Wide Local Excision in Primary Cutaneous Melanoma Management

Subjects: Surgery

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Surgical wide local excision (WLE) is an elective procedure involving the excision of a larger area of tissue surrounding the scar left after diagnostic excision of a primary cutaneous melanoma. It remains the current standard of care for primary cutaneous melanoma and aims to achieve locoregional disease control with minimal functional and cosmetic impairment. Despite several prospective randomised trials, the optimal extent of excision margin remains controversial, and this is reflected in the persistent lack of consensus in guidelines globally.

Keywords: melanoma ; margin ; excision ; recurrence ; survival

1. Is There Prognostic Benefit of Wide Margins Compared to Narrow Margins?

1.1. Melanomas < 2 mm Thick

For decades following Handley's initial report, WLE with margins of 3 to 5 cm was recommended and performed routinely until as recently as the 1970s. However, following Breslow's seminal work elucidating tumour thickness as a prognostic marker for local recurrence, it was postulated that locoregional control of thin lesions (pT1-pT2) might be sufficiently achieved through more conservative margins [1]. Evidence supporting this approach was provided from a retrospective analysis, and the first RCT, comparing 1 cm and 3 cm excision margins, was undertaken by the World Health Organization (WHO) Melanoma Group and published in 1988 [2][3]. After extended follow-up, they found that there was no statistically significant difference in either the disease-free survival (DFS) or overall survival (OS) (85.2% vs. 87.3%) for participants that were treated with a 1 cm compared to a 3 cm WLE margin at 7.5 years [4][5]. Four patients, clustered within the narrow 1 cm excision arm, had an LR as a first relapse. There were a number of limitations, not least that the protocol called for excisions to be undercut by an additional 1–2 cm within the subcutaneous fat, resulting in ambiguity in the true width of the margins. Furthermore, the number and characteristics of those lost to follow-up is unclear. Nevertheless, given the observation that all four events of LR occurred in those with melanomas thicker than 1 mm, they concluded that excision with narrower margins is a safe and effective procedure for those with primary melanomas thinner than 1 mm [4][5].

A further two randomised trials comparing 2 cm to 5 cm excision margins followed. The European Trial undertook the comparison for 326 patients with primary tumours less than 2.1 mm thick [6]. There were almost twice as many female patients (n = 204) than male (n = 122) but the two groups were comparable for prognostic characteristics including sex. After a median follow-up time of 16 years, 40 patients (12%) were lost to follow-up and a further 36 were not evaluable for DFS due to missing data. They found no significant difference in 10-year OS (87% for 2 cm vs. 86% for 5 cm, p = 0.56) or 10-year DFS (85% for 2 cm vs. 83% for 5 cm, p = 0.83). LRs occurred in one patient in the 2 cm arm compared to four patients in the 5 cm arm (overall LR rate = 1.5%) with no significant difference observed between groups [6]. The Swedish I trial enrolled 989 patients from six national regions with melanomas between 0.8 and 2.0 mm in thickness. Once again, groups were comparable for gender, age, tumour site, subtype, and thickness [7]. They found no statistically significant difference in either OS (HR 0.96; 95% CI 0.75–1.24; p = 0.77; median follow-up 11 years) or recurrence-free survival (RFS) (HR 1.02; CI 0.80–1.30; p = 0.88; median follow-up eight years). LR as a first relapse was rare, with five events in total observed (overall rate = 0.5%, one event in the 2 cm arm and four events in the 5 cm arm). There was no significant difference in LR events between the 2 cm and 5 cm arms (0.2% vs. 1.0%, respectively) or locoregional recurrence (15% vs. 12%, respectively, p = 0.22) [8]. Both trials, therefore, concurred that patients with melanomas between 1 and 2 mm thickness could be safely be treated with a WLE margin of 2 cm, and wider margins were unnecessary [6][7][8].

