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History of regional chemotherapy for cancer of the extremities

CHARLOTTE EIELSON ARIYAN & MARY SUE BRADY

Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, NY, NY 10065

Abstract

Patients with recurrent cutaneous or soft tissue malignancies of the extremity provide a unique opportunity to evaluate therapy targeted to the isolated limb. The most common clinical presentation of recurrent extremity malignancy occurs in patients with melanoma. The extremity is the site of primary melanoma in half of patients with the disease [1], and of those with a primary melanoma of Breslow depth ≥ 1.5 mm, 15% will develop a local or in-transit recurrence [2]. Palliation of extremity disease is important in these patients, as median survival after diagnosis of in-transit or locally recurrent disease >2 years [3, 4]. Radical approaches to eradication of extremity recurrence are rarely used, although in a *highly* selected group of patients undergoing amputation, 42% 5-year survival was reported [5]. As greater recognition of the palliative nature of extremity therapy has evolved, an emphasis on preservation of limb function has supplanted cure as a more realistic therapeutic goal. While occasional cure can be observed, it would be misleading to propose this as the likely outcome of eradication of recurrent extremity melanoma. Isolated limb perfusion (ILP) was developed as an alternative to amputation in patients with recurrent cancer of the extremity. The concept was that vascular isolation of the limb would allow delivery of higher (and potentially more effective) doses of chemotherapy to the disease in the limb than could be achieved with systemic therapy.

Keywords: *Clinical trials, isolated limb perfusion*

Overview

The early published experiences of the use of ILP in patients with extremity malignancies are notable for the heterogeneity of the treated patients. The studies are retrospective, and the treatment goals and assessment criteria are poorly defined. Standardized measurement of disease pre-treatment was nonexistent, and pathologic documentation of response to treatment was commonly not available. The clinical assessment of the limb both pre- and post-treatment was left to the discretion of the treating surgeon. Despite this, the initial studies of ILP represent an earnest effort to move the field of cancer therapy forward and formed the basis from which the field of regional therapy for extremity disease evolved. In this paper we will highlight those trials that contributed to the evolution of regional chemotherapy of the extremity, and ultimately culminated in randomized-controlled trials that today form our treatment paradigms.

Origins of isolated limb perfusion

Creech and Krementz reported performing the first ILP at Charity Hospital, New Orleans, Louisiana, in 1958. Indeed, following their initial report the essential technical components of the procedure remained unchanged over the ensuing 50 years. Isolation of the extremity was accomplished by open surgical cannulation of the vessels at the root of the limb and use of an extracorporeal circuit to provide a high-flow, hyperoxic perfusate, thereby achieving adequate tissue perfusion pressures and allowing relatively long treatment duration [6]. The chemotherapeutic agent used was melphalan, based on

in vivo data suggesting significant antitumor activity in mice [7, 8].

The first patient treated was a 76-year-old male who developed extensive satellitosis following excision of a primary melanoma of the leg and regional lymphadenectomy 2 years previously. At the time of his initial resection his lymph nodes were negative. One year later he presented with >80 tumor deposits in the leg, but refused amputation. A normothermic ILP was performed under spinal anesthesia. The patient was systemically heparinized and access was obtained through the common femoral artery and vein. The leg was isolated with an Esmarch tourniquet proximal to the cannulated vessels. The large venous and arterial catheters were connected to a high-flow oxygenated circuit. A flow rate was established and melphalan was injected in 4 doses at 5-minute intervals, for a total perfusion time of 23 minutes. The tourniquet was then released, the vascular cannulas removed, and the vessels surgically repaired. The patient had a remarkable complete response (CR) to the treatment, eventually dying of unrelated causes 16 years later [6, 9]. Despite the enticing success of this first patient, subsequent patients reported in this initial experience demonstrated only fair results. In the 18 cases of ILP for melanoma (both adjuvant and therapeutic) there were 2 deaths, and only 1 patient had a CR. Similar responses were seen in patients with limb sarcoma, although no patient in this initial report had a CR [10].

