PERSPECTIVE

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Melanoma Management

A surgical perspective report on melanoma management

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Practice points

- Excisional biopsy is the most reliable method for diagnosing melanoma. Punch biopsies are also acceptable if an excisional biopsy is not possible. Shave biopsies are least reliable as these often miss the deepest extent of the tumor.
- Wide excision is the cornerstone of treatment for melanoma. We typically do not deviate from NCCN guidelines in terms of margins.
- Melanoma *in situ*, particularly lentigo maligna subtype, have higher recurrence rates and should be considered for wider resection with up to 1 cm. In experienced centers, Mohs micrographic surgery can be considered.
- Sentinel lymph node biopsy should be performed on all melanomas greater than 1 mm in depth. It should also be considered for thin melanomas less than 1 mm but with worrisome features, such as high mitotic count and/or ulceration.
- A completion lymphadenectomy is routinely performed for positive sentinel lymph node biopsy. The results of the MSLT-2 trial may change this paradigm. Laparoscopic node dissection has been successfully used by some centers and can be considered.
- Locally advanced disease can be approached in several ways, though surgical resection with negative margins should be first line. Patients with a heavy burden of disease may benefit from isolated limb infusion or hyperthermic isolated limb perfusion. Additionally, intralesional injection therapy is a well-tolerated approach to controlling locoregional disease. Specifically, talimogene laherparepvec is preferred over other intralesional injection methods due to its efficacy and favorable side effect profile.
- Follow-up should include yearly or biannual dermatologic exams for stage I and II disease.

Management of melanoma includes wide excision with adequate margins and lymph node biopsy depending on the depth of the lesion, with subsequent completion lymphadenectomy for positive sentinel node. Locally advanced disease can be approached in several different ways depending on a variety of patient and disease-specific factors. These include surgical resection, isolated limb perfusion and infusion and intralesional injection therapy such as talimogene laherparepvec, IL-2 and Bacille Calmette–Guerin. Ongoing controversy exists regarding the utility of completion lymphadenectomy, and trials such as MSLT-2 will attempt to shed light on this issue. The future of melanoma management will likely focus on expanding the use of immunotherapy, allowing for narrower surgical margins, particularly in sensitive anatomic areas, and limiting the number of completion lymphadenectomies.

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Approximately 2.1% of the US population will be diagnosed with melanoma of the skin at some point during their lifetime, making it the sixth most common cancer in the USA [1]. An estimated 76,380 new patients are predicted to be diagnosed with melanoma in 2016 and about 10,130 patients will die of this disease, accounting for 1.7% of all cancer-related mortality [1]. Given these statistics,

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it is not surprising that melanoma is the most aggressive form of skin cancer [2]. A total of 5-year survival rates for early-stage melanoma, those who present with localized disease or primary tumors that are less than 1 mm in thickness, is usually greater than 90%. However, survival rates can range from 50 to 90% depending on tumor thickness, ulceration and mitotic rate [3]. If there is nodal involvement, survival is roughly half, depending on the nodal burden [3]. Within stage III, 5-year survival rates are between 20 and 70%, depending on the nodal tumor burden. Long-term survival with distant metastases has been less than 10%, however certain patients can have a more indolent course. The use of new systemic therapies in stage IV disease, either at presentation or recurrence, has also shown promise in providing long-term remission [2].

There is increasing interest in looking at genetic variations in clinical subtypes of melanoma. The currently described clinical subtypes of cutaneous melanoma are nonchronic sun-damaged melanomas and chronic sun-damaged melanomas. Different subtypes of melanoma have very different genetic profiles, some of which have different therapeutic implications. In an analysis of 102 primary melanomas, the nonchronic sun-damaged subtype was found to have the highest proportion of *BRAF* mutations (56%) compared with chronic sun-damaged, acral and mucosal subtypes (6, 21 and 3%, respectively), but 0% in nonchronic sun-damaged subtypes. *NRAS* mutations were found in 5–20% of subtypes [4].

