Safety and Feasibility of Minimally Invasive Inguinal Lymph Node Dissection in Patients With Melanoma (SAFE-MILND)

Report of a Prospective Multi-institutional Trial

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Background: Minimally invasive inguinal lymph node dissection (MILND) is a novel approach to inguinal lymphadenectomy. SAFE-MILND (NCT01500304) is a multicenter, phase I/II clinical trial evaluating the safety and feasibility of MILND for patients with melanoma in a group of surgeons newly adopting the procedure.

Methods: Twelve melanoma surgeons from 10 institutions without any previous MILND experience, enrolled patients into a prospective study after completing specialized training including didactic lectures, participating in a hands-on cadaveric laboratory, and being provided an instructional DVD of the procedure. Complications and adverse postoperative events were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0.

Results: Eighty-seven patients underwent a MILND. Seventy-seven cases (88.5%) were completed via a minimally invasive approach. The median total inguinal lymph nodes pathologically examined (SLN + MILND) was 12.0 (interquartile range 8.0, 14.0). Overall, 71% of patients suffered an adverse event (AE); the majority of these were grades 1 and 2, with 26% of patients experiencing a grade 3 AE. No grade 4 or 5 AEs were observed.

Conclusions: After a structured training program, high-volume melanoma surgeons adopted a novel surgical technique with a lymph node retrieval rate that met or exceeded current oncologic guidelines and published benchmarks, and a favorable morbidity profile.

Keywords: benchmarks, complications, endoscopic, groin dissection, inguinal, laparoscopic, lymph node count, melanoma, minimally invasive, seroma, videoscopic, wound infection

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The most frequent site of metastatic spread of melanoma is to the regional lymph nodes. In breast cancer, nodal evaluation serves primarily as a staging procedure, and complete axillary lymph node dissection offers little, if any, benefit for those with clinically occult disease, especially in those receiving standard adjuvant therapies.[1] In contrast, with melanoma, even isolated tumor cells within the lymph nodes are considered clinically relevant and staged as node-positive.[2] The goal of a lymphadenectomy is to remove and pathologically analyze lymph nodes for regional control, staging, directing adjuvant therapy decisions, and in a subset of patients, potentially improve survival.

Lymphadenectomy is the current standard for patients presenting with clinical nodal disease or a positive sentinel lymph node (SLN). Unfortunately, inguinal lymph node dissection is associated with significant morbidity. Three prospective trials have reported postoperative morbidity in approximately 70% of patients undergoing inguinal lymph node dissection through a conventional open approach,[3–5] including wound infection, wound dehiscence, and seroma formation. Numerous interventions have been attempted to minimize these complications, but these have not been successful.[6–8]

Minimally invasive inguinal lymph node dissection (MILND) is a novel approach to an inguinal lymphadenectomy. MILND is a 3-trocar technique that respects the anatomic boundaries of the femoral triangle, similar to its open predecessor. The procedure was first described in a cadaveric model and 1 patient in 2003,[9] and in 2006, a series of 7 patients with penile carcinoma was published.[10] Delman et al[11] modified the technique to be appropriate for patients with melanoma, and demonstrated the feasibility of this approach in a series of 5 patients, presented at the 2009 Society of Surgical Oncology meeting. Institutional series of 13 and 40 cases, respectively, have shown that the number of lymph nodes pathologically reported with MILND is comparable with the conventional open approach, yet short-term morbidity is decreased.[12,13]

The Safety and Feasibility of Minimally Invasive Inguinal Lymph Node Dissection trial (SAFE-MILND, NCT01500304) is a multicenter, phase I/II clinical trial designed to evaluate the safety and feasibility of MILND for patients with melanoma in a group of surgeons newly adopting the procedure. Herein, we report our findings, including the number of lymph nodes pathologically identified, adverse events (AEs), length of stay (LOS), and drain-days, and compare this with published reports for the conventional open approach.

METHODS

A select group of melanoma surgeons practicing in the United States, who performed at least 6 open inguinal lymph node dissections per year and had had no previous MILND experience, were identified and invited to participate in a structured training program to learn the innovative procedure. After obtaining institutional approval, each surgeon prospectively enrolled patients and submitted all data to a central site.