The introduction of hyperthermia in ILP

The next advance in regional perfusion of the extremity occurred with the recognition that hyperthermia could increase the efficacy of ILP. In 1967 Cavaliere reported the tumoricidal effects of heat (>40°C) in a rat hepatoma and human melanoma cell line. He then evaluated the effects of heat alone in humans with recurrent extremity tumors using ILP. Twenty-two patients (12 with sarcoma, 7 with melanoma, 3 with other cancers) were treated with hyperthermic perfusate in the absence of chemotherapy. The duration of hyperthermia ranged from 50 minutes to >6 hours. Six patients (27%) died in the immediate postoperative period. Of the 16 survivors, however, 12 patients were alive without evidence of disease at 3 to 28 months of follow-up [11].

The next logical step was taken by Stehlin, who combined regional chemotherapy with heated perfusion and reported his experience in 50 patients undergoing both therapeutic and adjuvant ILP. He used very high temperatures, with an average perfusate temperature of 46°C. Perfusions were performed for 45 minutes to 2 hours. Patients with melanoma received melphalan and sarcoma patients received melphalan and dactinomycin. Complications were significant and included postoperative edema (70%), hemoglobinuria (20%, 2 deaths), and bleeding (18%). At an average follow-up of 18 months, 50% of the patients with sarcoma were alive without evidence of disease. However, all the sarcoma patients also received radiation pre- or post-perfusion. Of the 37 melanoma patients, only 12 were performed for measurable disease. Of these, 10 of the 12 patients (83%) had a response defined as 'pronounced regression' for ≥3 months, but whether this represented a CR is difficult to determine [12].

This initial enthusiasm for regional extremity chemotherapy administered with varying degrees of hyperthermia resulted in several decades of literature that is difficult to interpret but was characteristic of medical reporting at that time (see Figure 1 with timeline). ILP was utilized for patients with a variety
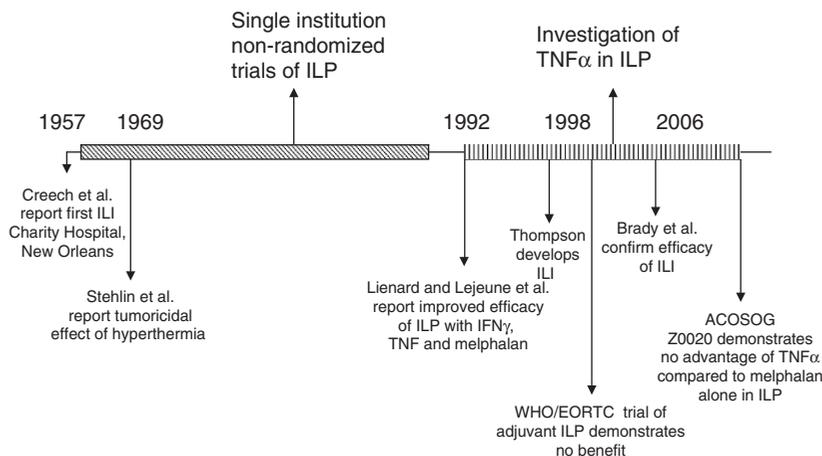

Figure 1. Milestones in the development of regional therapy for melanoma of the extremity. ACOSOG, American College of Surgeons Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; IFNγ, interferon γ; ILP, isolated limb perfusion; TNFα, tumor necrosis factor α; WHO, World Health Organization.

of tumors, using a variety of chemotherapeutic drugs, at various temperatures and treatment lengths. Reports ensued in which patients with measurable disease were treated; these were accompanied by reports of patients undergoing adjuvant perfusion due to a high risk of recurrence. In addition, efficacy was determined by survival, a less meaningful gauge of response in this highly selected patient population. We will review selected studies from this era when it is possible to distinguish between these 2 patient groups and, therefore, allow some reasonable assessment of historical response rates to ILP.

Clinical response to ILP in historical series

Many of the original ILP trials are difficult to interpret, in part because of a lack of standard staging and criteria for assessment of clinical response. At the time of the original limb perfusions by Creech, the staging systems for patients with melanoma only differentiated between local, nodal, and distant disease. The MD Anderson Staging System for Melanoma [13] (see Table I) was a 4-tiered system based on clinical evidence of disease and allowed differentiation between patients that were being evaluated for limb perfusion. Patients with stage I disease had primary melanoma, those with stage II disease had a local recurrence and regional nodal metastasis, stage III included patients with intransit metastases with or without nodal disease, and patients with stage IV disease had systemic metastases. Once adopted, this clinical staging system facilitated the interpretation of reports on the use of ILP in patients with melanoma, at least until the American Joint Committee on Cancer (AJCC) system evolved and incorporated pathologic staging. In addition, there was more consistency in evaluating what constituted a treatment response to ILP. A partial response (PR) was defined as a decrease in $\geq 50\%$ of the diameter of all lesions, without appearance of new lesions. A complete response was defined as the resolution of all visible disease [14]. Lastly, the Wieberdink scale of limb

toxicity made accurate reporting of limb morbidity following ILP more consistent (see Table II) [15].