Risk factors for melanoma include skin type, personal or family history of melanoma, multiple clinically atypical moles or dysplastic nevi and less common inherited genetic mutations. Genetic counseling is provided at our institution for all individuals who are considered at high risk, including those patients with a strong family history of invasive melanoma, with or without pancreatic cancer. Along with genetic factors, environmental factors include sun exposure and UV-based artificial tanning. Additionally, an interaction between genetic susceptibility and environmental exposure is seen in patients with an inability to tan and fair skin that burns easily. Nevertheless, melanoma occurs in all ethnic groups and in areas of the body with limited sun exposure [3].

At our institution, our multidisciplinary team of surgical, medical and radiation oncologists, dermatopathologists and dermatologists have extensive experience in treating melanoma. We aim to present the most up-to-date guidelines in the surgical management of malignant melanoma, particularly locally advanced melanoma and the different treatment options provided at our institution.

Presentation & workup

Pigmented lesions suspicious for melanoma undergo an excisional biopsy with 1–3 mm negative margins. The orientation of the excisional biopsy should be planned with definitive treatment in mind, such as a longitudinal orientation in the extremities and parallel to lymphatics. With the increasing use of lymphatic mapping and sentinel node biopsy, biopsies should be planned so as not to interfere with this procedure. Thus, wider margins for the initial diagnostic procedure should be avoided.

Excisional biopsy may be inappropriate for the certain sites such as the face, palmar surface of the hand, sole of the foot, ear, digits, subungal lesions or for very large lesions. In these instances, a full-thickness incisional or punch biopsy of the clinically thickest portion of the lesion is an acceptable option. The goal of these procedures is to obtain accurate primary tumor microstaging, without interfering with definitive local therapy. If the initial biopsy is inadequate to make a diagnosis or to accurately stage the tumor for treatment planning, a repeat biopsy with narrow margin excision should be considered. Shave biopsy may compromise pathologic diagnosis and complete assessment of Breslow thickness. However, it is acceptable in a low suspicion setting. For example, a broad shave biopsy may help to optimize accurate diagnosis of lentigo maligna. Experts realize that melanomas are commonly diagnosed by shave biopsy during screening in a dermatologist office and that any diagnosis is better than none even if microstaging may not be complete. Not surprisingly, most patients present to us with melanoma confirmed on shave biopsies, which we use to make adequate clinical management decisions.

Once confirmed on biopsy, patients should be carefully screened for any concurrent melanoma or skin lesions. Our workup includes a careful history and physical exam that includes family history of melanoma, personal history of melanoma or other skin cancers, history of blistering sunburn, as well as any prior dysplastic nevi. It is also germane to ascertain any neurological

symptoms such as new headache or back pain, as this may prompt a metastatic workup, particularly in high-risk patients. Physical exam involves careful inspection of the lesion itself as well as the entire region to check for in-transit disease. Meticulous evaluation of all major draining lymph node basins, most notably the inguinal, axillary and cervical should also be performed. A complete skin exam should also be performed by either a dermatologist or surgical oncologist two- to three-times per year.

Melanoma margins

The cornerstone of melanoma management is wide excision of the primary lesion with adequate margins. The depth of the lesion dictates the extent of excision. Multiple prospective trials, including a WHO study involving 612 patients and a Swedish trial of nearly 1000 patients, showed no difference between 2 cm margins and margins greater than 2 cm for lesions less than 2 mm in depth [5–7]. The WHO trial also compared 1 versus 3 cm margins for thin melanomas (less than 2 mm) and no difference in local recurrence nor overall survival was seen [5,6]. For lesions greater than 2 mm, subsequent studies showed equivalent overall survival and rates of local recurrence in melanomas using 2 cm margins versus 4 cm [8]. More recently, a 2016 UK study of 900 patients compared 1 versus 3 cm margins for lesions greater than 2 mm. This study showed no statistically significant difference in overall survival; however, they did find improved melanoma specific survival for patients in the 3 cm group versus 1 cm [9]. Of note, the follow-up for both these studies was around 8 years. A minimum of 1 cm margin is supported by a large case-control study of 11,290 patients, which showed local recurrence strongly associated with less than 1 cm margins for T1 melanoma [10].

