A feasibility study in oesophageal carcinoma using deep loco-regional hyperthermia combined with concurrent chemotherapy followed by surgery

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This phase I–II study investigated the feasibility of external deep loco-regional hyperthermia in localized primarily operable carcinoma of the thoracic oesophagus and gastro-oesophageal junction. Toxicity when combining neo-adjuvant hyperthermia with concurrent chemotherapy (CDDP and etoposide) was evaluated. Hyperthermia was given with a four antenna array, operating at 70 MHz arranged around the thorax. Temperatures were monitored rectally, intra-oesophageal at tumour level and intramuscular near the spine. In four steps, a thermal dose escalation was performed from 15–60 min of heating to 41°C with two patients in each step. The combined treatment courses were repeated every 3 weeks for a maximum of four courses. From January 1999–February 2002, 31 patients were included. Pre-treatment tumour stage mainly consisted of T3N1 (stage III) tumours, with a mean length of 6 cm. The maximum tumour temperature failed to reach at least 41°C in five patients during the test session of hyperthermia alone. Combined hyperthermia and chemotherapy was given 55 times in 26 patients. The amplitude was set at a ratio between top:bottom:left:right = 1:3:3:3, with a power range of 800–1000 W. Thermal data showed that it was technically feasible to heat the oesophagus; the median results were $T_{90} = 39.3^\circ C$, $T_{50} = 40^\circ C$, $T_{10} = 40.7^\circ C$ and a median $T_{\text{max}} = 41.9^\circ C$. In more distally located tumours higher temperatures were reached. In one patient, a transient grade 2 sensory neuropathy was seen. Further toxicity was mainly of haematological origin. Blisters or fat necrosis were not observed. Twenty-two patients underwent oesophageal-cardia resection with gastric tube reconstruction. There was no report of complications in the post-operative phase, which could be contributed to either the prior chemotherapy or the hyperthermia.

Key words: Oesophageal carcinoma, hyperthermia, neo-adjuvant chemotherapy.

1. Introduction

The prognosis of oesophageal cancer with invasion of the entire oesophageal wall or involvement of loco-regional lymph nodes remains poor. Long-term survival after potentially curative surgery is 5–20%\textsuperscript{1–3}. Several studies with neo-adjuvant chemotherapy have not supported the use of this pre-operative treatment\textsuperscript{4–6}. However, two recent randomized trials with cisplatinum based neo-adjuvant chemotherapy showed not only an improvement in the time to locoregional recurrence, but also an improvement in the overall survival of 3.5–6 months as compared to surgery alone\textsuperscript{7,8}. Despite this progress, the probability of local recurrence at 3 years after

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neo-adjuvant chemotherapy followed by surgery was still \( \approx 30\% \). Therefore, studies aiming at improvement of locoregional control are warranted.

Promising results have been achieved with the combination of heat and chemotherapy. The rationale for thermochemotherapy rests on the assumption that heat exposure increases tumour-cell kill by direct cytotoxicity and chemo-sensitization by interference with the repair of DNA damage and by a synergistic interaction with cytotoxic drugs. Phase II clinical studies were encouraging when heat was combined with cisplatinum (cDDP) in recurrent carcinoma of the uterine cervix, abdominal germ cell tumours and soft tissue sarcomas. Data on treatment of deep hyperthermia combined with cisplatinum-infusion in the thoracic region are scarce. In a rat model, the influence of hyperthermia was studied on the uptake of cisplatinum in the cervical spinal cord. No effect was seen when using mild hyperthermia (i.e. 42–43°C for 30 min), while after a heat dose of 43°C for 60 min a significant increase in cisplatinum uptake to toxic levels was demonstrated. These observations indicate that no toxicity to the normal nervous tissue is expected when combining cisplatinum with heat below 43°C. Clinical reports on hyperthermia in oesophageal carcinoma concern mainly Asian or Russian studies using intra-luminal applicators. Sugimachi et al. showed in a small trial with neo-adjuvant chemoradiotherapy randomizing between plus or minus intra-luminal hyperthermia that the clinical and pathological effects were in favour of the hyperthermia arm, with comparable side effects. A disadvantage of this intra-luminal heating technique is the limited penetration depth; the temperature rise drops to 50% at only 5 mm depth and, thus, seems to be insufficient to heat the majority of oesophageal carcinomas. Also, no longitudinal steering is possible, which results in temperature inhomogeneity in the longitudinal direction of the tumour. Li and Hou measured 25% temperature heterogeneity in the axial direction. Clinical data on the use of external locoregional hyperthermia in oesophageal cancer are lacking.