Training

All participating surgeons came to Mayo Clinic, Rochester, MN, for instructional training, which included viewing an instructional video, which was created by Mayo Clinic Media Support services, depicting the procedure in high-quality graphic detail, and adhering to effective adult learning principles. The 20-minute video included a 3-dimensional animated component of the relevant anatomy with key steps of the procedure outlined and visually depicted, and also a series of edited operative cases, highlighting the critical aspects of the procedure. The video can be seen at http://medprofvideos.mayoclinic.org/videos/minimally-invasive-inguinal-lymph-node-dissection-milnd. All attendees then participated in a hands-on cadaveric laboratory. During this training workshop, trainees performed MILND in a controlled environment under instructional supervision. During the hands-on cadaveric dissection, each participant functioned as an assistant for 1 case and as a surgeon for 1 case. Participants were provided a DVD copy of the educational video to allow them to review the operation in detail as needed after completion of the workshop.

Inclusion/Exclusion Criteria

Patients at least 18 years of age with melanoma, who were advised to undergo an inguinal lymphadenectomy secondary to clinical disease or a positive SLN biopsy, were eligible. Patients were not eligible for enrollment if they had a prior inguinal lymphadenectomy in the ipsilateral leg, prior radiation to the ipsilateral groin, or direct ulceration or invasion of the overlying skin. Patients with American Society of Anesthesiologists (ASA) class 4 or greater were also excluded. The decision to perform a combined pelvic lymphadenectomy was at the discretion of the operating surgeon.

Enrollment Scheme

A 2-stage enrollment scheme was used when a surgeon performed 5 cases and submitted surgical and pathologic data, and also 30 and/or 90-day postoperative visit results. The principal investigator reviewed these materials. If at most 4 lymph nodes were found on pathologic review in 3 or more of the cases, 2 or more cases converted to an open procedure, or 3 or more cases developed a grade 3+ adverse (excluding seroma or lymphedema), the surgeon would not be allowed to enroll additional cases.

Complications

Complications and adverse postoperative events were graded using the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v 4.0). Data collected included transfusion in the postoperative period, days the drain was in place, replacement of drains, duration of hospital stay, wound infections, wound dehiscence, seromas, arterial or venous injury, sensory and/or motor neuropathy, hemorrhagic and venous thromboembolic events, and other AEs in the 30 to 90-day follow-up period. Complications were captured on intent-to-treat basis.

Preoperative and postoperative limb volume measurements were obtained on both the operative and nonoperative lower extremity. Estimated leg volume recording by serial circumferential measurements at 4-cm intervals bilaterally from the heel to the groin was encouraged, but recording by other institutional established protocols was allowed including perometer and water displacement methods. The volumetric definition of lymphedema was an interlimb difference of at least 5% postop compared with baseline. This is adapted from the CTCAE v 3.0 criterion,[14] and has been utilized to identify the presence of lymphedema in prospective cohorts[15,16] and randomized controlled trials.[17,18] Patients undergoing a bilateral MILND procedure were eligible to be enrolled in the protocol, but were excluded from lymphedema calculations. Stopping rules were established including termination of the study, if 2 of the first 6 surgeons to complete cohort 1 lost enrollment privileges, or if, at any point in the study, 30% or more of the participating surgeons were not allowed to enroll additional patients as defined under the enrollment scheme above. A data safety monitoring board was established and monitored the trial.

Statistical Analysis

Descriptive statistics were used to summarize patient and surgical characteristics such as patient sex, age, body mass index (BMI), smoking history, limb volume, indication for inguinal node dissection (clinical nodal disease or SLN positivity), the number of lymph nodes pathologically identified, number of total positive inguinal lymph nodes, if deep pelvic lymphadenectomy was performed, and blood loss.

