ANTICANCER RESEARCH
International Journal of Cancer Research and Treatment
ISSN: 0250-7005

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Reprinted form
ANTICANCER RESEARCH *25*: 4407-4412 (2005)

ANTICANCER RESEARCH

International Journal of Cancer Research and Treatment

ISSN: 0250-7005

Editorial Office: International Institute of Anticancer Research, 1st km Kapandritiou-Kalamou Rd., Kapandriti, P.O.Box 22, Attiki 19014, Greece. Tel and Fax: 0030-22950-53389.

ANTICANCER RESEARCH supports (a) the establishment and the activities of the INTERNATIONAL INSTITUTE OF ANTICANCER RESEARCH (Kapandriti, Attiki, Greece) and (b) the organization of the International Conferences of Anticancer Research.

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Publication Data: ANTICANCER RESEARCH (AR) is published bimonthly. Each annual volume contains six issues. Annual Authors and Subject Indexes are included in the sixth issue of each volume.

Annual Subscription Rates 2005: Institutional subscription for Europe: Euro 1530 per volume. Institutional subscription for all other continents: Euro 1630 per volume. Personal subscription for Europe: Euro 740 per volume. Personal subscription for all other continents: Euro 800 per volume. Prices include rapid delivery and insurance. The complete previous volumes of Anticancer Research (Vol. 1-24, 1981-2004) are available at 50% discount on the above rates.

Subscription Orders: Orders can be placed at agencies, bookstores, or directly with the publisher. Cheques should be made payable to J.G. Delinassios, Executive Publisher of Anticancer Research, Athens, Greece and should be sent to the Editorial Office.

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Articles in ANTICANCER RESEARCH are regularly indexed in all bibliographic services, including Current Contents (Life Sciences), Science Citation Index, Index Medicus, Biological Abstracts, Chemical Abstracts, Excerpta Medica, University of Sheffield Biomedical Information Service, Current Clinical Cancer, AIDS Abstracts, Progress in Palliative Care, Cambridge Scientific Abstracts, Cancergram (International Cancer Research Data Bank), MEDLINE, Reference Update - RIS Inc., PASCAL-CNRS, Inpharma-Reactions (Datastar, BRS), CABS, Immunology Abstracts, Telegen Abstracts, Genetics Abstracts, Nutrition Research Newsletter, Dairy Science Abstracts, Current Titles in Dentistry, Inpharma Weekly, BioBase, MedBase and Investigational Drugs Database.

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Celiac Axis Infusion and Microembolization for Advanced Stage III/IV Pancreatic Cancer – A Phase II Study on 265 Cases

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Abstract. *Background: Despite various chemotherapeutic drugs and combinations given systemically, the impact of these agents on survival has not been convincing, and drug-related toxicity continues to be the limiting factor. Patients and Methods: Two hundred and sixty-five patients with locally advanced or metastasizing (UICC III/IV) pancreatic cancer underwent celiac axis infusion with Mitomycin, Mitoxantrone and Cisplatin combined with degradable starch microspheres in 5 courses and 1 course of isolated hypoxic abdominal perfusion and chemofiltration. Results: The study end-points were survival and quality of life. Seventy-five percent survival was 6 months, 50% (median) 9 months and 25% was 18 months. Eighty patients survived for one year and more. The longest actual survival time was ten years in a former unresectable stage IV patient. The quality of life improved in responders. No therapy-related hospitalization or increased morbidity was noted. The resectability rate after therapy in long-term survivors (>12 months) was 39%. Peritoneal carcinosis or progression of liver metastases occurred in 18%. The major cause of death in 48% was recurrence at the primary site. Conclusion: In good responders to arterial infusion and microembolization chemotherapy, the resectability rate increased remarkably. Relapses predominantly occurred at the primary site, and progression of distant metastases and peritoneal lesions may be reduced due to isolated abdominal perfusion.*

Pancreatic cancer patients present very late for therapy, and the two therapeutic options in most unresectable and metastasized tumors are systemic chemotherapy or best palliative care. Systemic chemotherapy created some clinical benefit response, especially when gemcitabine was used, but finally neither single nor combination chemotherapy translated into remarkable survival advantage.