This study investigated the feasibility of external heating of carcinomas of the thoracic oesophagus and the toxicity of combined hyperthermia with chemotherapy.

2. Patients and methods
2.1. Time schedule
During the study period, the standard pre-operative chemotherapy for treatment of squamous cell oesophageal cancer in the Academic Medical Centre consisted of cisplatinum and etoposide. To determine the feasibility of addition of hyperthermia to this standard neo-adjuvant chemotherapy regime, the ability to achieve therapeutic temperatures in the oesophagus was studied first. Therefore, a test session of hyperthermia prior to the chemotherapy was performed. When hyperthermia appeared to be feasible with adequate temperatures during this test session, the hyperthermia was continued during concurrent chemotherapy. A time interval of 1 week was kept between the test session and the first combined treatment, in order to avoid thermo-tolerance. A thermal dose escalation was performed in four steps from 15 min of heating at 41°C to 30, 45 and finally 60 min, with two patients in each step. The thermal dose escalation was applied to both the test session and the therapeutic session with chemotherapy. All patients were subjected to neurological examination before and after each hyperthermia session. The combined treatment courses were repeated every 3 weeks (figure 1(a)). The first evaluation took place after the second combined course of thermo-chemotherapy. Tumour response was assessed by endoscopy, endosonography and CT-scan. In the case of a responding
tumour (either complete response or partial response), another two cycles of hyperthermia and chemotherapy were given in weeks 7 and 10, followed by a second evaluation. Surgery had to be performed within 6 weeks from the start of the last cycle. In the case of stable or progressive disease at first evaluation, thermo-chemotherapy was discontinued and the patient was referred to surgery.

After 2 years of study, when preliminary data of three courses neo-adjuvant chemotherapy in adenocarcinomas showed positive results, it was decided to include also patients with adenocarcinomas of the oesophagus and to reduce the number of courses to three, without evaluation between the courses. The latter was based on the discrepancies of tumour response between CT-scan findings, endosonography and clinical symptoms during these evaluations.

### 2.2. Patient eligibility

Patients should have a Karnofsky performance score of >70, age of ≤75 years, a histological confirmed oesophageal carcinoma with a measurable tumour size which should be a potentially curable disease, adequate renal function (GFR > 60 ml min⁻¹), pre-treatment WBC > 3.5 × 10⁹ l⁻¹ and platelet count > 100 × 10⁹ l⁻¹ and a written informed consent. Patients were excluded in case of a tumour location in the cervical part of the oesophagus, any impossibility to introduce a thermometry catheter, severe cardiac disease, pre-existing myelopathy or neuropathy and previous radiotherapy or chemotherapy.

### 2.3. Thermometry placement

Through a flexible (naso) gastric tube, a double multi-sensor probe was deployed intra-luminal adjacent to the oesophagus tumour for temperature monitoring, under fluoroscopic guidance. Most patients were sedated with 2.5–5 mg midazolam i.v.
The upper and lower border of the tumour were marked at the skin on the back of the patient with lead wires and ink and documented by X-ray (figure 2). For normal tissue temperature monitoring, a rectal thermometer was given. For spinal cord measurement, a spinal intramuscular thermometry catheter at the level of the tumour was placed in the m. erector spinae (figure 3) upon the ligamentum flavum under local anaesthetics.

2.4. Multi-modality treatment

2.4.1. Hyperthermia. In the present study, locoregional hyperthermia was given using the AMC phased array of four 70 MHz antennae arranged around the thorax. The patient was lying in a prone position and held his arms over his head to provide access for the two side-antennae. The two other antennae were directed toward his back and belly (figure 4). Between the antennae and the patient, four water bags were placed in front of each antenna, serving a dual purpose: first to guide the field into the patient and secondly to provide skin cooling. The latter was achieved by circulating cold water of \( \sim 13^\circ C \) in the bolus.

