Thermal Dosimetry and Clinical Requirements

Kenneth H. Luk and Theodore L. Phillips

Abstract

Major problems in clinical hyperthermia include (a) inhomogeneity of heat distribution in designated tumor volumes due to tissue characteristics and differential blood flow, (b) limitations of heat delivery and control systems for adequate depth penetration and adjustments of temperatures, and (c) the lack of capability of accurate temperature measurements, especially in the area of noninvasive techniques for deep-seated tumors. Examples were given to illustrate the clinical requirements of hyperthermia of superficial, intermediate, and deep-seated tumors.

Introduction

Interests in hyperthermia in cancer therapy stemmed from clinical observations of tumor regression in patients with endogenous or exogenous very high fevers (25, 36). A number of reports have also indicated that ionizing radiation might be more damaging to tumor cells at elevated temperatures (32, 33).

Methods to attain local hyperthermia have included hot water, hot air, ultrasound, microwaves, and radio-frequency diathermy (5, 15, 17-19, 21). Regional hyperthermia has been attempted using regional perfusion of warmed blood (34, 35). Whole-body hyperthermia has been induced by bacterial toxins, immersion in molten wax, hot air inhalation, and thermal insulation suits (20, 25, 30, 36). In most of the clinical series reported, tumor temperatures either were not reported or could not be measured accurately.

In vitro and in vivo biological studies have attempted to answer the questions of mechanisms of tumor cell destruction (3, 7, 9, 14, 26, 27, 29); effects of hyperthermia alone, with radiation, or with chemotherapeutic drugs (2, 4, 6, 11, 16, 22, 28, 37); and the relationships of sequences of these modalities (1, 8).

Thermal enhancement ratios in the few biological determinations of skin, gut, cartilage, bone, and spinal cord seem to increase rapidly with increasing temperatures between 40 and 44°C (10, 12, 13, 23, 24, 31).

Minor changes of temperatures will cause significant differences in tumor cell kill and will affect the tolerance of critical normal tissues which may be in the volume of treatment included by radiation and/or hyperthermia. The authors will pose questions as to the clinical requirements of local hyperthermia in different parts of the anatomical structures relative to thermal dosimetry.

Table 1 categorizes the different groups of cancers to be considered for hyperthermia.

**Superficial Tumors**

Example 1: Chest Wall Recurrence of Breast Cancer. Fig. 1 presents the clinical problem of treatment of a chest wall recurrence of breast cancer. The patient was a frail postmenopausal woman who received previous radiation therapy to this site, did not respond well to hormonal manipulations with estrogen and androgen, and was not considered to be a candidate for chemotherapy. The lesions were coalescences of multiple small cutaneous nodules which eventually involved the skin of the right chest wall with seepage of serum and blood. Fig. 1A is a picture taken 3 months after 2450-MHz microwave hyperthermia with 4-MV electron beam radiotherapy (1800 rads/6 fractions/12 days).

Example 2: Abdominal Recurrence of Colon Cancer in the Laparotomy Scar. Fig. 2 is a CT scan of the cross-section of the abdomen of a 54-year-old man. The scan demonstrates a 4–5 cm mass of the anterior abdominal wall which was a recurrence of colon cancer one year after resection of tumor and chemotherapy. The tumor was firm to palpation and appeared fleshy when inspected through the wound opening. Fig. 2A is a repeat CT scan of the similar cross-section of this patient after 915-MHz microwave hyperthermia and 137Cs telotherapy (1800 rads/6 fractions/12 days).

The clinical requirements of hyperthermic treatments of this chest wall lesion in Example 1 would be (a) the application of heat to a depth of 1.5 cm so that the underlying lung tissues would not need to be unnecessarily heated, (b) adequate temperature achieved on the skin surface as well as at the depth of the chest wall since the tumor extended to there, (c) a relative homogeneity in the distribution of heat on the chest wall to avoid hot or cold spots, and (d) the ability to adjust thermal output to counteract the vascular thermoregulatory mechanisms since this lesion appeared to be quite vascular.

