



Michele R. Sassi. *Tribal Face of Rajasthan, India*. Photograph, 2007.

*The current treatment strategies for unresectable in-transit and recurrent extremity melanoma are reviewed.*

## Therapy for Unresectable Recurrent and In-Transit Extremity Melanoma

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**Background:** Unresectable recurrent and in-transit extremity melanoma presents a dilemma for the treating physician. While the disease is confined to the involved limb, the survival mimics that of multiple nodal metastases, with a 10-year survival rate of approximately 40%. This represents late-stage disease for which curative treatment options are limited.

**Methods:** To review the current treatment strategies for stage IIIB (N2c) in-transit and recurrent melanoma focusing on the options for unresectable disease, MEDLINE was searched for studies of known and experimental treatments for in-transit and recurrent extremity melanoma. Further results were obtained after review of the initial citations.

**Results:** For unresectable recurrences and in-transit metastases, therapies are limited to palliative (radiation), local (intratumoral injection, laser ablation and electroporation), regional (isolated limb perfusion/infusion), and systemic (chemotherapy) when local or regional techniques are not feasible.

**Conclusions:** In this patient population, intratumoral techniques have a limited role with current treatment regimens, but with the development of new drugs, these techniques may have more utility. If not contraindicated, regional techniques provide the greatest control and have minimal operative morbidity. Until new regimens are available, systemic therapy continues to be associated with considerable toxicity and only marginal response rates.

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**Abbreviations used in this paper:** BCG = bacille Calmette-Guérin, TNF- $\alpha$  = tumor necrosis factor-alpha, CR = complete response, PR = partial response, ILI = isolated limb infusion, ILP = isolated limb perfusion.

### Introduction

In-transit metastases from extremity melanoma are subcutaneous or cutaneous deposits of melanoma distant from the primary site but not reaching the draining nodal basin. While this is not considered stage IV disease, survival outcomes mimic those associated with advanced regional nodal disease, with 5-year survival rates of 24% to 54%.<sup>1</sup> Therapy for this pattern of recurrence is limited and options vary based on the volume of disease in the affected limb. Definitive surgical resection remains the preferred therapeutic approach. However, when surgery cannot be performed with a

reasonable cosmetic and functional outcome, other options must be utilized. This article reviews the current options available for treating unresectable recurrent and in-transit metastases of extremity melanoma.

## Radiation Therapy

Historically, melanoma was considered a radioresistant disease due to a lack of response observed with in vitro cultures treated with external-beam radiation.<sup>2</sup> Clinical experience does not support the in vitro data. Early studies evaluating the palliative effects of radiation demonstrated overall response rates of 60% to 79% for stage III disease.<sup>3,4</sup> While appropriate protocols for fractionated radiation are variable in that the dose per fraction, the number of fractions, and the time course of the fractionated therapy have not been standardized, symptomatic control is obtained for the majority of patients.<sup>4,7</sup> Only 9% achieve a complete response (CR) to radiation therapy, however, and even those who do will still develop distant metastases.<sup>5,7</sup> Although metastatic disease ultimately develops, some studies show that patients undergoing radiation (either higher fractions or higher total doses) have a significantly longer disease-free survival and overall survival (8 months vs 2 months).<sup>5</sup> The population most likely to benefit in this fashion are those with a complete initial response to radiation.<sup>4,5,7</sup> Therefore, while the precise algorithm for radiation therapy is still in evolution for recurrent or in-transit disease, there appears to be some benefit to using radiation to control disease and possibly prolong survival in patients who are not candidates for surgery or regional chemotherapy.

## Carbon Dioxide Laser Ablation

In patients who develop low-volume, multifocal, in-transit metastases, carbon dioxide laser therapy can be a valuable treatment adjunct and, in some reports, is a useful first-line modality.<sup>8,9</sup> As the volume of individual metastases increases, laser therapy becomes less effective and more difficult to perform. Larger lesions penetrate deeper into the subcutaneous tissue, diminishing the effectiveness of laser therapy while leaving a larger defect to heal. However, numerous small lesions may be easily treated, and reports of up to 450 small metastases have been ablated on an individual patient.<sup>9</sup> Treatments may be performed in an outpatient setting, and only local anesthesia is required. Wound healing rates are acceptable, with studies reporting almost all wounds healed by 6 weeks.<sup>9,10</sup> Ablations can be repeated multiple times; however, as the volume of disease increases, other modalities should be considered. Carbon dioxide laser ablation has been used both as a primary treatment modality, with regional therapies used for progressive disease, and as a salvage procedure after regional therapies have failed. The major limitation of laser therapy is that it can be used to treat only visible and superficial subcutaneous disease,

while deep subcutaneous lesions, large volume lesions, and microscopic disease cannot be treated. Nevertheless, laser therapy does provide excellent local control and can be used for both treatment and palliation of low-volume, multifocal extremity metastases.

## Intralesional Therapies

### *Bacille Calmette-Guérin*

Bacille Calmette-Guérin (BCG) was the first commonly utilized agent for intralesional injections in the setting of in-transit metastases. In 1974, Morton et al<sup>11</sup> reported their experience with intralesional injections of BCG. Regression occurred in 90% of the cutaneous lesions that were injected with BCG, and 17% of the patients injected had regression of uninjected nodules. They achieved a 31% disease-free survival at 6 to 74 months after injection. Later studies demonstrated improved local response rates with intralesional BCG injections, but the local complications in and around the injection site were severe. While local response rates were improved, survival results from these randomized control trials were inconsistent.<sup>12-14</sup> A subgroup analysis by Veronesi et al<sup>15</sup> showed improved survival in patients who converted to a positive BCG reaction from no initial reaction. In a large Eastern Cooperative Oncology Group (ECOG) trial (E1673) involving more than 700 patients, a survival difference in patients who received BCG with or without dacarbazine compared to the observation arm could not be identified.<sup>16</sup> In contrast to observations from data from Veronesi et al,<sup>15</sup> a subset analysis of the ECOG trial was not able to identify a difference in survival in patients who converted to a positive reaction after receiving BCG. Because of the associated injection-site morbidity and the inability to identify a survival benefit, intralesional injection with BCG has largely been abandoned in the management of in-transit metastases.

