Pulmonary metastatic melanoma: current state of diagnostic imaging and treatments

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Practice points

- The incidence of primary pulmonary melanoma is extremely rare, and thus, treatment modalities besides resection are challenging to find.
- International guidelines for surveillance imaging in melanoma patients are inconsistent and based mainly on expert consensus rather than evidence.
- Prevention in developing malignant melanoma (MM) is imperative. UV-B radiation is more closely associated with melanoma development.
- Approximately 10% of cases of cutaneous melanoma are familial.
- Primary MM of the lung and metastatic melanoma to the thorax can have varying radiographic presentations. However, the most common findings on chest computed tomography (CT) are solitary or multiple pulmonary nodules.
- CT, MRI and PET-CT scans are useful in staging and monitoring treatment responses.
- There have been significant advances in treatment options.
- For advanced disease, treatment options range from immunotherapy to surgical metastectomy with adjuvant radiotherapy.
- There are ongoing studies in the prevention (i.e., vaccines) and treatment for MM.

Abstract : Melanoma is the deadliest form of skin cancer with an estimated incidence of over 160,000 cases annually and about 41,000 melanoma-related deaths per year worldwide. Malignant melanoma (MM) primarily occurs in the skin but has been described in other organs. Although the respiratory system is generally afflicted by tumors such as lung cancer, it is also rarely affected by primary MM. The estimated incidence of pulmonary MM of the lung accounts for 0.01% of all primary lung tumors. The current understanding of pulmonary MM of the lung pathophysiology and its management are not well established. We aim to survey current clinical modalities with a focus on diagnostic imaging and therapeutic intervention to guide providers in the management of patients with a high index of suspicion.

Melanoma is the deadliest form of skin cancer with an estimated incidence of over 160,000 cases annually and approximately 41,000 melanoma-related deaths per year worldwide [1]. Malignant melanoma (MM) primarily occurs in the skin but has also been described in other sites and organs, including the oral cavity, paranasal sinuses, larynx, vagina and anorectal region [2]. However, the respiratory system is generally afflicted by highly aggressive tumors such as lung cancer and rarely affected by primary MM. This is evident among the limited number of published cases of primary MM of the lung (PMML) in the scientific literature and estimated incidence of PMML accounting for only 0.01% of all primary lung tumors [3]. In comparison, the majority of melanomas involving the lung are metastatic in origin, accounting for 5% of all malignant metastasis. As a result of their rarity, the

Future Medicine

pathophysiology of either etiology, their clinical presentation, diagnostic workup and therapeutic interventions are not well established. To date there is no succinct resource available; thus, this paper will mainly focus on pulmonary metastatic melanoma which comprises the majority of cases. We aim to survey current clinical modalities with a focus on diagnostic imaging and therapeutic intervention, including surgery and targeted therapy to guide providers in the timely management of patients with a high index of suspicion. Having an individualized approach with newer targeted treatment modalities may improve future outcomes.

Materials & methods

We searched the NIH public library (pubmed.gov) for patients with 'melanoma'. We looked at articles pertaining to melanoma, including case reports, case series, reviews, and investigator trials for the diagnosis and therapy for melanoma. The articles were reviewed to see if they met scientific and evidence-based merit for inclusion in our paper.

Etiology & classification of primary & metastatic pulmonary disease

In 1967, Jensen and Egedorf proposed the following clinical criteria for diagnosis of PMML: no previously removed skin tumors; no previously removed ocular tumors; a solitary lung tumor; tumor morphology compatible with a primary tumor; no other organ involvement; and autopsy without primary MM demonstrated elsewhere, especially not in the skin or eyes [4].

Multiple theories for the development of primary pulmonary disease have been proposed, including aberrant migration of melanocytes in utero as well as metaplastic differentiation of bronchial and/or neuroendocrine cells; however, the actual mechanism has not yet been elucidated [5,6]. One possibility is that epithelial cells exist in areas of squamous metaplasia in the lung and undergo differentiation to melanocytes to develop into MM [7].

Although primary melanoma of the lung has been reported in case series, its incidence is incredibly rare; the majority of melanoma cases which occur in the lungs and mediastinum are a result of metastatic disease, accounting for 5% of all malignant metastasis. Metastasis to the lungs and mediastinum are usually recognized before metastases to other sites are discovered [8]. In one population of 13,565 patients diagnosed with cutaneous MM, the five and 20-fold estimated risk of developing pulmonary metastasis was 13 and 23%, respectively. A retrospective review of 2485 patients found that only 2.6% had metastatic melanoma with an unknown primary lesion [9].

