Clinical Instrumentation Requirements with a Review of the Perth Hyperthermia Experience

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Abstract

The problems of precise clinical thermometry are enormous, and, because the degree of sensitization to ionizing radiation is strongly dependent on temperature and time at temperature, it is important that this problem be solved in a practical way. In lieu of accurate temperature-recording methods, it is imperative that any clinical treatment regimen which utilize heating be with temperatures which are elevated only moderately (to perhaps a maximum of 41°C).

With external heating methods, tumors with sluggish blood flow can be heated to a greater degree than normal tissues. This should be particularly true for hypoxic foci which are at some distance from cooling capillaries. Unfortunately, it seems unlikely that practical detectors can be designed to measure the temperatures of these crucial microenvironments. Hence, this is another reason why it may be necessary to be cautiously empirical about certain aspects of clinical treatment approaches utilizing hyperthermia.

J. A. G. Holt and A. J. M. Nelson's experience in 52 patients with head and neck cancer treated with 434 MHz microwave hyperthermia and ionizing irradiation in Perth, Western Australia, was reviewed during my visit there in the spring of 1978. The two-year disease-free survival of 47% for patients with advanced disease (T3, T4 or N2, N3) is promising. This is especially encouraging since these results were obtained with lower than conventional doses of irradiation and normal tissue tolerance was excellent. Phase I and II studies in this country appear warranted.

As an introductory remark, it perhaps would be prudent to state that presently available radiobiological information indicates that we should not be able to cure a human epithelial cancer, 1 cm in diameter, with ionizing radiation. This is important background because, if radiobiologists insist that we understand all the whys and wherefores of hyperthermia experimentally before it is used clinically, we may experience an inordinate delay in initiating a potentially useful modality into clinical practice. Incomplete understanding of the laboratory findings may continually put us off from doing something clinically useful with patients. This is said somewhat with tongue in cheek, but at the same time seriously to remind us that it is probably not unreasonable to proceed cautiously now with a combined approach (moderate hyperthermia in conjunction with irradiation and/or chemotherapy) in suitable patients with advanced cancer.

I am scheduled to discuss clinical instrumentation requirements. Let me say in advance that I do not anticipate that the situation will be clarified much by my presentation, and perhaps my presentation is not supposed to be clarifying. I may raise more questions, hopefully important ones, than I answer.

The necessity for recording both temperature and time at temperature of normal tissues and tumors whenever possible will not be reviewed. Of course, precise thermometry is especially important for some normal tissues (brain, liver, and heart, for example) which cannot tolerate prolonged exposures to temperatures which exceed 42°C (6, 8). But precise thermometry is not a trivial problem. In fact, the difficulties in accurately determining temperature, particularly in deep-seated tissues and tumors, are enormous. The tomographic thermometry technique, described by Christensen in this workshop (1), is an interesting approach and development. However, for these displays to be clinically useful, they undoubtedly will need to be 3-dimensional. This requirement compounds the reconstruction problem immensely. At temperatures, 41.5°C or less, precise thermometry is perhaps not so critical, since normal tissues tolerate this degree of hyperthermia well. So, the practical requirements for clinical thermometry will depend on the temperature to be utilized.

Except for heating of extremities by perfusion, uniform heating of volumes composed of heterogeneous normal tissues and tumors is unlikely to be achieved other than by whole-body heating techniques; since the temperature of normal tissues and tumors approximates that of blood, thermometry is relatively easy. But blood temperature must be closely monitored because with whole-body heating temperatures above 41.8—42°C are hazardous and, in fact, may be fatal. Nevertheless, this temperature is not high enough to consistently completely eradicate tumors, even with heating episodes lasting 2 to 3 hr (6, 8). Therefore, to be more effective, in most clinical situations whole-body hyperthermia will be used in conjunction with chemotherapy. With regional perfusion, uniform temperatures of 40—41.5°C can be achieved for up to 2.5 hr without causing important normal tissue injury (10). Better results accrue when chemotherapy and/or ionizing irradiation is used in conjunction with the perfusion.

