Past Clinical Studies and Future Directions

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Abstract

The biological rationale for hyperthermia and radiation is strong, initial results in superficial tumor sites have established efficacy in human cancer, and deep tumor sites are beginning to yield to our efforts at deep regional heating. Major thrusts of new clinical research should go toward improved equipment and defining techniques with existing devices, which can lead us into definitive Phase III trials to assess the role of regional hyperthermia in primary multimodality management of cancer. Detailed thermometry is an absolute requirement for all future clinical studies. Invasive techniques to achieve deep hyperthermia are under investigation and may prove to be useful. Whole-body hyperthermia with radiation and/or chemotherapy has been less well studied in the laboratory than has local hyperthermia, and studies to show clinical efficacy in humans are lacking.

A reiteration of the strong biological rationale for the potential of hyperthermia as a treatment of cancer in humans is espoused in the work in this supplement (7, 15). Past clinical trials and those in progress, treating superficial tumors with localized hyperthermia and radiation, confirm that heat has efficacy in the treatment of human cancers. On the other hand, studies to date utilizing deep regional hyperthermia teach us more about the complexity of the approaches and the many problems to be surmounted than about the efficacy or usefulness to our patients of such treatment. In spite of an attractive rationale for WBH, after years of clinical study, a clear statement cannot be made as to its efficacy and safety.

Where are we now and where are we going? A primary issue is efficacy of hyperthermia. In 1980, Overgaard (23) reviewed reports of over 3000 patients treated worldwide by a variety of EM and ultrasound techniques, and with highly variable attention to thermometry. From results in this group of patients, he concluded that heat alone has limited efficacy with reported CRs of only 13%, a rate comparable to that reported at Stanford (18). Further, Overgaard found several studies with heat-plus-X-ray and X-ray-only comparison arms. The studies were not randomized, but when summarized they did suggest that heat plus X-ray was superior to X-ray alone, with CRs approximately double in the heat-plus-X-ray-treated patients. In a study of superficial melanoma metastases, Kim et al. (16), using matched lesions in the same patient, reached the same conclusion. The prospective randomized study by Arcangeli et al. (1) again showed that the CR rate in heat plus X-ray was about double that in the X-ray only controls. Scott et al. (8) reviewed a series of patients with advanced head and neck tumors, or breast cancers with recurrent chest wall disease, who were treated with conventionally fractionated high-dose radiation plus twice weekly hyperthermia. In 31 patients, control lesions were treated by X-ray alone. This was not a randomized study; however, the smaller of the 2 treated lesions was assigned to the X-ray-only arm. Again, the CR rate was much better in the patients treated with heat plus X-ray, and this was achieved without added complications. These clinical reports are summarized in Table 1. A randomized study comparing X-ray with X-ray plus heat by the Radiation Therapy Oncology Group is nearing completion and, although the blinding has not yet been broken, the treatment arms are separating, suggesting that Arcangel’s results may be duplicated in the United States. In this volume, Perez and Sapareto (25) show data indicating that the CR rate predicts for prolonged response, and Meyer (19) reviews a large number of superficial hyperthermia studies. My conclusions from these various studies are as follows. (a) For superficial, easily heated cancer deposits, hyperthermia has efficacy in humans; (b) the efficacy of hyperthermia alone is limited and too low in terms of CR rate to make a large impact on the morbidity and mortality of human cancer. Heat alone may, however, provide important palliation for a limited number of previously treated patients; (c) heat plus X-ray shows a substantial advantage over X-ray alone; and (d) these studies of superficial tumors strengthen considerably the rationale for continuing investigations of approaches designed to achieve heating of deep tumor sites, where failure by current methods to achieve local-regional control of cancer leads to serious morbidity and mortality.

The studies of combined hyperthermia and ionizing radiation in superficial tumors have failed to show a serious detrimental effect in normal tissues, and the statement has frequently been made that the combination is safe. Caution is warranted, however. In animal studies, direct thermal injury, enhancement of the X-ray response by hyperthermia, and thermotolerance have all been demonstrated in normal tissues. Studies reported to date do not have large numbers of patients with effective hyperthermia to radiation-dose limiting tissues who survived long enough to accurately assess late effects. Because of this, the issue should remain open for hyperthermia of tumors at deep anatomical sites.

