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SENTINEL LYMPH NODE BIOPSY IN ELDERLY PATIENTS WITH
INTERMEDIATE THICKNESS MELANOMA

A Masters Thesis Presented

By

KATE H. DINH

Submitted to the Faculty of the

University of Massachusetts Graduate School of Biomedical Sciences, Worcester

in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

MAY 14, 2015

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The signature of the Dean of the Graduate School of Biomedical Sciences signifies that
the student has met all master's degree graduation requirements of the school.

Anthony Carruthers, Ph.D.,

Dean of the Graduate School of Biomedical Sciences

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ABSTRACT

Background: A landmark study suggested that wide excision of intermediate-thickness melanoma with sentinel lymph node biopsy (SLNB) and subsequent completion lymph node dissection (CLND) for regional disease may improve prognostication and disease-free survival (DFS) compared with those undergoing wide excision alone. However, these benefits were relatively small and not associated with an improvement in disease-specific survival (DSS). It remains unknown if SLNB and subsequent treatments are beneficial in elderly patients who have a decreased overall (OS) due to other causes.

Methods: Adults ≥ 70 years of age, who underwent surgical intervention for intermediate-thickness cutaneous melanoma from 2000-2013 were identified from a prospectively-maintained database. Clinicopathologic variables measured included age, gender, anatomic site, histologic type, tumor thickness, ulceration, receipt and result of SLNB, completion of CLND, OS, and DFS.

Results: Ninety-one patients underwent excision of an intermediate-thickness melanoma. Forty-nine patients (54%) received a SLNB. Seven of these biopsies (14%) were positive, and five patients went on to receive CLND. Five-year OS was 41% in patients who did not receive SLNB and 52% in patients who did receive SLNB ($p=0.11$). DFS was similar between groups independent of receipt of SLNB.

Conclusion: Among elderly patients with intermediate-thickness melanoma, patients who received SLNB had similar 5-year OS and DFS compared with those who did not receive SLNB. Routine SLNB for intermediate-thickness melanoma patients may not significantly change outcomes for this age group, and clinical decision-making should consider individual patient comorbidities and goals of care.

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LIST OF ABBREVIATIONS AND ACRONYMS

CLND – completion lymph node dissection

DFS – disease-free survival

MSLT – Multicenter Selective Lymphadenectomy Trial

OS – overall survival

SLNB – sentinel lymph node biopsy

DSS – disease-specific survival

NED – no evidence of disease

AWD – alive with disease

DOD – died of disease

DOC – died of other causes

DUC - died of unknown causes

CHAPTER I: INTRODUCTION

Melanoma is the fourth most common malignancy in American men and the seventh most common malignancy in women, with 76,000 cases diagnosed in 2014. The incidence rate of this malignancy appears to be increasing.¹ While disease-specific mortality has decreased among patients younger than 65 years, these rates have increased among those 65 years and older.²

The clinical practice guidelines from the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the Society of Surgical Oncology (SSO) recommend that patients with intermediate-thickness melanoma undergo sentinel lymph node biopsy (SLNB), with subsequent completion lymph node dissection (CLND), if the SLNB is found to have metastatic disease.³⁻⁵ These recommendations are based on the results of the landmark Multicenter Selective Lymphadenectomy Trial-I (MSLT-I). This trial randomized a total of 1269 patients with intermediate-thickness primary melanoma to wide excision with observation of lymph nodes or to wide excision with SLNB. The study reported a greater DFS in those undergoing SLNB, and subgroup analysis further demonstrated a benefit to CLND in the setting of a positive sentinel lymph node.⁶

However, it remains unclear if the results of the MSLT-I can be generalized to elderly individuals for a variety of reasons. First, the median age of the subjects in this trial was 53 years. Furthermore, despite the NCCN, ASCO, and SSO recommendations,

observational studies have shown that adherence to these guidelines is poor, particularly among elderly patients. In a study of patients with positive sentinel lymph nodes, the presence of non-adherence to guideline-recommended CLND was not associated with a reduction in survival.⁷ Finally, it is well known that patients >70 years have an increased likelihood of dying from other causes. While it has yet to be proven that SLNB and its subsequent CLND improve survival in the elderly with intermediate-thickness melanomas, national recommendations currently do not provide age-specific recommendations that take into account both mortality from disease and mortality due to other causes, the latter of which is a more dominant issue in the elderly population.

