

Point: Hyperthermia with Radiation for Chest Wall Recurrences

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Key Words

Recurrent breast cancer, hyperthermia, radiation

Abstract

Treatment of a locoregional recurrence of breast cancer after mastectomy remains a clinically challenging problem. Often these patients have undergone prior radiotherapy and chemotherapy. Therapeutic options usually include resection or additional radiation; however, the long-term control rates are often suboptimal with these approaches. Data from several randomized trials suggest that the addition of hyperthermia to radiation can increase the response rate for such local recurrences. Therefore, in settings where the available therapies are unlikely to yield local control (e.g., local/regional recurrence after prior radiation), a reasonable option to consider is radiation with hyperthermia as a radiation sensitizer. This article reviews the rationale and supporting literature for this recommendation. (*JNCCN* 2007;5:339–344)

Use of hyperthermia in the treatment of human cancer has a long and interesting history, dating back more than 5000 years. The earliest known medical reference is the Edwin Smith Egyptian papyrus scroll, which described a breast tumor treated with hyperthermia.¹ The use of heat in cancer therapy was also described by Hypocrites (470–377 BC) as, “those who cannot be cured by medicine can be cured by surgery. Those who cannot be cured by surgery can be cured by fire (hyperthermia). Those who cannot be cured by hyperthermia, they are indeed incurable.” This article defines hyperthermia as an elevation of temperature to a supraphysiologic level, between 40°C and 45°C. Higher temperatures may be used for thermal ablation, but are not reviewed in this article.

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Biologic Rationale

The rationale for combining hyperthermia with radiation rests on several mechanisms. Hyperthermia is known to cause direct cytotoxicity and also acts as a radiosensitizer.² Studies performed in vitro yield a pattern of survival curves similar to radiation survival curves (i.e., a dose response with increased cell death with longer/hotter treatments).³ The mechanisms of action of hyperthermia seem to be complimentary to the effects of radiation with regard to inhibition of potentially lethal damage and sublethal damage repair,⁴ cell cycle sensitivity,⁵ and effects of hypoxia and nutrient deprivation.⁶ In addition, hyperthermia may alter tumor blood flow/physiology to improve tumor oxygenation.⁷

Clinical Efficacy of Hyperthermia

Phase III series for various tumors treated with radiation and hyperthermia are summarized in Table 1. In general, the more recent series using modern techniques for hyperthermia with rigorous quality control and careful thermometry have yielded positive results. Significant benefits for locoregional control and local response have been shown for breast/chest wall recurrence,^{13,19} head and neck cancer,^{9,20} melanoma,¹⁵ bladder cancer,²¹ and esophageal cancer.²² Trials for cervical cancer²³ and glioblastoma multiforme¹⁶ show both local control and overall survival benefits.

The Radiation Therapy Oncology Group Hyperthermia Experience and the Technical Deficiencies of the 1980s

The Radiation Therapy Oncology Group (RTOG) conducted a randomized phase III study of radiation and hyperthermia versus radiation alone in superficial measurable tumors (RTOG 8104).¹¹ Between February 1981

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Table 1 General Summary of Randomized Clinical Data for Radiation With or Without Hyperthermia

Study	Patients, <i>n</i>	Tumor Type	End Point	Heat (%)	No Heat (%)
Valdagni et al. ⁸	44	N3 neck nodes	CR rate	82	37
Datta et al. ⁹	65	Head and neck	CR rate stage III	58	20
			CR rate stage IV	38	7
Kapp et al. ¹⁰	70, 179 lesions	Superficial tumors (mostly neck nodes and chest walls; melanoma)	CR rate	52 (6 HT)	51 (2 HT)
Perez et al. ¹¹	307	Superficial tumors (mostly neck nodes and chest walls)	CR rate	32	30
Sugimachi et al. ¹²	53	Esophagus	Pathologic CR	27	8
Vernon et al. ¹³		Chest wall Meta-analysis	CR rate	59	41
Emami et al. ¹⁴	173	Recurrent or persistent interstitial therapy	CR rate	55	53
Overgaard et al. ¹⁵	70, 134 lesions	Melanoma	2-y actuarial LC	46	28
Sneed et al. ¹⁶	112	GBM	2-y OS	31	15
Harima et al. ¹⁷	40	Cervix	CR	80	50
			3-y OS	58	48
van der Zee and Gonzalez ¹⁸	114	Cervix	CR	83	57
			3-y LC	61	41
			3-y OS	51	27
Jones et al. ¹⁹	108	Superficial tumors (mostly neck nodes and chest walls; melanoma)	CR (overall)	43	68
			CR (prior XRT)	23	68

Abbreviations: CR, complete response; GBM, glioblastoma multiforme; HT, hyperthermia treatment; LC, local control; OS, overall survival; XRT, radiation therapy.

and August 1987, 307 patients were randomized to undergo either radiation alone (4 Gy twice a week to a total of 32 Gy) or radiation followed immediately by hyperthermia (42.5°C for 45–60 minutes). The complete response rates were 30% versus 32% in these groups, respectively. Most of the patients had cancers of the head and neck region (48%) or chest wall recurrences from breast cancer (34%). In tumors smaller than 3 cm located in the breast, trunk, or extremities, a better complete response rate was noted with radiation and heat (62%) than with radiation alone (40%). Similarly, hyperthermia improved the durability of local control in lesions smaller than 3 cm but had no effect in lesions larger than 3 cm. Researchers postulated that smaller lesions were more heatable and thus received an adequate thermal dose. Detailed thermometry for the groups was not reported.

