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MELANOMA (KB KIM, SECTION EDITOR)

Current Treatment of Locoregional Recurrence of Melanoma

Malcolm Hart Squires III · Keith A. Delman

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Abstract Surgical resection is the mainstay of therapy for locoregional recurrence of melanoma and the best chance for long-term cure in patients with locoregional recurrence of melanoma. In addition to true local recurrence at the site of the primary lesion, locoregional relapse can occur as regional nodal disease or as satellite or in-transit metastases, which may be unresectable and can present significant treatment challenges. Options for unresectable locoregional recurrence include regional hyperthermic isolated limb perfusion or isolated limb infusion, topical therapies, intralesional injection therapies, laser ablation, radiation therapy, and systemic therapy. Given the risk of further relapse and the negative impact on prognosis and overall survival after locoregional recurrence of melanoma, most patients should be considered for aggressive locoregional therapy.

Keywords Melanoma · Recurrence · Locoregional · Isolated limb perfusion · Isolated limb infusion · Electrochemotherapy

Introduction

The incidence of melanoma continues to increase, with more than 76,000 newly diagnosed patients and more than 9,000 deaths projected annually in the USA [1]. Although most patients are diagnosed early and have disease confined to the primary lesion, up to 25 % of patients may ultimately develop recurrent disease locally or in regional lymph nodes [2]. Surgical resection carries the best chance of long-term survival, not only for early, newly-diagnosed melanoma, but also for local and regional recurrent disease.

M. H. Squires III · K. A. Delman (✉)
Department of Surgery, Division of Surgical Oncology, Winship Cancer Institute, Emory University, 1365C Clifton Road NE, 2nd Floor, Atlanta, GA 30322, USA
e-mail: kdelman@emory.edu

Locoregional recurrence of melanoma after initial resection is defined as recurrence locally at the site of the primary lesion, regionally in the draining lymph node basin, and/or anywhere in between. By convention, this recurrence is in the absence of distant metastatic disease. Local recurrence can represent either "persistent" disease due to inadequate initial excision or true recurrence adjacent to the scar after adequate prior wide local excision [2]. True local recurrence likely represents dermal lymphatic spread of malignant cells and is associated with worse prognosis [3]. Although overall rates of local recurrence are 2-3 % in large series, the risk of local recurrence increases significantly as the thickness of the primary melanoma increases and with the presence of ulceration [2, 4, 5]. Local recurrence, in turn, is significantly associated with increased risk of subsequent recurrence as in-transit, regional, and distant metastatic disease [2, 6].

Locoregional recurrence can also occur as in-transit metastases, defined as cutaneous or subcutaneous recurrence proximal to the primary lesion site and distal to the regional lymph node basin [7]. These locoregional cutaneous and subcutaneous metastases were historically distinguished by their distance from the site of the primary lesion, with local recurrence comprising any lesions occurring within 2 cm of the initial lesion and in-transit metastases recurring more than 2 cm from the primary lesion, although this distinction was shown to have no bearing on prognosis [8]. As opposed to distant superficial metastases resulting from hematogenous spread of disease, in-transit metastases represent tumor dissemination within the dermal and subdermal lymphatics [9, 10]. Up to 10 % of patients may ultimately develop in-transit superficial recurrent disease following wide local excision of their primary melanoma lesion, with a mean time to recurrence of 16 months [4, 9]. Both satellite and in-transit metastases are considered stage IIIB (without regional nodal metastases) or stage IIIC (with regional nodal metastases) disease by the most recent American Joint Committee on Cancer staging system and are associated with worse prognosis than local

recurrence [11]. Risk factors for in-transit recurrence include increasing depth, mitotic rate, and ulceration of the primary lesion and an initial positive sentinel lymph node (SLN) biopsy [9, 12, 13]. Patients with in-transit metastases are, in turn, at significant risk of further locoregional and distant recurrence [4, 12].

