Sentinel Node Procedure for Breast Cancer: training, safety, reliability and follow-up aspects

Printed by:
Optima Grafische Communicatie, Rotterdam

Sentinel Node Procedure for Breast Cancer: training, safety, reliability and follow-up aspects

De schildwachtklier procedure voor borstkanker:
Training, veiligheid, betrouwbaarheid en follow-up.

Proefschrift

ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de

rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

donderdag 8 juni 2006 om 11.00 uur

door

Antoinette Yda de Kanter

geboren te Rotterdam

Promotiecommissie

Promotoren: Prof.dr. A.M.M. Eggermont

Prof.dr. T. Wiggers

Overige leden: Prof.dr. P.C. Levendag

Prof.dr. I.H.M. Borel Rinkes

Prof.dr. J.W. Oosterhuis

To Marcel,
Kiki, Huib
and my parents

Contents

Introduction

History

The sentinel node was first described by Cabanas in 1977 describing the first node draining the primary tumour in the regional lymphatic basin in penile cancer [1]. It took several years before Morton et al. described their experience in 1992 with Sentinel Lymph Node Biopsy (SLNB) in melanoma [2]. Giuliano et al. essentially transferred the same technique of lymphatic mapping to breast carcinoma and reported the extensive experience in the John Wayne Cancer Center in 1994 [3]. He described how isosulfan blue was injected in a peritumoral fashion for lymphatic mapping. Krag et al. and Meijer et al improved the procedure by introducing a radioactive tracer and a hand held probe to detect the radioactive lymph node [4,5]. Various studies have shown that histopathological examination of the sentinel node is reliable in predicting axillary lymph node status in breast cancer. Consequently this procedure can replace routine axillary lymphadenectomy when the sentinel node is found to be negative. This was demonstrated in a randomized trial by Veronesi et al. [6]. The interest in the sentinel node concept in breast cancer is enormous because 60% of all patients is found node-negative and axillary lymph node dissection is associated with significant morbidity (lymphoedema and neuropathy of the involved arm) [7].

Accuracy

Inspired by promising single institutional results we started a prospective study after the value of the sentinel node in operable clinically node negative breast cancer patients. Initially there were three participating hospitals: a university hospital, an oncology centre and a community hospital. The differences in organisation of the surgery department between these hospitals allowed us to compare results and make some recommendations for implementation outside academic centres (**chapter 1**).

Ultrasound of the axilla in combination with fine needle cytology

The sentinel node procedure can prevent an unnecessary full lymph node dissection, but is for patients with a positive sentinel node an additional surgical procedure, identifying the need for a full lymph node dissection. We developed an interest for non-invasive methods that can detect positive lymph nodes to reduce the need for sentinel node biopsy. Because of promising results that we had demonstrated for ultrasound guided fine needle aspiration cytology (US-FNAC) of the clinically node-negative breast cancer patient [8], US-FNAC of the axilla had been introduced in our clinic as part of the pre-operative screening of clinically node negative breast cancer patients. In case of a positive cytology sentinel node biopsy was omitted. In **chapter 2** the results of this selection tool will be discussed. **Chapter 3** will discuss the single institution results of a validation study.

Micrometastases

In order to minimize the number of false-negative sentinel nodes, the pathologist examines the sentinel node more thoroughly than the large number of lymph nodes in a full lymph node dissection. With the examination of several levels and the use of immune histochemical staining even the smallest metastases are identified. The necessity of a full axillary lymph node dissection in case of diagnosing only a few metastatic cells in the sentinel node is questionable and evaluated in **chapter 4**.

Failure

Despite the pre-operative selection tool with ultrasound in combination with fine needle cytology and standardization of the procedure false negativity of the sentinel node occurred. The search for causes of failure was initiated. Most causes were found to be inherent to the implementation of a new procedure. In **chapter 5** the phenomenon that extranodal growth and/or extensive nodal involvement can block radioactive tracer and patent blue to reach the true sentinel node as a cause of false negativity of the sentinel node is discussed.

Safety

A point of concern was the safety of the procedure. The tracing of the sentinel node occurred with the help of a radioactive tracer and a blue dye. The government legislation concerning working with radioactive material is very strict and was hampering the implementation of the procedure in hospitals without a nuclear department. The exposure to radiation was investigated for those involved in the procedure in this study is reported in **chapter 6**.

Internal mammary chain hot-spots

A point of interest is the meaning of hot-spots of the internal mammary chain (IMC) on lymphoscintigraphy. Is this an indication for excision of such an IMC-sentinel node? [9] Despite several studies, up until now there is no national consensus about the clinical management. In **chapter 7** our long term follow-up results of our patients are described. These results could be of help to solve this question.

