk zone near the removed tumor bed will be heated. When applicator is made of a polymer base in which small steel spheres with a mass fraction are evenly distributed, then its average density is

$$\rho_1 = \frac{\rho_s \rho_p}{(1-\nu)\rho_s + \nu\rho_p}$$

and specific heat capacity is $c_1 = (1 - \nu)\ \rho_p + \nu\rho_s$, where c_p, c_s, ρ_p, and ρ_s are the heat capacity and density of polymer and steel, respectively. Assuming that $c_p \approx 1.5 \cdot 10^3$ J/(kg · K), $c_s \approx 0.5 \cdot 10^3$ J/(kg · K), $\rho_p \approx 1.2 \cdot 10^3$ kg/m^3, $\rho_s \approx 7.8 \cdot 10^3$ kg/m^3 and $\nu = 0.5$, then $\rho_1 \approx 2 \cdot 10^3$ kg/m^3, $s_1 = 10^3$ J/(kg · K) and

$$\Delta t \approx \frac{2 \cdot 10^6}{10^5} 6 = 120 \text{ s}$$

From the above calculations it was evident that the heating of the applicator was carried out in a few minutes, even considering the heat removal due to thermal conductivity. In Figure 3 the results of heating the spherical applicator with a diameter of 20 mm in the air coil of a laboratory inductor was shown. Based on the obtained data, it took less than 5 min to increase the temperature of the applicator by 10°C.

In the simplest model of the heated applicator, if under the influence of induction heating heat q_1 is released inside the applicator per unit of time, while part of the heat q_2 is emitted by the surface of the sample, it can be approximated that $q_2 = \sigma(T - T_0)$ where T is the sample temperature and T_0 is the ambient temperature; $\sigma = 0.020$ W/K is a constant proportional to the surface area, identical for all samples.

Given the initial condition $T(0) = T_0$, it follows that:

$$T = T_0 + \frac{q_1}{\sigma}\left(1 - \exp(-\alpha t)\right)$$

Filler mass fraction (%)	Filler mass (g)	polymer base mass (g)	Sample applicator volume (cm^3)
10	0.59	5.34	4.19
20	1.31	5.22	
30	2.18	5.08	
40	3.27	4.90	
50	4.67	4.67	
60	6.53	4.35	

Table 1: Percent of filler fraction and filler and polimer mass in different sample applicators

To establish the nature of the dependence of the efficiency of induction heat release q1 on the size of the filler particles, we investigated a single spherical particle of radius R, located in an alternating uniform magnetic field $B = B_m \cos \omega t$. At the initial stage of calculations, we considered the particle as a non-magnetic conductor. This assumption helped us to avoid violations of the uniformity of the magnetic field near the curved surface of the ferromagnet and to exclude the work spent on remagnetization of the sample from the calculations.

Thus, at a power consumption of 20 W, the samples with the nanodispersed filler practically did not heat up. An increase in the power to 40 W led to noticeable heating only for samples with a filler mass fraction of 60%, which was explained by the formation of conglomerates of nanoparticles at their high concentration. This ensured their direct contact and thus increased their effective size.

The data obtained in experiments with samples including filler made of spherical balls with a diameter of 0.5 mm, heated at a power consumption of 20 W, were shown in Figure 3. With such an inductor power, heating the samples to a hyperthermal temperature at ambient room temperature turned out to be possible only for samples with a mass fraction of a ferromagnetic material above 50%. Modeling parameters for a mass fraction of 20%, $q_1 = 0.225$ W for a mass fraction of 40%, and $q_1 = 0.375$ W for a mass fraction of 60%.

The data obtained in experiments with samples containing filler made of 1 mm steel spheres were shown in Figure 4. The results of these experiments indicated that when spheres with a diameter of 1 mm were used as

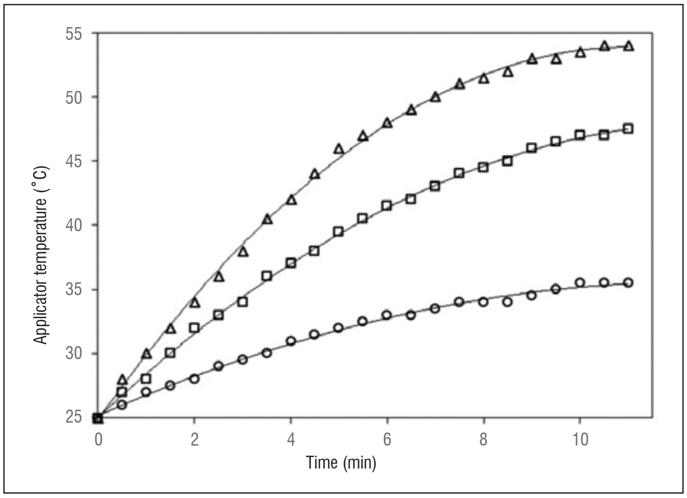

Figure 3. Experimental results after heating the applicator. The amplitude of the alternating magnetic field in the coil was 500 A/m. Filler: steel spheres with a diameter of 1 mm: ○: 20%, □: 40% and △: 60% of the filler in mass of sample applicator

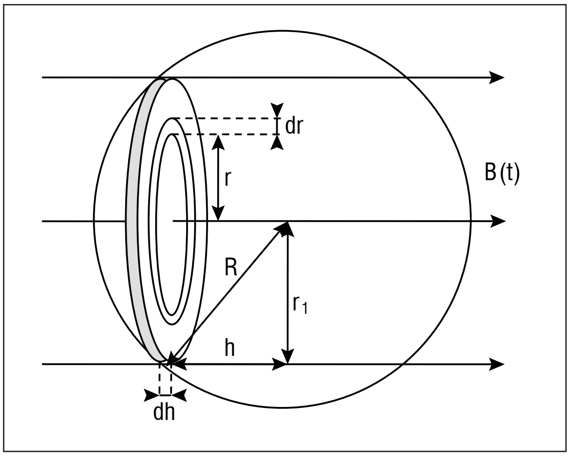

Figure 4. Shematic diagram of sample applicator parameters for heat release calculation

a filler, all prototypes with a mass fraction of spheres exceeding 20% were steadily heated to a temperature above 40°C even when a power of the unit equaled 20 W. The simulation was carried out based on the parameter $\sigma = 0.020$ W/K, as in the previous case.

The results obtained fully proved the possibility of contactless induction heating of non-conductive materials in biological tissues to achieve hyperthermic temperatures. Further research in this area and development and creation of an automated control system for long-term maintenance of the temperature of heated applicators at the target level is suggested. It is necessary to compare various methods for the control of the thermal power and to develop a technique and technology for monitoring and providing uniform temperature of the applicator. An important task for further research is also the development of different inductors for specific applications. We propose open external inductor with a magnetic core made of ferrite as the most promising model.

CONCLUSION

The performed assessments and calculations confirmed the possibility of creating clinically effective hyperthermia in the removed tumor bed by the method of local non-contact intraoperative hyperthermia. The proposed method can be used both independently and in combination with chemo- and radiotherapy, thus reducing the risk of recurrence for locally advanced forms of malignant tumors of the oropharyngeal region after surgical treatment.

Declaration of Interests

Authors declare no conflicts of interest.

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