ORIGINAL ARTICLE

Elective Lymph Node Dissection in Patients With Melanoma

Systematic Review and Meta-analysis of Randomized Controlled Trials

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Hypothesis: Elective lymph node dissection does not improve survival in patients with melanoma without clinically detectable lymph node metastases.

Objective: To determine whether elective lymph node dissection in patients with melanoma without clinically detectable regional metastases decreases overall mortality.

Design: Systematic review and meta-analysis of randomized controlled trials comparing elective lymph node dissection with delayed lymphadenectomy at the time of clinical recurrence.

Setting: Randomized controlled trials available by February 2001.

Subjects: The included trials comprised 1533 participants.

Intervention: Elective lymph node dissection compared with delayed lymphadenectomy or no lymphadenectomy in patients with melanoma without clinically detectable regional metastases.

Main Outcome Measure: Overall mortality in treatment groups as compared with control groups at the end of a 5-year follow-up period.

Results: Three randomized controlled trials met the inclusion criteria. The pooled odds ratio for overall mortality for the 3 trials was 0.86 (95% confidence interval, 0.68-1.09). Results are statistically nonsignificant, but they have potential clinical significance.

Conclusions: This systematic review of randomized controlled trials comparing elective lymph node dissection with surgery delayed until the time of clinical recurrence shows no significant overall survival benefit for patients undergoing elective lymph node dissection. Trials included in this review, however, contain significant bias. The question is not answered for all patients, and the results do not exclude the possibility that some subgroups may benefit from elective lymph node dissection. Further research is required.

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MALIGNANT melanomas comprise 5% of all skin cancers, but it accounts for 75% of all skin cancer deaths.[1] The incidence of malignant melanoma continues to rise all over the world.[2] Management of the regional lymph nodes in patients with melanoma is still a topic for debate in surgical oncology, and it has remained controversial since 1892, when Snow first recommended routine complete lymph node dissection in patients without clinical evidence of regional metastases.[3]

There are 2 different approaches toward lymphadenectomy: prophylactic or elective lymph node dissection (ELND) of the regional nodes draining the primary tumor vs delayed lymphadenectomy only when recurrences occur in the nodal basin. Surgeons performing ELND advocate it based on the Halstedian theory, which holds that metastases occur by passage of the tumor from the primary site to the regional nodes and then to more distant sites. Thus, prophylactic dissection of regional nodes should interrupt the metastatic cascade and prevent the spread of disease. Opponents of ELND consider prophylactic excision of lymph nodes unnecessary because the incidence of histologically positive regional nodes at the time of the resection of the primary melanoma in the patients with clinical stage I disease is only 20%.[4,5] Furthermore, patients undergoing routine ELND are at risk for considerable postoperative morbidity, and performing ELND increases the total costs of care per melanoma patient.[6]

See Invited Critique at end of article

Numerous articles that address outcome following ELND have been published, but although many of them are large retrospective and prospective studies, most

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METHODS

INCLUSION CRITERIA

We included only randomized controlled trials that compared ELND with delayed dissection or no dissection in patients with melanoma. Patients had to have a clinically and histologically diagnosed skin melanoma without clinically detectable regional lymph node metastases (stages I and II according to American Joint Committee on Cancer staging criteria).

SEARCH STRATEGY

We conducted sensitive electronic searches of MEDLINE (1966-February 2001) and Embase (1974-February 2001) using the recommended Cochrane Collaboration search strategy with MeSH headings "melanoma" and "elective lymph node" including all subheadings.

We reviewed the references of all relevant papers found in the searches, as well as those of review articles and textbooks, and we hand searched selected conference proceedings.

We conducted a search on the Controlled Trials Register from the Cochrane Library (Issue 4, 2000). No language restrictions were applied.

Where possible, we contacted the authors of the trials to verify the data and obtain additional unpublished data. We contacted experts in the field and asked them about any published or unpublished work that they might be aware of.

DATA EXTRACTION AND STUDY APPRAISAL

We extracted the following data from each study: randomization process including strategy for concealment of allocation, number of randomized patients, duration of follow-up, and number lost to follow-up. The main outcome measure was overall mortality at the end of a 5-year follow-up period for each trial. We sought mortality data in simple categorical form. Two reviewers independently extracted the data from each study, and any disagreements were resolved by discussion.

STATISTICAL METHODS

For each trial, we constructed 2×2 contingency tables, seperately enumerating the surviving and nonsurviving participants separately for the intervention and control groups. We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for 5-year overall mortality in the treated participants relative to the controls, using Peto's modification of the Mantel-Haenszel method with Cochrane Collaboration Review Manager 4.1 (The Nordic Cochrane Centre, Copenhagen, Denmark).

The number needed to treat (95% CI) was calculated for each trial using the Newcombe-Wilson hybrid efficient score method. We tested heterogeneity between trials using χ^2 distribution. Provided that no significant heterogeneity was identified, we pooled the summary estimates for the effect from each trial using Peto's fixed-effects model.

of them are nonrandomized.[7-9] The results are contradictory; therefore, the therapeutic value of prophylactic lymphadenectomy is still questioned.

