Evaluation of side effects after axillary lymph node dissection for breast cancer taking tumour staging status into account

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FRAUENKLINIK RECHTS DER ISAR DER TECHNISCHEN UNIVERSITÄT MÜNCHEN
(Direktorin: Univ.-Prof. Dr. Marion Kiechle)

Vollständiger Abdruck der von der Fakultät für Medizin der Technischen Universität München zur Erlangung des akademischen Grades eines Doktors der Medizin genehmigten Dissertation.

Vorsitzender: Univ.-Prof. Dr. D. Neumeier

Prüfer der Dissertation:
1. Univ.-Prof. Dr. M. Kiechle
2. Priv.-Doz. Dr. B. Kuschel

Die Dissertation wurde am 26.06.2008 bei der Technischen Universität München eingereicht und durch die Fakultät für Medizin am 23.09.2009 angenommen.
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1 Introduction and background information

1.1 Operation methods of the axillary region

As long term survival of breast cancer patients depends on the presence of distant metastases at the time of presentation, one of the main focuses of breast cancer management lies within the axillary region, as one of the primary metastatic pathways.

Therefore axillary lymph node involvement is one of the most important prognostic factors (in patients with breast cancer) and axillary lymph node dissection has become a standard procedure within breast cancer treatment. Since then it has been highly recommended to treat potential nodal metastases and to determine the need for adjuvant systemic treatment.

1.2 Conventional axillary lymph node dissection (ALND)

1.2.1 History and development of the ALND technique

Today’s knowledge about breast cancer treatment is based on surgical practice of many decades. The idea that breast cancer is a systemic disease has indicated substantial changes in breast cancer management and surgeon’s awareness.

Whereas current breast cancer management proclaims breast conservation (e.g. segmental mastectomy), the Halsteadian model of radical mastectomy introduced in 1894, was considered to be the ideal method of cancer surgery for at least a century [Cotlar et al, 2003; Stahlberg et al, 2001].

William Stuart Halsted’s (1852-1922) radical operation was based on an en bloc dissection of the entire breast, the pectoralis muscles and regional lymphatics. This operation method reached a 35-40% 5-year cure rate, which was an excellent result at this time [Cotlar et al, 2003].
In the 1930s a less radical method was introduced by D. H. Patey sparing the pectoralis major muscle. Known as the “Patey Operation” or “modified radical” it was one of many other following conservative procedures, indicating the transition towards a systemic hypothesis of breast cancer.

One reason for the trend to more conservative procedures was of course the use of radiation in breast cancer. Roentgen’s discovery of the x-ray in 1895 led to a fast
developing trend to combine radiation with breast cancer surgery. Improvement in radiotherapy technique made Professor R. Mc Whirter’s report from 1948 possible - patients were treated with simple mastectomy and radiation reaching a 62% cure rate [Cotlar et al, 2003].

Also the discovery and development of chemotherapy and endocrine therapy changed treatment possibilities and patterns. Now surgery wasn't the universal procedure to treat cancer, but the emphasis lay on systemic treatment to prevent cancer recurrence.

Another reason for change of conscience was the idea of comparing and reviewing operation procedures in large clinical trials. In the mid of the twentieth century the need for prospective and randomized studies was realized. Staging and prevention of axillary recurrence became important foundations in treatment management. Projects such as the National Surgical and Adjuvant Breast Project (NSABP) and Organizations such as the European Organization for Research and Treatment of Cancer (EORTC) initiated large trials comparing various surgical techniques. In 1990 routine axillary dissection Level I and II was recommended by the NIH Consensus Conference.

Despite the enormous transition to current surgical management of breast cancer, from the Halsteadian era until today axillary lymph node dissection is matter of many debates concerning the optimal technique.

In the following today’s standard technique for axillary dissection shall described.
1.2.2 Today’s technique


Fig. 2: Definition of the axillary lymph nodes in different levels

At the beginning the deepest part of the axillary fascia is incised, starting at the pectoral minor muscle through pulling the pectoralis major muscle a side with a hook.

Carefully spreading the tissue with a scissor, the axillary vein is searched for. It is important to identify the axillary vein at the beginning of the dissection so that it spared from manipulation.

It follows the en bloc resection of the fat and connective tissue, beginning at the lateral side of the axillary vein and continuing the dissection medial and caudal on the surface of the fascia of the latissimus dorsi and the subscapularis muscle.
When reaching the thoracodorsal vein and nerve bundle it is separated and spared. The superficial ventral branches of the axillary vessels are transected and alloyed. The nerves on the medial and dorsal side of the axilla such as long thoracic nerve and the thoracodorsal nerve must be spared whereas the intercostobrachial nerves should be manipulated as carefully as possible.

Is the fat and lymph node bundle isolated to the medial, dorsal and lateral side it only clings to one connective tissue tract. In lifting the pectoral minor muscle with a blunt hook the lymph nodes of level II can be dissected en bloc with the lymph node package of the axilla. If the lymph nodes of level III (infraclavicular) shall also be dissected the pectoralis minor muscle must be lifted with force or meanwhile transected at its insertion. Removing the pectoralis minor muscle completely for level III dissection is called the Patey procedure.

After blood stanching the axilla is drained to avoid infection and the cavity and wound margins are adapted.
The lymph node bundle is sent for pathological examination in order to define the tumor staging status (TNM). Classification of the axillary lymph node status is important to determine the need for adjuvant systemic treatment and for the postoperative long term survival.

1.2.3 Side effects

A mentioned above better understanding of the systemic nature of breast cancer and also better screening methods have led to great changes over the years of breast cancer management. Turning away from performing aggressive surgical techniques, thinking breast cancer is a regional disease solely, nowadays treatment rather focuses on breast conserving therapy and systemic treatment. As a result a substantial decline of breast cancer mortality is realized, which leaves a growing group of women living with breast cancer. Therefore today's therapy concepts lay their emphasis on improvement of quality of life and reducing long-term morbidity of cancer treatment.

These aspects have brought axillary lymph node dissection into question as late effects are frequent and severe having great impact on patients' quality of life. Shoulder-arm morbidity is one of the most important frequent side effects of ALND. It is a complex syndrome consisting of multiple symptoms such as sensitivity problems, loss of strength, restriction in movements and edema. Several studies [Ganz et al, 1999; Erickson et al 2001; Tanis et al, 2001; Veronesi et al, 2003] have subjectively and objectively evaluated these symptoms in clinical trials and revealed a tremendous number of women affected by shoulder-arm morbidity.

Kuehn T. et al (2000) reported sensitivity problems in 73% of the patients, an edema rate (> 10% difference in volume) of 22.7% and a restriction of isometric strength in 43.4% of the collective.

Yap et al (2003) found that 76.6% of the patients who had an axillary dissection experienced ipsilateral arm symptoms also including initial shoulder stiffness, medial arm numbness, and ipsilateral arm swelling. Patients without axillary treatment only reported arm symptoms in 10.8%, which proved the significant impact of axillary dissection on arm symptoms in his study group.
Ernst et al (2002) mentioned that after a follow up of five years or more 26% of the patients complained of shoulder pain and 10% are affected in their quality of life through impairment of range of motion and arm strength.

In a cohort study of 223 patients Maunsell et al (1993) found at three months after surgery, swelling in 24%, weakness in 55%, numbness in 58%, stiffness in 40% and limitation in range of movement in 32% of the patients.

A survey of 222 women who received ALND by Hack et al (1999) showed that 73% of the women were impaired in their range of arm/shoulder motion and 72% experienced pain, weakness or numbness. Arm edema is one of the most feared complications after axillary lymph node dissection as it results in a substantial degree of functional arm impairment [Erickson et al, 2001].

Causing limitation in range of motion due to weakness, pain and stiffness, it affects quality of life. Increasing the risk of infection, as the healing capacity of the affected tissue is reduced, lymph edema interferes with patients’ every day activities as special caution with affected the arm is of need. A known factor having significant influence and being associated with arm edema seems to be breast and axillary radiation [Erickson et al,2001; Yap et al,2003]. Yap et al (2003) reports of 21.3% self reported ipsilateral arm swelling when patients received axillary dissection and breast radiation, compared to 12.4% when radiation was not given.

Another influential condition has been published in previous studies and is reported by Yap et al (2003) who found that women with higher body mass indices suffer higher rates of arm swelling. Furthermore previous literature documented that side effects after ALND can lead to a wide range of psychological problems such as anxiety, depression, social avoidance and sexual dysfunction [Maunsell et al, 1993; Roses et al, 1999; Ververs et al, 2001]. Kuehn et al (2000) reported when asking for the most distressing problem regarding their breast disease that 22% answered with “fear of cancer recurrence”.

As a substantial number of women still have to be treated by ALND and even additional radio therapy, prevention strategies to minimize the risk of edema have been developed. Patients are taught to avoid trauma or injury, prevent infections, avoid arm constrictions and exercise the limb.
Although these strategies are mentioned to the patients at the hospitals there is no prove that they have an evidence based effect [Erickson et al, 2001]. Common treatments for lymphedema include complex physical therapy, massage, exercise, a compression garments, and lymphatic drainage. Additionally pharmacologic treatment such as antibiotics, benzopyrones, flavonoids, and diuretics is used.

