Reprinted from CANCER, Vol. 72, No. 2, July 15, 1993
Published by J. B. Lippincott Company Printed in U.S.A.

Long-term Results of Postoperative Intrathoracic Chemo-Thermotherapy for Lung Cancer with Pleural Dissemination

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Background. **To overcome the poor prognosis of lung cancer with pleural dissemination, the authors developed postoperative intrathoracic chemo-thermotherapy (PICT). In this report, they present the long-term results for 31 consecutive patients who underwent resection, followed by PICT for lung cancer with pleural dissemination between April 1985 and December 1991.**

Methods. **Among the patients, there were 26 cases of adenocarcinoma, 3 cases of squamous cell carcinoma, and 1 case each of large and adenosquamous cell carcinoma. Twenty-four of these patients had an initial diagnosis of pleural involvement at thoracotomy. The other seven patients had massive malignant effusion at the time of the initial diagnosis. PICT was started between days 10 to 14 postoperatively. When possible, three courses of this procedure were administered at intervals of 5–7 days.**

Results. **The 5-year cumulative and 5-year local relapse-free survival rates were 24.6% and 76.3%, respectively. The 3-year and 5-year cumulative survival rates for 14 patients without mediastinal lymph node involvement were 68.4% and 42.7%, respectively. Those rates for 17 patients with mediastinal lymph node involvement were 22.7% and 0%, respectively. The 3-year survival rate in the former group was significantly better than that in the latter group.**

Conclusions. **These results strongly suggest that in patients with pleural dissemination, PICT may be beneficial for regional disease control and improvement of survival, particularly for patients without mediastinal lymph node involvement. *Cancer* 1993; 72:426–31.**

Key words: chemo-thermotherapy, lung cancer, pleural dissemination, cisplatin, radiofrequency hyperthermia, long-term results.

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Accepted for publication February 25, 1993.

Thermal enhancement of the tumoricidal effect of cisplatin and other anti-cancer drugs has been demonstrated by many investigators in experimental in vitro[1–7] and in vivo[8] studies. However, because of the difficulties involved in homogeneously heating target lesions to more than 41.5°C, chemo-thermotherapy can be clinically applied only in special cases.[9,10]

Malignant pleural effusion or dissemination is a common complication of advanced lung cancer that can severely affect the performance status and shorten survival.[11–13] Although successful palliative treatment permits extra months to years of productive life, obviating the need for continuous hospital stay and repeated thoracentesis, cure cannot be expected. The lesion is not always detectable in a preoperative evaluation using a routine chest roentgenogram or a computed tomography scan. Consequently, surgical treatment in such patients is seldom effective because it amounts to no more than a noncurative resection.

We had hypothesized that the pleural surface might be selectively heated by applying radiofrequency waves through the chest wall. This hypothesis has been confirmed by exact temperature measurement in our clinical investigation.[14] In addition, there has been direct evidence supporting the efficacy of radiofrequency hyperthermia combined with chemotherapy on malignant pleural effusion.[15]

In an attempt to improve the poor results in patients with surgical treatment alone and to obtain local cure, postoperative intrathoracic chemo-thermotherapy (PICT) has been developed and attempted. This study reports the long-term results of PICT in patients with malignant pleural lesions.

Materials and Methods

Between April 1985 and December 1991, 31 patients with malignant pleural effusion or dissemination sec-

Table 1. Patient Characteristics

No. of patients	31
Mean age (range) (yr)	58. (29–74)
Sex ratio (male/female)	1.4/1
Histologic type	
Adenocarcinoma	26
Squamous cell carcinoma	3
Large cell carcinoma	1
Adenosquamous carcinoma	1
Primary tumor maximal diameter	
< 3.0 cm	18
3.1–4.9 cm	8
> 5.0 cm	5
N status	
N0	12
N1	2
N2	17
M status	
M0	29
M1	2
Operation	
Panpleuropneumonectomy	5
Pneumonectomy	3
Lobectomy	18
Segmentectomy or wedge resection	5

