Melanoma Research Review™

Making Education Easy

Issue 58 - 2023

In this issue:

Abbreviations used in this issue:

AE = adverse event; **AYA** = adults and young adults; **ECS** = extracapsular spread; **ICI** = immune checkpoint inhibitor; **LDH** = lactate dehydrogenase; **MEK** = mitogen-activated extracellular signal-regulated kinase; **NUM** = nail unit melanoma; **SN+** = SNB-positive; **TNM** = tumour, node, metastasis staging system; **TMB** = tumour mutational burden.

Welcome to the 58th issue of Melanoma Research Review

This month's issue begins with a small study that examined patient decision-making in deciding on a single adjuvant agent, anti-PD-1 treatment. This study is followed by the outcomes and toxicity from single-agent or combination immune checkpoint (ICI) therapy in younger patients. An interesting study included in this issue is a large multi-institutional evaluation of long-term outcomes after BRAF-MEK or BRAF inhibitor therapy. Finally, we conclude this issue with a report of a 7-gene prognostic signature biomarker test that aimed to identify high-risk patients with stage I to IIa disease.

We hope that you enjoy this update in melanoma research, and we look forward to receiving your comments and feedback.

Kind Regards,

Professor Michael Henderson
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Decision-making and health-related quality of life in patients with melanoma considering adjuvant immunotherapy

Authors: Atkinson TM et al.

Summary: This study aimed to collect data based on patients' demographics, health-related quality of life, and attitudes towards adjuvant immunotherapy treatment for melanoma. Forty-one per cent of patients opted for adjuvant anti-PD1 immunotherapy, and 59% opted for observation. Patients choosing adjuvant therapy scored higher on health-related quality of life, and social well-being at pre-treatment. Patients were more likely to perceive that their physician preferred adjuvant therapy, and to endorse positive statements about adjuvant therapy. Furthermore, they also had lower decision regret and higher satisfaction even if they experienced toxicity or recurrence. This study concluded that patients choosing adjuvant immunotherapy had lower decision regret and higher satisfaction over time, even if they had poorer outcomes in treatment.

Comment: This small but important study examined patient decision-making in deciding for adjuvant single agent anti-PD-1 treatment. In this study from Memorial Sloan-Kettering 41% of patients opted for adjuvant therapy and 51% for observation. There was little difference in health-related quality-of-life between the two groups; however, the patients who opted for therapy were more likely to believe this was what their clinician wished them to do and were more likely to take a position to be actively involved in their care and/or to do everything possible. The treatment group, despite being told otherwise, believed that there was a survival advantage to therapy. Patients who elected observation were more likely to believe they were in ill health, did not wish to come to the hospital frequently and were worried about their appearances but not about the usually anticipated side effects. Patients reported that the advice of friends, family and other doctors influenced their decision. This study highlights how patients come to their decisions and potentially informs clinicians how they might navigate the decision-making process with their patients.

Reference: Oncologist. 2023;oyac226
Abstract

Efficacy and safety of immune checkpoint inhibitors in young adults with metastatic melanoma

Authors: Wong SK et al.

Summary: This study included 676 patients; 190 aged ≤ 40 years, 313 between the age of 41-70 years and 173 aged ≥ 71 years. Patients aged ≤ 40 years had higher response rates and improved progression-free survival with combination ICI therapy compared to monotherapy. There was a similar progression-free survival rate among age groups, however, overall survival was inferior in patients >70 years. These patients also had lower response rates to combination therapy. ICIs had a similar incidence of severe toxicities, though hepatotoxicity was particularly common in younger patients versus patients younger than 40 years with monotherapy or combination ICI. The study concluded that there was comparable efficacy between younger and older patients, however, outcomes were superior when combination ICI was used compared to monotherapy in patients ≤ 40 years.

Comment: There is relatively little data on outcomes and toxicity from single-agent or combination immune checkpoint inhibitor therapy in younger patients (<40) compared to older patients. This is a relatively small retrospective study that highlights several important features. It would be anticipated that tumour mutational burden (TMB) would be higher in older patients, but this was not seen, although inflammatory signatures which may predict response to ICI therapy were more frequently seen in older patients. Combination ICI therapy in younger patients appeared particularly effective, but the number of patients >70 who received combination therapy was relatively small. The incidence of toxicity amongst all age groups was similar, but the pattern was different, with more frequent and significant hepatotoxicity in younger patients, while pulmonary and dermatological AEs were more common in older patients.