The aims of this study are to examine current practices in regional management of intermediate-thickness cutaneous melanoma in the elderly, and to determine if SLNB is associated with improved overall and disease-free survival.

CHAPTER II: METHODS

This retrospective review of our institution's prospectively-maintained melanoma tumor registry was performed after approval from our institutional review board. Our institution is a tertiary-care referral center for cancer, treating patients primarily from central Massachusetts and nearby regions of Connecticut and New Hampshire. Patients were included if they were ≥ 70 years and underwent surgical treatment for intermediate-thickness cutaneous melanoma between 2000-2013. The age cut-point of 70 years was chosen because of prior studies that showed differences in the natural history of disease in this age group, compared with patients younger than 70.⁸⁻¹⁰ Intermediate-thickness disease was defined as pathologically confirmed melanoma with a Breslow depth of 1-4 mm on biopsy or wide excision specimen. Biopsies that were performed at referring institutions were re-reviewed by pathologists at our institution. Patients were excluded if they were preoperatively diagnosed with regional or distant metastases.

Demographic data (age, gender), comorbidity information, and tumor characteristics (anatomic site, Breslow thickness, histologic subtype, presence of adverse features [ulceration or mitoses]) were collected. Comorbidity information from the medical record was used to calculate the Charlson comorbidity index.¹¹ The independent variable in our study was the receipt of SLNB. Data were collected on receipt of SLNB, positivity of SLNB, and receipt of CLND.

The primary study outcome was overall survival (OS), which was calculated from date of definitive primary melanoma surgery to date of death. Date of death and cause of death (when available) were confirmed with social security death records and the tumor registry. DFS was calculated from the date of definitive primary melanoma surgery to the date of recurrence detection.

Vital status was classified as: no evidence of disease (NED), alive with disease (AWD), died of disease (DOD), died of other causes (DOC), and died of unknown causes (DUC). NED was defined as patients without detected recurrent disease during follow-up examinations. AWD was defined as living patients with detected recurrent disease. DOD was defined as either (1) patients who had a cause of death that was directly disease-related, or (2) patients with advanced metastatic or locally aggressive disease, who had made decisions regarding goals of care related to their disease burden. DOC was defined as either (1) patients who had a cause of death obviously unrelated to disease, such as a trauma, or (2) patients who may have had an unclear cause of death, but they had recent follow-up prior to death with documented lack of melanoma recurrence. DUC was defined as either (1) patients without recent follow-up prior to death, or (2) patients with a melanoma disease burden but with a competing cause of death, such as those with two or more known primary malignancies.

Demographic and clinical characteristics were compared between the respective treatment groups in a univariate fashion, using t-tests and chi-squared tests for continuous and categorical variables, respectively. Kaplan-Meier curves, the log-rank test, and the

Cox proportional hazard model were used for survival analysis, both for OS and DFS. Multivariate analysis using the Cox proportional hazard model was done by adjusting for gender, age, primary site, and tumor thickness. The alpha level was set to 0.05 for all measures of statistical significance. Stata version 13 (StataCorp, College Station, TX) was used for all statistical analyses.

CHAPTER III: RESULTS

A total of 91 elderly patients with intermediate-thickness melanoma were identified out of 228 total elderly patients in the melanoma tumor registry. The patients were 55% male, and the mean age was 80.1 years (SD 6.7 years). Forty-nine patients (53.8%) underwent SLNB, while 42 (46.2%) underwent clinical observation of the nodal basin. Patients who received SLNB were significantly more likely to be male and younger than those who did not receive SLNB ($p < 0.05$). Patients who did not receive SLNB were more likely to have primary tumors of the head or neck ($p < 0.01$). There was no statistically significant difference between the two groups, with regard to Charlson Comorbidity Index, histologic type, or Breslow depth (Table 3.1). The reasons to forgo SLNB, when available, include patient preference and co-morbidities that would preclude further management (Table 3.2).

Of the 49 patients who received SLNB, seven (14.3%) were found to have metastatic disease. Of these seven patients, five went on to receive CLND. The remaining two patients demonstrated progression of disease before CLND could be performed (Figure 3.1).