Regional lymph nodes are a more common site of recurrence than either local or in-transit recurrent disease [2, 4]. Regional nodal recurrence rates of 3-9 % have been reported for patients following negative SLN biopsies, with increasing thickness and ulceration of the primary melanoma lesion and lesions located on the head or neck associated with greater risk of recurrence [14–17]. Patients with a positive initial SLN biopsy, by contrast, may have rates of regional recurrence as high as 35 %, with early recurrence associated with ulceration and greater depth of the primary melanoma, head/neck location, and greater number and greater size of positive lymph nodes on initial SLN biopsy and lymphadenectomy [18]. Independent prognostic factors for overall survival after locoregional recurrence of melanoma include features of the original primary lesion, such as thickness and presence of ulceration, and the stage of recurrence, namely, local, in-transit, or regional lymph node recurrence [4].

Surgical resection is the mainstay of therapy for locoregional recurrence of melanoma and is associated with the best outcomes. Options for unresectable locoregional recurrence, particularly in-transit metastases, include regional hyperthermic isolated limb perfusion (HILP) or isolated limb infusion (ILI), topical therapies, intralesional injection therapies, laser ablation therapies, radiation therapy, and systemic therapy. Systemic therapy can always be considered in patients with locoregional recurrence, particularly patients with unresectable disease or those who are candidates for enrollment in a clinical trial, but is outside the scope of this review and will not be discussed.

Surgical Management of Local and In-Transit Recurrence

Isolated local recurrence, once confirmed by biopsy, is best treated with re-excision, with National Comprehensive Cancer Network (NCCN) guidelines advocating 2-cm margins, although this margin selection has never been thoroughly investigated [19]. On the basis of subsequent pathologic staging of the thickness and ulceration of the excised recurrence, SLN biopsy may be indicated [19].

As in the case of local recurrence, surgical resection remains the first-line therapy for in-transit recurrent melanoma once biopsy or fine-needle aspiration biopsy has confirmed recurrent disease. Cosmetic appearance or function may preclude adequate resection, however, or patients may not be suitable candidates for surgical therapy. In these cases, other treatment options should be considered depending on the number and size of the lesions, the anatomic region (extremity versus trunk or head and neck location), and the dermal or subcutaneous location of the lesions [20].

NCCN guidelines recommend patients with biopsy-confirmed locoregional recurrence undergo staging with cross-sectional imaging, typically positron-emission tomography (PET), computed tomography (CT), or PET/CT to evaluate them for distant disease [19]. If workup reveals no evidence of extraregional disease, resection with negative margins is the standard of care. Recommendations for resection margins in wide local excision of primary melanoma do not apply in the setting of in-transit metastatic disease, and no studies have addressed the potential benefit of additional margin beyond a complete excision with R0 microscopically negative margins [19]. Individual, well-circumscribed lesions can be narrowly excised, with some groups advocating a 0.5-cm margin [10]. Multifocal locoregional metastases can be resected en bloc if their location is amenable to such an approach. When feasible, primary closure is preferable, although skin grafting or flap closure may be necessary to provide adequate coverage [21].

Particularly if patients have not previously undergone regional lymphadenectomy, many authorities advocate consideration of SLN biopsy in patients with resectable in-transit disease [22, 23]. Even in the setting of prior SLN biopsy or lymph node dissection, SLN biopsy for patients with recurrent in-transit disease may prove beneficial and guide decisions regarding regional therapy [24]. An SLN biopsy in the setting of in-transit disease may provide prognostic value; one study reported a significantly worse disease-free survival for patient with a positive SLN biopsy (16 months) versus patients with a negative SLN biopsy (36 months) [22]. Despite these data, others (including the authors) are cautious about applying SLN biopsy in the setting of stage IIIB or greater disease (local or in-transit recurrence) since the prognosis and treatment of these patients are largely driven by the recurrence itself.