RESULTS

Twelve surgeons from 10 institutions enrolled 88 patients between June 2012 and September 2014. None of the surgeons discontinued participation due to unacceptable outcomes as detailed in the "Methods" section. One patient withdrew preoperatively and 87 operative cases made up the study group. The median MILND procedures performed per participating surgeon were 6, with a range of 1 to 24. Mean patient age was 55.8, with 52 females (59.8%) and 35 males (40.2%). All patients had either 30 or 90-day follow-up; 83 patients had 30-day and 49 patients had 90-day follow-up; with 44 having both. The median length of follow-up was 72 days from surgery, with a range of 11 to 151.

The majority of patients (65, 74.7%) underwent a complete lymph node dissection secondary to a positive SLN, and 22 patients (25.3%) presented with clinical inguinal nodal disease. The median number of lymph nodes pathologically identified after the MILND was 10, with an interquartile range (IQR) of 6 to 13. The median total inguinal lymph nodes pathologically examined (SLN + MILND) was 12.0 (IQR 8.0, 14.0). Figure 1 is a histogram, which visually depicts the distribution of the number of lymph nodes pathologically identified for the cases completed via a minimally invasive approach. There was 44 (50.6%) cases with at least 1 MILND lymph node involved with metastatic disease, and in the other 43 (49.4%), the complete lymphadenectomy specimens were negative (range of positive lymph nodes at inguinal dissection 0–7, not counting prior positive SLNs). In the 65 patients whose indication for a completion lymphadenectomy was a positive SLN, 22 (34%) had further nodal disease. Seven patients underwent a combined pelvic lymphadenectomy and 3 (42.9%) had positive pelvic nodal disease.

Among the 87 patients in whom MILND was attempted, 10 (11.5%) were converted to an open procedure. The median hospital LOS was 1 day (IQR 1–2) for those successfully completed via a MILND and 3 days (IQR 2–4) for those converted to an open procedure. AEs are listed in Table 1 and are based on intent-to-treat analysis. Overall, 71% of patients suffered an AE; the majority of these were grades 1 or 2, with 26% of patients experiencing a grade 3 AE. No grade 4 or 5 AEs were observed. Hemorrhagic events included anemia (8), venous injury (2), intraoperative hemorrhage
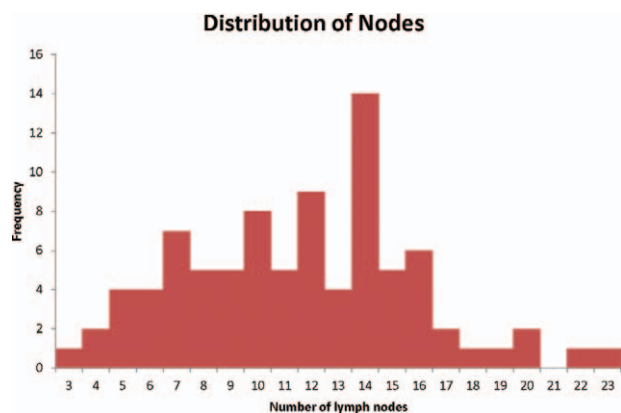
FIGURE 1. Histogram, which visually depicts the distribution of the number of LNs pathologically identified for the cases completed via a minimally invasive approach (N = 77). LN indicates lymph node.

(1), and postop hematoma (2). Only 1 patient required a blood transfusion and none required a take-back for bleeding. Two patients had a skin injury that required debridement or resection. Wound dehiscences were minor, with none requiring admission or debridement. Twenty patients experienced a wound infection, but only 11% of the patients received intravenous antibiotics or required radiologic intervention (grade 3). Twenty-five (28.7%) patients had a history of smoking, but only 9 (10.3%) smoked in the 1 month before the MILND procedure. Smoking history was associated with a higher rate of AEs (88% vs 65%; Fisher exact test $P = 0.036$).