The 5-year OS in patients who did and did not receive SLNB was similar: 52% and 41%, respectively ($p = 0.11$; Figure 3.2). OS was also not statistically different on multivariate analysis (hazard ratio (HR): 1.44, 95% confidence interval (CI): 0.62-3.34, $p = 0.39$).

Patients who did and did not receive SLNB had similar 5-year DFS: 77% and 79%, respectively ($p=0.87$; Figure 3.3). DFS remained not significantly different on multivariate analysis (HR: 1.65, 95% CI: 0.39-7.06; $p=0.50$).

Of the 91 study patients, 47 (51.7%) had died at the time of this study. Of the remaining 44, 1 was AWD, and 43 were NED. The causes of death could be determined in 30 cases. Of these, 9 died of disease and 21 died of other causes. In 17 cases, the cause of death could not be determined if the patients had been lost to follow-up prior to death or if their causes of death were ambiguous. In comparing the patients in whom the cause of death could be confirmed, patients who received SLNB were more likely to die from melanoma, while those who did not receive SLNB were more likely to die from other causes ($p=0.02$; Figure 3.4).

Table 3.1: Patient characteristics

Variable	Received SLNB (N=49)	No SLNB (N=42)	p- value
Male gender, N (%)	32 (65%)	18 (43%)	0.03
Age at diagnosis (years), mean (SD)	75.9 (4.2)	85.1 (5.6)	< 0.01
Charlson Comorbidity Index (unadjusted), mean (SD)	1.41 (1.32)	1.79 (1.60)	0.22
Site of primary tumor, N (%)			< 0.01
Head/neck	11 (22%)	27 (64%)	
Torso	16 (33%)	3 (7%)	
Upper extremity	12 (24%)	7 (17%)	
Lower extremity	9 (18%)	5 (11%)	
Other	1 (2%)	0 (0%)	
Histologic type, N (%)			0.27
Superficial spreading	19 (39%)	23 (55%)	
Nodular	11 (22%)	8 (19%)	
Lentigo maligna	2 (4%)	5 (12%)	
Acral lentiginous	3 (6%)	1 (2%)	
Nevoid	1 (2%)	0 (0%)	
Desmoplastic	3 (6%)	2 (5%)	
Unclassified	10 (20%)	3 (7%)	
Breslow depth (mm), mean (SD)	2.15 (0.91)	2.10 (0.81)	0.80

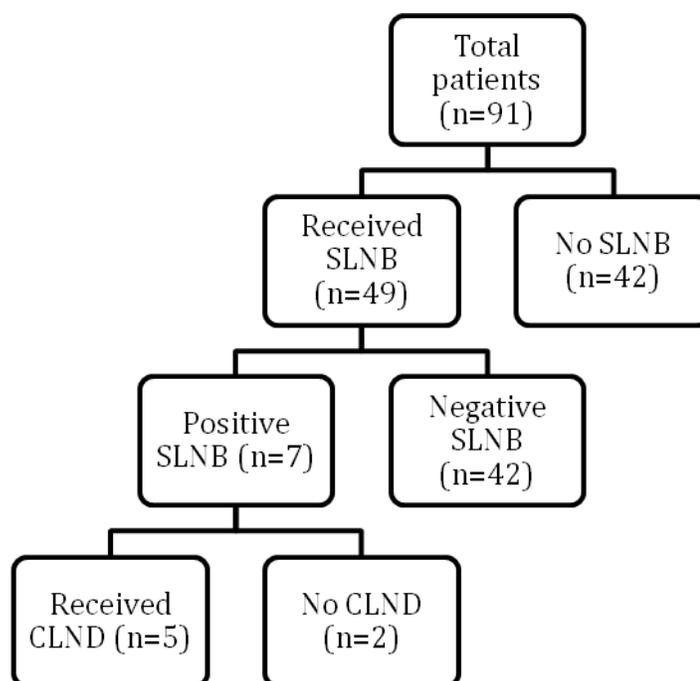
SLNB – sentinel lymph node biopsy; SD – standard deviation

Table 3.2: Reasons patients did not undergo sentinel lymph node biopsy (n=42)

