De-escalating management of primary and locally recurrent breast cancer

Valorisation

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Introduction

Breast cancer is the most common form of cancer to affect women and the second most common cancer worldwide. It is a potentially curable disease if diagnosed and treated at an early stage. Survival rates are still increasing, with a current 5-year overall survival of 90%. Treatment of breast cancer consists of excision of the tumor and one or more axillary lymph nodes, combined with (neo)adjuvant hormonal-, chemo-, immuno-, and/or radiotherapy in selected patients. Although survival rates and treatment modalities are improving, quality of life of breast cancer survivors is affected by the treatment associated morbidity. Due to its high incidence, breast cancer has an significant socio-economic impact. The majority of the costs concern healthcare costs followed by costs for productivity losses due to morbidity. Hence it is important to avoid exposure of patients to radical treatments that do not positively affect their survival, while causing lifetime morbidity.

Fortunately, breast cancer surgery has become less invasive over the years. The radical mastectomy described by Halsted has been replaced by the modified radical mastectomy and at present, the majority of breast cancer patients are now treated with breast conserving surgery. Axillary surgery has also become less invasive and the standard performance of an axillary lymph node dissection (ALND) has been replaced by the sentinel lymph node biopsy (SLNB) in clinically node negative breast cancer patients.

This shift towards less invasive treatment is also observed in patients with an ipsilateral breast tumor recurrence (IBTR). The general trend in breast and axillary management is to de-escalate, diminishing the risk of morbidity, while maintaining local and regional control and a high overall survival.

Relevance of scientific results in this thesis

This thesis addressed several topics of staging and management of the axillary lymph nodes in breast cancer patients with primary and recurrent disease. For a long time, an ALND was the standard procedure to assess the axillary lymph node status of all breast cancer patients. An ALND is associated with significant short- and long-term morbidity; such as upper extremity lymphedema in up to 20% of patients, seroma, shoulder dysfunction and nerve injury. Patients with ALND related lymphedema report a lower quality of life, higher level of depression and greater difficulty of functioning at work, socially and sexually compared to patients without lymphedema. Over the past years standard ALND was replaced by the less invasive SLNB as staging procedure. In SLNB, 1-2 axillary lymph nodes will be removed, while current benchmarks require at least 10 lymph nodes to be harvested during ALND. Complications associated with axillary surgery, still occur after SLNB, though less frequently and might me more associated

with axillary radiotherapy. Severe lymphedema occurs in 5% after a follow-up of 5 years.

In the first part of this thesis, a trend towards less extensive axillary surgery in primary breast cancer patients is shown, illustrated by an overall increase of the use of SLNB and a decrease in the use of completion ALND (cALND) after a positive SLNB. This trend is not only noticed in patients with small tumors (cT1-T2), but also in cT3-T4 breast cancer patients, as well as for patients treated with mastectomy. This reflects the confidence of physicians in the concept that not every tumor-positive sentinel lymph node will develop into clinically detectable axillary disease over time. Notably, sentinel node positive patients who were treated with cALND had a higher independent probability to receive adjuvant chemo(-immuno) therapy, irrespective of the final lymph node status. So, these patients experience not only the morbidity associated with ALND, but also with adjuvant therapy. Over the last decade, there is a growing interest in shared decision-making, in which physicians and patients share treatment preferences together. During this shared-decision making process, it is important to explore the risk of overtreatment and the costs related to treatments.

After showing that the use of extensive axillary surgery is decreasing, in the next chapter of this thesis interest is raised in not using axillary surgery in selected patients. In a study in elderly breast cancer patients (>75 years) omission of complete axillary staging had no impact on regional control and most of the patients died from non-breast-cancer-related causes. Therefore, even more restrictive axillary treatment might be indicated in this already vulnerable group of patients.

The second part of this thesis evaluates the de-escalation of axillary management in the recurrent breast cancer setting, aiming to prevent morbidity after axillary surgery even further Also, the impact of repeating the SLNB instead of standard ALND on recurrence rates and prognosis was investigated.
For patients with IBTR, adequate preoperative staging is imperative for tailoring optimal treatment plans. However, current guidelines do not provide a clear diagnostic path for this subgroup of patients. Within a large group of recurrent breast cancer patients, we showed a wide variation in the use of conventional imaging (chest X-ray, ultrasound of the liver, computed tomography scans of thorax and/or abdomen, skeletal scintigraphy), 18-F-FDG PET-CT or no preoperative imaging at all. Though, we did not observe a difference in the mean time to detection of distant recurrence, nor in the risk of regional recurrences after IBTR between the groups. Based on these results we cannot recommend a preferred type of preoperative staging. We do recommend to perform some kind of preoperative staging in every IBTR patient, because no staging could lead to unnecessary exposure to potentially harmful surgical and adjuvant treatments. 18-F-FDG PET-CT is one of the available staging modalities, but since

superiority to other modalities was not proven in this setting, further studies are needed to explore i.e. the cost-effectiveness.

