HHS Public Access

Author manuscript

J Surg Oncol. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

J Surg Oncol. 2022 January ; 125(1): 28–33. doi:10.1002/jso.26717.

Melanoma Trials that Defined Surgical Management: Overview of Trials that Established NCCN Margin Guidelines

Jeremy Sharib[1], **Craig L Slingluff Jr.**[2], **Georgia M Beasley**[1]

[1]Department of Surgery, Duke University

[2]Department of Surgery, University of Virginia

Abstract

Since the observation that clearance of all visible and microscopic tumor from cutaneous melanoma is critical to prevent recurrence, wide surgical margins have been central to surgical dogma. In the last several decades, more conservative margin widths have been vigorously studied by surgical investigators to lessen wound complications, need for reconstruction, and healthcare costs. This review summarizes surgeon-led clinical trials that define current guidelines and highlights the challenges to initiate and perform trials today.

Introduction

The incidence of cutaneous melanoma has been rapidly increasing in recent years.[1,2] In 2021, an estimated 106,110 new cases of melanoma will be diagnosed in the US. Eighty-four percent of new diagnoses are early-stage disease, diagnosed as cutaneous lesions without clinical lymphadenopathy.[3] While the last decade has seen dramatic changes in the management of melanoma that better align with disease biology, including targeted and immune therapy, the mainstay of treatment and staging for local disease is surgical resection via wide local excision of the primary lesion.[4]

The concept of wide local excision for cutaneous melanoma was initially described following the observation by Handley in 1907 of a patient with cutaneous melanoma who had multiple satellite lesions, in addition to metastases at distant sites.[5] Given these findings, surgeons of the day emphasized wide removal of the skin to 5-centimeter (cm) margins surrounding the primary lesions, as well as the underlying soft tissue through the fascia. For decades to follow, variation existed in surgical practice in part due to variability in melanoma biology, however, wide margins remained the standard despite the relatively low risk, <5%, of local recurrence.[6] Excisional technique and margin were also largely based on tumor location. Lesions on the trunk for example were likely to be excised with wider margin given the limited morbidity related to extended resection compared to more sensitive areas such as the limb, scalp or face. Surgical training and surgeon preference also played a role as there was no consensus regarding an optimal or consistent strategy. In 1977, Breslow determined that the risk of local recurrence correlated to depth of the primary tumor and

Corresponding Author: Georgia Beasley, DUMC 3118, Durham, NC 27710, Georgia.beasley@duke.edu.

presence of ulceration.[7] Given this finding, investigators began to question whether survival advantage from increasingly wide excision of thin tumors outweighs the excess morbidity and disfigurement related to a larger resection. Surgeons were well positioned to lead formal investigation of the appropriate resection margins for cutaneous melanoma as they were the primary contact for the majority of patients, who will only have localized disease. In this review, we will delineate the surgeon-led clinical trials that define major guidelines and current clinical practice for primary resection margins of cutaneous melanoma. We will also describe the challenges practicing surgeons face to conduct clinical studies utilizing private and public funding at large academic institutions.

Early trials that defined resection margins in cutaneous melanoma

Following Breslow's sentinel paper, several retrospective studies found that resection margins of 2 cm or less in melanomas with Breslow depth <1 millimeter (mm) were associated with low rates of local recurrence. A list of clinical trials that define surgical margins appears in Table 1. Given these retrospective findings, the World Health Organization (WHO) Melanoma Group sought to answer the question of whether narrower 1cm vs 2cm margins were safe in melanoma <2mm thick. The initial WHO trial, which opened in 1980, was led by surgical oncologist Umberto Veronesi, who also was responsible for seminal work related to breast-conserving approaches for localized breast cancer, and was the first multicenter multinational surgical trial for melanoma. The investigators randomized 703 patients in under 5-years in centers across Europe and South America. This represented the first prospective randomized trial supporting adequate disease control with narrow 1cm margins compared to 3 cm margins for melanoma tumors less than 2 mm in thickness.[6] Disease free survival (DFS) and overall survival (OS) rates were similar between the two groups. However, local recurrence rates in the study were <1% and each of the three patients who had local recurrence as the first recurrent disease had 1–2mm thick tumors and 1cm resection margins.[6] These data were supported by subsequent publication of the first Swedish trial in thin melanoma, which demonstrated the safety of 2cm margins compared with 5cm margins in melanomas <2mm thick.[8,9] Thus the safety of 1cm margins for thin melanoma <1mm and 2cm margins for <2mm was firmly established, but there remained an open question lesions >2mm thick.

