Available online at www.sciencedirect.com
SciVerse ScienceDirect
EJSO 39 (2013) 179–184
EJSO the Journal of Cancer Surgery
www.ejso.com

Assessment of a new scoring system for predicting non-sentinel node positivity in sentinel node-positive melanoma patients

K.P. Wevers [a], R. Murali [c,d], E. Bastiaannet [a], R.A. Scolyer [e,g,h], A.J. Suurmeijer [b], J.F. Thompson [e,f,g,i], H.J. Hoekstra [a,*]

[a] Division of Surgical Oncology, University of Groningen, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands
[b] Division of Pathology, University of Groningen, University Medical Center Groningen, The Netherlands
[c] Department of Pathology, Memorial Sloan-Kettering Cancer Center, NY, USA
[d] Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center, NY, USA
[e] Royal Prince Alfred Hospital, Sydney Medical School, The University of Sydney, Sydney, Australia
[f] Mater Hospital, Sydney Medical School, The University of Sydney, Sydney, Australia
[g] Melanoma Institute Australia, Sydney Medical School, The University of Sydney, Sydney, Australia
[h] Discipline of Pathology, Sydney Medical School, The University of Sydney, Sydney, Australia
[i] Discipline of Surgery, Sydney Medical School, The University of Sydney, Sydney, Australia

Accepted 17 October 2012
Available online 6 November 2012

Abstract

Background: When completion lymph node dissection (CLND) is performed in sentinel node (SN)-positive melanoma patients, a positive non-sentinel node (NSN) is found in approximately 20% of them. Recently, Murali et al. proposed a new scoring system (non-sentinel node risk score, N-SNORE) to predict the risk of NSN positivity in SN-positive patients. The objectives of the current study were to identify factors predicting NSN positivity and to assess the validity of the N-SNORE in an independent patient cohort.
Methods: All SN-positive patients who underwent CLND at a single institution between 1995 and 2010 were analyzed. Characteristics of the patient, primary melanoma, and SN(s) were tested for association with NSN positivity. Missing values were reconstructed using multiple imputation to enable multivariable analysis.
Results: CLND revealed positive NSNs in 30 (23%) of 130 SN-positive patients. Primary melanoma regression ($p = 0.03$) was independently associated with NSN positivity. After adjustment because of missing data on perinodal lymphatic invasion, N-SNORE proved to be a significant stratification model in our patient cohort ($p = 0.003$): 5.9% NSN positivity in the very low risk category and 75.0% NSN positivity in the very high risk category.
Conclusions: Presence of regression in the primary melanoma was independently associated with a higher risk of NSN positivity. The slightly modified N-SNORE scoring system provided useful stratification of the risk for NSN positivity. However, lack of perinodal lymphatic invasion data may have reduced its predictive value.

Keywords: Melanoma; Sentinel node; Predictors; Completion lymph node dissection; Non-sentinel node

Introduction

The incidence of melanoma is steadily increasing in the Western world. In the Netherlands its incidence has more than doubled in the past two decades, from 11.3 per 100,000 in 1989 to 26.3 per 100,000 in 2009.[1,2] In the United States the incidence rate in 2007 was 18.7 per 100,000 and it is estimated that more than 70,000 people will be diagnosed with melanoma in 2012.[3,4] Most melanoma patients in Western countries present initially with American Joint Committee on Cancer (AJCC) Stage I or II melanoma and 33–50% of these patients are diagnosed with Stage IA disease.[1,5]

The most important predictors of outcome in melanoma patients with clinically localized disease are Breslow thickness, ulceration, and the mitotic rate of the primary tumor.[5,6] The sentinel lymph node (SN) status, determined

* Corresponding author. Tel.: +31 (0) 50 361 23 17; fax: +31 (0) 50 361 48 73.
E-mail address: h.j.hoekstra@umcg.nl (H.J. Hoekstra).