Classification of cutaneous melanoma uses the tumor node metastasis staging system with stage I and II disease encompassing primary localized disease, whereas stage III represents regional metastatic disease and stage IV referring to melanoma with distant metastasis. Moreover, 5- and 10-year survival rates based on this classification range from 97 and 93% in patients with stage IA disease to 53 and 39% with stage IIC disease. Depending on substage, 1-year survival rates for metastatic disease range from 33 to 62% [10]. Previous studies have shown that the 1-year survival rate in patients with exclusive pulmonary metastatic melanoma was significantly better compared with metastases to other visceral sites, but at 2 years the survival rates were equivalent [11].

Risk factors

Intense, intermittent sun exposures as well as blistering sunburns in areas with less frequent sun exposure have been shown to increase the incidence of melanoma [12]. UV-B radiation with wavelengths between 290 and 320 nm is more closely associated with melanoma development compared with UV-A radiation with wavelengths 320–400 nm. It has been noted that there is a higher incidence of melanoma in regions closest to the equator where UV-B radiation is highest. Primary cutaneous melanomas in Hispanic, Asian and black individuals tend to occur more frequently in unusual anatomic sites such as the palms, fingers, nail beds, toes and soles [13]. For the majority of melanoma subtypes in ethnic minorities there are no established risk factors [14]. Review of the SEER data noted that the truncal region was the most common primary tumor site for whites and American–Indians, while lower extremities were the most common primary sites for Hispanics, African–Americans and Asian–Pacific Islanders. Minority populations tend to present with more advanced stages of disease and lower survival rates than white patients [15].

Although the greatest risk for melanoma is with UV-B exposure, UV-A has also been associated with the disease. Patients with a history of skin conditions such as psoriasis who were treated with oral methoxsalen and UV-A radiation appear to have increased risk of melanoma seen 15 years after treatment [16].

Approximately 10% of cases of cutaneous melanoma are familial [17]. In a study among melanoma families defined as kindreds in which melanoma occurred in two or more blood relatives, the likelihood of developing
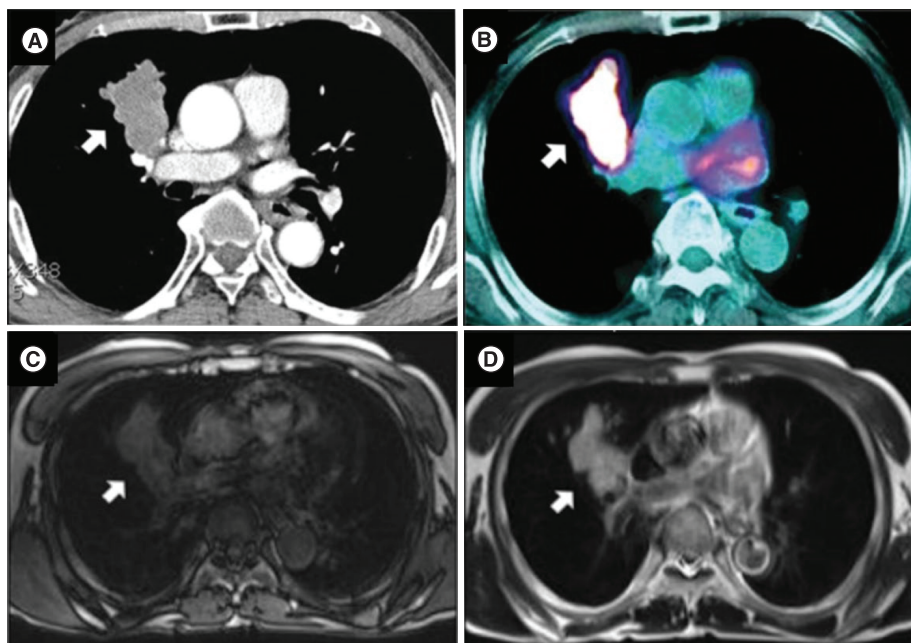
Figure 1. Pulmonary metastatic melanoma presenting as multilobulated mass. Chest computed tomography scan of malignant melanoma in the right-upper lobe of the lungs in a 69-year-old man. **(A)** A round, well-demarcated, multilobulated mass approximately 5 × 3.4 cm. **(B)** This nodule showed strong ^{18}F-fluorine-2-fluoro-2-deoxy-D-glucose (FDG) uptake on FDG-positron emission tomography. **(C & D)** Chest MRI revealed that the mass appeared to be hypointense on T1W1 and T2W1. White arrows indicate the lesion.

melanoma is greater among those family members who have dysplastic nevi [18]. Additional risk factors include a high number of nevi (>25) and atypical nevi [19]. Patients with a personal history of melanoma are also at higher risk for a second primary cutaneous melanoma. This risk appears to be greatest in the first 2 years after initial diagnosis and remains elevated for at least 20 years [20].

