

Chemotherapy of Melanoma of the Extremities by Perfusion: Fourteen Years Clinical Experience

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CHEMOTHERAPY of cancer by regional perfusion was introduced in 1957 in the Department of Surgery at Tulane University by the late Dr. Oscar Creech and the authors.^{10, 19, 30, 31} Technics had been developed in the surgical laboratories to perfuse specific anatomical regions of the body with chemotherapeutic agents by cannulizing the major artery and vein supplying the area.⁸ Further isolation was obtained by applying an external tourniquet and the area was sustained by circulation of whole blood through an extracorporeal oxygenated system utilizing a heart-lung apparatus. The isolation obtained permitted the addition of chemotherapeutic agents to the perfusion circuit in dosages higher than could be tolerated by systemic administration and limited only by local toxicity. The original plan was to treat various organs or regions such as the liver, lungs, pelvis, or limbs for palliation of advanced disease.

The first appropriate patient, a 76-year-old man with satellitosis of the thigh and leg from a melanoma of the foot excised a

year before, was seen in May of 1957. Melphalan,* or 1-phenylalanine mustard, was chosen for use which was a new agent under study for treatment of patients with advanced melanoma. The drug had been synthesized simultaneously by Bergel and Stock in London² and Larionov in Moscow.²² It was hoped that the agent would be of particular use for the treatment of melanoma as phenylalanine, a metabolite of melanin, would carry cytotoxic alkalating radicals into tumor cells producing melanin. Studies in mice with transplanted melanoma by Luck²⁵ were promising and were the basis for trials in patients with advanced disease. An amount equivalent to the single systemic dose was added to the perfusate which when confined to the lower limb provided a concentration of about eight times the level that could be obtained by systemic administration. On June 11, 1957, the first clinical perfusion was performed through the common femoral vessels. The satellites slowly regressed and the patient remained free of tumor for 14 years until his death at age 91 on July 29, 1971.

Because of this impressive response, the method was utilized for treatment of a wide variety of tumors and in many different anatomical regions. Objective regressions were seen in many types of cancer that did

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not ordinarily respond to the chemotherapeutic agents then available. The duration of remissions varied from a few weeks to many months, the best responses occurring in patients with melanoma of the limbs. Consequently, a series of prophylactic perfusions, in conjunction with conventional surgical treatment, was begun in an attempt to improve the salvage rate by eliminating residual microscopic deposits of tumor and in-transit metastases.

This technic has been used alone or in combination with excisional surgery in the treatment of melanoma of the limbs over a 14-year period ending in June, 1971. Less radical resections were required and major amputations were seldom necessary. In satellitosis of the limbs, chemotherapy by perfusion has been curative in a number of cases. It is felt the results obtained warrant continued use of the method and are presented for consideration.

Methods of Perfusion

Technics for perfusion for the upper and lower limb have been described in detail previously.⁹ However, improvements have been introduced and the procedures as presently performed will be described. The patient, under general anesthesia, is positioned on folded sheets with the shoulder or hip elevated about an inch above the operating table to facilitate the placement of a tourniquet about the base of the extremity. The entire limb is prepared and draped for inclusion in the operative field. The major artery and vein supplying the area are exposed and controlled with tapes. The patient is heparinized and transparent plastic catheters are inserted into the vessels. The catheters are then connected to the extracorporeal perfusion circuit (Fig. 1). At present, a disposable oxygenator (Travenol Perfuso-Pac®) is used. The pump is primed with 250 cc. of whole fresh blood and 250 cc. of Ringer's solution. Ninety-five per cent O₂ and 5% CO₂ are used for oxygen to prevent hypocarboxia and alkalosis

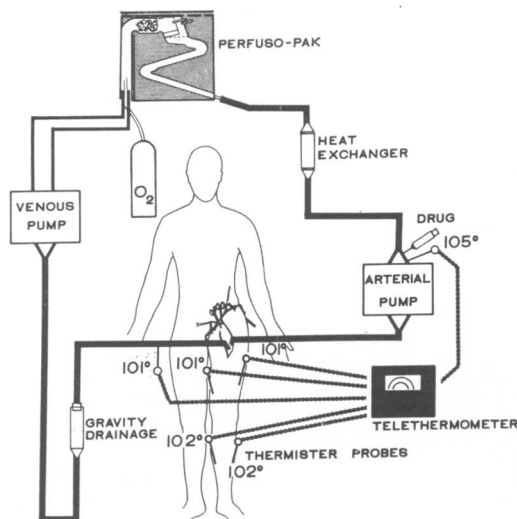


FIG. 1. Schematic diagram of perfusion circuit and equipment for a common femoral perfusion.

in the circuit as CO₂ is blown off through the oxygenator. With the bubble type oxygenator the plasma hemoglobins at the end of 45 minutes of perfusion range from 60 to 120 mg./100 ml. in samples taken from the perfusion circuit; however, levels from the patient after completion of perfusion have usually been below 20 mg./100 ml.

A gravity drainage collection device is used in the venous circuit and the arterial flow is regulated by the venous return. Flow rates for a common femoral or external iliac perfusion are maintained at 400 to 600 cc. per minute, while the flow rates for axillary perfusion are usually between 200 to 400 cc. per minute.