During the WHO and Swedish accrual period, in 1983, an American Intergroup trial led by surgical oncologists including Charles Balch similarly sought to define the surgical margins required for intermediate 1–4mm thickness melanoma.[5] In this multi-institutional study 93 participating surgeons from 77 institutions randomized 740 eligible patients (94% eligibility rate) to undergo wide local excision of lesions on the trunk or proximal extremity with 2cm vs 4cm surgical margins over 6 years.[5] Accrual was similar to other large surgical series in that 63% (468 patients) were treated and 75% of patients were accrued from on 15 high volume centers. Remarkably, long term follow up >5 years was achieved for 92% of patients and a median follow up of >10 years (5–16 years) was eventually published.[5] The investigators found similar 10-year OS rates between the 2cm and 4cm groups (70% vs 77%).[10] As in the WHO trial, local recurrence as the first site of recurrence (0.4% vs 0.9%) or at any time (2.1% vs 2.6%) were low, however, local recurrence was a poor prognostic sign associated with 10-year survival <5% compared to 82% without local recurrence.[10]

Local recurrence and ulceration were the only two variables associated with poor survival. The Intergroup also included a second cohort of patients with melanoma of the head/neck or distal extremity (272 patients) who underwent 2cm margins. Compared to patients treated with either 2cm or 4cm margins in the trunk/proximal extremity group, patients with lesions in the distal extremity (5.3%) and head and neck (9.4%) had higher local recurrence rates.[5] The Intergroup study establish the safety of 2cm margins for melanomas 1–4mm thick, which was incorporated into guidelines and became standard practice in the United States.[10] Early findings from this study, however, were controversial because they did not randomize patients with lesions of head and neck or distal extremity. Indeed, long term data on these patients demonstrated worse outcomes for such lesions when conservative 2cm margins were completed. This study was also the first to randomize to elective lymph node dissection vs observation for intermediate thickness melanoma. The results were perhaps a prelude to two future surgeon led Multicenter Sentinel Lymphadenectomy Trials (MSLT) begun a decade later.[11]

Following these early trials, surgical oncologists and plastic surgeons in the UK Melanoma group and the Swedish Cancer Society performed the two largest randomized controlled surgical trials to date to determine the necessary margins for intermediate- and high-risk cutaneous melanoma >2mm thick on the trunk or limbs. The UK trial, which accrued between 1992–2001 randomized 900 patients to either 1cm or 3cm excision margins at 59 hospitals in the UK, Poland and South Africa.[12] Locoregional recurrences were higher for the 1cm group (unadjusted hazard ratio (HR) 1.26; 95% confidence interval (CI) 1.00–1.59; p=0.05), but similar to prior trials, true local recurrences were low; 3.3% with 1cm margin and 2.9% with 3cm margins.[12] After a median follow-up 8.8 years, melanoma specific survival was significantly shorter for those in the 1 cm group compared to the 3 cm margin group (unadjusted HR 1.24; 95% CI 1.01–1.53; p=0.041), therefore the authors concluded 1cm margins were inadequate for high-risk melanoma.[13] However, whether the local recurrence rate was the cause of this finding is unclear. The investigators reported locoregional recurrence rates, which included nodal recurrence. Some have questioned whether the findings of this study are representative of the current strategies for melanoma management because it was done before sentinel lymph node biopsy was routinely performed.[13] However, all studies prior to the sentinel node biopsy era might be challenged in the same way. Randomization between study arms can be reasonably expected to have ensured that baseline risk was similar between study groups. Surgical complications were nearly double in the 3-cm group (8% vs 15%). In contrast, between 1992 and 2004, the Swedish trial randomized 936 patients to 2cm versus 4cm excision margins.[14] Local recurrences (HR 2.15; 95% CI 0.97–4.77; p=0.06) and melanoma specific survival (HR 0.95; 95% CI 0.78–1.16; p=0.61) were equivalent at a median follow-up 19.6 years.[14,15] By the time long term results were published for each trial, 2cm margins had been established for patients with >2mm thick melanoma, and no comparison was made between 1cm versus 2cm or 2cm versus 3cm. Together, these and prior studies support reducing margins from 5 cm to 2 cm for melanomas >2 mm thick, both based on reduced surgical morbidity and comparable oncologic outcomes. However, the results of the UK trial provide reason for caution in reducing margins to 1 cm in patients with melanomas >2 mm thick, unless it is demonstrated to be safe in a subsequent clinical trial. The results from these trials also

guide requirements for adequate design of future trials intended to spare patients surgical morbidity while minimizing local disease recurrence.