Reference: Eur J Cancer. 2023;181:188-97
Abstract

Risk stratification of sentinel node metastasis disease burden and phenotype in stage III melanoma patients

Authors: Hussain Z et al.

Summary: This retrospective cohort analysis included 1377 melanoma patients treated at an academic cancer centre. The study showed the incidence of SNB-positive melanoma (SN+) was 17.3%, and extracapsular spread (ECS) was 10.5%. There was no difference in disease-specific survival between groups IIIB and IIIC. Subgroup analyses showed that the optimal maximum tumour deposit size was 0.7mm for the subgroups, however, there was no cut point for the pT4bSN+ subgroup and patients with maximal tumour deposit site <0.7mm and no ECS had similar survival outcomes. Nodal risk categories were developed using the 0.7mm maximal tumour deposit size cut-point and the ECS status. The incidence of low-risk disease, according to the new nodal risk model, was 22.3% in the stage III cohort and 49% in the pT2b-pT3a and pT3b-pT4a subgroups. The study observed similar results for overall and distant metastasis-free survival.

Comment: The American Joint Committee on Cancer staging system is a monumental and effective prospective program that has evolved over the years beyond the standard TNM criteria. Stage III is a very heterogenous grouping and remains the most controversial despite the additional use of non-TNM criteria. This paper is one of several reports which have highlighted issues with the current staging system and focuses particularly on the role of maximum lymph node metastasis size and the presence of extracapsular extension. They identified a cut-off point for lymph node tumour diameter of 0.7 millimetres and ECS as predictive of outcome. The increased granularity of their proposed staging system has identified low-risk Stage IIIB and IIIC patients who may avoid systemic therapy and Stage IIIa patients who are likely to benefit. Forty per cent of T4b patients were classified as mid- or high-risk for recurrence, while for T1b-T2a melanomas, only 7.1% were classified as mid- or high-risk. The whole issue of stratification, particularly stage III disease, remains an area of active investigation.

Reference: Ann Surg Oncol. 2023;30:1808-19
Abstract

BRAF inhibitor cessation prior to disease progression in metastatic melanoma

Authors: Lee J et al.

Summary: This study assessed the long-term outcomes post-BRAF MEK or BRAF inhibitor therapy. Ninety-four patients who ceased targeted therapy without progression were identified retrospectively from 11 centres. The median follow-up from cessation was 42.9 months. At this period, 36 patients progressed; the median time to progression was 4.7 months, 30 were asymptomatic, and 7 had new brain metastases. Progression rates did not differ by the best response; the study observed 34% for complete response and 43% for partial response. The study also noted that treatment duration was strongly associated with the risk of progression. The median treatment duration was 18.3 months for those who progressed and 34.6 months for those who did not. The study concluded that the risk of progression after cessation of targeted therapy is strongly associated with treatment duration.

Comment: This is a multi-institutional evaluation of long-term (median 43 months) outcomes after BRAF MEK or BRAF (40%) inhibitor therapy (n=94). Although targeted therapy results in initial high rates of response, long-term control occurs in only one quarter. The paucity of data concerning the long-term outcomes of targeted therapy is addressed in the study. Take-away messages include baseline factors predicting response, e.g. LDH, and tumour burden do not predict outcomes post-therapy cessation. The median time to progression after therapy cessation was only four months. Most patients were asymptomatic at progression, including 19% with brain metastasis (only one patient had brain metastasis previously), highlighting the need for ongoing imaging surveillance for the first two years as progression after two years was very uncommon. Unlike immune checkpoint inhibitor therapy, the depth of response did not predict the risk of recurrence. The most important predictor of long-term response was the duration of therapy (with the potential for ongoing toxicity).

Reference: Eur J Cancer. 2023;179:87-97
Abstract

Treatment and outcome trends and predictors of overall survival of rectal melanoma

Authors: Emile SH et al.