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Key Words: Pancreatic cancer, celiac axis infusion, microembolization, isolated abdominal perfusion.

Based on the principle of dose-response, *i.e.* the concentration relationship, an extended phase II trial with a three-drug and DSM (Spherex) combination given intra-arterially *via* the celiac trunk or common hepatic artery should reveal whether pancreatic cancer shows a dose response behavior that results in increased resectability and prolonged survival.

Patients and Methods

Patient eligibility. Eligible patients were required to have histologically confirmed adenocarcinoma or poorly-differentiated carcinoma of the pancreas, that was not amenable to surgical resection as suggested by radiographic imaging and/or exploratory surgery. Patients who had prior palliative surgery in terms of biliary or gastric bypass, biliary stents as well as tumors not responding to systemic chemotherapy or in progression after systemic chemotherapy were also included into the trial. Prior radiation therapy 4 to 6 weeks before enrollment was not an exclusion criteria. Patients must have had adequate bone marrow reserves defined as WBC $\geq$3,500/mm^3 and platelet count $\geq$100,000/mm^3. Serum bilirubin should not have exceeded 1.5, 2.0 mg/dl.

Patients with a Karnofsky performance scale below 50-60% as well as progressive ascites were excluded from the study.

Pretreatment and follow-up evaluation. Baseline evaluation included full blood chemistry with tumor markers CEA and CA 19-9. Chest X-ray and CT scan at the start of the therapy should not have been older than 3 weeks. For follow-up control, serum chemistry, markers and ultrasound were performed before and after each cycle, CT scan and chest X-ray after 2 cycles each, and in cases of questionable complete remission, CT-PET-scan. In cases where there was a decrease of the tumor marker CA 19-9 by $\geq$50%, measurable decrease of tumor size in CT scan and improved performance scale, a staging laparotomy was performed after the third course of intra-arterial chemotherapy.

Therapeutic protocol. The protocol consisted of 6 courses at 4-week intervals. The first 3 courses (Table I) were administered *via* angiographically placed sidewinder catheters that were continuously rinsed with 20,000 IE heparin/24 hours. The drugs were given as daily bolus injections consisting of 3-5 ml of Xylocaine and 3 ml of DSM (Spherex) each with the corresponding drug Mitomycin, Mitoxantrone and Cisplatin® (Table II)*.

*®Cisplatin Lyophilisat Medac

Table I. *RCT for stage III/IV pancreatic cancer.*

Therapeutic protocol	
Cycle	Therapy
1. Angiographic catheter (Celiac axis)	Spherex/Xylocaine microembol. (MMC, Mitoxantrone, CDDP)
2. Angiographic catheter (Celiac axis)	Spherex/Xylocaine microembol. (MMC, Mitoxantrone, CDDP)
3. Angiographic catheter (Celiac axis)	Spherex/Xylocaine microembol. (MMC, Mitoxantrone, CDDP)
4. Staging laparotomy (+/– Jet port catheter)	
5. Hypoxic abdom. perfusion + chemofiltration (HAP-F)	(MMC, CDDP)
6. Angio- or Jet port catheter	Microemb. (MMC, Nov. CDDP)
In case of peritoneal mets:	Hypoxic abdom. perfusion - filtr.

Table II. *RCT for stage III/IV pancreatic cancer.*

Average dosages Angiographic technique		Isolated perfusion technique	
Spherex	3 ml		
Xylocaine	3 ml		
1. Mitoxantrone	10 mg	CDDP	70 mg
2. MMC	10-15 mg	MMC	30 mg
3. CDDP	50 mg		
4. CDDP	50 mg		

In case the celiac axis or common hepatic artery were free of visible tumor at second-look surgery for staging and/or resection, a Jet Port Allround Catheter (PfM, Cologne, Germany) was implanted end-to-side, and therapy continued through this arterial access.

