Combined Treatment of Residual, Recurrent and Unresectable Gastric Cancer

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A series of 25 patients with residual, recurrent, and unresectable gastric cancer received various combination of surgery, radiotherapy (RT), chemotherapy (CT), and hyperthermia (HT). They were placed into 7 categories; 1) CT and HT-14 patients; 2) RT and HT-15 patients; 3) surgery, RT and HT-2 patients; 4) surgery, RT, HT and CT-1 patient; 5) RT, HT and CT-1 patient; 6) RT and CT-1 patient; 7) RT alone-1 patient.

Three patients had curative resection. 21 patients received irradiation with tightly contoured portals to spare as much small bowel, kidney and marrow as possible. Hyperthermia was applied regionally once or twice a week for 23 patients using 8 MHz radiofrequency capacitive heating device (Thermotron RF-8). HT was given approximately 30 min after RT. 7 patients were treated with CT: 4 patients received HT and concomitant Mitomycin-C; 3 patients received HT and sequential 5-FU+Adriamycin+Mitomycin-C.

There was not any treatment related deaths. There was also no evidence of treatment related problems with liver, kidney, stomach, or spinal cord except only one case of transient diabetic ketoacidosis.

The tumor response was evaluable in 22 patients. None achieved complete remission. 11 (50%) achieved partial remission. The response rate was correlated with total radiation dose and achieved maximum temperature. 9 of 14 (64%) received more than 4000 cGy showed partial remission; especially, all 3 patients received more than 5500 cGy achieved partial response. 8 of the 12 patients (67%) who achieved maximal temperature more than 41℃ showed partial response in comparing with 25% (2 of 8 patients, below 41℃). The numbers of HT, however, was not correlated with the response.

3 of the 25 patients (12%) remain alive. The one who was surgically unresectable and underwent irradiation alone is in progression of the disease with distant metastases. The remaining two patients with curative resection are alive with free of disease, 24 and 35 months, respectively. The median survival by response are 11.5 months in responders and 4.6 months in non-responders.

Key Words: Gastric cancer, Radiotherapy, Chemotherapy, Hyperthermia

INTRODUCTION

Cancer of the stomach is the most common cause of cancer deaths in Korea. In 1988 the death rate from this disease in males and females is 38.8 : 100,000 and 23.9 : 100,000, respectively[1].

Surgery remains the mainstay of treatment for gastric cancer. Although the primary tumor may be surgically resectable in approximately 50% of patients, unresectable metastases to lymphatics and direct invasion of adjancent structures without clinically detectable disseminated disease is a frequently encountered clinical circumstance that precludes cure by surgical means alone[2]. Local regrowth or failures in the tumor bed, and regional lymph nodes or distant failures via hematogenous or peritoneal routes are all common mechanisms of failures after curative resection in clinical, reoperative[3,4] and autopsy series.

The potential benefit of adjuvant chemotherapy and irradiation are best illustrated by their value in patients with either locally advanced or disseminated disease. Although radiation alone has been shown to have curative potential in a small percentage of patients with resected but residual, or unresectable but localized disease, its greatest benefit has been when used in combination with chemotherapy[5,6]. However, in view of the limited tolerance of the stomach and other upper abdominal organs, the use of radiation dose modifier such as hyperthermia can improve the local control rate[7]

Over the last decade there has been encouraging reports demonstrating the remarkable effects of heat on tumor control when used in combination with radiation or some chemotherapeutic agents.

This paper reports personal experience with the use of hyperthermia, irradiation and chemotherapy for residual, recurrent and unresectalbe gastric cancer.

METHODS AND MATERIALS

1. Patient Selection

36 patients with advanced gastric cancer were admitted to this study during the period between November 1985 and December 1988. Among them 8 patients had evidence of either distant metastases or peritoneal spread at the start of treatment and 3 patients were lost to follow-up. The remaining 25 patients were considered eligible for this study. They were classified into 3 groups: 1) surgically unresectable-12; 2) recurrent, unresectable-10; 3) resected, but high risk for local regional failure-3.

The average age of patients were 52 years with 7 of the 25 being less than 40. The male to female ratio was 2 : 1 (Table 1).

2. Pathology

All patients had histologically proven adenocarcinoma; 1) poorly differentiatd-14 (56%); 2) moderately differentiated-5 (20%); 3) well differentiated-6 (24%).

