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Current Perspective

The end of wide local excision (WLE) margins for melanoma ?

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Abstract ***Clinical question:*** Is there nowadays any benefit of continuing the practice of routine wide local excision (WLE) for primary stage I/II cutaneous melanoma?
Background: WLE aims to eradicate potential microsatellites around melanomas and thereby reduce local recurrence rates and improve overall survival. Six large prospective randomised trials investigated WLE versus wider WLE, they all failed to show any effect on overall survival (OS).
Methods: A literature search was performed to identify data on outcome after omitting WLE. Additionally circumstantial evidence was gathered from pathology studies and outcomes of modified surgical techniques, as well as publications on morbidity.
Results: No prospective and one retrospective study was found. The retrospective study showed no difference in OS after correction for confounding factors. Pathology studies showed a low incidence of residual melanoma in WLE specimen (0–4.2%). Mohs surgery does not show a difference in recurrence rates or OS. WLE is associated with considerable postoperative morbidity, which increases with wider excision margins.
Conclusion: There is no solid prospective evidence to support the classic dogma of a 2-step approach with the use of WLE for primary cutaneous melanoma that has been completely excised on diagnostic excision biopsy. We recommend to setup and conduct a prospective

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randomised trial to compare the classical 2-step approach with WLE to a complete diagnostic excision only to abolish the routine practice of WLE in the future.

1. Clinical question

Is there nowadays any benefit of continuing the practice of routine wide local excision (WLE) for primary stage I/II cutaneous melanoma?

2. Background

Currently, the classical 2-step treatment paradigm for primary melanoma, is still the same one that has been taught over many decades, consisting of an initial diagnostic excision, followed by a wide local excision (WLE) with clinical safety margins. This practice was established empirically in the 1950s, without any proper level 1 prospective clinical trial evidence, which would nowadays be required to support treatment guidelines. However, it will require a prospective trial to abolish this ancient dogma.

The concept behind the WLE is that it aims to eradicate potential microsatellites around the melanoma and thereby prevent loco-regional recurrence and subsequently improve survival. Initially, 5 cm margins were considered routine by many.

Similarly, there initially used to be the concept of orderly progression, which lead people to believe that the use of sentinel lymph node biopsy (SLNB) would improve survival, as it might be possible to interrupt this process at the locoregional level and thus thereby improve survival [1]. However, this concept has since been disproven, as SLNB does not improve survival, as micrometastases are indicators and not governors of disease.

Six large randomised controlled trials have been undertaken to determine the optimal clinical safety margin of the WLE, ranging from 1 to 5 cm. All have failed to demonstrate a benefit in overall survival (OS) or recurrence free survival (RFS) for wider surgical margins [2]. This UK trial comparing margins of 1 and 3 cm for >2 mm melanomas found higher loco-regional recurrence rate, but no difference in survival after 5 years between the two groups [3]. On long-term follow-up, the investigators did find a higher melanoma specific survival (MSS) for the widest margin, but no difference in OS.

However, this trial was criticised for not reporting ulceration status, nor stratifying for sentinel node (SN) status, as SN staging was not mandatorily used, potentially causing a bias between the groups [4]. Since the initially advocated 5 cm margins, excision margins have decreased and current guidelines prescribe an excision margin of 1 cm for T1-T2 melanoma and 2 cm for T3-T4 melanoma [5,6]. This trend of decreasing margins led towards the recently launched phase III MelMarT trial (NCT02385214), comparing WLE safety margins of 1 and 2 cm for stage II melanomas (pT2b-pT4b, AJCC 8th edition).

The 2-step approach including a WLE is almost exclusively practised in the treatment of melanoma. For other solid tumours, such as for example breast or colorectal cancer, a complete surgical resection with tumour free margins is considered sufficient [7,8]. WLE can potentially cause large skin defects which may require reconstructive surgery and can be especially mutilating in the head- and neck area and at functional sites, such as for example the foot sole.

Melanoma treatment has radically changed over the past decade, mainly driven by huge advances in the systemic treatment. First these drugs showed their efficacy in stage IV patients, which has shifted to adjuvant therapies after initial surgical treatment of stage III melanoma [9–13]. Most recently even, the first reported positive outcome for adjuvant therapy after resection of stage II melanoma was reported [11].

