Langenbeck's Arch Surg (2000) 385:236–245

A. Bembenek
P.M. Schlag

Lymph-node dissection in breast cancer

Received: 25 September 1998
Accepted: 17 October 1998

A. Bembenek · P.M. Schlag
Surgery and Surgical Oncology,
Robert-Rössle-Klinik,
Charité Humboldt-University,
Lindenberger Weg 80, D-13122 Berlin,
Germany
Tel.: +49-30-94171400
Fax: +49-30-94171404

Abstract *Background:* Along with the ongoing modifications in treatment of primary breast cancer, the purpose and extent of lymph-node dissection has changed. The following is an overview of the current knowledge and practice of lymph-node dissection in breast cancer, with special regard to expected developments in the near future. Axillary dissection is described as a ten-step procedure, including dissection of level-I and -II and Rotter's nodes, without level-III nodes, providing at least ten lymph nodes for accurate staging information.
Discussion: Axillary dissection still offers the most efficient local control in node-positive patients, whereas, in primarily node-negative patients, irradiation seems to be equally effective. In general, lymph-node dissection does not alter overall survival but there is no doubt that surgical therapy still contributes to cure in early-breast-cancer patients and seems to be curative for certain patients with stage-I carcinoma. The lymph node status of the axilla is crucial for the indication of adjuvant therapy in early invasive breast cancer, but an increasing number of clinical node-negative patients could be managed with information based on features of the primary tumor, regardless of the nodal status. The most promising new concept for the selection of node-positive patients, while avoiding unnecessary morbidity of axillary dissection in early-breast-cancer patients, is the sentinel-node concept. The principle is based on the identification of the first "sentinel" lymph node reached by lymphatic flow. Thus, only proven node-positive patients undergo axillary dissection. Local failure of internal mammary lymph nodes is rarely recognized; however, internal mammary lymph nodes seem to have an underestimated prognostic significance in about 10–20% of axillary node-negative patients. This may lead to the withholding of systemic therapy for patients with early breast cancer. Nevertheless, there is no indication for a routine parasternal dissection today. The sentinel-node concept may also support the selection of diagnostic internal lymph-node biopsy and subsequent adjuvant therapy in cases with no axillary lymph-node metastases but with internal lymph-node metastases.

Key words Breast cancer · Lymph-node dissection · Lymph-node status · Lymphonodectomy · Sentinel-node biopsy

Introduction

The treatment of breast cancer has been one of the major clinical and surgical problems ever since the beginning of medicine. Hippocrates stated, in 400 BC, that “it is better not to apply any treatment”, whereas Galen (129–200 AD) tried to excise tumors by “accurate incisions surrounding the whole tumor, so as not to leave a single root.” From that time until now, the main part of breast-cancer therapy has been surgical. In addition to the removal of the tumor, the intention and extent of lymph-node dissection has changed, along with the understanding of the disease. In this article, we give an overview of the current knowledge of the disease and the surgical therapy.

Technique of axillary lymph-node dissection

Axillary dissection means a stepwise exposition and preservation of the anatomic “guideline structures” and an en bloc dissection of the lymphatic tissue according to different levels. The sequence of the surgical steps are not generally standardized, and several different techniques have been described, essentially guided, however, by the following anatomic structures [1, 2, 3].

The anatomic structures of the axilla which must be exposed in order to function as guidelines of dissection are: the lateral border of the major pectoral muscle, the minor pectoral muscle, the anterior border of the latissimus dorsi, the axillary vein (inferior border), the long thoracic (Bell’s) nerve and the thoracodorsal nerve and vessels. According to Berg and the Union Internationale Contra la Cancrum convention [2], the axilla is divided into three levels:

Level I (low axilla).	Lymphatic tissue lateral to the lateral border of the pectoralis minor muscle and inferior to the axillary vein
Level II (mid-axilla).	Lymphatic tissue between the medial and lateral borders of the pectoralis muscle and the interpectoral (Rotter’s) lymph nodes
Level III (apical axilla).	Lymphatic tissue medial to the medial margin of the pectoralis minor muscle, including those designated as subclavicular, infraclavicular or apical nodes

When performing an axillary dissection of level I and II through the incision of the tumor resection, the following steps are important:

1. Placement of the patient supine on the operating table, with his/her arm outstretched 90º on a sideboard.
2. Identification of the lateral border of the pectoralis major and preparation (in a superficial plane laterally towards the anterior border) of the latissimus dorsi, which is exposed.
3. Preparation from the lateral and posterior border of the pectoralis major through the axillary fascia to the lateral border of the pectoralis minor, retraction of the pectoralis major and excision of the interpectoral (Rotter’s) lymph nodes. The lateral pectoral nerve, because it is at risk on the middle and inferior part of the anterior face of the pectoralis minor, should be preserved.
4. Preparation of the lateral border of the pectoralis minor and retraction of the muscle upwards and medially so that the lymphatic tissue behind the muscle (level II) and the axillary vein can be exposed. Some authors propose to raise the arm across the face during this procedure, placing the hand near the opposite shoulder, in order to relax the pectoral muscles and facilitate manipulations on the pectoral muscles. Beyond this border, the pectoralis minor is divided by some surgeons [1]. We estimate that this is not necessary in most cases.
5. Liberation of the anterior and inferior aspects of the axillary vein, extending from the medial border of the pectoralis minor to the anterior border of the latissimus dorsi, without narrowing the vein.
6. The axillary contents are then dissected from the anterior-medial part to the posterior-lateral part, beginning with level II, followed by the tissue adhering to the lateral chest wall and inferior to the axillary vein. The long thoracic nerve, always placed behind the mid-axillary line, must be seen and preserved. However, there is no need for its preparation, because it is shed by the fascia of the serratus anterior muscle, which does not need to be touched during the dissection. Two or three intercosto-brachial nerves can regularly be seen and should be preserved if they are not affected by lymph-node metastases.
7. At the lateral part of the axilla, the thoracodorsal nerve, emerging laterally from behind the axillary vein, must be shown and left intact with accompanying vessels. Usually, 2–3 cm down from the inferior border of the vein, it crosses posteriorly the subscapular veins, which are prominent and mostly easy to identify, thus helping to identify the nerve. If the nerve is seen, it is traced downwards, until it enters the latissimus dorsi.
8. If the dissection inferior to the axillary vein [between the latissimus dorsi and the lateral chest wall, including the tissue behind the pectoralis minor (level II)] is complete, the whole specimen is excised, and the levels and their orientations are marked for histologic examination.
9. Placement of a suction drain, adaptation of the skin flaps with a resorbable suture and intracutaneous suture of the skin are the final procedures of the dissection.

If the dissection is performed through a separate incision, we prefer an incision along the lateral border of the pectoralis major.

Extent of the axillary lymph-node dissection

Number of nodes

Due to the direct correlation between involved lymph nodes and survival and the statistically significant cutpoint for the prognosis at ten removed lymph nodes, there is broad consensus for the necessity to remove a minimum of ten lymph nodes [4, 5, 6, 7]. Axillary sampling often fails to provide a sufficient number of nodes and is thus less effective as local treatment; thus, it is not an accepted alternative treatment to axillary dissection today [5, 8, 9]. The extent to which extent the axillary dissection should be performed has been questioned.

Level of dissection

According to the division of the axillary content into three levels [10] and Rotter's lymph nodes, the number of levels to be cleaned has been discussed. Analysis of the distribution of positive lymph nodes showed not only continuous involvement from level I to levels II and III, but a significant proportion of "skip metastases" occurring in level II and/or level III without involvement of level I (Table 1). The results of several studies reveal, in a significant number of nodal-positive patients, up to 30% skip metastases without involvement of level I. Only about 3%, however, show involvement of level III without positive nodes in levels I or II. Additionally, a discontinuous involvement of levels II or III has the same prognostic significance as sole involvement of level I [11]. Thus, for a representative staging, there is, in general, no need for routine dissection of level III. Some authors recommend total axillary dissection for better local control mainly in nodal-positive patients [12, 13]. However, dissection of levels I and II (which provide a sufficient number of lymph nodes), integrated in modern therapy strategies with systemic therapy for axillary node-positive patients, show acceptable low rates of local recurrence [4, 6, 14]. However, the incidence of seroma formation and long-term lymphedema in total axillary dissection is significantly higher than that seen in partial dissection [15, 16, 17]. Another argument against dissection of level III is that the lateral pectoral nerve usually must be sacrificed, resulting in a cosmetically undesirable partial atrophy of the major pectoral muscle and worsening the possibility of secondary breast reconstruction [5]. In conclusion, satisfying local control and adverse effects of complete axillary dissection override a possible small benefit in local control.

Therapeutic tumor resection in the axilla: local tumor control and survival benefit

Historic development

Bernard Peyrilhe, in 1773, first recommended removal of the cancerous breast along with axillary contents and the major pectoral muscle, a type of operation that became well known about 100 years later as Rotter and Halsted's radical mastectomy. The concept at this time was based on a primarily surgical approach to breast cancer, with the aim of cure by radical removal of all tumor tissue. The common idea was that breast cancer spreads sequentially from the primary site to regional lymph nodes and to distant sites, implicating that complete removal of the tumor and the afflicted lymph nodes should protect most patients from systemic disease. Due to a marked percentage of patients with tumor relapse after extended mastectomy, the common treatment of the disease became increasingly radical. In the late 1940s, interest in the internal chain of mammary lymph nodes increased, and a routine dissection of this region was first performed by Margottini and Bucalossi in 1948 [17]. Later, super-radical procedures followed, including the resection of supra-clavicular and even mediastinal nodes [18, 19]. As the success of the radical surgical interventions were more and more disappointing, the general concept of breast cancer changed. It was understood more and more as a primarily systemic disease, as most clearly articulated by Fisher in 1981 [20]. Following this paradigm, local treatments became less aggressive and staging procedures became increasingly important for the guidance of systemic therapy. However, even this point of view could not explain the better outcome of patients with early detection of cancer by routine mammography or the significant correlation of tumor size and metastasis. Taking into account both points of view, the "spectrum model" has recently been developed, explaining metastases as a "function of individual tumor growth and progression", stressing both local and systemic therapy [21].