An isolated hypoxic abdominal perfusion was performed at the fifth cycle for prevention and/or treatment of potential peritoneal seedings. For isolation of the abdomen, an arterial and venous stopflow balloon catheter were inserted into the femoral vessels and the balloon tips positioned to block the aorta and v. cava just beneath the diaphragm. The upper thighs were blocked by means of pneumatic cuffs. The average total doses of Mitomycin (MMC) and Cisplatin (CDDP) calculated for a median 70 kg/BW were 30 and 70 mg, respectively. The technique has been described elsewhere.

Evaluation of response. Quality of life and survival were selected as study end-points. The objective tumor response was assessed before and after each cycle, giving predominant attention to the course of the tumor markers CA 19-9 and CEA and to alterations in the Karnofsky performance status and pain response. Changes in serum levels of liver enzymes were noted, with special interest in alkaline phosphates, bilirubin, LDH and γGT.

During bi-monthly CT scans, special attention was directed to immediate changes in the tumor density. Hypodense areas, accompanied by sudden increase of tumor markers with subsequent deep decrease, were considered the result of necrosis. Fever occurring in the afternoon and evening between the third and eighth day at the latest was considered to be tumor necrosis fever.

Results

Overall survival. A total of 265 patients were enrolled over 10 years. One hundred and twelve patients (42%) were UICC stage III with locally advanced non-resectable tumors invading adjacent structures, such as the duodenum and common bile duct. One hundred and fifty-three patients (58%) were UICC stage IV with invasion or encasement of major vascular structures, such as superior mesenteric vessels, the common hepatic artery, celiac axis and liver metastases or local peritoneal lesions. Some of them had mild ascites. Immediate response after microembolization with elevation and decrease of CA 19-9 levels does not translate immediately into changes, *i.e.* reduction in diameter of pancreatic tumors, but in central necrosis. Therefore, the major end-point of this study was chosen as survival rather than X-ray response. The removal of necrotic tissue from a tumor in the head of the pancreas is depicted in Figure 1. The patient, a 47-year-old male with a bulky mass in the head of the pancreas, invading the mesenteric vessels and retroperitoneum, developed undulating fever a few days after each cycle. The CT scan showed extensive liquid structures throughout the tumor. At second-look, almost entire necrosis of the tumor was noted. After necrosectomy, the initial symptoms, such as fever, fatigue and night sweat, disappeared immediately.

The Kaplan-Meier estimate of cumulative survival of the entire group of 265 patients is shown in Figure 2: the 75% percentile was 6 months, the 50% percentile (median survival) was 9 months and the 25% percentile was still 18 months. The longest disease-free survival times were 117 months (former stage III) and 122 months (former stage IV a).

Long-term survival. A group of 80/265 patients who survived one year and over was studied in detail. In contrast to the total group of 265 patients with 42% stage III and 58% stage IV, the stage III to stage IV ratio was 57.5% to 42.5% (46/80 patients stage III, 34/80 patients stage IV) in this group of long-term survivors (Table III). Six out of 34 stage IV patients had a local relapse. Sixty percent of the tumors (49/80) were located in the head of the pancreas, 21% (14/80) in the tail, 8% (8/80) in the corpus, 4% (3/80) in the papilla, and 7% (6/80) were locally invading recurrences after Whipple resection, 3 of them with liver metastases.