Decreased range of motion, loss of strength and numbness also affects patients daily life routine severely as certain tasks cannot completed.

Besides arm morbidity, pain is a main complaint after ALND. Leading to psychological distress, mood disturbances and sleep interruptions pain interferes with social life in patients with cancer. Pain treatment schemes have to be developed for each patient individually.

1.3 Actual medical status/modern surgical procedures

The routine use of axillary lymph node dissection though, has aroused a great number of discussions recently, as this procedure remains the major cause of morbidity after breast cancer surgery. Less morbid and equally accurate methods of assessing axillary nodal status are needed.
Nowadays, new concepts such as the sentinel-node-technique and minimal invasive strategies such as endoscopic dissections are gaining more and more interest. Details and long term sequel of these modern operating techniques shall be summarized in the following pages.

1.3.1 Sentinel lymph node biopsy (SLNB)

1.3.1.1 Definition and procedure

Especially the sentinel-node-technique is a very fast developing field and has been evaluated in several clinical studies [Krag et al, 1998; Mc Masters et al, 2005; Ozmen et al, 2006]. Furthermore an Interdisciplinary Consensus of the German Breast Cancer Society [Kuehn et al, 2003] and also a Consensus Conference in Philadelphia, Pennsylvania [Schwartz et al, 2002] was held on the role of sentinel lymph node biopsy in carcinoma of the breast.

Per definition the sentinel node(s) is the first node or nodes to which lymph drainage and metastasis from breast carcinoma occurs.

Therefore the purpose of this procedure is to identify the first node/s to which metastasis has spread, by “visualizing” this primary lymphatic drainage.

The techniques that have been developed are based on the usage of radio colloid and additive blue dye by injection.

Sentinel-node-biopsy (SLNB) is the removal of all lymph nodes that are by definition sentinel nodes. Only the suspicious nodes that have been identified by radio colloid or blue dye are removed. The SLNB provides the lymph node that carries the highest probability of containing potential metastases.

To identify the axillary sentinel nodes several methods have been established, including peritumoral, which is the standard injection site, intratumoral, subcutaneous, intradermal and subareolar injection.
Commonly used are Tc 99m marked colloids, 20-100nm in size and 0.2-1.0 ml in volume. The amount of activity has to reach an appropriate level of target signal at the time of surgery. The total activity lies between 10 and 50 MBq.

After lymph node dissection the situs has to be searched for any remaining activity. When blue dye is used the volume injected depends upon the individual size of the patients, requiring from 1-3 ml of dye (thin patients), to a maximum of 5 ml dye (obese patients). This additive method is an intraoperative procedure which leaves room for short-term planning. Patentblau V (Fa. Geurbet) is authorized in Germany.
Clinical studies have shown that the identification of sentinel node/s lies between 82% and 98% when patients are selected properly and prediction of the tumour status of the axillary lymph nodes ranges between 88% and 100% [Hsueh et al, 1998; Mc Masters et al, 2000; Morrow et al, 2003]. These success rates reflect the high degree of accuracy of the SLND technique. Literature varies in the false negative rates of SLND still searching for the attributing factor [16]. Study series report rates from 4.5% [Gomatos et al, 2006], 5% [Tamaki et al, 2002], 5.6% [De Cicco et al, 1998] to 11.4% [Kuehn et al, 2001] and more.

These variations might be influenced by location of the tumour, whereas lateral located tumours increase the false-negative rates [Kuehn et al, 2001]. Also preoperative biopsy for diagnosis is presumed to play a role within the false-negative outcome. Yet “No single technical or patient parameter seems to predict a false-negative result” [Fukuma et al, 2002].
1.3.1.2 Learning phase

Concerning the learning phase and experience necessary to master this technique, different demands are required from the surgeons. In general the false-negative rate should be below 5% before embarking upon SLNB alone, without back up axillary dissection. In addition the conventional axillary dissection must be mastered and the surgeon should carry out about 50 breast cancer surgeries/year. Taking part in clinical studies is advised and a minimum of 20 SLNB/year have to be done.

As this new operating method is strongly linked to the nuclear medicine and the surgical pathology department a close cooperation of the surgical team with these institutes is very important.

1.3.1.3 Contraindications and restrictions

Contraindication for SLNB includes pregnancy, lactating women, allergic reactions to blue dye and radio colloid (they are very rare, e.g. urticaria, anaphylactic reaction), patients with a clinically positive axilla (N1) and patients with either multicentric or inflammatory breast cancer.

Furthermore locally advanced breast cancers (T>3cm; N+) and prior axillary surgery are considered contraindicated as lymphatic channels may be disrupted and the dye may be blocked or lead astray from identifying the sentinel node/s. Failed SLNB (inability to identify the sentinel node) usually leads to an immediate traditional axillary dissection.

“SLNB is considered to be a suitable replacement for axillary dissection as a staging and diagnostic procedure in T1 and T2 (usually 3 cm or less) breast carcinomas, as per TNM staging. SLNB has not been verified in larger cancers” (Proceedings of the Consensus Conference on the Role of Sentinel Lymph Node Biopsy in Carcinoma of the Breast, April 19-22, 2001, Philadelphia, Pennsylvania).

The SLNB is independent of the tumour location, age of the patient and type of surgery (mastectomy or breast conservation).
The risk of the radio colloid sentinel node technique in the theatre/operating room is minimal as the radiation exposure to patients, surgeons and other staffs is extremely low.

1.3.1.4 Benefits and disadvantages

A disadvantage of this new technique is the possibility of a cosmetic stain from the blue dye on the skin of the patient when injection is not placed properly. On the other hand SLNB avoids damage to the nerve and vascular structures in the axillary region which reduces the postoperative morbidity largely.

Schrenk P. et al (2000) reports and also other clinical studies [Swenson et al, 2002; Veronesi et al, 2003; Schulze et al, 2006 ] show a major advantage as SLNB causes less paraesthesia, numbness, pain, lymphedema, infection and restriction of arm motion compared with conventional axillary dissection. Gordon F. Schwartz et al (2002) states that, with SLNB “physical activity may begin much earlier than after formal node dissection, since the patient’s arm motion is virtually unrestricted after SLNB. Radiation therapy and adjuvant chemotherapy, if used, may begin sooner than after traditional axillary dissection.”.

One point not yet sufficiently researched on, is the need for completing the axillary dissection once a positive sentinel node has been identified. It is quite difficult to predict the likelihood of additional nodal diseases, as in 40-60% of the patients the sentinel is the only positive node [Morrow M. et al,2003].

All in all the sentinel procedure is certainly an alternative to conventional axillary dissection when considering each patient’s unique clinical circumstances. It may improve the overall morbidity for patients with selected negative axillary status.
1.3.2 Endoscopic axillary surgery

1.3.2.1 Endoscopic balloon dissection

Another modern approach to axillary lymph node dissection is the minimal invasive surgery which is common in several other specialities. So the increasing popularity of endoscopy finally also found its way to axillary dissection. Since 1993, when this new technique was introduced by Suzanne et al (1993), the feasibility of the endoscopic technique in the axillary region has been confirmed by several studies.

One of the techniques to perform axillary dissection is based on endoscopic balloon dissection. Therefore a preperitoneal distention balloon (PDB) is used. It is usually placed between the axillary fascia, serratus and latissimus dorsi muscles. The balloon then is inflated until an adequate working space is reached. After insufflation the PDB is removed and replaced with a 10 mm trocar (e.g. blunt-tipped), which is connected to the insufflator (e.g. CO₂) keeping the pressure at 8-12mm Hg. Through the cannular the endoscope is inserted and after inspecting the axillary contents, two smaller trocars (mostly 5mm) are placed at different angels under direct visualization.

Having introduced all of the surgical equipment, the key anatomical structures such as the axillary vein, the long thoracic and thoracodorsal nerves can be identified. Important points or reference are the latissimus dorsi muscles, the serratus muscles, the pectoralis major muscles and the chest wall. When the axillary space is clearly observed and thoroughly inspected instrumental manipulation of axillary contents can be performed. Having been placed in an endobag, the dissected axillary contents are removed through the 10 mm trocar. As excellent visualization of anatomical landmarks and enough working space can be reached, the method has proven to be feasible [Ho et al, 2002; Kuehn et al, 2001; Kocher et al, 1998].

Aim of the endoscopic axillary dissection was/is to minimize the surgical operating path and reduce tissue destruction. A number of studies [Avrahami R. et al, 1998; Kuehn T. et al, 2001] proved that it spares the nerve and vein requiring no traction. Additionally the technique reduces surgical scarring comparing the traditional large cut to three small incisions which improves the cosmetic result [Ho et al, 2002; Kuehn et al, 2001].
Kuehn et al (2001) also recorded a reduction of severe symptoms such as pain intensity, sensitivity disturbances, oedema and mobility in patients treated with endoscopic axillary dissection. Furthermore 73% of the patients with conventional surgery reported numbness, but the seroma rate and postoperative lymphorrhoea showed a similar number in the endoscopic group as well as the conventional group. Problematic also seem trocar-site metastases [Kocher et al, 1998] and the rate of tissue destruction is controversially reported in clinical studies.

