Hyperthermic Antiblastic Perfusion in Extracorporeal Circulation: Surgical Technique and Results in the Treatment of Extemities' Tumor

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Abstract

Regional perfusion in extracorporeal circulation is finding more and more applications in the treatment of extremities' tumors. In order to avoid any influence from surgical variables rises the necessity of a standardization of the technique.

In this paper we propose a new surgical technique with subsequent results based on the experience at the National Cancer Institute of Milan on 89 consecutive patients treated by regional hyperthermic antiblastic perfusion without significant complications.

Introduction

Regional perfusion with a cytotoxic drug has been used in the treatment of cancer of extremities in the past 25 years. The technique originally described by Creech[1] has not been substantially modified, however, as the operation is a complex one with some biochemical changes at the cellular level in the perfused limb. This procedure could result in serious complications including muscle necrosis and thromboembolic phenomenons. The complications rise even more when hyperthermia is added to cytotoxic drugs.

Any effort or modification that can bring the procedure to a safer level and minimize the complications, can bring about wider use of this therapeutic modality in the treatment of cancer of extremities. From these considerations[2] arises the necessity of a standardization of the technique, so that surgical variables cannot have any influence on the reported survivals. In the past 28 months at the National Cancer Institute of Milan we have developed a surgical approach for regional perfusion with cytotoxic drugs and hyperthermia. This technique has been employed on 89 consecutive patients without the complications that are commonly reported with this procedure.

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Patients and Methods

From March 1982 to July 1985, at National Cancer Institute, Milan Italy, 95 perfusions have been performed in a series of 89 patients. Table 1 shows the histologic type of the treated tumors. Except melanoma patients and Kaposi's sarcoma, all cases had been admitted to the hospital, as the only possible treatment could have been a demolitive surgery.

Table 2 shows the clinical stages of melanoma patients; 9 patients affected by so called high-risk melanoma of extremities (tumor thickness >1.5 mm.) underwent a prophylactic perfusion.

In Table 3 are reported the drugs and dosages used in various cancers.

Six out of eight melanoma patients treated with CDDP were submitted to this procedure when they did not respond to the first perfusion with L-PAM or DTIC.

Table 1
Patients

MELANOMA	76*
OSTEOGENIC SARCOMA	10
SQUAMOUS CELL CARCINOMA	3
SOFT TISSUE SARCOMA	3
ANGIOSARCOMA	2
KAPOSI	1
TOTAL	95

* 6 patients received a second perfusion
* 9 patients received a prophylactic perfusion for high risk Stage I

Table 2
Clinical Stage Melanoma Patients

I (HIGH RISK)	9
II	1
III A	30
III B	1
III AB	24
IV	5
TOTAL	70

Table 3
Drugs

	L-PAM	DTIC	CDDP	MTX	L-PAM + ACT D
	41 PATIENTS 1.0 mg/kg b.w.(A) 1.5 mg/kg b.w.(B)	27 PATIENTS 1.5 gr/M^2b.s.(A) 2.5 gr/M^2b.s.(B)	8 PATIENTS 200 mg/M^2b.s.(A) 400 mg/M^2b.s.(B)	—	—
OSTEOGENIC SARCOMA	—	—	10 PATIENTS 200 mg/M^2b.s.(A) 400 mg/M^2b.s.(B)	—	—
SQUAMOUS CELL CARCINOMA	—	—	—	3 PATIENTS 300 mg/M^2b.s.(B)	—
SOFT TISSUE SARCOMA	—	—	1 PATIENT 150 mg/M^2(B)	—	2 PATIENTS L-PAM 1 mg/kg bw (B) ACT D 0.014 mg/Kg bw(B)
ANGIOSARCOMA	—	—	2 PATIENTS 200 mg/M^2b.s.(A) 400 mg/M^2b.s.(B)	—	—
KAPOSI	—	—	—	—	1 PATIENT L-PAM 1 mg/Kg bw+ ACT D 0.014 mg/Kg bw(A)

A = Upper Extremity
B = Lower Extremity

Surgical Method

In addition to the standard work-up, peculiar to these types of patients, the vascular system of the affected limb to be perfused in older patients with artherosclerosis is evaluated by arteriogram. The circumference of the extremity is measured and registered, as a baseline for postoperative circulatory care.

If the patient suffers from varicose vein disease the extremities are wrapped with an ace bandage for two days prior to surgery. The groin and the abdomen are washed with Phisohex and Betadine the night before operation.