This theme of technical constraints limiting clinical effectiveness is also reflected in a second RTOG trial using interstitial radiation and hyperthermia.¹⁴ From January 1986 to June 1992, 184 patients with persistent/recurrent tumors after previous radiotherapy or surgery were randomized to interstitial radiation alone versus interstitial radiotherapy with interstitial hyperthermia. The study end points were the same between the arms. Complete response rates were 53% and 55%, and 2-year survival rates were 34% and 35%, respectively. The patient population was heterogeneous and included primarily patients with head and neck and pelvic tumors, most of which were 4 cm or larger.

A single-institution randomized trial was conducted at Stanford in the mid-1980s using hyperthermia and radiation for superficial tumors.¹⁰ Seventy patients with 179 individual lesions were randomized

to undergo 2 versus 6 hyperthermia treatments concurrent with radiation. The study included no control patients. Most lesions were chest wall recurrences from breast cancer (62%). This study showed no difference between 2 versus 6 hyperthermia treatments for all end points considered.

However, a follow-up dosimetric analysis from Stanford, published after the RTOG guidelines were established and based on a more homogeneous subset of 83 patients with single nodules from 1982 through 1992, suggested a dose–response for hyperthermia.²⁴ Thermal dose in the follow-up analysis was quantified using the cumulative area under the curve concept, also taking into account the Arrhenius model for thermal effects. Local response and duration of local control were associated with the cumulative hyperthermia dose delivered (defined as the cumulative equivalent minutes at 43°C for 90% of the target volume [CEM43°C T₉₀]), and patients receiving more than 10 minutes of CEM43°C T₉₀ fared better with improved complete response and duration of local control.

Enthusiasm for hyperthermia in the United States took a major downswing after the RTOG trials were published. Concurrently, an overall economic belt-tightening occurred in medicine, and managed care evolved. Many people argued that hyperthermia had come to a standstill. However, these negative trials highlight the deficiencies related to clinical implementation of hyperthermia in the 1980s. They do not refute the compelling biology of hyperthermia interactions with radiation and chemotherapy. Engineering refinements in commercially available equipment led to approval by the U.S. Food and Drug Administration. A few academic centers continued research in the physics, biology, and clinical implementation of hyperthermia. The National Institutes of Health and National Cancer Institute have continued to support hyperthermia research, and significant progress has been made.

RTOG and European Society for Hyperthermia Oncology Quality Assurance Guidelines

In response to the disappointing results from the early phase III trials, quality assurance guidelines were developed by RTOG to provide a framework for clinical hyperthermia.^{25–27} These were published in the early 1990s shortly after the first randomized trials were

completed and represent the concerted effort of many academic centers to define a better clinical framework for hyperthermia treatment. In parallel, a similar effort was undertaken by the European Society for Hyperthermia Oncology (ESHO), which also published a series of guidelines in a similar timeframe as the RTOG.^{28,29} These guidelines were applied to future studies.

Second- and Third-Generation Randomized Hyperthermia Trials

After the initial RTOG experience, a second generation of randomized hyperthermia trials was conducted that incorporated the quality assurance guidelines developed by RTOG and ESHO. Five randomized trials, comprising 306 patients, compared radiation with or without hyperthermia in the treatment of superficial localized breast cancer.

An international collaborative meta-analysis effort combined the results from these 5 randomized control trials with individual patient data for measurable recurrent breast cancer.¹³ Hyperthermia techniques differed somewhat between the various studies, but details of technique and thermometry are thoroughly documented. The complete response rates were 41% with radiation alone versus 59% radiation plus hyperthermia ($P = .007$; odds ratio, 2.3; 95% confidence interval [CI]; 1.4–3.8) favoring the hyperthermia arm. The local control advantage with hyperthermia was maintained in follow-up. Among patients experiencing a complete clinical response, 31% of the control patients (radiation alone) experienced a subsequent local failure versus 17% of those undergoing hyperthermia plus radiation. The benefits of hyperthermia were particularly evident in the subgroup of 210 patients who underwent prior radiation: complete response rates were 31% with radiation alone versus 57% with radiation plus hyperthermia.

