MANAGEMENT OF LOCO-REGIONALLY RECURRENT MELANOMA

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Abstract

Loco-regionally recurrent melanoma encompasses local recurrence (usually defined as being within 2cm of the primary tumour site), in-transit recurrence and regional lymph node recurrence. Survival in patients with loco-regional recurrence is considerably reduced compared with survival in patients without recurrence. The most appropriate treatment of loco-recurrence varies according to presentation. Local recurrence is best treated by surgical excision. In-transit recurrence is also treated by excision when possible, but may involve other forms of treatment, such as topical therapy (with dyphencyprone cream) or intra-tumoural injection therapy (eg. with Rose Bengal). For unresectable local and in-transit recurrence, regional limb chemotherapy (isolated limb perfusion or isolated limb infusion) remains the standard of care. When regional limb chemotherapy is not possible or has failed, alternative treatment options that are sometimes effective include topical therapy, intra-tumoural injection therapy or external beam radiation therapy. Rarely, amputation may need to be considered for in-transit disease confined to a limb when all other options have been exhausted. Regional lymph node recurrence is managed primarily by surgical resection involving formal lymphadenectomy of the neck, axilla or groin. For metastatic melanoma in the axilla a complete level I-III dissection is standard treatment. However, the extent of groin and neck lymphadenectomy for metastatic disease in these sites may vary. Currently, sub-inguinal ('superficial') lymph node dissection is often recommended for patients with palpable groin recurrence, but there is evidence suggesting that an ilio-inguinal dissection may be a safer alternative. Iliac dissection is required for clinically involved pelvic lymph nodes. For metastatic disease in cervical nodes, a full level I to V neck dissection is standard, but selective neck dissection with adjuvant radiation therapy may be an alternative. Post-operative radiation therapy improves regional recurrence-free survival for patients with resected high-risk stage III melanoma. Systemic therapy for loco-regional recurrence is the subject of ongoing research. The only currently approved adjuvant therapy for stage III melanoma is interferon-alpha. Newer agents under investigation include vaccines, ipilumimab and inhibitors of the BRAF pathway.

Loco-regionally recurrent melanoma refers to melanoma that has recurred between the primary site and the regional lymph nodes, following previous excision of a primary tumour. Five-year survival from melanoma is as high as 96% if it is diagnosed early, when the disease is localised to the primary site.[1] However, all patients are at risk for the development of local and/or regional recurrence. If loco-regional recurrence does occur, survival is dramatically reduced.[2]

Recurrence may occur in up to 36% of patients with American Joint Committee for Cancer (AJCC) stage I or II melanomas, of which loco-regional recurrence represents 63% to 87%. Sixty-five percent of recurrences occur within the first three years of follow-up. Patients with local or regional recurrence have a better prognosis than patients who relapse at systemic sites: five-year survival is 55% following local recurrence; 51% following regional node recurrence; and at best 20% following systemic recurrence.[2,3] Loco-regional recurrence is influenced by known primary tumour prognostic factors including Breslow thickness, ulceration, mitotic rate and the presence of lymphovascular or perineural invasion.[4,5,6]

The need for adequate management of loco-regional recurrence is of great importance if loco-regional relapse-free survival and melanoma-specific survival are to be improved. Asymptomatic AJCC stage IV disease may be found in up to 20% of patients presenting with loco-regional recurrence. These patients should undergo complete staging with whole body CT and/or FDG-PET scans, and should ideally be managed by a multidisciplinary team of clinicians.[7]

Local recurrence

A local recurrence of melanoma is usually defined as a tumour appearing in the skin or subcutaneous tissue within 2cm of the wide local excision site (although many would regard any recurrence clearly separated from the wide excision scar as an in-transit recurrence). For invasive melanomas of any thickness, randomised clinical trials and large cohort studies of excision margins have demonstrated local recurrence rates of 1-3% when a wide excision margin of at least 1cm has been obtained.[6,8]