A most important aspect of local or regional hyperthermia investigation involves thermometry. In the absence of reliable noninvasive techniques, temperatures must be measured by thermometers placed invasively into tumor and normal tissue in the target volume. This is often achieved quite simply in superficial tumors, but it is much more complicated and potentially morbid in deep tumor sites. Study of the X-ray response in heated transplanted rodent tumors has shown a degradation of tumor control if all of the tumor does not reach the target temperature (12). In randomized studies in pet animal tumors (dogs and cats), Dewhirst et al. (8) showed convincingly that it is the coolest temperature measured in the tumor that dictates

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2 The abbreviations used are: WBH, whole-body hyperthermia; EM, electromagnetic; CR, complete response.

the response. Oleson et al. have presented data confirming in humans that the minimum tumor temperature achieved is a critical parameter. Obviously, if we are to know what our minimum tumor temperatures are, a large number of sites in the tumor must be sampled. The ideal would be a 3-dimensional (mm) matrix of measurements serially obtained throughout the entire tumor, an ideal that cannot now be achieved. The compromise position is to sample as many sites as practicable. Thermometry probes with multiple sensing sites would be one approach. The method of "thermal mapping" developed by Gibbs (10) utilizes preplaced blind-ended catheters traversing the volume in several planes, orthogonally if possible. Noninteractive temperature-sensing probes are then advanced and retracted in steps, and the temperatures are recorded. He reports in this supplement (11) on the usefulness of the approach in comparing heating patterns produced by different heating devices in the same patient, and a detailed report will be published elsewhere.

Deep heating is a much more difficult problem than superficial heating. Several approaches with EM and ultrasound techniques have been suggested, but practical clinical experience has been rather limited. EM methods have included magnetic induction and propagated wave and near-field effects from an annular phased array. The largest reported experience is with magnetic induction by a concentrically placed coil, the Magnetron (4, 29-31). Most patients have received concomitant chemotherapy or X-ray and some favorable responses have occurred. Tumor temperatures in excess of 45°C have been reported; however, the thermometry usually consisted of single-point measurements, and details are lacking as to the location of the sampled sites. According to the criteria of Gibbs (11), one must conclude that thermometry in these studies have been inadequate to evaluate well the efficacy of heating. With magnetic coil induction, the heating in phantoms is maximal at the outer radius, and rapidly falls off to zero at the center (21, 24). From this one would predict that the clinical heating distribution for a concentric coil would be inhomogeneous, maximal near the surface, and near zero centrally. In those reported studies where multiple sites were monitored for temperature, the heating pattern was consistent with that predicted from the physical features of the device (11, 22). Clinically useful heating may be achieved in eccentrically located tumors, but is unlikely in deep central sites. Inductive coils have been used appositionally rather than concentrically (Helmholtz coil), but too few data have been reported to review. The inherent physical limitations are similar to those of the concentric coil. The annular phased array produces relatively more homogeneous heating in phantoms and pigs than does the concentric coil (13, 32). Initial clinical evaluation has shown the device to provide quite reasonable heating in deep tumors in the pelvis (11, 27). However, upper abdominal treatment has been less satisfactory, mainly due to systemic heating, and patient-device interface constraints complicate plans to treat thoracic tumors. Limited experience with the multitransducer ultrasound array (3, 17) suggests that selected tumors can be heated to depths of 15 cm. Inhomogeneities such as air-containing structures and bone-soft tissue interfaces cause severe problems from lack of wave propagation and wave reinforcement with hot spots, respectively.

In summarizing the reported studies of deep heating one concludes that our approaches are as yet not ideal. Hall (14) succinctly summarized the status of hyperthermia as having the biology with us but the physics against us. There is an obvious and critical need for creative new approaches or modification of those existing to give more optimal heating of tumors located deep within the body (28). However, given the strong biological rationale, the compelling results of treatment of superficial tumors and beginning success of achieving deep heating, we must proceed toward definitive study of deep tumors with the techniques at hand. As thorough as feasible documentation of heating patterns achieved is a mandatory requirement. Since the heating concept is regional rather than confined only to the tumor, special emphasis must go to sophisticated radiation treatment planning and execution to achieve relative localization of the radiation. At the University of Utah we are proceeding toward definitive trials, based on our initial experience with heating tumors in the pelvis, concentrating on advanced but potentially curable tumors in defined sites (bladder, cervix, endometrium, and rectum) with a series of protocols designed to critically define technical treatment techniques and patient management, including acceptable sedation and narcotics to allow dose escalation to therapeutic minimum tumor temperatures. The aim is to then participate with others with similar equipment in Phase II and Phase III trials to help define the role of hyperthermia in primary therapy of human cancer.

Considerable discussion was raised at this meeting concerning invasive techniques to achieve deep hyperthermia (2, 5, 9). These approaches show considerable promise for those clinical settings in which the heating devices or ferromagnetic materials can be placed within the tumor volume by transcutaneous or open surgical approaches to achieve a geometric distribution which will achieve the desired heating pattern. Often, the carriers for the devices can also be used for thermometry and for afterloading radiation brachytherapy. The potential for both local tumor and metastases control by WBH combined with radiation, chemotherapy, or both is highly attractive (6, 20, 26). Unfortunately, no clinical studies I am aware of or that were described at this conference clearly demonstrate efficacy of WBH as measured by relevant end points of cancer therapy. Well designed randomized trials to test the efficacy of WBH in multimodality regimens are badly needed.

References
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