The "Sentinel Node and Recurrent Breast Cancer" (SNARB)-study revealed that a repeat sentinel lymph node biopsy (rSLNB) was a feasible procedure with a high negative predictive value. This warranted the oncological safety and a rapid implementation of the rSLNB was initiated in the recurrent setting. This thesis showed that the risk of developing regional recurrence after a negative rSLNB was low, which supports the safety of rSLNB as a primary nodal staging tool in IBTR patients. Unlike SLNB in the primary setting, performing a rSLNB in patients with IBTR is more challenging, because of previous treatments of the breast and axilla. For some patients the rSLNB was unsuccesfull, which means that no sentinel lymph node could be visualized and/or harvested. Some assumed that in those patients possible positive sentinel lymph nodes would be left behind, which could develop into clinically detectable disease. This thesis reported that the risk of developing regional recurrences after an unsuccesfull rSLNB is low and showed that there is no need for additional axillary treatments. This may indicate that the value of rSLNB in clinically node-negative patients with IBTR might be disputed overall. Especially, since we showed that the outcome of rSLNB appears to have minor impact on the prognosis of patients with IBTR.
Therefore, the detection and removal of every metastatic lymph node might not be mandatory any longer. This creates new opportunities to further de-escalate axillary management, by omitting even the less invasive (r)SLNB procedure in patients with clinically node negative disease.

Target population

The results of this thesis are relevant for breast cancer patients with primary breast cancer and with an ipsilateral breast tumor recurrence, because it offers more information about axillary nodal staging and treatment in the primary and recurrent setting, the impact of axillary surgery on the use of adjuvant chemo (-immuno) therapy and the use of different pre-operative imaging modalities. Therefore, it is especially of interest for clinicians involved in multidisciplinary breast cancer treatment.
Lastly, the contents of this thesis are relevant for expert panels, which are responsible for the development of the national and international guidelines in breast cancer treatment.

Innovation and future

The de-escalation of breast and axillary surgery is a topic of debate in breast cancer treatment. This thesis provides next steps towards less invasive axillary surgery and towards possibly no surgical intervention in the axilla of breast cancer patients. To perform a standard ALND in clinically node negative (primary and recurrent) breast cancer patients is nowadays obsolete. Furthermore, since the outcome of rSLNB was

not an important prognostic factor, its value as a staging tool in IBTR-patients appears also to be disputable. The de-escalation of axillary surgery could theoretically increase the risk of regional recurrences, yet this disadvantage can be well balanced against the treatment associated morbidity of SLNB and ALND.
Ongoing studies are determining the value of SLNB versus no SLNB in the primary setting and results have to be awaited. In the recurrent setting, a randomized control trial would also be preferable, however such a trial is not feasible due to the low incidence of IBTR and recurrences after IBTR. The SNARB study is the largest study published on rSLNB, though did not include patients without an attempt of rSLNB. A multi-center prospective trial, including patients with rSLNB and without rSLNB, can be set up to evaluate and emphasize whether it is oncological safe to omit rSLNB in the recurrent setting. Though, due to a possible low accrual, such trials are frequently unable to inform clinical practice or benefit patients.
Highly accurate noninvasive techniques, such as axillary MRI and 18-FDG-PET-CT, are being evaluated for their ability to identify axillary tumor burden in clinically node negative patients. In the future, this might replace the relatively invasive SLNB. Research on these modalities in primary breast cancer is encouraging and trials should be conducted to confirm the use and cost-effectiveness of these techniques in the primary and recurrent setting. In the future axillary surgery might become the adjuvant treatment in the setting of breast cancer treatment.

Last, following the trend to de-escalate, the omission of a standard salvage mastectomy for all patients with an IBTR could be the next step. A prospective clinical trial investigating the feasibility of repeat breast conserving therapy for patients with an IBTR is currently designed.