The standard treatment of local and in-transit metastases is surgical resection with histologically negative margins. There is no randomised clinical trials evidence that wide margins of excision result in better outcomes for patients with local or in-transit recurrence, however for true local recurrence a margin of at least 1cm is sometimes suggested, including the previous primary excision scar. Sentinel lymph node biopsy has been proposed at the time of resection of a local recurrence for staging, but efficacy data are lacking.[9,10]

For unresectable loco-regional recurrence, treatment options include regional chemotherapy, intra-lesional chemoablation, radiation therapy and topical immunotherapy (see below for in-transit recurrence).[9,11]

In-transit melanoma recurrence

In-transit metastases appear as the initial site of recurrence in 2-31% of patients after primary treatment of melanoma. This is dependent on the initial stage of the melanoma and is more common among patients with a lower extremity primary tumour.[12,13,14] In-transit melanoma is thought to represent lymphatic metastatic spread, which manifests as cutaneous or subcutaneous tumour nodules located between the primary site and the regional lymph node field.

Limited in-transit disease may be treated adequately by surgical excision. The goal is complete excision of all lesions with clear histological margins. Wide excision and deforming surgery are not recommended. Unfortunately, recurrence of in-transit disease is common and patients should undergo close surveillance.[9]

For unresectable in-transit disease a number of treatment options are available. These include chemoablation, topical agents, infusional therapy and radiation therapy. Direct therapies include diathermy, cryotherapy and CO2 laser ablation. Ablation by intra-lesional injection of several compounds, including Bacille Calmette-Guerin has been reported.[15,16] Analysis of 15 non-controlled trials of intralesional Bacille Calmette-Guerin injections in patients with metastatic melanoma revealed complete responses in 19% and partial responses in 26%.[15] Cutaneous metastases have a response rate >80% in several reports. Subcutaneous metastases, however, are more resistant, with <20% responding to therapy.[15]

Recently, the use of PV10TM (Rose Bengal; Provectus Pharmaceuticals), a water-soluble xanthine dye, has been explored as an agent for the local control of melanoma metastases by intralesional injection. The efficacy of PV10 was investigated in a phase II trial, and demonstrated a 25% complete response rate and a 25% partial response rate among treated patients.[16,17,18] For more extensive disease, intralesional PV10 followed by external beam radiotherapy has been reported to provide effective local control with acceptable toxicity.[19]

Diphencyprone (DPCP) is a potent topical contact sensitiser that has most frequently been used as immunotherapy for cutaneous warts and alopecia areata.[20] Previously, topical DPCP has been combined with oral cimetidine or dacarbazine and radiotherapy to treat cutaneous melanoma metastases.[21,22] DPCP therapy involves the deliberate elicitation of contact hypersensitivity dermatitis at areas of recurrence or in-transit metastasis; the mechanism of action is presumed to be promotion of lymphocyte-mediated tumour destruction.[23,24] DPCP has been shown to be active in cutaneous in-transit melanoma, with >50% of patients showing complete tumour clearance, and another third of patients having slowing or partial clearance of their disease.[25] It represents an effective treatment option for head, neck and trunk disease, as well as low volume dermal limb disease.

Radiation therapy has also been shown to be of benefit in the treatment of unresectable in-transit melanoma.[26] Approximately 25% of palliatively irradiated melanoma in-transit metastases respond completely to treatment, and another 33% respond substantially. Small-volume macroscopic tumours may be controlled by radiation therapy where other treatment options have failed.[26,27] However, radiation therapy should be administered below the knee with caution.

Isolated limb infusion and perfusion

Regional limb chemotherapy with vascular isolation is the standard of care for extensive unresectable local or in-transit melanoma confined to a limb. Isolated limb perfusion (ILP) has a long track record in the treatment of cutaneous melanoma and is still widely used.[9,28] ILP is performed by cannulation of the major extremity artery and vein, with hyperthermic (40-42°C degree) perfusion of the limb for 60-90 minutes using a pump oxygenator. It is an effective treatment delivering high-dose cytotoxic chemotherapy, usually melphalan, regionally to the affected limb, with minimal risk of serious systemic toxicity. Overall response rates are 80%, with complete response rates of 40-60%. However, responses may be of limited duration, with most patients experiencing recurrence within 12-18 months. Survival correlates with response: five-year survival for non-responders is <7% while for complete responders survival approaches 50%.[28] Repeat perfusion can be considered for patients who recur following an initial response, and is often effective.