For regional or localized hyperthermia using the extrinsic heating methods listed in Table 1, uniform heating is not possible. A practical method of more uniformly heating to moderate temperatures with minimal morbidity, to be used in conjunction with ionizing irradiation, is sought. Perhaps the radio frequency heating system discussed in this workshop by Storm will be a practical approach (12). Careful thermometry will be necessary to assure that normal tissue tolerance is not exceeded. Tumor temperatures also will need to be determined.

With electromagnetic wave or ultrasound heating, tempera-
years of radiotherapy, the optimal timing of ionizing irradiation is exceedingly difficult problem clinically. After more than 75 years of radiotherapy, the optimal timing of ionizing irradiation has presented a complicated issue. Appropriately sequencing of ionizing irradiation has revealed that the maximal therapeutic gain occurs with a 1- to 6-hr interval between ionizing irradiation and subsequent heating. Nevertheless, the simultaneous use of both modalities is not necessarily advantageous. Fowler (2) and Stewart and Denekamp (11) have shown in vivo that hyperthermia interferes with the repair of sublethal injury or damage; however, this effect is likely to be greater than that for normal tissues. Because of an impaired blood flow in tumors, less of the absorbed heat is dissipated than from normal tissues; hence, preferential tumor heating should be attained.

Localized heating is permitted by ultrasound or electromagnetic (radio frequency or microwave) radiation; with these methods there is also the added advantage that tumor heating is likely to be greater than that for normal tissues. Because of an impaired blood flow in tumors, less of the absorbed heat should be dissipated than from normal tissues; hence, preferential tumor heating should be attained.

Whether the heat must be applied simultaneously with the ionizing radiation is conjectural at this time. The fact that maximal effects occur experimentally in vitro and in vivo when the 2 modalities are used simultaneously does not necessarily mean that the maximal therapeutic gain occurs with simultaneous treatment. For example, one postulates that at 41°C hyperthermia interferes with the repair of sublethal injury or damage from ionizing radiation and that sublethal repair occurs more promptly in normal cells than in hypoxic or nutritionally deprived tumor cells, then heating soon after irradiation might be anticipated to result in a better therapeutic gain. Hill and Fowler (2) and Stewart and Denekamp (11) have shown in vivo that the maximal therapeutic gain occurs with a 1- to 6-hr interval between ionizing irradiation and subsequent heating. Appropriate sequencing of ionizing irradiation has presented an exceedingly difficult problem clinically. After more than 75 years of radiotherapy, the optimal timing of ionizing irradiation alone is still being investigated and is presumably still not optimal. The addition of a new modality, of course, complicates optimization dramatically.

It will be necessary to do the initial clinical Phase I and II trials in patients with advanced disease, but developing a suitable regimen for treating patients primarily and with curative intent is the ultimate motivation for interest in hyperthermia in conjunction with ionizing irradiation. More effective control of localized tumors seems feasible with this approach.

As part of this presentation, George Hahn asked that I comment briefly on Dr. J. A. G. Holt's experience in Perth, Western Australia, using 434 MHz radiation in conjunction with megavoltage X-rays. This is perhaps an appropriate time for that review.

First, an impression about Dr. Holt. He is a very bright, energetic, devoted clinician with an excellent background in oncology. He is a Fellow of the Royal College of Surgeons. He decided to become a radiotherapist, training in radiotherapy at Bristol. He then spent 5 years at the Royal Marsden Hospital in London before going to the Peter MacCallum Clinic in Melbourne in 1959 and then on to Perth in 1960. Since that time, he has had a busy radiotherapy practice; he and his associates are responsible for providing the radiotherapy services for the virtually isolated 1.2 million people of Western Australia.