Table 1 Discontinuous metastases according to levels without involvement of level I. *LN+* lymph-node positive

Reference	Number of LN+ patients	Level I(%)	Levels II and III (%)	Level III (%)
[12]	65	22	4.6	3.1
[55]	255	9	3.5	2.4
[11]	461	12.8	2.7	

Table 2 Influence of axillary treatment on survival

Reference	Number of patients	Follow-up (months)	Compared treatments	Survival benefit (percentage of patients who survived) (%)	*P* value
[24]	498	144	Dissection versus ineffective dissection plus irradiation	5.5	0.05
[22]	1665	120	Watch policy versus dissection versus irradiation	None	0
[56]	2800	96	Watch policy versus irradiation	None	0
[57]	658	72	Dissection versus irradiation plus dissection	4	0.014

Surgical cure

Table 2 shows a tendency toward a survival benefit for a subgroup of patients with early breast cancer. One explication could be that some patients indeed suffer from a stage-I carcinoma with one or a few small axillary nodes (following the Halstedian concept of sequential spreading) and can, therefore, be cured by surgical therapy. It can be assumed that between 30% and 40% of the clinically node-negative patients have occult positive axillary nodes [22] and that 25% of them seem to follow the model of sequential spreading, having no distant metastases at the time of diagnosis. This means that a small percentage of about 5–10% of the early-cancer patients might be cured by tumor resection and axillary dissection [23].

Survival benefit

In general, it is accepted today that the approach to the axilla does not have a great influence on overall survival. However, it should be kept in mind that only a few studies dealt specifically with this subject.

The best-known study – and the only one that compared axillary irradiation therapy with axillary dissection and lack of treatment of the axilla in early (clinically node-negative) breast cancer patients – was the NSABP trial B-04 [22]. It revealed no survival benefit for any of the groups. Additionally, the local failure rate (in the axilla) of the untreated group was lower than estimated with regard to the frequency of positive nodes in the group of axillary dissection. In the dissection group, 38.6% positive nodes were found, whereas only 15% of the patients with untreated axilla developed local axillary recurrence. These results suggested that axillary tumor burden does not alter outcome and that axillary metastases do not progress or metastasize in every case. Because of several pitfalls in the protocol and performance of the study, it was open to criticism. Most patients randomized in the simple mastectomy group had partial axillary dissection, and the estimated number of patients in the axillary dissection group is still too small to draw any conclusions about it [23].

Table 3 Failure rate of untreated axilla, depending on tumor size [25]

Tumor size	Number of patients	Axillary failure (*n*)	Axillary failure (%)
<10 mm	32	3	9
10–20 mm	53	14	26
>20 mm	18	6	33
Total	103	23	22

Previous studies demonstrated a significantly lower survival for patients with unintentionally ineffective treatment of the axilla [24]. In other studies, several authors demonstrated prolonged survival and lower recurrence rates in patients treated with axillary dissection as compared to those undergoing only irradiation or no primary therapy of the axilla (Table 2). However, in all of these studies, the influence of adjuvant drug therapy on the effect of the local treatment remains undetermined, because patients received systemic therapy inconsistently. It is a general problem of recent studies that systemic adjuvant therapy confuses the influence of local treatment on overall survival and local recurrence.

Local control of early cancer

A formal axillary dissection undoubtedly provides effective local control in early and advanced breast cancer. For both, however, the indication is currently under discussion, and alternative treatments are currently being evaluated.

The failure rate of clinically node-negative, untreated axillary nodes depends only on tumor size (Table 3). No other feature of the primary tumor (histologic/nuclear grade, receptor status, etc.) showed a statistically significant correlation [25]. Even tumors up to a size of 1 cm were characterized by an axillary failure rate of 9% if

Table 4 Failure rate after axillary dissection in stage-I and -II breast-cancer patients. No additional systemic or local treatment of the axilla was given in any study. *Pathology LN+* lymph-node positive according to pathologic staging; *Pathology LN–* lymph-node negative according to pathologic staging; *n.a.* not applicable

Reference	Number of patients	Follow-up (months)	Type of surgery	Pathology LN+ patients (%)	Pathology LN– patients (%)	Failure rate (%)
[24]	204	60	Dissection	n.a.	n.a.	~5
[22]	654	120	Dissection	39	61	1.2
[8] (Group 1)			Dissection	All	0	3
			Sampling	All	0	12
[8] (Group 2)			Dissection	0	All	3
			Sampling	0	All	8
[14][a]	259	27	Dissection	38	62	0.08

[a] Radiation of the breast for all patients

Table 5 Failure rate after irradiation of the axilla without dissection. *LN+* lymph-node positive; *LN–* lymph-node negative

Reference	Number of patients	Follow-up (months)	Radiation dose (Gy)	Clinically – LN	Clinically LN+
[22]	646	120	50 (LN–); 60 (LN+)	3 (11/352)	12 (24/294)
[58]	263	120	50	1 (3/211)	29 (15/52)
[50]	370	73	44–55	1 (3/335)	3 (1/35)
[32]	48	48	45 (tangential)	2(1/48)	None
[59][a]	92	50	45 (tangential)	0 (0/92)	None

[a] Patients received adjuvant tamoxifen therapy

untreated [25], indicating that, even in small tumors, the axillary status should be evaluated and a subsequent treatment performed. Recent studies gave rise to the assumption that there are different subgroups of patients, with T1 tumors differing significantly in the rate of metastasis. Lymph or vascular invasion seem to be the most important predictors of metastasis, showing axillary involvement in up to 49% of the patients and, thus, indicating that the group of Tl tumors is a heterogeneous entity [26]. Perhaps further evaluation can separate a subgroup of patients with T1 tumors that could be spared further diagnostic or therapeutic procedures.