Pretreatments were not exclusion criteria. The ranking of pretreatments undergone by the patients before receiving intra-arterial chemotherapy is listed in Table IV. Approximately one-fourth (26%) of the patients had

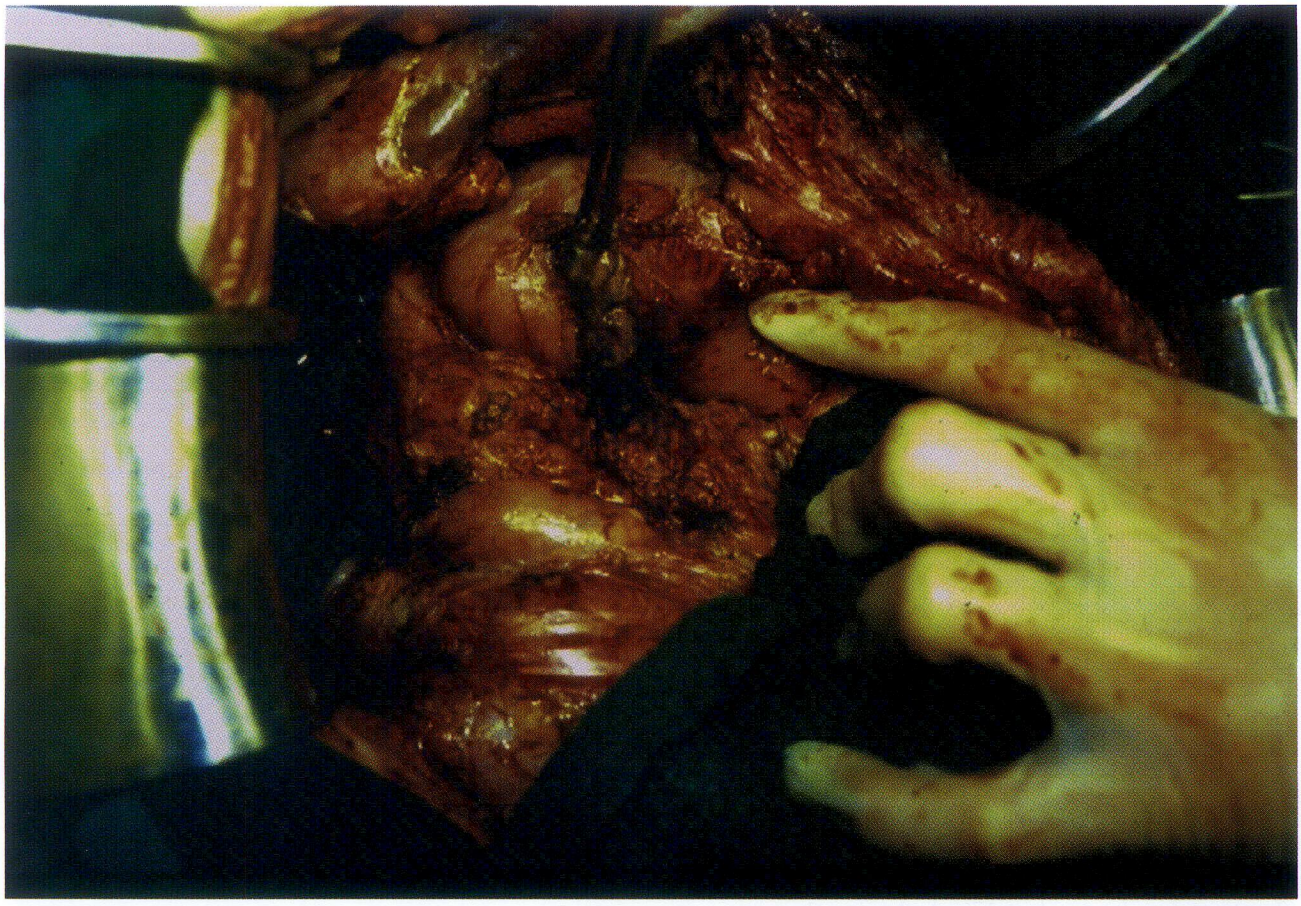
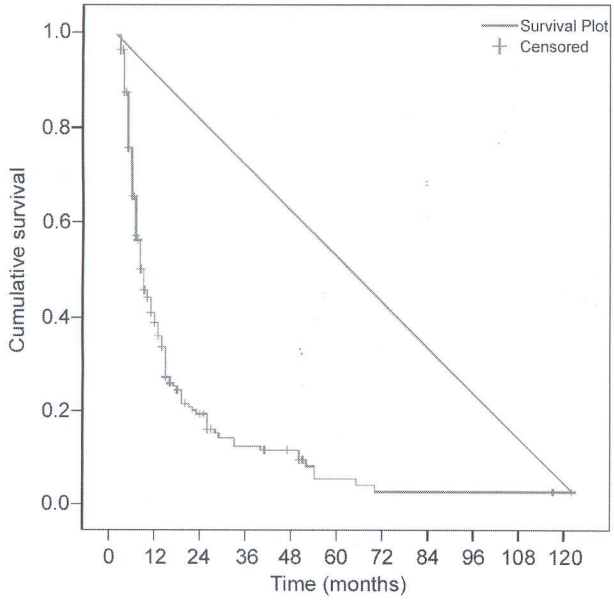