Contemporary surgical margin standards

As reviewed above, several randomized trials completed around the world supported more conservative margins than what had been done historically. Further, a Cochrane review of primarily prospective data supported that margins greater than 2cm can safely be avoided.[16] Based on data from these clinical trials initiated and run by surgeons, current National Comprehensive Care Network (NCCN) guidelines recommend wide excision with 1 cm margins for melanomas 1.0 mm or less, wide excision with 1–2cm margin for melanomas 1–2 mm in thickness, and 2cm margins for melanomas greater than 2 mm in depth. Tissue removed should include skin and subcutaneous tissue to the level of the fascia which contains all local lymphatic tissue. Certain anatomic sites including but not limited to digits, ears, the face, and the plantar surface of the foot may not be as easily amenable to rigid surgical criteria without significant concerns for poor cosmetic and functional outcomes and thus remain poorly studied.

The surgical community continues to pursue the question whether more conservative 1cm margins may be adequate in patients regardless of Breslow depth. It should be noted that in each of the large prospective randomized trials investigating margins to date have shown consistently low local recurrence rate (1.3%−4.3%) even for high-risk melanoma, and other than the UK trial, melanoma specific survival is equivalent for conservative and aggressive margins.[16] In contrast, the surgical morbidity and reconstruction rates are consistently higher for wider margins. Given the low rate of local recurrence, the current knowledge regarding the relationship to biology on distant recurrence in melanoma, and the high proportion of patients who present with primary lesions >2mm, many patients may endure undo morbidity to prevent an event that is unlikely to define their disease course. As outlined by the most recent Cochrane review, an adequately powered study designed to include contemporary primary treatment with sentinel lymph node biopsy is required to standardize conservative margins in clinical practice.[16]

This was the charge of surgical investigators in the Australia and New Zealand Melanoma Trials Group (ANZMTG) when they designed the ongoing MelMarT (Melanoma Margins Trial) trial series. MelMarT-I was a prospective multi-national, multi-institutional randomized controlled study comparing 1cm versus 2cm wide excision margins for primary cutaneous melanoma >1mm thick at 17 centers across 5 countries.[17] Unlike prior trials which investigated margins for primary resection, sentinel lymph node biopsy was required for all patients. Designed to address the primary endpoint of local recurrence and melanoma specific survival, nearly 10,000 patients would be required given the low event rates of the primary outcome. In what has now become a feasibility study, the authors screened a commendable 1358 patients over 18 months, but only randomized 400 patients, a much lower rate than prior surgical trials in melanoma margins, but high compared to surgical trials in general. While primary outcome data were s not mature enough to report, patients in the 2-cm margin group more often required reconstruction (34.9 vs. 13.6%; $p < 0.0001$) and had an increased wound necrosis rate (3.6% vs 0.5%; $p = 0.036$) compared to the

1 cm margin group.[17] Quality of life data based on the FACT-M questionnaire were no different between the 1cm and 2cm groups. This interim analysis demonstrates the ability for surgeons to design a robust non-inferiority trial of surgical disease and recruit and enroll patients at a high rate internationally. It also shows consistent surgical quality given the low rate of wound necrosis, though some readers have questioned why there is a nearly 35% rate of reconstruction required for 2cm margins.[17] Many issues related to the design and outcomes also arose. Despite a rapid accrual pace, the full cohort would require nearly 20 years at the current rate, with additional time for follow-up. Further, while necrosis and reconstruction rates differ, given the equivalency in surgical adverse event rate and quality of life related to 1cm versus 2cm margins, one may ask whether minimal margins are important. Finally, prior randomized trials have proven safety of 1cm margins for 1–2mm melanoma so the inclusion of these patients was likely unnecessary. The MelMarT-II study (NCT03860883), which represents an update to the original MelMarT protocol, based on the interim analysis, is ongoing. Patients with > 2mm thickness, or 1–2mm thickness with ulceration, are being randomized to either 1cm or 2cm margins. With a revised recruitment target of only 2998 patients, the primary outcome is now disease-free survival with secondary outcomes including local recurrence, melanoma specific survival, and surgery related adverse events. This trial should further clarify application of 1 cm margins to patients with melanoma in the most clinically relevant group based on current knowledge and international guidelines.