### *Interleukin-2*

Interleukin-2 (IL-2), a cytokine with a wide array of immunomodulatory effects, has been widely studied over the past 20 years. Atkins et al<sup>17</sup> reviewed 270 patients treated with high-dose IL-2 and demonstrated a 16% overall response rate (6% CR and 10% partial [PR]) for all sites. They achieved a median duration of response of more than 54 months for CRs and 8.3 months for PRs. This led the US Food & Drug Administration (FDA) to approve high-dose IL-2 for the treatment of stage IV melanoma. In a subsequent study, low-dose IL-2 was evaluated as adjuvant therapy with interferon in node-negative intermediate-thickness melanomas, but this study showed no difference in the observation arm compared with the treatment arm.<sup>18</sup> IL-2 has also been analyzed in combination with chemotherapy (known as biochemotherapy), and these results are mixed. However, in each of the phase III trials, biochemotherapy vs chemotherapy alone did not yield any significant difference in outcomes

except for increased grade 4 toxicities.<sup>19,20</sup> These toxicities limit the effectiveness of systemic IL-2.

Intralesional IL-2 therapy was studied for patients with soft-tissue as well as in-transit metastases. In a 2003 pilot study, Radny et al<sup>21</sup> evaluated intralesional IL-2 as salvage therapy for patients who failed surgery, perfusion, radiotherapy, or chemotherapy. CR rates were achieved in 15 of 24 patients and PR rates in 5 patients. Toxicities were mainly grades 1 and 2. The longest remission at that time was 38 months for patients with CR. In total, 209 of 245 metastases underwent CR, with progression of 7 cutaneous/subcutaneous metastases. Similarly, in a report from Germany, 2 patients who were not operative candidates and had multiple in-transit metastases received intralesional IL-2 with complete remission of their disease. Only local toxicities were seen and no systemic side effects occurred.<sup>22</sup> IL-2, as a local therapy, may be a useful adjunct for treatment of in-transit metastases or recurrent melanoma, but as with intralesional BCG, the time-intensive nature of this modality may be prohibitive. Further investigation is warranted.

### **Electroporation**

Electroporation, also known as electrochemotherapy (ECT), creates cell membrane defects or porations by generating short, high-intensity electrical pulses. These porations increase cell permeability and allow the increased uptake of cytotoxic drugs that are administered prior to the electrical pulsations. Moreover, the electrical stimulation causes a local vasoconstriction (limited to less than 24 hours), which allows the chemotherapy to increase its local activity prior to its clearance from the surrounding tissues.<sup>23,25</sup> The two drugs shown to have the highest efficacy when used with ECT are bleomycin and cisplatin. Their intracellular activity is potentiated more than 1,000-fold for bleomycin and 100-fold for cisplatin.<sup>26</sup> Intratumoral ECT with bleomycin yielded CR rates of 77% compared to 45% when given intravenously. Similarly, ECT with cisplatin compared to intravenous administration yielded CR rates of 67% and 48%, respectively.<sup>27</sup> Response rates from intratumoral injections of bleomycin with and without ECT decreased from 78% to 32% when electrochemotherapy was not utilized.<sup>28</sup> Subsequent reports of ECT for melanoma and other cutaneous tumors were consistent with the aforementioned studies and supported ECT as an effective modality, but treatment techniques varied widely.<sup>29</sup> Therefore, a multicenter study performed by the European Standard Operating Procedures for Electrochemotherapy (ESOPE) defined the parameters for using ECT with multiple histologies and varying chemotherapeutic agents. They achieved a response rate of approximately 85% in their study regardless of the drug used or the route of administration.<sup>30,31</sup>

The indications for ECT, which are similar to other intralesional techniques, are primarily for cutaneous

metastases that cannot be excised due to the number or location of the tumors. A major advantage of ECT is that it can be used in previously irradiated areas. It can also be employed to improve the quality of life in patients who have bleeding or painful lesions, and it may improve cosmesis.<sup>23,29</sup> Adverse effects of ECT are limited to minor irritation at the injection site and an “electric shock” sensation from the pulse current. These effects are transient and minimal, and the procedure can be performed in an outpatient setting with no need for local, regional, or general anesthesia.<sup>32</sup>

### **TNFERade**

Tumor necrosis factor-alpha (TNF- $\alpha$ ) is a potent immune system regulator with tumoricidal properties.<sup>33</sup> The use of TNF- $\alpha$  is limited secondary to its severe toxicities when given systemically.<sup>34</sup> One mechanism utilized to overcome these toxicities was to clone the TNF- $\alpha$  gene into a nonreplicating adenovirus downstream from a radiation and chemotherapy-induced promoter (Egr-1) and deliver it directly into the tumor.<sup>35</sup> This adenovirus complex is known as TNFERade.