3. Treatment Categories

They were plaed into seven categories: 1) chemotherapy and hyperthermia-4; 2) radiation and hyperthermia-15; 3) surgery, radiation and hyperthermia-2; 4) surgery, radaition, hyperthermia and chemotherapy-1; 5) radiation, hyperthermia and chemotherapy-1; 6) radiation and chemotherapy-1; 7) radiation alone-1 (Table 2).

4. Surgical Management

15 of the 25 patients underwent laparotomy. Of

Table 1. Patient Characteristics

	Number of patient	Percent (%)
Age (30–73)		
40세 미만(<40)	7	28
40세 이상(≥40)	18	72
Sex		
Male	17	68
Female	8	32
Median follow-up 10mo. (2–35mo.)		
Performance status by ECOG scale		
0 – 1	9	36
2 – 3	16	64
Location		
Cardia	4	16
Body and/or antrum	20	80
Entire stomach	1	4
Pathology ; Adenocarcinoma		
Well differentiated	6	24
Moderately differentiated	5	20
Poorly differentiated	14	56
Disease presentation		
Resected, but high risk	3	12
Unresectable	12	48
Recurrent, unresectable	10	40

mo. ; month

Table 2. Patient Group—Surgery (S), Radiotherapy (RT), Hyperthermia (HT), and Chemotherapy (CT)

Treatment categories	Patient number	Disease presentation		
		Resected, high risk	Recurrent	Unresectable
RT alone	1	0	0	1
CT + HT	4	0	0	4
RT + HT	15	0	9	6
S + RT + HT	2	2	0	0
S + RT + HT + CT	1	1	0	0
RT + HT + CT	1	0	1	0
RT + CT	1	0	0	1
Total	25	3	10	12

the 15 patients who underwent laparotomy, total gastrectomy was performed in 1 and distal subtotal gastrectomy in 2 patients. 8 patients with unresectable disease had bypass procedure and an additional 4 patients had only exploratory laparotomy with biopsy. The remaining 10 of the 25 patients did not undergo laparotomy. They were all with unresectable postoperative recurrent patients.

5. Radiation

Radiation, chemotherapy or hyperthermia was initiated as soon as the surgical wound had healded and the patients had stabilized which was usually 3 to 6 weeks postoperatively.

Radiation was delivered with Cobalt 60. 21 of the 25 patients received radiation. The radiation field usually included the tumor or tumor bed and major nodal chains (lesser and greater curvature; celiac axis including subpyloric, gastroduodencal, pancreaticoduodenal, splenic, suprapancreatic and porta hepatis when feasible; paraaortic to level of mid L-3 or L-4; paraesophageal with proximal lesions). Field design was influenced by the patterns of local regional failures in the University of Minnesota reoperative group which were in a distribution suitable for inclusion within a shaped radiation portal[3]. Such idealized ports needed to be modified dependent on initial extent of disease. With accurate field definition aided by CT scan, one-half to two-thirds of the left kidney could be spared in many patients, and the inclusion of the porta hepatis and pancreaticoduodenal nodes might cover only a minor portion of the right kidney.

Parallel opposed AP-PA portals with tightly contoured fields were used for the major portion of treatment. Field reduction and/or change into 3 ports (AP and parallel opposed shaped lateral ports) was planned after 20~23 fractions. Once-daily fractionation (5 days per week) using 180~200 cGy doses to a large field dose of 4000~4140 cGy and additional dose up to 6020 cGy was delivered to the primary bed. 20 of the 21 patients received a radiation as a part of combined treatment and one patients received only radiation; 4 patients received 3500~3960 cGy; 14 received 4000~5040 cGy; 3 received 5500~6020 cGy.

6. Hyperthermia

8 MHz radiofrequency capacitive heating machine (Thermotron RF-8, Yamamoto Vinyter Co., Osaka, Japan) was used for hyperthermia. The radiofrequency is applied through a pair of electrodes placed on opposite sides of the body and power is distributed locally or regionally through interaction of electric fields produced between the parallel-opposed electrodes. The surface of the metal plate of the electrode is covered with a flexible vinly sheet filled with temperature controlled 0.4% saline solution.

The surface of the body of the treated site was precooled before hyperthermia up to approximately 25℃, and then Aquasonic (Parker Lab., Inc., NJ) was applied and saline-soaked gauze was overlayed to improve the coupling of the electrodes and provide better contact over the irregularity of the body contour. Additionally, rectangular overlay bolus which is connected to circulating 10~20℃ water was placed between electrode and patient's body so that excessive heating of the skin and subcutaneous fat can be avoided.