ondary to lung cancer were treated by resection followed by PICT. The patient characteristics are shown in Table 1. There were 18 male patients and 13 female patients, and the patient age range was 29–74 years (mean, 58 years). There were 26 cases of adenocarcinoma, 3 cases of squamous cell carcinoma, and 1 case each of large and adenosquamous cell carcinoma. The maximal diameter of the primary tumor was 3.0 cm or smaller in 18 patients, 3.1 to 4.9 cm in 8 patients, and 5.0 cm or larger in 5 patients. Twelve patients had N0 disease, 2 had N1 disease, and 17 had N2 disease. The 17 patients with N2 disease included 2 with M1 disease. The extent of pulmonary resection consisted of pneumonectomy with total pleurectomy (panpleuropneumonectomy) in 5 patients, simple pneumonectomy in 3 patients, lobectomy in 18 patients, and a segmentectomy or wedge resection in 5 patients.

Of the 31 patients, 7 had massive malignant pleural effusion on the chest roentgenogram before operation (E2). However, in 17 patients, malignant effusion was first detected at thoracotomy (E1). The remaining seven patients had no clear effusion (E0), but pleural dissemination was proven by the intraoperative cytodiagnosis (D1 and D2) (Table 2). The degree of dissemination was classified as follows: D1, less than 10 visible disseminated nodules; D2, more than 11 visible disseminated nodules; and D0, no visible nodules but cytology-positive effusion.

The details of the heating method were described in our previous report.[14] Briefly, PICT was started between days 10 and 14 after the operations. Immediately after the intrapleural administration of 50–100 mg of cisplatin through the chest drainage tube, which had been left in place at the time of the surgery, radiofrequency (RF) hyperthermia was applied through the chest wall for 60 minutes to heat the pleura and pleural cavity. When possible, three courses of this PICT were administered at intervals of 5–7 days. A 13.56-MHz RF capacitive heating machine (HEH500C; Tateishi Electronics Co., Ltd., Tokyo, Japan) or an 8.00 MHz RF capacitive heating machine (Thermotron RF8; Yamamoto Vinitor Co., Ltd., Osaka, Japan) was used. Intrathoracic and peripleural temperature measurements were performed with a thermometric system with tetrafluorethylene-coated probes of a copper-constantan microthermocouple introduced through the described chest drainage tube or through a sensor guide placed in the pleural cavity at the time of surgery.

Survival curves were constructed by the method of Kaplan–Meier. The generalized Wilcoxon test was used for comparison of the survival curves.

Results

Table 2 shows the relationship between the D status and E status. Seven patients in the D2E2 category had massive pleural effusion, and the pleura was replaced by a bulky tumor. Five of the seven patients underwent pneumonectomy with total pleurectomy (panpleuropneumonectomy). In the other 24 patients, the pleural lesions were discovered when the chest was opened.

A total of 75 PICT treatment sessions were performed on the 31 patients (Fig. 1). A maximal peripleural temperature of higher than 43°C was attained in 47 (63%) sessions. The duration of an effective temperature of 41.5°C or higher was at least 40 minutes in 33 (44%) treatment sessions. The number of treatment sessions per patient was three in 16 patients, two in 12 patients, and one in 3 patients. Although the numbers are too small to draw firm conclusions, there was no correlation between the incidence of local recurrence

Table 2. Patient Distribution as Function of E and D Factors

	E0	E1	E2
D0	0	6	0
D1	6	7	0
D2	1	4	7*

* Patients with a large amount of malignant effusion before operation.

