

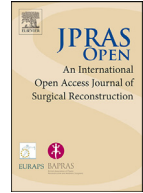


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Original Article

Can prophylactic incisional negative pressure wound therapy Reduce Wound Complications After Inguinal Lymph Node Dissection for Melanoma? Results from a Randomized Controlled Trial [☆]

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ABSTRACT

Background: Inguinal lymph node dissection (ILND) is associated with a high complication rate. Retrospective studies suggest that incisional negative pressure wound therapy (iNPWT) might reduce complications, especially seroma, following ILND.

[☆] This study was presented at the 10th World Congress of Melanoma in conjunction with the 17th EADO Congress, April 15–17, 2021.

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Keywords:

Negative-pressure wound therapy
PICO
VAC
Seroma
Complications
Lymph node dissection
Melanoma

Methods: This was a prospective multicenter, randomized (1:1), open-labeled, parallel-group trial. Patients with macrometastatic melanoma to the inguinal lymph nodes and eligible for ILND were randomized to receive either iNPWT for 14 postoperative days or conventional wound dressing. The primary outcome was seroma incidence. Secondary outcomes included surgical-site infection, wound rupture, wound necrosis, hematoma, rehospitalization and readmission rates between groups. All outcomes were registered 3 months after ILND and analyzed according to the intention-to-treat principle.

Results: The trial was terminated early due to a low recruitment rate as a consequence of a change in the national treatment protocol, and the estimated sample size was not reached. Twenty patients were included and randomized in the study. The trial showed less seroma formation between the iNPWT 6/11 (55%) and control 7/9 (78%) groups; however, this was not statistically significant ($p = 0.29$). Similarly, there were no differences in the rates of surgical-site infection ($p = 0.63$), wound rupture ($p = 0.19$), wound necrosis ($p = 0.82$), hematoma ($p = 0.19$), reoperation ($p = 0.82$) or readmission ($p = 0.34$) between groups.

Conclusion: There was a tendency toward fewer complications in the iNPWT group, however this trial was underpowered and could not confirm the hypothesis that iNPWT reduces complications after ILND. Future randomized controlled trials are required to fully evaluate the treatment potential of iNPWT.

Trial registration: The trial was prospectively registered at <https://clinicaltrials.gov/ct2/show/NCT03433937>.

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Introduction

Background

Melanoma is one of the most common cancers, with an increasing incidence¹. Melanoma on the trunk and lower extremities can metastasize to regional inguinal lymph nodes². Inguinal lymph node dissection (ILND) is the standard procedure indicated in patients with macrometastasis detected clinically or with imaging and without known distant metastasis. Iliac lymph node dissection is often added in the case of simultaneous lymph node metastasis in the lower pelvis. Seroma is the most common complication following ILND and can lead to increased hospitalization, multiple outpatient visits, and reoperation^{3,4} with negative impact on quality of life and health care costs. The high risk of complications following ILND has therefore received considerable attention and is the leading indication for the de-escalation of complete lymph node dissection in melanoma^{5,6}.

Incisional Negative Pressure Wound Therapy (iNPWT) has been shown to facilitate wound healing through vacuum-assisted closure⁷. In the last decade there has been a growing interest in prophylactic iNPWT to decrease complication rates after surgery⁸. Recent retrospective studies have shown promising potential for iNPWT in preventing wound complications after ILND^{9,10} however, randomized controlled trials have been lacking¹¹.

This trial aimed to investigate the efficacy of iNPWT in reducing complications following ILND. The trial was terminated earlier than anticipated due to a low recruitment rate as a consequence of altered national guidelines for the treatment of micrometastatic melanoma. Following the practice changing

MSLT-II and DeCOG trial results^{5,6}, complete lymph node dissection for micrometastatic melanoma was abandoned in Denmark in 2018¹², and the number of eligible patients dropped significantly.

This paper presents the trial results of 20 patients randomized to either iNPWT or conventional wound dressing after ILND for melanoma.

