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Review

A Review of Diagnostic Accuracy for Melanoma, Immunotherapy and Targeted Therapies

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ABSTRACT

Melanoma is a malignancy arising from the melanocytes. Australia has the highest melanoma rates in the world; real data show one Australian will be diagnosed with melanoma this year. Many British expatriates live and work in Australia. Awareness of commonly occurring anatomy locations for melanoma should be taught during patient education in dermatology clinics. Multiple theories of etiology exist, however, most notably is the BRAF mutation occurring primarily in the BRAF gene, which leads to uncontrolled cell signaling and proliferation, potentially driving melanoma development. Scientists have developed targeted therapies for the most common BRAF mutation, known as BRAF V600E mutation which represents a replacement of valine(V) for glutamic acid(E). This article will look at the risk factors, diagnostic accuracy, prognostic factors for cutaneous melanoma such as Breslow's depth; a measurement used to determine the depth of a melanoma tumor's invasion into the skin. And a review of local recurrence rates for primary melanoma indicates that there needs to be further research. Previous research has focused on melanoma-related deaths associated with a Breslow thickness threshold larger than 0.7mm – 0.75mm.

Daily sun protection cream or lotion is recommended for young people aged 20- 30years especially for UVA and UVB radiation related leisure activities, people with Fitzpatrick skin type I-III aged 70 years and above, people living in the tropics and frequent travellers and expatriates to the tropics. High-risk patients also need self-directed assessments of irregular and changing moles on the skin through use of physician approved mobile apps.

Keywords: Cutaneous melanoma; Melanoma staging; Dermoscopy; Skin cancer; Immunotherapy

Introduction

Most melanomas are caused by the sun. In fact, one UK study found that about 86 %of melanomas can be attributed to exposure to ultraviolet (UV) radiation from the sun[1,2]. 5-year survival among patients with localized melanoma is greater than 99%, whereas 5-year survival for those with distant or metastatic melanoma falls to 35%. These numbers are based on people diagnosed with melanoma between 2014 and 2020 in the United States. Similarly, 5-year survival among patients with localized squamous cell carcinoma (SCC) is 95%, whereas 5-year survival for those with regional SCC decreases to 58%[3]. Accurate screening for skin cancer coupled with earlier diagnosis can

optimize outcomes, minimize the number of invasive diagnostic procedures for benign lesions (skin biopsy), avoid associated morbidities and reduce health care costs[4,5]. Using the naked eye is the current standard of care for skin cancer examination and histopathologic testing remains the gold standard for skin cancer diagnosis[4,5].

Methods

Data extraction was performed by a reviewer, with verification by a second reviewer. A mixed-effects model was used in the data analysis. Data analyses were performed from May 2022 to December 2023[5].

Results

According to a meta-analysis of 100 studies found that using dermoscopy compared with clinical examination substantially improved diagnostic accuracy for melanoma (relative odds ratio [ROR], 5.7) and for keratinocyte cancer (ROR, 2.5). Sensitivity and specificity using clinical examination and images of melanoma were 76.9% and 89.1% for experienced dermatologists compared with 78.3% and 66.2% for inexperienced dermatologists and 37.5% and 84.6% for primary care physicians; using in-person dermoscopy and dermoscopic images, they were 85.7% and 81.3% for experienced dermatologists, 78.0% and 69.5% for inexperienced dermatologists and 49.5% and 91.3% for Primary care physicians.5 These results were statistically significant.

Discussion

Melanoma is a malignant tumor of melanocytes, which are the cells that make the pigment melanin and are derived from the neural crest. Although most melanomas arise in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate, including the uveal tract. Uveal melanomas differ significantly from cutaneous melanoma in incidence, prognostic factors, molecular characteristics and treatment. The thickness of the tumor (Breslow's depth) is the most important factor. Deeper tumors have a higher risk of metastasis. A review of the histology of an excised right thigh In-situ melanoma showed a peripheral depth of 1. 6mm and a deep depth of 4.8 mm, an ellipse of skin measuring 38 x13 x 9 mm on macroscopy. Microscopically, the skin specimen showed post -surgical changes only, no residual malignancy was seen. Although there is no Current standard guidance for excision margins for stage 0 or in situ melanoma, consensus margins recommend margins of at least 5mm for stage 0 melanoma, with a goal of achieving microscopically negative margins. However, 5 mm margins may be inadequate for some cases of in-situ melanoma and wider margins may be required[6,7]. Skin cancer is the most common malignancy diagnosed in the United States[8]. According to a cohort study in New South Wales, Australia, the analysis included a cohort of 144 447 Australian patients diagnosed with thin (T1) primary invasive melanomas (≤1.0 mm), consisting of 111 584 from the AIHW and 32 863 from the NSW-CanDLe initiative.9 The most common primary melanoma site was the trunk (36.3%) followed by the upper limbs (24.4%) and the lower limbs (22.1%)[9].