At first, little attention was devoted to the temperature of the arterial inflow. A coil of the arterial tubing was run through a bucket of hot water, producing temperatures in the arterial line of approximately 90° F. Later, the Marchand-Creech heat exchanger was included in the arterial line, making it easier to elevate the blood temperature to normothermic levels. For many years, the arterial blood was kept at 98° F. and external heat from an infrared light was applied to the tumor area. Since the

TABLE 1. *Subcutaneous Temperatures of Left Lower Limb Recorded During Perfusion*

Time Minutes	Leg Temperature in Degrees Fahrenheit				
	Arterial	Lateral Calf	Medial Calf	Lateral Thigh	Medial Thigh
0 On pump	104	96	97	97	95
5	103	97.5	99	98.3	96.5
10 On drug	104	99	100	99	98
15	104	100	102	100	98.5
20	102.5	101	103	100.5	99.8
25	101	101	103	100.5	100.5
30	100	101	103	100.5	101
35	104	101.5	102.5	101	101
40	102.5	102.5	103	101.5	102
45	102.5	102.5	103.5	102	102
55 Off pump					

E. F.—a 48-year old woman with primary melanoma of the left calf treated with Melpalan 86 mg. (1.2 mg./Kg. actual body weight) through the left common femoral artery.

work on hyperthermic perfusion of Cavaliere *et al.* in Rome,⁶ we have increased the temperatures in the perfusion circuit. The therapeutic rationale of hyperthermic perfusions requires elevation of the extremity temperature of 106° F. by arterial perfusion at 112° F., resulting in selective lysis of tumor cells. If chemotherapeutic agents are used at this temperature, too many complications occur. By increasing the arterial line temperature of 105° F., the temperature of the limb can be raised from 98° to 102° F. Thermister probes are placed subcutaneously to monitor the temperature of the limb during the perfusion. The extremity is wrapped with sterile drapes including a heating device (Aquamatic K pad®) set at temperatures between 102° to 105° F. Subcutaneous temperatures of the lower limb at the beginning of a perfusion are about 95° F. After 10 minutes of perfusion, limb temperature usually reach 98° F. at which point the drug is administered. After another 10–15 minutes of perfusion the temperatures range from 100° to 102° F. which are maintained for the duration of the perfusion. The temperatures recorded in a typical case are seen in Table 1. Hydrolysis of melphalan proceeds rapidly at 106° F. so the temperature in the

circuit is kept below 105° F. to avoid inactivation of the drug.

An external tourniquet consisting of several loops of an Esmarch bandage is placed about the root of the limb and held in position by Steinman pins placed through the skin and underlying subcutaneous fascia.

The position of the catheters and the area being perfused can be done by introducing three cc. of Fluorescite® into the arterial line and by observing the limb in a darkened room with a Woods' light. The distribution of the perfusate is determined by the yellow fluorescence in the skin. Satellites usually fluoresce more brightly than the surrounding skin. The distribution of the dye also indicates the position of the catheters, allowing adjustments to be made to correct the flow. If there is any question about distribution of the perfusate, a conventional arteriogram can be obtained.

The dosage of melphalan for the lower limb through the common femoral artery is from 1.0 to 1.4 mg./Kg. body weight and for the upper limb through the axillary artery from 0.6 to 1.0 mg./Kg. body weight. Table 2 indicates typical doses that may be given for a common femoral perfusion for a 70 Kg. patient. The drug is given in four aliquots at 3-minute intervals and perfusion

is continued for 45 minutes after the first aliquot. When nitrogen mustard is used, the total dose for lower limb is from 0.5 to 0.8 mg./Kg. body weight, not to exceed a total dose of 40 mg. Two to 3 mg. of this rapidly acting agent are given every 2 minutes until the entire amount is administered and the perfusion is continued for another 10 minutes. If large aliquots of nitrogen mustard are given at one time, neurotoxicity may follow. Triethylenethiophosphoramide (Thio-TEPA®) is given in the same manner as melphalan. When these two drugs are given together, the combined dose is calculated at 110% of either drug alone. Doses are varied according to the general condition and the age of the patient, the amount of fat or muscle in the extremity, and the size of the limb in comparison to the rest of the body.

At the completion of perfusion the perfusion circuit is rinsed with 250 cc. of 6% Dextran and 250 cc. of whole blood. The vessels are repaired with fine arterial sutures, and protamine sulphate is administered intravenously in doses equal to the previously administered heparin to counteract the anticoagulant effect. Planned excisional surgery is then carried out.

Specific Operative Procedures

For Stage I lesions of the thigh, an external iliac perfusion is performed, followed by a groin dissection including the iliac nodes, when enlarged, and the inguinal and femoral nodes. A wide excision of the tumor site is carried out and repaired with a split thickness skin graft. When the lesion is at or below the knee, a common femoral perfusion is performed, followed by a femoral node dissection and a wide excision of the primary lesion and repair with a split thickness skin graft. For upper limb Stage I lesions, the perfusion is carried out through the first portion of the axillary vessels, followed by an axillary

TABLE 2. Average Dosage for Common Femoral Artery Perfusion for 70 Kg. Man

Drugs	Average Total Dose
Melphalan	75 mg.
Thio-TEPA	75 mg.
Melphalan and Thio-TEPA	55 mg. and 30 mg.
Nitrogen mustard	35 mg.

node dissection and a wide excision of the primary lesion. The axillary dissection is performed by dividing the pectoral muscles and removing the lymph nodes from the apex of the axilla to the lateral border of the latissimus dorsi. For the past several years, in female patients with Stage I lesions, a modified axillary dissection has been performed without division of the pectoral muscles. In lesions arising within 15 cm. of the groin or axilla, an incontinuity dissection, including the skin and underlying soft tissue with the lymphatics to the regional nodes, is performed. In Stage II lesions, perfusion is followed by appropriate dissection of remaining nodes and a wide excision of metastatic or recurrent disease, particularly if there is a solitary or limited recurrence. With more extensive disease or satellitosis, perfusion alone is performed. Following regression of disease, a second procedure is performed which may include perfusion and/or excision of residual melanoma after a 3 to 6-week interval.