The locoregional technique relies on the constructive interference at the target of the waves emanating from four antennae. For the oesophagus, the antenna settings for the amplitude and phase were optimized with the aid of an e-field probe (REF, diameter 1 mm) mounted on a balloon catheter adjacent to the tumour. Prior to heating, the optimal phase setting was determined; the phase of the top antenna was set to 0°, then the phase of the three remaining antennae were optimized by setting the phase of each individual antenna to the angle, yielding a maximum in the power read-out of the probe.
Figure 3. CT scan showing the dorsal intra-muscular and intra-esophageal thermometry catheter (green and yellow arrow, respectively).

Figure 4. Patient in treatment position. Note the dorsal intra-muscular catheter (arrow).
To identify critical locations, treatment planning was performed using a generic ‘standard’ patient; in this procedure the patient’s anatomy was segmented into a limited number of basic tissue types (muscle, bone, fat, air) and the power distribution was computed on a cubic centimetre grid. These simulations identified a potentially serious problem in the myelum where for specific phase and amplitude settings the temperature rise in the myelum could far exceed that in the oesophagus. This result prompted two measures: the standard amplitude of the back antenna had to be reduced considerably and spinal temperature monitoring during treatment was mandatory.

For temperature monitoring, two parallel 21-point thermometry probes (spacing 1 cm, active length 20 cm) were placed into the oesophagus to map the temperature distribution in the peri-tumoural area. Initially, these were inserted in two opposing lumina of a three lumen naso-gastric tube, but after 20 hyperthermia sessions the probes were mounted on opposite sides of an inflatable balloon catheter (balloon length 80 mm, diameter 10 mm) for better intra-luminal fixation. The correct location was determined by the procedure mentioned earlier. It was not possible to monitor the tissue temperature in the entire region, as this would require extensive invasive thermometry, with the exception of a spinal intra-muscular catheter placed to monitor the most crucial spinal temperature by a 14-sensor thermocouple string (spacing 0.5 cm). The average depth of this catheter was 3 cm. A 14-sensor thermocouple string in a rectal catheter monitored the body temperature.

Tumour temperature uniformity was determined using $T_{10}$, $T_{50}$ and $T_{90}$, indicating the temperatures achieved in at least 10, 50 and 90% of the sensors in the tumour, respectively. Thus, $T_{10}$ is a measure for the maximum, $T_{50}$ for the mean and $T_{90}$ for the minimum tumour temperature.

After a phase of warming up (maximum 20 min), the effective heating period started when a tumour temperature was reached of 40–41°C, measured in at least one point in the tumour. One endeavoured not to exceed the maximum back temperature of 41°C. During these sessions, the patient was not sedated but experienced the after-effect of midazolam i.v., which was given during the positioning of the (naso) gastric tube. The adequacy of the patient was necessary to gain information for detecting hot spots and, thus, for preventing burning during hyperthermia.

Toxicity was scored according to the Common Toxicity Criteria version 2.0.

2.4.2. Chemotherapy. Chemotherapy consisted of cisplatinum and etoposide courses every 3 weeks. Cisplatinum 80 mg m$^{-2}$ i.v. was infused over 90 min on day 1. Hyperthermia was given simultaneously with the infusion of cisplatinum. Following hyperthermia, a fixed dose of 100 mg etoposide i.v. was given on day 1. On day 2, the same dose of etoposide was administered. On days 3 and 5, etoposide liquid (200 mg m$^{-2}$) was taken orally in three divided doses at fixed times at home (figure 1(b)).

Chemotherapy courses were delayed for 1 week if a white blood count of $<3.5 \times 10^9 l^{-1}$ or platelets $<100 \times 10^9 l^{-1}$ was present. A delay of a maximum of 2 weeks was accepted. When no improvement was seen after that period, neo-adjuvant treatment was stopped and the patient was referred to surgery. Dose reduction of etoposide to 75% was applied when a white blood count of $<1.0 \times 10^9 l^{-1}$ or platelets $<25 \times 10^9 l^{-1}$ was seen. In the case of renal insufficiency (creatinine clearance $<60 \text{ml min}^{-1}$ according to the Cockroft-Gault formula or serum creatinine $>150 \text{umol l}^{-1}$) or severe neurotoxicity ($>\text{grade 2}$), the treatment was stopped.
For the first 12 patients, the complete course was to be repeated in week 3 and, in the case of response at evaluation, a third and fourth course was given in weeks 7 and 10. For the last 14 patients, neo-adjuvant treatment was limited to three combined sessions without a mid-course response-evaluation.