Diagnostic imaging

PMML and metastatic melanoma to the thorax can have varying radiographic presentations, and due to its rarity many factors remain unknown. In addition, many radiographic findings are not specific to either pathologic entity albeit being helpful to narrow the scope of diagnoses. Accordingly, histological assessment coupled with a thorough dermatological exam for primary malignancies and metastases is warranted. Approximately 5–10% of patients with metastatic melanoma have a primary melanoma of unknown origin [21]. Noninvasive imagining techniques, such as computed tomography (CT), MRI and positron emission tomography (PET), are valuable in baseline tumor staging, preoperative planning and management of response to treatment [22,23]. Of these, chest CT is not only the least expensive option, but also currently the most sensitive imagining modality for pulmonary malignancies in extracutaneous melanoma [23,24].

The predominant finding on chest CT of pulmonary disease is a well-demarcated solitary nodule or mass with round contour and lobulation, similar to that of neuroendocrine tumors on film. Figure 1 shows imaging of a 5 × 3.4 cm sized mass with a multilobulated margin and homogenous enhancement in the right-upper lobe of a 69-year-old man with no significant smoking history (Figure 1A) [25]. Biopsy with immunohistochemistry was positive for human melanoma black 45, S-100 protein and vimentin leading to a diagnosis of PMML. In addition, a retrospective review of pulmonary metastatic cases from the NIH demonstrated 98% of its study population presented with nodular appearances on chest roentgenogram [26]. PET/CT have also become increasingly popular in the staging of metastatic extracutaneous melanoma as melanoma cells have a higher metabolic rate, thus, showing higher ^{18}F-fluorine-2-fluoro-2-deoxy-D-glucose (FDG) avidity compared with adjacent tissue. Figure 1B demonstrates an image of the patient mentioned previously with high metabolic activity of their PMML as detected by PET/CT. This inherent metabolic trait can therefore unmask subtle recurrences, micrometastases and indeterminate nodal metastases [23]. MRI findings of PMML include melanotic and amelanotic patterns. A melanotic pattern
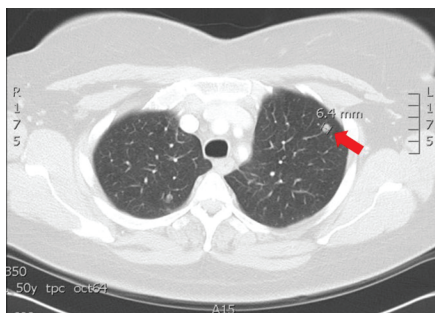
Figure 2.   Metastatic melanoma presenting with a single pulmonary nodule. Chest computed tomography (CT) scan with a left-upper lobe solid nodule from a 54-year-old woman who presented with 4 days of fever, nonproductive cough and scapular pain while being treated with antibiotics. The patient underwent a positron emission tomography (PET) scan 9 months after her initial CT chest scan, which demonstrated an increase in size of the known left-upper lobe noncalcified pulmonary nodule (red arrow) with focal ^{18}F-fluorine-2-fluoro-2-deoxy-D-glucose standardized uptake value (SUV) of 3.1. She underwent video assisted mediastinal lymph node dissection and thoracoscopic resection of the enlarging left-upper lobe nodule in the anterior segment. Left-upper lobectomy was performed and pathology was consistent with metastatic malignant melanoma. Follow-up PET scan revealed several new areas of hypermetabolic activity in the right vastus intermedius muscle with SUV of 16 and a PET avid soft-tissue nodule in the left-posterior-upper-thoracic region at the level of scapular spine with maximum SUV value of 12, which was later confirmed on biopsy to be metastatic melanoma. Despite extensive workup the site of primary melanoma was not identified.
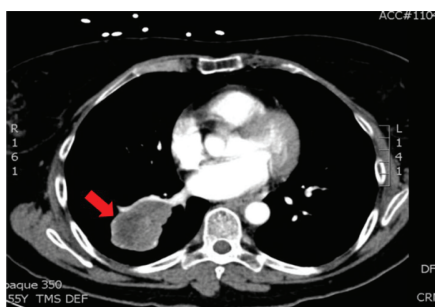

Figure 3.   Metastatic melanoma presenting with a focal pulmonary parenchymal mass. Computed tomography (CT) imaging demonstrates a 7.4 × 4.2 × 3.7 cm right-lower lobe mass (red arrow) from a 55-year-old woman, who presented to the hospital with confusion, severe right-sided headache and right facial droop. She had a history of a surgically excised melanoma on the anterior left chest 14 years prior with a positive sentinel node at that time. The patient then opted against systemic therapy. Endobronchial biopsy confirmed diagnosis of metastatic malignant melanoma.

distinguishes itself with hyperintensity on T1W1 and hypointensity on T2W1 while amelanotic patterned lesions are reversed with a stark hypointensity on T1W1 and hyperintensity on T2W1 (Figure 1C & D) [22,27].

