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Controversy

Is there a relation between type of primary melanoma treatment and the development of intralymphatic metastasis? A review of the literature ☆

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ABSTRACT

Background: Intralymphatic metastases (ILM) originate from tumor cell emboli entrapped in dermal lymphatics between primary tumor and regional lymph node basin. Because of this origin, sentinel lymph node biopsy (SLNB) might increase ILM by restricting lymph flow.
Methods: Pubmed, Embase, Cochrane and Medline were searched for articles on ILM between 1980 and September 2014. ILM Incidences were calculated after wide local excision (WLE), excision with elective lymph node dissection (ELND) or therapeutic lymph node dissection (TLND), WLE with SLNB with or without completion lymph node dissection (CLND) and delayed lymph node dissection (DLND) for patients developing nodal metastasis during follow-up.
Results: In 36 studies, 14,729 patients underwent WLE, 1682 patients WLE/ELND, 362 patients WLE/DLND and 11,201 patients WLE/SLNB. On meta-analysis, ILM occurrence was 3.4% (95% CI 2.8–4.2%). ILM occurred most frequently in the WLE/DLND group (5.5%, 95% CI 3.5–8.7%), followed by WLE/ELND (4.7%, 95% CI 3.1–7.0%), WLE/SLNB (4.5%, 95% CI 3.5–5.7%) and WLE alone (1.9%, 95% CI 1.4–2.7%). 1330 SLNB+ patients were identified and 5783 SLNB− patients. For these groups, on meta-analysis, ILM recurrence was 13.2% (95% CI 10.8–16.2%) and 3.4% (95% CI 2.5–4.5%), respectively ($p = 0.01$).
Conclusion: In this review SLNB is associated with an increase of ILM with an incidence of 1.9% for WLE vs. 3.4% for SNLB−. Selection bias in this review cannot be excluded. However, ILM occur four times more frequently after SLNB+ than SLNB− procedures and more often after SLNB+/CLND than WLE/DLND or WLE/ELND. ILM should therefore be viewed as a bio-marker of aggressive primary disease.
Synopsis: Sentinel lymph node biopsy is thought to increase intralymphatic metastasis by restricting lymph flow. This review demonstrates that there is an increase in metastasis, but this result has to be interpreted with caution due to possible selection bias. Aggressive tumor characteristics are likely the cause of this increase.

Introduction

The behavior of cutaneous melanoma is notoriously unpredictable. 5-year survival rates deteriorate as stage progresses. For stage IA, IB, IIA, IIB, and IIC these survival rates are 97%, 92%, 81%, 70% and 53%, respectively. 5-year survival for locoregional metastasis is 78% (stage IIIA), 59% (stage IIIB) and 40% (stage IIIC) [1]. Once melanoma has metastasized distantly survival is around 15–20%, although these rates are expected to improve upon the recent introduction of BRAF targeted drugs, checkpoint inhibitors and new generation immunotherapies [2–9]. Long-term follow-up reveals that ulceration and sentinel lymph node status are the strongest predictors for survival [10,11].

The concept of incidence of locoregional metastases increasing with tumor thickness was recognized decades ago [12–14]. Previously, in transit metastases (ITM) and satellite lesions (SL) were considered different entities, but The American Joint Committee on Cancer (AJCC) has classified both ITM and SL in 2002 as intralymphatic metastases (ILM) [15]. Historically, SL have been defined to reside within centimeters of the primary tumor location and ITM in the pathway between primary site and regional lymph node basin. The leading hypothesis is that both originate from tumor cell emboli entrapped in dermal lymphatic vessels between primary tumor and regional lymph node basin [16,17]. The appearance of

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ILM automatically upstages a patient's disease into stage IIIB/IIIC, decreasing 5-year survival to 59% and 40%, respectively [1]. Survival rates for patients with SL alone, SL/ITM, or ITM are identical and similar to that of patients with nodal disease [18]. Scar recurrence, 'true local recurrence', differs in pathophysiology, as these develop from residual cells of the initial melanoma, a result of false-negative margins or microsatellites.

Curative treatment for primary melanoma remains surgery (wide local excision, WLE) [2,19]. Four prospective additional elective lymph node dissection (ELND) trials showed no impact on survival [20–24]. ELND has become redundant after the introduction of the sentinel lymph node biopsy (SLNB) in 1992, which preserves its diagnostic advantage with less morbidity [21–23,25–27]. Patients with a positive SLNB undergo a completion node dissection (CLND). The MSLT-I study showed a small but significant disease-free and melanoma-specific survival benefit in patients with intermediate thickness melanoma (1.2–3.5 mm) and nodal disease following early treatment [28]. Most notably, a melanoma-specific survival improvement of 20% was reported for patients with intermediate thickness melanoma undergoing SLNB as opposed to observation, although the MSLT-I did not show improvement in recurrence free, distant metastasis free and melanoma specific survival for the entire population. The MSLT-II study will answer in the near future whether a CLND is indeed indicated after a positive SLNB [29,30]. Other treatment modalities have included therapeutic lymph node dissection (TLND), for metastatic nodal disease at the time of diagnosis, and delayed lymph node dissection (DLND), for patients developing metastatic nodal disease [31].