Clinical response to therapeutic ILP

The most common patients to be treated with ILP were those with measurable extremity melanoma. Early reports and series suggested CRs in the range of 39% to 82%, and overall survival of 42% to 55%, at 5 years. These studies are listed in Table III. These relatively large series suggested that reasonable long-term survival could be associated with ILP for extremity disease. It is interesting to note the trend toward lower response rates in more recent studies, perhaps suggesting more rigorous clinical assessments.

This trend is apparent in two recent studies, one retrospective and the other prospective, that confirm a lower percentage of complete responders than has been historically reported. The first is a retrospective review of the Sydney Melanoma Unit (SMU) experience with hyperthermic ILP with melphalan alone or in combination with actinomycin-D. An additional six patients were given different combinations of treatment consisting of actinomycin alone, cisplatin alone, or actinomycin and cisplatin together. The study reported that 56% of patients experienced a CR, which differed from Thompson's earlier experience in which 73% of patients were reported to have experienced a CR. In addition, at a median follow-up of 177 months, only 18.5% of patients were alive without evidence of disease. Of the 47 patients who had a CR, however, there was a 5-year survival of 40% and a 10-year survival of 28% [16].

The second report that provides evidence of more modest expectations for a CR following therapeutic ILP was from the recently completed ACOSOG Z0020 trial. This trial was designed and conducted to determine whether the addition of tumor necrosis factor (TNF) to melphalan in ILP was associated with a higher response compared with melphalan alone. One hundred and three patients were

Table I. MD Anderson staging for melanoma.

I	A Primary only
	B Primary excised
	C Multiple primaries
II	Local recurrence (within 3cm of primary)
III	A In-transit recurrence (no nodes)
	B Regional nodal recurrence (no in-transit)
	C In-transit and regional nodal recurrences
IV	A Distant cutaneous metastases
	B Distant visceral metastases

Table II. Wieberdink Toxicity Scale.

Grade	Description
I	No reaction
II	Slight edema or erythema
III	Considerable edema or erythema with blistering and slight motility reduction
IV	Extensive epidermolysis or damage to the deep tissues, causing important functional disturbances, threatening or manifest as compartmental syndrome
V	Major tissue damage necessitating amputation

randomized to hyperthermic ILP with melphalan versus melphalan and TNFα. Response rates were similar in both arms, with a CR in 25% of patients receiving melphalan and in 26% of patients receiving combination therapy. This trial demonstrated that in a carefully conducted prospective trial with accurate measurement of pre- and post-treatment disease, OR rates of 64% and CR rates of 25% can be anticipated with hyperthermic ILP for patients with melanoma [17].

Experience with adjuvant limb perfusion

The use of ILP as an adjuvant therapy for patients with high-risk extremity melanoma was first reported in 1975 by McBride and colleagues. This retrospective study included 202 patients with clinically localized melanoma invasive to at least the reticular dermis who underwent adjuvant ILP with melphalan. Of these, 92 patients were identified with ≥10 years of follow-up. The outcomes of these patients were compared with those of 71 patients with clinically localized melanoma treated at the same hospital but during an earlier era. The cases were not matched and the adjuvant ILP group had a higher percentage of females compared with the historical control group. In addition, the only characterization of the original melanoma is that it was 'invasive to the level of the reticular dermis'. While there was no significant difference in disease-free survival at 2 or 5 years, at 10 years the disease-free survival was better in patients who underwent adjuvant ILP (72% versus 45%, respectively; $P = 0.05$) [13].

Another retrospective study was published in 1988 that reported a large experience of adjuvant ILP in patients with extremity melanoma >1.5 mm in Breslow depth. Two-hundred twenty-seven patients underwent ILP at the time of wide excision and were compared to patients from a similar geographic area who underwent excision alone. There was no significant difference in 5-year disease-free survival between the groups. A secondary aim of the study was to identify, through multivariate analysis, the prognostic factors for survival, recurrence, and time to metastasis. This confirmed that Breslow thickness, patient age, Clark level of invasion, gender, and tumor ulceration were significant factors for survival. When the two groups were re-analysed again, adjusting for these prognostic features, there was still no difference in survival [18].

