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Name of Journal: ***World Journal of Clinical Oncology***

ESPS Manuscript NO: 22916

Manuscript type: Review

Answering reviewers

1. Reviewer asked that all references be placed before the full stop (period).
    a. This was done for all references in the manuscript.
2. The authors note that most melanomas (>70%) present with thin melanoma. Since worldwide this is not the case, I would suggest adding that these are U.S.A data.
    a. Addition: The cited reference [58] is specific to the United States and this was added to the opening sentence.
3. In "Patients with qRT-PCR positive sentinel nodes had significantly worse OS and DFS, demonstrating its potential value in detecting metastases in the sentinel nodes of patients with melanoma.[160, 161]", please add after "worse OS and DFS" than "histopathologically negative sentinel nodes".
    a. Review of the cited reference [160-161] confirms this and the phrase was added to the sentence. (page 21)
4. Address the new T1b category of thin melanoma with mitotic figures.
    a. Addition to manuscript: Mitotic rate has also been evaluated as a potential prognostic factor and has recently been incorporated into the AJCC staging system as prognostic for MSS.
5. Variability in sentinel node protocol from 0.7 -1.0; what is best practice? What is cut off in the literature you are citing?

    a. Addition to manuscript: Based on current evidence, Breslow thickness ≥0.75 mm appears to be the most consistent factor that independently predicts a >5% risk for SLN micrometastases.
6. Data on head and neck melanoma needs to address lentigo maligna and lentigo maligna melanoma which is almost always located on the head and neck and has been shown in many studies to have a better prognosis than traditional melanoma.
    a. Addition to manuscript: The subtype lentigo maligna melanoma, frequently occurs on the sun-exposed head and neck areas of older patients and carries an improved prognosis. However, lentigo maligna melanoma is treated as all other melanomas of the head and neck with regard to SLN staging.
7. Worldwide data not only American one should also be mentioned.
    a. We discuss data representing North America, Europe, Australia, and South America.
8. Side effects of at least blue dye have to be reported
    a. Addition to manuscript: Blue dyes also carry a risk of anaphylactic reaction, with the large study finding approximately 1%.
9. Other new dyes that are in use or are under clinical evaluation. For example ICG, combination of ICG with other compounds (ICG:HSA, ICG:nannocolloid), superparamagnetic iron oxide and others.
    a. Addition to manuscript: Several additional technologies are in development, including indocyanine green (ICG) conjugated with human serum albumin, ICG labeled with Technetium-99m, and superparamagnetic iron oxide tracer.
10. In case of MLTS I trial please also highline the question about: SLNB therapeutic or staging procedure and other critical issues found in literature Sentinel node followed by completion lymph node dissection versus nodal observation: staging or therapeutic

    a. Addition to manuscript: Although removal of microscopic disease confined to lymph nodes may be therapeutic in theory, it is unknown if SLNB has a therapeutic effect on survival.

11. Regarding the studies on the omission of CLND after positive SLN biopsy, the ongoing EORTC Minitub prospective registry should be mentioned.
    a. Addition to manuscript: Additionally, the European Organization for Research and Treatment of Cancer- Minimal Sentinel Node Tumor Burden study (EORTC- MINITUB) is also underway to evaluate survival of patients with minimal tumor burden who undergo nodal observation compared with those who undergo CLND
12. As so much is mentioned about the biological markers and as it is a comprehensive review I encourage the authors to use the data also from Genomic Classification of Cutaneous Melanoma.Cell. 2015 Jun 18;161(7):1681-96.
    a. Addition to manuscript: Recently, the Cancer Genome Atlas Network published a framework for genomic classification of cutaneous melanoma. Four subtypes were identified based on the most significantly mutated genes in 333 melanomas: mutant BRAF, mutant RAS, mutant NF1, and triple-wild-type. Although there was no survival association with the genomic classification, improved survival was found with samples enriched for immune gene expression associated swith lymphocyte infiltration. These data support the correlation of tumor infiltration by lymphocytes and survival in melanoma patients described previously.
13. The epitrochlear and popliteal sentinel nodes should be mentioned
    a. Addition to manuscript: Drainage in the upper extremities can be to the epitrochlear nodes, and to the popliteal nodes in the lower extremities.