A radiographic survey of 65 patients revealed the predominant presentation was one of solitary (Figure 2) or multiple pulmonary nodules [22]. A military pattern (so-called 'snowstorm') was only seen in five of the 65 patients and a lymphangitic pattern was seen in an additional five patients. Chest imaging of patients in this series further demonstrated the wide variability in radiographic presentations, including a parenchymal mass (Figure 3), bronchial obstruction by tumor, atelectasis, pleural effusion, single or multiple nodules, and mediastinal (Figure 4A) and/or hilar adenopathy [28]. Endobronchial metastases (Figure 4B) from melanoma have also been reported in other case series. Chung *et al.* reported such a case involving a hyperdense endobronchial metastasis with left-lower lobe intraparenchymal masses from melanoma [29,30]. Heyman *et al.* also documented an endotracheal metastasis from primary anorectal melanoma (reported in around 5% of those with extrapulmonary endobronchial metastases) [31].

In addition, flexible bronchoscopy is a valuable tool in the diagnosis and treatment of endobronchial lesions due to metastatic pulmonary melanoma. These tumors can have varying appearances from being amelanotic (Figure 5) or darker gray to even more pigmented lesions, which is consistent with prior reports [32]. When evaluating a patient with any of the pulmonary imaging findings above, metastatic melanoma must be included in the differential along with primary lung tumors and metastases from other solid organ tumors. Altogether, the use of various imagining modalities, including CT, MRI and FDG-PET/CT are invaluable tools in the proper evaluation of metastatic disease and assessment of treatment response.

Targeted therapy

Treatment options for advanced melanoma range from immunotherapy that targets inhibition of the MAPK pathway to surgical metastectomy with adjuvant radiotherapy (RT). Management of MM is complex and highly individualized based on history and patient prognosis.

The genetic mapping of melanoma has led to incredible breakthroughs in the molecular understanding of metastatic disease, particularly in the application of inhibition of known pathophysiologic mechanisms in MM. Known mutations in melanoma include v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), c-kit receptor
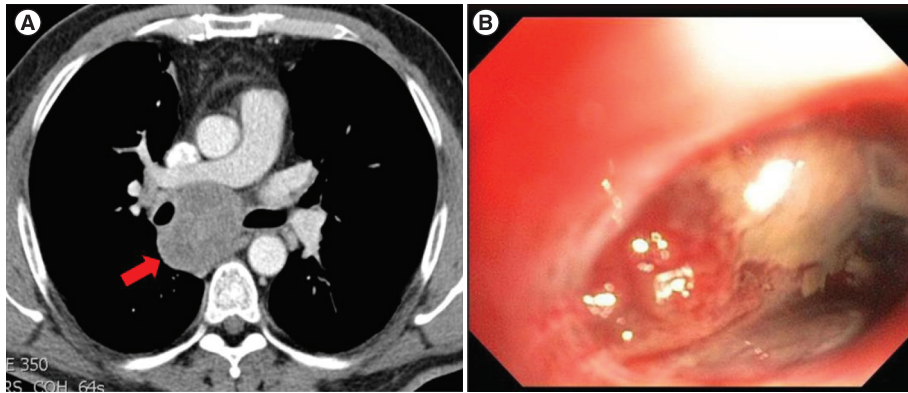
Figure 4.   Endobronchial metastasis from malignant melanoma. This patient was a 48-year-old man who presented to the emergency department with a cough productive of yellow-green sputum. **(A)** Chest computed tomography (CT) scan demonstrated a soft-tissue mass measuring 5.3 × 5.9 × 5.6 cm (red arrow) in the subcarinal space extending along the azygoesophageal recess complicated with esophageal displacement toward the left side. Ultrasound-guided biopsy demonstrated atypical epithelioid cells. **(B)** Bronchoscopy showed gray to black colored mucosa on the lateral wall of the superior segment off the pulmonary right-lower lobe.
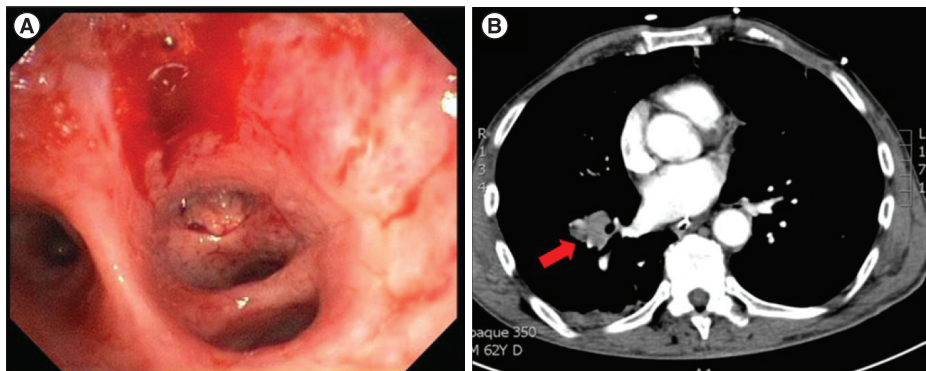

