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Integumentary Case Study

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NUR 586: Clinical Anatomy

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Case Study Overview

Chief Complaint: 48-year-old man with suspicious-looking mole on his back.

History:

- Max Burnell, a single, 48-year-old avid long-distance runner previously in good health, presented to his primary physician for a yearly physical examination.
- During the exam, a suspicious-looking mole was noticed on the back of his left arm, just proximal to the elbow.
- He reported he has had that mole for several years but thinks that it may have gotten larger over the past two years.
- He reported that he has noticed itchiness in the area of this mole over the past few weeks.
- He had multiple other moles on his back, arms, and legs, none of which looked suspicious.
- Upon further questioning, he reported that his aunt died in her late forties of skin cancer, but he knew no other details about her illness.
- Max is a computer programmer who spends most of the work week indoors. On weekends, however, he typically goes for a 5-mile run and spends much of his afternoons gardening.
- He has a light complexion, blonde hair, and reports that he sunburns easily but uses protective sunscreen only sporadically.

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Physical Examination

- Head, neck, thorax, and abdominal exams were normal, except for a hard, enlarged, non-tender mass felt in the left axillary region.
- In addition, a 1.6 x 2.8 cm mole was noted on the dorsal upper left arm.
- The lesion had an appearance suggestive of a melanoma.
- It was surgically excised with 3 mm margins using a local anesthetic and sent to the pathology laboratory for histologic analysis.

(Saladin, 2018)

How does the appearance of a malignant melanoma differ from that of a normal mole, or nevis, on gross inspection (i.e. the macroscopic appearance)?

Normal mole/Nevis	Melanoma
Uniform in color, typically one shade of brown	Not homogenous in color, may be several shades of brown or blue
Symmetrical	Asymmetrical
Even contour, smooth outline	Irregular border or outline
No larger than 6 mm or about the size of the end of a pencil eraser	Larger than 6mm in diameter
Smooth texture	Uneven texture, some areas raises above the skin and other areas even with the skin
	More likely to bleed or have reddish hallo

(Saladin, 2018)

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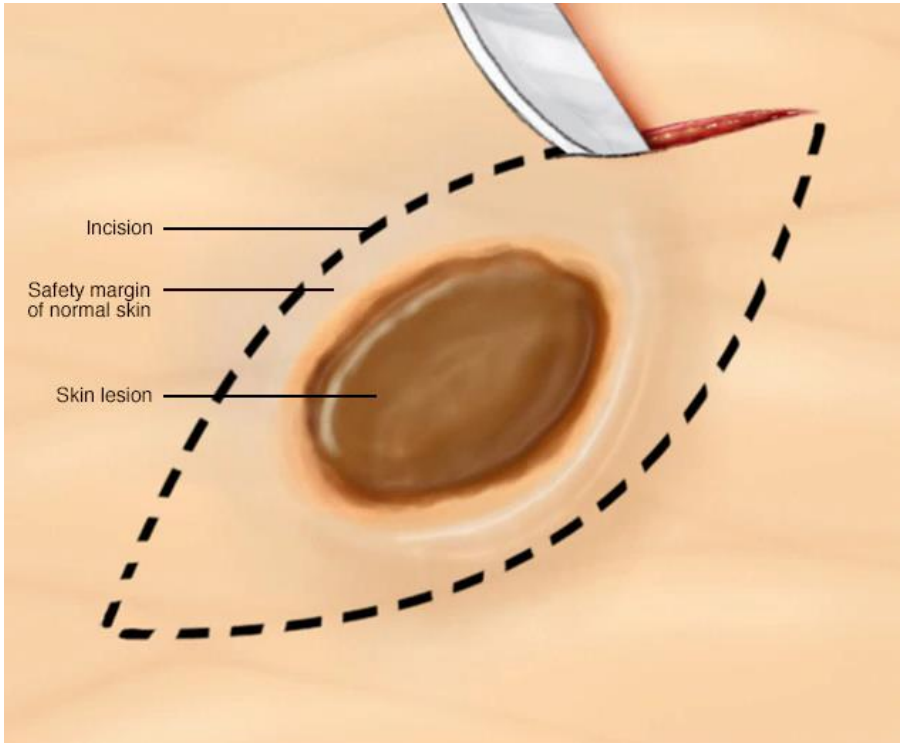
Why was it important to surgically excise and examine this mole?