2.4.3. Surgery. All patients were offered surgical resection with curative intent after the neo-adjuvant chemo-hyperthermia. Patients with a tumour distal to the carina primarily underwent a transhiatal resection without a thoracotomy and with only a limited lymph node dissection. When the tumour was located proximally to the carina, the tumour was mobilized via an anterolateral thoracotomy. Paratracheal and subcarinal nodes were resected en-bloc; nodes in the aortopulmonary window were left in-situ. Both after transhiatal and after transthoracic resection, a gastric tube reconstruction with cervical oesophago-gastrostomy was performed, using a one layer running suture.

3. Results

3.1. Patient and pre-treatment tumour characteristics

From January 1999–February 2002, 31 patients, 20 males and 11 females, were included in this study. Mean age was 62 years (range 43–75 years). Twenty patients had a squamous cell carcinoma and 11 patients had an adenocarcinoma. Pre-treatment tumour stage consisted mainly of T3N1 tumours (stage III) (table 1). Median length of the tumour was 6 cm, with a range of 2–12 cm. Six per cent of the tumours (2/31) were situated in the upper thoracic part of the oesophagus, 42% (13/31) in the mid-thoracic part and 52% (16/31) in the lower thoracic part.

3.2. Thermal outcome

3.2.1. Test sessions. Twenty patients underwent a test session of hyperthermia. In the next 11 patients, the test session was abandoned, because sufficient experience had been acquired to induce the right amplitude and phase settings of the antennae to reach adequate minimum tumour temperatures at the first session (learning curve). No acute toxicity had been encountered during the 20 test sessions.

In the first three patients, the initial amplitude setting was copied from previous cervix hyperthermia treatment in the department, where a standard ratio between top:bottom:left:right was set at 3:3:2:2. The incidence of high back temperatures prompted a change in default amplitude setting to 1:3:3:3, supported by

<table>
<thead>
<tr>
<th>Tumour stage</th>
<th>No of squamous cell carcinoma</th>
<th>No of adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0M0</td>
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<td>1</td>
</tr>
<tr>
<td>T2N0M0</td>
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<tr>
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</tr>
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<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>11</td>
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*Because of celiac lymph nodes, not because of distant metastasis.
the previously mentioned simulation results. The required power range to obtain these temperature levels was 800–1000 W. The maximum tumour temperature failed to reach at least 41°C in five out of 20 patients from the test session series. In two patients, this was due to technical problems (learning curve, dislocation of the probe), in two patients because of a tumour location above the carina and in one patient because scar tissue on her chest wall caused extreme pain during heating. These five patients went off study and received neo-adjuvant chemotherapy only.

3.2.2. Treatment sessions. Concurrent hyperthermia and chemotherapy was given 55 times in 26 patients. All patients had temperature measurements in two thermocouple strings along the tumour length. An average number of 12 tumour temperature points per patient was available (figure 5). For 55 sessions, the median results were \( T_{90} = 39.3°C \), \( T_{50} = 40.0°C \) and \( T_{10} = 40.7°C \), the difference \( T_{10} - T_{90} \) was 1.4°C. These results were almost identical for the test session. Most of the temperature heterogeneity was caused by heterogeneity in the axial direction, with often strong gradients at the axial borders. The profile found within one thermocouple string was usually repeated in the parallel string at the opposite side of the lumen. Hot spots were not a major problem (median \( T_{\text{max}} = 41.9°C \)) and were not the limiting factor during treatment. The mean back temperature was 38.6°C. In two patients (three sessions), the back temperature reached the critical level of 41°C.

A relation between tumour location and temperature was found. The more distally the tumours were located, the higher the temperature achieved. One found a \( T_{50} \) of 40.2 and 39.8°C, and a \( T_{90} \) of 39.4 and 38.9°C for distal and proximal locations, respectively.