Of the 77 procedures successfully completed by a minimally invasive approach, 16 (21%) developed a wound infection (1 grade I, 7 grade II, 8 grade III). Prophylactic antibiotics upon discharge were received by 23/77 (30%) of the patients. Moreover, 15/54 (28%) of the MILND procedures not prescribed prophylactic antibiotics developed wound infections versus 1/23 (4%) of those discharged on prophylactic antibiotics. None of the patients converted (0/10) received prophylactic antibiotics, and 4/10 (40%) of those who converted to an open procedure developed a wound infection (2 grade II and 2 grade III). Of the 87 patients, 21 (24%) had at least 1 wound-related event (wound infection, wound dehiscence, or skin injury/necrosis). The indication for lymphadenectomy did not seem to influence the wound complication rate. A wound-related AE was observed in 3/22 (14%) of those with clinical nodal disease and 18/65 (28%) of those with a positive SLN ($P = 0.183$) (chi-square test, $P = 0.183$).

The number of drain-days was available for 80 patients. The median number of drain-days was 27.6 (n = 72, IQR 19–34) among those who completed MILND and 24.6 (n = 8, IQR 13–28.5) among those who converted to open procedure. Patients whose indication for an inguinal lymphadenectomy was clinical nodal disease had their drains in place longer (median 30, IQR 27–38) than patients undergoing a MILND for a positive SLN (median 24.5, IQR 17–32, Kruskal-Wallis $P = 0.027$). The number of drain-days did not correlate with either wound infection, seroma (Kruskal-Wallis $P = 0.55$ and $P = 0.21$, respectively), or whether a Harmonic Scalpel or LigaSure was used (Kruskal-Wallis $P = 0.21$). A fibrin sealant was used in 15 (17.4%) cases and did not correlate with drain-days or postoperative seroma. Energy source utilized was not randomized and purely a surgeon choice. Harmonic scalpel was used in 69 cases (80%), LigaSure in 15 (17.4%), both in 2 (2.3%) cases, and the data are missing for 1 case. There were 10 (14.5%) cases of seroma in the Harmonic scalpel group and none in the LigaSure group, though this was not significant ($P = 0.12$). The median operative times were on average 12 minutes shorter and drain-days 2 days longer in the LigaSure group; however, the type of energy source used did not correlate with either of these outcomes.

Wound infection rate, operative time, and number of lymph nodes identified were not found to differ with respect to BMI. However, increasing BMI seemed to be associated with an increased rate of lymphedema; for BMI <25, 25 to 30, and >30, the lymphedema rates were 40%, 48%, and 72%, respectively. Among the 83 patients evaluated for lymphedema on day 30, lymphedema rates were somewhat higher among those with BMI >30 than those with BMI ≤30 (63.3% vs 41.1%; Fisher exact test $P = 0.07$). Of these 83 patients, 49 (59%) were re-evaluated at day 90, where lymphedema persisted in 11 (22%) and an additional 3 (6%) cases were reported.

DISCUSSION

In a multi-institutional, prospective trial evaluating a structured training program for MILND, the number of lymph nodes pathologically identified met the current oncologic guidelines and published benchmarks. The median number of lymph nodes pathologically identified (SLNB + MILND) was 12 (IQR 8, 14). These early cases in a surgeon's experience utilizing a new procedure were also associated with low morbidity and short hospital LOS.

The recommended minimum lymph node count for an inguinal lymphadenectomy published in the literature varies from 5 to 10.[19–24] Two studies arrived at a minimum number of 8 and 10 in an evidence-based manner based on the risk of understaging, regional recurrence, and/or overall survival.[20,23] Galliot-Repkat et al set a benchmark at 10, based on survival data in melanoma patients after lymphadenectomies and Bilimoria et al also used 10 as a threshold for quality, but these models did not differentiate between the

TABLE 1. List of Complications of All Attempted MILND Procedures on an Intent-to-treat Basis

Complications	Maximum Grade Complications (N = 87)			
	Grade 1	Grade 2	Grade 3	Total
Lymphedema	18 (21%)	26 (30%)	3 (3%)	47 (54%)
Wound infection	1 (1%)	9 (10%)	10 (11%)	20 (23%)
Hemorrhage	10 (11%)	2 (2%)	1 (1%)	13 (15%)
Seroma	3 (3%)	3 (3%)	6 (7%)	12 (14%)
Skin injury/necrosis	1 (1%)		2 (2%)	3 (3%)
Wound dehiscence	1 (1%)	1 (1%)		2 (2%)
Peripheral motor neuropathy			1 (1%)	1 (1%)
Other	2 (2%)	1 (1%)		3 (3%)
Total	37 (43%)	42 (49%)	23 (26%)	