Challenges and Hurdles for Surgical Margin Trials

Trials examining oncologic outcomes of surgical margins in melanoma have been critical in providing patients with safe, tolerable, and effective care. Wider margins that may result in increased wound dehiscence or need for complex closure without oncologic benefit can be an enormous burden and cost for patients and health care. Since many melanoma operations are performed in the outpatient setting, it is likely wound breakdowns and surgical site infections which also usually do not require readmission may also be under-reported compared to in-hospital procedures where tools like the National Surgical Quality Improvement Program (NSQIP) are more commonly applied. Furthermore, in the studies reviewed above, wider margins consistently led to higher rates of wound necrosis or need for complex closure. The RCTs to date have dramatically improved care for patients by decreasing morbidity of surgery in the setting of preserved oncologic outcomes. The surgeons and patients who had the foresight and motivation to participate in and complete these trials are inspiring. Trying to reduce any unnecessary surgical complications should always be at the forefront of surgical training and practice.

Given that well-designed clinical trials have reduced morbidity for patients, it is likely that additional trials, such as MelMarTII have the potential to further decrease surgical complications. Surgical margin trials and other surgical trials have no clear industry funding partner unlike pharmaceuticals or devices where industry partners can be a valuable resource. As such, the driving forces behind these trials are both surgeons and patients who recognize the need for such studies. In the United States, surgeon-driven surgical trials have been supported by the National Institutes of Health (NIH), cooperative groups, and other funding agencies. However, this has become increasingly difficult in the United States.

While many surgeons were not as quick to embrace trials to define evidence-based guidelines compared to medical colleagues, founding of the National Surgical Adjuvant Breast and Bowel Project (NSABP) in 1958, and led for over 25 years by surgeon-scientist Bernard Fisher, challenged aggressive surgical dogma and established the utility of systemic treatment in breast and colorectal cancers through rigorous surgical trials.[1] More recently, the American College of Surgeons Surgical Oncology Group (ACOSOG), created in 1998 by Sam Wells led to the design and completion of multiple practice changing multi-center clinical trials evaluating surgical therapies for breast and colon cancer, in addition to melanoma. Prior to the merger of ACOSOG into Alliance in 2014, ACOSOG was the only cooperative group whose primary mission was testing surgical approaches to treating cancer. Although NSABP and ACOSOG no longer exist in their original form, cooperative groups remain active in cancer clinical trials. One primary mission of the NCI (National Cancer Institute) cooperative groups is to reduce the burden of cancer and to improve the quality of life and survival in patients with cancer. Surgical trials that have potential to reduce morbidity of surgery while preserving oncologic outcomes therefore are very much in alignment with that mission. However, the path forward to doing surgical trials within cooperative groups may be more limited given competing novel therapeutic trials that may be more likely to be pursued by cooperative groups due to opportunity for industry partnerships.

Along with closure/merger of ACOSOG, other factors may threaten surgical clinical trials. A recent Nature editorial correctly noted the dramatic decline in support for surgical research "The flow of surgeons out of research is a problem that must be recognized and stopped."[18] Furthermore, success rates at obtaining NIH funding are at historic lows.[19] With less surgeons doing research in the US, less funding, and lack of a cooperative group with a primary mission to test surgical approaches, it is not surprising that MelMarT studies have been initiated outside the United States. Currently, a handful of sites in the United States are participating in MelMarT-II. However, to do so, centers in the U.S. needed to provide their own funding through philanthropy or other sources, which can be challenging. There are plans to open the trial through one of the National Cancer Institute (NCI) cooperative groups; but, it is possible the trial may meet enrollment numbers before activation in the cooperative group occurs, given the regulatory process. We need to continue to foster development of surgeon scientists that can lead efforts to improve quality of care. Funding agencies must also recognize the value of surgeon-driven research. Institutions should support surgeon participation, and cooperative groups should consider thoughtful surgical trials as of equal importance to pharmacological studies. Reducing the burden of cancer and improving quality of life can be accomplished with surgical trials that can be supported by cooperative groups or independent funding agencies and must be led by surgeons.

Disclosure:

G. Beasley has received clinical trial funding paid to Duke University from Delcath, Istari, Replimune, Oncosec, Checkmate. G. Beasley has done one-time advisory board for Cardinal Health, Regeneron. G. Beasley is supported by NIH K08 CA237726-01A1.

C Slingluff discloses research support to the University of Virginia from Celldex (funding, drug), Glaxo-Smith Kline (funding), Merck (funding, drug), 3M (drug), Theraclion (device staff support); funding to the University of Virginia from Polynoma for PI role on the MAVIS Clinical Trial; funding to the University of Virginia for roles

on Scientific Advisory Boards for CureVac. Also Dr. Slingluff receives licensing fee payments through the UVA Licensing and Ventures Group for patents for peptides used in cancer vaccines.