Methods

Trial design

This prospective multicenter, randomized (1:1), open-labeled, parallel-group study was conducted in Denmark (four sites); at the Departments of Plastic Surgery at Odense University Hospital, Herlev Gentofte Hospital, Rigshospitalet, and Roskilde Hospital. The trial results herein were reported following the published trial protocol and the Consolidated Standards of Reporting Trials (CONSORT) statement^{13,14}. All study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Odense University Hospital^{15,16}.

It was initially planned to include 110 patients over a 3-year timeframe¹³. However, shortly before the trial was initiated, complete lymph node dissection was no longer performed routinely for micrometastatic disease in Denmark following the MSLT-II and DeCOG trial results^{5,6,12}. Because of the sharp decline in ILND procedures, the steering committee and ethical board recommended that the trial be terminated after 20 patients. The study protocol was immediately amended in accordance with the recommendation.

Trial participants

Eligible patients were adults aged 18 years or older diagnosed to have melanoma metastasis in the inguinal lymph nodes with the indication of ILND following a multidisciplinary conference decision according to national guidelines¹². Indications for ILND were clinically (palpable, PET-CT or ultrasonographically) identified macrometastatic lymph nodes in the groin, and no distant metastasis. Patients should be able to communicate in oral and written Danish and should not suffer from dementia or any other psychiatric disorder, making them incapable of providing informed consent or adhere to follow-up.

Inguinal lymph node dissection

The ILND was performed as a standard lymph node dissection where all lymph nodes and adipose tissue were excised in the triangular region delineated by the sartorius muscle, adductor longus muscle, and the inguinal ligament, with clearance of the adjacent lower abdominal wall, up until approximately 5 cm above the inguinal ligament¹³. The wound was then closed using a 3.0 resorbable and a 4.0 non-resorbable suture and covered with an iNPWT dressing or Micropore™ tape, depending on treatment allocation. At the end of the procedure, two suction drains were placed from the surgical cavity through the skin distally or lateral from the inguinal wound and anchored using a 3.0 polypropylene suture. The suction drains were placed in a manner, which allowed the iNPWT to cover the surgical field. The drains were to be removed when there was a daily output of less than 20 mL per drain. A single dose of intravenous 1.5 g cefuroxime or equivalent antibiotic dosage was administered intraoperatively according to patient allergies and institutional protocol.

Interventions

Patients randomized to the iNPWT arm were assigned to wear a prophylactic iNPWT dressing (PICO, size: 10 × 20 cm; Smith & Nephew Medical Ltd, UK) over the closed inguinal incision for 14 consecutive days. The iNPWT dressing is a single-use battery-powered device that exerts 80 mmHg continuous negative pressure. The battery-powered iNPWT dressing lasts for 7 days and was thus to be changed on the 7th postoperative day. After removing the iNPWT dressing, a non-sterile Micropore™ tape dressing was then optionally used to cover the scar for up to 3 months

postoperatively. Patients in the control arm had a standard postoperative wound dressing consisting of the same optional non-sterile Micropore™ dressing applied for up to 3 months.

Randomization

Treatment allocation was determined by a computer randomization program in REDCap to either prophylactic iNPWT or a standard postoperative dressing in a 1:1 allocation. The randomization sequence used variable block sizes of four and six. Each study center had its own allocated block randomization to allow for an equal treatment allocation distribution between study sites.

Outcomes

The prespecified primary and secondary endpoints for this trial have been described elsewhere in detail¹³. In brief, postoperative complication endpoints were registered up to 3 months postoperatively and compared between the iNPWT and control groups. All postoperative complications were assessed and treated at the time of occurrence. Outcomes were registered at days 7 and 14 and 1 and 3 months postoperatively in the REDCap electronic case report form detailing whether an outcome had occurred up to each time point as previously described¹³.

The primary outcome was as follows:

- The number of patients treated for postoperative seroma, which was defined as a clinically recognized and punctured seroma, with an aspirated volume of 30 mL or more.