0748-7983/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejso.2012.10.014

by sentinel lymph node biopsy (SLNB), is also of great importance for prognosis and in most studies this represents the strongest predictor of outcome.[7] Furthermore, patients undergoing SLNB, with completion lymph node dissection (CLND) if metastatic nodal disease is identified, seem to have better regional tumor control and survival according to the most recent interim analysis of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I).[8]

Although CLND is usually performed in patients with a positive SN, one or more positive non-sentinel nodes (NSNs) are found in only 8–33% of patients undergoing CLND.[7,9,10] In other words, approximately 4 out of every 5 SN-positive patients who receive a CLND will not have additional involved regional nodes identified. In theory, removal of uninvolved nodes will not improve the prognosis. As a result CLND, which is accompanied by considerable morbidity and costs, seems an unnecessary operation in approximately 80% of SN-positive patients. Therefore, a tool for accurate preoperative prediction of NSN involvement is desirable, especially to identify a subgroup of patients with such low risk for NSN positivity that CLND can be safely avoided. Many studies have investigated clinical and histological factors that predict NSN positivity.[9–21] Recently, Murali et al. proposed a new scoring system for stratification of risk of NSN positivity which they termed the non-sentinel node risk score (N-SNORE).[21] The aims of the present study were to identify factors associated with NSN positivity in a cohort of Dutch patients and to independently assess the validity of the proposed N-SNORE.

Methods

All patients ($n = 130$) undergoing CLND after a positive SLNB at the Division of Surgical Oncology of the University Medical Center Groningen between 1995 and 2010 were included in this study.

To enable SLNB, lymphoscintigraphy with ^{99m}Tc nanocolloid was performed the day before surgery and patent blue was injected 15–20 min before the procedure. All basins identified by lymphoscintigraphy were explored surgically and all nodes that were hot and/or blue were removed.[22]

Histopathologic analysis of the SNs consisted of blocking in paraffin and cutting 4 μm thick sections at 4 different levels with 250 μm between each level. Sections at each level were stained with hematoxylin and eosin and immunohistochemically for S100 and Melan-A. If metastatic melanoma was identified by histopathology or immunohistochemistry, the SLNB was considered positive and CLND was performed. For NSNs, histopathological analysis was performed on hematoxylin and eosin stained sections of cross-sectioned lymph nodes, and additional immunohistochemistry was not performed routinely.

Details of the patients, their primary tumors, SLNB, and CLND were prospectively collected in a database. The recorded parameters included: age, sex, histologic subtype of primary melanoma, Breslow thickness, Clark level of invasion, ulceration, mitotic rate, lymphovascular invasion, satellites, regression, number of harvested SNs, number and proportion of involved SNs, extranodal spread of tumor, maximum size of largest melanoma deposit in lymph node, and whether metastasis was detected by hematoxylin and eosin staining alone or by additional immunohistochemistry.

Statistics

Missing data were imputed (multiple imputation[23]) using a model with all factors. For the multiple imputation, we generated 5 iterations and combined the estimates and standard errors using Rubin's Rules (micombine in STATA). Prior to running the model we checked whether the data was missing at random. We used multiple imputation by chained equations which assume a multivariate distribution exists without specifying its form. In STATA the ICE module was used to perform the multiple imputation. A model was built with all missing variables (as shown in Table 1) and outcome. Univariate and multivariable binary logistic regression analysis was used to identify independent predictors for NSN positivity. A full model including all variables that were deemed important for the outcome was built. Since Murali et al demonstrated a significant association with some of the variables, we included these variables in the model. A significance level of 5% was used to identify statistically significant results.

The N-SNORE as described by Murali et al. is a weighted score with a maximum sum of 11 points based on the following characteristics: sex (female = 0, male = 1), regression in primary melanoma (absent = 0, present = 2), proportion of harvested SNs containing metastatic melanoma ($\leq$50% = 0, >50% = 2), perinodal lymphatic invasion in SN (absent = 0, present = 3), and maximum size of largest tumor deposit in the SN ($\leq$0.5 mm = 0, 0.51–2.00 mm = 1, 2.01–10.00 mm = 2, >10.00 mm = 3). The authors created 5 risk groups based on the N-SNORE, which stratified the incidence of NSN positivity; very low (0%), low (5–10%), intermediate (15–20%), high (40–50%), and very high (70–80%).[21] Assessment of the proposed N-SNORE was done by chi-square testing. As the variable perinodal lymphatic invasion (3 of 11 points), defined as the presence of melanoma cells in lymphatic vascular channels in tissues beyond the capsule of the SN,[16] was not recorded in the patients in the present study, the score was adjusted by rearranging the scores for the risk groups and subtracting 3 points from the total.

For the analyses STATA/SE 10.0 version was used (ICE, MIM, MICOMBINE and LOGISTIC).

Results

A total of 130 SN-positive patients [75 males (58%) and 55 females (42%): median age 51.5 (range 5–88) years] underwent CLND. The clinicopathologic characteristics