The majority of clinical studies demonstrate that one of the most important prognostic factors for patients with early-stage melanoma is the status of the regional lymph nodes.[10] Morton et al[11] introduced the concept of intraoperative lymphatic mapping of the sentinel node, and sentinel lymphadenectomy to determine the tumor status of regional nodes and staging of patients with subclinical nodal metastases. This minimally invasive procedure is replacing ELND in many melanoma units, and it is suggested as a standard of care in the United States. In the United Kingdom, only a few centers treating patients with melanoma have technical facilities suitable for performing sentinel node biopsy, and there are a lot of arguments against it[12] based on morbidity, cost, and lack of evidence for efficacy. It will be some time before long-term follow-up for randomized controlled trial data for sentinel node biopsy are available. In the interim, a reconsideration of the data available for ELND is appropriate.

The present article reviews the randomized controlled trials that have examined the therapeutic value of ELND in patients with melanoma to reevaluate its validity.

RESULTS

We located 229 published papers reporting ELND in patients with melanoma. Four randomized controlled trials that evaluated the effectiveness of ELND on survival in patients with melanoma were identified[13-16] (**Table 1**). One trial (the Mayo Clinic Trial[16]) was excluded from the meta-analysis because although its methodological quality was acceptable, event data in the published papers were insufficient for analysis.[16] We contacted the author of the trial, but no additional data have so far been obtained. It has been included in the text of this review for discussion only.

Two articles' description of study design was sufficient enough to suggest that adequate concealment of allocation had taken place[13,14]; in other trials, concealment allocation was unclear.

Follow-up was reported in the Intergroup Melanoma Surgical Trial as 92%, while the World Health Organization (WHO) Melanoma Trials 1 and 14 did not report the number of patients lost during follow-up in their respective articles.[14-17] The authors verbally reported that they achieved 100% follow-up. Mortality data were available either from the published report or on contact with authors. The WHO Melanoma Trial 1 was reported in 2 publications. An early report gave the mortality data, but not all randomized patients had a 5-year follow-up.[13] The subsequent publication included a follow-up of 5 years for all patients, and the data were extracted from it.[17] The Intergroup Melanoma Surgical Trial was also reported in 2 publications. For our meta-analysis, we extracted data from the first publication,[14] as the second one refers to a long-term (10-year) follow-up.[18]

In 3 trials eligible for meta-analysis, the total number of participants was 1533; 768 were assigned to ELND; and 765, to delayed lymphadenectomy or no treatment (**Table 2**). A total of 416 deaths within 5 years of the

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Table 1. Characteristics of RCTs Comparing ELND With Delayed Dissection or No Treatment*

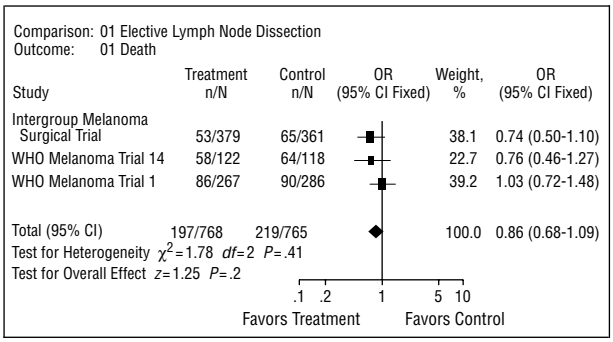
Trial	Year	No. of Patients	Site of Primary Tumor	Follow-up
Cascinelli et al[14]	1998	240	Trunk	132 mo (mean)
Balch et al[15]	1996	740	All sites	7.4 y (mean)
Sim et al[16]	1986	171	Extremities and trunk	4.5 y (median)
Veronesi et al[17]	1982	553	Extremities	8.2 y (mean)

*RCT indicates randomized controlled trial; ELND, elective lymph node dissection.

Table 2. Mortality Rates at 5 Years*

Trial	No LND	LND	RRR (95% CI)	ARR (95% CI)	NNT (95% CI)
WHO Melanoma Trial 14	0.54	0.47	0.12 (−0.12 to 0.31)	0.067 (−0.059 to 0.190)	15 (NS)
Intergroup Melanoma Surgical Trial	0.18	0.14	0.22 (−0.85 to 0.44)	0.04 (−0.01 to 0.09)	25 (NS)
WHO Melanoma Trial 1	0.31	0.32	−0.023 (−0.30 to 0.20)	−0.007 (−0.085 to 0.07)	−135 (NS)

*From the randomized controlled trials of immediate lymph node dissection (LND) vs delayed or no LND. RRR indicates relative risk reduction; ARR, absolute risk reduction; NNT, number needed to treat; and WHO, World Health Organization.



Meta-analysis of included randomized controlled trials comparing immediate lymph node dissection (treatment group) vs delayed or no lymph node dissection (control group) for mortality at 5 years. OR indicates odds ratio; CI, confidence interval; and WHO, World Health Organization.

primary tumor excision was recorded in 3 trials. Death occurred in 197 patients who underwent ELND compared with 219 from control groups. The pooled OR was 0.86 (95% CI, 0.68-1.09). **Figure 1** shows the results of the meta-analysis. There was no significant overall heterogeneity between trials ($P=.41$).