(Mayo Clinic,2020)

- The patient's mole has "an appearance suggestive of melanoma." One can assume the patient's mole had characteristics listed in the table on the previous slide.
- Additionally, the patient has several risk factors such as fair skin, male, sunburns easily, and family history of skin cancer (Saladin, 2018). For this reason, a surgical excision and biopsy of the lesion is appropriate for this high-risk patient to examine the cells under a microscope and determine whether they are cancerous.
- Because melanoma cancer metastasizes quickly, it is important to diagnose early to improve prognosis for the patient. Once this type of cancer metastasizes, it becomes difficult to treat which results in a poor prognosis (McCance & Huether, 2019).

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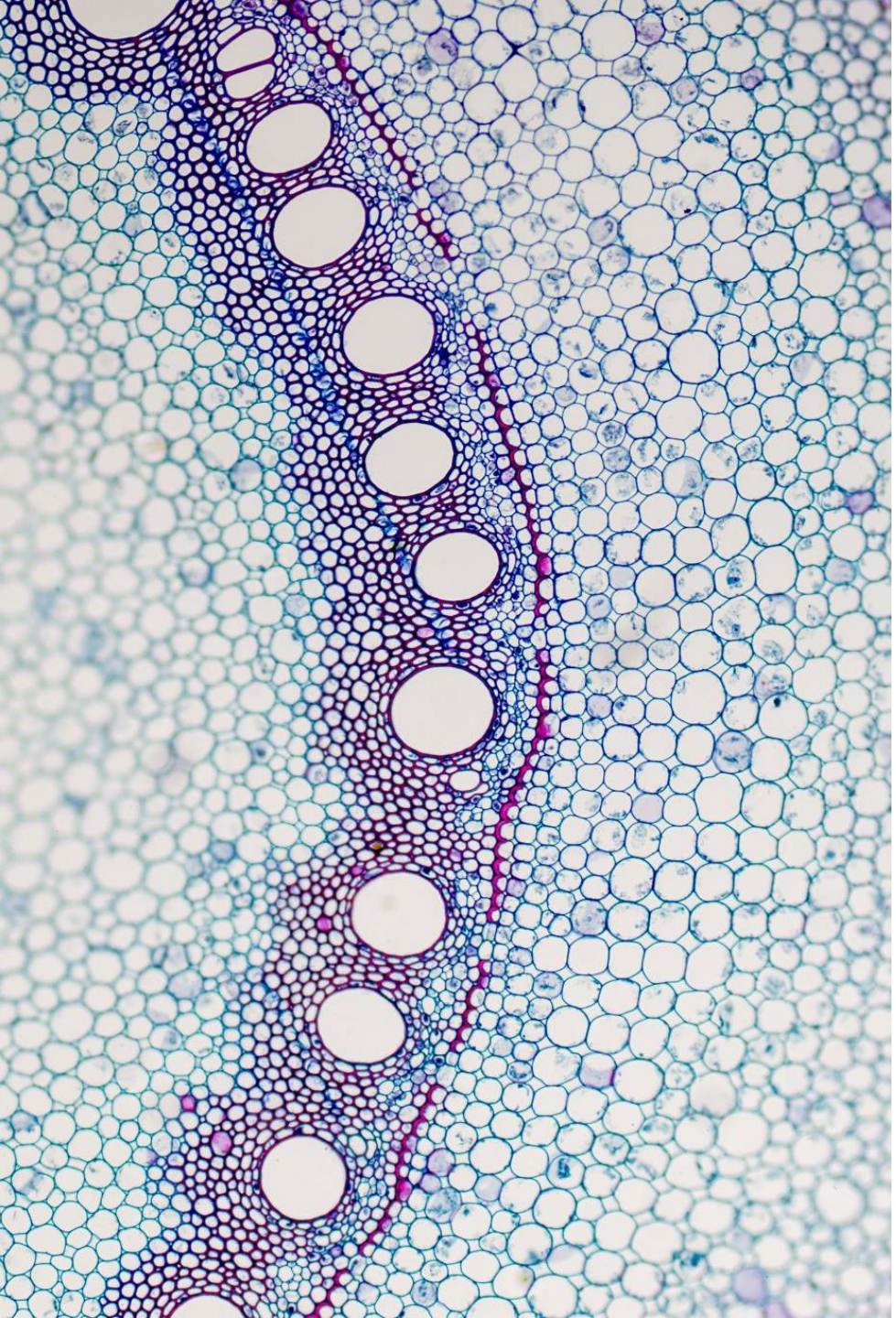

Pathology Report

The pathology report gave the following description of the tissue sample:

> "Diagnosis: Superficial spreading melanoma with vertical level V invasion. Coalescent nests of neoplastic cells were noted in the papillary and reticular dermis and in the subcutaneous layer. In addition, large pink-stained cells with pleomorphic nuclei were found spreading radially through the epidermal layer. Proliferating lymphocytic cells are noted in the dermis surrounding the malignant cells."