Secondary outcomes included the following:

- The cumulative volume of aspirated seromas, measured in milliliters aspirated in total.
- The cumulative number of aspirated seromas.
- The number of patients treated for a surgical site infection, defined as a clinical groin infection treated with antibiotics.
- The number of patients with wound dehiscence, defined as a wound edge dehiscence that required secondary suturing or NPWT treatment.
- The number of patients with wound necrosis, defined as the presence of dead tissue, who required debridement as per the attending physician's clinical decision.
- The number of patients with hematoma, defined as an inguinal surgical cavity filled by blood or clots, that required evacuation.
- The number of days until discharge, defined as the number of days from ILND until discharge.
- The number of patients requiring readmission, defined as the number of patients who were readmitted to the ward or had inpatient visits for reasons relating to the inguinal wound.
- The cumulative number of readmission days, defined as the total number of days that patients were readmitted to the ward or had inpatient visits for reasons relating to the inguinal wound.
- The number of patients requiring a reoperation, defined as opening of the wound/scar under general anesthesia for any complication (e.g. deep infection, hematoma, wound dehiscence, necrosis, and continuous lymph leakage) from the inguinal wound.
- The number of days with drains, defined as days from the ILND until the last suction drain was removed.
- The cumulative volume of collected fluid in suction drains, measured in milliliters.

The unplanned post-hoc analysis included the following:

- The cumulative incidence of complications, defined as the cumulative incidence of patients with at least one seroma, wound infection, wound rupture, wound necrosis, hematoma and/or reoperation. Each patient counted more than once if they had more than one type of complication (e.g. both seroma and infection). However, each unique complication type was only counted once, regardless of how many times the complication was registered in the patient.
- The cumulative number of all complications, defined as the cumulative number of seromas, wound infections, wound ruptures, wound necrosis, hematoma, and reoperations.

Table 1
Demographics and baseline information on participants in the study (n = 20).

| Variable | | iNPWT(N = 11) | Control(N = 9) | p-value |
|---|--------------|---------------|----------------|---------|
| Age (years) | Mean ± SD | 68 ± 11 | 70 ± 10 | n.s |
| Female (yes) | Number (%) | 4 (36%) | 6 (67%) | n.s |
| BMI (kg/m ²) | Median (IQR) | 27 ± 6 | 26 ± 5 | n.s |
| Diabetes (yes) | Number (%) | 1 (9%) | 1 (11%) | n.s |
| Tobacco use weekly (yes) | Number (%) | 1 (9%) | 1 (11%) | n.s |
| Alcohol consumption weekly (yes) | Number (%) | 8 (73%) | 3 (33%) | n.s |
| Lymph nodes removed (no.) | Median (IQR) | 10 (1) | 9 (1) | n.s |
| Lymph nodes with metastasis (no.) | Median (IQR) | 3 (2) | 2 (2) | n.s |
| Lymph node metastasis with perinodal growth (no.) | Median (IQR) | 0 (1) | 1 (1) | n.s |
| Iliac lymph node dissection (yes) | Number (%) | 3 (27%) | 1 (11%) | n.s |
| Days until discharge (no.) | Median (IQR) | 8 (5) | 7 (2) | n.s |
| Days until drain removal (no.) | Median (IQR) | 7 (1) | 7 (5) | n.s |
| Volume in suction drains (mL) | Mean ± SD | 964 (472) | 840 (755) | n.s |

This table shows the demographics and baseline information for patients in the iNPWT and control groups. There was no significant difference between the demographic and baseline variables between groups. iNPWT = incisional negative pressure wound therapy. No = number. SD = standard deviation. IQR = interquartile range. N.s = not significant.

- The number and qualitative analysis of treatment malfunctions in the iNPWT group, defined as any loss of seal, inadequate suction, and dysfunction leading to an unprotocolled change, failure, or removal of the iNPWT dressing.

The following baseline information was collected at the time of inclusion: patient age, sex, weekly use of tobacco (yes/no), weekly alcohol consumption (yes/no), BMI, and diabetes. The total number of lymph nodes removed, the number of metastatic lymph nodes and the number of lymph nodes with perinodal growth were retrieved from pathology reports. We also registered whether the ILND also included dissection of iliac lymph nodes.