3.3. Chemotherapy

All 26 patients received the first combined course of chemotherapy and hyperthermia and a second, third and fourth combination course was given in 19, eight and two patients, respectively. Reason for discontinuing the courses were patient’s refusal (three patients), haematological toxicity (two), nefrotoxicity (three), cardiac
problems (two), neurological complaints (one), stable disease (four) or progressive
disease (three) during interim-evaluation and gastro-intestinal toxicity (one). Five
patients did not receive the fourth course because of the adjustment of the standard
protocol from four to three courses. Chemotherapy was delayed nine times (seven
patients), eight times because of grade 3 haematological toxicity and once due to
renal toxicity. In three patients, a reduction to 75% of etoposide administration
was necessary because of pancytopenia.

3.4. Surgery

Of the 26 patients who had one or more combined hyperthermia/chemotherapy
sessions, 22 patients underwent surgery. Reasons for not entering the operation
procedure were death due to leucopenic complications in one patient and the
other three patients had distant metastasis found after re-screening prior to surgery.
In one patient, liver and omental metastases were found at laparotomy and under-
went no further resection. In total, 13 uncomplicated transhiatal and six uncompli-
cated transthoracic oesophageal resections were performed followed by gastric tube
reconstruction. One patient had a complicated transhiatal resection and died post-
operatively of multiple organ failure after 13 l. of blood loss during operation. One
patient received a palliative procedure because of an irresectable T4 tumour, found
during operation.

Of the 19 successfully operated patients, 17 patients had a microscopically radic-
al (R0) resection and two patients had a microscopically irradical (R1) resection.
Two patients (9%) had a pathological complete remission (pT0pN0), both were
pre-treatment staged with a T3N1 carcinoma; one patient with a adenocarcinoma
after two combined courses and one with a squamous cell carcinoma after four
courses. Five patients were pathologically downstaged, 11 stable disease and two
patients upstaged, which concerned the lymph node status in both patients. The
tumour length found during pathologic examination compared to the clinical length
was similar in six patients, smaller in nine patients and larger in four patients.

There was no report of complications during the post-operative phase, which
could be attributed specifically to the prior hyperthermia and/or chemotherapy.

3.5. Toxicity

No toxicity was seen during the test sessions of hyperthermia without chemother-
apy. One patient stopped prematurely the hyperthermia session because of discom-
fort. The majority of the patients had some complaints of discomfort, mainly due to
the prone position, but were able to complete the hyperthermia sessions. No blisters
or fat necrosis was observed. Chemotherapeutic toxicity is listed in table 2. In total,
24 times grade 3 and 16 times grade 4 toxicity were seen in 13 patients, which were
mainly of haematological origin (table 2).

During the combined courses of hyperthermia and chemotherapy, no acute
complaints were observed, except for one patient who experienced a grade 1 and a
grade 2 symmetrical ‘sock-like’ sensory neuropathy of her feet and lower legs after
the second and during the third combined course, respectively. This was the first
patient in whom adequate tumour temperatures were reached for 15 min. During
the second and third session, however, the mean back temperature also rose to 42.2
and 41.1°C, respectively. In none of the subsequent patients, a mean back tempera-
ture of ≥41°C occurred. These complaints were probably due to thermally enhanced
cisplatinum spinal cord cytotoxicity. The paraesthesia resolved spontaneously within hours and days and at last follow-up she was without any neurological complaints.

Unfortunately, one elderly patient died after the fourth course of chemotherapy due to grade 4 febrile neutropenia and nefrotoxicity in combination with shock. Complete tumour response was observed at autopsy (pre-treatment staged as T3N0).

3.6. Follow-up

Follow-up was complete in all 26 patients who entered the chemohyperthermia treatment. Mean follow-up period was 33 months for living patients (range 22–59 months). The 1 and 2 year actuarial survival rates are 69 and 62%, respectively, including the inoperable patients (figure 6). The 1 and 2 year survival rates for patients who underwent surgery after neo-adjuvant chemohyperthermia, including the palliative resected patient \( n = 21 \) are 86 and 76%, respectively. Two patients developed a mediastinal recurrence after resection (10%) and one an isolated supraclaviculair metastasis. All three patients were irradiated and are still alive.