Under general endotracheal anesthesia with patient in supine position the entire abdomen, both groins, and lower extremities are prepared with Betadine and draped. An Esmarch belt is loosely put around the root of the limb which will be used as a tourniquet later on. Two thermistor-probes are inserted deeply in the muscles of the thigh and of the calf, one on the cutis, at the same level, one in the subcutaneous tissue of the anterior part of the thigh, and, whenever possible, one inside the tumor. The extremity is wrapped in a sterile heating blanket. The draping is completed at this time and the lower quadrant with the groin of the side to be perfused exposed to the operative field. The external iliac vessels are reached by extra-peritoneal approach through a vertical lower paramedian skin incision which is extended to the femoral crease. The liver is palpated through a small opening in the peritoneum. In the absence of liver involvement the vessels are prepared. All the tributaries to the external iliac vein are tied and the vessels are cleaned of all the areolar and lymphatic tissue. The obturator vein is sectioned. Due to dissection and manipulation, the external iliac artery might go to a spastic state for which we routinely use a xylocaine solution to soak the artery and we remove the adventitia which results in an immediate vasodilatation. The internal iliac artery is identified and encircled by umbilical tape.

Two umbilical tapes are placed around the external iliac artery and the external iliac vein and long rubber budies are passed over the umbilical tapes. The patient is heparinized (3.3 mg. per Kg/body weight). The internal and external iliac arteries are occluded by tightening the umbilical tapes (Figure 1). The external iliac vein is left open to drain blood from the leg into the systemic circulation. The location of arteriotomy is chosen and using a no. 11 blade the wall of the artery is incised (Figure 2) and using a Potts' scissors it is enlarged (Figure 3) to the appropriate size. An arterial catheter proportional to the size of the artery is placed into the arterial lumen as shown in Figure 4. Once the catheter is in the proper position with good back bleeding the distal tourniquet is fastened around it. The catheter is left clamped. Using a similar technique a venotomy is done in the external iliac vein after it is occluded by the tourniquets (Figure 5).

At this point the catheters are connected to the extracorporeal machine which has been primed with one

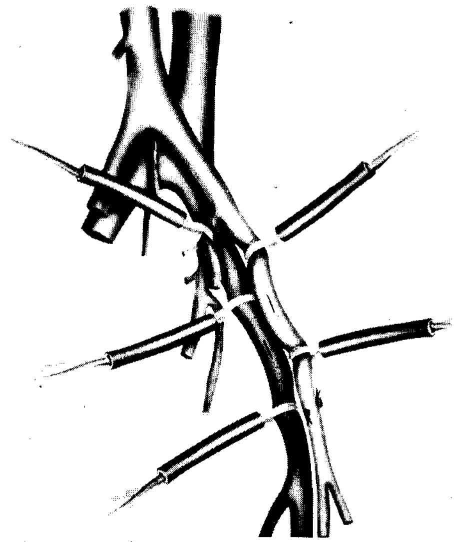

Figure 1: Preparation of external artery and vein, internal artery with umbilical tapes.