TABLE 3. Sites of 632 Perfusions in 522 Patients with Melanoma

Site	No. Pts.	No. Perf.
Limb	480	584
Upper	155	168
Lower	325	416
Head and neck	27	28
Pelvis	10	14
Breast	4	4
Brain	1	2
Total	522	632

TABLE 4. Sites of Primary Melanoma of the Upper and Lower Limbs Treated by Perfusion

Sites	Number Patients
Upper limb:	
Upper arm	43
Forearm	31
Trunk metastatic to axilla	30
Shoulder	16
Wrist	8
Subungual	6
Unknown primary metastatic to axilla	5
Elbow	5
Digit	3
Hand, dorsum	3
Hand, palm	2
Axilla	1
Scalp metastatic to humerus	1
Unknown primary metastatic to arm	1
Total	155
Lower limb:	
Leg	142
Foot, plantar	46
Foot, other	40
Thigh	24
Digit	21
Ankle	12
Knee	12
Subungual	7
Trunk metastatic to groin	6
Unknown primary metastatic to groin	5
Eye metastatic to leg	2
Unknown primary metastatic to femur	2
Groin, skin	1
Face metastatic to femur	1
Scalp metastatic to groin	1
Arm metastatic to leg	1
Unknown primary metastatic to thigh	1
Unknown primary metastatic to knee	1
Total	325

Clinical Material

In the 14-year period ending June 30, 1971, we have administered chemotherapy by regional perfusion to 522 patients with malignant melanoma. Table 3 indicates the sites of the 632 perfusions performed in these patients. As the results with melanoma in sites other than the limb have been of limited benefit, this report concerns our experience with the 480 patients with limb perfusions. One hundred and fifty-five patients had upper limb perfusions and 325 had lower limb perfusions. Most patients

with melanoma were white and only 23 were Negro. Distribution by sex was more even, with 208 males and 272 females in the series.

The primary sites of the melanoma for which limb perfusions were performed are shown in Table 4. The leg was the most common site of extremity lesions which occurred in 142 patients; the next most common site was the foot with 86 patients. The other sites are listed in order. Thirty patients with a locally controlled primary melanoma of the upper trunk with metastases to the axilla had axillary artery perfusions followed by axillary node dissection. Six patients with controlled lesions of the lower trunk with metastases to the inguinal nodes were similarly treated. Seven upper limb perfusions were performed on patients having an unknown primary lesion with metastases to the extremity. Fifteen patients were treated with metastatic lesions on the lower limb from a controlled primary lesion elsewhere or unknown site.

Melphalan has been used most extensively, having been used alone on 377 occasions. Thio-TEPA® has been used only on three occasions, but was combined with melphalan 169 times. Nitrogen mustard, usually given after unsuccessful melphalan perfusion, was used 27 times. Other drugs such as Actinomycin D, AB 100, Colchicine or Mitomycin-C were used alone or in combination on eight occasions.

Results of Treatment

The 480 patients with melanoma of the limbs were separated into three categories by the stage of disease. One hundred and eighty-two had localized or Stage I disease including 12 who had intact primary lesions, and 170 who had excisional biopsies which were referred for definitive treatment. There were 205 patients with regional or Stage II disease, including all patients with recurrence in the limb or regional nodes. There were 93 patients with

Stage III disease including 36 with the primary lesions in the limb but with systemic metastases; 27 had positive iliac nodes, and 30 had primary lesions outside of but with metastases to the limb.

Excluded from evaluation of Stage I and II disease were 25 patients who were treated less than one year ago, 15 who have been lost to follow-up and three who died of other causes, including trauma or stroke. Excluded from evaluation were 11 patients with Stage III disease for the same reasons. In assessing our results, follow-up reports are obtained at least once a year by examination of the patient or by report from the referring family physician.

All of the Stage I patients had invasive melanoma as determined by biopsy review of the primary lesions by members of the Tulane Department of Pathology, previously performed by Dr. Wallace C. Clark and presently by Dr. Richard J. Reed, which conformed to the criteria of invasive melanoma as established by Clark.⁷ This review is important, as patients with localized disease and with level of invasion confined to the upper papillary dermis (levels I and II according to the Clark criteria⁷ were excluded from the perfusion series. These patients were treated by local excision.

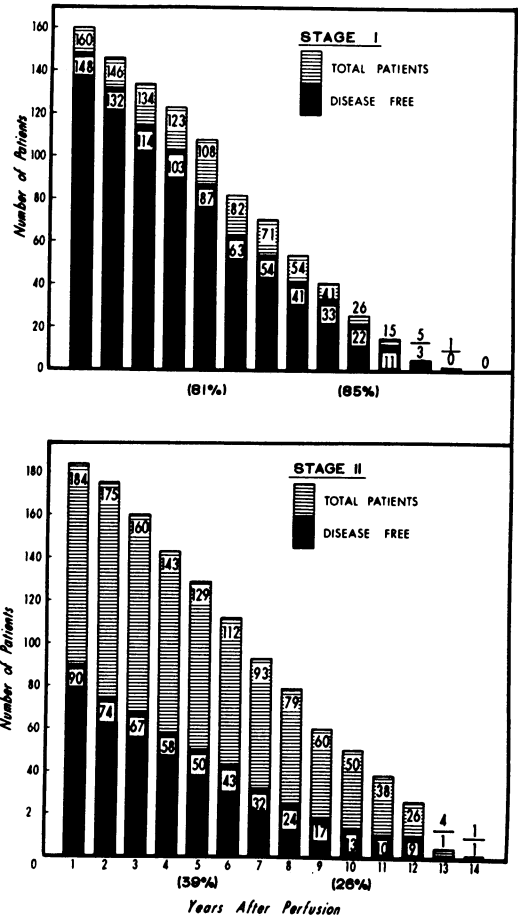


FIG. 3. Direct survival rate by year in numbers of patients treated by chemotherapy by perfusion in Stage I and Stage II melanoma of the limbs. Excision was carried out in all of the Stage I patients with one exception. In Stage II disease excisional surgery in addition to perfusion was carried out in about 2/3 of the patients, as indicated in the text. The following patients were excluded for these reasons: 25 patients who were treated less than one year; 15 lost to follow-up; and three dead from unrelated causes.