Surgical Management of Regional Nodal Recurrence

Patients with clinical suspicion of regional nodal recurrence should undergo fine-needle aspiration biopsy to confirm the diagnosis. Subsequent workup should then include staging PET/CT to rule out distant disease, including a pelvic CT scan for patients with clinically positive inguinofemoral lymph nodes. Complete lymph node dissection is indicated for patients who have not had a prior lymphadenectomy or who have previously undergone incomplete lymphadenectomy. As outlined by the NCCN guidelines, completion lymphadenectomy should entail “anatomically complete dissection of the involved nodal basin” [19]. For patients who have undergone previous lymphadenectomy, excision of the recurrence is still indicated, if feasible.

Axillary lymphadenectomy should include formal dissection of levels I, II, and III [25–27]. Since by definition, recurrence in the inguinal nodal basin represents "clinically macrometastatic disease," patients should undergo an inguinofemoral, deep iliac and obturator pelvic lymph node dissection [28]. Regional recurrence in the cervical lymph node basin requires a modified radical neck dissection that encompasses at least levels II, III, IV, and V [25, 29]. In patients with recurrent disease confined to the regional lymph node basin, completion lymphadenectomy offers the best potentially curative treatment option and can provide excellent long-term survival for select patients [30].

Following complete lymph node dissection for recurrent regional nodal disease, adjuvant radiation therapy may improve locoregional control [31]. In randomized controlled trials of patients at risk of nodal field relapse following therapeutic lymphadenectomy in the neck, axilla, or groin, adjuvant radiation therapy demonstrated significant reductions in regional recurrence rates, although it had no impact on disease-free or overall survival [32••, 33]. The addition of adjuvant radiation therapy does increase the frequency of postoperative lymphedema following axillary and groin dissections, an important morbidity to consider in these patients [34].

Regional Therapy: Hyperthermic Isolated Limb Perfusion

HILP, first described in the 1950s by Creech et al. [35], is a regional therapy for unresectable locoregional recurrence or in-transit metastases of the extremities involving high-dose chemotherapy. The procedure requires the dissection, isolation, and cannulation of the major artery and vein of the limb, either the external iliac or femoral vessels for the lower extremity or the axillary or brachial vessels for the upper extremity [36]. If indicated, therapeutic regional lymphadenectomy can be performed during HILP as the vessels are exposed. By isolating the limb proximally with a tourniquet, one can deliver high concentrations of chemotherapy regionally without it entering the systemic circulation, thereby avoiding most systemic toxicities. With use of an oxygenated extracorporeal circuit in order to maintain normal oxygenation and normal acid–base balance, the limb is perfused for 60–90 min with chemotherapy, typically the alkylating agent melphalan, before the perfusate is washed out [36]. Mild regional hyperthermia augments the effects of the melphalan and minimizes subcutaneous vasoconstriction [37].

HILP can be associated with significant morbidity, ranging from mild skin and soft-tissue effects in the treated extremity to severer vascular complications or compartment syndrome or even limb loss [36, 38•]. The commonest complication is lymphedema, the risk of which increases if completion lymph node dissection is performed concurrently [39]. A randomized prospective American College of Surgeons Oncology Group trial comparing HILP with melphalan alone versus melphalan plus tumor necrosis factor alpha found no improvement in response rates and significantly increased toxicity associated with the addition of tumor necrosis factor alpha; this combination is, therefore, rarely used [40]. Clinical response may be slow to develop following HILP, but complete response rates greater than 50 % and overall response rates of 80 % have been reported [38•, 41, 42]. Patients exhibiting a complete response can demonstrate durable long-term results and improved overall survival [43].