After systematic axillary dissection, including levels I and II, the failure rate is, in general, low (2–3%) regardless of the nodal status. Even in node-positive patients, the number of involved lymph nodes is not a predictive factor for local recurrence [27]. In contrast, the failure rate depends on the length of the follow-up, the tumor size and the type of the surgical procedure. Significant differences, with regard to the axillary failure rate, have been found between axillary dissection and nodal sampling (Table 4). Additionally, significant cutpoints for the failure rate are described for the removal of 5, 10 and 15 lymph nodes [6, 7] in clinically node-negative patients. This indicates that removal of fewer nodes results in an erroneous classification of the nodal status, lack of adjuvant treatment and, therefore, later growth of remaining, untreated lymph-node metastases in misclassified positive axillas.

Effective irradiation without dissection of the axilla seems to be as effective as axillary dissection in clinically node-negative patients but is associated with higher rates of recurrence in clinically node-positive patients (Table 5). This means that, for clinically node-negative patients with small tumor size, irradiation of the axilla seems to be a reasonable alternative treatment for local control if the axillary status is not necessary for the adjustment of adjuvant therapy. Patients who are clinically node positive should undergo axillary dissection for optimal local control.

Local control of advanced cancer

About 10 years ago, preoperative chemotherapy was introduced for patients with stage-III or -IV cancer [28, 29, 30]. The appropriate therapy after post-therapeutic restaging, however, remains to be determined. According to recent results, the indication for a surgical intervention after induction therapy is residual tumor tissue in the re-biopsy of the breast. Surgical therapy should include tumor resection and 14 axillary dissections, because simple mastectomy and axillary irradiation showed a high rate of axillary recurrence (11.8%) [28]. Recently, it has been stated that, for patients with negative re-biopsy, surgical therapy may be replaced by radiation therapy, an approach which resulted in a local recurrence rate of only 24% [28]. According to recent publications, there are three indications for axillary dissection in patients with stage-III to stage-IV breast cancer after induction therapy:

1. Patients with a positive re-biopsy of the breast
2. Patients with clinically positive axillary nodes, regardless of the breast biopsy
3. Patients in whom axillary lymph-node status determines eligibility for clinical trials

More randomized trials are needed to find the most appropriate therapy strategy for this group of patients.

Diagnostic evaluation of the nodal status

In accordance with changes in the general therapeutic concept of breast cancer, the diagnostic aspect of axillary dissection has become increasingly important.

Early cancer

The axillary nodal status is still the most important prognostic factor [31]. The distinction between a positive or negative axillary node status remains crucial for many of the currently applied therapeutic regimens. In addition, therapeutic consequences can be implicated not only by positive or negative axillary status, but also by the exact number of involved lymph nodes, which is shown to have a linear, inverse correlation to the disease-free 5-year survival rates [7, 11]. Modern therapeutic strategies take these findings into consideration by the adjustment of chemotherapy to the number of involved lymph nodes. Axillary lymph-node dissection (ALND) must provide a sufficient number of resected nodes in these patients. Most concepts require the evaluation of a minimum of ten nodes [4, 6, 32]

It has been shown that, in patients with intraductal carcinoma, the rate of axillary nodal metastases is lower than 0.08%; in some studies no positive nodes were found [33, 34]. Therefore, it is acceptable that a histologically unequivocal intraductal carcinoma without microinvasion does not require axillary dissection. In contrast, it also has been questioned whether the axillary status of low-risk patients with tumors smaller than 0.5–1 cm should be evaluated, because the number of positive nodes in such patients seems to be very small. However, according to several recent studies, even 5–8% of small tumors measuring 0.5 cm in diameter showed axillary metastases, as did 20% of tumors measuring 0.6–1.0 cm [35]. Additionally, it has been shown that even immunohistochemically proven “occult” micrometastases in otherwise node-negative patients had significant influence on survival [36], even if this correlation is still controversial. The conclusion is that, at present, this subgroup of patients should not undergo diagnostic or therapeutic strategies other than those conducted in patients with T1c or T2 tumors.

In general, however, the importance of the axillary nodal status for adjuvant therapy has decreased in the last years, since adjuvant therapy strategies are increasingly based on characteristics of the primary tumor, such as tumor size, receptor status or grading. Tumor size, for example, has partly replaced the nodal status as a guide for adjuvant therapy, mainly in patients with stage-I carcinoma. Several studies reported a survival benefit for all patients with tumors greater than 1 cm, regardless of nodal status, after systemic chemotherapy [37, 38]. Also, according to the International Consensus Panel of St. Gallen, patients with node-negative axillary status but belonging to the high-risk group (tumor >2 cm; grade-II or -III or ER-status negative) receive the same adjuvant therapy as patients with positive axillary status [39]. Taking these considerations into account, the impact of ALND on adjuvant therapy varies from 0% (stage I; age >60 years) to 17% of the patients (stage I; postmenopausal; age <60 years), depending on age, tumor size and menopausal status [40].

Advanced cancer

According to the current concept of preoperative induction therapy for advanced cancer [28, 30], surgical intervention is the second therapeutic step. Therefore, if a simple biopsy has proven advanced breast cancer histologically, no further dissection is needed to determine the exact nodal status. In contrast, measurable lymph-node conglomerates may be used as indicator lesions for the response to systemic therapy.