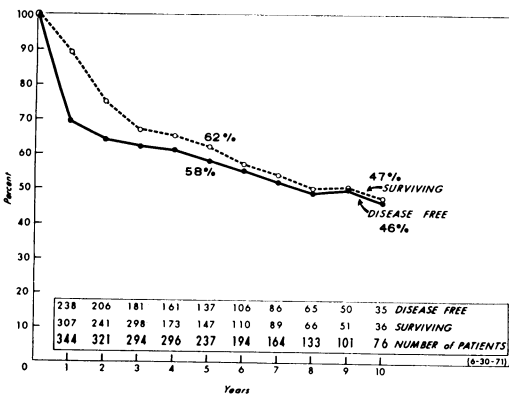


FIG. 2. Results of chemotherapy of melanoma of the limbs by perfusion comparing by year the per cent of patients disease free to the per cent of patients surviving.

Figure 2 shows the difference between Stage I and II patients surviving, with and without disease, and those classified as free of disease. By the third year, the curves begin to approximate each other and by the fifth year the direct disease-free rate is 58%. Ten additional patients were alive with disease, making the survival rate 62%. By the eighth year, only one patient remained alive with recurrences and the direct survival, disease-free rate at 10 years

TABLE 5. Results of Chemotherapy of Stage III Melanoma of the Limb by Perfusion

Year	Primary Elsewhere Metastases to Limb			Primary in Limb					
	Patients	Sur- viving	Disease Free	Positive Iliac Nodes			Systemic Metastases		
				Patients	Sur- viving	Disease Free	Patients	Sur- viving	Disease Free
1	27	9	6	21	10	1	34	9	2
2	25	6	4	16	2	1	32	4	2
3	23	4	2	15	0	0	31	3	1
4	22	3	2	15	0	0	27	1	0
5	20	2	1	14	0	0	25	0	0

is 46%. A second observation may also be made; that is, there continues to be a small attrition due to recurrence of melanoma. This attrition also is noted in age adjusted survival curves prepared by the End Results Program of the National Cancer Institute and confirms the clinical impression that the patient with melanoma never can be considered "cured."¹¹

Figure 3 shows the number of disease-free patients by Stage I and II according to year after treatment. Forty-three patients were excluded for the reasons listed above. The direct cure rate shows that 87 of 108 patients treated with Stage I disease and 50 of 129 with Stage II disease are free of disease at 5 years. At 10 years, 22 of 26 with Stage I, and 13 of 50 with Stage II are free of disease. At 12 years, the numbers of cases are limited—three of five in

Stage I, while nine of 26 in Stage II are free of disease.

The results of treatment for 93 Stage III patients are shown in Table 5, 11 patients were deleted for reasons listed above. These remaining patients fall in three categories: patients with primary lesions elsewhere with metastases of limb; patients with primary lesions in the limb with positive iliac nodes or with systemic metastases. These patients underwent perfusion to provide palliation because of local symptomatology such as bulky tumors, ulceration or pain, or to avoid amputation. While long-term survival is poor in Stage III melanoma, worthwhile palliation was achieved. At least one half of the patients had relief of symptoms for 2 months or more and all patients, except three who underwent amputation, had a useful limb. None of these patients survived more than 7 years. Only three were free of disease 3 years after treatment, while seven are alive. Those with metastases to the limb with the primary lesion elsewhere did better than the other two groups. Of the 21 with positive iliac nodes, ten patients survived, but only one was free of disease at the end of 1 year. All were dead at the end of 3 years. The observation made by McPeak *et al.*,²⁷ that positive iliac nodes indicate a hopeless prognosis, is again confirmed.

Figure 4 shows the per cent of disease-free patients according to sex, site, and stage at 5 years. The results suggest that

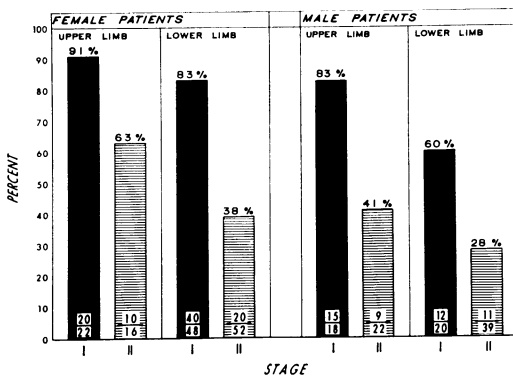


FIG. 4. Results of chemotherapy of melanoma of the limb by perfusion and excisional surgery five years after treatment according to sex, stage, and site.

women respond better than men, that upper limb lesions respond better than lower, and that Stage I disease responds better than Stage II. The only statistical significant differences exist between stage of disease with confidence levels varying from 90% in the upper limb women patients to 95% level for lower limbs in men, and 99.9% in the other two categories. The remaining differences are not statistically significant and only show trends. While the group is small, the salvage rate for women with upper limb involvement, Stage I patients is excellent, as only two of 22 patients had recurrence of disease by 5 years. This observation has modified our approach regarding prophylactic node dissection for this group and we now defer or perform a modified dissection.