The first single-institution randomized trial of adjuvant ILP was reported in 1984. One hundred and seven patients with extremity melanoma ≥1.5 mm Breslow depth and at least Clark's level IV were randomized to either wide local excision (WLE) with regional node dissection alone or in combination with hyperthermic ILP (42°C) with melphalan. After a mean follow-up of 550 days the study was stopped because of fewer recurrences in the ILP group. Of the 107 patients in the study there were 21 recurrences in the control group and only four in the adjuvant ILP group ($P = 0.0001$) [19]. When retrospectively matched for MD Anderson stage of disease [1], the adjuvant ILP group had significantly fewer recurrences, although the number of patients in the WLE group with recurrence was higher than expected for early stage disease. For example, in MD Anderson stage I disease the control group had a recurrence rate of 28% (versus 7% in the perfusion group), and stage II patients had a recurrence rate of 32% (versus 6% in the perfusion group), which were much higher than rates seen today for patients with stage I disease treated with surgery alone. The survival benefit for patients undergoing adjuvant ILP was maintained at 5 years, with 11 versus 3 patients dead of disease in the control and ILP groups, respectively ($P < 0.01$) [20].

This issue was subsequently addressed in a randomized, controlled trial performed over a 10-year period by a collaborative effort with the European Organization for Research and Treatment of Cancer (EORTC), the World Health Organization (WHO), and North American Perfusion Group Southwest Oncology Group (SWOG). Patients with extremity melanoma ≥1.5 mm thick, without evidence of distant disease, in-transit disease, or nodal

Table III. Response rates and survival following therapeutic ILP with melphalan in patients with melanoma.

Study	Patients	Conditions	CR (%)	PR (%)	OS (%)
Di Filippo 1989[39]	69	Hyperthermia	39	43	54.5 IIIA 47.3 IIIB at 5 years
Storm 1985[40]	26	Hyperthermia	50	31	NA
Minor 1985[41]	18	Hyperthermia	82	18	NA
Kroon 1987[42]	18	Normothermia	38	44	NA
Kroon 1993[43]	43	Normothermia	77	14	50 at 3 years
Klasse 1994[44]	120	Normothermia	54	25	42 at 5 years
Sanki* 2007[16]	120	Hyperthermia	56	15	18.5 at 177 months

CR, complete recovery; ILP, isolated limb perfusion; PR, partial recovery; NA, not applicable.
*Randomized controlled trial.

disease, were randomized to wide local excision ($n = 422$) or wide local excision with ILP ($n = 430$). Limb perfusion was performed with melphalan and hyperthermia for 1 h. While there was a decrease in local recurrence after ILP, after a median follow-up of 6.4 years, there was no difference in survival or time to development of distant metastasis[2]. As a result of this trial, ILP was no longer recommended as an adjuvant treatment for patients with extremity melanoma. Results of these trials are summarized in Table IV.

ILP with agents other than melphalan

Other chemotherapeutic agents have been evaluated for efficacy in ILP since it was first introduced. These include dimethyltriazeno imidazole carboxamide (DTIC), cisplatin, carboplatin, and thiotepa. The most experience has been with cisplatin, an inhibitor of DNA synthesis with significant potential for nephro- and neurotoxicity. When used in patients with at least MD Anderson stage IIIA melanoma, ILP with cisplatin resulted in 47% 5-year survival in 145 patients [21]. Additional series reported 11% CR at 3 years with high morbidity; 10% required an amputation and 20% had severe tissue toxicity [22, 23]. DTIC is another agent that has been used in ILP. Toxicity was low, but response rates were also lower than seen with melphalan, with 12% of patients having a CR and 29% experiencing a PR to ILP with DTIC [24]. In a retrospective, descriptive series of patients treated with therapeutic ILP with primarily DTIC or carboplatin, 26% of patients had a sustained CR at a median follow-up of 58 months (range 8 months to 17 years) [25]. Unfortunately, there is a lack of phase I or phase II trials to clarify the role of these other drugs, and melphalan remains the standard treatment.

