Dixon Anthony J (Orcid ID: 0000-0001-8071-7199)
Kyrgidis Athanassios (Orcid ID: 0000-0003-3896-0309)
Sladden Michael J (Orcid ID: 0000-0001-7281-2444)
Apalla Zoe (Orcid ID: 0000-0002-9255-8196)
Lallas Aimilios (Orcid ID: 0000-0002-7193-0964)
Longo Caterina (Orcid ID: 0000-0002-8218-3896)
Steinman Howard K (Orcid ID: 0000-0002-0333-2882)
Zouboulis Christos C. (Orcid ID: 0000-0003-1646-2608)

Multicenter Selective Lymphadenectomy Trial 1 - key primary data remain unavailable

There is a lack of adequate and appropriate reporting of key data from the Multicenter Selective Lymphadenectomy Trial 1 (MSLT1) of melanoma. In this trial, primary cutaneous melanoma (melanoma) patients were randomized into undergoing sentinel lymph node biopsy (SLNB) and then completion lymph node dissection (CLND) if node positive versus observation. No melanoma specific survival advantage was identified. Table 1 summarizes the published findings of MSLT1[1] in 2014. Substantial key trial data remain unavailable for peer review and scrutiny.

The trial's primary outcome is, *"To determine whether wide excision of the primary with intraoperative lymphatic mapping (LM) followed by selective lymphadenectomy will effectively prolong overall survival compared to wide excision of the primary melanoma alone"*[2]. We still await the overall survival data.

The 340 recruited patients with a primary melanoma of Breslow thickness under 1.2 mm have been omitted. The publication explains: *"Because of space constraints and event infrequency among patients with thin primary melanomas, data from this cohort are considered exploratory and are not reported on in this article."* Usage of the word "exploratory" is puzzling because 'exploration' is a key purpose of research. These patients recruited into this study have had their contributions overlooked. Full knowledge of these outcomes is necessary to ensure that guidelines for all melanoma patients are evidence based.

The approved MSLT1 protocol included identifying final surgery morbidity data from both intervention and observation trial arms. This data remains unpublished. The authors separately published some interim selected morbidity data from the trial but no intention to treat analysis.[3] 10-year morbidity data is especially important given the trial identified no melanoma specific survival benefit.

Published MSLT1 data remains incomplete, subject to classification bias, over presentation of secondary outcomes and might be misleading. Concerns include the selective reporting of secondary outcomes, especially with authors' definitions of "disease free survival" and "distant disease-free survival". Ongoing claims of a survival benefit for the intervention group are not supported by the data provided. Analysis used in MSLT1 included novel latent complex post-hoc subgroup analyses which were not specified in the trial protocol. MSLT1 defines intermediate-thickness melanoma as Breslow 1.20 to 3.50 mm. It is unclear whether this non-standard definition was prespecified or was defined only for the post-hoc analyses.

Limitations have already been discussed in the relevant Cochrane Collaboration Systematic Review[2]. The review reported the original MSLT1 authors' response to a letter by the Cochrane authors, which stated *"there are numerous additional analyses that have yet to be reported for the trial"*. Approaching seven years later, no further analyses have been published.

We have made diligent attempts asking the authors and their institutions to publish the missing data and / or allow independent evaluation but with no positive outcome to date. The MSLT1 study was funded by the National Institutes of Health in USA. In accepting funding, the authors undertook to fully publish the outcomes of the approved protocol.

MSLT2 study[4] was published in 2017. It compared SLNB positive melanoma patients who then underwent CLND with those randomized to observation. CLND did not alter melanoma specific survival. SLNB has implications for immunotherapy treatment of melanoma patients. To date, numerous clinical trials have required patients to undergo SLNB, with subsequent CLND if positive, to become eligible for the trial. Test characteristics of SLNB in predicting death are poor with a sensitivity and specificity both less than 40%[1,5]. Refined figures cannot be established due to missing data. In most areas of medicine, such a test would be abandoned. Patients cannot be expected to have an operation that poorly predicts and does not improve survival to qualify for drugs that might provide benefit. Ongoing drug trials excluding SLNB in the protocol are essential.

Trials that have such limitations in the reporting of data have variously been retracted, revised and / or independently analyzed. For example, in 2018 the New England Journal of Medicine (NEJM) retracted[6] the seminal dietary study (PREDIMED) published in 2013[7] as major inadequacies in data were identified. The NEJM published a corrected version[8].

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.21712

We have requested an independent analysis of the MSLT1 data to ensure the outcomes of this seminal trial are presented in detail. If an independent review identified critical deficiencies, bias or errors, then the original final report should be retracted and / or complemented by a more appropriate report detailing the important health outcomes of the trial as designed and prospectively filed in ClinicalTrials.gov database. The 2001 patients who enrolled in MSLT1 to contribute knowledge for future melanoma patients deserve full publication of all undisclosed findings.