Isolated limb infusion (ILI) was first reported by Thompson et al from the Sydney Melanoma Unit in 1994 as a less invasive alternative to ILP.[29] Catheters are inserted percutaneously, and melphalan, with or without actinomycin D, is circulated manually with a syringe via a three-way tap after vascular isolation of the extremity with a tourniquet (which determines the proximal extent of treatment). Outcomes for ILI have been shown to be similar to those for ILP, with the Sydney Melanoma Unit reporting a 38% complete response rate and a complication rate similar to that of ILP.[30]

Complications of both ILP or ILI can be significant, with localised effects including compartment syndrome, neuropathy, skin reaction, blistering and lymphoedema.[31] Some patients may require simple excision of in-transit disease proximal to the tourniquet after their ILI. In addition the patients must be fit for general anaesthesia.

Amputation for extensive in-transit recurrence may be a last resort for patients who have symptomatic localised disease and have failed other therapies.[32] At the Sydney Melanoma Unit, 6% of their total ILI-treated patients ultimately underwent amputation. Most of these patients suffered from deeply infiltrative lesions associated with severe pain or bleeding from ulcerated and necrotic lesions. Amputation of the affected limb resulted in effective symptom relief in all patients.[32] Five-year survival rates following amputation historically have been as high as 28%.[33]

Regional lymph node recurrence

Prior to the widespread implementation of sentinel lymph node biopsy, a minimally invasive procedure for identifying patients who harbour occult microscopic disease in regional lymph nodes,[34,35] regional lymph nodes were the most common initial site of recurrence. The risk of nodal recurrence for intermediate thickness melanomas (Breslow thickness 1-4mm) is 15-20% at five years.[36] With the introduction of sentinel lymph node biopsy regional recurrence rates are now <5%, however patients who have not undergone sentinel lymph node biopsy (and those with false-negative sentinel lymph node biopsy) may still present with lymph node recurrence.

Therapeutic lymph node dissection is the treatment of choice for both microscopic and macroscopic metastatic disease in regional lymph nodes, as complete resection offers the best chance of loco-regional control and survival for patients without metastatic disease at systemic sites. Nodal disease may present at an advanced stage with invasion/encasement of neurovascular structures or with ulceration through the skin. Care of these patients requires a team approach including general surgery, plastic surgery, vascular surgery and radiation oncology.

Axilla

Patients with metastatic lymph node disease in the axilla should undergo a complete (level I-III) axillary dissection. The goal is for removal of all lymph nodes, as surgical excision provides the best chance of cure. Surgical resection is curative in up to 50% of patients with palpable nodal disease.[37,38] Lymphoedema rates are <10% following a level I-III axillary dissection for melanoma. Recurrence within the surgical field may occur, the risk being determined by characteristics of the dissected lymph node field, such as the number of positive nodes and the presence of extracapsular spread. The prognosis following in-field recurrence is typically poor.[39]

Groin

A groin dissection is recommended for clinically palpable disease in the groin. Previously a 'radical' groin dissection (combined inguinal and pelvic lymph node dissection) including inguinal, iliac and obturator nodes, was often performed for metastatic melanoma in the groin. More recently, a trend has been seen towards a 'superficial' (inguinal only) node dissection in patients without evidence of disease above the level of the inguinal ligament on CT or PET/CT imaging.

However, these scans will not identify microscopic disease, and patients with metastases in sub-inguinal lymph nodes have a 20-30% chance of harbouring pelvic lymph node metastases. A positive Cloquet's node, four or more positive nodes on inguinal dissection, and palpable inguinal nodes are predictors of pelvic nodal status. Elective pelvic dissection may therefore be considered for selected patients when planning treatment.[40,41]

Inguinal lymph node dissection is associated with significant post-operative complications, including wound infection and seroma formation.[42] The addition of pelvic lymph node dissection is associated with somewhat higher rates of lymphoedema.[41]

Current decisions relating to the extent of lymph node dissection for AJCC stage III melanoma of the groin are largely institution based, with randomised trials required, but unlikely to be undertaken in the foreseeable future.