Figure 5.   Pulmonary metastatic melanoma presenting as a focal mass with irregular margins. (A) Bronchoscopy showing a pale exophytic lesion in the right-lower lobe anterior segmental airway in a 62-year-old man. Endobronchial cryobiopsy was significant for metastatic malignant melanoma. **(B)** Chest computed tomography (CT) was notable for right hilar lymphadenopathy and a 2-cm lesion with irregular margins (red arrow) was noted on the right-posterior chest wall.

tyrosine kinase (c-kit) and neuroblastoma RAS viral oncogene homolog (NRAS) [33,34]. *BRAF* mutations have been found in the majority of melanomas and are largely associated with more aggressive disease [33]. Two *BRAF* inhibitors, vemurafenib and dabrafenib, have been approved for use in advanced disease with tumors demonstrating *BRAF* mutations. In patients with stage IIIC or IV disease, *BRAF* inhibition with vemurafenib compared with standard cytotoxic chemotherapy demonstrated to be 5-months (5.9 vs 7.6 months) progression-free survival (PFS) and a 7-month (14.5 vs 7.6 month) overall survival (OS) advantage [35]. Despite these initially promising results, most patients treated with *BRAF* inhibition continue to exhibit disease progression after their initial treatment course [36].

Given these disappointing findings, experimentation with downstream inhibition of the *BRAF* pathway, via *MEK* inhibition remains an area of great interest. Trametinib, a highly potent *MEK* inhibitor has demonstrated activity in patients with *BRAF*-positive melanoma. The Phase III METRIC trail demonstrated a 6-month survival rate of 81% in the trametinib group compared with 67% in the standard chemotherapy arm (even though nearly half of the chemotherapy arm patients crossed over to trametinib following disease progression) [37]. Several other *MEK* inhibitors have been studied, including cobimetinib, binimetinib and selumetinib each showing activity in patients with *BRAF*-positive disease. Several ongoing and recently published trials have evaluated dual *BRAF/MEK* inhibition. A Phase III study evaluating dabrafenib and trametinib demonstrated an objective response rate (complete and partial) of 69 versus 53% in the dabrafenib/placebo arm [38].

Although *BRAF* mutations have been found in >50% of metastatic melanomas, c-kit mutations have been seen in 15–20% of tumors. Imatinib, known for Bcr-abl inhibition has demonstrated activity against c-kit; however, Phase II trials have shown minimal success [39]. In similar fashion, anti-angiogenesis studies have evaluated *VEGF* inhibition with limited results [40].

Similarly, the potential roles of RT in the treatment of patients with melanoma are limited. Although RT is considered effective in some settings, its use has decreased in recent years with the advent of new therapies that may also target the risk of systemic disease. Among patients with metastatic disease undergoing RT, stereotactic body RT (SBRT) and stereotactic radiosurgery in addition to surgery and other ablative modalities are used, and both modalities are still under active investigation regarding metastatic disease management [41]. SBRT delivers hypofractionated (high dose per fraction) treatment with high degrees of accuracy to the tumor site while minimizing exposure to the surrounding normal tissue. The modality delivers six- to ten-times the standard daily dose per fraction to the tumor in 3–10 treatment sessions over several weeks. A previous retrospective study suggested that a starting single fraction equivalent dose ≥48 gray is required to be effective for controlling metastatic melanoma with comparable local control rates with SBRT of other tumor etiologies [42].