Despite of improved long-term morbidity the endoscopic axillary dissection cannot be implemented for routine axillary dissection because of long operating times which interfere with the daily clinical rhythm [Kuehn et al, 2001].

1.3.2.2 Endoscopic axillary exploration (EAE)

Therefore the more specialized variant, the Endoscopic axillary exploration (EAE) presented by Tsangaris T. N. et al (1999) with sentinel lymphadenectomy, might be a suitable method. This minimally invasive approach is a combination of the endoscopic access to the axillary and the sentinel node technique.

Fig. 6: Endoscopic axillary exploration (EAE) with sentinel lymph node mapping and biopsy
It is performed with blue dye injection (isosulfan blue) for lymphatic mapping and biopsy, as previously described above and the lymph node/s are dissected and extracted through a cannular. Again a balloon dissector was inserted and later on insufflation of Co² was initiated.

The advantage of this specialized technique is the remaining reduction of severe impairment and scarring through minimal manipulation, as well as shorter operating times. Tsangaris T. N. et al (1999) deliberately states that a level I and II dissection is not an optimal usage of the EAE.

Again this method cannot be used for locally advanced breast cancers (T>3cm; N+) and is limited to all the contraindications of the SLNB.

1.3.3 Axillary Dissection with Access Minimized (ADAM)

Given the current trend to minimal invasive approaches, another technique has been developed concerning axillary dissection.

The Axillary Dissection with Access Minimized (ADAM) introduced by Paepke S. et al (2003) completely avoids the axillary access. A separate incision in the axillary region is abstained and breast tumour removal, axillary dissection, lymph node sampling or SLNB is performed through the mammary cut (25-80mm).

Paepke S. et al (2003) amplified this specific surgical technique, which has been so far only performed for tumours localized in the upper outer quadrant by Singletary et al (1999), to tumours localized centrally or in the inner quadrant. ADAM is performed through a single incision using laparoscopic assistance.
A tract is created bluntly between the breast tissue and the pectoralis major muscle, then the axillary fascia is incised. The endoscope is introduced through the created access into the axillary region and after visualizing axillary landmarks and structures for orientation, the dissection and extirpation of lymph nodes can take place.
Because of the longer operating tract long hooks, scissors and plucks might be needed. To avoid wound infection, a separate drainage is placed for 3 to 4 days to both operation sites (axilla and mamma). There is no difference in the operating times comparing conventional axillary dissection and ADAM. The cosmetic result is thoroughly comparable with the conventional breast conserving surgery. Mobility of the arms and shoulders seems unaffected even immediately after surgery [Paepke et al, 2003].

Although a few similar concepts using endoscopic equipment have been published in Japan by Tamaki et al (1998) and by Fukuma et al (2002) the idea of the ADAM technique, using a single incision only, seems a nouvelle approach.

Advantage of this method surely is the avoidance of a separate incision in the axilla and therefore maintaining the subcutaneous lymphatic drainage and reduction of postoperative sensibility changes and pain sensation changes. Whether tumour cell spillage from the mammary site to the axillary region can take pace, still has to be observed.

Nevertheless, although technical feasibility has been proved, this new technique still has to be verified in larger clinical studies to predict the postoperative results.

After introducing these novel techniques and discoveries, which have strongly influenced current breast cancer management one has to be aware, that the conventional axillary lymph node dissection (ALND), still is a standard method in clinical routine. Although as said above, the SLNB is considered to be a suitable replacement for axillary dissection its restrictions still make the ALND a highly important procedure to predict lymphatic tumour growth. Especially in larger cancers (T3, N+; >3cm) and patients with positive nodal status, the complete axillary clearing is the routine technique to improve tumour control.

Highly important and main focus for these patients lies in the postoperative morbidity and the complication rate after axillary lymph node dissection. In order to find prevention strategies these long-term sequels have to be assessed.

Purpose of the present study was to analyse the of the patients subjectively assessed morbidity after ALND correlated to the type of surgery, nodal status and initial tumour size. Working hypothesis when conducting this retrospectively trial was that a reduction of pain, as well as an improvement of range of motion is achieved in
course of time and that the initial size of the tumour is of no significance to the postoperative morbidity outcome.

The self-assessment questionnaire was developed to assess the extent of pain and limitation of arm mobility in a follow up phase up to 12 months after surgery.

For estimation of the long-term morbidity after ALND the present study used only subjective measures of pain and arm morbidity gained by questionnaire.
2 Method
2.1 Structure of the Questionnaire

A total number of 516 patients, who had undergone either breast conserving therapy or mastectomy including axillary dissection for invasive breast cancer, were enrolled in the present study.

A self-assessment questionnaire listing 45 items was mailed to the patients together with a prepaid envelope. The mean age of the women, at the time of their operation was 58 Years. The study accrued patients receiving treatment between the years 1999 to 2002.

The subjective estimation of the long-term sequel of axillary dissection (Level I and II) was evaluated. The extent of symptom intensity for pain and limitation of arm mobility were rated using a five-point self-report scale (0 - 4) in the questionnaire.

<table>
<thead>
<tr>
<th>Degree of intensity symptoms</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>No pain slight</td>
<td>mediocre</td>
<td>severe</td>
<td>strongly severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no use of medication needed</td>
<td>use of medication on occasion</td>
<td>permanent use of medication needed</td>
<td>permanent use of medication needed, no full improvement</td>
<td></td>
</tr>
<tr>
<td>Limitation in range of motion</td>
<td>None slight</td>
<td>mediocre</td>
<td>severe</td>
<td>strongly severe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hardly noticed in daily life</td>
<td>noticed in daily life partly disturbing activity</td>
<td>disturbing daily life constantly</td>
<td>functional loss in daily life</td>
<td></td>
</tr>
<tr>
<td></td>
<td>normal physical activity</td>
<td>normal physical activity</td>
<td>normal physical activity disturbed</td>
<td>normal physical activity severely disturbed</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Scale of self-assessed symptoms

Besides demographic data, responses regarding axillary symptoms as pain, morbidity, analgetical treatment and others were included in the questionnaire. No clinical examination was performed on any of the patients. A covering letter assured
the confidentiality of the data and emphasized the voluntary nature of participation. At the end of the questionnaire, a space was left to allow the patients to add their comments and any criticisms about the items or further information of their disease. Written informed consent to participate in the study was obtained from all patients.

2.2 Statistical analysis by SPSS

Statistical analysis was performed using SPSS 11.5 © (Inc., Chicago, IL) computer system. Analyses were completed with a Medion © Professional Computer, Intel ®. All data were entered into a spreadsheet developed with the SPSS database system.

First, for all variables a descriptive analysis was performed. Absolute and relative frequencies were calculated for each item of the questionnaire. The information shown in frequency-tables was then transformed in graphical appearance, as histograms.

Furthermore the items pain, limitation in range of motion and use of analgesic drugs were calculated in cross tables and differences were then evaluated with the chi-square-test or exact test of Fisher when appropriate. In identifying and comparing the patients at risk for pain, restriction of arm morbidity and use of analgesic drugs, we reclassified the patients into 4 groups: T1, T2, T3, and T4 in order to survey correlation to the initial tumour size. In another step the patient collective was divided into 3 groups: N1 (0-10), N2 (11-20), N3 (21-30) to correlate operative radicalness to perceived pain and impairment of arm mobility. Again cross tab calculations were formed and estimated with chi-square-test or exact test of Fisher.

Then, differences in intensity of pain, impairment of arm mobility and use of analgesic drugs were assessed with analysis of variance with repeated measures according to therapy and the different time points. In case of significance t-test was used as well as Post-hoc test.

As a measure of significance, the P value was set at 0.05 as level of significance; P items lower than 5% were therefore valued as significant.

Graphical presentation was chosen for each table specifically, using histograms, box plots, bar charts or tables.
3 Results
3.1 Patients and disease characteristics

A sample of 516 women was obtained by a self-administered questionnaire. 336 patients (65.1%) completed the questionnaire. The mean time passing since surgery and filling out the questionnaire was 25 months (range 7.5 – 45). The mean age was 58 years (range 27-83).

All the women had either breast conserving surgery or mastectomy and all received Level I/II axillary dissection.

Concerning operation techniques, it was documented if any immediate or delayed reconstruction was performed.