TNFERade is synergistic with radiation in that the combination effect is greater than either modality alone with no resultant increase in normal tissue damage.<sup>36</sup> A phase I study by Senzer et al<sup>37</sup> evaluated multiple tumor types with TNFERade and radiation. They demonstrated pathologic CR in 3 melanoma patients, including a patient who previously had no response to radiation alone. Likewise, McLoughlin et al<sup>38</sup> evaluated 3 patients with advanced melanoma who had a CR after TNFERade with a durable response of at least 2 years. Building on these trials, MacGill et al<sup>39</sup> evaluated a preclinical mouse model of metastatic melanoma and demonstrated that TNFERade, in addition to the effects of local treatment, reduces distant disease. These early clinical trials support the use of TNFERade for extremity in-transit disease, but larger clinical trials are needed to validate its use for regional and distant metastases.

### **Systemic Chemotherapy**

Systemic chemotherapy with or without biochemotherapy for melanoma has modest response rates at best (11.4% to 17.1%).<sup>40,41</sup> This modality is usually selected for distant metastatic disease and not for locoregional control; however, there are some circumstances where systemic chemotherapy may be appropriate. Patients who have high-volume in-transit disease may be candidates for chemotherapy since purely local or intralesional therapies are not realistic. Similarly, systemic chemotherapy becomes an option for patients who are not surgical candidates for regional therapies such as limb perfusion or infusion.

Dacarbazine has been the standard for chemotherapeutic agents in metastatic melanoma and the only one approved by the FDA, and yet the treatment responses

are limited and not durable. A response rate of only 20% with a median duration of response of 4 to 6 months has been reported.<sup>42</sup> Temozolomide, an oral chemotherapeutic agent with the same metabolite as dacarbazine, has been shown to be of equivalent efficacy to that of dacarbazine and with a similar toxicity profile.<sup>43</sup>

Combination chemotherapies have been shown to have improved outcomes in single center studies, but they also have associated increased toxicities. However, as data from larger trials are evaluated, these data seen in the single institution studies have not been reproduced, and the response rates appear to be equivalent or marginally better — approximately 18% for combined therapy vs about 10% for dacarbazine alone ( $P = \text{NS}$ ).<sup>44-47</sup> Therefore, since the response rates and duration of response are limited with chemotherapy, other modalities should be considered for the treatment of locoregional recurrence or in-transit metastases for melanoma.

## Regional Therapies

### *Hyperthermic Isolated Limb Perfusion*

Hyperthermic isolated limb perfusion (HILP) as described by Creech et al<sup>48</sup> in 1958 is a regional treatment for in-transit metastases using high-dose chemotherapy or biochemotherapy bypassing the systemic complications. This surgical procedure entails dissecting and isolating the external iliac vessels for the lower extremity or the axillary vessels for the upper extremity. Regional node dissection can be performed if clinically indicated at the time of vascular dissection. The vessels are directly cannulated and the limb is isolated via a tourniquet. The chemotherapy is then infused and recirculated through the limb via a cardiopulmonary bypass machine to reheat and re-oxygenate the removed blood. This allows for drug concentrations 15 to 25 times higher in the target tissue than what can be achieved systemically. This technique effectively excludes the bone marrow and gastrointestinal tract from the perfusion circuit and spares the patient the common toxicities of systemic chemotherapy. Similarly, the perfusate is washed out from the limb with 2 liters of a balanced electrolyte solution, and the liver and kidney are not exposed to the harmful effects of metabolizing and excreting the chemotherapy.<sup>49,50</sup> Isolation of the limb also allows regional hyperthermia to be achieved, which has been shown to augment the effects of the delivered chemotherapy.<sup>51</sup> HILP for melanoma is usually performed under a mild hyperthermia (38° to 40° C). While raising the basal temperature increases response rates, it can also increase regional toxicities.<sup>52,53</sup>

The chemotherapeutic agents most widely used in HILP are melphalan (United States and Europe) and TNF- $\alpha$  (Europe alone). Early studies comparing melphalan to other antineoplastic agents demonstrated that melphalan was a significantly better chemotherapeutic agent with improved response rates.<sup>54,55</sup> While

dacarbazine has the greatest effect against melanoma when given systemically for metastatic disease, it is less effective than melphalan when administered regionally.<sup>56,57</sup> Outcomes from multiple studies yield typical CR rates for melphalan HILP between 50% to 70%, with recurrences rates of 40% to 50% if CR is achieved.<sup>49,58-60</sup> When TNF- $\alpha$  is added to melphalan, improved CR rates of 60% to 80% have been reported, but the data are not uniform and the patient inclusion criteria differ among studies.<sup>61,62</sup> A recent multicenter randomized trial by the American College of Surgeons Oncology Group (ACOSOG Trial Z0020) of HILP with melphalan vs melphalan with TNF- $\alpha$  showed CR rates of only 25% and 26%, respectively, far below what had been previously reported.<sup>63</sup> They also reported a significantly higher number of complications with melphalan plus TNF- $\alpha$  vs melphalan alone (16% vs 4% grade IV adverse events,  $P = .04$ ). These data have been refuted by Lejeune and Eggermont<sup>64</sup> in a correspondence stating that these results were reported after only a 3-month interval follow-up, which is inadequate to assess the true response of HILP. They also noted that the patient and tumor characteristics were not delineated in the study so the target group may not have been applicable to the utilized treatment paradigm. It will be interesting to evaluate the data at longer outcome timepoints to see if TNF- $\alpha$  did in fact impact the CR of melphalan. At this time, however, TNF- $\alpha$  is not approved for regional therapy of in-transit metastases in the United States.