SLNB in addition to WLE alone has been suspected of causing ILM by inducing lymphatic stasis or entrapment of melanoma cells [32,33]. Pathophysiology on which this hypothesis is built is that the lymph flow from the skin reaches the nodal basin within minutes, with melanoma cells still in lymphatic channels *en route* to the lymph node basin at the time of SLNB or nodal dissection [33,34]. Estourgie et al. published a fourfold risk of ITM recurrence in SLNB positive patients as compared to SLNB negative patients, thereby raising the question whether surgical treatment of the regional lymph node basin can be responsible for ITM, although the same research group refuted this finding in a larger population [35,36]. Although various authors have studied this phenomenon, most notably Morton et al. in the aforementioned MSLT-I trial and van Poll et al. using data of the Melanoma Institute Australia, a definite answer as to whether the incidence of ILM should be attributed to unfavorable primary tumor characteristics alone or is increased by the SLNB procedure by means of a review of all available data has not yet been published [10,16,28,37,38].

The objective of this review was to provide an extensive body of evidence, answering the question whether ILM frequencies increase after performing SLNB.

Methods

Pubmed, Embase, Cochrane Library and Medline were searched for articles using the terms 'melanoma' and 'recurrence' or 'in transit metastasis' or 'ITM' or 'SL' or 'intralymphatic metastasis' or 'local recurrence' or 'satellite' or 'sentinel node' or 'survival' between January 1980 and September 2014. Articles were excluded if they had not been written in English, if they did not distinguish between a local recurrence and ILM, if incidence for ILM as a first recurrence (FR) was not reported, if studies exclusively reported on SLNB− or SLNB+ or if treatment strategy was unclear. Duplicates, case reports, letters to the editors and case series were excluded. Data regarding ILM as FR derived from our institution's SLNB database (UMCG database) were added to the review.

ITM was classified as recurrent melanoma in the pathway between primary melanoma location and the regional nodal basin, with the lesion more than two or five centimeters from this location, depending on the definition used in the article. All other cutaneous and subcutaneous metastases between the re-excision scar and the location of ITM were classified as SL. As consensus is now that ITM and SL are the same entity, all ITM and SL were combined into one value, 'ILM'.

For all included articles the number of patients with ILM as first recurrence (FR) were calculated per treatment group: for WLE alone, for WLE with ELND, WLE and DLND or TLND and WLE with SLNB. The last group was stratified into tumor-negative SLNB (SLNB−) patients and tumor-positive SLNB (SLNB+) patients undergoing CLND. When assessing risk of ILM as FR, WLE was compared to the WLE/SLNB− group. WLE/SLNB+ was compared to WLE/DLND, WLE/ELND and WLE/TLND groups. As only SLNB+ patients undergo additional CLND, this division groups together the most similar procedures regarding interruption of lymph flow. Additional study characteristics were collected: study design, number of patients, mean/median Breslow thickness, age at diagnosis, and melanoma ulceration status.

Statistical analysis

For a comprehensive review of the data, all data were summarized in tables and analyzed using version 18 SPSS, (IBM, Chicago, Illinois, USA). Descriptive statistics were used to calculate frequencies of ILM for the different treatment strategies. Chi-square tests were used to check for significant differences.

Subsequently, all studies were assigned a weight based on the amount of included patients and entered into a meta-analysis. Meta-analyses were performed stratified for treatment, SLNB results and anatomical localization of the primary tumor. Proportions of ILM and the corresponding 95% CI were calculated and entered in a datasheet. Meta-analyses were performed with the 'metan' module using STATA/SE version 12.0 (StataCorp, College Station, Texas, USA) with the original data as reported in the studies. Pooled ILM proportions and their 95% CI were calculated using a random effects model.

Results

Study characteristics

19,620 studies were identified and assessed according to the inclusion criteria. 36 studies with a total of 33,622 patients were included for analysis (Table 1), including our ongoing academic medical center database (UMCG database). 6 studies were excluded because they exclusively reported on SLNB− or exclusively on SLNB+ patients ($n = 684$ patients) [11,39–43]. Median follow-up ranged from >12 months–11 years. Fifteen out of 36 studies reported mean Breslow depth and 6 reported exclusively median Breslow depth. One study reported Breslow depth using incremental depths [44]. Melanoma ulceration status was reported in 23 studies; in 15 of those data were only available for part of the population. Twelve studies provided treatment/recurrence data on WLE (14,729 patients), 5 on WLE/ELND (1682 patients), 1 on WLE/DLND (362 patients) and 18 on WLE/SLNB (11,201 patients). For the remaining 5648 patients in 7 studies, treatment was not specified. No study reported outcomes exclusively for TLND.

In 23 of the 36 included studies a clear definition of ITM/SL was not provided. ITM was defined as (sub)cutaneous disease recurrence between locoregional lymph node basin and 2, 3 or 5 centimeters from the original scar in $n = 5$, $n = 1$ and $n = 4$ studies, respectively. The remaining 3 studies defined ILM as recurrence