Reason	Number of cases*
Patient would not be a candidate for CLND and/or adjuvant therapy	11
Patient did not want more aggressive treatment beyond excision	11
Physician recommended against SLNB because of patient age and/or comorbidities	10
Tumor board consensus decision	3
SLNB attempted, but no sentinel nodes found intra-operatively	2
Not documented	16

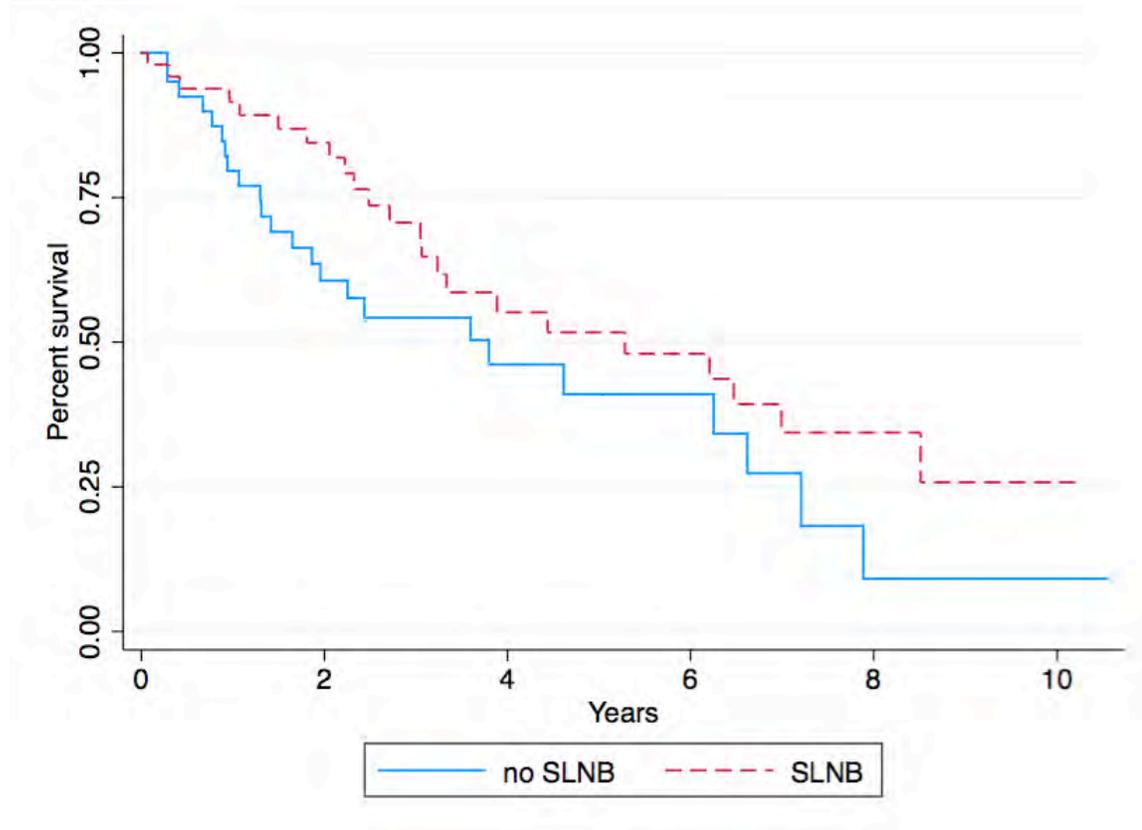
*The cases sum up to greater than the total number of cases because some patients had multiple reasons cited.

Figure 3.1: Lymph node evaluation in elderly patients with intermediate-thickness cutaneous melanoma



