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R. Cavaliere

G. Moricca

F. Di Filippo

L. Aloe

G. Monticelli

See next page for additional authors

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Hyperthermic Perfusion 16 Years After its First Clinical Applications

R. Cavaliere,* G. Moricca,* F. Di Filippo,* L. Aloe,* G. Monticelli, and F. S. Sartori****

It is known that above-normal temperatures (42°-42.5°C) provoke selective damage to neoplastic cells. We used heated circulating blood as a method for heat transfer on patients with limb tumors. From October 1964 to December 1979, we treated a total of 198 patients with hyperthermic perfusion for melanoma of the limbs (91), osteosarcoma (57), and soft tissue sarcoma (50). For melanoma patients, the five-year survival rate, excluding Stage IV, was 60%. For patients with soft tissue sarcoma, the five-year survival rates were 53% and 56% for hyperthermic perfusion and hyperthermic antiblastic perfusion, respectively. For 29 patients with osteosarcoma, hyperthermic perfusion was combined with systematic amputation of the limb for a 60% survival rate over a five-year period. Newer studies with osteosarcoma patients involve a multistep treatment that saves the tumor-bearing limb without reducing survival rates. Our 16-year clinical trial demonstrates that hyperthermia is effective in curing some tumors of the limbs, especially osteosarcoma and melanoma. We believe that perfusion remains the most reliable heat transfer method for loco-regional treatment and perhaps even for whole-body treatment for limb tumors.

It is known that above-normal temperatures (42°-42.5°C) provoke selective damage to neoplastic cells (1-9). Many published reports on the treatment of tumors by hyperthermia have demonstrated that, however the treatment is applied, hyperthermia is capable of producing positive results that, in some tumors, could not be obtained with conventional treatments.

As previously published (10-12), we used heated circulating blood to apply as a method for heat transfer on humans. Sixteen years after the first clinical applications, we consider the results that we obtained with hyperthermic perfusion to be satisfactory for treating limb tumors. In some tumors, however, hyperthermic perfusion did not bring about complete control of the disease; thus, various therapy protocols presently employ a multi-step treatment to optimize the selective effect of the heat.

Materials and Methods

Our technique for performing hyperthermic perfusion, which was standardized after the first series of trials, can be summarized as follows:

* Regina Elena Institute for Cancer Research, Rome, Italy

** First Orthopedic Clinic of the University of Rome, Rome, Italy

Address reprint requests to Dr. Cavaliere, Regina Elena Institute for Cancer Research, Viale Regina Elena 291, Rome, Italy

For the upper limbs, the axillary artery and vein are cannulated and connected to a heart-lung machine, previously primed with an isotonic solution. An electromagnetic flowmeter and polygraph are inserted into the arterial line to record perfusion flows and pressures. A thermistor is inserted just next to the arterial cannula to monitor the actual temperature of the blood entering the artery. No tourniquet is used at the root of the limb when hyperthermic perfusion is performed. Needle probes of the thermocouples are inserted into the muscles of the arm and forearm and into different parts of the tumor; other probes are inserted into the rectum and mid-thoracic esophagus. All thermometers are connected to a computerized control system.

When perfusion begins, the temperature of the arterial line is 38°C and is gradually raised to 42.5°C and even to 43°C in the heat exchanger. Perfusional pressure, kept slightly higher than the systemic pressure, is constantly regulated according to the modifications in the central venous pressure. Flows are predetermined but subject to adjustments depending on the amount of return venous flow.

After 45-60 minutes of perfusion, when the temperature of the tumor reaches 42°C, the hyperthermic treatment begins. Perfusion takes from two to four hours, depending on the size and the histological type of tumor, and, of course, on the condition of the patient. Afterwards, the circuit is washed out with an isotonic solution containing 1 million

I.U. of anti-callycrein, and the vessel incisions are sutured. During hyperthermic treatment and for a few days thereafter, controlled osmotic diuresis and low-level metabolic alcalosis are maintained. The lost blood is reintegrated.

For the lower limbs, the surgical approach involves the iliac or femoral vessels. The procedure for hyperthermic perfusion is the same.