It has been questioned for some years now whether axillary dissection is necessary in all patients with invasive cancer. Many concepts have been investigated to avoid unnecessary morbidity and hospitalization of axillary dissection. For example, mathematical models using many different prognostic factors have been developed to select patients with node-negative axillas who don’t need axillary dissection [41, 42]. Currently, the most promising concept is the sentinel-node (SN) concept.

SN concept

The standard method for the evaluation of the axillary-node status, until recently, was systematic axillary dissection. However, in specialized centers that have passed the learning curve, there is increasing evidence that the SN concept can identify correctly the axillary-nodal status with an accuracy of about 95–100% [43, 44]. A SN can be identified in between 80% and 99% of patients with stage-I or -II carcinoma [43, 45, 46]. This means that, with regard to the high rate of node-negative patients with T11 tumors (70–75%) [26, 35], the morbidity of unnecessary ALND could possibly be avoided in about 60–75% of patients with early-stage carcinoma. As mentioned above, systemic therapy does not always depend on the nodal status. Thus, if the information “nodal positive” is sufficient for the next therapeutic step of a selected group of patients (for example, high-risk patients), these patients may be spared from axillary dissection.

Beyond this, it has been shown that about an additional 8% of occult metastases can be identified by immunohistochemical staining or genetic methods in otherwise negative lymph nodes [36]. These new detection methods can be applied, for technical reasons, only to a few nodes (like the SN), but not to all lymph nodes of a formal dissection. This suggests that, even with a failure rate of 5% incorrect SNs, the overall accuracy of the nodal status prediction may increase with this new method.

Until recently, the SN biopsy was followed regularly by a systematic limited axillary dissection (levels I and II) because the method was regarded as mostly experimental. An exception was made by Reuhl et al., who performed the SN technique several times without subsequent axillary dissection in patients with ductal carcinoma in situ (data not published). Due to high accuracy in the prediciton of axillary involvement for clinically node-negative patients with small tumors, the first prospective clinical trial for SN biopsy without subsequent axillary dissection in Europe has been initiated (for clinically node-negative patients with tumors up to 1 cm) by the group of Veronesi. However, if the exact number of involved lymph nodes is warranted for the choice of systemic treatment, a systematic ALND remains necessary.

Techniques of the SN biopsy

At the moment, the SN technique is usually applied if the tumor is palpable or can be marked exactly by a localization procedure. There are two substance classes for lymphatic mapping in general use today: radiolabeled colloids and vital dye (isosulfan blue).

Vital dye

Blue-dye injection is used by the group of Giuliano et al., one of the pioneers of the SN biopsy in breast cancer. Briefly, 3–5 ml isosulfan blue vital dye (Lymphazurin, Hirsch Industries, Richmond, Va.) is injected into the tumor and the parenchyma surrounding the tumor. If the tumor has already been resected (for example, to prove malignancy), the solution is injected into the wall of the tumor cavity. After 5 min, a transverse incision is made just below the hair-bearing region, and the blue-stained lymphatic tract or lymph node is identified by blunt dissection. The dye-filled tract is dissected to the first blue node, which is excised. If a node was identified before the dissection of the lymphatic tract, the tract may also be traced proximally to ensure that the excised node was the first colored node (i.e., the SN) [45].

Radiolabeled colloids

It is important to know that the size of the tracer colloid is crucial for the quality of the transport with the lymph flow and the length of time it is stored in the lymph nodes. It has been found that the size of the colloid shows an inverse correlation to the speed of its transport along the lymphatic channels and has a direct correlation to the duration of storage in a lymph node. There are several substances that have been used as tracer colloids. In the USA, the most used is ^{99m}Tc-sulfur colloid [44, 47] with an average particle size of about 10–50 nm. This agent shows a relatively fast movement from the tumor to the lymph nodes and a fast extraction out of the lymph node with the efferent flow due to its ability to pass through the vascular epithelial cell gaps. In Germany and Europe, heterogeneous solutions of albumin derivatives with a particle size ranging from 80 nm to 200 nm are widely used. They undergo phagocytosis by macrophages and show a long storage time in the lymph nodes; in contrast, the transport from the injection time to the lymph node is significantly longer. They require early injection but offer the possibility of several preoperative y-camera pictures for the determination of SN localization in advance and show a constant activity during the operative procedure.

After informed consent is given, 0.5–1 ml of the radionuclide is injected into the skin and the parenchyma surrounding the tumor 17 h before surgery. After 1 h and just before surgery, pictures are taken with the y-camera. If a SN can be demonstrated, it is localized intraoperatively with the y-probe and selectively excised using the incision of the tumor resection or a separate incision at the border of the major pectoral muscle or any other access to the axilla. If there are two or more nodes, we excise both or take out the one with the greatest activity.

Comparing the two techniques, the radionuclide technique needs more technical effort but is surgically easier to handle and less invasive, because the node can be localized using a y-probe without dissection of a lymphatic channel. Recently, a combination of the two methods was evaluated. First results showed a high predictive accuracy and high detection rates but some difficulties with the different kinetics of the marker substances [44]. The value of this technique remains to be evaluated. The development of the SN concept and its growing number of applications let us think about its application in other lymph-node groups that are difficult to evaluate – first of all, the internal mammary lymph nodes.