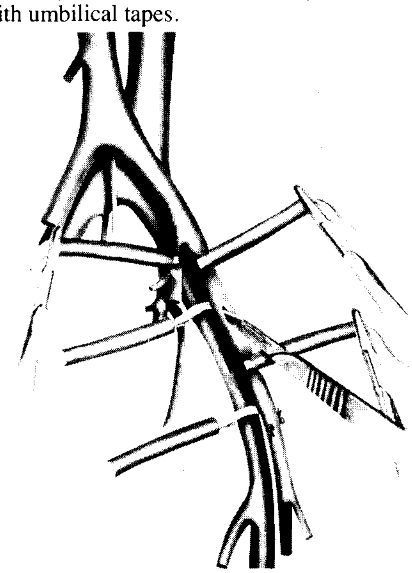

Figure 2: Incision of artery wall by no. 11 blade

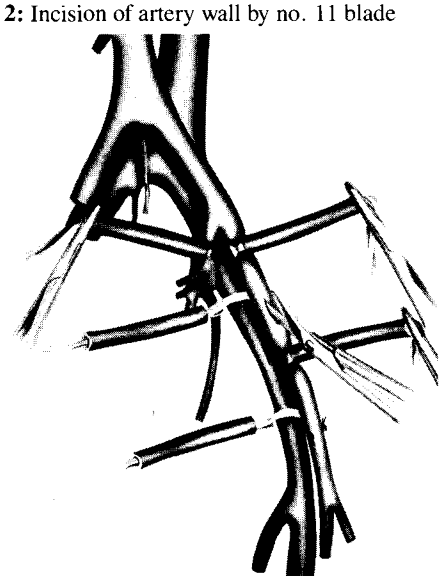

Figure 3: Enlarging the incision by Potts' scissors

unit of packed red blood cells and 1,000 cc. Plasmagel. Once the perfusion has begun the Esmarch's tourniquet is tightened around the root of the extremity and anchored to a Steinman pin which is driven into the superior anterior iliac spine (Figure 6). At this point the venous return and the level in the oxygerator reservoir are checked. If there is any kind of obstructions to the flow the catheters are manipulated until the flow becomes satisfactory.

The temperature of the extremity is checked frequently until the desired level is reached (usually 40.5-41.0°C in the muscle) which takes an average 30 minutes. At this time the cytotoxic drug is given in a single bolus. The perfusion time will last 60 minutes from the time of injection of the drug.

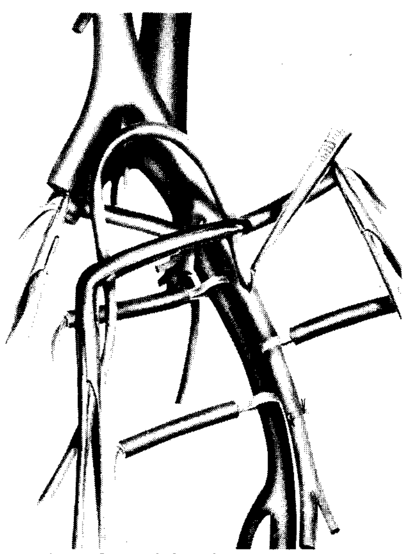

Figure 4: Insertion of arterial catheter

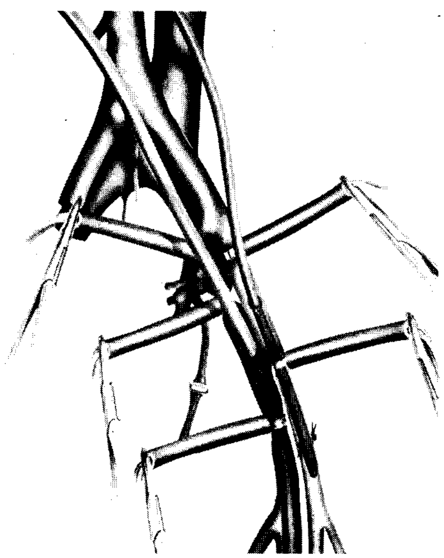

Figure 5: Positioning of vessels' catheters with the obturatory vein and all the tributaries of the external iliac vessels closed.

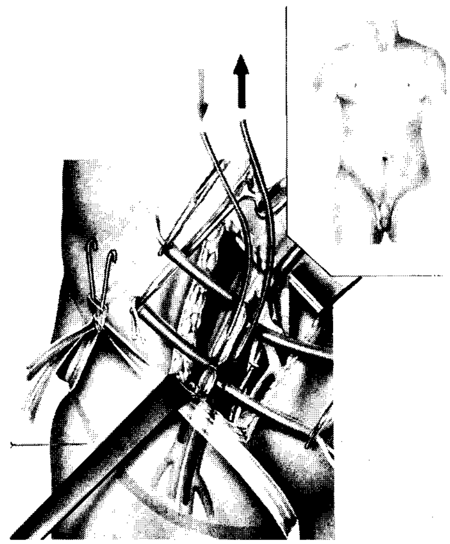

Figure 6: An Esmarch's tourniquet is placed to stop the superficial circulation.