The Intergroup trial enrolled a further 486 patients with intermediate thickness (1–4 mm) melanomas of the trunk or proximal extremity, from multiple institutions in four countries (United States, Canada, Denmark, and South Africa) and

randomised them to either 2 cm or 4 cm margins. After a median follow-up of six years, the authors found no significant difference in either OS (79.5% vs. 83.7%) or LR rate (0.8% vs. 1.7%) for the 2 cm margin patients vs. the 4 cm margin patients, respectively [9]. In long-term analysis, 468 patients (6/244 lost from the 2 cm arm, 12/242 lost from the 4 cm arm) were followed up to a median of 10 years [10]. The rate of LR as a first relapse was similar in both groups (0.4% and 0.9% for 2 and 4 cm margins, respectively) and the trial found no significant differences in the 10-year disease-specific survival (DSS) between those who underwent a 2 cm compared to a 4 cm excision margin (DSS 70% vs. 77%, $p = 0.074$). The authors concluded that the 2 cm margin is safe for those with melanomas < 4 mm in thickness; however, in subsequent analyses, some have interpreted this nearly significant finding as an indication that there may still be a potential adverse effect of margins ≤ 2 cm [10][11].

1.2. Melanomas > 2 mm Thick

Of the first four trials undertaken, only the Intergroup trial included patients with primaries thicker than 2 mm, and this subgroup was smaller (213/486 patients, 44%) [9]. Furthermore, none of the preceding trials had included patients with melanomas of > 4 mm thickness. Therefore, two further trials were undertaken in patients with melanomas ≥ 2 mm thick, first by the UK Melanoma Study Group (UK MSG) comparing 1 cm with 3 cm margins, and subsequently by the Swedish Melanoma Study Group comparing 2 cm to 4 cm margins. Consistent with preceding RCT evidence, the UK MSG trial found no statistically significant difference in either disease-specific (HR 1.24; 95% CI 0.96 to 1.61; $p = 0.1$) or overall survival (HR 1.07; 95% CI 0.85–1.36; $p = 0.6$) for patients treated with 1 cm and 3 cm excision margins at a median follow-up of five years. However, they did report a statistically significant difference in the locoregional recurrence rate (HR 1.26; 95% CI 1.00–1.59; $p = 0.05$). Although at that time the authors noted a difference in the number of deaths due to melanoma in the 1 cm excision arm ($n = 128$) compared to the 3 cm excision arm ($n = 105$), this was not found to be statistically significant (HR 1.24; 95% CI 0.96 to 1.61; $p = 0.1$) [12]. However, in further analysis of these data, which extended the median follow-up to 8.8 years, Hayes et al. found that the 1 cm margin was associated with a statistically significant reduction in DSS compared to the 3 cm arm (absolute difference 5.95%), leading the authors to conclude that the survival of 1 in 16 patients could potentially be disadvantaged by excision margins < 3 cm at 10 years (HR 1.24 [95% CI 1.01–1.53], $p = 0.041$) [13].

In contrast, the Scandinavian trial recruited patients < 75 years of age with melanomas thicker than 2 mm (median BT 3.1 mm), from 53 hospitals in Sweden, Denmark, Estonia, and Norway, and randomised them to either a 2 cm or a 4 cm excision margin. With a cohort of 936 patients, it represents the largest RCT published; however, with changes to clinical practice favouring routine excision with narrow margins towards the end of the enrolment period, the trial was terminated early and the overall accrual did not meet the planned sample size to show equivalency. Clinicopathological features were similar in both groups. At initial follow-up after a median 6.7 years, no significant difference was observed between the two groups for both 5-year OS (65% in both groups, $p = 0.69$) and 5-year RFS (56% in both groups, $p = 0.82$). The number of deaths due to melanoma was also equal (134/465 in the 2 cm arm vs. 138/471 in the 4 cm arm) (HR 0.99; 95% CI 0.78–1.26, $p = 0.95$). Once again, LR as a first event was rare (overall rate 3%), and although there were twice as many occurrences within the 2 cm margin group compared to the 4 cm margin group, this finding did not reach statistical significance ($n = 20$, 4.3% vs. $n = 9$, 1.9%; $p = 0.06$). When nodal metastasis and in-transit metastases were combined into a hybrid endpoint of locoregional recurrence, the outcome was equal (139 vs. 138 events) in the two treatment groups (HR 1.00; 0.79–1.28; $p = 0.96$) [14]. The long-term follow-up was the most complete of all the RCTs, with a median of 19.6 years and <1% loss to follow-up (2/936). Consistent with their initial findings and those of previous RCTs, there was no significant difference observed between the survival curves for either OS (HR 0.98; 95% CI 0.83–1.14; $p = 0.75$) or DSS (HR 0.95; 95% CI 0.78–1.16; $p = 0.61$) [15].