For many years now we have been performing a sympathectomy at the time of perfusion. We use the same surgical approach to prepare and expose the vessels of the limb to be perfused. For the upper limbs, this involves removing part of the sympathetic chain between the proximal part of the stellate ganglion and the third dorsal ganglion. The proximal part of the stellate ganglion is left in situ to avoid causing the Bernard-Horner syndrome. For lower limb tumors, the sympathectomy involves removing the last three lumbar ganglions.

Results

From October 1964 to December 1979, we treated a total of 198 patients with hyperthermic perfusion for limb tumors.

Melanoma of the limbs

We treated 91 patients with limb melanoma either by hyperthermic perfusion or hyperthermic antiblastic perfusion (Table I). We have adopted the tumor classification system of the M.D. Anderson Hospital and Tumor Institute (Houston, Texas). Today, perfusion is being performed to treat Stage I melanoma, if Clark's histological level is III or more (13), and/or if the tumor is at least 1.5 mm thick, according to Breslow (14). A lymphadenectomy is performed only when the lymph nodes are involved.

Our five-year survival rate for patients treated for melanoma, excluding Stage IV, was 60%. There are no great differences between the results obtained with hyperthermic perfusion and those obtained with hyperthermic antiblastic perfusion. As has been reported previously (12, 15), in cases of loco-regional spreading melanoma, hyperthermic perfusion without the use of antiblastic drugs appears to be more effective. However, these results will soon be more accurately confirmed by a randomized study presently underway.

TABLE I

Melanoma of the Limbs

*Stages	Hyperthermic Perfusion Patients (30)	Hyperthermic Antiblastic Perfusion Patients (61)
I	3	7
II	3	10
IIIA	6	14
IIIB	6	9
IIIAB	6	12
IV	6	9

* According to the tumor classification system of the M.D. Anderson Hospital and Tumor Institute (Houston, Texas)

Hyperthermic perfusion, as we have stated, can also be combined with the administration of antiblastic drugs. For the treatment of melanoma, 1-1.2 mg/kg of body weight of melphalan is used, and for osteosarcoma and soft tissue sarcoma, 0.8 mg/kg, followed by 0.015 mg/kg of actinomycin-D. The duration of the hyperthermic antiblastic treatment never exceeds 120 minutes.

Osteosarcoma

Between October 1964 and December 1979, 57 patients with osteosarcoma underwent hyperthermic treatment. The first nine were subjected to hyperthermic perfusion without further treatment, and three of them today are free of disease, 8, 10, and 11 years after treatment. In the other six cases, the patients died of metastases.

To improve our results, we combined hyperthermic perfusion and/or hyperthermic antiblastic perfusion with systematic amputation of the limb a few weeks after perfusion. The time lapse between perfusion and amputation was arbitrarily set at four weeks, based on previous results which suggested that the presence of perfused tumor cells helped significantly in preventing further metastases.

We treated 29 patients according to this procedure with a 60% rate of success over a five-year period, according to the Kaplan-Meier actuarial method (16), 12 with hyperthermic perfusion and 17 with hyperthermic antiblastic perfusion. This rate is far better than those obtained with conventional treatment, where major radical surgery is performed (12). Furthermore, analyses of tumors that were excised during amputation showed that hyperthermic perfusion had caused extensive necrosis and that the tumors were surrounded by a zone of bone sclerosis (the stop effect), similiar in appearance to the sclerotic borderline of a benign tumor (Fig. 1).

In 1975, we began new studies to see whether or not it was possible to save the tumor-bearing limb without reducing the survival rates. This involves a multi-step treatment, including hyperthermic antiblastic perfusion, en-bloc resection when possible, bone reconstruction (with metallic endoprostheses or autoplastic bone grafts), and adjuvant chemotherapy. Of the nine patients who were treated with this procedure, five are alive and free of disease, with the limb intact, 19-51 months after treatment.