198 women, have been treated with breast conserving therapy, while 138 patients had undergone mastectomy. It was also questioned whether the women had undergone any adjuvant or neoadjuvant therapy, which is listed in table 3.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Patient and disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluated patients $n = 336$</td>
<td></td>
</tr>
<tr>
<td><strong>Age (in years)</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>58</td>
</tr>
<tr>
<td>Range</td>
<td>27-83</td>
</tr>
<tr>
<td><strong>Time since surgery (in months)</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>25</td>
</tr>
<tr>
<td>Range</td>
<td>7.5-45</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Mastectomy ($n$)</td>
<td>138</td>
</tr>
<tr>
<td>Breast conserving therapy ($n$)</td>
<td>198</td>
</tr>
<tr>
<td><strong>Side of breast carcinoma</strong></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>156</td>
</tr>
<tr>
<td>Left</td>
<td>163</td>
</tr>
<tr>
<td>Both</td>
<td>17</td>
</tr>
<tr>
<td><strong>Immediate Implante</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14</td>
</tr>
<tr>
<td>No</td>
<td>322</td>
</tr>
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</table>
### Table 3: Patient and disease characteristics

**Evaluated patients** $n = 336$

<table>
<thead>
<tr>
<th>Immediate reconstruction with muscle-skin-flaps</th>
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<th>No</th>
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<td>Yes</td>
<td>5</td>
<td>331</td>
</tr>
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<td></td>
<td></td>
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</tbody>
</table>

<table>
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<th>Chemotherapy</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
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<td></td>
<td>Yes</td>
<td>193</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
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</tr>
</thead>
<tbody>
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<td>197</td>
<td>133</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiotherapy</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
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<td>248</td>
<td>88</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
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<table>
<thead>
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<th>Neoadjuvant therapy</th>
<th>Chemotherapy</th>
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<th>No</th>
</tr>
</thead>
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<td></td>
<td>Yes</td>
<td>27</td>
<td>309</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>T1a</th>
<th>T1b</th>
<th>T1c</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>12</td>
<td>30</td>
<td>140</td>
<td>107</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal status</th>
<th>N -</th>
<th>N +</th>
<th>Nx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>206</td>
<td>111</td>
<td>19</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of dissected lymph nodes</th>
<th>N1 (01 - 10)</th>
<th>N2 (11 - 20)</th>
<th>N3 (21 - 30)</th>
<th>Nx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>22</td>
<td>139</td>
<td>27</td>
<td>148</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Patient and disease characteristics
Adjuvant endocrine treatment was performed in 197 (58.6%) patients and 193 patients were treated with adjuvant chemotherapy (57.4%).

A total of 248 (73.8%) patients had undergone radiotherapy.
As shown in the histogram below 96.4% of the patients received at least one of these adjuvant treatments.
3.2 Main results of symptoms in course of time

Main focus of the study was to evaluate the subjective estimation of symptom intensity for pain and limitation of arm mobility correlated to the time after surgery. Therefore a five-point self-report scale (0 – 4) at different time points, e. g. directly after the operation, at the hospital, first weeks at home, after 6 months, after 12 months, was used in the questionnaire.

Already many clinical studies have described the degree of pain and arm morbidity in course of time using objective and subjective registrations. Our follow up described results on subjective assessment of the patients and up to 12 months only. Additionally objective parameters such as analgesic use and different kinds of postoperative therapy (antibiotic treatment, physical therapy, lymphatic drainage) were taken into account.

The results demonstrate that complaints significantly (p< 0.0001 for the parameters pain and impairment of arm mobility) diminish in course of time in the patient collective, which is shown by the two following graphical charts.
3.2.1 Impairment of pain

The frequency tables show that directly after surgery 16.1% of our patient collective estimated their pain degree as strongly severe, whereas after 12 months 0.7% of the patients declared to have strongly severe pain. Following the scale point strongly severe step by step the percentage of the patients, drops at each time point as said above from 16.1%, to 8.1%, to 6.4%, to 1.3% ending at the last time point with 0.7%.
Chapter 3

Results

Pain directly after surgery

Fig. 15: Pain directly after surgery

Pain before leaving hospital

Fig. 16: Pain before leaving hospital

Pain after 4 weeks

Fig. 17: Pain after 4 weeks

Pain after 6 months

Fig. 18: Pain after 6 months
Additionally 14.2% of the women had no pain straight after surgery and 37.5% documented to have none after 12 months. At time point II:14.5% , at time point III:16% and at time point IV:29.9% of the patients affirmed to have no pain.

But not only the maximum and the minimum of the pain scale has improved over time, but also the middle items of the pain scale have shown recovery over course of time.

The maximum percentage rate directly after surgery lies at mediocre pain with 26.8%, also at mediocre pain at time point II and III with 30.0% and 36.4%, after 6 months maximum percentage holds slight pain with 32.1% and at time point IV 37.5% patients had no pain. Therefore an improvement of the whole scale of pain symptoms can be concluded from these frequency tabs and graphs.

As the emphasis of this study lies on the long-term sequel of the axillary dissection it was evaluated if the axillary region alone subjectively causes more problems than the breast surgery.

Pain being more severe in the axillary region than in the breast itself was declared by 35.9 % of the patients. And 26.3 % of the patient collective (n= 323) felt the same degree of pain in the breast and in the axillary region.
Pain is more severe in the axillary region than in the breast

Considering breast surgery technique the women’s estimated degree of pain was also evaluated separately for breast conserving surgery and mastectomy. There is no significant difference between the two operating methods for the item pain (p=0.4). The means of symptom intensity for pain in course of time are visualized for both groups in the following box plot graph and table 4.

Fig. 20: Pain is more severe in the axillary region than in the breast

Fig. 21: Mean intensity of pain: mastectomy vs breast conserving therapy
Finally the extent of pain in course of time was compared between patients with positive and negative axillary lymph nodes. Results showed that until up to 4 weeks after surgery node negative patients seem to have reported significantly more pain ($p=0.015$, $p=0.003$, $p=0.028$). At the time points of 6 and 12 months no significant difference between the two groups could be found (see table 5).
When leaving the aspect of node positive or negative aside and simply looking at the number of dissected lymph nodes forming three groups: N1 (0-10), N2 (11-20) and N3 (21-30) no significant differences could be surveyed when correlating the three groups to the intensity of pain in course of time (p≥0.197).

<table>
<thead>
<tr>
<th>PAIN</th>
<th>AFTER SURGERY</th>
<th>BEFORE LEAVING HOSPITAL</th>
<th>AFTER WEEKS</th>
<th>4 AFTER MONTHS</th>
<th>6 AFTER MONTHS</th>
<th>12 AFTER MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (0-10)</td>
<td>Mean 1,95</td>
<td>1,70</td>
<td>1,45</td>
<td>1,00</td>
<td>0,63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n 20</td>
<td>20</td>
<td>22</td>
<td>20</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>N (11-20)</td>
<td>Mean 2,04</td>
<td>1,80</td>
<td>1,68</td>
<td>1,21</td>
<td>1,01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n 134</td>
<td>132</td>
<td>132</td>
<td>130</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>N (20-30)</td>
<td>Mean 2,07</td>
<td>1,62</td>
<td>1,42</td>
<td>1,00</td>
<td>0,79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n 27</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>Mean 2,04</td>
<td>1,76</td>
<td>1,62</td>
<td>1,15</td>
<td>0,93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n 181</td>
<td>178</td>
<td>180</td>
<td>176</td>
<td>161</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Mean intensity of pain: N1 vs N2 vs N3

Fig. 23: Mean intensity of pain: N1 vs. N2 vs. N3

Also of great interest was the fact if patients received a separate incision in the axillary region besides the incision in the breast. No separate incision was made if patients received mastectomy and partly if the tumour was located in the upper outer quadrant. In none of the patients the ADAM technique, as described before was
performed. Our results showed that after 1, 6 and 12 months patients with a separate axillary incision had more pain ($p=0.043, p=0.027, p=0.035$) than those without an extra incision. P-values at a minor significance only. The number of patients varies due to incomplete reporting.

3.2.2 Impairment of arm mobility

When taking impairment of arm mobility into account, quite similar results can be found in course of time. Here the calculated frequencies showed that directly after surgery 23.0% of the patients estimated their degree of arm mobility as strongly severe impaired (max. at time point I = strong pain with 26.8%), whereas after more than 12 months 2.1 % declared to have strongly severe impairment of arm mobility (max. at time point IV = no pain with 37.9%).

Complete resolution of impaired arm mobility was achieved in 37.9% of the cases. Here again the charts underline the theory of reduction of arm mobility after 12 months.
Chapter 3   Results

Impairment of arm mobility

At the hospital station

Fig. 25: Impairment of arm mobility at the hospital station

In the first weeks at home

Fig. 26: Impairment of arm mobility in the first weeks at home

Until 6 months after surgery

Fig. 27: Impairment of arm mobility after 6 months

Until 12 months after surgery

Fig. 28: Impairment of arm mobility after 12 months
Summarising the results on pain and arm mobility in our study population of patients, the impairment of those two items in course of time has improved significantly. Although these results prove that most of the patients do feel less pain and arm movement restriction in time, still 19.4% are left with mediocre pain and 19.6% with mediocre impairment of arm mobility after 12 months.