1.3. MelMarT

With the majority of data supporting the hypothesis that primary cutaneous melanomas may be managed with narrow margins with similar safety and efficacy to that of wider margins, yet with potentially substantially less associated morbidity and cost, there remained a lack of any direct comparison between the extent of “narrow” margins previously evaluated, namely 1 cm and 2 cm [16]. The Melanoma Margins Trial (MelMarT) II trial (ClinicalTrials.gov ID: NCT03860883) is an international multicentre, randomised controlled phase III clinical trial, investigating the hypothesis that a 1 cm wide excision margin is non-inferior to a 2 cm wide excision margin for patients with primary, cutaneous, pT2b-4b melanomas [14].

Its design was unique compared to previous RCTs in a number of key criteria reflecting contemporary practice. MelMarT represents the first and only trial sentinel lymph node biopsy as an essential inclusion criterion for pathological staging. Furthermore, it has a pragmatic design, meaning that those patients with positive SNB will be managed according to the

treating unit's local protocol, allowing for the effects of surgical margins to be evaluated within the new, current context of the availability of adjuvant therapies for high-risk disease. In contrast to preceding RCTs, MelMarT was designed as a formal non-inferiority trial; the trial design initially included pT2a melanomas and given the particularly low event rate in this cohort, a sample size of nearly 10,000 patients was required to provide enough statistical power to definitively address the safety and efficacy of 1 cm vs. 2 cm margins. Consequently, it was prudent to conduct a pilot feasibility study to determine if patient recruitment could be achieved at a sufficient rate across multiple centres internationally.

2. Socio-Economic Implications of Excision Margins

The implications of surgical decision making extend beyond prognosis, affecting the quality of life of individual patients as well as presenting a socio-economic challenge to healthcare systems globally. Increasing the radial surgical margin from 1 cm to 2 cm increases the size of the resulting defect from 2 cm to 4 cm in diameter. Although this difference may at first seem trivial, it can present a substantial difficulty in repairing the wound, especially if affecting anatomic sites such as the head and neck, where critical structures need to be preserved for both functional and cosmetic considerations, or the distal extremities, where tissue laxity is limiting. It often necessitates the conversion from a simple primary closure to a complex repair involving skin grafts or flaps, which has been reflected in trial data. The Intergroup trial reported 46% of patients treated with 4 cm margins had a skin graft compared with only 11% with 2 cm margins [9]. In the Scandinavian study, for those treated with 2 cm margins, primary closure of the wound was possible in 69% of cases and the use of skin grafts was more frequent in the 4 cm group (12% vs. 47%) [14]. This was similar to the findings of the MelMarT feasibility report, in which over a third of patients in the 2 cm arm required reconstruction with either a skin graft or a local flap, twice that which was required in the 1 cm arm (39.4% vs. 13.6%, respectively; $p = 0.0001$). This difference was even more pronounced in the patients with head and neck melanoma (1 cm: 8.3% vs. 2 cm: 68.8%; $p = 0.002$), although this should be interpreted with caution given the small patient numbers resulting in wide confidence intervals [17]. Given that those with head and neck melanoma have been largely excluded from trials, thus representing < 1% ($n = 44$) of pooled participants to date, it is possible that the true reconstructive burden remains underestimated. Despite substantial heterogeneity between trials, meta-analysis has also found a significant difference in the risk of requiring a skin graft or local flap (RR 0.30; 95% CI 0.19–0.49, $p < 0.00001$) [18]. In two meta-analyses, the estimated number needed to harm (NNH) was three, indicating that for every three patients undergoing a wider excision, one patient would undergo a reconstruction who would otherwise not require it if a narrower margin had been used [18][19].