Use of immune agents in ILP

Investigations into the mechanisms of Bacillus Calmette-Guerin (BCG) therapy led to the discovery of important cytokines involved in immunoregulation. Injections of mice with BCG and endotoxin resulted in release of a factor that induced necrosis in a murine model of sarcoma within 24 hours, with approximately 20% of the tumors disappearing completely [26]. This factor was called TNF and was later purified by protein separation [27]. Further studies demonstrated that the addition of interferon (IFN) α, β, or γ to TNFα had a synergistic tumoricidal effect in murine models [28].

Correlative studies in human trials with systemic TNFα therapy resulted in severe side effects similar to those seen in septic shock, which limited its utility. In ILP, however, the toxicity of systemic TNFα exposure could be abrogated by vascular isolation of the limb, making it an appealing agent. In addition, TNFα was felt to facilitate the efficacy of chemotherapy by its effects on tumor and normal vasculature and thereby allow increased exposure of tumor to chemotherapeutic agents [29].

Posner was the first to use TNFα in a human trial of ILP. In this study 6 patients received escalating doses of only TNFα during hyperthermic ILP. Only 1 patient had a CR that lasted 7 months, and 2 patients had a PR of <1 month duration [30]. Despite the disappointing results of TNFα alone, further treatment based on encouraging laboratory studies resulted in a phase II trial combining high-dose TNFα, IFNγ, and melphalan in ILP. Interferon was added because of potential antitumor synergism [28, 31]. Nineteen patients had MD Anderson stage IIIA or IIIB melanoma with measurable recurrent extremity disease. Overall the tumor burden was large, with a median of 10 lesions per patient (range 1 to >100). An additional 4 patients had recurrent sarcoma. The treatment was toxic; all patients had a systemic inflammatory response requiring dopamine prophylaxis. Two patients required an amputation due to limb toxicity. At a mean follow-up of 11 months, however, 89% of patients ($n = 21$) had a CR and 11% ($n = 2$) had a PR to the combination treatment [32]. This initial report resulted in tremendous interest in the addition of TNFα to ILP, resulting in many single-institution,

Table IV. Adjuvant ILP with hyperthermia and melphalan in patients with melanoma.

Study	Patients	Number in trial		5-year survival (DF) (%)		Comments
		WLE	WLE + ILP	WLE	WLE + ILP	
McBride 1975[13]	≥Clark III	71	92	55	76	$P = 0.1$
Ghussen 1984[19], 1989[20]	≥1.5mm, ≥Clark IV	54	53	52	88.7	$P = 0.001$ RCT
Franklin 1988[18]	≥1.5mm	238	227	73	77	$P = 0.9$
Koops 1998[2]	≥1.5mm	412	420	62	62	RCT
Edwards 1990[45]	>2mm	150	149	77	84	0.33
		25	25	44	85	$P < 0.01$

DF, disease free; RCT, randomized controlled trial; WLE, wide local excision.

nonrandomized trials (Table III). The role of IFN as a component of the ILP was separately addressed in a phase II trial. Sixty-four patients were randomized to receive TNFα and melphalan alone or in combination with IFNγ. No significant benefit was observed with the addition of IFN (CR 69% versus 78%; not significant), and its use has subsequently waned [33].

The role of TNFα in ILP has recently been addressed by a prospective, randomized trial conducted by the American College of Surgeons Oncology Group (ACOSOG) of ILP using melphalan alone compared with melphalan and TNFα. One hundred and three patients with recurrent melanoma of the extremity were enrolled. The trial was stopped early because at interim analysis there was no evidence of improved efficacy in the melphalan/TNFα arm but 2 patients in the group required amputation (25% CR with melphalan versus 26% CR with melphalan and TNFα; $P = 0.89$). At 6 months, only 89 patients were evaluated; however, there remained no significant improvement with the addition of TNFα (42% CR with combination versus 20% in single therapy; $P = 0.101$). Overall complications were not significantly higher in patients receiving combination therapy (33% had adverse events of at least grade 3 with melphalan alone versus 37% with melphalan and TNF), however the rate of grade 4 adverse events occurred in 1% of the melphalan-alone arm and in 11% of the melphalan/TNFα arm. In addition, there was one amputation secondary to disease progression in the melphalan group, whereas the combination therapy resulted in 2 patients with amputations secondary to toxicity [17, 34]. This trial had been criticized for the early time point for assessing response (3 months) and for the lower response rates observed with TNFα compared with prior trials (Table V). In addition, the original analysis allowed for 12% of patients to be excluded from the analysis for various reasons. However, when analysed again with intention-to-treat analysis, there still was not a statistical difference between groups [34]. The results of this trial, as well as the difficulty obtaining TNFα for ILP in the United States, make it unlikely TNFα will continue to be evaluated in ILP in the United States.