The treated site was inaccessible directly. So, the temperature was measured indirectly using a thin Teflon-coated microthermocouple (Sensortek Inc., NJ) which was inserted into the nasogastric tube. The location of it was confirmed fluoroscopically.

Hyperthermia was applied regionally once a week for 2 patients and twice a week for 21 patients. The total number of hyperthermia for each patient ranged from 3 to 12 depending on the different fractionation scheme of treatment, performance status. the interval of each hyperthermia was at least 72 hours. The maximum monitored temperature was kept at 41℃ for 30-40 minutes. When combined with radiation, hyperthermia was done approximately 30 minutes after radiation.

7. Chemotherapy

7 patients were treated with chemotherapy as a part of combined treatment: 4 patients received hyperthermia and concomitant Mitomycin-C (4 mg/m² IV in 5% dextrose in water before hyperthermia); 3 patients received hyperthermia and sequential 5-FU+Adriamycin+Mitomycin-C (Table 3).

During treatment, patients were seen in status check at least once a week with notations consisted of tolerance, weight, blood counts, and liver function test in every two weeks.

RESULTS

1. Toxicity

Overall acute tolerance to combined modality treatment was good as judged by symptoms, hematologic parameters and necessity for medical support. There was not any treatment related

deaths. There was also no evidence of treatment related problems with liver, kidney, stomach, or spinal cord attesting to excellent chronic tolerance of treatment methods used in this series.

The planned course of treatment was not significantly altered as a result of gastrointestinal side effects. While approximately 50% of patients required antiemetics because of anorexia, nausea, or vomiting, symptoms were alleviated in most by premedication with prednisone, perphenazine or metoclopramide. 3 of the 25 patients (12%) were unable to complete their treatment; two because of poor GI tolerance, one because of distant metastases. The average weight loss in the total group of patients was 1.9 kg. Five of the 25 patients (20%) lost more than 4 kg.

Hematologically, white cell counts of less than 2500 occured in 5 of the 25 patients (20%), and three patients (12%) required whole blood transfusion because of the hemoglobin level of less than 10.0.

One of the 25 patients who were treated with combination of hyperthermia and radiation showed transient diabetic ketoacidosis.

Table 3. Chemotherapy Regimens

A. Mitomycin——HT
   1. Dose (before HT)
      4mg/m² in 5% dextrose in water
   2. Schedule
      twice a week until 10 sessions of HT

B. FAM——RT and HT——FAM
   1. Dose
      a. 5 Fluorouracil 600mg/m² (day 1——weeks 1, 2, 5, and 6)
         Adriamycin 30mg/m² (day 1——weeks 1 and 5)
         Mitomycin 10mg/m² (day 1——week 1)
      b. 50–75% dose reduction in first cycle after RT but full doses in pre–RT cycle and in other post–RT cycles if blood counts are satisfactory.
   2. Schedule——One 6 week cycle is given before RT with RT starting week 7. Cycles resume 2 to 4 weeks after completion of RT——5 additional cycles at 8 week intervals.

2. Temperature Measurement

Temperature measurement was undertaken in 23 patients who received hyperthermia as a part of combined treatment. 4 microthermocouples were applied for each hyperthermia; one each on the anterior and posterior skin surface of the treated site, one in the axilla, and one in the stomach. It was impossible to measure thermal distribution of the tumor, so that intragastric temperature was measued. The measured temperature was peritumoral rather than intratumoral temperature. Although the location of the microthermocouple was confirmed fluoroscopically every time, it could be slightly shifted by the respiration and the movement of the intragastric gas could make temperature change.

3. Tumor Response

The tumor response was evaluable in 22 patients except 3 postoperative cases. The patients were followed by UGI series, CT scan and endoscopy. The follow-up studies were checked at least

Table 4. Response by Treatment Modalities

Response/Modality	HT + CT (4)	RT + HT (15)	RT + HT + CT (1)	RT + CT (1)	R T (1)	Total (22)
Objective response						
No response	3	7	0	1	0	11
Partial response	1	8	1	0	1	11
Complete response	0	0	0	0	0	0
Subjective response						
No response	2	2	0	0	0	4
Partial response	1	5	0	1	0	7
Complete response	1	8	1	0	1	11

HT ; Hyperthermia, CT ; Chemotherapy, RT ; Radiotherapy, ( ) ; Number of patients

1 month after completion of the treatment.