A study identified Acral and cutaneous melanoma tissue microarray with 32 samples from patients with acral melanoma and 14 samples from patients with cutaneous melanoma. 90% of acral samples and 57.1% of cutaneous samples were positive for HOXB13. Acral tumours staining positively for HOX13 included both primary (8 out of 9) and metastatic (19 out of 21) samples, indicating that positional identity might be retained at distant metastatic sites[10]. The study was hinged on the Anatomic location which determines oncogenic specificity in melanoma.

Risk Factors

A systematic review and meta-analysis of 23 studies and 21 risk prediction models Carried out at the Melanoma institute of Australia, discovered the need to identify the best performing risk prediction model for sentinel lymph nodes biopsy positivity in melanoma[17]. Twenty-one risk prediction models were identified encompassing a collective 168000 model development patients. A total of 15 unique predictor variables were identified, of which the most utilized was the Breslow depth (15 studies), followed by ulceration (14 studies), age (12 studies), Clark level (8 studies), mitoses (8 studies) and anatomic location of the primary melanoma (7 studies)[11-16].

What is the role of climate in melanoma virulence?

There is a staggering lack of meta-analyses or systematic reviews that examine the relationship between climate change and skin cancer. Climate change is a dynamic phenomenon that is anticipated to have adverse effects on human health, including skin cancer[20]. Particularly, melanomas are the deadliest form of skin cancer and 65%-90% of melanomas are attributed to UV radiation[21].

It was estimated that some 59 000 (65%) of about 92000 melanomas that occurred worldwide in 1985 were caused by sun exposure[21]. People who have benign sun damage in the skin are more likely to develop a skin cancer than those who do not. Incidence of skin cancer in some populations has been observed to fall in a temporal pattern consistent with an effect of increasing efforts to control sun exposure on skin cancer risk[22]. Several factors affect human exposure to UV radiation, including latitude, altitude and behaviours related to occupational and leisure activities[23].

Previous studies that examined the relationship between shift work and skin cancer risk have provided inconclusive results. However, occupation such as shift work have been studied to be associated with increased incidence of melanoma. A study defined shift work as working between 1:00 AM and 2:00 AM for at least 6 months[24]. Based on the literature, individuals who practice outdoor sport-related activities receive high ultraviolet radiation exposure, have a high risk for skin cancer, have a high prevalence for pigmented lesions and may benefit from electronic sun protection educational interventions[25]. Behaviors related to temperature and exposure to UV radiation and occurrence of skin cancer have also been researched relatively frequently and have been identified as an important determinant of skin cancer incidence in the context of climate change, a factor that may increase risk and a key potentially modifiable risk factor[26].

Melanoma and skin types

Screening detection for all US adults >70 years old with Fitzpatrick skin type I-III (Hartman et Al 2020). Dermatologist usually perform Total body skin examination TBSE for detecting incidental skin cancer in higher- risk patients. In low resource countries, this approach to early diagnosis may identify in situ melanoma in the early stages and address the problem of healthcare cost if this is done annually. A large

portion of Literature show that regular and consistent use of sun protection factors 30 or 50 can prevent the risk of developing melanoma, other skin cancers like squamos cell carcinoma SCC and effective in reducing the number of moles acquired in early life, which are a risk marker for melanoma[30]. Sunscreen should be applied generously and frequently and is recommended for young people aged 20- 30years especially for UV radiation related leisure activities, people with Fitzpatrick skin type I-III aged 70 years and above, people living in the tropics and frequent Travellers and expatriates to the tropics.

What is the diagnostic accuracy for melanoma?

What does a melanoma look like? As majority of people often detect skin cancer at the later stages, it is worthwhile to educate on the subtle skin changes associated with melanoma. Most malignant changes occur gradually and increase in size and diameter over time. Most patients we have had consultations with have described dry white skin changes around the periphery of the suspected melanoma. It is non-tender, brown colour and non-pruritic. As a rule, patients should look out for changing mole or 'ugly duckling' mole that looks different in size and diameter from other benign moles on the body. A cohort study conducted by Kaiser Permanente Northern California of 59,279 primary care patients demonstrated that a store-and-forward tele dermatology workflow involving capture of high-resolution dermoscopic images and image retrieval to a large computer monitor (in contrast to a smartphone screen) was associated with a greater probability of cancer detection despite fewer face-to-face visits compared to direct referral (Marwaha et al., 2019).

- **A is for Asymmetry:** One half of a mole or birthmark does not match the other.
- **B is for Border:** The edges are irregular, ragged, notched or blurred.
- **C is for Color:** The color is not the same all over and may include different shades of brown or black or sometimes with patches of pink, red, white or blue.
- **D is for Diameter:** The spot is larger than 6 millimeters across (about ¼ inch – the size of a pencil eraser), although melanomas can sometimes be smaller than this.
- **E is for Evolving:** The mole is changing in size, shape or color.