Isolated Limb Infusion

ILI is a simpler, less invasive alternative to HILP for the treatment of in-transit extremity metastases that was first proposed by Thompson et al. [44] in the 1990s. Rather than open, surgical exposure of the extremity vessels, vascular access to the artery and vein is obtained percutaneously, via the contralateral femoral or iliac vessels in the case of lower-extremity ILI [42]. Under fluoroscopic guidance, 5 F or 6 F arterial and venous catheters are then positioned appropriately in the vessels of the limb to be treated, with the catheter tip typically at the level of the knee or elbow joint [42]. As in HILP, a proximal tourniquet is placed to isolate the affected limb from the systemic circulation and the extremity is warmed externally. An extracorporeal circuit is connected to the catheters for circulation of chemotherapy, but no supplemental oxygenation is provided. Unlike in HILP, the low-pressure circulation in ILI, typically performed for 30 min, creates a hypoxic and acidotic environment in the extremity, increasing the efficacy of melphalan [45].

Overall response rates for ILI ranging from 43 to 88 % have been reported, with complete response rates of 30-41 % [38•, 42, 45, 46]. Although the overall regional morbidity of HILP and is comparable to that of ILI, ILI is associated with a much lower risk of severe limb-threatening complications and systemic toxicities [38•, 47]. The advantages of ILI include the shorter operative time, the minimally invasive approach, significantly decreased risk of major complications involving the treated limb, and the ability to easily repeat the procedure for subsequent recurrences [38•, 42]. The disadvantages of ILI for the treatment of locoregional recurrent melanoma include its ability to treat less overall area of the affected extremity and the lower clinical response rates and shorter durability of response compared with HILP [36]. No prospective comparisons of HILP versus ILI have been conducted, and although no survival difference between the two treatments has been demonstrated, a complete response to either modality is associated with improved overall survival [38•, 47, 48].

For patients with unresectable lower-extremity recurrence and concurrent pelvic lymph node disease, an algorithm proposed by Beasley et al. [47] advocates first-line HILP, to make possible the performance of a completion lymphadenectomy as the external iliac and femoral vessels are exposed. For all other patients with unresectable in-transit metastases localized to an extremity, Beasley et al. [47] advocate ILI as the first-line regional therapy. HILP can then be used as a salvage therapy for patients who fail to respond to ILI [24]. For patients with progressive disease following regional therapy, another HILP or ILI can be a safe and efficacious procedure, with complete response rates of 20-45 % reported, although toxicities were noted to increase [46, 49, 50]. PET/CT has not been proven effective at predicting response to regional therapy, although a recent study demonstrated that posttherapy surveillance scans detected subclinical distant disease or regional nodal disease outside the treatment field that was still amenable to resection in 47 % of patients [51•].

Topical Therapy

Diphencyprone (DPCP) is a topical immunotherapy agent that functions as a contact sensitizer and is commonly used in the treatment of alopecia and warts [52]. Preliminary research suggests that the immunomodulatory effects of DPCP may involve upregulation of the T_H17 lymphocyte pathway [53]. Several small series of patients undergoing weekly topical application of DPCP, either alone or in combination with other agents, for treatment of superficial in-transit melanoma metastases have reported encouraging partial and complete response rates for extensive recurrences not suitable for other therapies [54, 55]. Durable responses of 54 months, 30 months, 17 months, and 9 months, respectively, were reported for the four patients with a complete response among one study cohort of seven patients [55].

Imiquimod is a topically applied immunomodulator and Toll-like receptor agonist that has also been explored for the treatment of in-transit melanoma metastases [52]. Imiquimod has been shown to activate Toll-like receptor 7 and induce cytokine secretion that leads to downstream activation of effector cells and T_H1 lymphocytes [56, 57]. Several small series investigating topical application once or twice daily either alone or in combination with other agents such as topically administered 5-fluorouracil have reported regression rates of 50-90 % for superficial lesions treated over the course of months [58, 59].

Intralesional Therapy

Intralesional therapy involves the direct injection of a therapeutic agent into the melanoma lesion and is most commonly used for subcutaneous and intradermal recurrent or in-transit lesions not amenable to surgical resection. A potential advantage of this approach is the ability to induce a systemic immune response against melanoma antigens as a de facto autologous vaccine, thereby inducing regression of other lesions [10]. Additionally, agents can be delivered directly into lesions at much higher concentrations locally, with less risk of systemic toxicity [52].