Statistical analysis

We described the baseline characteristics of patients with means ± standard deviations (SD) for continuous parametric variables, median and interquartile range (IQR) for nonparametric continuous variables, and rounded frequencies (%) for categorical variables. The Skewness/Kurtosis test was used to test for normal distributions of continuous variables. Primary and secondary outcomes were compared between the iNPWT and control groups using an unpaired *t*-test, Chi-squared, or Mann-Whitney test depending on the data type and distribution. Prespecified subgroup analyses excluding patients with dissection of the iliac lymph nodes were also performed for the primary and secondary complication endpoints. STATA 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP) was used for the statistical analysis and conducted with a two-tailed significance level of 0.05 and reported with 95% confidence intervals (CI) when applicable. All analysis was conducted on the intention-to-treat principle.

Results

We included 20 patients between July 2018 and July 2020, all of whom underwent randomization. Eleven patients were allocated to the iNPWT group, and nine to the control group (Fig. 1). There was no statistically significant difference in age, sex, BMI, comorbidity, tobacco use, and alcohol consumption between groups (Table 1). The number of removed lymph nodes, iliac dissections, days until discharge, and days till drain removal were comparable between the groups. All patients were included in the intention-to-treat analysis.

There were fewer patients with seroma in the iNPWT 6/11 (55%) compared to the control 7/9 (78%) group; however, this difference was not statistically significant, *p* = 0.29, Fig. 2. No seromas occurred during the first seven days after ILND in either group. Similarly, no difference in the number of treated seromas between the iNPWT (median: 3, IQR: 6) and control (median: 4, IQR: 7) groups was evident,

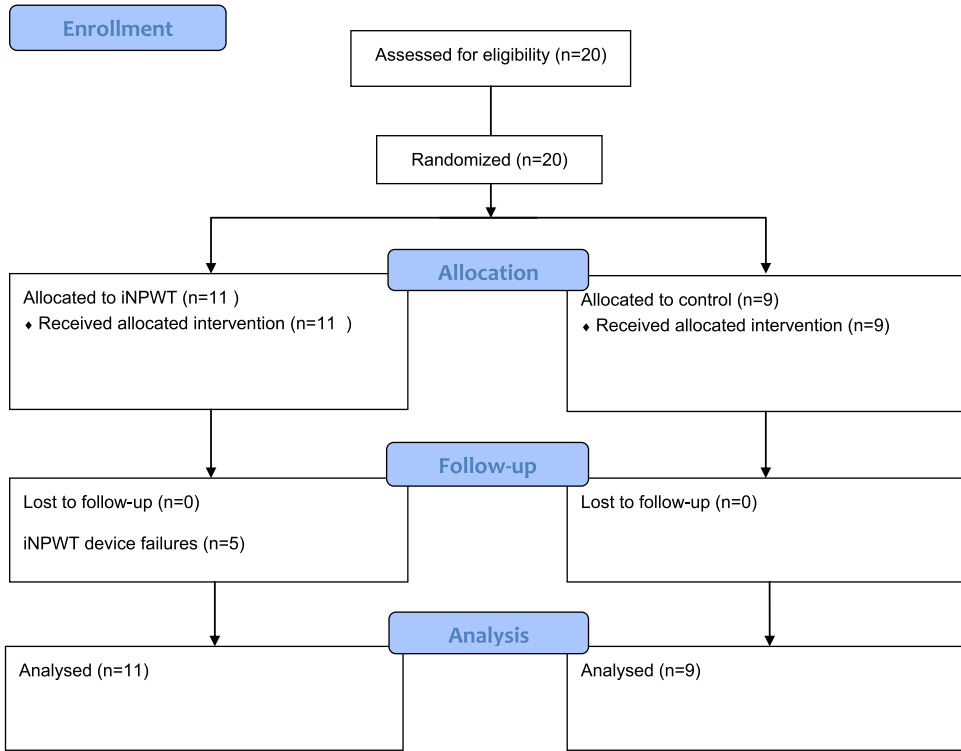


Fig. 1. Flowchart. This figure shows the flowchart of the included patients.