COMMENT

The aim of our study was to review the effectiveness of ELND in patients with melanoma, restricting the review and meta-analysis to reports of randomized controlled trials. All 4 randomized trials included in this review fail to demonstrate any benefit from ELND in patients with melanoma. We conducted an appropriate search according to Cochrane Collaboration strategy to avoid missing papers. Reviewing an abstract of one study published in German, we were suspicious that the study might be a randomized controlled trial,[19] but this study was excluded on confirmation from the author that the study was not a randomized controlled trial, and thus did not fulfill our inclusion criteria.

All trials contained significant methodological bias. One of the main problems is that preoperative lymphoscintigraphy was not performed in all trials, and ELND was carried out based on anatomical knowledge. In recent years, it has been shown that this nuclear medicine procedure is important to define all nodal basins at risk for metastases and to guide the surgeon to dissect all in-transit areas at risk because of anomalous drainage patterns. Only in the Intergroup Melanoma Surgical Trial did all patients undergo preoperative lymphoscintigraphy, while in WHO Melanoma Trial 14, lymphoscintigraphy was used to identify the first drainage basin only when it became available and it was not performed in all patients. In WHO Melanoma trial 1 and in the Mayo Clinic trial, lymphoscintigraphy was not performed at all. It is conceivable that sentinel node biopsy will improve the efficacy of ELND.

The WHO Melanoma Trial 1 was a study confined only to melanoma in the distal two thirds of the extremities, and 82.8% of the patients had melanoma on lower limbs. The majority of the patients were women (81.4%), and although this demographic distribution reflected the patient population from which the study was drawn, it is a group at relatively low risk for metastatic disease, and this may have caused significant bias.

In the Mayo Clinic Trial, the study groups were not similar. It was a 3-arm study with small group sizes that are insufficient for any reliable interpretation and conclusions, especially when many different prognostic variables need to be controlled in the multivariate analysis.

The Intergroup Melanoma Surgical Trial was the only one to use the method of prerandomization and to stratify patients into subgroups according to independent prognostic features. There is clear evidence that the patients were exactly matched by those variables that could have influenced outcome. In this trial, subgroup analysis was performed, and a subgroup with nonulcerated melanoma, Breslow thickness between 1.0 and 2.0 mm, and age 60 years or younger emerged as a group that may benefit from ELND. Age was not a stratified criteria, and the fact that it is emerging as a prognostic factor may be more of a statistical than a biological phenomenon. In this subgroup analysis, the possible mathematical artifact imposed by age might influence survival analysis of subgroups.[20]

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The only trial with a long-term follow-up[18] of 10 years had similar findings as those seen in this meta-analysis, with an overall survival rate of 77% vs 73% ($P=.12$) in patients receiving ELND compared with those recieving nodal observation.

In this systematic review and meta-analysis, we found that the overall mortality of patients with melanoma was not statistically significantly decreased among participants randomized to ELND compared with those in the control group. The conducted trials reviewed above are, however, of questionable validity. Thus, in our opinion, current evidence is insufficient to confirm that ELND does not improve survival in patients with melanoma. Further studies are needed to evaluate the benefits of ELND, and new large-scale randomized controlled trials seem to be necessary to resolve this issue. It is hoped that the randomized controlled trials of sentinel node biopsy and lymphadenectomy will have sufficient power to provide a definitive answer.

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Invited Critique

The optimal surgical management of the regional nodal basin in cutaneous melanoma has long been an area of controversy. Four prospective trials have been conducted to determine whether ELND is superior to observation; unfortunately, no survival benefit has been observed. Lens et al report the results of a meta-analysis combining data from 3 of these trials. Using the end point of overall survival at 5 years, they observed a nonsignificant pooled odds ratio of 0.86 in favor of ELND. The authors assert that the trials are of questionable validity and call for an additional large-scale trial to resolve this issue. It is unlikely that another prospective randomized trial of ELND will be conducted given the development of sentinel lymph node biopsy (SLNB). The goals of surgery directed at the regional nodal basin for cutaneous melanoma include identification of metastases and therapeutic removal of these metastases. Sentinel lymph node biopsy has surpassed ELND as a staging modality and has been widely accepted by surgeons throughout the world. Although Lens et al recognize the continued controversy regarding SLNB, the advantages in staging and subsequent risk stratification outweigh the potential risks, and SLNB has been adopted by most melanoma centers worldwide.[1] Furthermore, it is recognized that some patients are indeed cured with ELND; however, these numbers may be small, and accurate identification of these patients remains difficult.[2] Approximately 20% of patients will be found to harbor microscopic metastases at ELND; perhaps one quarter to one half of these will achieve a survival benefit from ELND. The majority of patients subjected to ELND will not benefit, further supporting SLNB in the management of cutaneous melanoma. While Lens et al attempt to end the controversy regarding ELND in cutaneous melanoma through the performance of a meta-analysis, the development of SLNB has essentially sealed the fate of ELND.

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