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Conventional cancer treatment alone or with regional hyperthermia for pain relief in lung cancer: A case—control study

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KEYWORDS
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Summary
Objective: To investigate the effect of combining conventional treatment with regional hyperthermia on cancer pain in lung cancer patients.
Design: Case—control study.
Setting: One Korean university hospital and three complementary cancer clinics.
Main outcomes and measures: Main outcome was effective analgesic score (EAS, PI[1 + (M/10)], 1: anti-inflammatory drug consumption at a regular dosage, M: weekly dose (mg) of oral morphine equivalent and PI: pain intensity) at four time points (baseline (days −30 to 0), time 1 (days 1—60), time 2 (days 61—120), and time 3 (days 121—180)). Propensity score matching between the hyperthermia and control groups was performed using a 1:5 ratio. A linear mixed effects model was employed to measure EAS changes over time in the two groups.
Results: At baseline, there were 83 subjects in the control group and 32 subjects in the hyperthermia group. At time 3, there were 49 subjects in the control group and 16 subjects in the hyperthermia group. Analyses showed rate of change of EAS, treatment × time was significant ($p = 0.038$). This significant difference was mainly observed for time 1 (mean difference: 101.76 points, 95% confidence interval: 10.20—193.32 points, $p = 0.030$).
Conclusions: Our results indicate an increase in cancer pain in lung cancer patients administered regional hyperthermia, particularly during the early stage of hyperthermia treatment.

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Introduction

Lung cancer is one of the most common forms of cancer worldwide and the leading cause of cancer-related death in Korea.[1,2] Despite advances in lung cancer diagnosis and treatment methods, lung cancer has a five-year survival rate of only 15.6%.[3] In this regard, lung cancer patients seek complementary and alternative treatment methods, and regional hyperthermia is a complementary treatment method that attracts Korean cancer patients.[4]

The rationale behind regional hyperthermia is that an increase in the temperature of the tumor mass (to 39—42 °C) can inhibit the repair of radiation-induced damage, induce changes in perfusion and re-oxygenation, produce heat-shock responses, stimulates immunological activity, and has a direct cytotoxic effect that improves tumor responses to radio- and chemotherapy.[5—7] According to randomized controlled trials (RCTs) and cross-sectional studies conducted on the effects of regional hyperthermia treatment, its side effects are either minimal or nonexistent, and it provides partial relief from cancer-related pain.[8—10] However, the majority of studies conducted on the effects of regional hyperthermia treatment on pain relief focused mainly on patients' subjective assessment of pain before and after hyperthermia treatment, indicating some difficulty in accurately evaluating cancer pain.

The present study investigates the effects of combining regional hyperthermia plus conventional cancer treatment on cancer pain in lung cancer patients.

Materials and methods

As of April 2013, three clinics were providing external electromagnetic hyperthermia treatment in Kwangju City and Chonnam Province (Korea). Between January 2010 and April 2013, 35 patients at Chonnam National University's Hwasun Hospital received at least one hyperthermia treatment session at one of the three clinics. These 35 subjects were used as a reference data set for patient matching. Between January 2010 and April 2013, 2795 subjects were diagnosed with lung cancer at the authors' institution. Of these, 2209 were treated using conventional cancer treatment only. 551 of these patients without information regarding the primary tumor site, cytologic type, or TNM stage were excluded, and 35 were treated conventional cancer treatment and regional hyperthermia treatment (the hyperthermia group). The conventional treatment group (the control group) was composed of 83 patients, who were propensity score matched using a ratio of 1:5. Data collection and data transfer procedures between institutions were approved by the institutional review board of Chonnam National University's Hwasun Hospital.

External electromagnetic hyperthermia

The hyperthermia group was composed of 35 patients that underwent more than one session of external electromagnetic hyperthermia treatment at three complementary cancer treatment clinics in Kwangju City and Chonnam Province after being diagnosed with lung cancer at Chonnam National University's Hwasun Hospital. Conventional cancer treatment with hyperthermia was provided to all 35 subjects. For pretreatment planning, a moderate hyperthermia (MHT) protocol was selected, which elevated the temperature of the tumor mass to 39—42 °C using 13.56-MHz RF electromagnetic radiation two to three times weekly for 60 min per session; numbers of treatment sessions were based on considerations of patient condition.[5] The treatment was provided using the EHY-2000 unit (Oncotherm Ltd, Ibolya, Hungary). Treatment durations ranged from 1 to 42 weeks (mean: 10.3 weeks), and the number of treatment sessions ranged from 1 to 47 (mean: 19.3).

Effective analgesic scores

To measure effective analgesic scores (EAS), information on pain intensity and opioid analgesic doses was collected from patients' electronic medical records at our institution for four time points, that is, baseline (days −30 to 0), time 1 (days 1—60), time 2 (days 61—120), and time 3 (days 121—180). Day 1 was defined as the start of regional hyperthermia. In the control group, day 1 was defined as the day post-diagnosis corresponding to the time elapsed between diagnosis and hyperthermia therapy start of the corresponding matched pair in the hyperthermia group. Given that it was not possible to accurately measure pain intensity and opioid analgesic doses at desired time points, the mean value of pain intensities during each time period measured as determined using a standard scale of pain intensity (numeric scale: 0—10 at the hospital or outpatient department) by nurses was defined as the pain intensity (PI) by retrospectively analyzing electronic medical records.[11] For opioid analgesic dose, the same dose of an oral agent or an agent in a patch were administered daily from the date of first prescription until the prescription was revised. For injections, it was assumed that an injection was complete at the time of administration. The opioid analgesic amount used during the study period was converted into an oral morphine (mg) equivalents using an opioid conversion table, and these values were used to calculate weekly doses.[12—15] EASs were calculated using the following formula: PI[1 + (M/10)], where 1 indicates the administration of an anti-inflammatory drug at a regular dosage; M, the weekly dose (mg) in oral morphine equivalents, and PI, the pain intensity on a 1—10 scale.[16] EAS is known to be suitable for evaluating the pain associated with chemotherapy and radiotherapy in cancer patients, particularly in retrospective studies.[16—18] In this study, an increase in EAS was taken to indicate a problem with adequate analgesia, and a decrease, the successful treatment of pain.

Covariates

The covariates included in the analysis were; age, gender, initial diagnosis (year), tumor site, cytologic type, TNM stage, initial weight loss, initial ECOG performance status, surgery, chemotherapy, radiotherapy, concurrent chemoradiotherapy (CCRT), and palliative radiotherapy.