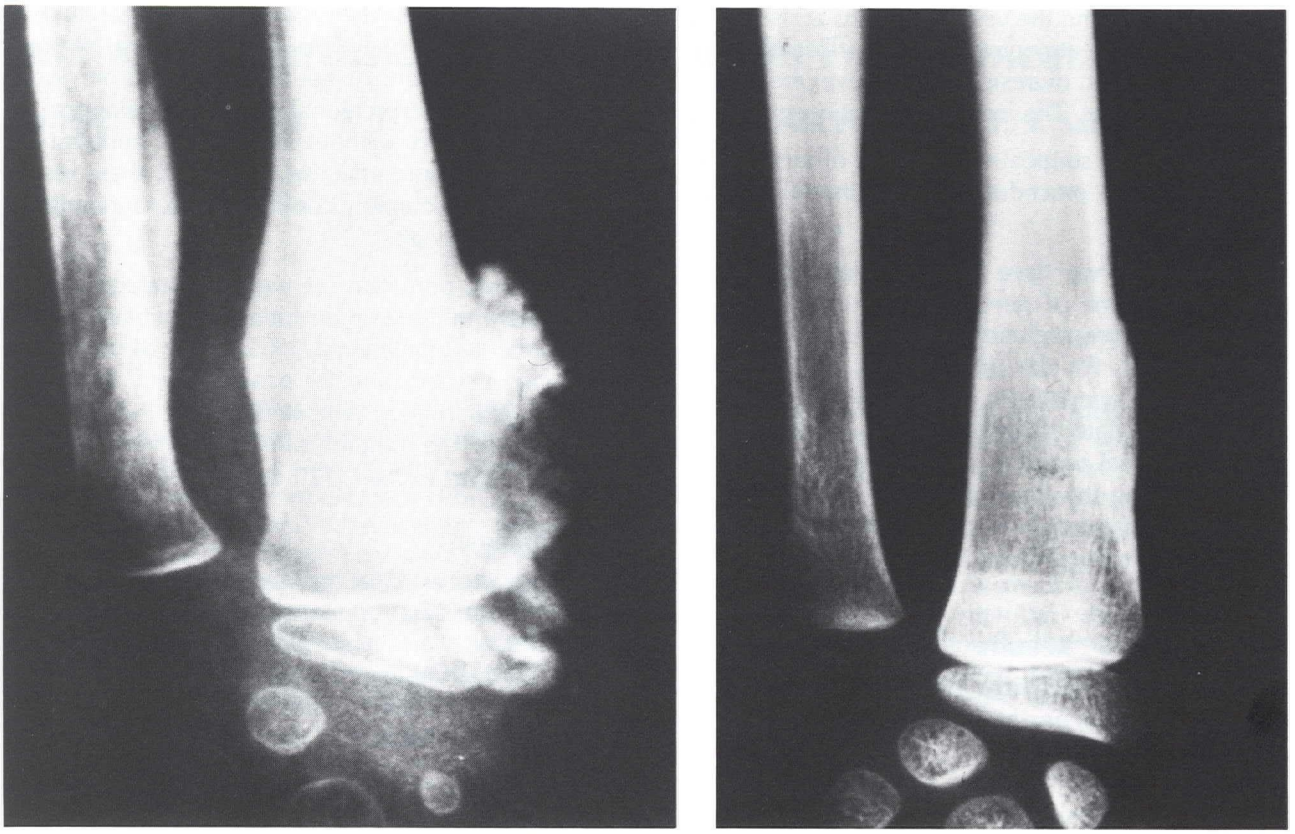

Fig. 1
Osteogenic sarcoma of distal part of radius.
Left: Before perfusion; right: Clinical results two years later, with complete bone repair.

Soft tissue sarcoma

Between October 1964 and December 1979, we treated 50 patients with soft tissue sarcoma either by hyperthermic perfusion or hyperthermic antiblastic perfusion, followed by excision of the tumor or amputation, depending on the histological type of the cancer, its size, and site. The five-year survival rates were 53% and 56% for hyperthermic perfusion and hyperthermic antiblastic perfusion, respectively. Therefore, no significant differences exist between the two techniques.

However, even if we consider that all the patients with soft tissue sarcoma had previously been treated with radio-chemotherapy, we cannot be entirely satisfied with our results. Recurrences have appeared, so that hyperthermic perfusion alone does not completely achieve loco-regional control of the tumor.

With these considerations in mind, we have begun a new treatment protocol in which hyperthermic perfusion, as a first step, is followed, at random, either by an endo-arterial infusion (adriamycin) or radiotherapy. After the tumor has been excised, adjuvant chemotherapy is administered only in advanced stages (II, III, IVA, according to the American Joint Committee classification).