Objective responses observed within 1-2 months after treatment were categorized as: 1) complete response (CR), complete regression of all clinically detectable disease; 2) partial response (PR), at least a 50% reduction in tumor volume; 3) no response (NR), less than 50% volume reduction.

Of the 22 patients, none achieved complete tumor remission, 11 (50%) partial remission, 10 (45%) stable disease and 1 (5%) showed distant metastases. In view of subjective complaints, 18 (82%) showed partial or complete relief of their discomfort (Table 4).

18 of the 22 patients received radiation. 4 patients received 3500~3960 cGy; 1 of 4 (25%) showed partial remission. 11 patients received 4000 ~5040 cGy; 6 of 11 (55%) showed partial remission. 3 patients received 5500~6020 cGy; 3 of 3 (100%) showed partial remission.

20 of the 22 patients underwent hyperthermia. The maximum achieved temperature was 40~41℃ in 8, 41~42℃ in 5, 42~43℃ in 3, and more than 43℃ in 4 patients. The partial tumor remission rate was 25%, 60%, 67% and 75%, respectively (Table 5).

Table 5. Response by Achieved Maximum Temperature

Temperature (°C)	Patient number	Response			Response rate (%)
		CR	PR	NR	
below 41	8	0	2	6	25
41 —— < 42	5	0	3	2	60
42 —— < 43	3	0	2	1	67
over 43	4	0	3	1	75
Total	20	0	10	10	

Survival

As of March 1990, 3 of the 25 patients (12%) remain alive. The one who was surgically unresectable and underwent irradiation alone is in progression of the disease with distant metastases. The remaining two patients who were in the resected, but high risk group, are alive with free of disease, 24 and 35 months, respectively (Fig. 1).

The median survival by response are 11.5 months in responders and 4.6 months in nonesponders (Fig. 2).

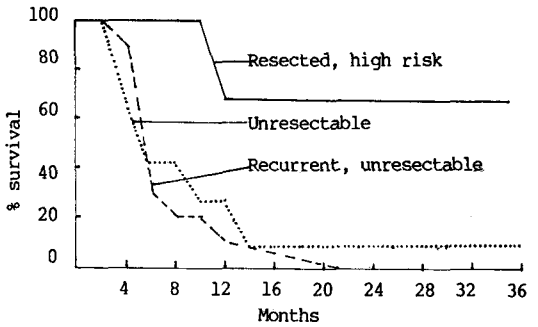

Fig. 1. Survival curves in the group that had a curative resection but were at high risk for local recurrence, in the group with surgically unresectable, and in the group with recurrent, unresctable.

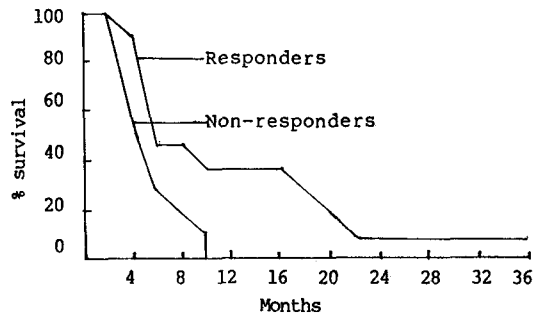

Fig. 2. Survival curves in the responders and non-responders.

DISCUSSION

The management of residual, recurrent or unresectable gastric cancer presents challenges in the field of radiation oncology. The long-term benefit of irradation for the residual disease and unresectable groups had been established. Wieland and Hymmen used 6000 cGy when feasible (150 to 200 cGy daily) with a result of 11% (9 of 82) 3-year and 7% (5 of 72) 5-year survivals[8]. Takahashi compared historical controls with patients with inoperable disease or patients who had undergone palliative procedures and received postoperative irradiation[9]. The average survival for the group treated by radiation therapy was longer by 9 to 10 months, which 74% survival (32 of 43 patients) at 1 year and 28% survival (12 of 43 patients) at 2.5 years. In my study, 1 of 25 patients was treated with radiation alone (5940 cGy in 7 weeks). He had unresectable disease in the cardia, distal esophagus, celiac and perigastric lymph nodes. He is alive at 35 months, but with disease progressing recently. Although some cures have

been obtained with irradiation alone, indicating that gastric cancer is radiosensitive, this is not a valuable approach because the bulk of disease and the limited tolerance of the stomach and surrounding organs prevent from a suitable therapeutic ratio between cure and complication. The preferred use of radiation as an aid to local regional control would be in combination with operative removal of all gross disease in the primary area and lymph nodes, with radiation usually in combination with chemotherapy being used to treat microscopic or subclinical residual disease.