Internal mammary lymph nodes

Since the period of super-radical resections in the late 1940s and 1950s, the prognostic and therapeutic impact of internal mammary nodes (IMN) has been widely neglected.

Therapeutic dissection

It has been shown, in several studies, that extended radical mastectomy with dissection of the IMN did not improve long-term survival in large groups of patients, with tumors of all sizes [48, 49]. The treatment of local failure is not an indication, because parasternal recurrences in patients undergoing adjuvant therapy [cyclophosphamide–methotrexate–5-fluorouracil (CMF) in cases of axillary involvement and conventional breast irradiation after conservative surgery] occur in very few (about 0.11%) of the patients [50]. Due to the fact that only some patients with T1 tumors do not undergo adjuvant therapy, the overall risk of local relapse by IMN is low. If the rare case of a recurrence occurs, it can be sufficiently treated, for example, by radiation therapy [51]. Recent studies have re-evaluated routine tangential irradiation of the IMN in stage-I/II patients and did not find an increase in clinically important skin or pulmonary complications, but a long-term benefit of this treatment remains to be proven [52].

Prognostic significance

Involvement of IMN, however, is strongly related to axillary-node involvement, and its prognostic significance is the second most important factor for survival (after axillary-node status, and followed by tumor size). In patients with negative axillary nodes, IMN have the same prognostic significance as axillary nodes [53, 54].

Therefore, the information about the IMN status seems to be of great interest in axillary-node-negative patients. Cody et al. reported a rate of about 17–20% IMN-positive patients with negative axillary nodes, independent of the tumor size [54]; Veronesi et al. found an involvement in 6–16% of axillary-node-negative patients, depending on the size of the tumor and the patient's age [53].

Among patients without axillary involvement, the risk of recurrence or death at 10 years is twofold greater for IMN-positive patients if they receive no adjuvant therapy [54]. Thus, for a certain percentage of axillary-node-negative patients with small T1 tumors and positive IMN, who would not receive adjuvant therapy due to axillary status, tumor size or histologic features, the underestimation of the nodal status could lead to a failure to receive adjuvant therapy, resulting in a decrease of survival.

Nevertheless, no-one would claim the routine indication for a systematic parasternal dissection in axillary-node-negative T1 tumors. Thus, the problem of the evaluation of the INM status remained unresolved until now. Computed tomography/magnetic resonance imaging and lymph scintigraphy were not sufficiently reliable; newer methods such as positron-emission tomography scan remain to be evaluated. Even for this problem, a strikingly logical concept seems to be the SN biopsy. Reuhl et al. showed that SN biopsy is feasible [46], but the detection rate of a SN is, for unknown reasons, still lower than would be estimated. Further investigation of this subject must be undertaken.

Conclusions

Axillary dissection offers the most efficient local control in node-positive patients whereas, in primarily node-negative patients, irradiation seems to be equally effective. In general, lymph-node dissection does not alter overall survival, but surgical therapy undoubtedly makes a large contribution toward cure in early-breast-cancer patients and can be curative for patients with stage-I carcinoma. The lymph-node status of the axilla is still crucial for adjuvant therapy in early invasive breast cancer, but an increasing number of clinically node-negative patients could be managed with information based on features of the primary tumor, regardless of their nodal status.

The most promising new concept for the selection of node-positive patients, avoiding unnecessary morbidity of axillary dissection in early breast cancer patients, is the SN concept. The principle is based on the identification of the first "sentinel" lymph node reached by lymphatic flow from the tumor to the lymph-node stations. For identification, vital dye or a radioactive colloid is peritumorally injected and the first marked node resected and examined.

Internal mammary lymph nodes are rarely recognized in local failure but seem to have an underestimated prognostic significance in about 10–20% of axillary-node-negative patients. This may lead to the withholding of systemic therapy for patients with early breast cancer. Nevertheless, there is no indication for a routine parasternal dissection today. The SN concept may also support the selection of patients for diagnostic internal lymph-node biopsy and subsequent adjuvant therapy in cases with no axillary metastases but with internal lymph-node metastases.

References

1. O'Higgins N (1994) How I minimize morbidity in axillary dissection. Eur J Surg Oncol 20:80–81
2. Ball ABS, Waters R, Thomas M (1987) Formal axillary dissection. Br J Hosp Med 44:396–399
3. Riddell VH (1948) Radical mastectomy Br J Surg 36:108–129
4. Axelsson CK, Mouridsen HT, Zedeler K (1992) Axillary dissection of level-I and -II lymph nodes is important in breast cancer classification. Eur J Cancer 28:1415–1418
5. Cady B, Sears HF (1986) Usefulness and technique of axillary dissection in primary breast cancer. J Clin Oncol 4:623–624