Morbidities from HILP with or without TNF- $\alpha$  can be significant and are due to the local effects of the chemotherapy itself, the application of hyperthermia, the systemic leak of the chemotherapy from the isolated limb, or the surgical intervention. The local effects include skin and soft-tissue damage ranging from mild erythema and epidermolysis to extensive tissue damage requiring fasciotomy that results in a limb amputation rate of 0.5% to 1.5%.<sup>63,65,66</sup> Vascular complications occur in up to 10% of patients and are due to stenosis and/or thrombosis at the arteriotomy/venotomy site or to deep venous thrombosis (DVT) formation with a resultant pulmonary embolus.<sup>67-69</sup> Lymphedema is the most commonly reported morbidity and occurs at a frequency of 12% to 36%. This occurs in the acute setting and persists years after the perfusion.<sup>70-72</sup> Groin dissection performed at the time of perfusion increases this risk.<sup>73</sup> Tissue temperatures higher than 40° C or a greater concentration of melphalan are significant risk factors for developing local tissue damage.<sup>74</sup>

Systemic effects such as myelosuppression and hypotension occur when the melphalan perfusate leaks from the isolated limb or when the washout is incomplete. If TNF- $\alpha$  is used in the perfusate, then the toxicities can be even more severe.<sup>49,63</sup> This necessitates the continuous monitoring of chemotherapy leakage from the limb during the perfusion using a radiolabeled trac-

er that can be measured systemically. If leakage occurs, the resultant increase in systemic radioactivity will be detected at a point distant from the isolated limb and the perfusion can be halted if necessary. Lastly, the surgical morbidity is well defined for any lymph node basin dissection that includes but is not limited to infection, lymphedema, and paraesthesias.<sup>8</sup>

### Isolated Limb Infusion

Isolated limb infusion (ILI) as described by Thompson et al<sup>75</sup> from the Sydney Melanoma Unit is the minimally invasive counterpart to isolated limb perfusion (ILP), which appears to be of similar efficacy but more easily performed. Instead of surgical exposure of the iliac or axillary vessels, vascular access is obtained in the radiology department via a percutaneous route in the groin (the contralateral groin if dealing with lower extremity in-transit metastases) and into the vessels feeding the affected limb. The leg is prewarmed with a warming blanket prior to bringing the patient to the operating room. Prewarming decreases the amount of time under general anesthesia. A pneumatic tourniquet is placed on the proximal aspect of the limb to “isolate” the limb from the systemic circulation. The temperature is monitored through temperature probes placed in the extremity, and once temperatures of 38° to 40° C are achieved, the infusion is begun. Like ILP, the chemotherapy is circulated through an extracorporeal circuit with a heating coil, then into the arterial catheter, and subsequently removed through the venous catheter to be rewarmed and recirculated. Unlike ILP, ILI is performed in an acidotic and hypoxic milieu, which has been shown to augment the effects of melphalan.<sup>76</sup>

Clinical results for ILI demonstrated CR rates of 23% to 44% and PR rates of 27% to 56%. Median duration of responses ranged between 12 to 18 months.<sup>75,77-80</sup> However, if CR was achieved, the median duration of response was 24 months compared with 9 months if PR was achieved. Median survival times were significantly longer if CR was achieved vs PR (42 vs 32 months,  $P = .04$ ).<sup>78</sup> The lower rates of 23% for CR and 27% for PR seen by

Brady et al<sup>77</sup> may be attributed to treating patients with a higher volume of disease and to using a shorter infusion time. Otherwise, the remainder of the studies reported outcomes similar to results achieved with ILP. Zager et al<sup>81</sup> reported on a series of 64 patients with a median follow-up of 12 months. The authors reported a 68% overall response with 32% complete responders.

The morbidity from ILI differs significantly from ILP. Surgical access is not required, and patients with serious comorbidities can still undergo ILI. In the operating room, the duration of general anesthesia for ILI is limited, and the need for blood transfusions has practically been eliminated. While the regional toxicities of ILI and ILP are comparable, the systemic toxicities do not appear to be equivalent. The routine use of a pneumatic tourniquet prevents the systemic leakage of chemotherapy from the limb, and the washout of the chemotherapy prior to deflating the tourniquet removes most of the remaining chemotherapy.<sup>75</sup> Unlike ILP, given the minimal invasiveness of ILI, patients who have progression of disease after therapy can receive a second infusion with minimal morbidity. Access to the affected limb can be obtained percutaneously weeks to months after the primary infusion with no increased complications. There is a significant increase in regional toxicity with a second infusion, but a high rate of response can be achieved.<sup>79</sup>

The morbidity of ILI in the postoperative setting is well defined. Nausea is commonplace but appears to be the only systemic toxicity reported. Myelosuppression and hypotension are rarely seen. Up to 52% of patients will experience nausea, but with the perioperative use of 5-HT<sub>3</sub> receptor blockers, the amount has been curtailed and is limited to the first 24 to 48 hours.<sup>75</sup> Inflammation and erythema become most evident peritumorally, but erythema and edema of the extremity distal to the tourniquet is expected to some degree in all patients.<sup>77</sup> Mild to severe pain in the limb has also been reported, but these local toxicities are self-limited and resolve within 3 months to 1 year.<sup>77,79</sup> Unlike ILP, there were no reported grade V toxicities<sup>82</sup> when melphalan



Figure. — Development of severe grade III regional toxicity 6 days after an ILI (A), which subsequently resolved by the patient's 3-month postoperative follow-up visit (B). Photographs courtesy of Keith A. Delman, MD.

was used as a sole agent. However, the addition of other chemotherapeutic agents as well as repeat infusions increased the grade V toxicities to up to 28% in those who underwent repeated ILI. The incidence of grade V toxicity associated with ILI has not been reported frequently in the literature.<sup>83</sup> The Figure shows the development of severe grade III regional toxicity 6 days after an ILI that subsequently resolved by the patient's 3-month postoperative follow-up visit.