The early success of treating inoperable non-small-cell lung cancer with stereotactic radiosurgery has led to the investigation of this technique for the treatment of limited pulmonary metastatic disease. In a multicenter Phase I/II study in which the dose was escalated from 48 to 60 gray in three fractions to increments of 6 gray to patients with limited pulmonary metastasis, no dose-limiting toxicity was observed and the 1-year local control rate was 100% [43]. Equally important, the role of RT has also demonstrated palliative benefit in the management of metastatic disease to relieve tumor-related symptoms. While palliative RT does not provide a chance for a cure, it improves overall quality of life and may prolong survival time. For patients with progressive metastatic disease this therapy can be an effective option to manage symptoms associated with spinal cord compression and particularly as an adjunct to surgery. Finally, patients with brain metastases can also benefit from RT by itself or as an adjunct to other therapies including surgery and steroids [44].

Immunotherapy

High-dose interferon had long been the adjuvant treatment of choice in advanced disease; however, it has limited efficacy in advanced disease and is associated with significant side effects, including flu-like illnesses, anorexia, fever and most notably latent autoantibody induction [45]. Following the disappointing results with high-dose interferon, IL-2 was evaluated. Although in combination with surgical resection, IL-2 demonstrated a small survival advantage; it too was associated with extensive and severe multiorgan toxicities, and IL-2 therapy ultimately failed to control extensive disease [46]. Despite this finding, a small proof-of-concept study evaluating the efficacy of low-dose inhaled IL-2 for pulmonary melanoma showed promising results, including control of disease, prophylaxis for recurrence following lung resection and decreased systemic toxicity [47].

Cancer vaccines are also being studied in the treatment of metastatic melanoma. Monotherapy with glycoprotein 100 (gp100), a vaccine made up of HLA-A20201 peptide from the melanosomal protein, has limited antitumor activity when given as monotherapy with an overall objective response rate of 2.9% [48]. Schwartzentruber *et al.* demonstrated that treatment in conjunction with high dose IL-2 has shown an increased response rate of 22%, and a similar study conducted by Rosenberg *et al.* showed a 42% response rate [49,50].

Antitumor activity can be further potentiated by upregulation of cytotoxic T-lymphocytes. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) acts to downregulate this pathway; CTLA-4 targeted blockade has shown promising results. Ipilimumab, a human monoclonal antibody that blocks CTLA-4, has demonstrated improved survival in patients with MM. In a study of 676 patients with unresectable stage III or IV melanoma, cohorts were randomized to ipilimumab, gp100, combined ipilimumab and gp100 treatment, or placebo in a 1:1:1:1 ratio [51]. Results demonstrated increased survival in patients treated with ipilmumab with or without gp100 (10 vs 6.4 months, respectively).

Following the success of CTLA-4 pathway blockade, interest increased in identifying additional potential immune-checkpoint targets. The programmed cell death 1 receptor ligand (PD-L1) pathway demonstrates similar downregulatory activity. Agents targeting programmed cell death protein-1 (PD-1) and its receptor ligand, PD-L1 have recently demonstrated efficacy in MM. The KEYNOTE-002 trial evaluated the efficacy of pembrolizumab, a PD-1 inhibitor in 540 patients with metastatic, ipilumumab-resistant disease. Patients were randomized to low-dose pembrolizumab, high-dose pembrolizumab or standard cytotoxic chemotherapy. PFS at 6 months was found to be 34, 38 and 16%, respectively. In a similar fashion, objective response rates were noted to be 21, 26 and

4% [52]. Nivolumab, a second PD-1 inhibitor demonstrated similar results. In CHECKMATE-066, nivolumab was compared with traditional cytotoxic chemotherapy in 418 untreated patients with MM. Here, 1-year survival rates were 73% with nivolumab therapy compared with 42% in the standard arm. Similarly, the objective response rate was 40 and 14%, respectively [53]. In 2016, results from a head-to-head CTLA-4 versus PD-1 blockade were released. PFS at 12 months was 39% in the short-cycle pembrolizumab group, 28% in the long-cycle pembrolizumab group and 19% in the ipilimumab cohort. Similar findings were demonstrated in 1- and 2-year OS as well as objective response rates [54]. A follow-up Phase III clinical trial (CHECKMATE-067), involved dual CTLA-4/PD-1 blockade with nivolumab and ipilimumab and demonstrated markedly improved 3-year OS at 58% in the combination arm compared with 52 and 34% in the nivolumab alone and ipilimumab alone, respectively [55].