Figure 1. *Removal of necrotic tumor tissue after regional chemotherapy (RCT).*



	Survival time	Standard error	95% Confidence interval
25% Percentile	18	2.02	
Median	9	0.69	(8;10)
75% Percentile	6	0.28	

Figure 2. *Kaplan-Meier estimates of overall survival. RCT for advanced pancreatic cancer.*

Table III. *Advanced pancreatic cancer. Clinical stages for 265 patients vs. 80/265 long-term survivors.*

UICC stage	All patients n=265	Long-term survivors >12 months n=80
1. UICC III	112/265 (42%)	46/80 (57.5%)
2. UICC IV	153/265 (58%)	34/80 (42.5%)

Table IV. *Pretreatment in long-term survivors (>12 months) of pancreatic cancer.*

1. Palliative operation	21/80	26%
2. Biliary stent	10/80	12%
3. Expl. laparotomy	17/80	21%
4. None	11/80	14%
5. Whipple resection	8/80	10%
6. Palliative operation + syst. chemo	5/80	6%
7. Syst. chemo	4/80	5%
8. Syst. chemo + radiation	2/80	3%
9. Radiation	2/80	3%

Table V. *RCT for stage III/IV pancreatic cancer operations in long-term survivors (>12 months) of pancreatic cancer after neoadjuvant RCT.*

1. Explorative laparotomy	31/80	39%	} =54%
Tumor biopsy, Jet-Port			
2. Palliative surgery	12/80	15%	
3. TU-resections	31/80	39%	
Whipple-operation	15/80 (19%)		
Corpus/tail resection	12/80 (15%)		
Enucleation	4/80 (5%)		
	31/80 (39%)		
4. No operation	6/80	7%	

Table VI. *Causes of death in long-term survivors of pancreatic cancer stage III/IV (n=75/80).*

1. Progression at the primary site	36/75	48%
Head of the pancreas	19/75 (25%)	
Local recurrence after Whipple	12/75 (16%)	
Progression of local recurrence	4/75 (5%)	
Progression of tail of the pancreas	1/75 (1%)	
2. Non tumor-dependent	17/75	23%
3. Distant metastases	14/75	19%
Liver	6/75 (8%)	
Peritoneum	5/75 (7%)	
Lung	3/75 (4%)	
4. Unknown	8/75	11%

palliative bypass surgery, mainly biliodigestive anastomoses, another 12% a biliary stent, 10% a Whipple resection followed by recurrence (6 patients) or liver metastases alone (2 patients) and a total of 17% had prior chemotherapy and/or radiation.