Asking the women for their general impairment after lymph node dissection 17.2% declared to have no impairment and 41.1% stated to be only slightly impaired by the dissection. Nevertheless 11.3% of the collective reported severe and 3.1% reported strongly severe impairment, when asked for general impairment.
Again, when dividing the patients collective into those, which received breast conserving surgery and those with mastectomy, there is no significant difference (p=0.37) for impairment of arm mobility between the two types of surgery in course of time.
Chapter 3

Results

ARM MOBILITY AT HOSPITAL STATION IN THE FIRST AFTER 6 UNTIL 12 MORE THAN MONTHS MONTHS

<table>
<thead>
<tr>
<th></th>
<th>AT HOSPITAL STATION</th>
<th>IN THE WEEKS</th>
<th>FIRST</th>
<th>AFTER 6 MONTHS</th>
<th>UNTIL 12 MONTHS</th>
<th>MORE THAN 12 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MASTECTOMY</td>
<td>Mean n 2.48 2.32 1.64 1.22 1.10</td>
<td>118 117 118 112 115</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BET</td>
<td>Mean n 2.35 2.14 1.56 1.16 1.05</td>
<td>189 189 186 166 161</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>Mean n 2.40 2.21 1.60 1.19 1.07</td>
<td>307 306 304 278 276</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Mean impairment of arm mobility: mastectomy vs. breast conserving therapy

Also when examining arm mobility in node positive and node negative patients, only directly after surgery node negative patients reported significantly less impairment of arm mobility (p=0.037). Otherwise no significant difference within these two groups could be detected when asking for impairment of arm mobility in course of time.

<table>
<thead>
<tr>
<th></th>
<th>AT HOSPITAL STATION</th>
<th>IN THE WEEKS</th>
<th>FIRST</th>
<th>AFTER 6 MONTHS</th>
<th>UNTIL 12 MONTHS</th>
<th>MORE THAN 12 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N -</td>
<td>Mean n 2.50 2.28 1.63 1.18 1.08</td>
<td>193 192 188 175 176</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N +</td>
<td>Mean n 2.19 2.06 1.51 1.17 1.07</td>
<td>106 106 106 95 92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>Mean n 2.39 2.20 1.59 1.18 1.07</td>
<td>299 298 294 270 268</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8: Mean impairment of arm mobility: N- vs N+

Fig. 32: Mean impairment of arm mobility: N- vs N+
Considering the dissected lymphatic nodes only, also no significant difference in arm mobility was found when comparing the three groups at different time points.

<table>
<thead>
<tr>
<th>ARM MOBILITY</th>
<th>AT HOSPITAL STATION</th>
<th>IN THE FIRST WEEKS</th>
<th>AFTER 6 MONTHS</th>
<th>UNTIL 12 MONTHS</th>
<th>MORE THAN 12 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (0-10)</td>
<td>Mean 2.05</td>
<td>1.90</td>
<td>1.50</td>
<td>0.95</td>
<td>0.79</td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>N (11-20)</td>
<td>Mean 2.35</td>
<td>2.15</td>
<td>1.53</td>
<td>1.20</td>
<td>1.05</td>
</tr>
<tr>
<td>n</td>
<td>133</td>
<td>132</td>
<td>132</td>
<td>118</td>
<td>115</td>
</tr>
<tr>
<td>N (21-30)</td>
<td>Mean 2.19</td>
<td>1.77</td>
<td>1.36</td>
<td>0.83</td>
<td>0.88</td>
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<td>25</td>
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</tr>
<tr>
<td>TOTAL</td>
<td>Mean 2.30</td>
<td>2.07</td>
<td>1.50</td>
<td>1.12</td>
<td>0.99</td>
</tr>
<tr>
<td>n</td>
<td>179</td>
<td>179</td>
<td>177</td>
<td>161</td>
<td>158</td>
</tr>
</tbody>
</table>

Table 9: Mean impairment of arm mobility: N1 vs N2 vs N3

And again the item separate incision in the axillary region was correlated with the patients’ perceived impairment of arm mobility in course of time. Here results showed no statistically significant difference between the two examined groups ($p \geq 0.203$).
3.3 TNM relevance of the measured factors

After comparing women’s subjective assessment of pain and restriction of arm mobility at 5 different points of time, a second parameter, the tumour staging status was included into the calculations.

By taking this approach, the parameters pain and impairment of arm mobility are being correlated to the staging of the primary breast cancer. This aspect has not been discussed in any other study before, but might be quite important considering the facts of cancer as a systematic disease.

In order to find answers, if there is any connection between staging of the breast and the long-term sequel of axillary dissection (Level I and II) we reclassified the patient collective into their specific staging group such as T1, T2, T3 or T4.

3.3.1 Impairment of arm mobility

After implementing post hoc test to test significance (p level 0.05) of the mean difference of impairment of arm mobility between each T group at the different time points, a strong correlation between these two items could not be distinguished.
All p values but 3 were above the significance level of 0.05. Only the values of T1 and T4 (0.035) at the hospital station, of T1 and T3 (0.015) and T2 and T3 (0.049) after more than 12 months of surgery were under the level of significance.

33.3% of the T4 group had no impairment of arm mobility after surgery and in the first weeks at home. 8.3% of the T4 patients stated strongly severe impairment during these time periods, whereas 14.9% of T1 patients complained about strongly severe impairment after the first weeks.

After 6 months 0% of the T4 collective, compared to 4.1% of the T1 group coped with strongly severe impairment. Twelve months after surgery 14.3% of T4 had strongly severe impairment (T3 = 0%), but 28.6% had no sign of restriction of arm mobility.

So looking only at the extremes such as strongly severe and no impairment, comparing the T1 collective with the T4, no significant link is obvious. Looking at the graphical figures also taking the T2 and T3 group into account, this is confirmed.

![Impairment of arm mobility after surgery](image-url)
Chapter 3

Results

Impairment of arm mobility in the first weeks at home

![Chart showing impairment of arm mobility in the first weeks at home]

Fig. 36: Impairment of arm mobility in the first weeks at home

Impairment of arm mobility until 6 months after surgery

![Chart showing impairment of arm mobility until 6 months after surgery]

Fig. 37: Impairment of arm mobility after 6 months
Chapter 3   Results

Impairment of arm mobility until 12 months after surgery

Fig. 38: Impairment of arm mobility after 12 months

Impairment of arm mobility in the following months (after 12 months)
3.3.2 Impairment of pain

Also the information shown in the frequency-graphs below, on impairment of pain imply that there is no strong correlation between staging of the breast cancer and the item pain.

Therefore again the post hoc test, analyzing each T for every time point separately and correlating the T groups between each other was used and resolved in nearly all p values above 0.05. Values under 0.05 were gained for correlation between T1 and T2 (0.019) and T1 and T4 (0.011) directly after surgery, for T1 and T4 (0.021) before leaving hospital and finally for T1 and T4 (0.025) in the first weeks at home.

Directly after surgery 53.8% of the patients with T4 status claimed to have no pain, 7.7% to have slight, 0% to have mediocre, 23.1% to have strong and 15.4% to have strongly severe pain impairment.

In the T1 group 5.8% stated to have no, 19.1% slight, 31.8% mediocre, 24.9% strong and 18.5% strongly severe pain directly after surgery. Within group T2 directly after surgery maximum percentage lies at strong pain with 26.7% and minimum at strongly severe pain with 12.9%. Maximum at group T3 lies at strong pain and no pain with 28.6% and minimum lies at slight pain with 7.1%.

After 12 months 28.6% of the patients with T4 diagnosis have no pain, slight pain and mediocre pain. Strong pain impairment was affirmed by 0% of this group, although 14.3% had strongly severe pain impairment.

In group T2 and T3 0% have strongly severe pain after 12 months, whereas 33.3% (T2) and 16.7% (T3) have no pain after this amount of time.
Chapter 3   Results

Pain directly after surgery

Fig. 40: Pain directly after surgery

Pain at leaving hospital

Fig. 41: Pain at leaving hospital
Chapter 3

Results

Fig. 42: Pain in the first 4 weeks

Fig. 43: Pain after 6 months
3.4 Use of analgesic drugs

But not only the two items pain and limitation in range of motion were evaluated in order to estimate the degree of long-term sequel after axillary dissection. In order to get more objective information on the impact of pain on the patients, we examined the item “use of analgesic drugs” more closely.
24.1% of the patients stated to have needed analgesic drug support directly after surgery. Only 12.5% were on medical treatment for their pain before leaving the hospital, whereas in the first weeks back at home only 12.0% and in the first few months only 7.0% of the women took medication for pain. The last histogram shows that 14.1% took analgesic drugs only when needed.
When again evaluating the patients with mastectomy and breast conserving therapy separately considering the use of analgesics, there is no significant difference between the two types of operation - p-values are above 0.05 at each time point.

Directly after surgery 22.8% of the mastectomy group (group 1) and 24.1% of the breast conserving group (group 2) affirmed use of analgesics (p-value: 0.793). Before leaving hospital 11.1% of group 1 and 13.3% of group 2 took analgesics (p-value: 0.556). 11.1% of the mastectomy collective and 12.8% of the breast conserving collective took pain medication in the first weeks (p-value: 0.659). In the first months after surgery 8.8% of the mastectomy patients and 5.7% of the breast conserving therapy made use of analgetical treatment. (p-value: 0.287).

Irregular usage of analgesics was stated by 12% of group 1 and 15.6% of the group 2 patients (p-value: 0.366).

