Morbidity after lymph node dissection in patients with cancer: Incidence, risk factors, and prevention
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CHAPTER 8

General discussion and future directives
Lymph node dissection is still a fundamental part of cancer treatment, and continues to be a source of treatment-related morbidity. As long as this is the case, efforts should be made to minimize morbidity by further improving surgical techniques and postoperative management, and by offering appropriate interventions and rehabilitation, if needed.

Our research has shown that postoperative wound complications are still a major source of short-term morbidity from inguinal lymph node dissection (ILND), despite efforts to optimize surgical techniques and postoperative management of open ILND. A central aim of our research was to identify risk factors for wound complications after ILND in patients with penile cancer, and to try to replicate the findings of previous studies as well as explore additional risk factors in patients with melanoma. In general, we could only partially confirm the results of previous studies. Moreover, the findings in our penile cancer cohort were inconsistent with the findings in the melanoma cohort. None of the additional risk factors included in our research were associated significantly with complications.

Inguinal lymph node dissection is a rather uncommon procedure, due to the low incidence of cancers leading to inguinal lymph node metastases. As a consequence, the number of studies that have addressed risk factors for wound complications after ILND is also limited. The observed differences in complication rates and identified risk factors across studies may, in part, be due to variations in research methodology, such as the definition of outcomes, or the statistical approach used. It is also likely that the influence of many risk factors is small, and therefore difficult to detect in the relatively small samples that have been investigated thus far. So, despite best efforts, there is still insufficient evidence about the factors that consistently elevate the risk of surgical wound complications after ILND.

Since complication rates of this procedure remain high, there is a clear need for further improvement in the quality of care, as well as a need for further research in larger series of patients. We would recommend that this procedure only be performed in high-volume medical centers, and that a multi-center, prospective complication registry be established, based on clear and commonly agreed upon definitions of and criteria for classifying complications.

Meanwhile, we should look for options to limit postoperative wound complications after inguinal lymph node dissection. The effectiveness of introducing simple interventions, such as local antiseptic treatment in the preoperative and early postoperative phase (e.g., using chlorhexidine scrubs), could be explored. In addition, the effectiveness of fibrin sealants and collagen sponges for tissue management could be further evaluated in this population of patients. Tissue sealing products may reduce seroma formation by improving tissue apposition, which would reduce the need for repeated puncture and limit skin traction. This could potentially reduce overall wound complication rates.

Minimally invasive (videoscopic) surgery for inguinal lymph node dissection may be a promising alternative to open ILND. Results from observational studies suggest that this procedure potentially limits morbidity, without compromising the quality of the surgery, but evidence from randomized controlled trials is still needed. There is one recently registered randomized controlled trial on this subject, which is currently ongoing.
Lymphoedema

Lymphoedema is another major source of morbidity after lymph node dissection in several anatomical regions. Most interventions to reduce the incidence of lymphoedema lack a solid evidence base, and the available research suffers from serious limitations. Our systematic review of conservative (i.e., non-pharmacological and non-surgical) interventions for prevention of upper limb lymphoedema after breast cancer treatment included 10 randomized controlled trials of several types of intervention: manual lymph drainage alone or in combination with exercise or compression; different postoperative shoulder rehabilitation protocols; and the safety of strength training. For most interventions, the quality of the evidence was low, due to methodological limitations and heterogeneity of the findings. Therefore, clinical uncertainty in this area remains.

In our own trial on prevention of lower-limb lymphoedema after inguinal lymph node dissection, we were unable to demonstrate a statistically significant risk-reducing effect of class-II graduated compression stockings. This finding should not, however, be considered as definitive proof of the absence of any protective effect of compression stockings after inguinal lymph node dissection. Our trial was relatively small, and the dropout rate was higher than anticipated. To our knowledge, our is the only full-scale randomized controlled trial on the use of graduated compression stockings to prevent lymphoedema of the lower-limbs. Additional trials are needed.

No randomized studies have yet been performed to evaluate other interventions for prevention of lower-limb lymphoedema. The (cost-) effectiveness of possible preventive treatments, in particular manual lymph drainage and surveillance with early intervention, needs to be investigated. Future high quality randomized controlled trials are therefore still needed to strengthen the evidence base on the prevention of both upper-limb and lower-limb lymphoedema after lymph node dissection in patients with cancer.