SLNB – sentinel lymph node biopsy; CLND – completion lymph node dissection

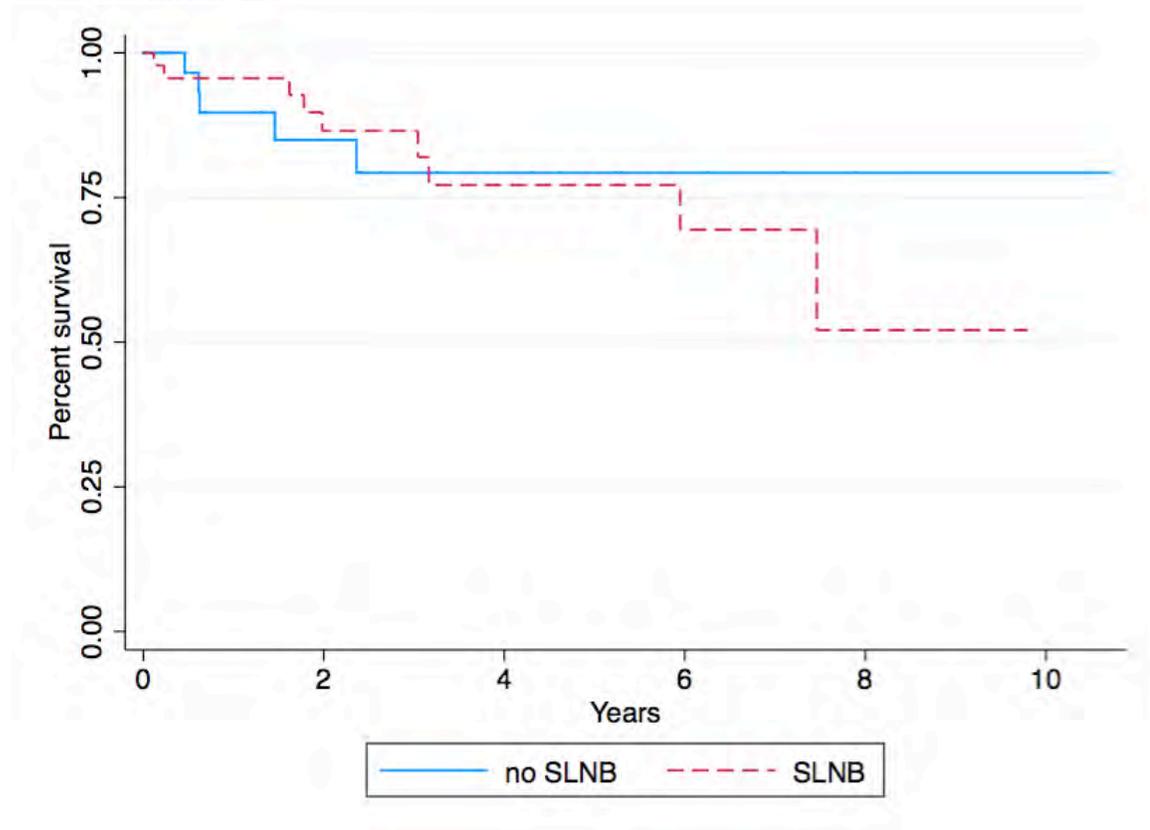
Figure 3.2: Overall survival for elderly patients with intermediate-thickness cutaneous melanoma



p=0.11

SLNB – sentinel lymph node biopsy

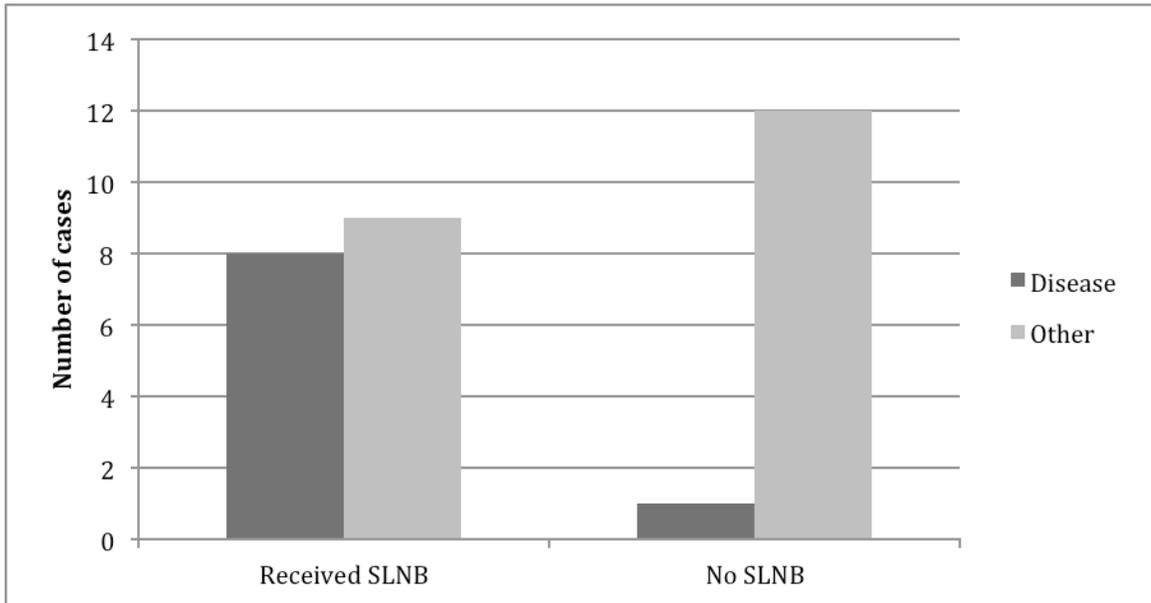
Figure 3.3: Disease-free survival for elderly patients with intermediate thickness cutaneous melanoma