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What do levels I, II, III, IV, and V vertical invasion refer to when describing melanomas?

- **Level I** – also referred to as “melanomas in-situ,” includes lesions up to 2mm with no nodal or distant metastases, cells localized to the epidermis (not invaded through the basement membrane)
- **Level II** - melanoma tumor has just begun to invade the basement membrane and travel into the papillary dermis (second layer of the skin), includes larger lesions greater than 2mm without positive nodes or distant metastases
- **Level III** - melanoma tumor is filling and expanding deeper through the papillary dermis, this level includes lesions of any
- **Level IV** - melanoma tumor has invaded the reticular dermis
- **Level V** - melanoma tumor has invaded the subcutaneous fat layer beneath the dermis and penetration into the third layer of the skin (the subcutis)

(McCance & Huether, 2019; OncoLink Team, 2018)

Why is it useful to determine the level of invasion of this lesion?

- Melanoma is the most serious form of skin cancer with an estimated 87,110 cases and 9,730 deaths in the United States in 2017 (McCance & Huether, 2019).
- Statistically, it is imperative for a patient's prognosis to identify and treat melanoma before it invades deeper into the skin or metastasizes to other areas of the body.
- The level of invasion is determined by a health care provider to help guide/determine treatment options for the patient after surgical excision as well as give the patient a prognosis.
- Melanoma metastasizes quickly and is unresponsive to chemotherapy; for this reason, the average patient lives only 6 months after diagnosis. However, if the cancer is caught prior to metastasis, patients have a 5-year survival rate (Saladin, 2018).

Propose an explanation for why proliferating lymphocytes were noted around the borders of the lesion.

- Melanomas are considered one of the most immunogenic tumors, inducing both innate and adaptive immune responses.
- Among these immune responses, the most abundant immune cell type in the tumor microenvironment (TME) are lymphocytes, especially CD8+ T-lymphocytes, besides tumor-associated macrophage (Gonzalez et al. 2018).
- During melanomagenesis or tumor initiation, immunogenic antigen-presenting on the tumor cell will induce naive T-lymphocyte cells from surrounding lymph nodes.
- The T-lymphocytes will then proliferate and invade the tumor microenvironment.
- It is this invasion of the TME that makes proliferating lymphocytes detectable in the dermis surrounding melanomas.

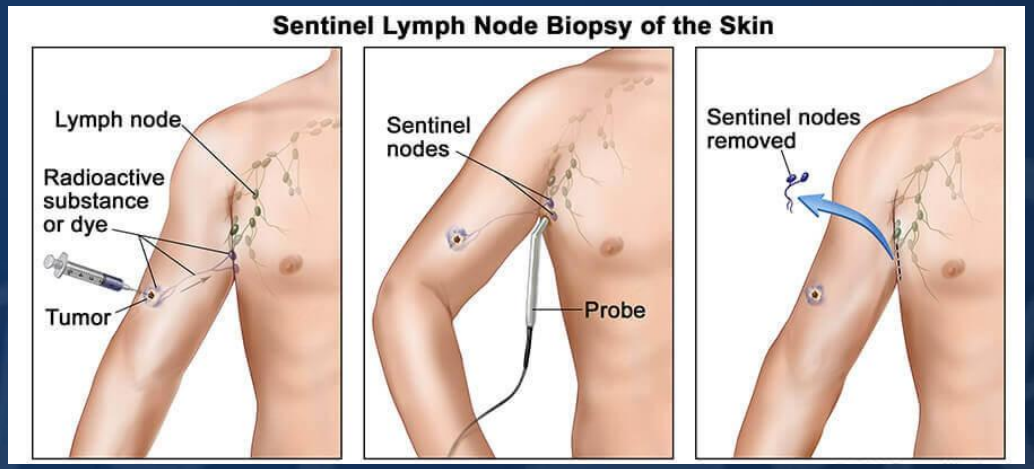
Max is told that he has a malignant melanoma and that it may have already metastasized. He is advised that he may need additional surgery to verify that his tumor has metastasized...