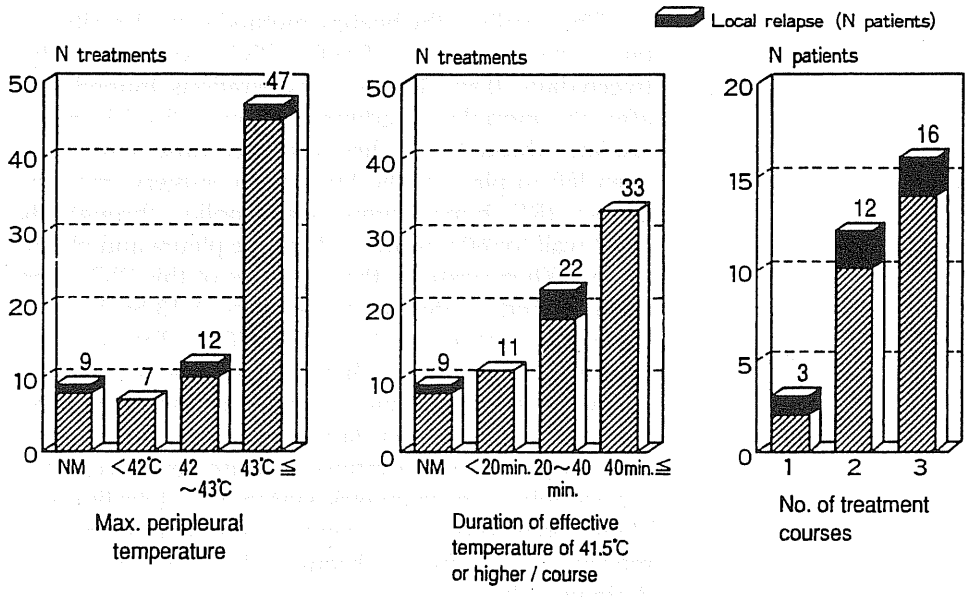

Figure 1. Heating conditions. (Left) Correlation between maximal temperature attained with each therapy and the number of treatments. Center. Correlation between duration (minutes) of an effective temperature of 41.5°C or higher and the number of treatments. (Right) The number of treatments administered to each patient. The black columns indicate the number of patients with local recurrence.

and the maximal temperature, duration of maintaining a temperature higher than 41.5°C, or the number of treatment courses.

There were no major complications during the treatment. Of the 31 patients, 12 had no complications, and the remaining 19 experienced one or two minor complications during or after the treatment (Table 3). As shown in Figure 2, the overall 3-year and 5-year cumulative survival rates were 44.2% and 24.6%, respectively. The 5-year local relapse-free survival rate was 76.3%, and only five patients had local recurrence. The major cause of death was distant metastasis. The survival rates were compared with respect to lymph node involvement (N status) (Fig. 3) and showed a significant difference in the 2- and 3-year survival rates between patients with and without mediastinal lymph node metastasis (N0 plus N1 group versus N2 group). The median survival rates for patients with and without lymph node metastasis were 43 months and 16 months, respectively. The 3-year and 5-year cumulative survival rates were 68.4% and 42.7% for the N0 plus N1 group and 22.7% and 0% for the N2 group. Five patients are alive and well more than 3 years after the PICT treatment, and all of them were in the N0 plus N1 group. The survival rates were compared with respect to the E factor (Fig. 4). Although the patient group with E2 disease had a poorer prognosis than did the other groups, the difference was not significant. Of seven patients with E2 disease, one patient with panpleuropneumonectomy is alive and well 28 months after the treatment.

After PICT was completed, pleural fluid was collected from 25 patients, and the cytologic diagnosis became negative for tumor cells in 20 of those patients. Of the five patients with positive cytologic findings, two died of local recurrence and two died of distant metastasis. One patient with severe degenerative positive cells in the cytology is alive and free of disease more than 3 years after the treatment.

Table 3. Complications During or After Postoperative Intrathoracic Chemo-Thermotherapy

Nausea, vomiting	6
Pain	4
Skin burn	3
Moderate nephrotoxicity	2
Fat necrosis	1
Nausea, vomiting, and skin burn	1
Nausea, vomiting, and pain	1
Skin burn and moderate nephrotoxicity with hyperkalemia	1

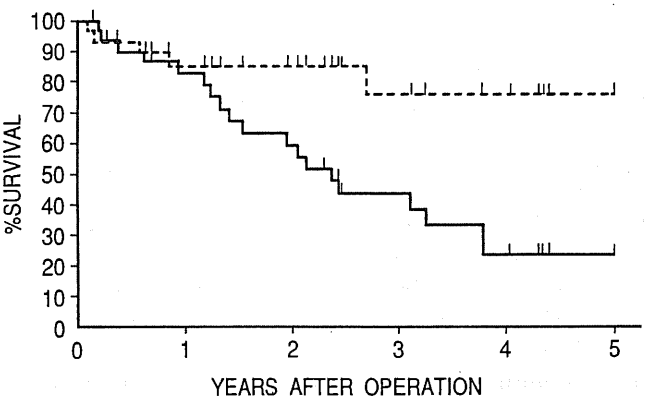

Figure 2. Survival rate (solid line) and local relapse-free survival rate (dotted line) after combined treatment by resection and PICT.