6. Graversen HP, Blichert-Toft M, Andersen JA, Zedeler K (1988) Breast cancer: risk of axillary recurrence in nodal-negative patients following partial dissection of the axilla. Eur J Surg Oncol 14:407–412
7. Sosa JA, Diener-West M, Gusev Y, Choti MA, Lange JR, Dooley WC, Zeiger MA (1998) Association between extent of axillary lymph-node dissection and survival in patients with stage-I breast cancer. Ann Surg Oncol 5:140–149
8. Benson EA, Thorogood J (1986) The effect of surgical technique on local recurrence rates following mastectomy. Eur J Surg Oncol 12:267–271
9. Kissin M, Thompson E, Price A (1982) The inadequacy of axillary sampling in breast cancer. Lancet 1:1210–1212
10. Berg JW (1955) The significance of axillary node levels in the study of breast carcinoma. Cancer 8:776–778
11. Canavese G, Catturich A, Vecchio C, Tomei D, Gipponi M, Bruzzi B, Baddellino F (1998) Prognostic role of lymph-node level involvement in patients undergoing axillary dissection for breast cancer. Eur J Surg Oncol 24:104–109
12. Danforth DN, Findlay PA, McDonald HD, Lippman ME, Reichert CM, D'Angelo T, Gorrell CR, Gerber NL, Lichter AS, Rosenberg SA, De Moss ES (1986) Complete axillary dissection for stage I–II carcinoma of the breast. J Clin Oncol 4:655–662
13. Senofsky GM, Moffat FL, Davis K, Masri MM, Clark KC, Robinson DS, Sabates B, Ketcham (1991) Total axillary lymphadenectomy in the management. Arch Surg 126:1336–1342
14. Siegel BM, Mayzel KA, Love SM (1990) Level I and II dissection in the treatment of early-stage breast cancer. Arch Surg 125:1144–1447
15. Larson D, Weinstein M, Goldberg I, Silver B, Recht A, Cady B (1986) Edema of the arm as a function of the extent of axillary surgery in patients with stage I/II carcinoma of the breast treated with primary radiotherapy. Int J Radiat Oncol Biol Phys 12:1575–1582
16. Aitken DR, Minton JP (1983) Complications associated with mastectomy. Surg Clin North Am 63:1331–1352
17. Kissin MW, Della Rovere GQ, Easton D, Westbury G (1986) Risk of lymphoedema following the treatment of breast cancer. Br J Surg 73:580–584
18. Dahl-Iversen E, Tobiassen T (1969) Radical mastectomy with sternal and supraclavicular dissection for mammary carcinoma. Ann Surg 170:889–891
19. Wangensteen OH, Lewis F, Arelge SW (1956) The extended or supraradical mastectomy for carcinoma of the breast. Surg Clin North Am 36:728–734
20. Fisher B (1981) A commentary on the role of the surgeon in primary breast cancer. Breast Cancer Res Treat 1:17–26
21. Hellman S, Harris J (1987) The appropriate breast carcinoma paradigm. Cancer Res 2:339–342
22. Fisher B, Redmond C, Fisher ER, Bauer M, Wolmark N, Wickerham DL, Deutsch M, Montague E, Margolese R, Foster R (1985) Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 312:674–681
23. Harris JR, Osteen RT (1985) Patients with early breast cancer benefit from axillary treatment. Breast Cancer Res Treat 5:17–21
24. Langlands AO, Prescott RJ, Hamilton T (1980) A clinical trial in the management of operable cancer of the breast. Br J Surg 67:170–174
25. Baxter N, McCready D, Chapman JA, Fish E, Kahn H, Hanna W, Trudeau M, Lickley L (1996) Clinical behaviour of untreated axillary nodes after local treatment for primary breast cancer. Ann Surg Oncol 3:235–240
26. Barth A, Craig PH, Silverstein MJ (1997) Predictors of axillary lymph node metastases in patients with T1 breast carcinoma. Cancer 79:1918–1922
27. Fisher BJ, Perera FE, Cooke AL, Opeitum A, Venkatesan V, Dar AR, Stitt L (1997) Long-term follow-up of axillary node-positive breast cancer patients receiving adjuvant systemic therapy alone: patterns of recurrence. Int J Oncol Biol Phys 38:541–550
28. Danforth DN, Zujewski J, O'Shaughnessy J, Riseberg D, Steinberg SM, Atee N, Noone M, Chow C, Chaudhry U, Lippman M, Jacobson J, Okunieff P, Cowan KH (1998) Selection of local therapy after neoadjuvant chemotherapy in patients with stage IIIA, B breast cancer. Ann Surg Oncol 5:150–158
29. Hortobagyi GN, Blumenschein GR, Spanos W (1983) Multimodal treatment of locoregionally advanced breast cancer. Cancer 51:763
30. Machiavelli MR, Romero AO, Perez JE, Lacava JA, Dominguez ME, Rodriguez R, Barbieri MR, Acuna LA, Acuna JM, Langhi MJ, Amato S, Ortiz EH, Vallejo CT, Leone BA (1998) Prognostic significance of pathological response of primary tumor and metastatic axillary lymph nodes after neoadjuvant chemotherapy for locally advanced breast carcinoma. Cancer J Sci Am 4:125–131
31. Weidner N, Cady B, Goodson WH (1997) pathologic prognostic factors for patients with breast carcinoma. Surg Oncol Clin North Am 6:415–461
32. Cady B, Stone MD, Wayne J (1993) New therapeutic possibilities in primary invasive breast cancer. Ann Surg 218:338–349
33. Silverstein MJ, Waisman JR, Gamagami P (1990) Intraductal carcinoma of the breast (208 cases). Cancer 66:102–108
34. Parker RG, Berkbigler D, Rees K, Leung KW, Legorreta AP (1998) Axillary dissection in ductal carcinoma in situ. Am J Clin Oncol 21:109–110
35. Shetty MR, Reiman HM (1997) Tumor size and axillary metastases, a corralation ocurrence in 1244 cases of breast cancer between 1980 and 1995. Eur J Surg Oncol 23:139–141
36. International Breast Cancer Study Group (1990) Prognostic importance of occult axillary lymph node micrometastases from breast cancers. Lancet 335:1565–1568
37. National Institutes of Health Consensus Panel (1992) Consensus statement: treatment of early-stage breast cancer. J Natl Cancer Inst Monogr 11:1–5
38. Early Breast Cancer Trialists' Collaborative Group (1988) Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. N Engl J Med 319:1681–1692
39. Goldhirsch A, Wood WC, Senn HJ, Glick A, Gelber RD (1995) International Consensus Panel on the Treatment of Primary Breast Cancer. Eur J Cancer 31A:1754–1759
40. Dees EC, Shulman LN, Souba W, Smith BL (1997) Does information from axillary dissection change treatment in clinically node negative patients with breast cancer? Ann Surg 226:279–287