Melanoma *in situ*

Since the consensus guidelines put forth in 1992, the treatment of melanoma *in situ* (MIS) consists of wide excision with 5 mm margins. However, a large prospectively collected series by Kunishige *et al.* of over 1000 patients showed that this may in fact be inadequate [11]. Only 86% of melanomas were successfully removed (pathologically negative margins) with 6 mm margins. Almost 99% of melanomas were completely removed with 9 mm margins [11]. Several other studies have corroborated this point. Felton *et al.* calculated that 16 mm margins were required to clear 97% of MIS [12]. Despite the fact that 5 mm margins may not result in complete clearance of disease, the overall recurrence rate is quite low. One study by Joyce *et al.* reports a recurrence rate of 0.5% for margins greater 3 mm [13].

The most recent 2016 guidelines from the National Comprehensive Cancer Network (NCCN) on adequate margins for wide excision are as follows: MIS requires a 0.5–1 cm margin, malignant melanoma less than 1 mm requires 1 cm margin; malignant melanoma between 1 and 2 mm, requires a 1–2 cm margin; and any lesion with a depth greater than 2 mm requires 2 cm margins. Special circumstances such as cosmetic areas where a full 2 cm margin is not feasible may preclude obtaining these margins. In these cases, 1 cm margin may be acceptable. We do not offer Mohs excision for melanoma due to inability to achieve reliable frozen margins [14]. In particular, Mohs may be unsuitable for detecting single atypical cells at the margins of MIS.

Sentinel node biopsy

The utility of sentinel lymph node biopsy (SLNB) in melanoma has been well established. Trials have shown that elective lymph node dissection in stage I and II melanoma has no survival advantage over nodal observation [15]. The largest trial to date that evaluates whether complete lymph node dissection (CLND) in the presence of a positive sentinel node confers any survival benefit is MSLT-1. This randomized controlled trial showed no disease-specific survival benefit in CLND in the whole cohort. However, in posthoc subgroup analysis, there appears to be a disease-specific survival advantage in the patients with intermediate thickness melanoma (1–4 mm) when compared with patients who underwent nodal observation [16]. Breslow thickness correlates with positive SLNB rates. SLNB should be conducted in melanomas greater than 1 mm. For lesions 0.75–1 mm and no evidence of ulceration or mitoses, SLNB should be considered and discussed with the patient.

Completion lymphadenectomy

MSLT-2 is a Phase III randomized trial comparing CLND and nodal observation by ultrasound in melanoma patients with positive sentinel node based on either pathology (H&E, immunohistochemistry) or reverse transcription PCR. Accrual

is complete, but no preliminary data are available yet. Bamboat and colleagues published a retrospective study of 167 patients with positive SLN who underwent nodal observation. When compared with patients who underwent immediate CLND, not surprisingly, the observation group has a higher rate of having nodal disease as the first site of recurrence. However, melanoma-specific survival was not different between the two groups [17]. Pasquali *et al.* recently surveyed approximately 200 surgeons from 25 countries regarding their opinions on CLND in patients with positive sentinel node. 92% recommended CLND and nearly half of the surgeons have enrolled patients in the MSLT-2 trial. In patients with positive inguinal SN, 36% would perform superficial inguinal dissection, 30% would perform a superficial and deep dissection, and 36% chose either based on the number of positive SNs, Cloquet node status and lymphatic drainage patterns [18].

The reliability of using Cloquet's node to dictate deep groin dissection has been inconclusive. Strobbe *et al.* found low sensitivity in Cloquet's node predicting pelvic nodal status [19], while Koh *et al.* actually found Cloquet's node to be superior to imaging in their series [20]. At our center, we also question the utility of Cloquet's node in predicting pelvic nodal status and do not use it to evaluate for deep pelvic lymphadenectomy. In patients with palpable groin nodes, our staging typically includes PET/CT scan to identify occult pelvic disease. In patients that have suspicious pelvic nodal disease on imaging, we routinely perform superficial and deep pelvic lymphadenectomy. If there are macroscopic-positive superficial nodes we offer a deep dissection.