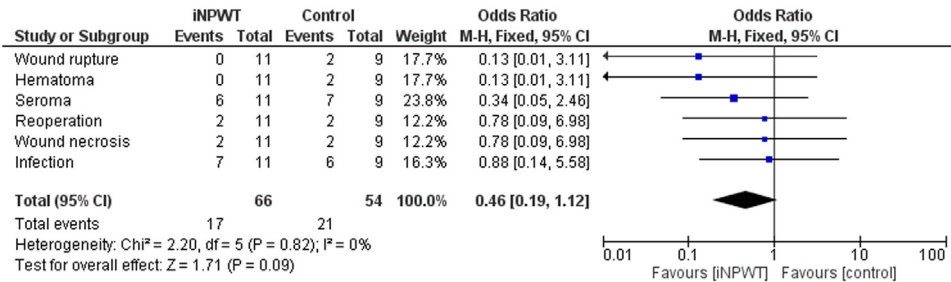


Fig. 2. Complication incidences between the iNPWT and control groups. This forest plot figure shows the incidence and odds ratio for complications in the iNPWT and control groups. Complications are shown for patients treated with ILND with or without iliac lymph node dissection. There was no significant difference in individual or overall complication rates between groups. iNPWT = incisional negative pressure wound therapy.

$p = 0.46$. We found no difference in the cumulative volumes of seromas between the iNPWT (median: 450 mL, IQR: 1410 mL) and control (median: 365 mL, IQR: 2590 mL) groups, $p = 0.61$.

No statistically significant difference was observed in the rates of surgical site infection between the iNPWT (7/11, 65%) and control (6/9, 67%) groups, $p = 0.63$. There were no patients with wound rupture in the iNPWT (0/11) group compared to 2/9 (22%) in the control group, however this was not statistically significant ($p = 0.19$). No statistically significant difference in rates of wound necrosis was evident between the iNPWT (2/11, 18%) and control (2/9, 22%) groups, $p = 0.82$. There were no patients with hematoma in the iNPWT (0/11) group compared to 2/9 (22%) in the control group; how-

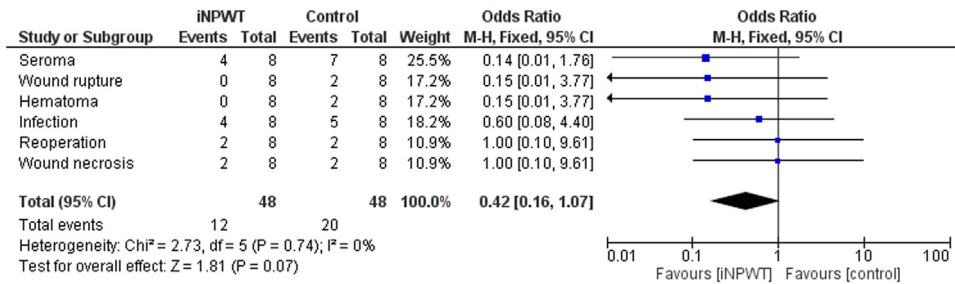


Fig. 3. Stratified complication incidences between the iNPWT and control group. This forest plot figure shows the incidence and odds ratio for complications in the iNPWT and control groups. Complications are shown for patients treated with ILND only (patients with iliac lymph node dissection excluded from this analysis). There was no significant difference in individual or overall complication rates between groups. iNPWT = incisional negative pressure wound therapy.

ever, this was not statistically significant, $p = 0.19$. No difference in reoperation rates were observed between the iNPWT (2/11, 18%) and control (2/9, 22%) groups, $p = 0.82$. As expected, given the current results, there was also no difference in readmission rates between the iNPWT (4/11, 36%) and control (3/9, 33%) groups, $p = 0.88$. In patients who were readmitted to the ward, there was no significant difference in the total number of days in hospital between the iNPWT (median: 7, IQR: 2) and control (median: 2, IQR:22) groups, $p = 0.46$.