Why does Max's physician think that his cancer has already metastasized?

- The analysis of Max's pathology results was done using the Clark level criteria.
- This criterion uses a level number to grade how deep an invasion is, and the higher the level number, the deeper into the tissue the invasion extends.
- Max's results indicated a superficial spreading melanoma with a vertical level V invasion.
- This description, according to the Clark criterion means that the melanoma has metastasized into the subcutaneous tissue.

What additional surgical procedure might help Max's physician determine whether his cancer has metastasized?

- To further confirm a metastasis, a sentinel lymph node biopsy can be performed. This procedure requires an injection of a radioactive dye into the bloodstream, and the dye is subsequently picked up by the lymphatic nodes that have the metastasis. The lymph node is then surgically removed, and a pathological test is performed to confirm whether it is positive or negative for metastasis.
- The rationale is that a positive test indicates that the melanoma has learned the complex pathway of immune evasion. Once the melanoma has been able to metastasis into the sentinel lymph node, there is a higher risk that there will be a distant spread.



(National Cancer Institute, 2020)

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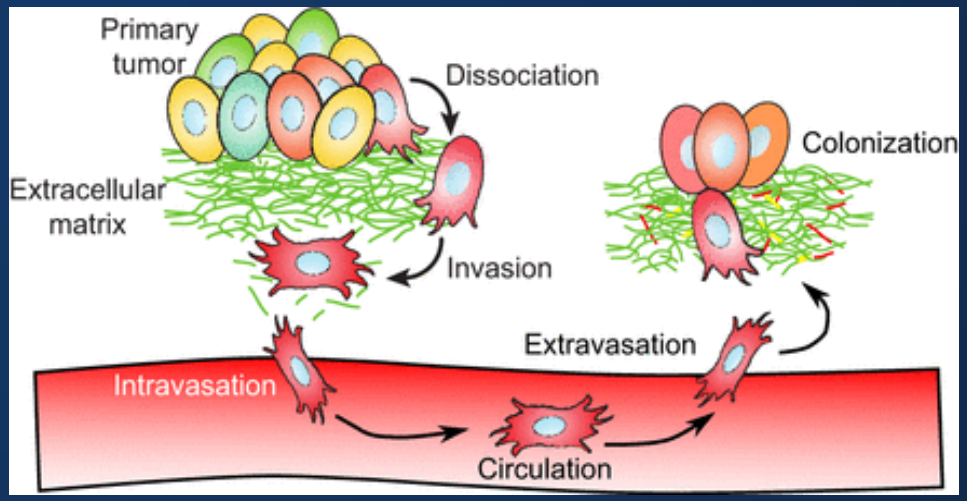
The surgical procedure alluded to in the last question showed that Max's cancer had indeed spread to another part of his body...

How do malignant melanomas normally spread to other areas of the body?

- Though melanomas typically begin in the epidermis as a superficial lesion, malignant melanomas may eventually spread to any area of the body through the lymphatic system or blood vessels. Usually, these lesions grow in a horizontal pattern, a phase known as radial growth (Cersosimo, 2006).
- However, once melanoma begins to grow vertically, ultimately piercing the endothelium of capillaries, the tumor cells move into the bloodstream and lymphatics permitting them to create distant metastases (McCance & Huether, 2019).
- Nguyen and Massagué (2007) describe the process of metastasis in phases including "vessel formation, evasion of immune surveillance, embolism, capillary adhesion, extravasation and organ-specific colonization" (p. 342).
- The vessels provide the nutrients the tumors need to grow and prepare for metastasis.
- The tumors evade immune surveillance by "immune suppressive effects or by loss of target antigen expression" (Vinay et al., 2015, p. 186).
- Embolism involves the individual tumor cells or groupings of tumor cells entering circulation. If the cells survive in circulation, they must then "extravasate the vasculature to invade the target tissue parenchyma, where metastatic foci are established" (Miles et al., 2008, p. 305).
- Once the tumors are within the lymphatic system, they "may simply follow an interstitial pressure gradient or may secrete cytokines that induce growth of lymphatics towards the tumor or within the tumor" (Zybtek et al., 2008, p. 7).
- The tumor cells then occupy the extracellular matrix (ECM), extend to lymphatic vessels, then flow through the lymphatic system reaching the lymph node subcapsular sinus (Zybtek et al., 2008).