Summary: This study was an analysis of the national cancer database and included 641 patients (58.5% female). The study notes an overall survival rate of 26%, a median survival duration of 17.9 months, and significantly decreased use of chemotherapy and surgery, however, there was increased use of immunotherapy across the time periods. Moreover, the overall survival rate was longer in the last time period than in the first two (21.8 vs 16.8 vs 16.5 months; p=0.09). Surgical excision was included as an independent predictor of improved overall survival, whereas older age, positive resection margins and metastasis were predictors of poor survival rates.

Comment: This is a large retrospective study from the US national cancer database (with all the usual reservations) of rectal-only melanoma, which is usually combined in most series with anal melanoma, given the rarity of this condition. In general rectal melanomas present later and in a more advanced stage than anal melanoma and not surprisingly the results are poorer, overall survival was 35% and approximately one-third of patients presented with metastatic disease. Over the time period 2004-2019, there were major changes in the management with the abandonment of chemotherapy and a significant uptake of immunotherapy. There was a swing towards local excision rather than major rectal excision, with no difference in survival between the two procedures. Immunotherapy improved survival in patients with metastatic disease but not in those patients receiving it as adjuvant therapy. The authors summarise not unreasonably that early diagnosis with complete excision (clear margins) offers the best chance for these patients with a condition where outcomes have not dramatically improved in recent years.

Reference: Eur J Surg Oncol. 2023;S0748- 7983(23)00087-2.
Abstract

Earlier recurrence detection using routine FDG PET-CT scans in surveillance of stage IIB to IIID melanoma

Authors: Helvind NM et al.

Summary: This retrospective population-based nationwide cohort study used prospectively collected data from 5 national health registries to compare the hazard of recurrence, cumulative incidence and absolute risk of recurrence in patients with cutaneous melanoma. Included in this study were 1480 patients with stage IIB to IIID cutaneous melanoma. In cohort 2 there were higher cumulative incidences of overall and distant recurrence, with a peak difference at three years. The hazard of recurrence rate was higher in cohort two during the first two years, with hazard rates for overall and distant recurrence of 1.16 and 1.51, respectively. The patterns persisted in absolute risk estimates.

Comment: Unfortunately, there is little good evidence on which to base surveillance programs after treatment for localised melanoma. This study is unique in that it is large and population-based and compared the addition of PET CT scanning to routine review. The authors identified the first two years as the time period when imaging identified significantly more cases of metastatic disease, (51% increased risk of recurrence within the first two years of surveillance for stage IIB to IIID patients). The optimal sequencing of imaging could not be determined although given their data the authors concluded that imaging six monthly for the first two years and then annually for 5 years would be reasonable. Various historical factors including the introduction of sentinel node biopsy, avoidance of completion lymphadenectomy etc highlight the need for randomised studies several of which are currently accruing data.

Reference: Ann Surg Oncol. 2023; online ahead of print
Abstract

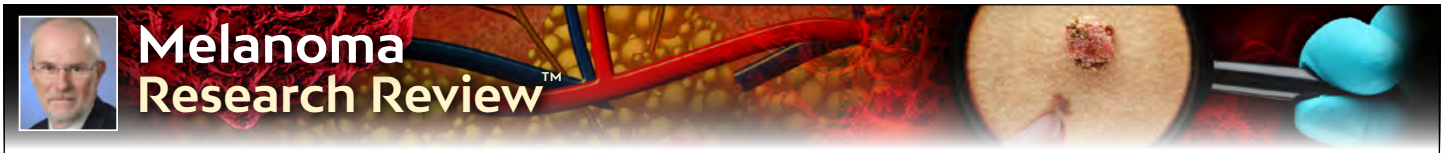
Risk of recurrence of nail unit melanoma after functional surgery versus amputation

Authors: Oh BH et al.