TABLE 2. Comparison of Lymph Node Count in Our Trial With the MIA Open Inguinal Lymphadenectomy Experience and 2 Prospective Multi-institutional Trials Utilizing an Open Approach to Inguinal Lymphadenectomy

	Mean	Median	Range	8 or More	11 or More
MIA[25]	12.1	11	3–27	90%	62%
Current study	11.6	12	3–23	80%	60%
Sunbelt[26]	11	—	2–37	—	—
MSLT-I*	—	11	—	—	—

*Personal communication with Dr Mark Faries.
MIA indicates Melanoma Institute of Australia; MSLT-I, Melanoma Sentinel Lymph Node Trial 1.

regional nodal basins.[21,25] The median number of lymph nodes pathologically identified in our study of newly trained surgeons was 12. For the cases that were completed via a minimally invasive approach, 68% had 10 or more lymph nodes and only 20% had less than 8 total inguinal nodes. This compares favorably with the Melanoma Institute of Australia's (MIAs) finding, as shown in Table 2, with a mean of 12.1% and 90% of their inguinal lymphadenectomy cases having at least 8 lymph nodes examined.[26] Our methodology was also similar to that of MIA in including prior SLNB lymph nodes into the count of total regional nodes examined. Unlike their study, we did not include prior lymph nodes removed via an excisional biopsy. Comparing our study with multi-institutional trials of the open procedure is probably the best comparison for the adequacy of the lymph node count. The mean lymph node count for inguinal lymphadenectomies was 11 in both the MSLT-I trial (Mark Faries, personal communication) and the Sunbelt Melanoma Trial[27] (Table 2).

Minimally invasive lymph node dissection has been shown to have favorable short-term outcomes compared with the open approach, and this is supported by the current multi-institutional study. Although 71% of patients enrolled suffered an AE, we were probably overly stringent in documenting all events prospectively, as noted by grade 1 fatigue, contact dermatitis, and an episode of syncope all being counted as AEs. Many of these events would likely not have been identified in a retrospective review, or counted as a complication in national registries or prospective trials. Excluding acute lower-extremity edema (3 cases), 20 (23%) patients suffered grade 3 AEs, including 10 patients who received intravenous antibiotics, 6 seromas that required a drain to be replaced, 2 skin injuries that required debridement, 1 patient requiring a blood transfusion, and 1 femoral nerve injury. The complication rate reported in this study would be expected to decrease as more experience is gained with performing this procedure. The learning curve for this trial has recently been reported,[28] and how baseline laparoscopic skills influenced outcomes will be the subject of future publications from this study. Unlike prior studies which have demonstrated decreased morbidity when an inguinal lymphadenectomy is performed for clinical nodal disease as opposed to microscopic disease, that is, positive SLN,[8,29] this was not our experience. The drain-days were on average longer for those with clinical disease, but the seroma rate and wound complication rate were not statistically different.

The current Centers for Disease Control (CDC) definition of postoperative wound infections does not include cellulitis treated with oral outpatient antibiotics, secondary to this being very subjective and unreliable. In our study, only 11% of patients experienced a grade 3 wound infection, 8/77 (10%) completed via MILND, and 2/10 (20%) of those converted. We noticed a lower infection rates in those discharged on prophylactic antibiotics. This care management was at the discretion of the treating surgeon, and this finding is worth further exploration. The infection rate reported in this study of inguinal lymph node dissections compares very favorably with the literature for the open procedure, as does our wound dehiscence and