Neck

Although radical neck dissection has been the gold standard for metastatic melanoma in cervical nodes, modified radical neck dissection does not appear to compromise regional control in patients and allows preservation of the internal jugular vein, sterno-mastoid muscle and accessory nerve.[43] Radical neck dissection should routinely include levels II to V. Management of clinically apparent disease of the parotid gland should include a superficial parotidectomy, with neck dissection also indicated due to a 30% risk of occult neck node involvement.[44] Similarly, superficial parotidectomy should be considered with modified radical neck dissection where parotid nodes may be at risk, such as for primary lesions of the face and scalp. Most melanomas of the head and neck spread in a reasonably predictable manner based on the anatomical site of the primary melanoma. Knowledge of these patterns can be useful in limiting the extent of nodal dissection to those levels most at risk of metastatic disease (selective neck dissection). However, in the setting of clinically apparent nodal disease in the neck, selective node dissection may be associated with a higher recurrence rate than modified radical neck dissection.[45] Post-operative radiation therapy may help to reduce the risk of regional relapse after selective neck dissection.[45,46]

Radiation therapy

Following therapeutic lymph node dissection for regional lymph node recurrence, patients with extranodal spread of melanoma, an increased number of tumour-positive lymph nodes, and increasing size of involved nodes have a greater risk of recurrence in the operative field. Post-therapeutic lymph node dissection in-field recurrence can cause serious morbidity including pain, ulceration, malodour, lymphoedema and impaired function, as well as carrying a poor prognosis.

The results of a recent randomised controlled phase III intergroup trial conducted by the Australian and New Zealand Melanoma Trials Group and the Trans-Tasman Radiation Oncology Group demonstrated that adjuvant radiotherapy after nodal dissection for high risk patients substantially reduced the risk of further lymph-node field relapse (but with no significant effect on overall survival).[46] Adjuvant radiotherapy was associated with acceptable early toxicity. Lymph-node field relapse was predicted by extranodal spread of melanoma, increased number of tumour-positive lymph nodes, and increasing size of involved nodes.[46] Adjuvant radiation therapy should therefore be considered for patients with proven nodal metastases and a high risk of regional recurrence.[47,48,49]

For bulky, unresectable nodal disease, some studies have suggested a benefit with palliative radiation therapy. Quoted overall response rates are up to 84% for bulky disease,

with large fractions being beneficial. The median disease-free survival was seven months for those with inoperable disease, and the median overall survival 18 months.[50]

Adjuvant systemic therapy

Patients with AJCC stage III disease are at high risk of dying from melanoma, with <50% 10-year survival. These patients should be considered for adjuvant systemic therapy. The only drug with demonstrated efficacy as adjuvant therapy for high risk melanoma is interferon-α. Trials have shown that high-dose interferon improves progression-free survival by approximately 10% at five years. A recent meta-analysis of patients with high-risk cutaneous melanoma concluded that interferon-α2b adjuvant treatment resulted in small, but statistically significant improvements in both progression-free survival and overall survival.[51]

Patients with unresectable AJCC stage IIIc melanoma should be considered for systemic therapy. The current standard of care is dacarbazine, with response rates in the order of 10%. However, newer agents such as inhibitors of BRAF (for example vemurafinib) or the anti-CTLA4 antibody ipilumimab, have both shown significant improvements in survival compared with dacarbazine.[52,53] The utility of these newer agents as adjuvant therapy for resected stage III disease is the subject of ongoing clinical trials.

In summary, loco-regional recurrence of melanoma encompasses a wide clinical spectrum, ranging from easily resectable disease to the very difficult management problem of extensive in-transit and/or nodal disease. Treatment options vary for each individual, and are best addressed in a multi-disciplinary team setting where there can be discussion among relevant medical and surgical teams to develop an appropriate treatment plan for that patient.

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