Surgical treatment

Surgical metastasectomy has been used in patients with limited pulmonary involvement by MM. In one study of 86 patients who underwent resection of pulmonary metastases, 16% had improved disease burden after a median follow-up of 35 months. The estimated 5-year survival in this study was 33% [56]. A second series of patients undergoing metastectomy demonstrated a median survival of 19 months and a 5-year survival of 21% if they had complete pathologic resection [56]. Patients had the greatest benefit from metastasectomy if there were no extrathoracic metastases, which resulted in a disease-free interval from their cutaneous lesion of >5 years. Moreover, patients must be carefully evaluated for surgical candidacy to maximize survival benefit. In a Phase II study of 64 patients with stage IV metastatic disease, patients underwent complete surgical resection of their cancer. Median disease-free survival was only 5 months; however, OS at 3 and 4 years were 36 and 31%, respectively [57]. The patients most likely to benefit from complete resection remain those with a positive response to systemic therapy [58]. Resection of pulmonary metastatic disease was examined in the International Registry of Lung Metastases. Among the 282 patients, there were no long-term survivors who underwent incomplete resection; however, achieving complete surgical resection lead to 5- and 10-year survival rates of 22 and 16%, respectively [58]. A 2007 review of 1720 patients demonstrated a median survival following resection of 7.3 months; nevertheless, patients with a disease-free interval of >5 years prior to resection demonstrated a 1-year survival advantage (19 vs 7 months) [59].

The role of bronchoscopy beyond diagnosis for metastatic disease is largely limited to palliation, and evaluation of its utility as a therapeutic intervention is limited. Local tumor debulking utilizing a combination of cryotherapy, neodymium-YAG laser and endobronchial stenting has been shown to be both safe and efficacious in temporarily relieving symptoms. There have also been case reports of bronchoscopically deployed brachytherapy in an effort to deliver high-fraction radiation therapy directly to the tumor [60]. Although these observations are promising from a palliative perspective, benefits may be short lived and there is currently no evidence based data to support the widespread use of bronchoscopy within the context of MM treatment.

Novel therapeutic approaches

With the marked success of immune checkpoint inhibition in several neoplasms, extensive research continues to implicate the role of the immune system and its manipulation in MM prognosis. Specifically, novel understanding of the mechanism in which IL-33 function modulates tumor development has demonstrated promising avenues of immunotherapy treatment strategies. *In vivo* studies by Qi *et al.* reported that IL-33 administration can effectively inhibit the development of pulmonary metastasis of breast cancer in a mouse [61]. In their studies, IL-33 promotes the production of IL-33 specific receptor expression on natural killer cells, thus, mediating their recruitment to the tumor microenvironment. The subsequent systemic activation and local recruitment of natural killer cells results in significant tumor rejection in the lung. This novel mechanism for IL-33-mediated suppression of metastatic pulmonary cancer may provide potential therapeutic avenues for targeting metastatic tumors of various primary sources.

A group in Tokyo has focused on the application of siRNA using nanotechnology to regulate melanoma metastasis. In a recent study, they were successful in evaluating the inhibitory effect of anti-RelA (siRelA) conjugated with their novel functional peptide CH2R4H2C nanomicelle to target the NF-κB signaling pathway in metastatic pulmonary melanoma mouse models [62]. Using a validated metastasis model injected with the B16F10 mice melanoma cell line, they demonstrated a significant reduction in pulmonary nodules from mice treated with seven systemic injections of their novel formulation compared with naked siRelA groups. The positive findings of this approach may prove to be another important antimetastasis treatment strategy if it is also found to be effective in human trials.

The development of resistance to chemotherapy also continues to be the major impediment in the treatment of metastatic melanoma patients. The mechanisms conferring this intrinsic drug resistance in melanoma cells remain poorly understood. Among the more well-supported hypotheses, studies have implicated overactivity of the enzyme glutathione-S-transferase in melanoma cells, which conjugates glutathione leading to intracellular detoxification [63]. Mechanisms related to altered DNA repair have also been uncovered as neoplastic cells exhibit increased base excision repair (BER) of DNA damage via overexpression of key BER proteins, including human APE1, DNA polymerase β and FEN1 I and an upregulation of O^6-methylguanine-DNA methyltransferase, an enzyme involved in repair of DNA damage caused by alkylation [64]. However, advances in pharmaceutical science have also been made to circumvent this issue. Notably, Lian *et al.* recently derived a novel compound RJT-101, a camptothecin derivative, which theoretically blocks the overexpression of topoisomerase I unique to melanoma cells to induce cellular arrest and attenuate tumor growth [64]. *In vivo* randomized controlled studies demonstrated significant reduction in metastatic pulmonary nodule size when given three subcutaneous injections of the novel therapeutic per week compared with the delivery vehicle alone. A survival curve also showed that RJT-101 treatment significantly prolonged the survival of tumor-bearing mice without significant difference of body weight compared with the control group.