The salvage according to special categories for Stage II disease is of interest (Table 6). Several categories of patients had perfusion and additional excisional surgery; included are untreated patients with primary and regional metastases intact, with five of 18 free of disease after 5 years and 23 of 30 patients with solitary recurrences had no further disease. Few patients with satellitosis or extensive recurrences had additional excisional surgery. Of 39 patients with satellitosis treated by perfusion, 11 are free of lesions. An example of good response in a patient with satellitosis is shown in Figure 5 A & B. Patients with extensive regional metastases responded poorly, only four of 23 had no disease at 5 years. Thirty-six patients of 39 with satellitosis were treated by perfusion alone, eight underwent perfusion more than once (Table 7). Such a patient is demonstrated in Figure 6 A and B. Ten patients were free of disease for 5 to 14 years following perfusion, eight others had temporary control from 1 to 4 years.

Table 8 compares the results of treatment in Stage I disease according to year for patients who underwent perfusion and wide

TABLE 6. Results of Chemotherapy of Stage II Melanoma of the Limb Five Years after Perfusion According to Special Categories

Special Categories*	5 Years after Perfusion	
	No. Pts.	No. Disease Free
Previously untreated primary with regional metastasis*	18	5
Solitary cutaneous or subcutaneous metastasis*	12	8
Solitary regional node*	18	15
Satellitosis—previously negative nodes†	22	6
Satellitosis—previously positive nodes†	17	5
Extensive regional metastases**	23	4
Primary unknown, metasis to limb* (skin, nodes, or bone)	8	5

* Most patients had additional excisional surgery.

† 36/39 no additional excisional surgery.

** Perfusion only in most cases.

excision of the primary site versus those who had perfusion, regional node dissection and wide excision. The second category contains almost five times as many patients and shows slightly better salvage rates in each cohort, but none of the dif-

TABLE 7. Results of Chemotherapy of Melanoma of the Limb by Perfusion Alone for Satellitosis Developing After Conventional Surgical Treatment

36 patients treated 5 or more years ago
19 with negative nodes
5 Free of disease
1 Controlled 1 year—alive at 10 years following excisions × 10 for recurrent disease
1 Controlled 4 years—dead at 7 years
1 Controlled 2 years—dead at 3 years
1 Controlled 1 year—dead at 3 years
10 Dead at 1–4 years
17 with positive nodes
5 Free of disease
1 Controlled 4 years—dead at 5 years
1 Controlled 3 years—dead at 5 years
1 Controlled 2 years—dead at 7 years
1 Controlled 1 year—dead at 2 years
8 Dead at 1–2 years



FIG. 5 A & B. A 38-year-old woman with a pigmented nevus of the right ankle of long duration, who noted growth of the lesion during the third trimester of pregnancy in May, 1961. Wide excision in May was followed by groin dissection in June, 1971. In May, 1962 appearance of dermal metastases of right thigh occurred (A top). In July, 1962 the patient was perfused with 50 mg. of melphalan and 15 mg. of Thio-TEPA® through the common femoral artery. Complete remission followed and the thigh is shown 18 months later. The patient is alive and well at present (B bottom).

ferences are statistically significant. While many feel that prophylactic node dissection is important as pointed out by Polk, statistical evidence to prove this point is lacking.²⁸

Only one patient was treated for primary disease by perfusion alone. This patient was a 68-year-old woman who refused to undergo amputation for melanoma of the palm, but agreed to undergo perfusion. Figure 7 A and B shows the favorable result of treatment, i.e., the patient has had no evidence of melanoma for 11 years.

Complications and Deaths

Of the 480 patients, 209 patients died of recurrent tumor. Table 9 lists the operative deaths and complications. Nine patients died shortly after treatment; six were due to chemotherapy with leukopenia and septicemia, and three were operative deaths due to myocardial infarction, chronic congestive heart failure, and anesthesia, respectively. Systemic complications from chemotherapy consisted of leukopenia with white blood count under 2,000 per cubic mm. in 26 cases and under 1,000 in 17

FIG. 6 A & B. In February, 1961 a 36-year old white male noted changes in nevus on left calf. Excision followed by groin dissection was carried out in May, 1961. In December, 1961 excision of a local recurrence followed. Dermal metastases of left calf appeared in May, 1962 (A top). In May, 1962 perfusion was carried out with 70 mg. of melphalan and 30 mg. of Thio-TEPA®. In June and in October, 1962 perfusion with 90 mg. of melphalan was performed followed by temporary improvement on each occasion. In February, 1963 the patient was perfused with 60 mg. of nitrogen mustard through the common femoral artery. Complete regression followed and patient's leg is shown in July, 1971 (B bottom).



cases. Fourteen patients had severe alopecia; 10 had pulmonary complications such as atelectasis and pneumonia; three had pulmonary emboli. Miscellaneous complications included three with postoperative psychoses, one with complete loss of the nails. The deaths and complications are separated according to those occurring before July 1, 1968 and those occurring since then. Only one operative death has occurred in the past 5 years and the number of complications are acceptable when one considers that this procedure involves the

intra-arterial use of highly toxic drugs, extracorporeal circulation, and radical excisional surgery. The large number of complications early in the experience must be attributed to the development of a new procedure. Node dissection is usually accompanied by increased wound complications. High doses of alkylating agents have been shown to inhibit wound healing²⁰ and precautions must be taken to avoid the resultant complications, i.e., suction drainage, careful suturing, retention of skin stitches for 12-14 days, etc.