Our objectives were two-fold: 1) loco-regional control of the tumor without the need for radical surgery; 2) distant control of the disease through the enhancement of the immune system and adjuvant chemotherapy. Our preliminary results have confirmed that this multi-step treatment can achieve loco-regional control of the disease. In terms of regained functionality, the results are very satisfactory, better than those obtained with conservative surgery. Of ten patients treated, only two died (12 and 19 months after treatment) due to lung metastasis. To confirm these preliminary results, this procedure will have to be performed on a greater number of patients. We have also had positive results with hyperthermic perfusion alone, in cases of primary soft tissue sarcoma, when the tumor is not excessively large (Figs. 2-4).

Discussion

Today, 16 years after our first clinical experiences treating cancer of the extremities by hyperthermic perfusion, some

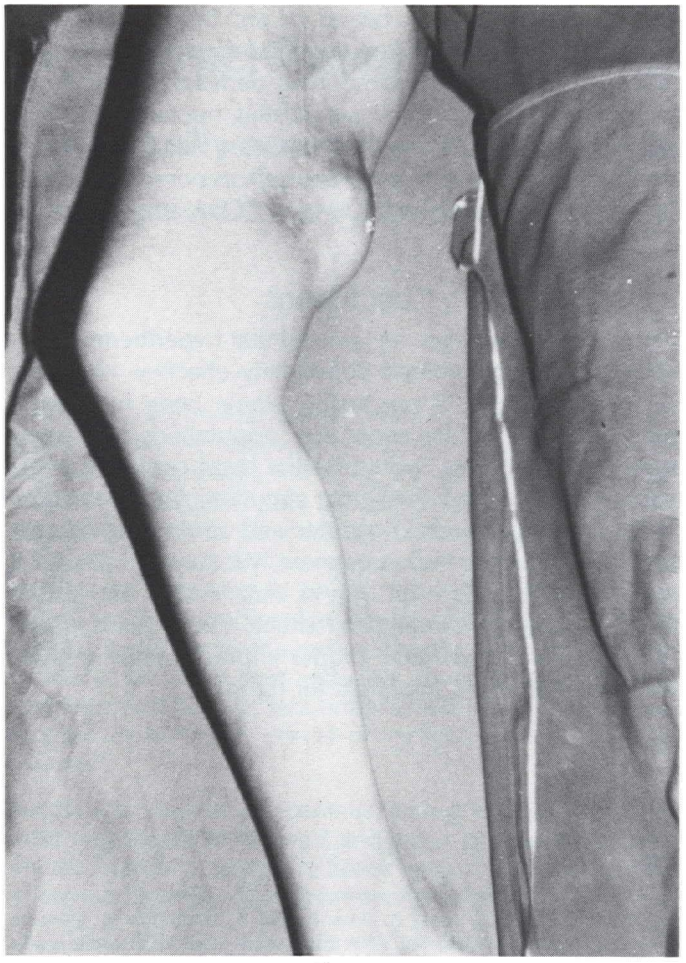

Fig. 2
Large recurrent fibrosarcoma of the thigh before hyperthermic perfusion.

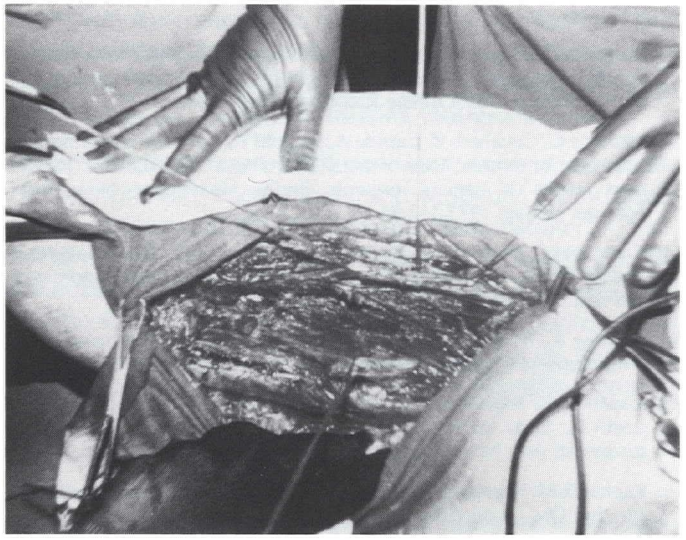

Fig. 3
Radical conservative excision of the tumor mass, sparing the sciatic nerve and femoral vessels.