4. Discussion

The feasibility and toxicity of loco-regional hyperthermia with concurrent chemotherapy was studied. The thermal data indicate that it was technically feasible to heat the oesophagus to a median temperature of 40.0°C. Although the maximum tumour temperatures were considered adequate, the \( T_{50} \) and \( T_{90} \) values were suboptimal. The optimal temperatures in thermo-chemotherapy, however, are still unclear. In order to sensitize radiotherapy by using hyperthermia, a temperature of at least 41°C is required. However, it is not clear whether heat sensitization for chemotherapy demands an equally high intra-tumour temperature. It has been suggested that cisplatinum cytotoxicity is already enhanced with mildly elevated temperatures, even under 41°C. In the present study, the tumour temperature was measured intra-luminal and not intra-tumoural, so that the actual intra-tumoural temperature could be slightly higher than measured.

The second aspect of this study was toxicity. None was seen during the test sessions of hyperthermia alone, but substantial grade 3 and 4 toxicity was found after the combined treatment with chemotherapy. However, a comparable toxicity score has been reported with chemotherapy alone. The most feared complication of hyperthermia was myelopathy, because of the close anatomic relation with the oesophagus. Nevertheless, this complication occurred in only one patient and was reversible within 2 days. This was one of the first patients, with a measured mean
temperature in the m. erector spinae of 42.2°C. This complication prompted a change in the power distribution over the four antennae, resulting in a factor 3 reduction of the amplitude of the top (back) antenna, compensated by a 50% rise in the left and right antenna. No myelopathy was encountered anymore in the following patients and temperatures in the back probe could be kept below 40°C. No complications were seen during or after surgery, which could be attributed to the neo-adjuvant chemotherapy or hyperthermia.

One tried to evaluate tumour responses and found a 9% complete remission rate. However, partial remission and progression are difficult to assess because one compares a clinically staged tumour with a pathological one. No grading of pathologic remission was performed. Kitamura et al.\textsuperscript{20} investigated the clinicopathological features of patients with a markedly effective response compared to those showing a less effective response to hyperthermo-chemo-radiotherapy. He found a 22% (33/151) complete remission rate, but the CR rate was significantly more present in the T1–T2 group compared to the more advanced staged tumours. Most of the tumours (87%) in the present series were staged as T3, which could explain the lower CR rate. The five patients who could not be adequately heated in the test session of hyperthermia alone were among the first 14 patients. In the following part of the study, no patients were off-study for technical impossibility to heat, which suggests a learning curve for heating the oesophagus. Another improvement made after seven patients was the replacement of the (naso) gastric tube by a balloon.

![Survival curve from start of treatment for all patients entering the chemohyperthermia, including the not resected patients (n = 26).](image)
catheter, which reduced involuntarily movement of the thermometry. No further progress was achieved in later patients, especially not in the tumour temperatures, suggesting that increasing $T_{90}$ beyond 40°C is very unlikely with this technique. It is speculated that this may be attributed to structures located near the proximal oesophagus, e.g. large vessels and trachea that may contribute to a significant cooling effect. It was clear that more distally located tumours were more easily heated than proximally located tumours. Tumours above the carina could not be adequately heated.

Increasing the tumour temperature without additional side effects could be a new challenge for the future. A combination of external hyperthermia plus intraluminal hyperthermia could potentially lead to higher tumour temperatures. More studies are needed to investigate the optimal therapeutic temperature when combining heat with cisplatinum.

Another issue of interest is radiotherapy combined with surgery; however, a variety of prospective studies using either pre-operative radiation\textsuperscript{21,22} with accelerated schemes, conventional fractionation with moderate-to-high dose as well as post-operative radiotherapy\textsuperscript{7,23} didn’t show a clear benefit in survival although a tendency to increased local control was present in some series. Attempts to improve response rates in this disease is currently sought in combined modality approaches.

Since it was concluded from this phase I study that hyperthermia was feasible in esophageal cancer, a phase II study was started combining loco-regional hyperthermia with a milder chemotherapy scheme (paclitaxel and carboplatin) plus moderate dose radiotherapy (41.4 Gy) in a neo-adjuvant setting.

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References