TABLE 8. *Chemotherapy of Melanoma of the Limbs by Perfusion**
Results of Treatment of Stage I Melanoma

Year	Perfusion and Excision			Perfusion, Excision, Dissection		
	Patients	Disease Free		Patients	Disease Free	
		No.	Per Cent		No.	Per Cent
1	27	23	85	133	125	93
2	26	22	85	120	110	92
3	24	19	79	110	95	88
4	24	19	79	99	84	85
5	24	19	79	84	68	81
6	23	17	74	59	46	78
7	22	16	73	49	38	78
8	20	15	75	34	26	77
9	17	13	77	24	20	83
10	13	10	77	13	12	92
11	9	6	67	6	5	83
12	5	3	60	1	0	0
13	1	0	0	0	0	0

* Number and percentages of patients treated in any given year surviving without evidence of disease.

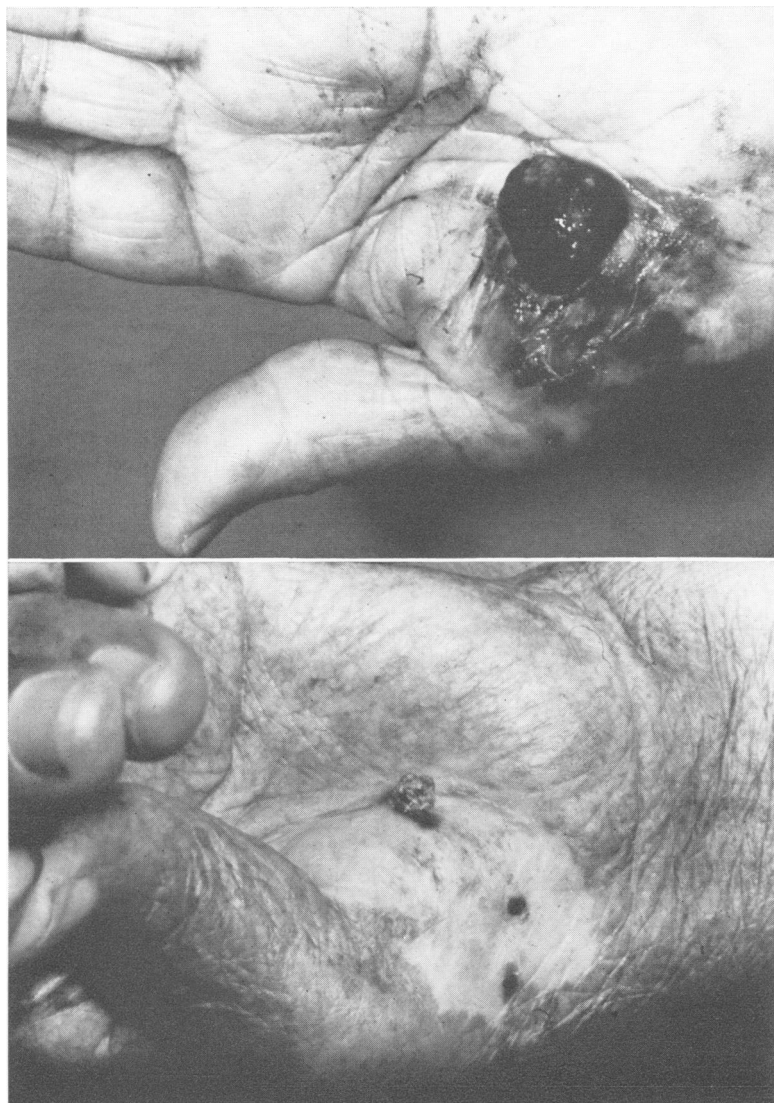
Discussion

The main advantages offered by regional perfusion of chemotherapeutic agents consist of increased tumoricidal effects and decreased systemic toxicity. The improved tumor response is due to the following factors: intra-arterial lung administration; increased dosage; increased tissue oxygen tension; elevated limb temperature; decreased systemic toxicity; and possibly autoimmunization. Intra-arterial administration is a particularly effective way of giving chemotherapeutic agents.^{3, 17, 35} Regional perfusion permits an increase in local dosage of from six to ten times that obtained by systemic administration. We have shown that increased tissue oxygen tension potentiates the effect of alkylating agents,²¹ an observation confirmed by others.^{14, 23} The technic makes it possible to maintain the perfusate temperature at the most efficacious level for drug action. The isolation of the limb and the removal of active agents at the end of the procedure reduce systemic toxicity. Finally, the use of this method to treat melanoma may produce autoimmunization caused by local destruction of tumor initiating an immune response in a host

whose ability to make antibody has not been depressed by systemic administration of immune suppressive drugs. The best examples are the responses seen in patients with satellitosis, with a 35% disease-free rate at 5 years, late responses of lesions outside of the perfused area, spontaneous remissions of new lesions developing long after perfusion, and serial biopsies of satellites showing heavy round cell infiltration accompanying resolution of tumor after a delayed interval.

What benefit has chemotherapy by perfusion for melanoma produced beyond that of conventional surgical treatment or systemic chemotherapy alone? The lack of uniformity in other methods of evaluation, treatment, and analysis make a comparison difficult. Added to the problem are the variations in histologic grading, level of invasion, stage and site of disease, previous and concurrent therapy, and variations in surgical technics. The summation of results following surgical treatment reported by Ackerman and delRegato in 1962¹ was an accurate reflection of response to treatment to that time. They concluded that the response of superficial melanoma was excel-

FIG. 7 A & B. A 68-year old negro female with a small black pigmented area of the palm of the left hand for many years noted the onset of pain, growth, and ulceration with bleeding in July, 1960 (A top). In October, 1960 a perfusion with 50 mg. of melphalan and 30 mg. of Thio-TEPA® through the brachial artery was performed. Complete remission followed shown in picture B (bottom) one year later. Slight muscle and nerve damage followed the perfusion. Patient is alive and well at present.



lent and the 5-year survival rate of invasive melanoma without regional node involvement was about 30%. When microscopically positive nodes were present, the 5-year rate was about 15% and when nodes were clinically positive, the survival rate was less than 10%.