There was a trend toward slightly fewer overall complication incidences in the iNPWT group (17/66, 25%) than the control group (21/54, 39%); however, this was not statistically significant (Odds ratio: 0.5, 95%CI: 0.2; 1.1, $p = 0.09$).

In a subgroup analysis of patients without dissection but with iliac lymph nodes, there was again a trend towards slightly fewer overall complications in the iNPWT 12/48 (25%) group compared to the control 20/48 (42%) group; however, this difference was again not statistically significant (Odds ratio: 0.42, 95%CI: 0.16; 1.07, $p = 0.07$, Fig. 3).

There were a total of 53 complications (38 seromas, 8 wound infections, 5 wound necrosis and 2 reoperations) in 11 patients in the iNPWT (median number of complications per patient: 5, IQR: 1) group and 62 complications (46 seromas, 7 wound infections, 3 wound ruptures, 2 wound necrosis, 2 hematomas and 2 reoperations) in 9 patients in the control (median number of complications per patient: 7, IQR: 2) group. This difference in the total number of complications was however not statistically significant ($p = 0.41$).

Device malfunctions occurred in 5/11 (44%) patients in the INPWT group. In three cases, the malfunction was due to inadequate suction; in one case, the iNPWT device was removed due to deep wound infection, and the last case was due to wound dehiscence with epidermolysis resulting in fewer days with the INPWT device attached.

Discussion

This multicenter, randomized clinical trial compared the complication profiles of 11 patients having a standard-size iNPWT dressing to 9 patients using standard postoperative dressings over the inguinal wound for 2 weeks after ILND for macroscopic regional melanoma metastasis. Despite the limited case number caused by the early termination of the trial following restricted indications for ILND (excluding micrometastatic disease), there was a tendency towards fewer wound complications in the iNPWT group compared to the control group, including a lower number of seromas, both of which were non-significant. Thus, the trial indicated some benefit, but was unable to provide a final conclusion on the hypothesis that iNPWT can reduce seroma (and other wound-related complications) following ILND.

The clear weakness of the study is that it was underpowered, failing to reach the target recruitment ($n = 110$). When the trial was first conceived, ILND for melanoma was commonly performed for both micro- and macrometastatic groin disease, with micrometastatic disease accounting for approx. 90% of our total volume of ILNDs¹⁰. Each site performed more than 30 ILNDs annually at that

time, and therefore a maximum inclusion period of 2 years to enroll the estimated 110 patients was anticipated. In 2017, the MSLT-II and DeCOG trials, which evaluated melanoma patients with micrometastatic lymph node metastases, showed no added 3-year survival benefit for patients treated by complete lymph node dissection compared to observation and delayed lymph node dissection (in the case of later macrometastatic disease)^{5,6}. These two practice-changing trials lead to a change in national guidelines, and effective as of January 2018, we abandoned ILND for micrometastatic disease in Denmark¹². This caused a sharp decline in the number of ILND procedures performed, which is consistent with international treatment patterns^{17–19}. The MSLT-II trial also showed that 25% of patients with micrometastatic disease undergoing observation would experience locoregional lymph node recurrence and later require lymph node dissection. We therefore anticipate a modest increase in the number of patients requiring ILND in the years to come. However, given the rapid and sharp decline in ILNDs the recent years, it was deemed unreasonable to extend the inclusion period of this trial by several years.

The study also has several strengths. First, the study had a low risk of selection bias due to its randomized design, which had previously been lacking in this setting¹¹. Secondly, the risk of management and performance bias were low because all patients were assessed and followed using the same pre-defined criteria. Thirdly, the study possessed a low risk of detection bias due to the objective outcome recording. Fourth, the post-randomization bias risk was low attributable to the use of a prespecified intention-to-treat analysis. Fifth, the presented study had a low risk of reporting bias because the statistical analysis in this paper was performed in accordance with the previously published protocol and intention-to-treat analysis¹³. Lastly, the trial had complete information on all included patients owing to the pragmatic and clinically relevant design. The added unprotocolled analysis, which we believe is of significant interest to the reader and planning of future studies, has clearly been labeled in the methods section as such.

