The American Journal of Surgery (2015) 210, 1178-1184

The American Journal of Surgery®

Southwestern Surgical Congress

Risk factors associated with lymphedema after lymph node dissection in melanoma patients

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KEYWORDS:
Lymphedema;
Melanoma;
Lymph node dissection;
Risk factors

Abstract

BACKGROUND: Secondary lymphedema is a frequent complication after lymphadenectomy in melanoma patients, although few studies in melanoma adequately characterize risk factors for lymphedema, and of these, sample size is limited. This study aims to identify risk factors associated with the lymphedema after axillary lymph node dissection (ALND) and inguinal lymph node dissection (ILND) in a more robust cohort of melanoma patients.

METHODS: We identified 269 ALND or ILND melanoma patients treated between 2008 and 2014. Demographic, clinical, and postoperative data were collected by review of the electronic medical record. Univariate and multivariate analysis were used to determine independent predictors of lymphedema.

RESULTS: Fifty-six (20.8%) of the patients developed lymphedema after lymph node dissection with a median staging group of 3. ILND (odds ratio [OR] = 4.506, $P < .001$, 95% confidence interval [CI]: 2.289 to 8.869) and peripheral vascular disease (PVD; OR = 3.849, $P = .020$, 95% CI: 1.237 to 11.975) were significant predictors of lymphedema in multivariate analysis. Obese body mass index approached significance (OR = 1.802, $P = .069$, 95% CI: .955 to 3.399).

CONCLUSIONS: PVD and ILND were the 2 factors associated with the highest risk of lymphedema in melanoma surgery with PVD increasing risk 2-fold in ILND patients and 3-fold in ALND patients. These findings may improve surgeon-patient communication of care goals and surgical risk assessment.

Lymphedema, or the presence of chronic edema due to decreased lymph transport, is one of the more significant complications that can occur after a lymph node dissection of the axillary or inguinofemoral lymph nodes. Typically, these lymph node dissection procedures are performed in the setting of node-positive breast cancer and melanoma. For axillary dissection in this setting, lymphedema rates of 6% to 15% have been reported, and for inguinal dissection rates can be even higher at 29% to 41%.[1,2] Although risk factors for lymphedema in breast cancer patients having axillary

Partial funding support for this article including faculty effort has come from the University of Michigan Comprehensive Cancer Center support grant P30CA046592 (M.S.C.), the University of Michigan Department of Surgery (M.S.C.), and Department of Dermatology (T.J. and A.D.).

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Manuscript received April 10, 2015; revised manuscript August 12, 2015

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http://dx.doi.org/10.1016/j.amjsurg.2015.08.014

dissections have been described in the literature, these risk factors in melanoma patients, especially in patients having inguinal dissections, have not been studied as robustly. This is felt to be due to several factors including under-recognition, misdiagnosis, and lower number of cases as compared with breast cancer.[1] Traditionally, the importance of lymphedema has been viewed as secondary in the context of an untreatable side effect of a beneficial therapy.[2] However, lymphedema is a painfully disfiguring complication associated with numerous histologic changes of the cutaneous tissues, including fibrosis, loss of normal sensation, impaired function, and increased risk of inflammation and recurrent infection of the affected limb.[1,3–5] Moreover, these patients can experience significant decreases in health-related quality of life and life-long increased rates of limb infection.[1,2,6–11] Given the high number of patients developing lymphedema after inguinal lymph node dissection (ILND) for metastatic malignant melanoma, the impact of these chronic issues related to quality of life and infection on the health care system is not trivial. In the current era of the Affordable Care Act with a growing focus on patient-centered outcomes, improvements in risk profiling will be an important component in decreasing the incidence of this debilitating complication.

Postoperative lymphedema after axillary lymph node dissection (ALND) has been well studied in breast cancer patients, and although the pathophysiology and treatments for breast cancer and melanoma differ, the surgical techniques associated with complete lymph node dissection are very similar. Therefore, in the context of studying risk factors that would be associated with lymphedema in melanoma patients, it is reasonable to 1st look at similar characteristics observed in breast cancer patients. These factors, include age, body mass index (BMI), sex, race, type of cancer, cancer stage, tobacco use, diabetes, history of heart failure, chemotherapy, radiation therapy, incision location, operation time, ALND, sentinel lymph node biopsy (SLNB) or prior surgery on the limb, extent of surgery at the time of LND (ie, in breast cancer this would be modified radical mastectomy vs breast-conservation surgery), and number of nodes removed (ie, ≤ 5 vs >5 removed).[4,7,9,12–18] These studies have noted that increasing BMI, specifically morbid obesity, is associated with an increased risk of wound complications, including lymphedema in the setting of both axillary and inguinal lymphadenectomy. In addition, certain combinations of surgery and adjuvant therapy have been reported to increase the risk of lymphedema. A study by Ozaslan and Kuru[17] found that women who had the combination of full axillary dissection and axillary radiotherapy carry an increased risk of developing lymphedema. Although the literature on lymphedema in breast cancer is fairly robust including large meta-analyses,[19] in the melanoma population, there remains a gap in evaluating the risk factors of secondary lymphedema after nodal dissection for melanoma in part due to a lack of a large sample size for adequate statistics, variances in defining and reporting this complication, and limitations in longer-term follow-up. We feel the melanoma population may have some unique characteristics especially when compared to breast cancer and genitourinary (GU) cancers where ALND and ILND are most commonly performed. Because most of the ALND literature is for breast cancer patients, there are some differences anatomically in the surgical approach. Unlike in breast cancer, ALND in melanoma is not combined with removal of the breast and its lymphatic collaterals (modified radical mastectomy). In addition, a large portion of melanoma ALNDs are in men which may affect lymphedema development. Similarly, with comparing GU inguinal dissections and melanoma inguinal dissections, there are other differences. Most of the inguinal dissections in the GU literature also include iliac and pelvic dissections with ILND; although in this study with melanoma patients, we only looked at inguinofemoral dissections and excluded any dissections above the inguinal ligament. In this manner, our cohort has several unique characteristics that are different from the grouped meta-analyses in the literature. The objective of this study was to enhance the literature by evaluating risk factors for lymphedema in a larger cohort of melanoma patients using a highly robust database of patient characteristics, comorbidities, and follow-up. This study retrospectively examines the prevalence of lymphedema in patients having ALNDs or ILNDs for melanoma. The primary aim of the study was to examine associations between comorbidities, intraoperative technique, postoperative treatment, and lymphedema. Although there are limited studies in melanoma investigating the relationship between lymphedema development and ALND or ILND, several patient characteristics have been postulated as risk factors including adjuvant therapy, radiation therapy, and lymphocele formation.

Methods

Study population

This study cohort was identified as a subset of melanoma patients seen at the University of Michigan Comprehensive Cancer Center Melanoma Clinic between 2008 and 2014. Overall, 310 patients were included in this subset cohort from our institutional review board–approved, prospectively maintained melanoma database. A retrospective chart review was then performed on each patient to define and capture the clinical and operative variables for our data set. Clinical data points collected included patient demographic information, preoperative comorbidities, intraoperative details, postoperative complications and morbidities, and adjuvant therapy details. To better assess lymphedema rates on a single limb after nodal dissection, patients undergoing bilateral ALND or bilateral ILND were excluded from this analysis, as were patients undergoing simultaneous ALND and ILND. Patients receiving preoperative adjuvant chemotherapy or immunotherapy were also excluded from this cohort to evaluate a more homogenous population having postoperative adjuvant treatment, which is considered more standard. When excluding patients with dissection of multiple nodal basins