Summary: This retrospective analysis aimed to determine risk factors associated with recurrence in minimally invasive nail unit melanoma (NUM). This study evaluated 140 NUM cases (33 with amputation and 107 with functional surgery). In the amputation group, the mean Breslow thickness values were 3.14 ± 2.62 mm, recurrence occurred in 30.3% of patients and distant disease occurred in 30.3% of patients. In the functional surgery group, recurrence occurred in 21.5% of patients, distant disease occurred in 7.48%, and the mean Breslow thickness values were 0.70 ± 1.36 mm. Those with the greatest risk factor for recurrence or distant disease included male sex, greater Breslow thickness values, amelanotic colour, ulcers, and nodules. The optimal Breslow thickness value was 0.8mm for stratifying recurrence risk post-surgery.

Comment: Traditionally, amputation has been recommended for melanomas of the nail plate (subungual melanoma). This is a comparatively large retrospective study of patients collected over 14 years, which explored the possibility of complete removal of the nail unit rather than amputation based on a protocol emphasising preoperative imaging and frozen section intraoperative evaluation of the deep margin. The authors identified a cut-off Breslau thickness of 0.8 mm as safe for the preservation of the digit. Although many subungual melanomas present at an advanced stage, a modest proportion present early, and this data give support to the increasing use of digit preservation for suitable cases.

Reference: J Am Acad Dermatol. 2023;S0190-9622(23)00063-4.
Abstract



Independent commentary by Professor Michael Henderson

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Melanoma survival by age group

Authors: Wojcik KY et al.

Summary: This population-based study investigated the disparities for adolescents and young adult patients (AYA) and classed them by stage, tumour thickness and insurance type in California. There were 81,597 cases of cutaneous melanoma diagnosed in patients aged 15-64 years from 2004-2015. In the adjusted, age-specific models, AYA patients with stage IV melanoma had worse survival rates than what was observed among older adults. In addition, thicker tumours and public insurance were associated with worse survival outcomes for AYAs than observed in models for older adults, however, AYAs experienced better survival when the disease was detected in the earlier stages. In conclusion, that to improve AYA survival, early detection, greater awareness, and screening for AYA melanoma would reduce poor survival rates.

Comment: This is an interesting but perplexing report based on data from the California Cancer Registry. The population of California is diverse and add to this the issues with registry-sourced data, the implications for interpreting this data are significant. Furthermore, the definition of AYA is 15-39, considerably wider than most definitions which include patients aged 22, 25 or 30. Nevertheless, this study did identify issues of concern; firstly, this age group presented with more advanced melanomas compared to older patients. They were fewer cases of melanoma in situ which is surprising given the Australian experience. Males appeared to do significantly worse than females, as might be expected, but the outcomes for stage four patients were considerably worse than for older patients. There are no obvious reasons for this disparity if this is, in fact, the case. Although the time period for this study is wide, it does include the era of modern targeted and ICI therapy.

Reference: J Am Acad Dermatol. 2023;S0190-9622(23)00003-8.
Abstract

Identification of high-risk patients with a seven-biomarker prognostic signature for adjuvant treatment trial recruitment in American Joint Committee on Cancer v8 stage I–IIA cutaneous melanoma

Authors: Meyer S et al.

Summary: This study used prospectively-collected whole-tissue sections to assess consecutive stage I-IIa patients for disease-free survival, melanoma-specific survival, and overall survival rates. High-risk patients had significantly worse disease-free survival, melanoma-free survival, and overall survival than low-risk patients. In addition, models with the 7-marker signature risk category plus clinicopathological/demographic covariates substantially outperformed models with clinicopathological/demographic variables alone in predicting all studied outcomes. This study concluded that patients with American Joint Committee on Cancer stage early-disease, the 7-marker signature reliably prognosticates melanoma-related outcomes, independent of classification.

Comment: This study is a further report of a 7-gene prognostic signature (Immunoprint) focusing on patients with stage I-IIa disease. The panel characterises patients as high risk or low risk and identified 91% of recurrences and 100% of deaths. High scores were noted in 13% of patients with stage Ia disease, 53% of stage Ib and 68% of stage 2a disease. High scores were significantly associated with overall survival, distant disease-free survival and melanoma-specific survival. Whether immunoprint is sufficiently discriminative for routine use has not been established, and clearly, much larger cohorts with survival data will be required before this panel can be recommended for routine use.

Reference: Eur J Cancer. 2023;182:77-86
Abstract

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