The increased reconstructive burden associated with wider margins brings with it significant clinical and socio-economic ramifications, including additional risks of morbidity; prolonged hospital stay; disfiguration; chronic pain; and functional loss requiring rehabilitation [10][20][21]. The Intergroup study found that the principal factor that influenced length of hospital stay was the need for skin grafting to close the wound; the hospital stay for those who had a skin graft was 3.5 days longer than for those whose wound was closed primarily (6.5 days vs. 3.0, $p < 0.01$). Balch et al. found that the use of a skin graft was associated with delayed ambulation postoperatively as well as a slightly higher rate of wound infection compared to those who had primary closure (5.7% vs. 2.8%, $p = 0.07$) [9][10]. In the UK MSG trial, there were a greater number of surgical complications in the wider 3 cm arm compared to the 1 cm arm (15% vs. 8%) and the most common complications were partial or complete graft loss (2% in the 1 cm group, 4% in the 3 cm group) and wound dehiscence (2% in both groups) [12][13]. Although the MelMarT-I trial found no significant difference in the overall surgical adverse event rate between the two groups, they did identify a statistically significant increase rate of wound necrosis (including partial/total loss of skin graft) in the wide (2 cm) arm (3.6 vs. 0.5%, $p = 0.036$), which they attribute to the increased rate of reconstruction in the 2 cm arm [17]. When surgical adverse events were explored in a recent meta-analysis, the number of pooled participants was particularly small (862–1762), and they found no significant difference in events between narrower (1–2 cm) and wider margins, specifically for wound dehiscence (RR 0.96; 95% CI 0.54–1.71; $p = 0.88$) and wound infection (RR 1.22; 95% CI 0.68–2.17; $p = 0.50$) [18].

There remains a paucity of quantitative evidence regarding the cost-effectiveness of WLE margins; indeed, none of the published trials or meta-analyses, including the Cochrane review, included any assessment of cost-effectiveness of wider excision margins. An indication of the economic impact of implementing narrower margins can be appreciated from retrospective analysis. In a single-centre UK-based study, 1184 patients diagnosed with pT1b to pT4b primary cutaneous melanoma underwent WLE with either a narrow 1 cm ($n = 229$, 19.3%) or wider 2–3 cm margin ($n = 995$, 80.7%) [21]. In line with trial data, the authors found the odds of needing a reconstruction significantly increased to greater than 3:1 in the wider margin group compared to the narrower margin group. Furthermore, the need for reconstruction significantly increased hospitalisation rates (26.6% vs. 63.0%, OR = 4.7; $p < 0.0001$) collectively and individually for the head and neck (26.8% vs. 53.9%), and upper (18.9% vs. 42.3%) and lower extremities (34.8% vs. 77.3%). The use of the narrower 1 cm margin significantly reduced hospitalisation rates in the upper and lower extremities (7.1% vs. 28.5%; $p = 0.004$, 37.9%

vs. 58.5%; $p = 0.005$, respectively). Analysis of resource usage and financial tariff data for 889 patients treated from 2012 onwards found that, in cases where reconstruction was required, there was a significant increase in the mean and median overall procedure cost per patient of £180 ($p < 0.0001$) and £346 ($p = 0.0004$) respectively [21].

The MelMarT-II trial will provide much needed high-quality evidence by incorporating a standalone health economic analysis performed for the UK cohort of patients, determining the cost-effectiveness of implementing a 1 cm compared to 2 cm wide local excision margin for primary invasive cutaneous melanomas, which will be crucial to inform national guidelines. This will be particularly pertinent to policy makers within the UK, as within the centrally funded National Health Service (NHS) there is an ever-increasing demand on limited resources; however, the data it provides will be of interest multi-nationally as melanoma represents an increasingly significant challenge to many different modern healthcare systems.