Most reports on combined treatment deal with results in the patients with unresectable cancer and show suggestive improvement for irradiation plus 5-FU over that achieved with either irradiation alone or 5-FU alone[5,10]. In the Mayo clinic series, a randomized double blind study of patients with unresectable disease, 5-FU was used during the first 3 day of radiation (3500~4000 cGy at 900 ~1200 cGy/week). For the combined therapy versus radiation therapy groups, mean survival was 12 versus 5.9 months, and 5-year survival rate was 12% (3 of 25 patients) versus 0% (0 of 23)[5]. The randomized GITSG study (protocol 8274)[11] including 90 patients with unresectable or residual disease showed that the combination of radiation therpay plus 5-FU followed by maintenance 5-FU plus methyl-CCNU was superior to 5-FU plus methyl-CCNU alone with regard to long-term survival. Patients with residual disease after resection had better long-term survival rates than those whose cancers were never resected[11]. Min et al found the combination of radiation therapy plus 5-FU followed by maintenance 5-FU after curative resection was superior to curative resection alone in advanced gastric cancer[12]. For the combined therapy versus curative resection only, 5-year survival rate was 27% versus 18%. Irradiated patients received 5000 cGy in 8 weeks in split course fashion (2500 cGy in 3 weeks, followed by 2 weeks' of 5-FU was given on days 1,2 and 3 of each radiation therapy sequence, followed by 5-FU maintenence chemotherapy).

For lesions which are resectable, the data from the Minnesota reoperative series[3] and a series from Memorial hospital[4] confirm that local recurrence in the tumor bed and nodal areas is a significant problem in the pathological subgroups with extension through the wall, nodal involvement or both in combination. Gunderson et al[7] reported that when irradiation is combined with surgical resection of all or a majority of tumor, both survival and local control appear to be better than in the unresected patient group. Only 4 of 29 patients (14%) with curative resection, or resection but residual disease, had later evidenc of failure within the irradiated field as opposed to 6 of 9 or 66% in the group with unresectable disease. In randomized trial from Moertel et al[13], 62 patients with involved nodes were randomized to no further treatment or postoperative irradiation (3750 cGy over 4~5 weeks) plus 5-FU (15 mg/kg IV bolus on days 1~3). The 5-year survival rate in patients assigned to receive additional treatment was 23% versus 4% in those treated by surgery. Local failure was documented as a component of initial progression in 39% of treated patients versus 55% of those treated with surgery alone. Although a preponderance of data suggests improved survival in unresectable gastric cancer with radiation plus chemotherapy, Dent et al[14] and Tsukiyama et al[15] reported conflicating results. Those conflicting results from the above positive results indicate a need for continued investigation about improving local control rate. In my study, 3 of the 25 patients had curative resection but were at high risk for locoregional failure and received postoperative irradiation plus hyperthermia (2 of the 3 patients), and one of the three patients had irradiation plus hyperthermia plus sequential FAM chemotherapy. One of the three patients was dead 20 months after treatment, and the remaining 2 patients are still alive 24 months and 35 months, respectively without evidence of recurrence.

The biological rationale for the use of hyperthermia alone or in combination with radiotherapy or chemotherapy, to treat malignant tumors, have been well established[16~18]. The effect of local hyperthermia alone is reported to produce response in 51% of patients[19] and when combined with radiation, the complete response rate is often more than doubled in comparing with radiation alone[20]. However, most reported clinical studies were made concerning superficial tumors. Unfortunately the engineering or technical aspects of hyperthermia to raise the temperature of deep-seated tumors to a therapeutic range with acceptable side effects on the surrounding normal tissues has not been satisfactory. Several Japanese reports[21~23] suggested the usefulness of radiofrequency capacitive hyperthermia combined with radiotherapy for the treatment of refractory deep-seated tumors. In agar phantom and human tumor study, Song et al[24] demonstrated that radiofrequency capacitive heating is potentially useful. In the phase I trial of

Minnesota University[25], radiofrequency capacitive hyperthermia was useful and response rate was depended with combined total radiation dose; the response rate of the full-dose radiotherapy group and low-dose group was 69% versus 43%, respectively. In my study, the response rate was also depended on the total radiation dose. 18 of the 25 patients were evaluable for the response. one of four (25%) patients who received 3500~3960 cGy, 6 of 11 (55%) received 4000~5040 cGy, and 3 of 3 (100%) received 5500~6020 cGy showed objective response.