References

1. Manson JE, Rexrode KM, Garland FC, Garland CF, Weinstock MA: The case for a comprehensive national campaign to prevent melanoma and associated mortality. Epidemiology 11:728–34, 2000 [PubMed: 11055639]
2. Guy GP, Ekwueme DU: Years of potential life lost and indirect costs of melanoma and non-melanoma skin cancer: a systematic review of the literature. Pharmacoeconomics 29:863–74, 2011 [PubMed: 21846158]
3. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2015. CA Cancer J Clin 65:5–29, 2015 [PubMed: 25559415]
4. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, Segal NH, Ariyan CE, Gordon RA, Reed K, Burke MM, Caldwell A, Kronenberg SA, Agunwamba BU, Zhang X, Lowy I, Inzunza HD, Feely W, Horak CE, Hong Q, Korman AJ, Wigginton JM, Gupta A, Sznol M: Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 369:122–33, 2013 [PubMed: 23724867]
5. Balch CM, Urist MM, Karakousis CP, Smith TJ, Temple WJ, Drzewiecki K, Jewell WR, Bartolucci AA, Mihm MC Jr., Barnhill R, et al. : Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial. Ann Surg 218:262–7; discussion 267–9, 1993 [PubMed: 8373269]
6. Veronesi U, Cascinelli N, Adamus J, Balch C, Bandiera D, Barchuk A, Bufalino R, Craig P, De Marsillac J, Durand JC, et al. : Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. N Engl J Med 318:1159–62, 1988 [PubMed: 3079582]
7. Breslow A: Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg 172:902–8, 1970 [PubMed: 5477666]
8. Ringborg U, Andersson R, Eldh J, Glaumann B, Hafström L, Jacobsson S, Jönsson PE, Johansson H, Krysander L, Lagerlöf B: Resection margins of 2 versus 5 cm for cutaneous malignant melanoma with a tumor thickness of 0.8 to 2.0 mm: randomized study by the Swedish Melanoma Study Group. Cancer 77:1809–14, 1996 [PubMed: 8646678]
9. Cohn-Cedermark G, Rutqvist LE, Andersson R, Breivald M, Ingvar C, Johansson H, Jönsson PE, Krysander L, Lindholm C, Ringborg U: Long term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumor thickness of 0.8–2.0 mm. Cancer 89:1495–501, 2000 [PubMed: 11013363]
10. Balch CM, Soong S, Ross MI, Urist MM, Karakousis CP, Temple WJ, Mihm MC, Barnhill RL, Jewell WR, Wanebo HJ, Harrison R: Long-term results of a multi-institutional randomized trial comparing prognostic factors and surgical results for intermediate thickness melanomas (1.0 to 4.0 mm). Intergroup Melanoma Surgical Trial. Ann Surg Oncol 7:87–97, 2000 [PubMed: 10761786]
11. Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, Balch CM, Berman BS, Cochran A, Delman KA, Gorman M, Kirkwood JM, Moncrieff MD, Zager JS, Lyman GH: Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. Ann Surg Oncol 25:356–377, 2018 [PubMed: 29236202]
12. Thomas JM, Newton-Bishop J, A'Hern R, Coombes G, Timmons M, Evans J, Cook M, Theaker J, Fallowfield M, O'Neill T, Ruka W, Bliss JM: Excision margins in high-risk malignant melanoma. N Engl J Med 350:757–66, 2004 [PubMed: 14973217]
13. Hayes AJ, Maynard L, Coombes G, Newton-Bishop J, Timmons M, Cook M, Theaker J, Bliss JM, Thomas JM: Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: long-term follow-up of survival in a randomised trial. Lancet Oncol 17:184–192, 2016 [PubMed: 26790922]
14. Gillgren P, Drzewiecki KT, Niin M, Gullestad HP, Hellborg H, Mansson-Brahme E, Ingvar C, Ringborg U: 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial. Lancet 378:1635–42, 2011 [PubMed: 22027547]

15. Utjés D, Malmstedt J, Teras J, Drzewiecki K, Gullestad HP, Ingvar C, Eriksson H, Gillgren P: 2-cm versus 4-cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: long-term follow-up of a multicentre, randomised trial. Lancet 394:471–477, 2019 [PubMed: 31280965]