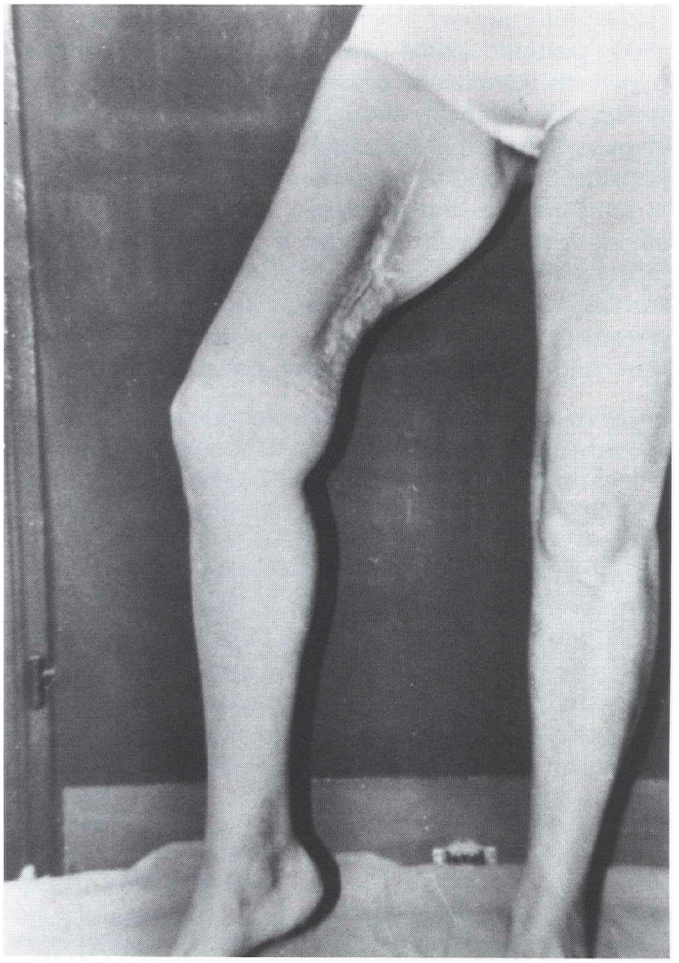

Fig. 4
Clinical results, one year later, with a complete range of movements.

definitive observations can be made. Clinically, we have demonstrated that hyperthermia is effective in curing some tumors of the limbs, even in cases in which poor results were obtained with conventional treatments. Many techniques have been developed to obtain above-normal temperatures in a particular part of the body as well as in the entire body, but in light of our results, we believe that perfusion still remains the most reliable heat transfer method, certainly for loco-regional treatment and perhaps even for whole-body hyperthermia. Hyperthermic perfusion permits us to control and maintain above-normal temperatures over the entire tumor site uniformly and constantly.

Although the first clinical applications of this technique presented complications, once we became more familiar with the physiopathology of hyperthermia, complications were reduced to a minimum. The operative mortality rate has been reduced to approximately 3%, which is considered normal in a routine operation.

Another difficulty we encountered was what we have called "post-perfusional limb syndrome." During follow-up, patients complained of persistent, diffused, and often burning pain, probably brought about by the autonomic nervous system. Since this could represent a form of reflex-sympathetic dystrophy, we performed a sympathectomy at the same time as the perfusion, which did not greatly complicate the surgical operation in terms of exposing and preparing the vessels of the limb. As a result, the pain described was no longer observed. The association of the sympathectomy with perfusion considerably reduced edema and postperfusional venous stasis.

The survival rates of patients with limb tumors, principally with advanced osteosarcoma and melanoma, are extremely satisfying. Complete loco-regional control has been obtained, a result of remarkable value, particularly in osteosarcoma, because it permits us to save the limb. In fact, we have begun a protocol treatment which involves, whenever possible, the en-bloc resection of the tumor in order to preserve the tumor-bearing limb. These considerations take on an even greater importance in that osteosarcoma mainly affects patients in their second decade of life. Of the nine patients treated, five are alive with no sign of disease, for a period ranging between 19 and 51 months.