To our knowledge no prospective trials have assessed the benefit of WLE compared to a complete diagnostic excision with clear margins only. Considering the developments in systemic therapy treatment for melanoma, including adjuvant therapies, we question the continued practise of routine WLE in stage I/II melanoma?

3. Literature search and selection

To address the research question a literature search was conducted. Pubmed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for publications with relevant data on patient outcome after omitting re-excision for primary cutaneous melanoma (Fig. 1). A combination of controlled thesaurus terms and title/abstract/keyword terms, including synonyms, were used. A schematic representation of the search strategy is as follows: (melanoma) AND (wide local excision OR single stage excision OR guideline compliance OR guideline non-compliance) AND (survival OR recurrence). For PubMed and Embase.com filters created by the BMI for clinical trials and epidemiologic studies were used. The searches were performed on 19th March 2021.

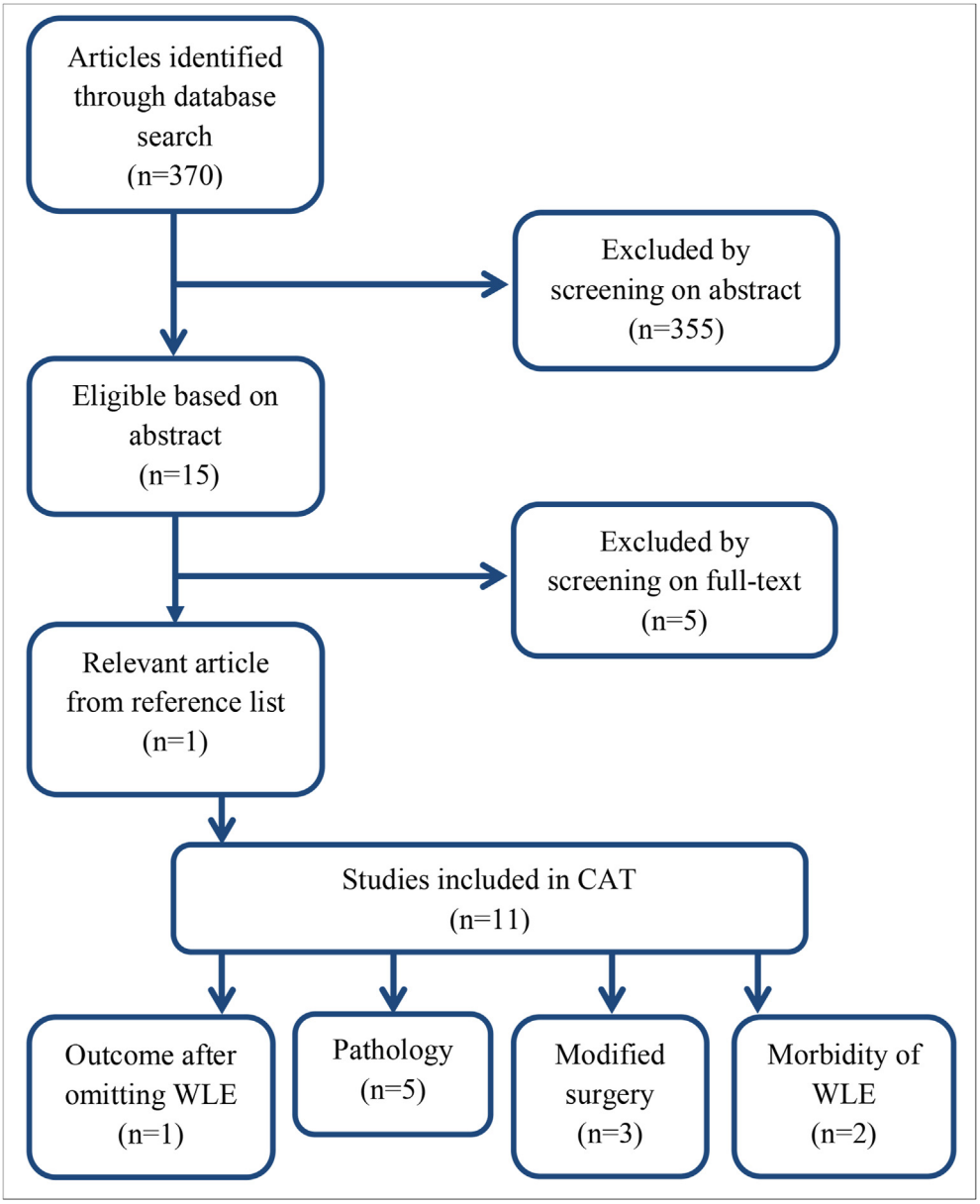

Fig. 1. Flowchart of literature search in Pubmed, Embase and Cochran CENTRAL database.