The lack of a generally agreed upon criterion for defining clinically relevant lymphoedema is an important limitation in the current available evidence, and a major obstacle to designing high quality trials in the future. Most of the methods used for diagnosing lymphoedema in clinical trials are based on volumetry, which has important limitations. The literature reflects a wide range of cut-off values used for defining clinically relevant volume change from baseline or volume difference between treated and untreated limbs. This suggests that these cut-offs are, to some extent, arbitrary. Changes in (limb) volume do not necessarily imply the presence of lymphoedema. Volumetric methods are unsuitable for assessing the presence of lymphoedema in other relevant areas of the body, such as the genital area and abdomen after inguinal lymph node dissection, the breast or thorax after axillary lymph node dissection, and the head and neck region after neck dissection. It should also be recognized that lymphoedema is a condition characterized by more than change in volume, such as changes in inflammatory state and tissue compliance. Currently, there are no valid and reliable measures for lymphoedema that include the latter outcomes, and thus more methodological work is required.
Shoulder morbidity after neck dissection

Our study on the incidence and impact of shoulder disability after neck dissection showed that, overall, about half of the patients experienced shoulder pain after neck dissection. For most patients, shoulder complaints did not recover within the study period, regardless of the type of dissection. Patients with a selective neck dissection experienced less functional loss and less disability than patients with a radical or radical modified neck dissection, even if, in the latter case, the accessory nerve was spared. This underscores the fact that, despite preserving anatomical continuity, the accessory nerve still suffers substantial damage if the lymph node dissection is extensive. Therefore, whenever possible and whenever deemed oncologically safe, neck dissection should be performed as selective as possible.

Even more conservative and less invasive neck dissection may be possible in patients with clinical N0 neck status. In the foreseeable future, sentinel lymph node dissection (SLND) may become a viable alternative to elective neck dissection. Evidence suggests that SLND could replace elective neck dissection in some types of cancer. Still, while SLND has become widely accepted in the treatment of breast cancer, controversy remains about its value in head and neck cancer, and further development and validation of the technique in the latter group of patients is necessary.

Our results, that show that neck dissection not only results in a high incidence of shoulder pain and disability, but also in compromised health-related quality of life (HRQoL), underscores the need for reducing morbidity following this surgical intervention. Unfortunately, the current evidence on the effectiveness of shoulder rehabilitation after neck dissection is also very limited. Results from a non-randomized study suggest that physiotherapy in the postoperative phase may be helpful in preventing shoulder disability. The only strong evidence for the effectiveness of physiotherapy for shoulder disability associated with neck-dissection comes from randomized controlled intervention trials in patients with shoulder disability. The exercise program as employed in these studies—progressive resistance exercise aimed at improving scapulo-thoracic stability—may also be effective in preventing shoulder disability after neck dissection.

Considering that not all patients experience shoulder pain and disability in the longer term, we should select and invite patients for a preventive program based on their clinical risk profile. The results from our cohort study could be used for this purpose. That study indicated that patients who exhibit loss of function of the accessory nerve, who experience shoulder pain, and who exhibit scapular instability at discharge from the hospital are at greater risk for developing shoulder disability. These patients could therefore be eligible for early rehabilitation.

Initiating ‘preventive’ rehabilitation in this population of patients will be challenging. The burden of adjuvant radiotherapy, the presence of psychosocial problems, limited financial resources and low health literacy may lead to non-adherence and loss to follow-up. We need qualitative studies to better understand the patients’ perspective after neck dissection, including their symptom burden, their perceived need for rehabilitation, their preferences for different approaches to rehabilitation, and perceived barriers to following (p)rehabilitation programs.
When one evaluates the effectiveness of early shoulder rehabilitation after neck dissection in a randomized controlled trial, incorporation of patient-reported outcomes for shoulder disability is essential. Of the scales included in our clinimetric study, the Neck Dissection Impairment Index 24 or the Shoulder Pain and Disability Index 25,26 appear to be best suited for this purpose. The results of our item response theory (IRT) analysis supported the possibility of combining these two scales to obtain a Rasch scale, which has potential advantages in terms of clinical interpretation. However, such a combined scale also has some shortcomings, including larger floor effects and less ability to discriminate between patients with and without (a self-reported) need for treatment, as compared to the two original scales. Thus, although the IRT approach to assessing shoulder disability after neck dissection is promising, it still requires further work.

The availability of IRT-based health status questionnaires, including those on assessing shoulder disability after neck dissection, would facilitate e-health applications that are rapidly gaining in popularity due to their potential for providing low-cost, personalized supportive care to patients with cancer. Such e-health initiatives, and particularly those that involve a personal internet portal, typically incorporate routine screening for symptoms and rehabilitation needs. The availability of IRT-based measures facilitates the development of computer adaptive testing in such portals. This makes it possible to assess a wide range of health problems in a reliable manner, while keeping patient response burden to a minimum.

Conclusion

Advances in surgical diagnosis and treatment procedures, such as the introduction of the sentinel node procedure, have reduced the need for lymph node dissection and thus the incidence of treatment related morbidity in some patient groups. Nevertheless, in patients with regional lymph node involvement, a more extensive resection of the regional lymph nodes is still an indispensable part of treatment with curative intent. As a result, morbidity associated with lymph node dissection is a reality for many cancer survivors. The results of the studies in this thesis can contribute to improvement of care by broadening the evidence base regarding the incidence and risk factors of wound complications after inguinal lymph node dissection, the prevention of lymphoedema after inguinal and axillary lymph node dissection, and the incidence, impact and assessment of shoulder disability after neck dissection. In addition, we have identified critical knowledge gaps and provided suggestions for a patient-centered research agenda.
REFERENCES