We still do not know whether or not the mortality rate should be attributed to an incomplete capacity of the enhanced immune response that perfusion appears to evoke in the host, as far as pre-existing micrometastasis is concerned. This appears to be the most suitable explanation because we have neither recurrences nor metastases in the perfused area.

Conclusions

Our clinical experience has proved that hyperthermic perfusion can be considered completely effective in curing some limb tumors. Theoretically, whole body hyperthermia, exposing all the neoplastic populations to above-normal temperatures, would be the most complete treatment of tumors. We believe that circulating blood remains the best method for heat transfer and could also be employed for a whole-body treatment. We have employed a whole-body treatment on only a very limited number of patients, using an aortal-caval shunt; these first applications indicate that with the proper improvements, it could become an effective treatment for tumors.

References

1. Mondovi B, Strom R, Rotilio G, Finazzi Agro A, Cavaliere R, Rossi-Fanelli A. The biochemical mechanism of selective heat sensitivity of cancer cells. I. Studies on cellular respiration. Europ J Cancer 1969; 5:129-36.
2. Mondovi B, Finazzi Agro A, Rotilio G, Strom R, Moricca G, Rossi-Fanelli A. The biochemical mechanism of selective heat sensitivity of cancer cells. II. Studies on nucleic acids and protein synthesis. Europ J Cancer 1969;5:137-46.
3. Mondovi B. Biochemical and ultrastructural lesions. Proc, Int Symposium on Cancer Therapy by Hyperthermia and Radiation, Washington, DC, April 28-30, 1975.
4. Mondovi B, Strom R, Finazzi Agro A, et al. Effect of polyenic antibiotics on Ehrlich ascites and Novikoff hepatoma cells. Cancer Res 1971;31:505-09.
5. Giovanella BC, Mosti R, Heidelberger C. Biochemical and biological effects of heat on normal and neoplastic cells. Proc Ann Assoc Cancer Res 1969;10:28.
6. Giovanella BC, Morgan CA, Stehlin JS, Williams LJ. Selective lethal effect of supranormal temperature on mouse sarcoma cells. Cancer Res 1973;33:2568-78.
7. Giovanella BC, Mondovi B. Selective heat sensitivity of cancer cells. In: Rossi-Fanelli A, Cavaliere R, Mondovi B, Moricca G, eds. Recent results in cancer research. Berlin, Heidelberg, New York: Springer Verlag, 1977:1-6.
8. Strom R, Scioscia Santoro A, Crifo C, Bozzi A, Mondovi B, Rossi-Fanelli A. The biochemical mechanism of selective heat sensitivity of cancer cells. IV. Inhibition of RNA synthesis. Europ J Cancer 1973; 9:103-12.
9. Strom R, Crifo C, Bozzi A, Rossi-Fanelli A. Inhibition by elevated temperature of ribosomal RNA maturation in Ehrlich ascite cells. Cancer Biochem Biophys 1975;1:57.
10. Bourdon G, Halpern MB. Immunité antitumorale induite par l'administration de cellules tumorales homologues at isologues traitées par chauffage ménagé. CR Acad Sci Paris 1976;282(D): 1571-74.
11. Cavaliere R. Regional hyperthermia by perfusion. In: Proc, International Symposium on Cancer Therapy by Hyperthermia and Radiation. Baltimore: Am College Radiology Press, 1976.
12. Moricca G, Cavaliere R, Caputo A, Biogotti A, Clistro F. Hyperthermic treatment of tumors: Experimental and clinical applications. In: Recent results in cancer research. Berlin, Heidelberg, New York: Springer Verlag, 1977:112-51.
13. Clark WH Jr, Fromm EAL, Bernardino EA, Mihm MC. The histogenesis and biological behaviours of primary human malignant melanomas of the skin. Cancer Res 1969;29:705-26.
14. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 1970;172:902-08.
15. Cavaliere R, Moricca G, Di Filioppo F, Caputo A, Santori FS, Monticelli G. Heat transfer problems during local perfusion in cancer treatment. Ann NY Acad Sci 1980;335:311.
16. Kaplan ELM. Non parametric estimation from incomplete observation. Am Stat Oss J June 1938.