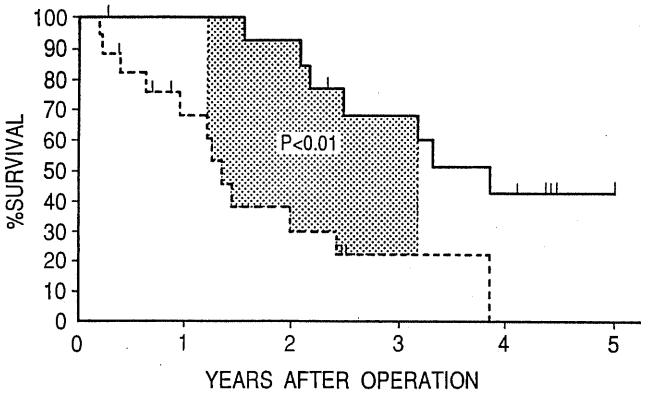

Figure 3. Survival rates of patients with N01 disease (solid line; n = 14) and N2 disease (dotted line; n = 17).

Discussion

Several investigators have shown that hyperthermia acts synergistically with cisplatin in in vitro tumor models.[1–7] Marmor[13] showed that hyperthermia and cisplatin act synergistically against murine tumors in vivo. Wallner et al.[3] reported that hyperthermia and cisplatin act synergistically at 39–43°C against drug-sensitive HA-1 cells. They found a similar degree of synergism between hyperthermia and cisplatin even in cisplatin-resistant cells. Wallner and Li[4] reported that simultaneous heating and cisplatin exposure gave maximal potentiation of cisplatin.

The mechanism(s) by which hyperthermia kills cells remains a matter of controversy, as does the means by which elevated temperatures increase the cytotoxicity of anti-cancer drugs. Three general possibilities that have been proposed are: (1) an increased level of drugs within cells[7,16]; (2) significant enhancement of the DNA cross-linking effect of the drugs[7,17]; and (3) heat-induced inhibition of DNA repair.[18,19] In alkaline elution studies with cisplatin plus hyperthermia using a human squamous cell cancer cell line, Herman et al.[5] demonstrated that the degree of cross-linking was significantly increased at 42°C versus 37°C, especially immediately after 1-hour exposure to the drug. They also reported that the intracellular accumulation of cisplatin was increased by concomitant hyperthermia of more than 42°C in vitro. They speculated that the most likely explanation for the supra-additive cytotoxicity observed with hyperthermia and cisplatin is increased efficiency of formation of drug-induced DNA lesions (cross-links) at elevated temperatures.

RF hyperthermia has been used to treat superficial and deep-seated tumors. It generally is accepted that the addition of local hyperthermia to radiation therapy can substantially improve local tumor control.[20,21] However, although many in vitro and in vivo experimental studies have demonstrated the effectiveness of chemo-thermotherapy, the clinical efficacy is controversial. The main problems confronting the clinical application of chemo-thermotherapy are: (1) the difficulty of achieving homogeneous heating of bulky tumors to higher than 41.5°C; (2) the low concentration of cisplatin in the tumor attained by intravenous administration; and (3) natural or acquired resistance of the tumor cells to heat or cisplatin.