This study has several potential shortcomings, some of which are inherent to the meta-analysis process. Significant heterogeneity is present in the patient selection criteria and treatment parameters. In addition, concurrent systemic chemotherapy was used in a nonrandomized manner. This reflects the necessary medical management in this population of patients at high risk for systemic relapse or already existing distant metastases. Nonetheless, this meta-analysis is a very important collaborative study that

helps to define the role of hyperthermia in breast cancer chest wall recurrence.

The authors recently completed a single institution prospective, randomized trial of radiation and hyperthermia for superficial tumors.¹⁹ Patients who were about to receive a course of local radiation for a superficial lesion less than 3 cm in thickness were eligible. Furthermore, in recognition of the concept that the tumor must be heatable to potentially experience a therapeutic gain, patients were assessed for heatability before randomization. Between July 1994 and July 2001, 122 patients were enrolled. Most patients (70/108) in this trial experienced chest wall recurrences. Based on test dose criteria, 109 patients were deemed heatable and randomized to treatment with no additional heat (i.e., radiation alone) versus additional hyperthermia with radiation. The hyperthermia dose CEM43°C T₉₀ was defined prospectively based on prior studies,¹ and the hyperthermia arm received 10 minutes or more CEM43°C T₉₀. This was the first study to use the concepts of prospective dose/prescription to hyperthermia, and stringent quality assurance was used. The complete response rate in the hyperthermia arm was 66% versus 42% in the no hyperthermia arm. The odds ratio for complete response was 2.7 (95% CI, 1.2–5.8; *P* = .02) favoring the hyperthermia arm. These results are similar to those of the meta-analysis. Previously irradiated patients experienced the greatest incremental gain in complete response: 23.5% in the no hyperthermia arm versus 68.2% in the hyperthermia arm.

A recent retrospective review of treatment for chest wall recurrence from 7 institutions was presented at the American Society for Therapeutic Radiology and Oncology 2006 meeting.³⁰ Among 71 patients treated between 1993 and 2005, the complete response rate was 67% in those treated with hyperthermia and radiation versus 31% treated with radiation alone. Although these are retrospective data, they generally agree with those of the meta-analysis and recent randomized series.

Technical Considerations

Although the authors strongly believe that hyperthermia is a useful adjunct to radiation, they recognize that its delivery requires special expertise. Quality hyperthermia requires the coordinated efforts of physicists, technologists, nurses, and physicians. However,

because these resources are not available at all facilities, patients who might benefit from this technology should be referred to facilities that have modern equipment and expertise in this area.

Alternative Strategies

Additional strategies to address local chest wall recurrence include surgery and photodynamic therapy. A review of the literature for these modalities shows single-institution series for surgical approaches, with descriptions of 22 to 38 patients accumulated over long intervals (i.e., 20–35 years).^{31–33} A series of 35 patients from Memorial Sloan-Kettering over 35 years underwent resection followed by reconstruction using mesh or a mesh “sandwich.”³³ No operative deaths occurred and no respirator was needed. Of these patients, 20 were alive from 5 to 120 months, with a median of 50 months. One of 35 patients experienced further chest wall recurrence. Photodynamic therapy series describe the off-label use of photodynamic therapy in chest wall recurrence for groups of 8 to 14 patients, most with multiple lesions.^{34–38} Results indicate high complete response rates, albeit with small patient numbers and relatively short follow-up. Although results from surgical and photodynamic therapy approaches are good, they likely represent a highly selected subgroup of patients accumulated at major academic centers that see a large volume of recurrent breast cancer. The broader applicability of these approaches in the general oncologic community is unclear.

Conclusions

Chest wall recurrence of breast cancer presents many clinical challenges. Data from several studies suggest that hyperthermia plus radiation is a viable option that should be considered, particularly in patients who have undergone prior radiation, in whom the dose of additional radiation that can be delivered is limited. These recent positive trials for hyperthermia reflect an evolution in hyperthermia approaches, based primarily on the establishment of quality assurance guidelines to ensure the accurate delivery of the desired thermal dose.

Two frequent concerns about the use of hyperthermia are related to the overall availability of clinical hyperthermia treatments and its cost-effectiveness. An informal survey of National Comprehensive

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Cancer Network member institutions shows that hyperthermia research and clinical programs are available at a few. Hyperthermia treatment is Medicare and Medicaid approved, and CPT codes exist for both superficial and deep hyperthermia procedures. On July 25, 2006, the Centers for Medicare and Medicaid Services made available the Hospital Outpatient Prospective Payment System proposed rule, which includes a proposed increase of 3.2% overall for all Medicare outpatient services, but a decrease for some individual procedures. In this recent announcement, hyperthermia codes are proposed to increase by 45.9%. These favorable changes in reimbursement represent recognition of the clinical value of hyperthermia as shown in modern phase III series. Given the economic viability and solid clinical data showing improved locoregional control in difficult clinical settings, the authors hope that more oncologists will consider joining the renaissance in clinical hyperthermia.

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