(749 words)

Anthony Dixon,[1] Athanassios Kyrgidis,[2] Christopher Zachary,[3] John Dixon,[4] Catalin Popescu,[5] Michael Sladden,[6] Zoe Apalla,[2] Stuart Anderson,[7] Giuseppe Argenziano,[8] Demetrios Ioannides,[2] Alexander Nirenberg,[1] Aimillios Lallas,[2] Samuel Zagarella,[9] Caterina Longo,[10] Harvey Smith,[11] Howard Steinman,[12] Thrasivoulos Tzellos,[13] Lloyd Cleaver,[14] Ken Leahey,[15] Christos Zouboulis[16] and J. Meirion Thomas[17]

[1] Australasian College of Cutaneous Oncology, Melbourne, Australia
[2] Aristotle University of Thessaloniki, Greece
[3] University of California, Irvine, California, USA
[4] Swinburne University of Technology, Melbourne, Australia
[5] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[6] University of Tasmania, Launceston, Australia
[7] Maffra Medical Group, Maffra, Australia
[8] University of Campania, Italy
[9] University of Sydney, Sydney, Australia
[10] University of Modena and Reggio Emilia, Modena, Italy
[11] Oxford Dermatology, Perth, Australia
[12] Campbell University, North Carolina, USA
[13] Arctic University of Norway, Tromsø, Norway
[14] A T Still University, Kirksville, Missouri, USA
[15] Harbour Medical Services, Adelaide, Australia
[16] Brandenburg Medical School Theodor Fontane and Faculty of Health Sciences Brandenburg, Dessau, Germany
[17] Royal Marsden Hospital, Chelsea, London, United Kingdom

Corresponding author: Professor Anthony J. Dixon PhD MB BS
Email: anthony@acco.edu.au

Funding: None
Conflicts of interest: None to declare

References

1. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. *N Engl J Med.* 2014;370(7):599-609.
2. Kyrgidis A, Tzellos T, Mocellin S, et al. Sentinel lymph node biopsy followed by lymph node dissection for localised primary cutaneous melanoma. *Cochrane Database Syst Rev.* 2015(5):CD010307.
3. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg.* 2005;242(3):302-311; discussion 311-303.
4. Faries MB, Thompson JF, Cochran AJ, et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. *N Engl J Med.* 2017;376(23):2211-2222.
5. Zagarella S. Sentinel Lymph Node Biopsy Still Provides No Benefits for Patients With Melanoma. *Am J Dermatopathol.* 2020;42(7):481-483.
6. Estruch R, Ros E, Salas-Salvado J, et al. Retraction and Republication: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet. N Engl J Med 2013;368:1279-90. *N Engl J Med.* 2018;378(25):2441-2442.
7. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med.* 2013;368(14):1279-1290.
8. Estruch R, Ros E, Salas-Salvado J, et al. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med.* 2018;378(25):e34.

Table 1. Summary of data from the MSLT1 trial on sentinel lymph node biopsy.

Total patients	2001 patients underwent randomization							
Classification based on thickness	Thin melanoma <1.2mm Breslow		Intermediate 1.2 to 3.5mm		Thick melanoma > 3.5 mm Breslow		All thicknesses	
Number in each thickness	340 patients		1347 patients		314 patients		2001 patients	
Randomized to	Intervention*	Observation	Intervention*	Observation	Intervention*	Observation	Intervention*	Observation
Number randomized	[a]	[a]	813	533	186	128	999 [d]	661 [d]
Underwent SLNB	141	[a]	770	22	173	9	943 [d]	31 [d]
Underwent observation	[a]	91	35	500	12	117	47 [d]	617 [d]
Included in follow up	[a]	[a]	805	522	185	126	990 [d]	648 [d]
Completed the trial	[a]	[a]	505	326	80	65	585 [d]	391 [d]
Died from all causes [c]	[a]	[a]	180	128	87	52	267 [d]	180 [d]
Died from melanoma	[a]	[a]	133	103	68	43	201 [d]	146 [d]
Died from other causes	[a]	[a]	47	25	19	9	66 [d]	34 [d]
Lost to follow up	[a]	[a]	120	68	18	9	138 [d]	77 [d]
Surgery related morbidity	[b]	[b]	[b]	[b]	[b]	[b]	[b]	[b]
Overall death rate [c]	[a]	[a]	22.1% [c]	24.0% [c]	46.8% [c]	40.6% [c]	26.7% [d]	27.2% [d]
Melanoma specific death rate	[a]	[a]	16.4% [e]	19.3% [e]	36.6% [e]	33.6% [e]	20.1% [e]	22.1% [e]

Legend:

[a] Data on patients with thin melanoma was included in the protocol, collected, but has not yet been published

[b] 10 year safety / morbidity including surgical related morbidity has not yet been published

[c] Overall mortality was the defined primary outcome in the trial protocol. Death from other caused is listed for intermediate and thick melanoma patients, but complete analysis of overall survival has not yet been published

[d] Percentages in the total patient columns are incomplete, missing patients with thin melanoma outcomes

[e] There was no significant difference identified between intervention versus observation melanoma specific mortality.

* Intervention group patients were randomized to sentinel lymph node biopsy, & if then positive, completion lymph node dissection

Data published in final report of MSLT1. Morton DL, Thompson JF, Cochran AJ, et al. N Engl J Med 2014;370:599-609