seroma rates (Fig. 2). Coit et al reported a 64% in hospital wound complication rate. Overall, 45% of patients suffered a major wound complication including frank purulent drainage or wound dehiscence.[4] This high complication rate is similar to that documented in other prospective studies.[3,5] Wound dehiscence occurred in 45% of patients in the study by Serpell et al,[5] and 53% in the trial by Chang et al.[3] It should also be appreciated that the significance of a wound dehiscence has a markedly different connotation for an open inguinal lymphadenectomy compared with a 1 cm trocar site incision. In the MD Anderson series, a major wound dehiscence, defined as the requirement for a vacuum-assisted wound device, occurred in 13% of cases.[3] Three of the patients in the current study developed a seroma that was observed, 3 were aspirated, and 6 had a second drain placed. These seroma rates compare favorably with the open procedure as shown Figure 2. Martin et al have published the only prospective review of the perioperative complications after MILND. They also included in their definition of a wound infection any use of antibiotic. In 40 patients, their overall complication rate was 47.5%; lymphedema was not recorded, but their infection (40%), seroma (22.5%), and flap necrosis rate (2.5%) were similar to ours.[13]

Retrospective studies have also demonstrated a lower complication rate and shorter hospital LOS for MILND compared with an open approach.[12,13,30] A comparison of LOS between our contemporary study and historical references of the open trials is not appropriate, because LOS has decreased over time for a multitude of reasons. This is reflected in the Memorial Sloan Kettering study published in 1991 in which the mean LOS was 7 days for those without a wound complication and 13 days for those experiencing a wound complication,[4] and in the Serpell et al[5] study in which patients were kept in the hospital until the drain was removed.

Lymphedema is the most dreaded long-term complication of inguinal lymphadenectomy. The incidence and potential quality of
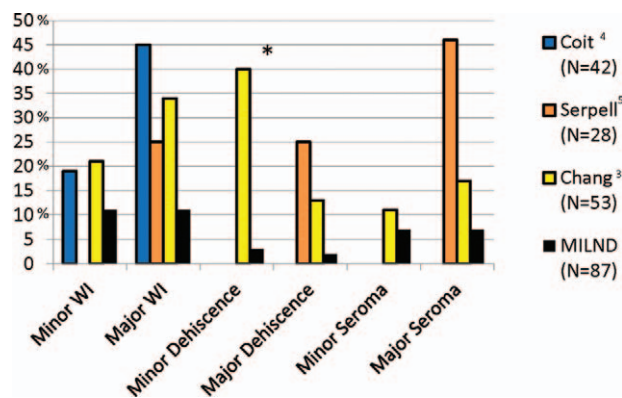
FIGURE 2. Comparison of complications from this prospective study versus prospective open trials. *In the study by Coit et al, wound infections and wound dehiscences were grouped.

life impact of lymphedema in the lower extremity after a groin dissection is magnified over that commonly experienced in the arm after an axillary lymph node dissection. Chang et al[3] reported a 3-month incidence of 45% for open groin dissections based on 2 prospective studies. Lower-extremity lymphedema often occurs early, but may undergo reduction or disappear completely after 6 months,[31] whereas others have reported a mean time to maximum lymphedema of 14.7 months.[32] Spillane et al[33] reported an incidence of approximately 16% in patients seen at least 6 months after their inguinal lymphadenectomy. Forty-one percent of patients enrolled in our trial developed lymphedema (17 grade 1, 22 grade 2, and 2 grade 3) within 30 days of MILND. Fifty-four percent of patients enrolled in this trial developed lymphedema at some time, with only 3% grade 3. Reporting the incidence of worst outcome (54%) may not be reliable as only about half of the patients returned for 90-day follow-up. Acute postoperative limb volume changes seem common after this procedure; however, it is not clear at this time what the long-term incidence of lymphedema will be and how that will compare with the open procedure.

Minimally invasive lymph node dissection is a novel approach to inguinal lymph node staging and treatment.[11,12] We report an excellent safety profile and lymph node count from a prospective multi-institutional trial for this procedure. These results were obtained after a rigorous training program of surgeons with a high-volume melanoma practice and extensive experience with open inguinal lymphadenectomies. We have established that high-volume melanoma surgeons can safely and adequately perform MILND after a structured training program.

ACKNOWLEDGMENTS

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