Being distressed by the relative ineffectiveness of ionizing irradiation in curing advanced, but localized, tumors, he has been motivated to pursue new approaches which might enhance the local control rate. Therapy while under hyperbaric oxygen conditions appeared to cause a modest enhancement, but not enough to satisfy his impatience to have a significant impact on the cancer cure rate. Hyperthermia in conjunction with irradiation seemed another method worth exploring. In the 1960's, Dr. Holt used heating pads and blankets for extremity lesions and subsequently utilized a hot-paraffin technique. In 1973, he introduced 434-MHz heating to his irradiation regimen (3).

His desire to select what he considers the right treatment for each patient has prevented him from doing a conventional clinical trial. This has necessitated the inclusion in his clinical reports of considerable subjective, anecdotal data which are difficult to interpret. Furthermore, thermometry has been virtually nonexistent, confounding interpretation even more. Nevertheless, it is fair to say that no one has solved the problem of accurately measuring temperature throughout the heated volume, except for superficial tissues and tumors. The normal tissue temperatures attained by Holt and associates are sufficiently low that reactions or complications have been virtually nonexistent, so it appears that their approach has been safe, even though further scientific evaluation is desirable.

After visiting Dr. Holt's clinic and reviewing a portion of his experience of treating more than 1500 patients with 434-MHz heating and ionizing irradiation, I believe his accomplishments should be given some acknowledgment. I submit that the series of patients which has been reported by Nelson and Holt (7) is no less evaluable than those presented at this workshop.

A standard European 434-MHz diathermy unit of 200 watts (Erbe Elektromedizin, Tubingen, West Germany) is shown in Fig. 1. This is the unit which Dr. Holt uses to heat patients with small, localized tumors. The notorious Tronado unit (4), which has been spruced up a bit and mounted in a horizontal position,
is shown in Fig. 2. There are 3 rings of diathermy units, each with 4 diathermy units like that shown in Fig. 1, coupled in sequence in each ring; the total power with this unit is 2400 watts.

The report by Nelson and Holt in 1977 (7) has generated considerable interest, as well as skepticism. I visited Dr. John Holt and Dr. Allan Nelson in Perth for 10 days in April, 1978, being particularly interested in reviewing the 52 patients with advanced head and neck cancer reported in that paper who were treated with 434 MHz radiation and megavoltage X-rays. Heating was for 20 to 30 min, with probable tumor temperatures of 39.5°C ± 1°C. Heating was prior to ionizing irradiation.

I reviewed the charts on all 52 patients and was able to examine personally 23 of the 32 surviving patients. Several surviving patients whom I did not see are in nursing homes in their home communities; others whom I did not examine lived several hundred miles away and were unable to come during my visit.

Table 1 shows that, although these 52 patients were reported as having advanced head and neck cancer, I believe that 15 of the patients should be considered as having less than advanced disease [T1N0 (3 patients), T2N0 (12 patients)]. Four of the patients who had T2N0 tumors had recurrent disease, which is a little less favorable, but I still have considered them as early-stage patients.

In the 15 patients with early-stage disease, with a treatment approach which uses heating on alternate days and daily (5 days/week) doses of ionizing irradiation that are somewhat less than those usually used without hyperthermia, there has been very good local control. If the 80-year-old patient who died without evidence of disease at 4 years is excluded, all of the early-stage patients are alive without disease after 2 or more years.

The results of the other 37 patients, considered to have advanced disease, are shown in Table 3. Eighteen of the patients survived without evidence of disease at 2 years. These patients were treated, as previously mentioned, with doses of radiation that were less than those usually used for patients with advanced head and neck tumors. The doses ranged from 4000 rads/6 weeks to 6300 rads/7 weeks. Only 6 of the 37 patients had doses in excess of 5500 rads in 6 to 7 weeks.

In the patients whom I examined, no significant normal tissue morbidity was noted. My conclusion is that the results seem encouraging enough to warrant Phase II trials of this approach in other institutions.

Ned Hornback of the Indiana University School of Medicine in Indianapolis visited Dr. Holt about 3 years ago, and subse-
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References


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