41. Kiricuta CI, Tausch J (1992) A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. Cancer 69:2496–2501
42. Ravdin PM, De Laurentiis M, Vendely T, Clark GM (1994) Prediction of axillary lymph node status in breast cancer patients by use of prognostic indicators. J Natl Cancer Inst 86:1771–1775
43. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, Costa A, De Cicco C, Geraghty JG, Luini A, Sachini V, Veronesi P (1997) Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph nodes. Lancet 349:1864–1867
44. Barnwell JM, Arredondo MA, Kollmorgen D, Gibbs JF, Lamonica D, Carson W, Zhang P, Winston J, Edge SB (1998) Sentinel-node biopsy in breast cancer. Ann Surg Oncol 5:126–130
45. Giuliano AE, Dale PS, Turner RR, Morton DL, Evans SW, Krasne DL (1995) Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg 222:394–401
46. Reum T, Kaisers H, Markwardt J, Haensch W, Hohenberger P, Schlag PM (1998) Axillaausrtiumung bei klinisch nodal-negativem Mammakarzinom. Dtsch Med Wochenschr 123:583–587
47. Krag DN, Weaver DL, Alex JC, Fairbank JT (1993) Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol 2:335–340
48. Lacour J, Le M, Caceres E, Koszarowski T, Veronesi U, Hill C (1983) Radical mastectomy versus radical mastectomy plus internal mammary dissection. Cancer 51:1941–1943
49. Veronesi U, Valagussa P (1981) Inefficacy of internal mammary nodes dissection in breast cancer surgery. Cancer 47:170–175
50. Recht A, Pierce SM, Abner A, Vicini F, Osteen RT, Love SM, Silver B, Harris JR (1991) Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol 9:988–996
51. Donegan WL, Spratt JS (1995) Surgical management. In: Donegan WL, Spratt JS (eds) Cancer of the breast, 4th edn. Saunders, Philadelphia, pp 443–504
52. Kaija H, Maunu P (1995) Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomized trial. Radiother Oncol 36:172–176
53. Veronesi U, Cascinelli N, Bufalino R (1983) Risk of internal mammary lymph-node metastases and its relevance on prognosis of breast cancer. Ann Surg 198:681–684
54. Cody HS III, Urban JA (1995) Internal mammary lymph node status – a major prognostic factor in axillary node negative breast cancer. Ann Surg Oncol 2:32–37
55. Gaglia P, Bussone R, Caldarola B, Lai M, Jayme A, Caldarola L (1987) The correlation between the spread of metastases by level in the axillary nodes and disease-free survival in breast cancer. A multifactorial analysis. Eur J Cancer Clin Oncol 23:849–854
56. Cancer Research Campaign Working Party (1980) Cancer research campaign (King's/Cambridge) trial for early breast cancer. Lancet 12:55–60
57. Cabanes PA, Salmon RJ, Vilcoq JR, Duaran JC, Fourquet A, Gautier C, Asselain B (1992) Value of axillary dissection in addition to lumpectomy and radiotherapy in early breast cancer. Lancet 339:1245–1248
58. Osborne MP, Ormiston N, Harmer CL, McKinna JA, Baker J, Greening P (1984) Breast conservation in the treatment of early breast cancer. Cancer 53:349–355
59. Wong JS, Recht A, Beard CJ, Busse PM, Cady B, Chaffey JT, Come S, Fam S, Kaelin C, Lingos TI, Nixon AJ, Shulman LN, Troyan S, Silver B, Harris JR (1997) Treatment outcome after tangential radiation therapy without axillary dissection in patients with early-stage breast cancer and clinically negative axillary nodes. Int J Radiat Oncol Biol Phys 39:915–920
60. Haffly BG, Ward B, Pathare P, Salem R, McKhann C, Beinfield M, Fischer D, Reiss M (1997) Reappraisal of the role of axillary lymph node dissection in the conservative treatment of breast cancer. J Clin Oncol 15:691–700
61. White RE, Vezeridis MP, Konstadoulakis M, Cole BF, Wanebo HJ (1996) Therapeutic options and results for the management of minimally invasive carcinoma of the breast: influence of axillary dissection for the treatment of T1a and T1b lesions. J Am Coll Surg 183:575–582