Articles were screened for relevance on their title and abstract. There were no restrictions on date of publication or language. Only articles that presented clinical data were included. Only one publication reported on patient outcome after omitting re-excision, therefore additional evidence was sought in pathology studies and articles describing modified surgical excision. Additionally, articles on morbidity of WLE were reviewed. Reference lists of relevant articles were hand searched for potentially missed articles. We did not include the large randomised controlled trials on the optimal resection margins, because no comparison to diagnostic excision only was made in these trials.

4. Critical appraisal of the evidence

4.1. Clinical outcome data

We identified one single study that described patient outcome after omitting WLE for primary cutaneous melanoma [12]. In this retrospective Dutch cohort study of 464 patients, 182 patients (39%) did no undergo a WLE. Overall survival was significantly lower in the non-WLE group (HR 1.5; CI 1.04–2.02). However, after adjusting for age, gender, Breslow thickness and tumour site, the authors found no evidence for non-WLE as a hazard for lower overall survival. Unfortunately, data on local recurrence or melanoma-specific

survival were not available. It is not mentioned what the indications were for omitting a WLE. The authors found no other publications on the effect of WLE on OS and note that the guidelines recommend two stage excision based on RCT's comparing WLE margins, not RCT's comparing one complete excision versus two-stage excision.

4.2. Pathology outcome data

The rationale behind WLE is that by taking an extra margin of healthy skin potential microsatellites are removed, which if left untreated could cause local recurrences. Therefore, indirect evidence for the benefit of WLE can be found in pathological research describing the occurrence of malignant melanoma cells in WLE specimen.

Five studies in our literature search reported on these outcomes. Goldrick *et al.* [13] and de Waal *et al.* [14] examined the incidence of residual tumour cells in WLE specimen after complete diagnostic excision and found an incidence of 0% and 0.5%, respectively. Both studies retrospectively examined a cohort of >1000 patients treated at regional hospitals. A study by Bolshinsky *et al.* [15] reported a higher incidence of 4.2% in 807 WLE specimen after complete diagnostic excision, with the lentigo maligna subtype being most at risk for residual melanoma. The authors differentiated between residual tumour cells of the primary melanoma and local metastasis, with the latter defined as 'a deposit separate from the scar, usually rounded in outline microscopically'. Of the 34 tumour positive samples, 33 were classified as residual primary melanoma and one as local metastasis.

Hocevar *et al.* [16] combined examination of WLE specimen with recurrence and overall survival data. They found residual melanoma in 3.6% of stage I and II melanoma after primary diagnostic resection. They also found a higher rate of sentinel lymph node biopsy positivity in the group with residual melanoma compared to the group without residual disease (44% vs 22%) and higher local recurrence rates (16% vs 2.7%). Consequently, OS after 5 years was significantly lower (64% vs 87.5%).

Contrary to these findings, a prospective study by Molenkamp *et al.* [17] did not find an effect of positive resection margins of primary diagnostic excision or presence of residual melanoma in WLE specimen on disease free or overall survival.

The range in incidence could be explained by differences in histopathological examination of the WLE specimen. The specificity of histopathological examination increases with the amount of sections studied, this is however a more time consuming and costly procedure. Practice of histopathological examination differs per study and center.

4.3. Modified surgery

Despite the consistency of guidelines in their recommendation for surgical margins, WLE is not feasible for every anatomic site. Another surgical strategy has been developed for melanoma at sites where anatomic reconstruction is unfeasible or decidedly mutilating. Mohs micrographic surgery (MMS) enables complete excision of melanoma with the narrowest margin by histopathologic examining of the resection border. This technique aims for complete primary excision with a minimum margin of healthy skin; therefore we examined the literature on outcomes of MMS versus WLE.

In our search we found three relevant publications. Chin-Lenn *et al.* [18] retrospectively studied 151 patients with facial melanoma from the Alberta Cancer Registry, 60 treated with MMS and 91 with WLE. They found no difference in 5-year local recurrence rates (6.2% vs 7.9%, $p = 0.58$), distant recurrence (8.8% vs 18.8%, $p = 0.37$) or disease specific survival 92.4% vs 82.8%, $p = 0.59$).