The objective of hyperthermia in Example 2 would be to heat a somewhat spherical tumor mass to a temperature of 42–44°C. However, the skin was not involved, and there was no need to heat the skin to this temperature which might produce thermal damage. It would be desirable to cool the skin while allowing heat to build up s.c.

With the tumor reaching a depth of 5 cm, it is important also to take into consideration a temperature gradient which might exist when heat is applied in a single direction, in part due to the rate of deposition of heat energy and in part due to dissipation of heat by transference via blood flow or tissue contiguity.

Large and small bowels may be quite sensitive to heat damage. In the large bowels, feces may act as an absorber of heat without any means of dissipation; therefore, the bowel can reach much higher temperatures than desired. The possibility exists that necrosis of the colon can occur from excessive heat...
Table 1

<table>
<thead>
<tr>
<th>Categories of cancers to be considered for hyperthermia</th>
<th>Superficial tumors</th>
<th>Moderately deep tumors</th>
<th>Deep-seated tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest wall recurrence of breast cancer</td>
<td>Unresectable primary breast cancer</td>
<td>Cancer of lung, esophagus</td>
<td></td>
</tr>
<tr>
<td>Scar recurrence of colon or bladder cancer</td>
<td>Head and neck cancers</td>
<td>Cancer of pancreas</td>
<td></td>
</tr>
<tr>
<td>Metastatic cancer of lung, colon, etc.</td>
<td>Sarcoma of extremities</td>
<td>Cancer of liver, kidney</td>
<td></td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>Intracranial neoplasms</td>
<td>Retropertioneal sarcomas</td>
<td></td>
</tr>
<tr>
<td>Squamous cell or basal cell carcinoma of skin</td>
<td></td>
<td>Cancer of ovary, colon</td>
<td></td>
</tr>
<tr>
<td>Mycosis fungoides and cutaneous lymphoma</td>
<td></td>
<td>Cancer of prostate</td>
<td></td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td></td>
<td>Cancer of bladder</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cancer of cervix, uterus</td>
<td></td>
</tr>
</tbody>
</table>

damage. On the other hand, the small intestines (especially the intestinal crypt cells) are rapid cell renewal systems which may be easily damaged by hyperthermia or by radiation and drug effects enhanced by hyperthermia. Therefore, in this clinical setting, it is important that the intestines will not be heated.

**Moderately Deep Tumors**

**Example 3: Intracranial Neoplasm.** Fig. 3 is a CT scan of a large right temporoparietal lobe tumor with a central cystic component. The patient experienced personality changes as well as early motor deficits. The histopathology was astrocytoma.

**Example 4: Nasopharyngeal Carcinoma.** Fig. 4 represents cross-sections of the cranium of a patient with carcinoma involving the nasopharynx as well as the ethmoid sinus. His symptoms included pain and nasal obstruction.

More than any other regions of the body, it is most critical to be able to heat accurately a very limited volume of tissue in the brain. Accomplishing this goal is not easy since the heating system must go through the scalp, the skull, and some brain tissues. Heat is reflected at the interphase of scalp and bone, causing local hot spots in the scalp and inadequate heat dose to the tumor.

Before attempting to heat this tumor, one must have a relatively good idea of whether this tumor is vascular. The rate of heat accumulation or dissipation will be quite different as a function of blood supply. It may be futile to heat a very vascular tumor since the surrounding brain tissues may be heated to a higher temperature. Focusing devices or multiple portals of heat entry possibly can partially compensate for the above problems.

A major therapeutic gain is a prerequisite for hyperthermia of brain tumors. Damage to normal brain tissue by heat would not be acceptable because of the gravity of such morbidities.

Nasopharyngeal carcinoma and cancers of the head and neck require a high dose of radiation for control, and local failures are not uncommon. It could be advantageous to combine hyperthermia with radiation or chemotherapy. However, clinical hyperthermia in this example is a challenging problem.