19.7% of the patients who underwent mastectomy and 21.3% of the patients who received breast conserving therapy confirmed that they took analgetical medication because of pain in the axillary region (p-value: 0.733). Now calculations were implemented considering the different staging status of the patients. Within the patients collective the groups T1-T4 were compared on the use of analgesics. Again the results show that in terms of significance that there are no distinctions between the four staging groups.

When asked for usage of analgesics in order to ease axillary pain 21.6% of T1, 19.0% of T2, 23.1% of T3 and 23.1% of T4 affirmed this (p-value: 0.894). Directly after surgery analgetical drugs were taken by 25.8% of T1, 21.7% of T2, 7.1% of T3 and 23.1% of the T4 patients (p-value: 0.441).

Before leaving hospital 13.3% of T1, 12.3% of T2, 7.1% of T3 and 15.4% of the T4 group needed pain medication (p-value: 0.920). Analgetical treatment was made use of by 12.6% of T1, 10.4% of T2, of 14.3% of T3 and 15.4% of T4 patients in the first weeks (p-value: 0.804).

During the first months 7.8% of T1, 3.8% of T2, 7.1% of T3 and 23.1% of T4 needed analgetical assistance. Here the p-value with 0.076 lies only slightly above the significance line of 0.05, therefore the T4 patient group can be said to have made significantly more use of analgetical treatment.
This result is exceptional considering that at all the other time points no difference between the tumour groups could be found.

In the whole these results on analgetical use underline the other pain related outcomes already presented above.

3.5 Postoperative parameters

Also general postoperative parameters as physical therapy, lymphatic drainage, antibiotic therapy and sensitivity changes were taken into account (view table 10 for summary). As can be seen from the figures in the following table the full count of 336 evaluated patients is not always reached. This variation is due to incomplete reporting.

3.5.1 Postoperative therapy

<table>
<thead>
<tr>
<th>Table 10</th>
<th>Postoperative therapy</th>
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<tr>
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<td>Physical therapy</td>
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<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Physical therapy</td>
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<td>Lymphatic drainage</td>
<td>Antibiotic therapy</td>
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<td>190</td>
</tr>
</tbody>
</table>

Table 10: Postoperative therapy
3.5.2 Sensitivity changes and readjusting to the “healthy arm”

The item “relearning” in our questionnaire has proven that 42.2% of the women had to readjust every day life handlings to their “healthy” arm instead of using their usually used now operated arm.

When comparing the mastectomy group with the patient group who were treated with breast conserving therapy no significant difference can be distinguished (p>0.05) regarding this item.

The intensive usage of the “healthy” side finds its reasons in different postoperative complications after axillary dissection, e. g. sensitivity changes or loss of strength. Sensitivity problems were found in 220 patients (65.5%).

And again no significance difference between patients receiving mastectomy and breast conserving therapy (p> 0.05) could be proved.
3.5.3 Subjective complaints and general problems in every day life

In order to get an idea of these complications some of the patients described their symptoms and added associated problems in their every day life routine.

A summary of the most mentioned problems in general and specific examples of daily life are listed in table 11.
Table 11: The most frequent subjective complaints after axillary dissection - patients free associations

**General problems:**

- Numbness of the upper arm
- Scar pains
- Feeling of tenseness
- Limitation through arm swelling / edema
- Restriction of force / fast weakness, loss of strength
- Limitation in stretching movement / working over-head
- Limitation in putting pressure on something, e.g. ironing
- Constant fear for wounding operated arm → relieving posture

**Examples from daily life routine - limitations while:**

- Cleaning windows
- Scrubbing floors
- Opening bottles / Screwing movement
- Lifting heavy things from cupboards, shelves,…
- Carrying heavy bags, e.g. shopping
- Grapping / holding things forcefully
- Hair drying
- Stirring movements, e.g. baking a cake
- Gardening
- Handwriting and typing, e.g. working on the computer
- Sport activities

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3.6 Retrospective consent to axillary lymph node dissection

Last item of the questionnaire concerned the given consent of the women to axillary lymph node dissection, when looking back on the surgery and the postoperative consequences. 90% of the patients stated, that they would again choose lymph node dissection as a part of their treatment.
Further impressions on this particular question could be gained by personal comments of the patients, given at the end of the questionnaire underlining the quite ambivalent experiences with or opinions on this intervention. Some of the comments are listed underneath:

- Consent to lymph node dissection, because “An uncertain diagnosis is too great of a psychological strain.”
- “The dissection of the lymph nodes is important for the rest of one’s life, as it gives security after the surgery.”
- “As long as the sentinel node technique is not to 90% save, I would prefer the lymph node dissection.”
- “Today I would prefer the sentinel method.”
- “Although it leads to a reduced quality of life, I would still give my consent to the lymph node dissection.”
- “One bears side effects and impairment for security.”
- “Security/health comes before beauty/impairment.”
- “If I had to decide again, I’d would have the sentinel node remove fist and then make further decisions.”
4 Discussion and conclusions

Having demonstrated our approach and all our results, the question whether especially pain and arm mobility when assessed subjectively will diminish in course of time, will be discussed with the focus on other result in literature. The aspect of the initial tumour size and the impact of positive or negative axillary lymph nodes on sequel in course of time will also again be reviewed.

4.1 Estimation of the long-term sequel of axillary lymph node dissection: objective vs. subjective

A number of studies have evaluated long term morbidity after ALND using mostly subjective and/or objective assessment [Ivens et al, 1992; Maunsell et al, 1993; Hack et al, 1999; Ernst et al, 2002]. Most authors have evaluated a wide range of symptoms. However, quite a large number of trials have focused on specific complaints, especially arm edema [Erickson et al, 2001; Mc Laughlin et al, 2008]. In the study presented here we mainly used subjective measures (patients´ subjective assessments and judgment of impairment) for evaluation of pain and arm mobility. Objective parameters such as analgesic usage were used in order to distinguish correlations to the subjective reports of the patients. Clinical evaluations such as range of shoulder movement or arm circumference were left aside, since different assessment strategies are used in literature which makes comparison of existing data problematic. The problem of comparability has been lined out in literature before [Kuehn et al, 2000; Ernst et al, 2002; Yap et al, 2003; Mc Laughlin et al, 2008], but uniform definitions or standard techniques have not been released so far. Furthermore “The reported rates of lymphedema may be influenced by each patient’s interpretation of their own arm swelling and concomitantly by existing sensory changes. Therefore, the definition and prevalence of what constitutes clinically significant lymphedema is unclear.” [Mc Laughlin et al, 2008, p 5220].

We are also convinced that clinical tests are not sensitive enough to adequately register the different degrees of symptom intensity (especially low degrees of symptoms intensities) and patient’s symptoms are often underestimated when only measured by objective parameters. Kuehn et al (2000) for example, found that subjectively assessed symptoms were generally classified as more severe than
clinically evaluated symptoms. We conclude that objective measurements can quantify the problems but cannot grasp the impact patients have to cope with.

Many symptoms may not be persistent, but rather occur divergently and therefore slip through clinical measurements which are set at certain times.

Another crucial point is, that symptoms such as stiffness, numbness and weakness are very hard to measure as the previous strength and mobility has to be taken into account [Ivens et al, 1992].

Furthermore ALND associated complications are not only affecting patients physically but also psychologically. This psychological influence on physical impairment is hardly possible to determine but not to underestimate [Hack et al, 1999; Maunsell et al, 1993]. Our data on women’s impressions and comments about their given consent to axillary lymph node dissection (view results: 3.6.) emphasize their fear of cancer recurrence and strong hopes for security within the patients when asked about their breast disease.

Therefore we assume that the symptoms breast cancer patients must cope with are best reflected when self-reported.

4.2 Improvement of symptoms in course of time

Main focus and purpose of the current study was to evaluate impairment of symptoms (pain and arm mobility) after axillary dissection measured by the patients’ subjective assessments. The results of this trial suggest that the morbidity of axillary dissection improves in course of time, but that complaints can remain substantial after a follow up time of 12 months.

Although a number of studies [Ernst et al, 2002; Kuehn T. et al, 2000] concluded that the symptoms do not diminish and rather reach a stable state, our evaluations show quite a reduction of complaints after 12 months. Our results support previous work from Liljegren et al (1997) who reports that 40-50% of the patients felt an improvement of symptoms in course of time. Still our figures clearly show that one fifth of the patient collective are left with mediocre pain and impairment of arm mobility, which proves that morbidity remains substantial. ALND associated
complications can adversely affect quality of life, e.g. delaying resumption of normal activities and return to work.

Therefore the current trend to more selective and less invasive procedures could be of great benefit for breast cancer patients.

Results from several trials have shown that the SLNB is a most effective procedure with significantly less side effects such as arm swelling, impairment of arm movement, pain, etc. [Mc Laughlin et al, 2008; Morrow et al, 2003; Schwartz et al, 2001].

Nevertheless considering the international consensus recommendations conventional axillary lymph node dissection remains the most effective surgical treatment of clinically node positive patients and patients with locally advanced breast cancer. Security and tumour control should always be first goal when choosing the adequate operating technique.