16. Sladden MJ, Balch C, Barzilai DA, Berg D, Freiman A, Handiside T, Hollis S, Lens MB, Thompson JF: Surgical excision margins for primary cutaneous melanoma. Cochrane Database Syst Rev:Cd004835, 2009 [PubMed: 19821334]

17. Moncrieff MD, Gyorki D, Saw R, Spillane AJ, Thompson JF, Peach H, Oudit D, Geh J, Dziewulski P, Wilson E, Matteucci P, Pritchard-Jones R, Olofsson Bagge R, Wright FC, Crampton N, Cassell O, Jallali N, Berger A, Kelly J, Hamilton S, Durrani A, Lo S, Paton E, Henderson MA: 1 Versus 2-cm Excision Margins for pT2-pT4 Primary Cutaneous Melanoma (MelMarT): A Feasibility Study. Ann Surg Oncol 25:2541–2549, 2018 [PubMed: 29850955]

18. More surgeons must start doing basic science. Nature 544:393–394, 2017

19. Hromas R, Abkowitz JL, Keating A: Facing the NIH funding crisis: how professional societies can help. Jama 308:2343–4, 2012 [PubMed: 23183908]

Synopsis:

This review summarizes clinical trials results that have informed current guidelines for surgical margins in melanoma. The review also highlights the challenges to initiate and perform trials today.

Table 1:

Summary of Margin Trials in Melanoma

Study	Cooperative Group	Country of origin	First Author	Dates of Enrollment	Trial Description	Patients	Primary Outcome	Date Published
WHO	World Health Organization	EU USA	Veronesi U	July 1980 – April 1985	1cm vs 3cm margins Melanoma <2mm thick Trunk or limbs	1cm margin: 305 pts 3cm margin: 307 pts	No difference in OS, DFS All 3 local recurrence in 1cm group in patients with >1mm tumors	May 5, 1988
Swedish 1	Swedish Melanoma Study Group	Sweden	Rinborg U	February 1982 – December 1990	2cm vs 5cm margins Melanoma 0.8–2mm thick Trunk or limbs	2cm margin: 373 pts 5cm margin: 396 pts	No difference in OS, DFS Local recurrences rare (<1%)	January 5, 1996
Intergroup Melanoma Surgical Trial*	ECOG, SWOG, NSABP, NCI Canada, CALGB	USA Canada	Balch C	January 1983 – October 1989	2cm vs 4cm margin + SLNBx Melanoma 1–4mm thick	Group A) 2cm margin: 238 pt 4cm margin: 230 pt Group B) 2cm margin head/neck	No difference in OS, DFS Local recurrence associated with 5% 10-yr survival Head/Neck lesions associated with local recurrence	April 8, 1993
Swedish 2	Swedish Melanoma Study Group	Sweden	Gillgren P	January 1992 – May 2004	2cm vs 4cm margin + SLNBx Melanoma >2mm thick Trunk or limbs	2cm margin: 465 pts 4cm margin: 471 pts	No difference in OS, DFS	October 24, 2011
UK Trial	United Kingdom Melanoma Study Group	United Kingdom	Thomas JM	January 1993 – July 2001	1cm vs 3cm margin + SLNBx Melanoma >2mm thick Trunk or limbs	1cm margin: 453 pts 3cm margin: 447 pts	Increased local recurrence in 1cm group (HR 1.26 95% CI 1.00–1.59, p=0.05) No difference in OS, DFS	February 19, 2004
MelMarT1	Australia & New Zealand Medical Trials Group	Australia New Zealand	Moncrieff M, Gyorki D	January 2015 – June 2016	1cm vs 3cm margin + SLNBx Melanoma >2mm thick Trunk or limbs	1cm margin: 198 pts 2cm margin: 202 pts	LR and DSS were not assessed 2cm margin associated with high wound necrosis and reconstruction QoL similar between groups	May 30, 2018
MelMartTII	Melanoma and Skin Trials Limited	Australia New Zealand		December 2019 –	1cm vs 2cm margin >2mm or 1–2mm with ulceration	1cm margin: 1499 (target) 2cm margin: 1499 (target)	Primary Outcome: DFS Secondary Outcomes: LR, Distant DFS, DSS, OS, QoL, Safety	ongoing

Abbreviations: ECOG-Eastern Cooperative Oncology Group, SWOG-Southwestern Oncologu Group, NSABP-National Surgical Adjuvant Breast and Bowel Project, NCI-National Cancer Institute, CALBG-Cancer and Leukemia Group N, USA-United States of America, EU-European Union