p=0.87

SLNB – sentinel lymph node biopsy

Figure 3.4: Causes of death in elderly patients with intermediate-thickness cutaneous melanoma



p=0.02

SLNB – sentinel lymph node biopsy

CHAPTER IV: DISCUSSION

In this retrospective study, about half of the elderly patients with intermediate-thickness melanoma underwent SLNB. The patients for whom SLNB was deferred were more likely to be female, older, and have head/neck primary tumors. The most common reasons for deferral were generally related to the patients' age and comorbidities, a lack of candidacy for CLND and/or adjuvant therapy if the SLNB were positive, and patient desire to not to pursue aggressive treatment.

This compliance pattern is consistent with trends seen in the National Cancer Database (NCDB). Bilimoria et al. showed that only 50% of patients of all ages with a metastatic sentinel lymph node went on to receive CLND. Patients aged >75 years were even less likely to undergo a CLND after a positive sentinel lymph node (42.7%).¹² The NCDB data does not contain information as to the reasons why patients defer CLND despite clinical guidelines. However, a retrospective patient series at Memorial Sloan-Kettering Cancer Center showed similar rates of CLND. Chart reviews from that study demonstrated that the most common reason for forgoing CLND was patient refusal (45%), although the study could not ascertain the exact reason for this decision.⁷ While these studies examined CLND rather than SLNB, the patients and clinicians in our retrospective study believed that there would not be much utility in doing a SLNB if it was already known that a subsequent CLND or additional treatment would be deferred.

In these cases, a SLNB would only provide prognostic information while subjecting patients to potential complications.

Our study demonstrates that elderly patients have similar OS and DFS, independent of receipt of a SLNB. Several other retrospective studies have compared the oncologic outcomes of patients of all ages who undergo SLNB with those who undergo observation.¹³⁻¹⁹ The trend in these studies shows that SLNB is associated with improved DFS but, similar to our study, not with DSS or OS.

A randomized trial that compares elderly patients who undergo CLND with those who undergo observation for positive SLNB could elucidate the relationship between subclinical lymph nodes and survival. This is one of the aims of MSLT-II, which is still ongoing with a 10-year follow-up period. The trial includes adult patients ≥ 18 years, but subgroup analysis may provide some information about the role of SLNB and CLND in the elderly.²⁰

Our study has several important limitations. It is a retrospective study of patients treated at a single institution. The patients were not randomized to SLNB. Furthermore, because our institution is a tertiary-care referral center for cancer, the patient follow-up for medical issues unrelated to melanoma is variable. However, follow-up for melanoma is consistently performed at our institution, which allows for more reliable recurrence documentations. Therefore, patients with DUC were more likely to be DOC rather than DOD, although we did not incorporate this assumption in our calculations.

The decision to undergo a surgical procedure for any patient, and especially the elderly, is a complex process that involves discussion between the physician, patient, and patient caretakers. This study shows that elderly patients who received SLNB had similar OS and DFS independent of receipt of SLNB. Routine SLNB for intermediate-thickness cutaneous melanoma may not significantly change outcomes for this age group and may not be necessary in this patient subpopulation. Therefore, clinical decision-making should continue to take into account both tumor- and patient-specific factors.

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