Still momentarily the ongoing debate about this patient collective, which might be over treated with ALND, encourages new ideas to extend the field of application for SLNB, e.g. patients with primary systemic therapy, patients with locally advanced breast cancer, etc. [Bauernfeind et al, 2007; Lelievre et al, 2006; Specht et al, 2005]. But for the evaluation of these new ranges of use it is important to balance the risks and possible benefits.

4.3 Relevance of the tumour staging status and type of surgery

Another significant aspect of this examination was the tumour staging status of our patients and its correlation to their degree of symptom intensity. This question has not been discussed in any other study before, but might be quite important considering the facts of cancer as a systematic disease.

Are the parameters pain and impairment of arm mobility correlated to the staging of the primary breast carcinoma or is there a connection between staging of the breast and the long-term sequel of axillary dissection? To find answers we reclassified the patient collective into their specific staging group such as T1, T2, T3 or T4.

As shown through several cross-tables, graphical charts and verified through several tests, there is not a higher risk for pain or limitation in range of motion, when having a
higher oncological staging level (p> 0.05). The information shown in the frequencygraphs has proven our theory, that the primary status of breast carcinoma has no significant correlation to the staging of the primary breast carcinoma and the longterm sequel of axillary dissection.

We conclude that the staging of the primary breast carcinoma has no direct impact on arm mobility or on impairment of pain. Evidence from our cross tabs rather state, that the staging of the breast exerts no influence on these two symptoms evaluated in course of time.

When evaluating the correlation between the types of surgery which were used (mastectomy or breast conserving therapy) and impairment of arm mobility, pain and usage of analgesic drugs, no significant difference (p>0.05) in the postoperative effect between the two types of surgical management could be distinguished. These results are similar to others in literature, reported by Kuehn et al (2000) and Ernst et al (2002). Kuehn et al (2000) reported that the type of surgery (breast conserving therapy of mastectomy) does not influence either the subjective or the objective symptoms. Also Ernst et al (2002) mentioned not to have found any significant difference relating to pain, loss of arm strength and limitation of shoulder movement when comparing patients who received mastectomy and breast conserving therapy. Comparability of our results underlines our theory that neither type of surgery of the breast nor primary stating status of breast cancer influences the symptoms evaluated.

Not evaluated in our study was the impact of reconstructional procedures either with implants or muscle-skin flaps, as number of cases was far too small for proper evaluation (19 vs. 317 cases). Data on this topic is very rare as reconstructional breast surgery has been evaluated considering to timing, method and cosmetic outcome, but not correlated with symptoms in course of time after ALND. In our collective the number of patients treated with immediate or delayed reconstruction is underrepresented and does not influence statistical outcome of our analysis.

We also looked into the aspect of nodal status (N+ or N-) and the number of dissected axillary lymph nodes and their influence on symptoms in course of time. Here results on the impact of the nodal status showed no significant difference in perception of pain or arm impairment after 6 and 12 months after surgery. Although our results show a significance up to 4 weeks after surgery in favour of patients with
a negative lymphatic status, we conclude a bias because of the small number of cases evaluated. Results in literature about the impact of extent of axillary lymph node dissection and its influence on postsurgical symptoms is controversial. Ernst et al (2002) reported no difference for the items shoulder pain, abduction and arm strength in patients with positive vs. negative lymph nodes after 5 years. Also Kuehn et al (2000) did not find increase of subjective or objective symptoms when comparing complete axillary clearing including Level III. Harvesting a larger number of lymph nodes did not result in higher morbidity in course of time. Schulze et al (2006) observed impact of metastatic disease in the axillary region and the incidence of lymph edema and also reported lack of significant difference between patients with positive or negative lymph nodes.

More important for the postoperative morbidity seems to be the type of procedure selected for axillary lymph node dissection. Several authors have shown that a higher number of removed lymph nodes leads to more arm functioning impairment [Liljegren et al, 1997; Albert et al, 2006)]. Although in our patient collective the number of dissected lymph nodes showed no influence on the symptoms in course of time (similar to Kuehn et al, 2000), this might be due to the small number of cases and discrepancy between the groups (N1,N2,N3) which were evaluated. Furthermore a bias could result as the pathologic preparation of the lymphatic nodes might not always result in the exact number of dissected nodes. Data of larger trials comparing SLNB and ALND, gained profound results in favour for removing less lymph nodes from the axillary region as performed in the SLNB technique [Mc Masters et al, 2000; Mc Laughlin et al, 2008]. Therefore patients with negative nodal status and those without any contradicitional features the sentinel node concept as mentioned before is an appropriate alternative [Schrenk P et al, 2000], as it avoids dissection of nerve or vascular structures. The sentinel method when performed regarding to the international consensus guidelines, is momentarily gold standard for a special patient collective.

Another aspect when focusing on arm morbidity and debating on management of the axilla could be the fact of sparing the subcutaneous lymphatic drainage. Using a single incision only, how performed by Paepke et al (2003), seems an interesting approach to eliminate postoperative axillary morbidity and has to be kept in mind when discussing side effects of axillary dissection.
In our study collective the ADAM procedure was not performed, but still the influence of separate incision was evaluated, as in patients receiving mastectomy and in patients with tumours located in the upper outer quadrant a separate incision was avoided. Results for the perceived pain by the patients showed a statistically trend for better outcome when receiving a single incision only. We conclude that the ADAM approach should be examined and compared with SLNB, as well as ALND in long-term studies in order to gain reliable data.

Of course when mentioning all these different procedures the aspect that the success of a surgical procedure is dependent on the out carrying surgeon, shall not be left aside.

4.4 Discrepancies and possible variations of the current study

Although there most likely is a discrepancy between self-assessed symptoms and any results from physical examination, our study completely focused on the subjective judgement and perceptions of the patients themselves. Considering that quality of life is mainly a subjective and very individual topic, it was important for us to concentrate on this self-assessing viewpoint.

Considering the symptoms of the patients only pain and impairment of arm mobility were assessed in this trial, whereas swelling or lymphedema was not included. Still this parameter has been described in literature as a very frequent symptom after ALND and must be considered as one of the major complications after operation [Yap et al, 2003]. Although nowadays ALND is not as radical as in former times, lymphedema occurs in approximately 16% of the patients. The prevalence of lymphedema via objective and subjective parameters has been assessed in many trials before, also comparing incidence after ALND vs SLNB [Mc Laughlin et al, 2008]. Here several aspects have to be considered as multiple factors are associated with development of lymphedema. Influential items are history of infection or injury, higher body mass index, higher body weight and history of radiation. As in our study most of these facts were not documented, evaluation of lymphedema in course of time in our self-administered questionnaire was not reasonable.
Besides another source of variation is the fact that axillary dissection was performed by different surgeons in this trial. Concerning the learning phase and experience necessary to master ALND it seems plausible that a surgeon who is familiar with this operative technique for many years versus a younger colleague still in training will manage less tissue destruction, e.g. preserving lymphatic pathways or blood vessels. Another point when considering variation could be the duration between breast carcinoma treatment and administration of the questionnaire. Although only a maximum of 4 years lies between questioning and surgical treatment, a number of patients left parts of the self-assessment-scale blank and had to be excluded due to incomplete reporting. As we have such a large number of cases (n=336) their number should not be of any consequence.

A further bias could result in the fact that the time passing since surgery and the answered questionnaire (mean = 25 months), might be too short for symptoms emerging after many years. “Furthermore, approximately 25% of women ultimately developing lymphedema after axillary lymph node dissection (ALND) will do so after 3 years.” [Mc Laughlin et al, 2008, p5220]. Therefore severe cases with, e.g. lymphedema with a initial high fraction of positive axillary lymph nodes could be underrepresented in this evaluation.
5 Summary

Purpose of the current study was to investigate the intensity of pain and impairment of arm mobility breast cancer patient’s subjectively assessed after axillary dissection. A self-report questionnaire was mailed to 516 patients who received axillary dissection as part of breast cancer treatment. The subjective assessment of intensity of pain and impairment of arm mobility of 336 (65.1%) women was evaluated by using a five-point self-report scale (0 - 4) in the questionnaire. Influence of the type of surgery (breast conserving and mastectomy), tumour staging status and nodal involvement on these items was examined. Statistical analysis of all data was achieved by using SPSS 11.5 © (Inc., Chicago, IL) computer system.

Our results show that women’s estimated degree of pain and arm morbidity decreases significantly in course of time. Nevertheless one fifth of our collective remain with mediocre pain and arm impairment 12 months after surgery (19.4% are left with mediocre pain and 19.6 % with mediocre impairment of arm mobility). Also the objective parameter “use of analgesics” declined over the follow-up of 12 months. Extent of surgery (breast conserving or mastectomy) seems of no significant difference according to these 3 evaluated items. Also the tumour staging status and nodal metastasis (N+ vs N-) is of no influencing relevance to patient’s estimated pain level, drug consume or arm impairment. Furthermore the number of dissected lymph nodes in our collective showed no impact on the items pain and arm impairment in course of time. However this might be due to the small patient collective and discrepancy between the number of cases in the evaluated groups (N1,N2,N3).