(Albritton & Miller, 2017)

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Describe some of the current theories of the etiology of malignant melanoma.

- Certain etiological factors predisposing patients to melanoma have been known for years, such as genetic predisposition and UV exposure. An accumulation is seen of genetic changes that trigger oncogenes, damage DNA mending genes, and inactivate tumor suppressor genes (McCance & Huether, 2019). The *BRAF* oncogene has been found to cause two-thirds of melanoma cases in men, but virtually not a causative factor in women (Saladin, 2018).
- Recently, several whole genome (WGS) or whole exome sequencing (WES) studies have exposed specific gene drivers in several types of melanomas, with mucosal and acral melanomas of particular concern, as they arise in sun-shielded body locations with little or absent UV exposure (Krauthammer, 2018). “The fact that these melanomas have a distinct non-UV signature is of great interest and may hint at a common mechanism that affects melanocytes in the oral cavity and esophagus” (Krauthammer, 2018, p. 1074).
- Some theories have delved deeper into the etiology behind UV exposure as well. Bhandaru et al. (2015) “asked if ser-1981 phosphorylation of ATM is associated with melanoma progression and prognosis” (p. 2) since several other sites have been recognized and stated to regulate ATM activity. “Results revealed that both loss of, and gain in, p-ATM expression were associated with progression of melanoma from normal nevi to metastatic melanoma” (Bhandaru et al., 2015, p. 4). Researchers continue to develop new and more current theories into the etiology of malignant melanoma.

Two treatments available for Max's malignant melanoma and their effectiveness:

Treatment for melanoma depends on the cancer type and whether it is localized or metastatic (Saladin, 2018). Since it is known that Max's disease has metastasized, treatment will likely consist of immunotherapy, cryotherapy, radiation therapy, or other various types of infusions. It is important for the patient to understand that once metastasis emerges, melanoma is fatal with 5-year survival rates of 20-63% (Yu et al., 2019).

Treatment Option 1:

Immunotherapy involves using the body's own immune system to prevent and treat disease.

Interleukin-2 (IL-2) is one of the most successful and widely known treatments for metastatic melanoma. A retrospective study by Buchbinder et al. (2019) found high doses of IL-2 exhibited robust antitumor action, response rate 22.5%, in metastatic melanoma patients.

Another common immunotherapy, ipilimumab, has been shown to effectively increase overall survival rates. Schadendorf et al. (2015) studied information from 2985 patients with metastatic melanoma and ipilimumab treatment and found the average overall survival was 9.5 months and the three-year rate was 21%.

Treatment Option 1:

Radiation therapy in the treatment of metastatic melanoma is typically used in adjunct to immunotherapy. Aboudaram et al. (2017) discovered that in combination, radiation therapy and immunotherapy at a 10-month follow-up had a response rate that was considerably higher than the control (immunotherapy alone) group (64.7 vs. 33.3%, *P*=0.02).

The incidence of malignant melanoma has increased over the past few decades. Propose an explanation for this trend.

- The number one cause of melanoma is UV exposure through repeated sunburns and indoor tanning. Fair skin individuals are at the highest risk to develop melanoma, yet these individuals live in a society that sees “tanned” skin as a positive attractive feature. Men and women use tanning beds before weddings, trips, and other big events to get that “glow” for pictures. Many people also believe getting a “base tan” will prevent them from getting sun burns on vacations, so their respective risk of developing skin cancer is lessened. This is just not true. A person is more likely to develop skin cancer from use of indoor tanning than develop lung cancer from smoking (Wehner et al., 2014).

- The increase in malignant melanoma is directly correlated, in my belief, to the pressure of society to have “tan” skin and also the lack of proper healthcare. Current generations demand instant gratification, so preventative care or the need for primary physicians seems unwarranted. Why pay for a medical visit if nothing is wrong? By the time these patients seek medical care, it is likely the melanoma may have metastasized.

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References Continued

Aboudaram, A., Modesto, A., Chaltiel, L., Gomez-Roca, C., Boulinguez, S., Sibaud, V., ... & Meyer, N. (2017). Concurrent radiotherapy for patients with metastatic melanoma and receiving anti-programmed-death 1 therapy: a safe and effective combination. *Melanoma research*, *27*(5), 485-491. https://doi.org/10.1097/CMR.0000000000000386

Albritton, J. L., & Miller, J. S. (2017). 3D bioprinting: improving in vitro models of metastasis with heterogeneous tumor microenvironments. *Disease models & mechanisms*, *10*(1), 3-14.