Monitoring for early postoperative tissue toxicities includes a physical examination to evaluate any changes in the treated extremity, including increasing tenseness overlying the muscle groups, increasing pain and erythema, epidermolysis, and sensorimotor deficits. Twice-daily creatine kinase (CK) levels are drawn. As noted by Lindner et al,<sup>78</sup> the risk of developing severe limb toxicity increases with CKs greater than 1,000 IU; however, multiple patients develop CKs of greater than 1,000 IU with no manifestations of severe limb toxicity requiring intervention. We note at both our institutions that CK values peak around 72 to 96 hours and then decrease gradually. Both institutions aggressively hydrate the patients to limit the nephrotoxic effects of myoglobinuria. Zager et al<sup>81</sup> suggest that intravenous corticosteroids may help after an ILI to lessen the regional inflammatory response in the muscle from reperfusion injury. Decadron 4 to 6 mg every 6 hours intravenously may lead to less postoperative edema, erythema, and extremity pain.<sup>74</sup> The authors usually use corticosteroids after CK values peak over 1,000 U/L or if the infused leg develops severe edema and erythema that is uncomfortable to the patient in the absence of compartment syndrome symptoms.<sup>65,74</sup> The corticosteroids are tapered as the symptoms abate and the CK levels come down towards baseline. If any evidence of compartment syndrome arises, a fasciotomy should be performed early in the course to decrease the risk of limb loss. Patients are ambulatory by day 2 and are monitored for at least 4 days or longer if there is a significant increase in the CK value.

## Conclusions

When in-transit metastases of melanoma are not amenable to surgical resection, various modalities can be utilized to treat this disease. The potential advantages of each therapy must be weighed against the toxicity of the therapy itself and of the biologic or chemotherapeutic agents used. Radiation therapy should be used only in the palliative setting. Carbon dioxide laser therapy has a role for small-volume, visible disease. Unlike BCG, newer intralesional injection agents are promising, with minimal apparent side effects, but the ability to treat innumerable lesions is limited. ILP is indicated for advanced locoregional recurrences, but the procedure is maximally invasive and the leakage of the chemotherapy or biologic agent remains a worrisome outcome,

especially with the use of TNF- $\alpha$ . ILI is a minimally invasive procedure that can be repeated with ease and the initial toxicities are limited and well described.

No randomized, controlled trials have compared these different modalities and, currently, there is no standard of care for treating these patients. We believe that each modality can play a role in treating unresectable recurrent and in-transit melanoma, but the use of ILI is well tolerated, effective for disease control, and easily repeatable.

## Disclosures

*No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.*

## References

1. Balch CM, Soong SJ, Atkins MB, et al. An evidence-based staging system for cutaneous melanoma. *CA Cancer J Clin*. 2004;54(3):131-149; quiz 182-184.
2. Barranco SC, Romsdahl MM, Humphrey RM. The radiation response of human malignant melanoma cells grown in vitro. *Cancer Res*. 1971;31(6):830-833.
3. Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. *Int J Radiat Oncol Biol Phys*. 1991;20(3):429-432.
4. Seegenschmiedt MH, Keilholz L, Altendorf-Hofmann A, et al. Palliative radiotherapy for recurrent and metastatic malignant melanoma: prognostic factors for tumor response and long-term outcome. A 20-year experience. *Int J Radiat Oncol Biol Phys*. 1999;44(3):607-618.
5. Olivier KR, Schild SE, Morris CG, et al. A higher radiotherapy dose is associated with more durable palliation and longer survival in patients with metastatic melanoma. *Cancer*. 2007;110(8):1791-1795.
6. Overgaard J, Overgaard M, Hansen PV, et al. Some factors of importance in the radiation treatment of malignant melanoma. *Radiation Oncol*. 1986;5(3):183-192.
7. Konefal JB, Emami B, Pilepich MV. Malignant melanoma: analysis of dose fractionation in radiation therapy. *Radiology*. 1987;164(3):607-610.
8. Hayes AJ, Clark MA, Harries M, et al. Management of in-transit metastases from cutaneous malignant melanoma. *Br J Surg*. 2004;91(6):673-682.
9. Hill S, Thomas JM. Use of the carbon dioxide laser to manage cutaneous metastases from malignant melanoma. *Br J Surg*. 1996;83(4):509-512.
10. Gibson SC, Byrne DS, McKay AJ. Ten-year experience of carbon dioxide laser ablation as treatment for cutaneous recurrence of malignant melanoma. *Br J Surg*. 2004;91(7):893-895.
11. Morton DL, Eilber FR, Holmes EC, et al. BCG immunotherapy of malignant melanoma: summary of a seven-year experience. *Ann Surg*. 1974;180(4):635-643.
12. Cohen MH, Jessup JM, Felix EL, et al. Intralesional treatment of recurrent metastatic cutaneous malignant melanoma: a randomized prospective study of intralesional Bacillus Calmette-Guérin versus intralesional dinitrochlorobenzene. *Cancer*. 1978;41(6):2456-2463.
13. Quirt IC, DeBoer G, Kersey PA, et al. Randomized controlled trial of adjuvant chemoimmunotherapy with DTIC and BCG after complete excision of primary melanoma with a poor prognosis or melanoma metastases. *Can Med Assoc J*. 1983;128(8):929-933.
14. Tan JK, Ho VC. Pooled analysis of the efficacy of bacille Calmette-Guérin (BCG) immunotherapy in malignant melanoma. *J Dermatol Surg Oncol*. 1993;19(11):985-990.
15. Veronesi U, Adamus J, Aubert C, et al. A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med*. 1982;307(15):913-916.
16. Agarwala SS, Neuberg D, Park Y, et al. Mature results of a phase III randomized trial of bacillus Calmette-Guérin (BCG) versus observation and BCG plus dacarbazine versus BCG in the adjuvant therapy of American Joint Committee on Cancer Stage I-III melanoma (E1673): a trial of the Eastern Oncology Group. *Cancer*. 2004;100(8):1692-1698.
17. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999;17(7):2105-2116.
18. Hauschild A, Weichenthal M, Balda BR, et al. Prospective randomized trial of interferon alfa-2b and interleukin-2 as adjuvant treatment for resected intermediate- and high-risk primary melanoma without clinically detectable node metastasis. *J Clin Oncol*. 2003;21(15):2883-2888.