ILND for melanoma is associated with a considerable risk of morbidity and long-term impairments in quality of life^{20,21}. Recent trials have propelled the de-escalation of lymph node dissection in melanoma^{5,22}. However, ILND is still a standard procedure in the management of patients with macrometastasis of melanoma²³. Proper patient selection for ILND and improved postoperative care are paramount to reduce the disproportional morbidity burden, especially for groin dissections. Prior to and inspiring this trial, we evaluated the effect of prophylactic iNPWT for ILND in melanoma in a retrospective study and found that iNPWT significantly reduced seroma formation and was more cost-effective than conventional wound care¹⁰. In that study, we used a standard 10 × 20 sized iNPWT exerting 125 mmHg vacuum pressure, which was less than the 80 mmHg used in the current randomized study. The lower incidence of seroma following iNPWT application after ILND in melanoma has recently also been confirmed in a retrospective study by Moncrieff et al.⁹. They used a two-layered iNPWT dressing exerting 75 mmHg negative pressure that was cut and tailored for each patient, and the dressing was changed every 3–4 days in the outpatient clinic. Both retrospective studies found a higher effect size than the effect size from this randomized study. In contrast, we applied a standardized, off-the-counter iNPWT dressing on all patients, which was only (protocolled) to be changed after seven days. Some patients in this trial encountered device malfunctions due to inadequate suction on the wound defect. While the rate of device malfunctions was not described in the two retrospective studies, it is possible that a more flexible choice of iNPWT dressings tailored to each patient's inguinal wound incision length and crease could have reduced the rate of device malfunctions by optimizing dressing fit and suction. An inguinal seroma can also displace the fit of the overlying iNPWT, making regular dressing changes and adjustments necessary more often than we proposed. An other area of uncertainty is the optimal magnitude of negative pressure suction. In theory, a higher negative pressure could damage the epidermis, while too little vacuum to facilitate wound healing would lead to the treatment being ineffective²⁴. Currently, it is not known whether a higher magnitude of negative pressure (e.g., 125 mmHg), is better at preventing wound complications than lower settings (e.g. 75–80 mmHg) and future studies in this setting is warranted²⁵.

In this study, there was a tendency toward fewer complications in the iNPWT group, which is consistent with the results of the above-mentioned two larger, retrospective studies^{9,10}. The previous retrospective studies have, however, inherent selection, performance, and detection biases, which may contribute to a potential overestimation of the iNPWT treatment effect. On the contrary, this

randomized trial was underpowered and may have missed the true treatment effect. Ultimately, this trial could not confirm the hypothesis or the promising treatment effect that iNPWT reduces complications after ILND compared to conventional wound dressing, found in the two retrospective studies. On pooled analyses, there was a trend toward fewer overall complications in the iNPWT group, which at least suggests a possible benefit of iNPWT and should be an incitement for future randomized trials.

Conclusion

This trial demonstrates that iNPWT for ILND is feasible in a multicenter randomized trial setting. Although the targeted sample size was not reached owing to early termination of recruitment, there was a tendency toward fewer complications, most pronounced for seroma, in the iNPWT group. Thus, iNPWT showed some promise, which should encourage adequately powered future randomized controlled studies to uncover the true treatment potential of iNPWT after ILND.

Ethics approvals

The trial was approved by The Regional Committees on Health Research Ethics (S-20170085) and registered with the Danish Data Protection Agency (2008-58-0018). Informed consent was obtained from all participants prior to participation in the study.

Declaration of Competing Interest

None.

Funding

The company Smith&Nephew granted the iNPWT devices used in this study to JAS (grant number IIS 486). The grant was unrestricted. The grant provider did not have influence on the study design, data collection, data analysis, decision to terminate the trial earlier than anticipated, interpretation of results, or report writing.

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