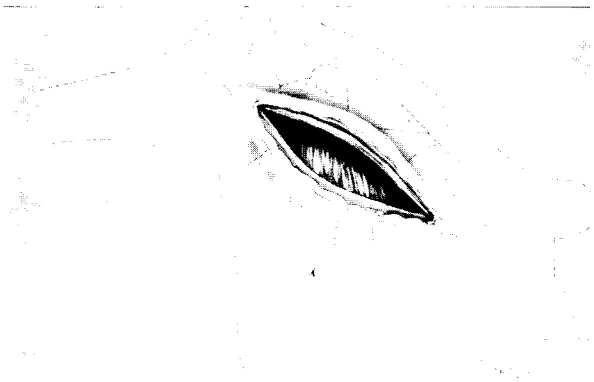

Figure 11: Preparation of major and minor pectoralis

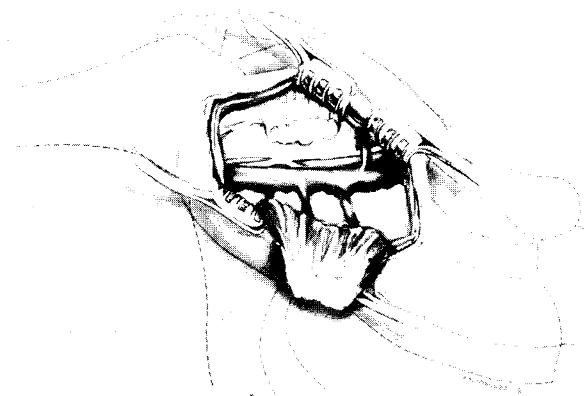

Figure 12: Disconnection of minor pectoralis

An identical technique is used for perfusion of upper extremities, where the approach to axillary vessels is obtained dividing the fibers of pectoralis major, and disconnecting the pectoralis minor (Figures 11, 12 and 13). The only difference is in the impossibility of using the Satinsky clamp when we close the vasotomies.

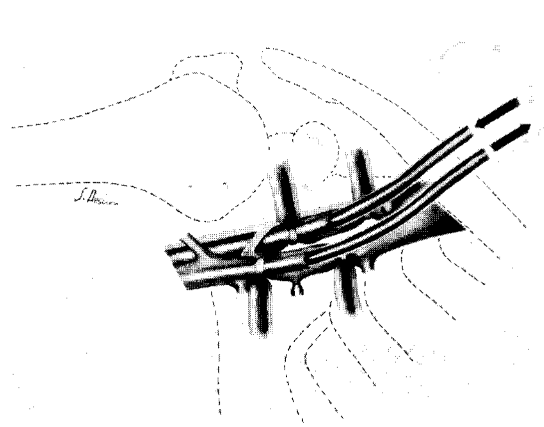

Figure 13: Final position of vessel's catheters

Extracorporeal Circuit

The extracorporeal circuit is in Tygon[a] of $^{1}/_{4}''$ or $^{3}/_{8}''$ internal diameter; all the connectors, with corresponding diameter, are disposable plastic.

We use a Bio Console Pump.[b] The bubble oxygenator, [c,d,e] with heat exchanger, may be of infant size, for we need a blood flow higher than 1.5L/min. The temperature of the thermostated water bath[f] is maintained about 1 °C higher than the one to be reached in the arterial line of the circuit and in the limb.

Priming

The priming is constituted by a plasma expander,[g] and packed Red Blood Cells. The hematocrit is adjusted to about 20%. Heparin is added routinely (8,000 U.I./liter), pH is regulated at 7.38 by $NaHCO_3$, 1 mEq/ml; Lidocaine 400 mg., Tobramicine 100 mg., and Glucose 10 gm. are added at the beginning of the circulation.

Oxygenation

The oxygenation of the blood circulation in the E.C.C. is obtained by an O_2/CO_2, 97 percent/3 percent gas mixture. Its flow is regulated following blood flow in the oxygenator and on the control of several pH, pCO_2 and pO_2 determinations during the hyperthermic antiblastic extracorporeal circulation.

Filtration

As microembolization is a constant risk during E.C.C., we use blood filters[h] when adding the Packed red blood cells to the priming fluid and another filter[i] in the arterial line of the circuit.

Perfusion Flow Rate

The perfusion flow rate is detected by a transducer with disposable insert and selected as the flow that maintains a stable level in the oxygenator and the whole system with a mean pressure in the arterial phase of the extracorporeal circuit lower 10-15 mmHg than the mean arterial pressure (MAP) of the patient. This method permits a constant reduction of leakage from the perfused district to the general circulation. In order to analyze leakage we inject in the general circulation, 10 u. of labelled albumin with I^{131} and 100 u. TC^{99m} and in the extracorporeal circuit, 100 u. labelled albumin with I^{131}. A scintillation counter placed over the heart checks the value of the eventual leakage from the extracorporeal circuit to the systemic circulation.

Blood gas samples are drawn from the venous and arterial lines and if after 30 minutes of perfusion there is still acidosis, due to arterial occlusion during insertion and connection of the catheters, (usually it takes seven to eight minutes) it is corrected by addition of sodium bicarbonate to the perfusate.