Second-look surgery. Seventy-four out of 80 patients, surviving between 12 and 122 months, underwent second-look operations (Table V). In 54%, only palliative surgery (12/80 patients) or staging laparotomy with tumor biopsies could be performed. A total of 31/80 patients (39%), however, were amenable to tumor resections including 15 Whipples, 12 corpus-tail-resections and 4 excavations and drainages of major tumor necroses.

Survivors. Five patients are still alive after 25, 27, 50, 117 and 122 months, respectively. The latter 3 had explorative surgery showing local inoperability of stage IVa, IVa and stage III tumors of the head of the pancreas. After downsizing, Whipple resection at second-look surgery was feasible. The patients surviving for 25 and 27 months (stage IV) were in progression during systemic chemotherapy with Gemcitabine and responded to celiac axis infusion with MMC, Novantron, CDDP. One had Whipple and the other had corpus-tail resection thereafter.

Causes of death. The causes of death in the group of long-term survivors provide better information regarding the biological behavior of the tumor and necessary improvements in therapy (Table VI).

Twenty-three percent of all patients – almost one-fourth – died of causes other than the tumor itself. Only 19% died from distant metastases: 8% from liver, 7% from peritoneal and 4% from lung metastases.

The major cause of death was progression at the primary site. As much as half of all patients (48%) died from local relapse or progression of the primary tumor.

Side-effects. The toxicity profile observed from the administered intra-arterial dosages was most favorable. Hematological toxicity from systemic escape of intra-arterial drugs did not exceed WHO grade 2 and a minority of patients experienced grade 1 or 2 nausea and vomiting. Seventy-80% of the patients reported improved quality of life after regional chemotherapy. Dose adjustments from systemic toxicity were never needed. None of the patients required prolonged hospitalization for treatment-related hematological complications. Four cases with immediate tumor necrosis (Figure 1, Table V) were hospitalized for surgical necrosectomy and drainage. The major complication from isolated abdominal perfusion was a 30% rate of inguinal lymph fistules.

Discussion

Based on Burris' randomized trial (1) comparing Gemcitabine with 5-FU for treatment of advanced unresectable disease, Gemcitabine has emerged as the standard current chemotherapy for pancreatic cancer. It has also shown activity in tumors refractory to 5-FU in terms of quality of life (2). Combination therapies of Gemcitabine with 5-FU (3), Cisplatin (4), Irinotecan (5), Oxaliplatin (6), Cisplatin and 5-FU (7) or ISIS-2503 (8) have failed to show improvement or a significant impact on the dismal clinical course of pancreatic cancer. Although in a few phase III studies (3, 9, 10) there was some improved response rate and progression-free survival, this, however, did not translate into prolongation of overall survival. Since even infusional 5-FU (10) and Capecitabine (11) in 2 studies generated response rates and median survivals in advanced pancreatic cancers comparable with Gemcitabine, it can be assumed that none of the drugs or combinations tested so far can demonstrate statistically significant improvement in results (13-16). Toxicity continues to be the limiting factor in administering adequate doses of drugs or combinations.

Interestingly, in the trial conducted by Maisey *et al.* (10), the combination of 5-FU with MMC showed a superior response rate to 5-FU alone, which, however, did not translate into a survival advantage. Nevertheless, a non Gemcitabine-containing regimen showed comparable results. Again, therapy was associated with increased toxicity and, in some cases, 5-FU therapy had to be suspended until the toxicity was resolved. In a randomized phase II comparison of dose-intense Gemcitabine (12), superior activity and survival could be achieved by increasing the dose and adapting the optimal "fixed-dose rate".

An interesting point was illustrated by Klapdor (17), who, not only stuck to one fixed drug regimen, but combined first, second- and third-line therapies and monitored the course of tumor markers as sensitive indicators of tumor behavior. The currently most active drugs were administered systemically as well as locoregionally. The response rates of 30-35% PR and 35-40% MR and SD have never been achieved before in any single-line regimen.