Development of isolated limb infusion

The most significant recent advance in the field of regional chemotherapy for extremity tumors occurred with the development of isolated limb infusion (ILI) by John Thompson of SMU [35]. ILI offers several distinct advantages over ILP, particularly with regard to ease of performance. While response rates have not been directly compared, the experiences from SMU as well as MSKCC suggest that ILI may supplant ILP as the standard regional chemotherapy approach for most patients [35, 36].

ILI is performed by placing angiographic catheters into the involved limb via the contralateral extremity. This obviates the need for open surgical cannulation of the vessels. A blood pressure cuff inflated to 350 mm Hg and positioned at the most proximal portion of the involved limb is used to isolate the extremity from the systemic circulation. Melphalan and dactinomycin are rapidly infused into the arterial catheter, and then the limb infusate (chemotherapy and limb blood volume) is manually circulated through a blood warmer using manual pressure. After 20 to 30 minutes a crystalloid infusion followed by venous outflow extraction serves to flush the extremity of chemotherapy, and the procedure is terminated. Since a membrane oxygenator pump is not used the infusion is low flow, normothermic, hypoxic, and acidotic. No pump priming is required, the duration of the procedure is short, and patients who may not tolerate ILP due to comorbid conditions can be treated with ILI. In addition, the procedure can be repeated with more ease than ILP. While hyperthemia cannot be achieved due to

Table V. Trials with tumor necrosis factor (TNF) in melanoma and sarcoma.

Study	Additional Agent	Patients	CR (%)	PR (%)	Comments
Lienard 1992[32]	Melphalan, IFNγ	23 Stage IIIA, Stage IIIAB bulky melanoma or recurrent sarcoma	89	11	
Vaglini 1994[24]	Melphalan, IFNγ	11 Stage IIIA melanoma	64	NA	One death from multiorgan failure
Fraker 1996[46]	Melphalan, IFNγ	26 Stage IIIA/IIIAB melanoma	76	16	
Eggermont 1996[47]	Melphalan, IFNγ	186 sarcoma	18	57	IFNγ first 55 patients only
Grunhagen 2004[48]	Melphalan	87, in-transit melanoma	69	26	Good response with high disease burden
Noorda 2004[49]	Melphalan	90 unresectable melanoma	59	NA	No increased response in increase tumor burden
Rossi 2004[50]	Melphalan	20	70	25	
Cornett 2006[17]	Melphalan +/- TNFα	64 melphalan	25	39	$P = 0.89$ (for CR)
		65 melphalan + TNFα (3–4 mg)	26	43	

CR = complete recovery; IFN = interferon; NA = not applicable; PR = partial recovery.

the absence of a high-flow heated circuit, acidosis and hypoxia may actually serve to increase melphalan activity [37].

Thompson's group reported the first experience with ILI in 1998. They treated patients with recurrent melanoma of the extremity or recurrent sarcoma. Of the 82 patients who had a minimum of 6 months follow-up, 39% had a CR and 52% had a PR, with a median follow-up of 16 months [38]. This data was substantiated by Brady and colleagues, who reported a phase II trial of ILI with melphalan and dactinomycin in patients with stage IIIB or IIIC melanoma or unresectable soft tissue sarcoma. In this study, at 1 year 23% of patients had a CR with a median duration of 12 months, and 27% had a PR with a median duration of 11 months [36].

Conclusion

The field of extremity chemotherapy for soft tissue tumors has evolved substantially over the last 50 years, although until recently the technical components of the procedure remained essentially the same. As the palliative nature of the procedure has been increasingly recognized, a shift toward less morbid and less invasive approaches has occurred. The development and acceptance of ILI for patients with cancer of the extremity will facilitate testing of new agents for regional therapy due to its ease of performance and tolerability. Perhaps when used in conjunction with efficacious systemic approaches, regional therapy can move from a palliative approach to extremity disease to a strategy in which regional tumor necrosis will facilitate eradication of occult systemic disease.

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