At the end of the perfusion the limb is washed with ten liters of Ringer's lactate[l] which takes about 10 minutes during which the limb is not being perfused and remains hypoxic. As the temperature of the limb is elevated, and the oxygen demand remains high, we lower the temperature of the blanket to cool off the surface of the leg, in order to decrease oxygen demand and tissue acidosis in the skin.

To limit this terminal hypoxic period to the washing time only, we close the vasotomies using a Satinsky clamp allowing the extremity to be perfused by blood right after the wash is done (Figure 7). There is no

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a Tygon Norton Industrial Plastics, Akron, OH 44309
b Bio Console Bio Pump, Bio-Medicus, Minnetonka, MN 55344
c Venothermoxygenator Infant, Polystan, Copenhagen, Denmark
d S-070 Blood oxygenerator, Shiley Inc., Irvine, CA 92714
e HI-FLEX 700, Dideco, Mirandola, Italia
f EXACAL 3001 Neslab Instruments, Inc., Portsmouth, NH 03801
g Plasmagel, Roger Bellon, Neuilly sur Seine, France
h Ultipor SQ40S, Pall Biomedical Corp., Glen Cove, NY 11548
i Ultipor LPE 1440, Pall Biomedical Corp., Glen Cove, NY 11548
l Ringer's lactate, S.A.L.F. Laboratories Bergamo, Italy

problem for the vein as it is large enough; however the artery, particularly in women, is small and does not always allow application of this technique in the repair of the arteriotomy (Figures 8 and 9). We do not transfuse the leg after the wash. The temperature of the limb is brought down to the preoperative level gradually. The heparin action is neutralized with protamine sulfate depending upon the clotting time.

The wound is irrigated with Betadine solution and closed in layers after leaving an Emodren[m] catheter in the retroperitoneal space. The fasciotomy of the lateral compartment is performed (Figure 10) in order to avoid the external popliteus nerve failure.

Results

Table 4 reports the immediate local response (evaluated within one month from perfusion), in melanoma patients according to the used drugs. Only seven patients showed no response.

L-PAM seems to offer better results in terms of immediate response, but if we consider (Table 5) the new relapses after perfusion, it is possible to see that 27 out of 32 submitted to perfusion with L.-PAM developed further distrectual metastates, while only 8 out of

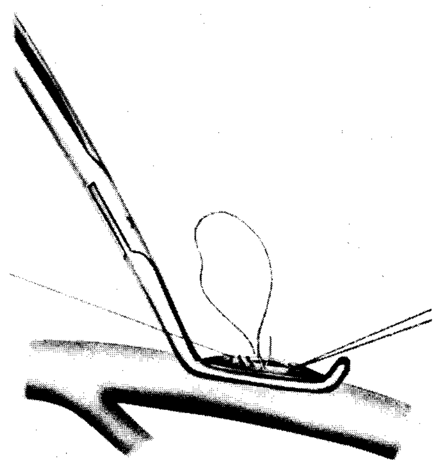

Figure 7: A Satinsky's clamp is placed to reduce the hypoxic period

27 patients treated with DTIC developed metastases. However, these data are not comparable, because of the different median follow-up time (24 months for L.-PAM, versus 12 months for DTIC).

Table 6 shows the actual status of these patients, after

m Emodren, drainage catheter, Lepetit SpA, Milano Italy

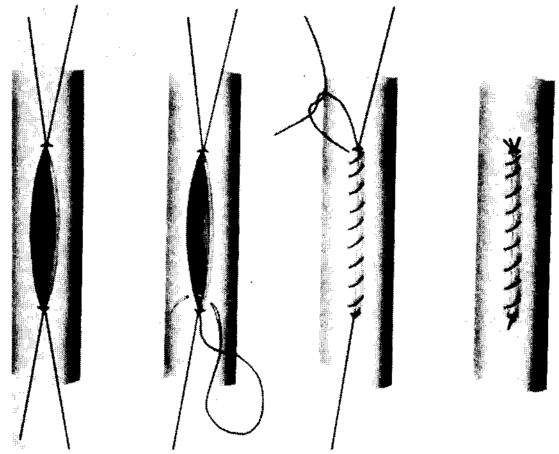

Figure 8: Technique of repairing vessels when there is no possibility to place a Satinsky's clamp