Therefore intensity of pain, arm impairment and usage of analgesic drugs appear to diminish in course and remain unaffected by primary staging of the breast carcinoma, type of surgery as well as nodal status. Still even after 12 months part of the study population is left with substantial degree of pain as well as impaired arm movement - daily activity is affected and restricted/limited.
6 Acknowledgements

The author would like to thank Professor Dr. Marion Kiechle for chaperoning this project/doctoral thesis and for critical reading of the manuscript.

Thanks in large part to the kindness and considerable mentoring provided by O.A. Dr. St. Paepke, my long-time supervisor. His inspiring and encouraging way to guide me through this piece of work, as well as his invaluable comments during this dissertation played a central role to the outcome of this project.

I will also give a special thanks to Dr. Ulrike Schwarz-Boeger for technical assistance and advice.

I am very grateful to R. Busch who gave helpful suggestions during my statistical analysis.

Also I thank my colleagues for inspiring discussions during the whole working process.
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Erfassung von Nebenwirkungen

Fragebogen
Zur Einschätzung der Belastung nach operativer Entfernung der Lymphknoten der Achselhöhle

Sehr geehrte Patientin,


Wir wissen jedoch, dass die Operation zu Schmerzen, Bewegungseinschränkungen, Missemfindungen und Lymphödemen mit Schwellung des Armes in unterschiedlichem Ausmaß, u. ä. m. führen kann. Für uns ist es wichtig, diese sich evtl. aus der Operation ergebenden Beeinträchtigungen erfassen zu können. Dafür benötigen wir Ihre Mitarbeit!
Vor Ihnen liegt ein Fragebogen, der erarbeitet wurde, um möglichst genau den Umfang der Behandlung und die daraus resultierenden Beschwerden im Zeitverlauf zu erfragen. Da die Operation zum Teil länger zurückliegt sind wir auf möglichst genaue Angaben aus Ihrer Erinnerung angewiesen. Am Ende des Fragebogens haben Sie Platz, eigene Gedanken zu äußern oder Veränderungen zu beschreiben, die Sie in den vorliegenden Fragen nicht genügend beachtet fanden.

**Hinweis zum Datenschutz**
Die von uns erhobenen Daten finden in anonymisierter Form Eingang in eine Gesamtauswertung aller von uns befragten Patientinnen. Die Daten können demzufolge nicht zur befragten Person zurückverfolgt werden, so dass der Schutz Ihrer persönlichen Daten gewährleistet ist.

Wir danken Ihnen herzlich für Ihre Mitarbeit!

Prof. Dr. med. M. Kiechle  Dr. Paepke  Evelyn Klein
Klinikdirektorin  Projektverantwortlicher  Doktorandin

**Erläuterung der Graduierung, die zur Beantwortung mehrerer Fragen angegeben sind**

<table>
<thead>
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<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Markierung mit X</th>
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</thead>
<tbody>
<tr>
<td>0 =</td>
<td>keine Ausprägung</td>
<td>keine Beeinträchtigung</td>
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<td>1 =</td>
<td>wenig ausgeprägt, gering beeinträchtigend</td>
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<td>2 =</td>
<td>mittelgradige Ausprägung oder Beeinträchtigung, d.h. im Alltag bemerkbar, teilweise auch als störend empfunden, normale Arbeit oder Funktion nicht gestört, Medikamenteneinnahme bei Bedarf notwendig</td>
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<td>3 =</td>
<td>starke Ausprägung oder Beeinträchtigung, d.h. im Alltag durchgängig als störend empfunden, normale Arbeit oder Funktion gestört, Medikamenteneinnahme durchgängig notwendig</td>
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<td>4 =</td>
<td>sehr starke Ausprägung oder Beeinträchtigung, d.h. im Alltag durchgängig zum Funktionsverlust führend, Medikamenteneinnahme durchgängig notwendig, Medikamente führen nicht zur vollständigen Besserung</td>
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</table>
Fragebogen zur Erfassung von Nebenwirkungen nach operativer Entfernung von Lymphknoten aus der Achselhöhle bei Patientinnen mit Brustkrebs

Name, Vorname, Geburtsdatum:

Adresse:

I. Daten zur Operation

Operationsdatum (Monat/Jahr)

Operationsart:
Hier bitte ankreuzen Entfernung der Brust
Entfernung eines Knotens aus der Brust
Entfernung eines größeren Teiles (Segment/Quadrant)
Entfernung des Wächterlymphknotens (Sentinel)
Operation mit sofortiger Einlage eines Implantats
Operation mit Rückenlappenplastik und Implantateinlage

Operationsseite Rechts
Links
Beidseits

Operation der Achselhöhle:
Erfolgte die Eröffnung der Achselhöhle über einen Extraschnitt ja / nein
II. Medikamentöse Behandlung

Hormonbehandlung vor der Operation nach der Probeentnahme ja / nein
Chemotherapie vor der Operation nach Probeentnahme ja / nein
Strahlentherapie nach der Operation ja / nein
Hormontherapie nach der Operation ja / nein
Chemotherapie nach der Operation ja / nein
Keine medikamentöse oder Strahlenbehandlung nach der Operation ja / nein

Sollten mehrere der genannten Behandlungsverfahren angewendet worden sein so bitten wir um Ankreuzen aller durchgeführten Behandlungen.

III. Einschätzung der Schmerzen nach Entfernung der Lymphknoten aus der Achselhöhle

III.1. Zeitpunkt und Ausprägung der Schmerzen

<table>
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<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Unmittelbar nach der Operation</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Vor der Entlassung nach Hause</td>
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<td></td>
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<tr>
<td>In den ersten 4 Wochen zu Hause</td>
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<tr>
<td>Nach 6 Monaten</td>
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<tr>
<td>Nach 12 Monaten</td>
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</tbody>
</table>

Waren die Schmerzen in der Achselhöhle stärker als in der Brust?

ja / nein / gleich
III.2. Einnahme von Schmerzmitteln

Haben Sie aufgrund der Schmerzen in der Achselhöhle Schmerzmittel eingenommen?

ja / nein

Wenn ja,

Unmittelbar nach der Operation ja / nein

Vor der Entlassung ja / nein

In den ersten Wochen zu Hause ja / nein

Hier bitte den Zeitraum angeben:

In den darauf folgenden Monaten ja / nein

Hier bitte den Zeitraum angeben:

Unregelmäßige Einnahme von Schmerzmitteln bei selten auftretenden Schmerzen ja / nein

IV. Einschätzung der Bewegungseinschränkungen

Haben Sie nach der Entfernung der Lymphknoten Bewegungseinschränkungen der Armes bemerkt oder einen Verlust der bisherigen Kraft und Geschicklichkeit?

IV.1. Zeitpunkt und Ausprägung der Bewegungseinschränkung

Im Zeitraum des Aufenthaltes auf der Station 0 1 2 3 4

In den ersten Wochen zu Hause 0 1 2 3 4

Bis zu 6 Monaten nach der Operation 0 1 2 3 4

Bis zu 12 Monaten nach der Operation 0 1 2 3 4

In den darauf folgenden Monaten 0 1 2 3 4
V. Einschätzung von Empfindungsveränderungen

Haben Sie seit der Operation Veränderungen der Empfindung im Bereich des Oberarmes?

ja / nein

VI. Umlernen

Haben Sie nach der Operation lernen müssen, Tätigkeiten, die Sie bisher mit dem Arm der operierten Seite ausführten mit dem anderen Arm auszuführen?

ja / nein

Wenn ja, welche:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

VII. Nachbehandlung

Waren nach der Entlassung aus dem Krankenhaus

1. Antientzündliche Behandlungen (Antibiotikagabe) ja / nein

2. Punktionen (z.B. von Flüssigkeitsansammlungen im Wundbereich) ja / nein

3. Physiotherapeutische Behandlungen ja / nein

4. Lymphdrainagen ja / nein

notwendig?

Wenn die oben genannten Behandlungen notwendig waren bitte die Dauer mitzugeben.
VIII. Bewertung aus ihrer ganz persönlichen Sicht

Wenn Sie alle aufgeführten Faktoren zusammenfassend bewerten, wie ausgeprägt ist der Grad der Gesamtbeeinträchtigung durch die Entfernung der Lymphknoten aus der Achselhöhle?

0  1  2  3  4

Würden Sie rückblickend aus heutiger Sicht der Entfernung der Lymphknoten aus der Achselhöhle zustimmen eingedenk der Tatsache, dass dadurch die Entscheidungen hinsichtlich der nachfolgenden Behandlung (Chemotherapie, Hormontherapie) sicher getroffen werden konnte.

ja  /  nein

Oder ablehnen und damit in Kauf nehmen, dass die Entscheidung zur nachfolgenden Behandlung nicht sicher getroffen werden könnte.

ja  /  nein.

Persönlicher Kommentar:

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Mit herzlichem Dank für Ihre Mitarbeit!

Die Mitarbeiter der Frauenklinik des Klinikums rechts der Isar
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03.11.2006 Erhalt der Approbation

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München, April 2010