3. Interpretation of RCT Data in the Landscape of Contemporary Melanoma Management

A Cochrane review in 2009 pooled 3297 patients from the then five completed RCTs (WHO, Intergroup, European, Swedish, and UK) found no overall survival advantage for wide excision margins (3–5 cm) compared to narrow margins (1–2 cm), (HR 1.04; 95% CI 0.95–1.15; $p = 0.400$). In the absence of a plausible rationale for narrow margins providing an overall survival benefit, there remains the possibility that margins > 2 cm may result in a small but nevertheless clinically important difference in overall survival (up to a 15% relative reduction in overall mortality), which may have yet to be detected due to insufficient primary data. Small sample sizes have meant that all the trials were underpowered to show the equivalence or non-inferiority of narrow margins compared to wide margins. Accordingly, it was also not possible to produce definitive guidance on the optimal minimum margins by the T stage. The lack of data is further compounded by the absence of any consistent definition for “narrow” (1–2 cm) and “wide” (3–5 cm) excision margins between trials [16][18].

Subsequent meta-analyses have similarly found no statistically significant difference in either survival or recurrence outcomes between narrow and wide excision groups, with the exception of that reported by Wheatley et al. in 2016. They included six RCTs and concluded that narrow margins (1–2 cm) may be harmful compared to wide margins (3–5 cm) given a statistically significant difference in DSS (HR 1.17 95% CI 1.03–1.34, $p = 0.02$). This potential survival disadvantage was not reflected in their summary estimate OS (HR 1.09 95% CI 0.98–1.22; $p = 0.1$) and it is also notable that DSS was only reported in four RCTs (Swedish, Intergroup, UK, and Scandinavian), leading to a substantial risk of selective reporting bias [11]. The most recent meta-analysis, which pooled data from 4579 patients across all seven trials (including the recent MelMarT pilot study) once again found no statistically significant difference in outcomes between narrow (1–2 cm) and wide excision (2–5 cm) for overall death, (RR 1.00; 95% CI 0.93–1.07, $p = 0.97$), death due to melanoma (RR 1.11; 95% CI 0.96–1.28, $p = 0.16$), rates of locoregional recurrence (including LR, in-transit metastasis and regional nodal metastasis individually), or rates of distant metastasis. Once again, they concluded that the analysis was still likely underpowered and thus unable to define the optimal excision margins for primary melanoma, with insufficient information contained within the primary studies to perform any subgroup analysis by BT [18].

Data analysis has been further complicated by the creation of hybrid endpoints in some RCTs, which has led to concerns being raised regarding the interpretation of their data [22]. Specifically, in their long-term analysis of the UK MSG trial, it was proposed that the significant finding of poorer DSS in the 1 cm arm compared to the 3 cm arm was directly attributable to the initial finding of an increased rate of locoregional recurrence associated with the use of a narrower margin. Due to lower than estimated incidence rates of local and in-transit recurrence, the authors combined the rate of nodal recurrence (the incidence of which was over five times greater in both the 1 cm and 3 cm study arms) to create a hybrid endpoint of locoregional recurrence that was defined after the trial began. An alternative explanation for this finding, however, is that the survival disadvantage was due to a higher incidence of biologically more aggressive disease in the narrow margin group that was undetected at the time of the intervention, rather than resulting from the narrow margin intervention itself [13][22]. The possibility that there were between-group differences in rates of SN positivity leading to differences in outcome has been raised and dismissed as unlikely by some, given the degree of protection inherent in the randomisation process as well as the fact that in all of the studies, all other known prognostic characteristics were well-matched between groups [11][13]. However, it is notable that despite randomisation, careful stratification, and well-matched baseline clinicopathological characteristics, in the recent MelMarT feasibility study, the rate of SN positivity was noted to be higher in the 1 cm compared with the 2 cm group (22.9% vs. 15.2%, $p= 0.058$), demonstrating that such a chance imbalance is indeed feasible [17].

This highlights another, and arguably the most clinically significant, limitation in the existing evidence for surgical margins: the absence of SNB as a staging criterion in all but one of the RCTs. This procedure has become standard care in

patients with pT2 and above tumours, as a result of the increased accuracy of initial staging it affords, and the fact that, where identified, the presence of regional nodal metastases has been shown to be the single most important independent predictor of both recurrence and survival in patients with intermediate thickness melanoma (1–4 mm) [23][24][25].