Follow-up of sentinel node negative patients and futility of ultrasound

An other follow-up question is the incidence of axillary lymph node recurrences in SN-negative patients [10]. After our validation study and other national studies the sentinel node procedure was implemented in the Netherlands as a safe procedure with an acceptable false negative rate. The implementation was started without knowing the late effects, so an important question during follow-up is the incidence of axillary recurrences and their influence on overall survival. In **chapter 8** the 5-year follow-up results of sentinel node patients, treated without a full axillary lymph node dissection is discussed. We also evaluated the results of ultrasound of the axilla in the follow-up in order to detect recurrences before the patient.

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CHAPTER 1

Controlled introduction of the sentinel node biopsy in breast cancer in a multi-centre setting: the role of a coordinator for quality control.

A.Y. de Kanter, A.N. van Geel, M.A. Paul, C.H.J. van Eijck, S.C. Henzen-Logmans, R.H. Kruyt, E.P. Krenning, A.M.M. Eggermont, T. Wiggers

European Journal of Surgical Oncology 2000; 26: 652-656

Controlled introduction of the sentinel node biopsy in breast cancer in a multi-centre setting: the role of a coordinator for quality control

A. Y. de Kanter*, A. N. van Geel*, M. A. Paul†, C. H. J. van Eijck‡, S. C. Henzen-Logmans¶, R. H. Kruyt‖, E. P. Krenning§, A. M. M. Eggermont* and T. Wiggers*

*Departments of *Surgery, ¶Pathology and ‖Radiology, University Hospital Rotterdam/Daniel den Hoed Cancer Center, †Department of Surgery, Zuiderziekenhuis Rotterdam and Department of ‡Surgery and §Department of Nuclear Medicine, University Hospital Rotterdam/Dijkzigt Hospital, The Netherlands*

Aims: It is proposed that sentinel node biopsy should replace axillary lymph-node dissection. We analysed the role of a coordinator in the introduction of the sentinel node biopsy in breast cancer in a multi-centre setting to assure standardization and quality control.

Methods: We included 232 operable breast cancer patients. Part of the procedure was an ultrasound examination of the axilla with fine needle aspiration cytology. The sentinel node was identified with 99m-Technetium and Patent Blue.

Results: The results of the procedure, sensitivity and false negativity, were the same for the three participating hospitals. We think this is mostly due to the coordinator who supplied information about the technique, pitfalls and results to all teams.

Conclusions: Our experience regarding the organization aspects of introducing the sentinel node procedure in a multi-centre setting now serves as a model in organizing its application in a much wider number of hospitals.

Key words: **sentinel node; learning curve; quality control.**

Introduction

Axillary lymph node dissection (ALND) is still part of the standard treatment of breast cancer patients for staging purposes. There is no evidence that ALND improves local tumour control in patients without lymph-node metastases. ALND has many complications; lymphedema, hypesthesia, stiffness, pain and weakness of the shoulder.[1,2] Since SN biopsy has proven to be a reliable predictor of the axillary lymph-node status it is proposed that SN biopsy should replace ALND.

Potential replacement of ALND by imaging techniques such as computer tomography, ultrasound, SPECT and positron emission tomography has been evaluated in a number of studies, but as yet none of these methods is accurate enough to replace ALND, which at this time remains the gold standard.[3–8]

Sentinel node biopsy is a procedure that could replace ALND if sensitivity is as accurate as in an ALND. The SN hypothesis was firstly described by Cabanas and further developed by Morton and others.[9–15] Results seem promising. However, the introduction of the sentinel node as a standard procedure is still under discussion.[16] Before the introduction the following requirements should be met: consensus about an acceptable false-negative rate, analysis of causes of false-negative sentinel nodes, a definition of the role of lymphoscintigraphy and optimization and standardization of all aspects of the procedure. Concern regarding this new technique and its general use in surgical practice has been expressed because in most studies on sensitivity and accuracy the SN procedure has been performed in a single institution by only one or two surgeons.

We studied the sensitivity and accuracy of the SN procedure in a multi-centre setting. Special attention was paid to difficulties in implementation. A study coordinator was responsible for the quality of the procedure in all three participating hospitals. In the first period the coordinator was responsible for the design of the protocol, instruction of all involved individuals, and for organizing the interaction between the departments of Nuclear Medicine, Surgery and Pathology. During the second period we analysed the failures followed by apposition (if necessary) and continuation of quality control of the procedure.

Correspondence to: A. Y. de Kanter, C/O Department of Surgical Oncology, University Hospital Rotterdam/Daniel, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands. Tel: +31-10-4391506.