The first description of intralesional immunotherapy for melanoma was reported by Morton et al. [60] using bacille Calmette–Guérin (BCG) in the 1970s. They reported regression rates of 90 % for intradermal lesions into which BCG had been injected, along with 17 % for regional lesions into which BCG had not been injected. More recently, combination therapy with injected BCG and topically administered imiquimod in a small cohort of patients demonstrated complete regression in 56 % of patients, and when combined with surgical resection of solitary resistant lesions in an additional 33 % of patients, it provided a durable response [61].

Intralesional Immunotherapy

In addition to its role as a systemic agent, interleukin-2 (IL-2) has been explored as an intralesional immunotherapy for in-transit metastatic melanoma, with the ability to deliver significantly greater local concentrations by direct injection than standard systemic treatment can safely reach. Several small series have demonstrated clinical response in more than 50 % of patients and 80-90 % of lesions into which IL-2 had been injected, although response rates in untreated regional lesions were less impressive [10, 62, 63]. Combination therapies with topical agents such as imiquimod have also shown promise, as deeper subcutaneous lesions less responsive to imiquimod demonstrated significant regression to injected IL-2 [64].

Granulocyte–macrophage colony stimulating factor (GM-CSF) has been used as intralesional immunotherapy with encouraging results, and intralesional vaccination with an oncolytic herpes simplex virus encoding GM-CSF, constructed to selectively replicate in tumor cells and secrete GM-CSF, is now being investigated [65, 66]. Patients exhibiting a response to direct intralesional injection of this virus construct have demonstrated increased dendritic cell activity locally and decreased numbers of regulatory T cells and suppressor T cells in lesions into which the virus construct had been injected, along with increased antigen-specific T cells both locally and systemically [66]. An objective response rate of 28 % was reported in a phase II trial of 50 patients, and interim results of the phase III Oncovex (GM-CSF) Pivotal Trial in Melanoma (OPTIM) involving 436 patients with stage IIIB, IIIC, or IV melanoma demonstrated an objective response rate of 26.4 %, with improved durable response rates and prolonged time to treatment

failure achieved with vaccination versus subcutaneous injection of GM-CSF alone [67, 68].

Other cytokines, including interferon-α and interferon-β, have also been investigated as intralesional therapeutic agents [69, 70]. Another promising agent administered as intralesional injections is rose Bengal (PV-10), a chemoablative agent that in vitro and in vivo studies have shown to be both directly cytotoxic to melanoma cells and immune response stimulating, as demonstrated by regression rates of 40 % in regional lesions into which rose Bengal had not been injected [71]. Additional intralesional immunotherapies include velimogene aliplasmid (Allovectin), an injectable plasmid agent encoding the heavy chain (HLA-B7) and light chain (β_2-microglobulin) of major histocompatibility complex class I [72]. Direct injection of the plasmid increases major histocompatibility complex class I expression on tumor cells, stimulating immune system recognition of foreign melanoma antigens and inducing antitumor responses in both lesions into which the plasmid had been injected locally and untreated distant lesions [73]. Following encouraging phase I and phase II trial results, a phase II trial of velimogene aliplasmid has completed accrual and interim results are expected [72, 74].

Laser Therapy

Local therapy with lasers for multifocal, superficial in-transit disease is a minimally morbid, well-tolerated treatment for patients with lesions not amenable to surgical resection. Phototherapy with a pulsed dye laser is a treatment option at some institutions for visible, superficial intradermal lesions, particularly when lesions are located on the head, neck, or trunk, sites not amenable to other regional therapies such as limb infusion [10]. The laser lyses tumor cells and induces a local inflammatory response, and can be combined with topical agents or other modalities to achieve local control of micrometastases or for palliation [75]. Carbon dioxide laser ablation offers another therapeutic option for low-volume, multifocal superficial metastases [76]. Carbon dioxide laser ablation may allow treatment of more deeply extending lesions, although wound healing becomes a concern with targeting of larger-volume disease [39].