In all trials presented, except one (3), only chemonaive and non pretreated patients were enrolled. In our study, the only exclusion criteria was a Karnofsky index below 50-60%. Mild ascites was accepted for enrollment. In this highly unfavorable subset of patients, the results, which included a resectability rate of 39% in long-term survivors, *i.e.* 12% in the entire trial and no toxicity-related hospitalization, seem superior to previously reported systemic chemotherapy or chemoradiation regimens in more favorable patients. Survival time and quality of life, *i.e.* clinical benefit response, were the primary end-points. It has been suggested that the burden from treatment-related adverse effects should not be added to those already suffering with the disease (7).

Former phase II studies with Mitomycin and Cisplatin or Mitoxantrone in intra-arterial infusion chemotherapy for advanced pancreatic cancer have already shown acceptable median survival times of 10 months and good quality of life (18-20). In a non-randomized study (3), regional chemotherapy with Mitomycin and Mitoxantrone was compared with best palliative care in patients refusing chemotherapy. The advantage in survival time was highly significant with regional chemotherapy. The same results were seen in a randomized phase III trial of regional chemotherapy *versus* systemic chemotherapy, however, the study had to be discontinued early because of much higher toxicity and significantly shorter survival in the systemic group (21).

The low incidence of distant metastases to the liver is suggested to be due to simultaneous intra-arterial therapy of the liver through the arterial catheter. Liver metastases seem to have a better blood supply than the pancreatic primary tumor itself (to be published elsewhere), and finally because of a higher blood flow through the hepatic artery.

Potential or pre-existing peritoneal lesions are supposed to be affected with hypoxic isolated abdominal perfusion. It is supposed, therefore, that the incidence of peritoneal metastases at second-look surgery and as cause of death was very low (7%). Isolated perfusion, however, is not suitable, and should not be used for the treatment of primary tumors, as some authors have attempted (22, 23), because the local drug exposure with hypoxic abdominal perfusion at the poorly-vascularized pancreatic primary tumor can not compete with the drug exposure achieved with a catheter placed by Seldinger's technique to cover a much smaller area of blood supply. Management of stop flow perfusion techniques requires a great deal of individual experience in terms of the initiation of hypoxia and the administration time of drugs (to be published).

Median survival times ranged between 3 to 6 months throughout all studies published so far. In our study, the 75th percentile was 6 months, the 50th survival (median) 9 months and the 25th was 18 months. The outstanding difference in these results compared with other trials is the percentage of patients surviving longer than the median time, *i.e.* the area under the curve exceeding the 50% mark.

Although a special effort was made to concentrate the therapy on the area of primary tumor invasion, the major cause of death (48%) was recurrence at this site. Special efforts are thus warranted to optimize targeted tumor eradication.

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Received June 20, 2005
Accepted July 11, 2005

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Manuscripts. Submitted manuscripts should not exceed fourteen (14) pages (approximately 250 words per double - spaced typed page), including abstract, text, tables, figures and references (corresponding to 4 printed pages). Papers exceeding four printed pages will be subject to excess page charges. All manuscripts should be divided into the following sections: (a) First page including the title of the presented work [not exceeding fifteen (15) words], full names and full postal addresses of all Authors, name of the Author to whom proofs are to be sent, key words, an abbreviated running title, an indication "clinical", "epidemiological", or "experimental" study, and the date of submission. (Note: The order of the Authors is not necessarily indicative of their contribution to the work. Authors may note their individual contribution(s) in the appropriate section(s) of the presented work); (b) Abstract not exceeding 150 words, organized according to the following headings: Background - Materials and Methods - Results - Conclusion; (c) Introduction; (d) Materials and Methods, or Patients and Methods; (e) Results; (f) Discussion; (g) Acknowledgements, and (h) References. All pages must be numbered consecutively. Footnotes should be avoided. Review articles may follow a different style according to the subject matter and the Author's opinion. Review articles should not exceed 35 pages (approximately 250 words per double-spaced typed page) including all tables, figures and references.

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