19. Keilholz U, Punt CJ, Gore M, et al. Dacarbazine, cisplatin, and interferon- $\alpha$ -2b with or without interleukin-2 in metastatic melanoma: a randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. *J Clin Oncol*. 2005;23(27):6747-6755.
20. Rosenberg SA, Yang JC, Schwartzentruber DJ, et al. Prospective randomized trial of the treatment of patients with metastatic melanoma using chemotherapy with cisplatin, dacarbazine, and tamoxifen alone or in combination with interleukin-2 and interferon  $\alpha$ -2b. *J Clin Oncol*. 1999;17(3):968-975.
21. Radny P, Caroli UM, Bauer J, et al. Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. *Br J Cancer*. 2003;89(9):1620-1626.
22. Pföhler C, Steinhäuser S, Wagner A, et al. Complete remission of cutaneous satellite and in-transit metastases. After intralesional therapy with interleukin-2 in 2 patients with malignant melanoma [in German]. *Hautarzt*. 2004;55(2):171-175.
23. Larkin JO, Collins CG, Aarons S, et al. Electrochemotherapy: aspects of preclinical development and early clinical experience. *Ann Surg*. 2007;245(3):469-479.
24. Gehl J, Skovsgaard T, Mir LM. Vascular reactions to in vivo electroporation: characterization and consequences for drug and gene delivery. *Biochim Biophys Acta*. 2002;1569(1-3):51-58.
25. Sersa G, Cemazar M, Parkins CS, et al. Tumour blood flow changes induced by application of electric pulses. *Eur J Cancer*. 1999;35(4):672-677.
26. Orłowski S, Bełehradek J Jr, Paoletti C, et al. Transient electroporation of cells in culture: increase of the cytotoxicity of anticancer drugs. *Biochem Pharmacol*. 1988;37(24):4727-4733. Epub 2007 Jul 5.
27. Sersa G, Miklavcic D, Cemazar M, et al. Electrochemotherapy in treatment of tumours. *Eur J Surg Oncol*. 2008;34(2):232-240. Epub 2007 Jul 5.
28. Byrne CM, Thompson JF, Johnston H, et al. Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy). *Melanoma Res*. 2005;15(1):45-51.
29. Giardino R, Fini M, Bonazzi V, et al. Electrochemotherapy a novel approach to the treatment of metastatic nodules on the skin and subcutaneous tissues. *Biomed Pharmacother*. 2006;60(8):458-462. Epub 2006 Aug 14.
30. Marty M, Sersa G, Garbay JR, et al. Electrochemotherapy: an easy, highly effective and safe treatment of cutaneous and subcutaneous metastases. Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. *Eur J Cancer Suppl*. 2006;4(13):3-13.
31. Mir LM, Gehl J, Sersa G, et al. Standard operating procedures of the electrochemotherapy: instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the Cliniporator(TM) by means of invasive or non-invasive electrodes. *Eur J Cancer Suppl*. 2006;4(11):14-25.
32. Rols MP, Bachaud JM, Giraud P, et al. Electrochemotherapy of cutaneous metastases in malignant melanoma. *Melanoma Res*. 2000;10(5):468-474.
33. McDermott MF. TNF and TNFR biology in health and disease. *Cell Mol Biol (Noisy-le-grand)*. 2001;47(4):619-635.
34. Chapman PB, Lester TJ, Casper ES, et al. Clinical pharmacology of recombinant human tumor necrosis factor in patients with advanced cancer. *J Clin Oncol*. 1987;5(12):1942-1951.
35. Rasmussen H, Rasmussen C, Lempicki M, et al. TNFerade biologic: preclinical toxicology of a novel adenovector with a radiation-inducible promoter, carrying the human tumor necrosis factor alpha gene. *Cancer Gene Ther*. 2002;9(11):951-957.
36. Hallahan DE, Maucrier HJ, Seung LP, et al. Spatial and temporal control of gene therapy using ionizing radiation. *Nat Med*. 1995;1(8):786-791.
37. Senzer N, Mani S, Rosemurgy A, et al. TNFerade biologic, an adenovector with a radiation-inducible promoter, carrying the human tumor necrosis factor alpha gene: a phase I study in patients with solid tumors. *J Clin Oncol*. 2004;22(4):592-601. Epub 2004 Jan 15.
38. McLoughlin JM, McCarty TM, Cunningham C, et al. TNFerade, an adenovector carrying the transgene for human tumor necrosis factor alpha, for patients with advanced solid tumors: surgical experience and long-term follow-up. *Ann Surg Oncol*. 2005;12(10):825-830. Epub 2005 Aug 9.
39. MacGill RS, Davis TA, Macko J, et al. Local gene delivery of tumor necrosis factor alpha can impact primary tumor growth and metastases through a host-mediated response. *Clin Exp Metastasis*. 2007;24(7):521-531. Epub 2007 Jul 25.
40. Atkins MB, Lee S, Flaherty LE, et al. A prospective randomized phase III trial of concurrent biochemotherapy (BCT) with cisplatin, vinblastine, dacarbazine (CVD), IL-2 and interferon  $\alpha$ -2b (IFN) versus CVD alone in patients with metastatic melanoma (E3695): an ECOG-Coordinated Intergroup trial. *Proc Annu Meet Am Soc Clin Oncol*. 2003;22:708. Abstract 2847.
41. Flaherty LE, Olencki TE, Stover L. A patient with metastatic melanoma. *Melanoma Care Options*. 2005(3). <http://www.melanomacare.org/pdfs/issue03.pdf>. Accessed March 26, 2008.
42. Anderson CM, Buzaid AC, Legha SS. Systemic treatments for advanced cutaneous melanoma. *Oncology (Williston Park)*. 1995;9(11):1149-1158; discussion 1163-1164, 1167-1168.
43. Quirt I, Verma S, Petrella T, et al. Temozolomide for the treatment of metastatic melanoma: a systematic review. *Oncologist*. 2007;12(9):1114-1123.
44. Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol*. 1999;17(9):2745-2751.
45. Del Prete SA, Maurer LH, O'Donnell J, et al. Combination chemotherapy with cisplatin, carmustine, dacarbazine, and tamoxifen in metastatic melanoma. *Cancer Treat Rep*. 1984;68(11):1403-1405.
46. Legha SS, Ring S, Papadopoulos N, et al. A prospective evaluation of a triple-drug regimen containing cisplatin, vinblastine, and dacarbazine (CVD) for metastatic melanoma. *Cancer*. 1989;64(10):2024-2029.
47. Margolin KA, Liu PY, Flaherty LE, et al. Phase II study of carmustine, dacarbazine, cisplatin, and tamoxifen in advanced melanoma: a Southwest Oncology Group study. *J Clin Oncol*. 1998;16(2):664-669.
48. Creech O Jr, Krementz ET, Ryan RF, et al. Chemotherapy of cancer: regional perfusion utilizing an extracorporeal circuit. *Ann Surg*. 1958;148(4):616-632.
49. Fraker DL. Management of in-transit melanoma of the extremity with isolated limb perfusion. *Curr Treat Options Oncol*. 2004;5(3):173-184.
50. Grunhagen DJ, de Wilt JH, Graveland WJ, et al. Outcome and prognostic factor analysis of 217 consecutive isolated limb perfusions with tumor necrosis factor- $\alpha$  and melphalan for limb-threatening soft tissue sarcoma. *Cancer*. 2006;106(8):1776-1784.
51. Stehlin JS, Giovanella BC, de Ipolyi PD, et al. Results of hyperthermic perfusion for melanoma of the extremities. *Surg Gynecol Obstet*. 1975;140(3):339-348.
52. Di Filippo F, Calabrò A, Giannarelli D, et al. Prognostic variables in recurrent limb melanoma treated with hyperthermic antilimbic perfusion. *Cancer*. 1989;63(12):2551-2561.
53. Kroon BB, Klaase JM, van Geel AN, et al. Application of hyperthermia in regional isolated perfusion for melanoma of the limbs. *Reg Cancer Treat*. 1992;4:223-226.
54. Fraker DL. Hyperthermic regional perfusion for melanoma and sarcoma of the limbs. *Curr Probl Surg*. 1999;36(11):841-907.
55. Thompson JF, Gianoutsos MP. Isolated limb perfusion for melanoma: effectiveness and toxicity of cisplatin compared with that of melphalan and other drugs. *World J Surg*. 1992;16(2):227-233.
56. Aigner K, Hild P, Henneking K, et al. Regional perfusion with cisplatin and dacarbazine. *Recent Results Cancer Res*. 1983;86:239-245.
57. Vaglini M, Belli F, Marolda R, et al. Hyperthermic antilimbic perfusion with DTIC in stage IIIA-IIIAB melanoma of the extremities. *Eur J Surg Oncol*. 1987;13(2):127-129.
58. Klaase JM, Kroon BB, van Geel AN, et al. Prognostic factors for tumor response and limb recurrence-free interval in patients with advanced melanoma of the limbs treated with regional isolated perfusion with melphalan. *Surgery*. 1994;115(1):39-45.
59. Vroenenraets BC, Hart GA, Eggermont AM, et al. Relation between limb toxicity and treatment outcomes after isolated limb perfusion for recurrent melanoma. *J Am Coll Surg*. 1999;188(5):522-530.
60. Vroenenraets BC, Nieweg OE, Kroon BB. Thirty-five years of isolated limb perfusion for melanoma: indications and results. *Br J Surg*. 1996;83(10):1319-1328.
61. Fraker DL, Alexander HR, Andrich M, et al. Treatment of patients with melanoma of the extremity using hyperthermic isolated limb perfusion with melphalan, tumor necrosis factor, and interferon gamma: results of a tumor necrosis factor dose-escalation study. *J Clin Oncol*. 1996;14(2):479-489.
62. Liénard D, Eggermont AM, Kooops HS, et al. Isolated limb perfusion with tumor necrosis factor- $\alpha$  and melphalan with or without interferon-gamma for the treatment of in-transit melanoma metastases: a multicentre randomized phase II study. *Melanoma Res*. 1999;9(5):491-502.
63. Cornett WR, McCall LM, Petersen RP, et al. Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumor necrosis factor: American College of Surgeons Oncology Group Trial Z0020. *J Clin Oncol*. 2006;24(25):4196-4201.
64. Lejeune FJ, Eggermont AM. Hyperthermic isolated limb perfusion with tumor necrosis factor is a useful therapy for advanced melanoma of the limbs. *J Clin Oncol*. 2007;25(11):1449-1450; author reply 1450-1451.
65. Lens MB, Dawes M. Isolated limb perfusion with melphalan in the treatment of malignant melanoma of the extremities: a systematic review of randomised controlled trials. *Lancet Oncol*. 2003;4(6):359-364.
66. Vroenenraets BC, Eggermont AM, Hart AA, et al. Regional toxicity after isolated limb perfusion with melphalan and tumor necrosis factor- $\alpha$  versus toxicity after melphalan alone. *Eur J Surg Oncol*. 2001;27(4):390-395.
67. Eggimann P, Chiroló R, Chassot PG, et al. Systemic and hemodynamic effects of recombinant tumor necrosis factor alpha in isolation perfusion of the limbs. *Chest*. 1995;107(4):1074-1082.
68. Hoven-Gondrie ML, Thijssens KM, Van den Dungen JJ, et al. Long-term locoregional vascular morbidity after isolated limb perfusion and external-beam radiotherapy for soft tissue sarcoma of the extremity. *Ann Surg Oncol*. 2007;14(7):2105-2112. Epub 2007 Apr 25.
69. Noorda EM, Vroenenraets BC, Nieweg OE, et al. Isolated limb perfusion with tumor necrosis factor- $\alpha$  and melphalan for patients with unresectable