Electrochemotherapy

Electrochemotherapy combines high-intensity electrical pulses to create cell membrane poration with the concurrent intravenous or intralesional delivery of low-dose cytotoxic drugs, most commonly cisplatin or bleomycin [20]. The transient disruption of cell membrane integrity and the local vasoconstriction resulting from the electrical stimulus increase the intracellular delivery and local efficacy of the chemotherapeutic agent. A recent review reported overall response rates of 50–90 % in 11 series to date, and electrochemotherapy has been shown to be effective both in a local control setting for cutaneous lesions not amenable to resection because of disease extent, and for the palliative treatment of painful or bleeding lesions [20]. Indications include proximal lesions of the extremities or lesions on the head, neck, or trunk; renal failure or allergies to the chemotherapeutic agents are the primary contraindications to this therapy [52]. The advantages include a minimal side effect profile in appropriately selected patients, the ability to perform the intervention with the patient under local anesthesia, sparing of surrounding uninvolved tissue, and the ability to use electrochemotherapy in the setting of prior radiation therapy [39].

Radiation Therapy

Although there may be an adjuvant role for radiation therapy following complete nodal dissection of recurrent regional disease, especially when a high likelihood of further recurrence exists, current NCCN guidelines also recommend radiation therapy as a palliative option for unresectable nodal, satellite, or in-transit disease. The efficacy of radiation therapy is typically greatest in the adjuvant setting for microscopic residual disease in a limited field, either following completion lymphadenectomy and removal of all gross disease or following resection of in-transit metastases with clear margins [10]. Extrapolating results for the use of radiation therapy from treatment of primary stage III disease suggests some patients with locoregional recurrence who are unable to undergo resection or regional chemotherapy might achieve improved locoregional control and possibly even improved survival with radiation therapy [77, 78]. External beam radiotherapy can be particularly useful for recurrent lesions of the head and neck, where other treatment modalities are unavailable [79].

Historically, melanoma has been considered a relatively radioresistant malignancy, and early preclinical and clinical investigations suggested that hypofractionated, or higher dose per fraction, radiation therapy might be beneficial [80, 81]. This has prompted some institutions to favor hypofractionated radiation therapy, in which 30 Gy is typically delivered in five fractions, versus more standard fractionation of 2 Gy per daily fraction in 3 weeks or more [82]. The only randomized controlled comparison of fractionation schedules to date was performed in the palliative setting, and demonstrated no difference in response rates and slightly higher rates of toxicities associated with hypofractionation [83, 84]. Although the widespread adoption of hypofractionation is supported by retrospective and case-series data, a recent randomized trial by Burmeister et al. [32••] demonstrating improved locoregional control with adjuvant radiation therapy following lymphadenectomy for melanoma used conventional standard fractionation

and has generated renewed interest in this approach to radiation therapy.

Conclusion

Locoregional recurrence of melanoma may affect up to 25 % of patients and can present significant treatment challenges. In the absence of distant metastases, complete surgical excision to achieve clear margins remains the ideal treatment for resectable local and in-transit recurrent disease, and complete lymph node dissection is indicated for regional nodal disease. For unresectable local or in-transit disease confined to an extremity, HILP or ILI, indicated for the presence or absence of concurrent regional lymph node disease, respectively, offers the best chance of durable response and improved survival. For recurrent, unresectable locoregional disease located on the trunk, head, or neck, potential efficacious treatment options include intralesional or topical therapy, laser therapy, electrochemotherapy, radiation therapy, and systemic therapy.

Compliance with Ethics Guidelines

Conflict of Interest Malcolm Hart Squires III and Keith A. Delman declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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