As the underlying molecular blueprint of melanoma continues to be elucidated, even more specific targets shall become available as treatment options. Researchers have already identified key proteins implicated in the metastatic potential of MM in the hopes of arresting this deadly disease [65]. With the varying presentations of pulmonary metastases from advanced melanoma and new therapies targeting this disease on the horizon, clinicians should maintain a high index of suspicion for MM when encountering newly discovered pulmonary lesions. This holds true for both minority groups with unknown risk factors and patients of European ancestry with a history of intense intermittent sun exposure, even if the exposure is infrequent.

Discussion

Melanoma is the deadliest form of skin cancer. A well-established relationship exists between MM and UV radiation, specifically UV-B radiation. A familial history of dysplastic nevi is another pertinent risk factor for developing MM. Among the various sites MM can spread to, including the oral cavity, paranasal sinuses and anorectal region, metastases to the lung remain rare. However, pulmonary metastatic melanoma has a better prognosis than when other organs are involved, with a 5-year OS of 17% [62]. In selecting the most appropriate therapeutic strategy, the clinical and histological features of the lesion, the patient aspect, and the body area involved should be considered.

Treatment options for advanced melanoma range from immunotherapy that inhibits the MAPK pathway to surgical metastasectomy with adjuvant RT. Among therapeutics that inhibit *BRAF* signaling, vemurafenib and dabrafenib have both been approved for use in advanced disease. Trametinib, a highly potent *MEK* inhibitor has also demonstrated activity in patients with *BRAF*-positive melanoma. In addition, subsets of metastatic melanoma are remarkable for c-kit signaling mutations; however, limited efficacy has been uncovered using imatinib. Immunotherapy has shown promise by modulating antitumor activity via upregulation of cytotoxic T-lymphocytes. Dual therapy with both PD-1 and CTLA-4 blockade using nivolumab and ipilimumab, respectively, was successful in markedly improving survival in MM patients compared with either therapy alone.

Surgical metastasectomy is a treatment for patients with limited pulmonary involvement typically indicative of an isolated and/or focal mass. Past studies on patients with complete resections of their pulmonary metastases have demonstrated improved 5- and 10-year survival rates of 22 and 16%, respectively.

Recent advances in the evaluation of new treatment approaches, including the evaluation of additional molecular targets have also shown promise. Nanomicelles engineered to carry siRNA to target the NF-κB signaling pathway have shown a significant reduction in metastatic pulmonary nodules in animal models. Another study uncovered the antitumor effects of IL-33, which has been shown to modulate the pulmonary metastases in mice with primary breast cancer. There is still a need to evaluate its therapeutic potential in modulating melanoma tumor activity.

Conclusion

MM represents the deadliest form of skin cancer with a surprisingly high burden of disease. The disease has a high metastatic potential, with the lung being one of the most common sites of spread. In selecting the most appropriate therapeutic strategy, the clinical and histological features of the lesion, the patient aspect, and the body area involved should be considered. Treatment options for advanced melanoma typically range from immunotherapy that inhibits the MAPK pathway to surgical metastasectomy with adjuvant RT. Palliative RT is also important

in the control of tumor-related burden associated with metastatic disease. Recent research advances have yielded potential new treatment modalities to improve upon the current available therapeutic options for MM. Specifically, insights to the antitumor activity of IL-33 could become an invaluable multimodal approach to treating patients with pulmonary metastatic melanoma. In addition, improved understanding of the chemoresistant mechanisms underlying MM has allowed opportunities for pharmaceutical science to circumvent this issue. The application of a camptothecin derivative, which has been shown to limit rapid-cell turnover specific to MM is evidence of this fact and may eventually become another option to treat patients with complex MM.

Future perspective

With the advent of new and combination therapies, the treatment of MM has resulted in an increase in overall PFS. Prevention and early detection will always remain the mainstay in successfully treating this disease. Trials in therapeutic vaccines are also underway. The future in treating more advanced MM and associated metastatic disease will lie in finding specific mutations and individualizing treatment. As researchers are actively pursuing these targeted therapies, our understanding of this deadly disorder has also grown, allowing us to provide better care even for those patients who present with metastatic disease.

Author contributions

KS Zhang, T Pelleg, S Campbell and S Ie contributed to conceptualization of the study. All the authors contributed to investigation and resources of the study. KS Zhang, T Pelleg and S Campbell contributed to writing the original draft. KS Zhang, Catalina Rubio, AL Loschner and S Ie contributed to writing review and editing. KS Zhang contributed to project administration. S Ie supervised the study.

Financial & competing interests disclosure

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