Recent reports have shown better survival rates. The monograph on *End Results in Cancer* from the National Cancer Institute in 1968¹¹ states that the prognosis for melanoma has shown improvement since the 1940's. The upward trend in survival

has occurred in both localized and regional cases with rates consistently higher for women in each time period and each stage classification.

Data obtained through the courtesy of Mr. Herman Heise from the End Results Program of the National Cancer Institute have been used to compare with our Stage I patients treated by perfusion and excisional surgery. The End Results Program patients have been treated by definitive excision, which includes a wide variety of procedures ranging from conservative to

TABLE 9. Major Complications Following Chemotherapy by Perfusion, Node Dissection and/or Wide Excision and Skin Graft*

Complications	6/11/57- 7/1/66-		No.
	6/30/66	6/30/71	
Wound:			68
Infection	18	7	
Bleeding	8	3	
Seroma**	4	5	
Dehiscence with second-ary closure	8	0	
Infection with dehiscence	4	4	
Ischemic necrosis	6	1	
Limb other than wound:			90
Edema (severe and/or persistent)	29	12	
Nerve and muscle damage***	20	3	
Thrombophlebitis	12	5	
Arterial thromboses***	5	0	
Venous thromboses***	4	0	
Systemic:			80
Leukopenia			
Less 2000/mm ³	26	0	
Less 1000/mm ³	16	1	
Severe alopecia	12	2	
Pulmonary (atelectasis, pneumonia, etc.)	8	2	
Pulmonary emboli	2	1	
Miscellaneous (p.o. psychoses, etc.)	7	3	
Deaths:****			9
Agranulocytosis with septicemia	6	0	
Myocardial infarction	0	1	
Congestive heart failure	1	0	
Anesthesia	1	0	

* Complication occurred following 157 of 584 perfusions.

** Requiring five or more aspirations.

*** Requiring amputation in one patient of each category.

**** Death due to myocardial infarction occurred in 1968, other deaths occurred prior to 1964.

radical. The age adjusted 5-year survival rates for upper and lower limbs in men is 78% and 74% and for women, 86% and 80%. The sample sizes are large—194, 249, 292, and 621 patients consecutively and are the only readily accessible source of material with large enough groups for accurate evaluation. When these rates are compared

to the direct survivals listed in Figure 4 it will be seen that the Tulane groups responded better in all instances except for lower limbs in men—60% compared to 74%. It must be pointed out that these survival rates are calculated on the basis of data submitted by three central registries and nine hospitals which are categorized as referral centers. Data from central registries, which provide the great majority of the cases, invariably have more favorable end results than referral hospitals. Also, age-adjusted survival cures are about 5 to 10% higher at 5 years than the direct survival rates. Although they are based on histologically proven cases, the End Results data also include superficial melanoma, representing perhaps as many as 3% of the cases. This lesion is now recognized as having a very favorable prognosis even when treated by local excision.^{4, 13} Thus, when the direct disease-free rates obtained in the perfusion experience are compared to the End Results Group rates, the adjunctive perfusion group rates are improved by 10% to 15% at 5 years for the various categories.

In regional recurrent disease, there are several categories in which perfusion alone or with excision has provided 5-year survival rates that are not usually duplicated. These groups include patients with satellitosis treated by perfusion, 11 of 39 of whom are disease-free at 5 years, and patients with solitary nodal cutaneous or subcutaneous recurrence of whom 23 of 30 are disease-free at 5 years. Although there have been occasional dramatic responses in patients with extensive disease, cures have been few, 4 of 23 being disease-free at 5 years. Nevertheless, functional limbs were salvaged until the patients died of systemic metastases. In recent years, major amputation for melanoma has developed as a complication or failure of treatment in only four patients.

Prior to the introduction of perfusion, systemic chemotherapy had little to offer

the patient with melanoma. While providing temporary relief, chemotherapy did little to influence the course of disease.³² Chemotherapy of melanoma has improved particularly since the introduction of 4-amino 5-imidazole carboxamide. The Central Oncology Group, of which Tulane is a member, has treated 276 evaluable patients with advanced disease and reported ten complete remissions and 51 partial remission,¹⁶ the longest lasting over 2 years. Using a combination of three agents, imidazole carboxamide, a nitrosourea derivative (CCNU), and vincristine for 5-day courses every 4 to 6 weeks, we have treated 35 patients.⁵ Three patients had complete responses, two patients had remissions at 18 months, and eight had partial responses. The South West Cooperative Study Group had a similar experience, with 20% responding by use of a slightly different combination of imidazole, BCNU, and vincristine.²⁴ However, systemic chemotherapy for melanoma must still be considered to offer only temporary palliation.