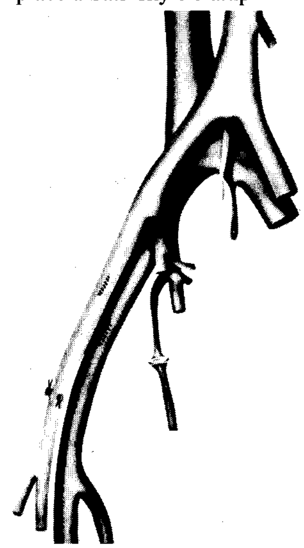

Figure 9: Anterior view of the repaired vessels

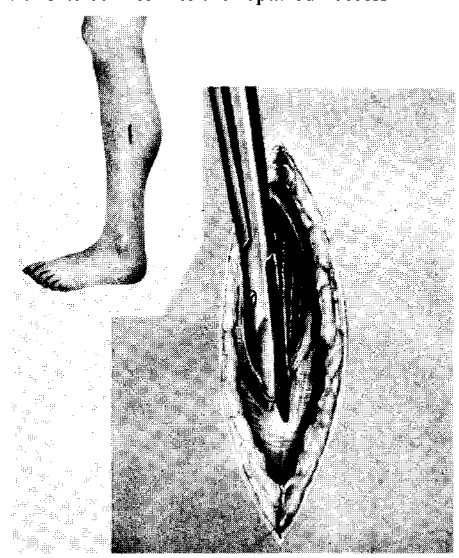

Figure 10: Fasciotomy of the lateral compartment of the leg

Table 4

Stage IIIA—IIIAB Malignant Melanoma Immediate Local Response According to the Drug

	CR.	PR. >50%	PR. <50%	N.R.	NOT EVALUABLE
L-PAM	17	8	7	—	—
DTIC	4	7	11	5	—
CDDP	2	1	2	2	1

Table 5

Relapse after Perfusion (Malignant Melanoma)

	LOCAL RELAPSE	LOCAL RELAPSE PLUS DISTANT METASTASES	DISTANT METASTASES ONLY
L-PAM	10/32	6/32	11/32
DTIC	5/27	1/27	2/27
CDDP	—	3/8	—

Table 6

Malignant Melanoma: Stage IIIA—IIIAB—IV Final Status According to the Drug

	NED	AWD	DOD
L-PAM MEDIAN FOLLOW-UP 24 MONTHS	10*	5	16
DTIC MEDIAN FOLLOW-UP 10 MONTHS	14**	11	2
CDDP MEDIAN FOLLOW-UP 12 MONTHS	3	3	2

*7 patients underwent local excision of residual nodules

**10 patients underwent excision of residual nodules

removal of residual tumors after perfusion.

We emphasize that nine patients treated with the L-PAM underwent a prophylactic perfusion for high risk malignant melanoma.

Table 7 shows the local response in non-melanoma patients; these evaluations, except Kaposi's sarcoma, were histologic evaluations, expressed in percentage of necrosis, on the specimens or on the biopsies. It has to be stressed that all these patients were candidates for major surgery (amputation or disarticulation). They underwent hyperthermic antiblastic perfusion as "the last step" before demolitive surgery.

In osteogenic sarcomas, the radiological regression with rearrangement of the bone was so impressive that until now four patients underwent conservative surgery, plus endoprosthesis (one of these patients developed a single lung metastasis after 16 months). They are still alive and disease free after 10 months after the bone resection. Three patients were amputated, one for a retraction of the tissues of the knee due to a previous radiotherapy, (the histologic examination of this case revealed 100% necrosis) and the other two were amputated for technical reason (even in these cases the histologic specimens confirmed good results in term of necrosis). Three patients are still in treatment and waiting for a possible conservative surgery.

The three cases of extensive squamous cell carcinoma showed such an impressive clinical regression, that they underwent radical wide excision and skin-grafts. The histologic examination revealed a necrosis greater than 95 percent with minimal residual of tumoral cells. These squamous cell patients are still alive and disease free, respectively 32, 29, 13 months from perfusion.

Minor results have been obtained in angiosarcomas and soft tissue sarcomas: out of five patients, one with soft tissue sarcomas and one with angiosarcoma are dead two and five months after perfusion. One patient with angiosarcoma, treated with CDDP, was amputated for local complications (diffuse burns with gangrene). In patients with Kaposi's sarcoma, not only the disease in the perfused limb showed a complete response, but also the lesions not directly treated regressed considerably (about 50 percent). Table 8 shows the actual status of this patients with the relative follow-up.