Our institution has adopted a minimally invasive approach to both superficial groin and deep-pelvic lymphadenectomy in selected patients. For superficial groin dissection, we use a laparoscopic approach that entails a 10 mm camera port inferior to the apex of the femoral triangle, and two 5 mm ports outside the medial and lateral borders of the femoral triangle. With the help of transillumination through the skin flap along with skin markings of the triangle, we can dissect out the entire nodal packet to just above the level of the inguinal ligament. In our experience, the postoperative recovery is much shorter in patients who underwent laparoscopic groin dissection compared with open. Nodal retrieval has been comparable to the open approach. A safety and feasibility study involving 87 patients who underwent minimally invasive lymphadenectomy demonstrated adequate lymph node retrieval with favorable morbidity profile [21]. Smaller case series have also observed a significant reduction in hospital stay. Larger studies with extended follow-up are needed to examine whether minimally invasive approach improves lymphedema outcomes [22].

For pelvic lymphadenectomy, we use a robotic approach. Although there are limited data on its outcome and efficacy compared with an open approach, studies have shown shorter hospital stay with comparable operating time and nodal yield [23].

Locally advanced disease

When local, satellite or in-transit recurrence is suspected, the NCCN guidelines recommend that these are biopsied or undergo fine-needle aspiration to confirm diagnosis. Once the diagnosis is confirmed, these patients should undergo staging studies either by CT scan, PET/CT scan or MRI. Locally advanced disease should be excised with negative margins if the entire extent of disease can be resected, deeming the patient with no evidence of disease. This approach may offer the best chance for long-term disease-free survival. We typically aim to obtain 1 cm margins and a negative deep fascial plane, though there is no standard of care. It is important to note that the depth of the primary tumor does not affect margin width when managing recurrent disease. Dong *et al.* reviewed 648 patients with local recurrence from cutaneous melanoma. All patients were initially treated with resection of the local recurrence. After resection, 124 patients (19%) did not have any further disease progression, 196 (30%) had another local recurrence and 150 (23%) had a distant recurrence. Those with progression of disease went on to receive local, intra-arterial perfusion or systemic therapies. 77% of the 124 patients who did not have further disease progression after resection of their local recurrence, had a median follow-up of 39 months [24].

Although patients with locally recurrent or in-transit disease are at high risk for occult nodal involvement, management of these lymph nodes with an SLNB lacks consensus guidelines. SLNB in those who have already had prior biopsy has been shown to be technically feasible, with a 94% success rate in one study [25]. Yao and colleagues found that in 30 patients who underwent SLNB for recurrent melanoma, 14 (47%) were found to have positive SLN and 11 (78%) of those

underwent CLND [26]. The patients with a positive sentinel node had a median disease-free survival of 16 versus 36 months in those with negative sentinel node. Of note, in this study there was no difference in overall survival (p = 0.025). Beasley *et al.* also discovered a high rate of positive lymph nodes in patients with in-transit disease. In their study of 33 patients, 30 had positive lymph nodes and 10 (33%) of these 30 patients had positive lymph nodes. Nine of these subsequently underwent completion lymphadenectomy, and additional positive lymph nodes were found in four of these patients [25]. It is interesting to note that 79% of the patients in this study had undergone prior SLNB or CLND of the same lymph node basin as the expected drainage of the in-transit recurrence [26,27]. Overall, there is no consensus on whether or not patients with locally advanced disease should undergo an SLNB, and if positive whether or not they should undergo a CLND.

Unresectable locally advanced melanoma is difficult to treat and has limited effective therapeutic options. Since the 1950s, hyperthermic isolated limb perfusion (HILP) and later modified isolated limb infusion (ILI), has been developed to help combat this elusive disease. ILP is a surgical technique that involves obtaining vascular access to either axillary or femoral vessels, and administering hyperthermic chemotherapy with melphalan. Limb temperatures typically reach 39–41°C, which has been reported to have a positive effect on complete response (CR) [28]. It is essential that the limb vasculature is isolated from systemic circulation with the use of a tourniquet and that collateral vessels are ligated to minimize the risk of systemic toxicity from the high-dose chemotherapy, which is usually given at 15- to 25-times higher than would be tolerated with systemic chemotherapy [27]. In Europe, the addition of TNF-α has been shown to improve CR, however this has not been consistently reproducible [29,30]. The largest US study was a multicenter trial by the American College of Surgeons Oncology Group Z0020 in which patients received either melphalan or melphanal and TNF-α. A total of 25% of patients in the melphalan group had a CR at 3 months, compared with 26% in the melphalan and TNF-α group, with no statistically significant difference in overall survival or CR [31]. Additionally, the use of TNF-α had increased toxicity such as cardiovascular events including tachycardia, hypotension, decreased systemic vascular resistance, increased cardiac output and even liver dysfunction [32]. As a result, in the USA, HILP is performed with melphalan alone. Moreno-Ramirez and colleagues published a systematic review on ILP analyzing 22 studies which included over 2000 patients. The primary endpoints were overall response rate and survival. The average overall response rate to ILP in this meta-analysis was 90%, with a range of 64–100% and the average 5-year overall survival was 36%. The recurrence rate was reported on average as 40%, with a median survival of 10.5 months until local recurrence [32].