There is still a potential therapeutic aspect of SNB that needs to be accounted for when extrapolating evidence to guide modern practice. The second Multicenter Selective Lymphadenectomy Trial (MSLT-II) found that for 823 patients with a positive SN diagnosed and removed at the time of WLE, no nodal recurrence was observed in 80% of patients at 10 years follow-up [26]. If SNB had been employed in previous RCTs, not only would those patients with poorer prognostic disease at the time of wider excision have likely been identified, but the removal of the sentinel node in those patients may have achieved regional nodal disease control in most cases, bringing the rate of the hybrid locoregional recurrence reported in the UK MSG trial into questionable, if any, significance.

References

1. Breslow, A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann. Surg. 1970, 172, 902–908.
2. Veronesi, U.; Cascinelli, N.; Adamus, J.; Balch, C.; Bandiera, D.; Barchuk, A.; Bufalino, R.; Craig, P.; De Marsillac, J.; Durand, J.C.; et al. Thin stage I primary cutaneous malignant melanoma. Comparison of excision with margins of 1 or 3 cm. N. Engl. J. Med. 1988, 318, 1159–1162.
3. Breslow, A.; Macht, S.D. Optimal size of resection margin for thin cutaneous melanoma. Surg. Gynecol. Obstet. 1977, 145, 691–692.
4. Veronesi, U.; Cascinelli, N. Narrow excision (1-cm margin). A safe procedure for thin cutaneous melanoma. Arch. Surg. 1991, 26, 438–441.
5. Cascinelli, N. Margin of resection in the management of primary melanoma. Semin. Surg. Oncol. 1998, 14, 272–275.
6. Khayat, D.; Rixe, O.; Martin, G.; Soubrane, C.; Banzet, M.; Bazex, J.A.; Lauret, P.; Vérola, O.; Auclerc, G.; Harper, P.; et al. Surgical margins in cutaneous melanoma (2 cm versus 5 cm for lesions measuring less than 2.1-mm thick). Cancer 2003, 97, 1941–1946.
7. Ringborg, U.; Andersson, R.; Eldh, J.; Glaumann, B.; Hafström, L.; Jacobsson, S.; Jönsson, P.E.; 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 1996, 77, 1809–1814.
8. Cohn-Cedermark, G.; Rutqvist, L.E.; Andersson, R.; Breivald, M.; Ingvar, C.; Johansson, H.; Jönsson, P.E.; 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 2000, 89, 1495–1501.
9. Balch, C.M.; Urist, M.M.; Karakousis, C.P.; Smith, T.J.; Temple, W.J.; Drzewiecki, K.; Jewell, W.R.; Bartolucci, A.A.; Mihm, M.C.; 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. 1993, 218, 262–267.
10. Balch, C.M.; Soong, S.J.; Smith, T.; Ross, M.I.; Urist, M.M.; Karakousis, C.P.; Temple, W.J.; Mihm, M.C.; Barnhill, R.L.; Jewell, W.R.; et al. Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1–4 mm melanomas. Ann. Surg. Oncol. 2001, 8, 101–108.
11. Wheatley, K.; Wilson, J.S.; Gaunt, P.; Marsden, J.R. Surgical excision margins in primary cutaneous melanoma: A meta-analysis and Bayesian probability evaluation. Cancer Treat. Rev. 2016, 42, 73–81.
12. Thomas, J.M.; Newton-Bishop, J.; A'Hern, R.; Coombes, G.; Timmons, M.; Evans, J.; Cook, M.; Theaker, J.; Fallowfield, M.; O'Neill, T.; et al. Excision margins in high-risk malignant melanoma. N. Engl. J. Med. 2004, 350, 757–766.
13. Hayes, A.J.; Maynard, L.; Coombes, G.; Newton-Bishop, J.; Timmons, M.; Cook, M.; Theaker, J.; Bliss, J.M.; Thomas, J.M.; UK Melanoma Study Group; et al. Wide versus narrow excision margins for high-risk, primary cutaneous melanomas: Long-term follow-up of survival in a randomised trial. Lancet Oncol. 2016, 17, 184–192.
14. Gillgren, P.; Drzewiecki, K.T.; Niin, M.; Gullestad, H.P.; Hellborg, H.; Månsson-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 2011, 378, 1635–1642.
15. Utjés, D.; Malmstedt, J.; Teras, J.; Drzewiecki, K.; Gullestad, H.P.; 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 2019, 394, 471–477.