Complications

Table 9 shows the complications noted in these 95 patients were:

Table 7
Sarcomas
Evaluation of Hystologic Response

	PATIENTS		% NECROSIS
OSTEOGENIC SARCOMA	10	9	100%
		1	N.R.
SQUAMOUS CELL CARCINOMA	3		95%
ANGIOSARCOMA	2	1	60%
		1	80%
SOFT TISSUE SARCOMA	3	1	90%
		2	NOT EVALUABLE *
KAPOSI	1		100% **

*Patients Still in Treatment
**Clinical Finding

Table 8
Overall Survival

	NED	AWD	DOD
OSTEOGENIC SARCOMA MEDIAN FOLLOW-UP 12 months	9*	1	—
SQUAMOUS CELL CARCINOMA MEDIAN FOLLOW—UP 20 months	3	—	—
SOFT TISSUE SARCOMA FOLLOW-UP 12 months	—	2**	1
ANGIOSARCOMA MEDIAN FOLLOW-UP 4 months	1***	—	1
KAPOSI FOLLOW-UP 39 months	—	1	—

*1 patient underwent lung resection for metastases
**2 patients are still in treatment
***1 patient was amputated for local complication

a) deep thrombophlebytis in three patients affected by osteogenic sarcoma, perfused with Cis-platinum and three superficial thrombophlebitis. These complications resolved within two to three weeks.
b) G.I. bleeding, in three patients, two affected by malignant melanoma, perfused with Melphalan; one affected by osteogenic sarcoma, perfused with Cis-platinum. In these patients the platelet count was normal. All responded to medical treatment.
c) long term edema of the lower extremities in two patients affected by malignant melanoma; the first one perfused with Melphalan, the second one with DTIC; both submitted to regional node dissection. A transitory edema in 12 patients was observed that resolved spontaneously in two to three weeks.
d) five cases of transitory bone-marrow depletion that lasted two to three weeks.
e) two cases of amputation (one in a patient affected by angiosarcoma and one in another affected by melanoma both treated with Cis-platinum) due to local complication in the extremity such as burns and vessel destruction.

Discussion and Conclusions

Isolation perfusion plus hyperthermia and antiblastic drugs seems to find more and more indications in the treatment of malignancies localized in the extremities.

In regard to stage III malignant melanoma, our results confirm what already appeared in the past literature both as far as the local control of the disease and the overall survival, increasing up to 55 percent at five years.[3,4,5,6,7]

No significant difference in survival seems to rise when L-PAM, has been the most commonly employed agent, is used alone,[8] or associated with Act-D, [9] or to other drugs CDDP plus DTIC and VDS.[10]

Table 9
Complications in 95 Perfusions

EDEMA	14
BLISTERING	4
BURNS	1
AMPUTATION	2
BONE MARROW DEPLETION	5
G.I. BLEEDING	3
DEEP THROMBOPHLEBITIS	3
SUPERFICIAL THROMBOPHLEBITIS	3

Even using DTIC, as in our[11] and in Didolkar's experience,[12] the results do not show an significant improvement. In favour of DTIC is its minor toxicity, both local and general.

It is quite difficult at present to evaluate the action and the role of Cis-platinum, which showed very high toxicity in patients affected by melanoma, versus a practically absent toxicity in patients affected by osteogenic sarcomas. We are now performing studies on the kinetic and tissue distribution of this drug.

In regard to prophylactic perfusion with L-PAM in high risk stage I malignant melanoma the results of our randomized clinical trial number of patients and follow up do not allow any evaluation at present.

These young patients were taken into consideration for perfusion, as the only possible treatment could be amputation or disarticulation.

The huge tumor regression due to perfusion allowed four patients to be submitted to conservative surgery, while three more patients are waiting for the same conservative treatment. Even in three patients amputated for technical impossibility of conservative surgery, the tumoral necrosis was practically complete.

In squamous cell carcinomas, the perfusion obtained results superior to any other provision: the sub-total necrosis of these lesions allowed a limb-salvage with a wide excision and plastic reconstruction.[16]

There is no satisfactory explanation for the regression of lesions outside of the perfused arm in the patient with Kaposi's sarcoma.

We may conclude that perfusion plays an important role in a multidisciplinary approach to malignancies of extremities, when the problem of limb-salvage has to be considered.

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