

## **PROMISING TRENDS IN THE DEVELOPMENT OF SYSTEMIC HYPERTHERMIA IN MULTIMODALITY THERAPY FOR MALIGNANT NEOPLASMS**

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Over the past 30 years odd, investigations in hyperthermic oncology presupposing application of high temperature (40–43°C for whole-body exposure and 42–47°C for local treatment) for enhancing the efficacy of combination or multimodality therapy have been undertaken in all developed countries. The first studies of medicotechnical, experimental and clinical aspects of hyperthermic oncology at the State Institution «N.N. Alexandrov Research Institute of Oncology and Medical Radiology» began as early as in 1968 [1, 7]. To date, the Institute has gained experience of more than 5,000 whole-body hyperthermia procedures with induced hyperglycemia and multidrug chemotherapy in multimodality treatment of cancer patients with various nosologic forms of malignant tumors. Our experience of many years' standing enables to conclude that indications for multimodality therapy including hyperthermia are (1) far-advanced and generalized forms of malignant tumors for which conventional treatment methods are ineffective or seem to be known to have no prospects; (2) presence of conditions and factors worsening the disease prognosis; (3) unresectable tumor forms to be transformed into a resectable state as a result of regression; (4) non-radical and conditionally radical surgical interventions; (5) neoplasms developing resistance to cytostatic therapy in the course of the treatment (chemo- and radioresistant tumors).

According to our data, patients with the following nosologic forms of malignant tumors are eligible for different options of whole-body hyperthermia/hyperglycemia: soft tissue and bone sarcomas, melanomas, renal cell carcinoma, unresectable forms of primary and metastatic hepatic tumors, breast cancer, small-cell lung cancer, some other nosologic forms of tumors (moderately and poorly differentiated retroperitoneal sarcomas). In these cases whole-body hyperthermia with hyperglycemia and chemotherapy may be used both as part of primary programmed treatment (adjuvant and/or neoadjuvant setting), and a component of salvage therapy for patients with disease progression in the course or after the programmed treatment.

For the time being, appropriate optimal programs of multimodality therapy with whole-body hyperthermia are still unavailable for patients with different nosologic forms of malignant tumors. Such programs may be developed in co-operative studies applying common criteria for patient eligibility, establishing common treatment protocols and comprehensive evaluation of treatment outcomes. Nevertheless, nowadays there is no doubt about the fact that controlled whole-body hyperthermia/hyperglycemia with chemotherapy (drug doses lower than the course ones) administered according to the techniques we have developed [3, 4] improves oncological efficiency of the therapy for patients with advanced disease. A comparative analysis of treatment efficacy using the 5-year survival rate criterion in identical comparably matched arms of patients with melanoma, soft tissue sarcomas, renal cell carcinoma (the total number of patients in this sample being 244 in the study arm and 267 in the control arm) demonstrated that the use of whole-body hyperthermia in multimodality treatment programs increased the 5-year survival rate 2.2-fold compared to that in the control arm where the complex treatment was carried out without the hyperthermia/hyperglycemia component (39.4% vs 17.2%, that is higher by 22.2%). No less significant ( $p < 0.05$ ) are the comparative rates using the 10-year survival criterion: for stage IV skin melanoma – 24.7% vs 12.9% (36 patients in

the study arm and 41 in the control) and poorly differentiated soft tissue sarcomas – 61.5% vs 31.1% (133 and 152) in particular.

The potential and reserves of multimodality therapy using hyperthermic techniques are far from being exhausted. There is a number of practicable ways and new promising trends for the improvement of this method. Among them are the following:

1. Creation of perfect universal multifunctional hyperthermic systems operating in a wide range of electromagnetic wave frequencies and therefore enabling to provide the needed (individual in each case) thermal exposure rate in tumors regardless of their sites, volumes and consistency. In this respect, deserving consideration are computer-based systems for whole-body hyperthermia – Ptich (Minsk, Belarus), YuG-VChG (Nizhny Novgorod, Russia) operating in the frequency range of 13.56 MHz, and especially the latest model of BSD.2000.3D unit for deep regional hyperthermia. This system includes an electromagnetic hyperthermic unit proper (frequencies from 915 MHz to 434 MHz) and an MR-imager. It provides MRI monitoring of hyperthermia with determining not only the temperature levels but also such values as tumor volume, blood flow, necrosis in the tumor, etc. On October 20, 2003 Prof. P. Wust (Berlin) reported about the employment of this unit for the treatment of patients with pelvic sarcomas, rectum cancer, prostatic cancer, intraperitoneal sarcomas, soft tissue sarcomas of the extremities and others at the International Interuniversity Workshop for Diagnostic and Therapeutic Radiology (Minsk) [6]. The reporter claimed that his method was simpler than others, partial hyperthermia being better tolerated, requiring no anesthesia, and being appropriate for use in outpatient setting. Undoubtedly, the unit and the method are an important step forward having prospects in the issue of hyperthermic oncology. However, they are used only in regional hyperthermia and cannot be applied in patients with stage IV disease which considerably limits the scope of indications for and the potential of the hyperthermic method.
2. Combined (sequential) or concomitant (concurrent) use of local and whole-body hyperthermia. Our investigations (Patent № 6001 of the Republic of Belarus) demonstrated a feasibility in principle to obtain higher temperature rates locally in tumors (43–47°C) in whole-body hyperthermia setting (40–42°C) for different nosologic forms of malignant neoplasms. Hence, concurrent application of whole-body and local hyperthermia makes it possible to safely raise the temperature in the tumor by 3–4°C compared with the body core, which is naturally impossible when using only systemic hyperthermia. Thus, conditions are provided to increase the degree of the sensitizing and damaging effect of hyperthermia/hyperglycemia on the tumor, which selectively potentiates and accelerates inactivation (devitalization) of the tumor cells.
3. Combined administration of whole-body hyperthermia/hyperglycemia and biotherapy (interferon, interleukin-2, etc.). A randomized study carried out by our Institute's researcher O.G. Sukonko has established the fact that systemic hyperthermia and biotherapy following nephrectomy improves 5-year survival of high-risk renal cancer patients 1.5-fold compared to that of patients treated with systemic hyperthermia alone (68.2% vs 45.1%).
4. Employment of whole-body hyperthermia (especially its concomitant option) in combination with hemosorption on activated carbon (Patent № 6538 of the Republic of Belarus). The method reduces endogenous intoxication, lowers the toxic reactions to anticancer drugs and enhances sensitivity of malignant neoplasms to cytostatics.
5. Concurrent use of hyperthermia and chemoembolization of arteries supplying blood to tumors. The study including 47 patients with bone and soft tissue sarcomas, conducted at N.N. Alexandrov Research Institute of Oncology and Medical Radiology (Patent № 6456 of the Republic of Belarus) found that systemic chemotherapy (doxorubicin) in combina-

tion with chemoembolization of arteries supplying blood to tumor (cisplatin) and local electromagnetic hyperthermia (42–45°C, 60 min) reduced the tumor volume by more than 50% in 76.7% of the cases and caused complete response in 2.1%. Grade III-IV posttherapeutic pathomorphism occurred in 42.1% of the cases. With tumors locating on the extremities, limb-sparing surgery succeeded in 86.8% (33/38).

The treatment of patients (31) with inoperable primary or metastatic hepatic cancer also showed the expedience of concurrent administration of local and especially whole-body hyperthermia with chemoembolization of the hepatic artery (Patents № 2751 and № 5836 of the Republic of Belarus): each third patient presented with 3-year survival.

6. Realizing the potential of multimodality therapy within the programs of organ-sparing and function-sparing treatment of cancer patients. This issue is of great scientific and practical importance for framing the concept of providing optimal conditions for performing the above operations improving the quality of cancer patient's life. It is critical for patients with locally advanced malignant neoplasms of the extremities. Our data indicate that the inclusion of electromagnetic hyperthermia in treatment programs for patients with locally advanced soft tissue sarcomas increases the rate of limb-sparing operations 7-fold compared to that with surgery alone and reduces the rate of amputations 3-fold compared to that with combination treatment (without hyperthermia). Of vital importance is the choice of hyperthermia and reconstructive and restorative surgery techniques. Thus, the combination of local thermoradiochemotherapy with complex vascularized flaps grafting allowed to perform limb-sparing operations in 92.3% of patients with poorly differentiated locally advanced malignant neoplasms locating on the extremities, the 5-year survival rate being no less than 65%.

## Conclusion

Thus, theoretical, experimental and clinical research indicates that controlled induced hyperthermia and hyperglycemia are a powerful chemo- and radiomodifying factor. There is no doubt about the expediency of inclusion of whole-body hyperthermia in particular in the programs of multimodality therapy for cancer patients with advanced forms of the disease (in case of no contraindications). The search for optimal programs of multimodality treatment for patients with malignant neoplasms including local, whole-body, combined and concurrent hyperthermia is quite justified and advisable.

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