Clinically, because chemo-thermotherapy has been performed only for cases of advanced inoperable tumors or progressive disease despite surgery, the effectiveness was judged only from the response rate in terms of image diagnosis and the degree of alleviation of the symptoms, such as pain.[22] Only a few reports have evaluated the long-term results after the treatment.[9]

RF hyperthermia proved to be suitable as an effective heat delivery system for peripleural lesions because RF energy distorted by air in the lungs or in the postoperative intrathoracic cavity accumulates in the peripleural area. Evidence of this had been presented in our previous investigations.[14,15] However, when 50–100 mg of cisplatin was administered into the pleural cavity, a free-platinum concentration greater than 10 μg/ml was maintained for at least 1 hour.[23] Thus, we think that total cell kill can be achieved if the tumor cells are directly attacked with a combination of hyperthermia by PICT and a high cisplatin concentration similar to the level shown to be effective in vitro.

In the current study, there was no clear correlation between local recurrence and the maximal peripleural temperature, duration of an effective temperature, or number of treatments. Two of five patients with local

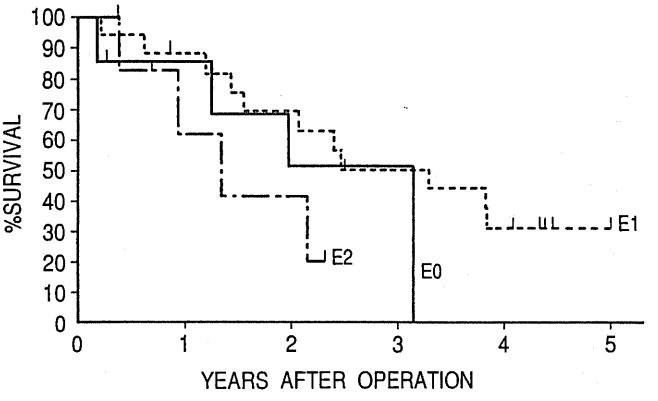

Figure 4. Survival curves of the three groups subdivided as a function of the degree of malignant effusion. E0 (n = 7); E1 (n = 17); E2 (n = 7).

recurrence were treated with three courses of PICT, achieving a temperature higher than 42.0°C. However, the recovered pleural effusion was continually positive for tumor cells after each completion of the treatment. This finding suggests that each tumor must have its own level of sensitivity to hyperthermia or cisplatin. In vitro chemo-thermo–sensitivity tests using specimens resected during operations are thought to be useful for the selection of patients before PICT, and a study of this is being conducted in our institute.

Buhr et al.[24] reported that patients with positive pleural lavage findings had a significantly poorer 2-year survival rate, even those with disease diagnosed as the early tumor stages, but the authors did not describe the type of recurrence or metastasis. When massive symptomatic pleural effusion is found in patients with lung cancer, the prognosis is extremely poor. Various methods of pleurodesis have been described,[25–27] and many agents have been subjected to trials. Although many agents have been used, including antineoplastic agents, radioactive isotopes, and talc, the agent most commonly used for sclerosis is tetracycline. Although various agents are capable of preventing recurrence of the effusion, their effects often are temporary.

We developed PICT for lung cancer with the objective of eradicating residual tumors after resection and improving the local cure. All 31 patients in this study had malignant effusion or dissemination at the time of operation. In addition, seven patients had massive malignant effusion at the time of the initial diagnosis. Patients with only positive findings in the pleural lavage were excluded from this study. The overall cumulative 5-year survival rate was 24.6%, and only 5 of our 31 patients experienced local disease recurrence. This implies that resection followed by PICT results in substantial long-term survival and local control of disease. Our study indicates that long-term survival can be expected in patients without mediastinal lymph node involvement and that such patients are the most suitable for this therapy. In addition, this therapy is thought to be indicated, even for patients with the most advanced disease with massive malignant pleural effusion, if patients with distant metastasis are excluded by careful preoperative screening.

In conclusion, our results strongly suggest that the PICT using RF hyperthermia and a high concentration of cisplatin is effective in the treatment of carcinomatous pleuritis. Our findings also indicate that when PICT is performed for patients without mediastinal lymph node involvement, long-term survival can be expected. The encouraging results have provided justification for future randomized trials between our approach and that of standard intrapleural therapy, such as tetracycline, bleomycin,[27] or cisplatin alone, for dealing with residual lesions after surgery.

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