In addition to HILP, ILI is another option for management of locally advanced disease that is unresectable. Unlike HILP, it is a percutaneous method of obtaining vascular access to the affected limb. Chemotherapeutic agents are then infused at a lower rate, 80–120 ml/min compared with 400–600 ml/min in HILP [33]. As in HILP, the temperature goal is greater than 37°C. ILI has had similar response rates to HILP, with overall CR rates ranging from 43 to 72% [27]. Since ILI is less invasive and reported to have fewer toxic side effects, it is a reasonable option for patients with poor performance status [34]. Another advantage of ILI is that since no surgical incisions are made, there is decreased scar tissue and tissue plane disruption, which may make it a better initial option, followed by HILP if there is recurrence after ILI. On the other hand, HILP should be considered if there is palpable lymphadenopathy requiring a CLND, as both procedures can be conducted simultaneously [27].

Intralesional injection therapy is another option for patients with in-transit disease. Bacille Calmette–Guerin and IL-2 are both approved for intralesional injection therapy for in-transit disease. However, Bacille Calmette–Guerin has fallen out of favor after a study in 2004 from University of Pittsburg found that Bacille Calmette–Guerin injection showed no benefit as compared with observation and was associated with the development of abscesses in two-thirds of the patients [35].

Intralesional IL-2 has had more success in treating patients with locally recurrent disease or in-transit metastases. Two recent studies on the use of IL-2 for in-transit melanoma showed a CR rate of 32–51% [36,37]. In both studies, about 50% of patients had systemic and/or radiotherapy after their initial surgical excision. Hassan *et al.* could not identify any tumor characteristics or prior treatment factors that can predict CR to IL-2 therapy [37]. Both studies showed that CR

to IL-2 is associated with improved overall and progression-free survival. The disadvantage of IL-2 is that it is time consuming since it must be given multiple times per week and that it lacks a bystander affect, in that lesions that are not injected are unaffected.

Another method for intralesional injection therapy that has recently gained acceptance and has been used more frequently at our institution is injection of talimogene laherparepvec (T-VEC). This modified herpes simplex virus works by delivering granulocyte macrophage colony-stimulating factor (GM-CSF) and inducing tumor cell lysis [38]. T-VEC has shown some promise in patients with unresectable stage IIIB and stage IV melanoma. Andtbacka *et al.* recently found that at 44 months, tumors injected with T-VEC had a significantly improved overall response rate compared injection with GM-CSF 26.4 versus 5.7%, respectively [39]. T-VEC is preferred over the other intralesional injection methods at our institution due to its improved efficacy for stage III disease and favorable side effect profile, as well as its effect on bystander lesions.

Overall, locoreginal recurrence of melanoma is a complex issue that requires a multidisciplinary approach. Current NCCN guidelines state that the optimal treatment for in-transit disease or locally advanced melanoma is surgical resection with negative margins. However, if this is not feasible, then ILI or HILP can be considered for patients with unresectable locally advanced disease confined to an extremity. Additionally, intralesional therapies such as T-VEC can be considered in patients with cutaneous, subcutaneous, nodal lesions and even stage IIII distant disease. At our institution, we have been utilizing T-VEC for in-transit disease. Very rarely will we pursue HILP due to its toxicity.