The variations in survival rates for surgical treatment of melanoma of the limbs are considerable and Knutson *et al.* in a recent report have compiled the results from 17 papers representing 2,339 cases.¹⁸ The 5-year salvage rate following surgical treatment varied from 10% to 59%, but no breakdown was given by site, stage, type of surgical treatment, etc. In Knutson's own series, age-adjusted survival rates for upper extremity were 58% and for lower extremity were 52%. In James' compilations of survival rates published in 1966, the 5-year survival for upper extremity lesions was 46% and 33% for lower extremities.¹⁵ Reports on perfusion therapy of melanoma by Stehlin,³⁴ Rochlin,²⁹ Shingleton,³³ and McBride²⁶ are more consistent for extremity melanoma and compare closely with our results. It will require a prospective randomized study to determine the benefit of adjunctive perfusion. Such a

study in progress under the direction of Shingleton at Duke sponsored by the Central Oncology Group, but it will be several years before useful data can be obtained. The above authors generally agree that the use of perfusion for curative purposes will reduce local recurrences in the limb.

Summary and Conclusions

From June 1957 through June 1971, 480 patients with melanoma of the limbs were treated by chemotherapy by perfusion on 584 occasions.

Of 108 patients with Stage I melanoma, 87 were free of disease at 5 years and 22 of 26 at 10 years, following perfusion, wide excision of the primary site, and in most instances regional node dissection.

Of 119 patients with Stage II disease, 50 were free of disease at 5 years and 13 of 50 at 10 years. These patients received perfusion and excisional surgery except those with satellitosis or extensive disease of the limb who were treated by perfusion alone in most instances.

The best survival rates based on sex, site, and stage resulted in women with Stage I upper limb lesions of whom 20 of 22 were free of disease at 5 years.

In Stage II disease, the patient with satellitosis of the limb responded well, ten of 36 were free of disease at 5 years and were treated by perfusion alone. With solitary nodal, cutaneous, or subcutaneous recurrence, 23 of 30 patients were free of disease at 5 years but only four of 23 were free of disease with extensive recurrences in the limb.

Ninety-three patients with Stage III disease were treated by perfusion for palliation. Over half had useful palliation but only 18 survived 1 year after therapy.

Chemotherapy by perfusion as an adjunct to conventional excisional surgery in Stage I adds approximately 15% to the 5-year survival rate for invasive melanoma; reduces the incidence of regional recur-

rence, and eliminates the need for major amputation. In Stage II disease, the survival rates are doubled in most categories; chemotherapy by perfusion is the therapy of choice for satellitosis.

Acknowledgment

The authors wish to acknowledge the interest and assistance of their colleagues and the many house officers on the Tulane Service who have participated in this project. They also wish to recognize the valued assistance of the perfusion nurses, the technicians and secretaries who have aided in the program. Finally they wish to recognize the faithful assistance of Miss Beulah Creel, R.N., who maintained the records and conducted analyses for our reports throughout the entire project.

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DISCUSSION

DR. GILBERT S. CAMPBELL (Little Rock): First, I would like to express my sincere gratitude to Dr. Edward T. Kremetz for the courtesy and advice he has given us in setting up our modest program on chemotherapy of melanoma at the University of Arkansas.

We feel that some limb complications following perfusion from melanoma are the direct result of unphysiological perfusion rather than the chemotherapeutic agent utilized during perfusion. In an obese patient, a tight tourniquet can obliterate venous outflow more efficiently than it can obliterate collateral arterial inflow. Consequently, with prolonged perfusion, abnormally high pressures may develop in the vessels of the isolated extremity. We insert a needle in the artery of the perfused limb distal to the arterial cannula to record pressure before and during perfusion. The arterial pressure distal to the cannula is held below the patient's systemic arterial pressure, and sometimes this necessitates accumulation of blood in the pump oxygenator (bleeding out the limb, so to speak, in order to avoid overperfusion).

If the arterial pressure in the perfused limb is lower than systemic arterial pressure, one doesn't have to worry about a leak of the phenylalanine nitrogen mustard into the systemic circuit since the gradient is in the other direction. We no longer monitor for leaks nor have we observed any systemic complications following extremity perfusion for melanoma.

DR. J. BRADLEY AUST (San Antonio): I would be remiss not to pay homage to the late Dr. Oscar Creech, who, with the current authors, gave birth to the concept of isolated perfusion chemotherapy.

We have just heard the results of 14 years' experience. There can be no doubt of the valuable palliation afforded patients suffering locally recurrent disease, especially satellitosis.

My second comment relates to the suggestion of 10 to 15 per cent better 5-year survivals using isolated perfusion at the time of definitive surgery, which, if true, is a very important adjunct. If my host, Bill Shingleton, were here, he would make the following comments. He and I, among others, feel strongly that the time for a controlled clinical study is at hand. Such a study will be needed to determine whether operation alone or operation plus perfusion can offer a higher cure rate. Unfortunately, the groups practicing isolated perfusion receive their patients upon referral because they are going to do isolated perfusion, and it is difficult for them to enter upon a controlled study.

Therefore, our plea is that those of us who have lesser dedication to isolated perfusion, and perhaps less emotional involvement in the problem, go ahead and do a controlled, randomized clinical study—conventional surgical treatment versus conventional operation plus perfusion. Perhaps in 5 to 10 years we can answer the crucial question.

Finally, I have a question of the authors. Since there were approximately 20 per cent deaths in Stage I disease, what percentage developed local recurrence, since we would hope that the major impact of perfusion and operation would be to eliminate local recurrence? Distant metastasis beyond the isolated perfused area is beyond the scope of our control at the time of therapy.

So if you could answer that question for us, it might give us further hope that we could accomplish greater things.

DR. HUGH E. STEPHENSON, JR. (Columbia): I, too, would like to voice appreciation to Dr. Kremetz for his pioneering efforts and for his attempts to guide and stimulate us in what is such a major breakthrough in the assault on melanoma.

The first slide (slide), our first perfusion case, actually was an instance of satellitosis in a woman who lived 8 additional years. This has been our best result to date.