16. Sladden, M.J.; Balch, C.; Barzilai, D.A.; Berg, D.; Freiman, A.; Handiside, T.; Hollis, S.; Lens, M.B.; Thompson, J.F. Surgical excision margins for primary cutaneous melanoma. Cochrane Database Syst. Rev. 2009, CD004835.
17. Moncrieff, M.D.; Gyorki, D.; Saw, R.; Spillane, A.J.; Thompson, J.F.; Peach, H.; Oudit, D.; Geh, J.; Dziewulski, P.; Wilson, E.; et al. 1 versus 2-cm excision margins for pT2-pT4 primary cutaneous melanoma (MelMarT): A feasibility study. Ann. Surg. Oncol. 2018, 25, 2541–2549.
18. Hanna, S.; Lo, S.N.; Saw, R.P. Surgical excision margins in primary cutaneous melanoma: A systematic review and meta-analysis. Eur. J. Surg. Oncol. 2021, 47, 1558–1574.
19. Haigh, P.I.; Difronzo, L.A.; McCready, D.R. Optimal excision margins for primary cutaneous melanoma: A systematic review and meta-analysis. Can. J. Surg. 2003, 46, 419–426.
20. Newton-Bishop, J.A.; Nolan, C.; Turner, F.; McCabe, M.; Boxer, C.; Thomas, J.M.; Coombes, G.; A'Hern, R.P.; Barrett, J.H. A quality-of-life study in high-risk (thickness ≥ or 2 mm) cutaneous melanoma patients in a randomized trial of 1-cm versus 3-cm surgical excision margins. J. Investig. Dermatol. Symp. Proc. 2004, 9, 152–159.
21. Lo, M.C.; Heaton, M.J.; Snelling, A.; Moncrieff, M.D. Reconstructive burden and financial implications of wider excision margins for invasive primary cutaneous melanoma. J. Plast. Reconstr. Aesthet. Surg. 2020, 73, 313–318.
22. Moncrieff, M. Excision margins for melanomas: How wide is enough? Lancet Oncol. 2016, 17, 127–128.
23. Gershenwald, J.E.; Thompson, W.; Mansfield, P.F.; Lee, J.E.; Colome, M.I.; Tseng, C.H.; Lee, J.J.; Balch, C.M.; Reintgen, D.S.; Ross, M.I. Multi-institutional melanoma lymphatic mapping experience: The prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. J. Clin. Oncol. 1999, 17, 976–983.
24. Morton, D.L.; Cochran, A.J.; Thompson, J.F.; Elashoff, R.; Essner, R.; Glass, E.C.; Mozzillo, N.; Nieweg, O.E.; Roses, D.F.; Hoekstra, H.J.; et al. Sentinel node biopsy for early-stage melanoma: Accuracy and morbidity in MSLT-I, an international multicenter trial. Ann. Surg. 2005, 242, 302–311.
25. Morton, D.L.; Thompson, J.F.; Cochran, A.J.; Mozzillo, N.; Nieweg, O.E.; Roses, D.F.; Hoekstra, H.J.; Karakousis, C.P.; Puleo, C.A.; Coventry, B.J.; et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N. Engl. J. Med. 2014, 370, 599–609.
26. Multicenter Selective Lymphadenectomy Trials Study Group. Therapeutic Value of Sentinel Lymph Node Biopsy in Patients with Melanoma: A Randomized Clinical Trial. JAMA Surg. 2022, 157, 835–842.