Metastatic disease

Metastatic melanoma proliferates by escaping immunosurveillance, a process in which the immune system targets cancer cells. The mainstay for metastatic melanoma is immunotherapy which works by helping the body's immune system destroy malignant cells. Two specific T-cell receptors, CTLA-4 and PD-1, are targets for immunomodulators. These receptors normally function to limit the immune response. Therefore blocking these receptors removes the inhibition on T-cell activation. First-line agents for metastatic disease include ipilumumab, which is a CTLA-4 inhibitor, and/or pembrolizumab and nivolumamb, which are both PD-1 inhibitors [32]. Additionally, melanomas with mutations in the *BRAF* gene may have a better response to targeted therapy with either dabrafenib or vemurafenib or combination therapy with both BRAF and MEK inhibition [33].

Limited metastatic disease can be considered for resection. This depends on the patient's overall performance status as well as location and extent of disease. In general, patients who present with limited metastatic disease eligible for resection should first undergo a course of immunotherapy. After restaging with imaging, they are considered for resection. There is no consensus on the size of margins with resection but in our practice we try to maintain an adequate amount of healthy tissue around the specimen.

Follow-up

Patients with a history of melanoma need to be monitored closely for signs of recurrence and/or metastasis. All follow-up visits consist of a comprehensive review of systems, particularly focusing on symptoms that may suggest disseminated disease such as new headaches, changes in vision or back pain. This may prompt further workup such as an MRI of the brain. Physical exam includes thorough inspection of the scar, as well as all draining lymph node basins, paying particular attention to any new nodules along lymphatic path. All patients with a history of melanoma need regular follow-up with dermatology, medical oncology and/or surgical oncology at least twice a year for the first 1–2 years, then at least yearly.

We adhere to the NCCN guidelines in regard to follow-up for these patients. In general, follow-up for thin melanomas not requiring a sentinel lymph node biopsy during initial resection includes clinic visits every 6–12 months for 5 years, then annually as indicated. We do not typically image these patients unless otherwise indicated. Patients with thick melanomas are followed more closely. This includes an exam every 3–6 months for 2 years, then every 3–12 months for the next 3 years. Imaging is often indicated in these patients, though the frequency and type of the study is chosen on a case-by-case basis. Patients with stage III disease undergo cross sectional imaging with a CT scan every 3–12 months. Sometimes an ultrasound of the lymph nodes may be necessary if physical exam is equivocal, or for a patient with a positive sentinel node who refused completion node dissection.

Conclusion

Melanoma management is an ever changing field with exciting new therapies available to lessen the burden of disease and prolong life. Surgery has been and will likely continue to be the mainstay of therapy, though its role could certainly change as newer treatment modalities arise. Wide local excision with negative margins is the cornerstone of treatment, and sentinel lymph node biopsy is required if the initial depth is greater than 0.75 mm with the presence of ulceration and/or high mitotic rate or for all melanomas with a depth greater than 1 mm. Completion lymphadenectomy is currently the standard of care for the management of a positive sentinel node. This can be accomplished by the standard open technique, as well as laparoscopic techniques which are becoming popular among higher volume centers. ILI, ILP and now T-VEC injections are utilized in the management of in-transit and locally advanced unresectable disease with some success. Distant solitary metastatic masses should be resected if possible. For widespread disseminated disease, immunotherapy is now first-line therapy with impressive response rates and we always consider patients for enrollment on a clinical trial. Close follow-up and continued counseling to decrease risk factors are essential aspects to help prevent recurrence and for early detection of recurrence.

Future perspective

Melanoma management will continue to evolve as more and more studies shed light on the natural history of this disease. We foresee surgery remaining a central role in the management of melanoma, with wide local excision for the primary lesion. With the advent of newer immunotherapy and injectable options, surgery may play a smaller and smaller role for in-transit disease. Already we are seeing impressive results with injectable T-VEC and IL-2, and these therapies continue to develop. Management of nodal disease may follow the same path as breast cancer, with a lesser emphasis on completion lymphadenectomies. This of course will depend on the MSLT-2 trial, but if this study fails to demonstrate clear superiority of completion lymphadenectomy over nodal-basin observation, then there will be a push to limit the indications for lymphadenectomy. This procedure is potentially quite morbid with an overall complication rate of 28% [40]. We could also expect to see an expanded role for immunotherapy. The current guidelines recommend immunotherapy for stage IV disease and strong consideration for stage III disease. However, we may see this being used in patients with stage II disease who are at higher risk of recurrence. Systemic immunotherapy may also start to be utilized for in-transit disease as well.

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