The temperature measurement in deep hyperthermia has many problems. There is no applicable non-invasive thermometry system until now. Invasive thermometry can confirm the thermal distribution of the tumor, but it is practically difficult in fractionated hyperthermia. Furthermore, three-dimensional thermal mapping is more difficult. In my study, intragastric temperature was measured using nasogastric tube instead. The meausred temperature is the peritumoral rather than the intratumoral temperature. The response was correlated with the temperature achieved. Only 2 of 8 (25%) below 41℃ and 8 of 12 (67%) above 41℃ showed objective response. The number of hyperthermia for each individual was 3 to 12, but the response was not correlated with the number of hyperthermia received.

Many authors[22~25] recommended precooling for sometime before hyperthermia is effective for deep-heating. It can avoid the excessive heating of the skin and subcutaneous fat.

Hiraoka et al[23] and Lee et al[25] demonstrated that intratumoral low-density on posttreatment CT seems to be a good parameter for assessing the tumor response in addiation to tumor regression.

Recently, new approach using hyperthermia such as continuous hyperthermic peritoneal perfusion in combination with the administration of cisplatin and mitomycin C have been performed for treating peritioneal recurrence and prophylaxis of peritoneal dissemination[26~28].

For the effective use of hyperthermina alone or combined with other modalities, Bae[29] proposed that following questions should be solved: 1) specific information regarding damage to all major dose-limiting organs and tissues; 2) quality-assured noninvasive thermometry; 3) optimum temperature, duration, number and frequency of hyperthermia; 4) optimum radiation parameters in combination with hyperthermia; 5) standardization of evaluation of response rate.

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= 국문초록 =

수술후 잔존 위암, 재발성 위암 및 절제 불가능한 위암의 병용 요법

부산메리놀병원 치료방사선과

배 훈 식

1989년 보건사회부 통계에 의하면 1988년도 한국 성인 남녀의 제일 많은 암 사망원인은 위암으로 밝혀졌다.

위암의 최신의 치료방법은 조기발견에 의한 근치절제술이지만 수술 후 잔존위암, 재발성 위암 및 절제 불가능한 위암의 치료는 난점으로 지적되어 있다.

저자는 1895년 11월부터 1988년 12월까지 메리놀병원 치료방사선과에서 치료를 받았던 36예중 분석이 가능한 25예를 대상으로 다음과 같은 결론을 얻었다.

1, 방사선치료, 복합 항암제 치료, 및 온열치료의 병용요법은 비교적 안전하였으며 병용요법의 독성에 의한 사망은 없었다.

2, 병용요법에 의한 객관적 반응의 결과는 종괴축소로 판별하였으며 종괴절제술을 시행하였던 3예를 제외한 22예에서 측정이 가능하였다. 종괴의 완전 소실을 보인 예는 없었으며 11예(50%)에서 50%이상의 종괴 축소를 보였다. 그러나 주관적 반응으로 증상의 소실 혹은 완화를 보인 예는 18예(82%)이었다.

3. 총 방사선조사 선량과 온열치료시 도달된 최고 온도는 종양반응의 예후 예측인자로 확인되었다. 4000 cGy 이상 조사된 14예중 9예(64%)에서 부분 반응을 보였으나 4000 cGy 미만의 4예중 1예(25%)에서 부분반응을 보였다. 온열치료시 도달된 최고 온도가 41℃ 미만인 8예중 2예(25%), 41℃ 이상인 12예중 8예(67%)에서 부분 반응을 보였다.

4, 25예중 3예(12%)는 현재 생존하고 이중 1예는 절제 불가능했던 위암 환자로 5980 cGy의 방사선치료만 받았던 예로 현재 35개월째 생존하고 있으나 최근 원발 병소의 진행과 원격 전이가 관찰되었다. 나머지 2예는 근치절제술 후 절단면에서 암세포 침윤이 관찰되었던 예로 1예는 방사선치료와 온열치료, 1예는 복합 항암제치료는 시행받았으며 전자는 35개월, 후자는 24개월째 무병 상태로 생존하고 이다.

반응정도에 따른 정중 생존기간은 무반응군은 4.6개월 반응군은 11.5개월이었다.