soft tissue sarcoma of the extremities. *Cancer*. 2003;98(7):1483-1490.

70. Grünhagen DJ, van Etten B, Brunstein F, et al. Efficacy of repeat isolated limb perfusions with tumor necrosis factor alpha and melphalan for multiple in-transit metastases in patients with prior isolated limb perfusion failure. *Ann Surg Oncol*. 2005;12(8):609-615. Epub 2005 Jun 22.

71. Möller MG, Zager JS, Lewis JM, et al. Single agent experience of hyperthermic isolated limb perfusion of extremity sarcomas. *Ann Surg Oncol*. 2007;14(2):72.

72. Vrouenraets BC, Keus RB, Nieweg OE, et al. Complications of combined radiotherapy and isolated limb perfusion with tumor necrosis factor alpha +/- interferon gamma and melphalan in patients with irresectable soft tissue tumors. *J Surg Oncol*. 1997;65(2):88-94.

73. Noorda EM, Vrouenraets BC, Nieweg OE, et al. Repeat isolated limb perfusion with TNFalpha and melphalan for recurrent limb melanoma after failure of previous perfusion. *Eur J Surg Oncol*. 2006;32(3):318-324. Epub 2006 Jan 18.

74. Thompson JF, Eksborg S, Kam PC, et al. Determinants of acute regional toxicity following isolated limb perfusion for melanoma. *Melanoma Res*. 1996;6(3):267-271.

75. Thompson JF, Kam PC, Waugh RC, et al. Isolated limb infusion with cytotoxic agents: a simple alternative to isolated limb perfusion. *Semin Surg Oncol*. 1998;14(3):238-247.

76. Siemann DW, Chapman M, Beikirch A. Effects of oxygenation and pH on tumor cell response to alkylating chemotherapy. *Int J Radiat Oncol Biol Phys*. 1991;20(2):287-289.

77. Brady MS, Brown K, Patel A, et al. A phase II trial of isolated limb infusion with melphalan and dactinomycin for regional melanoma and soft tissue sarcoma of the extremity. *Ann Surg Oncol*. 2006;13(8):1123-1129. Epub 2006 Jun 21.

78. Lindnér P, Doubrovsky A, Kam PC, et al. Prognostic factors after isolated limb infusion with cytotoxic agents for melanoma. *Ann Surg Oncol*. 2002;9(2):127-136.

79. Lindnér P, Thompson JF, de Wilt JH, et al. Double isolated limb infusion with cytotoxic agents for recurrent and metastatic limb melanoma. *Eur J Surg Oncol*. 2004;30(4):433-439.

80. Mian R, Henderson MA, Speakman D, et al. Isolated limb infusion for melanoma: a simple alternative to isolated limb perfusion. *Can J Surg*. 2001;44(3):189-192.

81. Zager JS, Gershenwald JE, Aldrink J, et al. Isolated limb infusion for locally recurrent and in-transit extremity melanoma: a multi-institutional experience. *Ann Surg Oncol*. 2006;13(2):75. Abstract.

82. Wieberdink J, Benckhuysen C, Braat RP, et al. Dosimetry in isolation perfusion of the limbs by assessment of perfused tissue volume and grading of toxic tissue reactions. *Eur J Cancer Clin Oncol*. 1982;18(10):905-910.

83. Bonenkamp JJ, Thompson JF, de Wilt JH, et al. Isolated limb infusion with fotemustine after dacarbazine chemosensitisation for inoperable loco-regional melanoma recurrence. *Eur J Surg Oncol*. 2004;30(10):1107-1112.