Bhandaru, M., Martinka, M., McElwee, K. J., & Rotte, A. (2015). Prognostic significance of nuclear phospho-ATM expression in melanoma. *PLOS One*, *10*(8), 1-15. https://doi.org/10.1371/journal.pone.0134678

Buchbinder, E. I., Dutcher, J. P., Daniels, G. A., Curti, B. D., Patel, S. P., Holtan, S. G., ... & Richart, J. M. (2019). Therapy with high-dose Interleukin-2 (HD IL-2) in metastatic melanoma and renal cell carcinoma following PD1 or PDL1 inhibition. *Journal for immunotherapy of cancer*, *7*(1), 1-7. https://doi.org/10.1186/s40425-019-0522-3

Cersosimo, R. J. (2006). Cutaneous malignant melanomas. *US Pharm*, *7*, 3-15. https://www.uspharmacist.com/article/cutaneous-malignant-melanomas

Gonzalez, H., Hagerling,C., & Werb, Z.(2018). Roles of the immune system in cancer ; from tumor initiation to metastatic progression. *Gene and development* 32(19-20), 1267-1284

Krauthammer, M. (2018). Unraveling the etiology of primary malignant melanoma of the esophagus. *Journal of thoracic disease*, *10*(9), 1074. https://dx.doi.org/10.21037%2Fjtd.2018.03.91

Mayo Clinic (2020). Excisional Biopsy [Photograph]. Retrieved from https://www.mayoclinic.org/diseases-conditions/melanoma/diagnosis-treatment/drc-20374888

McCance, K. L., & Huether, S. E. (2019). Pathophysiology-E-book: the biologic basis for disease in adults and children. Elsevier Health Sciences.

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References

Miles, F. L., Pruitt, F. L., van Golen, K. L., & Cooper, C. R. (2008). Stepping out of the flow: capillary extravasation in cancer metastasis. *Clinical & experimental metastasis*, *25*(4), 305-324. https://doi.org/10.1007/s10585-007-9098-2

National Cancer Institute (2020). Sentinel Lymph Node Biopsy of the Skin [Photograph]. Retrieved from https://www.cancer.gov/news-events/cancer-currents-blog/2017/lymph-node-surgery-melanoma

Nguyen, D. X., & Massagué, J. (2007). Genetic determinants of cancer metastasis. *Nature Reviews Genetics*, *8*(5), 341-352. https://doi.org/10.1038/nrg2101

OncoLink Team. (2018, September 26). Understanding your pathology report: Melanoma. OncoLink. https://www.oncolink.org/cancers/skin/melanoma/treatments/understanding-your-pathology-report-melanoma

Saladin, K. S. (2018). Anatomy & physiology: The unity of form and function. McGraw-Hill.

Schadendorf, D., Hodi, F. S., Robert, C., Weber, J. S., Margolin, K., Hamid, O., ... & Wolchok, J. D. (2015). Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *Journal of clinical oncology*, *33*(17), 1889. https://dx.doi.org/10.1200%2FJCO.2014.56.2736

Vinay, D. S., Ryan, E. P., Pawelec, G., Talib, W. H., Stagg, J., Elkord, E., ... & Signori, E. (2015). Immune evasion in cancer: Mechanistic basis and therapeutic strategies. *Seminars in cancer biology* (35) 185-198. http://dx.doi.org/10.1016/j.semcancer.2015.03.004

Wehner, M. R., Chren, M. M., Nameth, D., Choudhry, A., Gaskins, M., Nead, K. T., ... & Linos, E. (2014). International prevalence of indoor tanning: a systematic review and meta-analysis. *JAMA dermatology*, *150*(4), 390-400.

Yu, C., Liu, X., Yang, J., Zhang, M., Jin, H., Ma, X., & Shi, H. (2019). Combination of immunotherapy with targeted therapy: theory and practice in metastatic melanoma. *Frontiers in Immunology*, *10*, 990. https://doi.org/10.3389/fimmu.2019.00990

Zbytek, B., Carlson, J. A., Granese, J., Ross, J., Mihm, M., & Slominski, A. (2008). Current concepts of metastasis in melanoma. *Expert review of dermatology*, *3*(5), 569-585. https://dx.doi.org/10.1586%2F17469872.3.5.569

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