First, there are many critical structures in the vicinity. For example, the optic globe contains proteinaceous fluids which may be quite sensitive and alterable by heat. Also, the lenses are avascular structures which may accumulate excessive amounts of heat due to lack of heat loss. Hyperthermia must be delivered in a sharply defined volume. Insertion of a locally heated applicator to the nasopharynx may be adequate for mucosal disease, but it probably will not be able to take care of disease extension such as into the ethmoid sinus. On the other hand, externally applied heat may encounter physical limitations such as bone absorption of heat and tissue inhomogeneity including air spaces.

**Deep-seated Tumors**

**Example 5: Pancreatic Carcinoma.** Fig. 5 is a CT scan of the abdomen of a patient who presented with abdominal pain and weight loss. The pancreatic carcinoma was outlined in ink, and a metallic clip from a previous biopsy was seen in the center.

Pancreatic carcinoma is increasing in incidence in recent decades and is associated with a very poor prognosis with currently available treatment modalities of surgery, radiotherapy, and chemotherapy.

Critical organs in its surroundings include the liver, small intestines, kidneys, and spinal cord. These organs all have different rates of blood flow through them; e.g., renal blood flow averages 1200 ml/min/300 g tissue in humans.

There are different tissue densities, air contents, and irregularities of shape. The tolerance of these organs to heat has not been fully understood. The small intestines are quite sensitive to heat damage. The liver and kidneys may not be heated to high temperatures because of their blood supply. The spinal cord, however, does not have a profuse blood supply, and enhancement of myelitis had been demonstrated in animals with heat and radiation (24). Therefore, it is prudent to plan to avoid bringing these organs to high temperatures relative to the tumor volume.

**Discussion**

Before clinical hyperthermia can become a practical and successful tool in cancer therapy, either as an independent modality or as an adjuvant to radiotherapy or chemotherapy, further advances need to be made in the areas of heat delivery, distribution, measurement, and precise control. In contrast to ionizing radiation, the relative blood supply to the tumor and the thermoregulatory physiological responses of the body may play an important part in the ability to achieve certain temperatures in the tumor as compared with the surrounding normal tissues, and they are directly responsible for the accomplishment of a therapeutic gain. Similar to radiation therapy, the morbidities of moderate temperatures to critical normal tissues, with or without radiation or chemotherapy, will present as a limiting factor in the degree and duration of such heat deliveries.

The application of hyperthermia to cancer therapy in different parts of the human body poses various sets of problems. These problems include the homogeneity of heat delivery in the designated tumor volume and the avoidance of normal tissues. What is implied is the basic understanding of the biological effects of heat in various tissues as well as the effects of heat with the additions of other enhancement factors, such as drugs or radiation. Much research in this area is still needed.

The technological development of heat delivery systems has to dovetail with the specific requirements of heating the various parts of the body. This may mean different systems of heat delivery, more than one portal of heat entry, and the sophistication of precise control.
K. H. Luk and T. L. Phillips

Underlying all these developments (and without which the research studies would be meaningless), is the capability of accurate thermal dosimetry. The examples above were chosen to illustrate the clinical requirements of hyperthermia in the hope of stimulating discussion and furthering research in these areas.

Acknowledgment

The authors are grateful to Dr. Jeanne M. Quivey for permission to use the CT scans in Figs. 3 to 5.

References

Fig. 1. Chest wall recurrence of breast cancer.
Fig. 2. Abdominal recurrence of colon cancer in the laparotomy scar.
Fig. 3. Intracranial neoplasm.
Fig. 4. Nasopharyngeal carcinoma.
Fig. 5. Pancreatic carcinoma.
Cancer Research

Thermal Dosimetry and Clinical Requirements
Kenneth H. Luk and Theodore L. Phillips


Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/39/6_Part_2/2300

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.