American Joint Committee on Cancer (AJCC) recommended the following TNM criteria for primary tumour staging in 2018[28].

a. T1: ≤1 mm (a: <0.8 mm without ulceration; b <0.8 mm with ulceration or 0.8-1 mm with or without ulceration)
b. T2: 1.1 to 2 mm (a: without ulceration; b: with ulceration)
c. T3: 2.1 to 4 mm (a: without ulceration; b: with ulceration)
d. T4: >4 mm (a: without ulceration; b: with ulceration)
e. N - Nodal involvement. detected in lymph nodes next to the main site where the melanoma was found.
f. M - Metastasis. measures spread of the tumor to distant body sites.

Immunotherapy drugs enhance the immune system's ability to fight cancer; they are used to treat melanoma.

- **atezolizumab:** blocks the interaction between programmed cell death protein 1 ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) on immune cells.
- **interleukin-2:** IL-2 binds to IL-2 receptors (IL-2R), which are expressed by melanoma cells, triggering a cascade of events that may lead to the death of cancer cells. It was the first immunotherapy approved for metastatic melanoma.
- ipilimumab binds to CTLA-4, preventing it from interacting with its ligands, CD80 and CD86.
- nivolumab specifically binds to the PD-1 receptor on T cells thereby prevents it from interacting with its ligands, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2).
- pembrolizumab works by blocking PD-1 receptor on T cells, this inhibition allows T cells to resume their anti-tumor activity.
- Relatlimab works by blocking the Lymphocyte-activation gene 3 (LAG-3) pathway. This prevents LAG-3 from interacting with its ligands, thus blocking the inhibitory signal and allowing T cells to become more active.

Targeted therapies which specifically target cancer cells, are used to treat melanoma include:

- binimetinib, trametinib targets and blocks MEK1 and MEK2 proteins that are part of the MAPK/ERK signalling pathway. In melanoma, the MAPK/ERK pathway is overactive due to mutations in the BRAF gene.
- cobimetinib, also targets and blocks the activity of MEK (MAPK/ERK kinase) proteins and is often used in combination with a BRAF inhibitor e.g vemurafenib.
- dabrafenib selectively inhibits the BRAF kinase, which is a key enzyme in the mitogen-activated protein kinase (MAPK) pathway.
- encorafenib specifically targets the BRAF V600E mutation, which is a common genetic alteration found in many cancer cells, including melanoma. This mutation leads to a constitutively activated BRAF kinase, driving uncontrolled cell growth.
- vemurafenib also competitively binds to the ATP-binding site of BRAF V600E kinase, preventing its activation.

Vaccine therapy is a cancer treatment that uses a substance or group of substances to stimulate the immune system to find the tumour and kill it. It is currently being studied in the treatment of stage III melanoma that can be cured by surgical removal.

Recurrence

The results of a European, multicenter, randomized trial compared margins of 2cm (n=161) versus 5cm (n=165) in 326 patients with primary melanomas with a thickness of 2.1mm or less. The study included 141 patients with melanomas measuring 1mm or less[17,18]. There was no statistically significant difference in 10-year Disease-free survival DFS or overall survival OS between the 2 groups. Local recurrence occurred in 1 patient treated with a 2 cm margin and 4 patients treated with 5cm margins[17,18]. DecisionDx-melanoma uses gene expression profiling [GEP] test to empower patients to make more informed decisions. A study identified DecisionDx-melanoma provided significant and independent risk stratification of patients with cutaneous melanoma, beyond American Joint committee on cancer Eighth edition (AJCC8) stage, which may help inform more personalized patient management decisions[31].

The limitation of DecisionDx-melanoma is that it provides personalized results for patients with stage I-III cutaneous

melanoma. There still needs to be further research to add to the studies on local recurrence of cutaneous melanoma.

Conclusion

Total body photography and sequential digital dermoscopic imaging may be considered for selected high-risk patients, but cost and variable patient adherence with follow-up are barriers to use; long-term lesion follow-up is best conducted by dermatologists[27]. Physician-directed mobile apps such as DermEngine, handyscope, VisualDx and DermExpert are useful tools that aid primary care physicians to identify a changing mole or 'ugly duckling sign'. Tele dermatology and artificial intelligence may further enhance the capabilities of imaging systems. Miiskin and Molescope are equally useful apps which enable users to securely upload images online and share their history electronically with physicians. These apps are intended for use with smartphone dermoscopic attachments. Watchful surveillance is also key. Treatment options for early detected melanoma should include skin biopsy, Wide local excision WLE and long- term follow–up of 5 - 20 years for signs of recurrence and invasive melanoma.

Author Contributions

Abiola Odeyinka MD has responsibility for conceptualization, design, writing, revision of the manuscript.

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