Hanson *et al.* [19] used the American National Cancer Database and compared 5-year overall survival for 50.397 head and neck melanoma patients treated with MMS and WLE. Patients treated with MMS (n = 3510) even had a higher 5-year OS (HR 1.18, CI 1.083–1.288; $p = < 0.001$). The authors offer no explicit reason for this finding, except for that MMS is predominantly used in academic centres, which together with treatment at high volume facilities have been linked to improved overall survival. Demer *et al.* [20] essentially performed a similar study for melanoma of the trunk and extremities. In 4,413 patients treated with MMS compared to 184,449 patients treated with WLE there was no difference in OS (HR 1.097, CI 0.950–1.267; $p = 0.21$).

4.4. Morbidity

WLE causes skin defects that can be difficult to close and occasionally requires additional surgery. We reviewed the literature to assess the extent of morbidity caused by WLE. The MelMarT trial published a feasibility pilot report including the need for reconstructive surgery and wound necrosis rate. Both were significantly higher in the 2-cm group compared to the 1-cm group (34.9 vs 13.6% and 3.6 vs 0.5%) [21]. In an article titled 'Primum non nocere' the morbidity of WLE for pT1a melanomas was described. They found complications of WLE in 25% of 231 included patients, including wound and scarring problems [22].

5. Discussion

Data on refraining to use WLE is scarce. In the publication by Haniff *et al.* it seemed to have detrimental effects on survival, but this was no longer the case after correcting for confounding factors [12]. There might

have been ample good reasons for non-adherence with the guidelines, for example in elderly and/or frail patients with many significant comorbidities.

Incidence of melanoma tumour cells in WLE specimen varies from 0 to 4.2% in the literature [13–17]. This means that ≥96% will not be able to benefit from a routine WLE at all, as they do not harbour any disease. Moreover, the remaining small minority of patients also do not seem to benefit, as none of the studies has shown any significant impact on OS, only a reduction in local recurrences with wider margins.

We argue that these microsatellites are governors of disease, and the overwhelming majority will also harbour metastases within their SLN. Since they are already upstaged to stage III on the detection of microsatellites within the diagnostic excision and/or metastases identified on SLNB, and as such will automatically qualify to be eligible for adjuvant systemic therapy, we question the benefit of routine WLE in this current day and age?

A frequent argument to continue this practice is the limited costs and morbidity associated with the 2-step WLE procedure. Although this is correct within an individual patient, the impact on a worldwide societal level is still significant. Complication rates (wound break down, bleeding, infections, need for reconstruction, failure of graft take, scarring, psychological stress, etc.) are not to be underestimated and are generally estimated to be within the range of 5–10%. Considering 325,000 newly diagnosed melanomas worldwide annually, this means that between 16,250 and 32,500 individuals will develop these issues yearly. Let alone the cost impact, which is easily tens of millions of euro's/dollars each year.

There are still current ongoing studies looking into the value of adjuvant systemic therapy already for high-risk stage II melanoma; CheckMate 76K (NCT04099251), and EORTC 2139/Columbus-AD (NCT05270044) as well as the already mentioned positive Keynote-716, which will change treatment for stage IIB/C melanoma in the near future. We anticipate that, with correct biomarkers, this will shift to high risk IB/IIA in the future. This all-further questions the need to continue the practice of WLE for stage I/II melanoma.

The situation is very similar to the historical situation in breast cancer that it was routine to perform a Halsted breast amputation in all cases, which shifted towards surgical de-escalation in the seminal paper by Veronesi *et al.* demonstrating that breast conservative surgery was also a safe possibility [23]. This caused a shift in paradigm from 'maximum tolerable' to 'minimum effective' [24]. This shift was made possible due to developments in radiotherapy and systemic therapy for breast cancer (chemotherapy and hormonal therapy) that have been long awaited in melanoma, but are now finally here.

In conclusion, there is no solid evidence to support the classic dogma of a 2-step approach with the use of WLE for primary cutaneous melanoma that has been completely excised on diagnostic excision biopsy.

We recommend to setup and conduct a prospective randomised trial to compare the classical 2-step approach with WLE to a complete diagnostic excision only to abolish the routine practice of WLE in the future.

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Conflict of interest statement

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