The participating hospitals were: a university hospital in which every 3 months a new resident performed the procedure under the guidance of one surgical oncologist (A), a cancer centre with five surgical oncologists performing the SN procedure (B) and a general teaching hospital with one experienced surgeon responsible for the SN procedure (CC).

We report here on the results obtained in this setting and the role of the coordinator in standardizing procedures in the different hospitals and assuring quality control.

Role of the coordinator

The role of the coordinator was two-fold; firstly the supervision of the implementation of the procedure, and secondly to refine the procedure upon the collected data. We started with a procedure based upon data in the literature. The sentinel node tracing-technique was mainly self-made and refined by visiting one of the few sentinel node performing hospitals.

Eligibility of all patients with proven breast cancer was checked by the study coordinator. Informed consent about the sentinel node procedure was obtained by the surgeon and, if necessary, the coordinator was asked to explain more about the procedure to the patient.

All nuclear departments were instructed to use the same dose radioactive tracer and material. If possible the coordinator injected the 99m-Technetium-nanocolloid herself and while injecting instructed others how to determine the injection sites and possible pitfalls. To create a standard procedure we performed a 1-day procedure if possible. For a 1-day procedure the intervals between injection and lymphoscintigraphy were 2 hours, and between lymphoscintigraphy and operation less than 6 hours.

All lymphoscintigraphy scans were performed in the same position. All scans were reviewed by the coordinator and explained by the surgeons. If there was a mark on the patient's skin there was an explanation written regarding which node was marked and which scanning direction was used.

If possible the coordinator was present at each procedure. All surgeons were instructed to inject the blue dye in the same dose and place with regard to the tumour and to use the same approach. This approach was developed in the first few weeks of the study and during regular meetings problems were solved and standardized.

Information about the technique and pitfalls/results were continuously supplied to all teams by the coordinator. Another important task of the coordinator was to instruct the surgeon how to use the probe, in particular the direction of scanning was a pitfall (in one line towards the sites of injection). The operation theatre personnel were instructed about the essential functions of the probe and how to handle it. Uneasiness about the radioactivity of the breast, sentinel node and swabs was reduced in cooperation with the division of radiation protection.

After the instruction and teaching period the coordinator was in charge of controlling the quality of the procedure.

Patients and methods

From December 1996 till November 1998, 241 consecutive patients with operable breast cancer visited one of the three participating hospitals. The study population consisted of 240 women and one man. The diagnosis of the primary tumour was established with mammography, palpation and cytology. In case of strong clinical suspicion of malignancy, a diagnostic and therapeutic lumpectomy was performed before SN biopsy ($n=71$). No frozen sections of the lumpectomy were performed because of proper pathological diagnosis and to avoid SN/ALND in DCIS patients.

Patients with palpable nodes, necessity for neoadjuvant chemotherapy or multifocal tumours were excluded ($n=9$). The remaining 232 patients were included. Part of the sentinel node procedure was an ultrasound of the axilla with fine needle aspiration cytology (FNAC). If cytology showed tumour cells, these patients were scheduled for ALND. If cytology was negative, patients were scheduled for SN biopsy. Informed consent for the sentinel node biopsy was obtained from all. Identification of the SN was performed with 30–40 MBq 99m-Technetium nano-colloid (Solconanocoll®) injected subcutaneously and peritumorally at least two and a half hours before operation. In cases of a preceding lumpectomy the radioactivity was injected cranially of the scar in healthy breast tissue. If the operation was planned for the next day the amount of tracer was doubled ($n=12$). Two hours post-injection a lymphoscintigraphy was made in anterior, anterior–oblique and lateral views. For logistic reasons no scan was made in 23 patients. Visible nodes were traced with a cobalt stick and marked on the patients' skin with a felt pen. At the beginning of the operation 0.5 ml Patent Blue was injected intradermally above the tumour, or in cases of a preceding lumpectomy cranially of the scar. Subsequently the SN was identified with guidance of a RMD-CTC4 or C-trac probe and the blue-stained lymph vessel. For the first 10 patients in the study the sentinel node was traced in the specimen after resection of the axillary lymph nodes. Later on we identified and removed the sentinel node first before a complete ALND was performed. All axillary specimens were processed for histological examination using haematoxylin and eosin (H&E) staining. The SN(s) were examined with multiple sections (four to eight) and immunohistochemical staining (IHC) using cytokeratine antibody (CAM 5.2) in order to improve the detection of (micro) metastases.

Results

We enrolled 232 patients in this study, 63 in the university hospital, 107 in the cancer centre and 62 in the municipal hospital. Table 1 shows the characteristics of the procedure. Ultrasound examination and FNAC diagnosed metastases in 33 patients (16% of all breast cancer patients examined with U.S., 35% of all node positive patients).

In 69% the tumour in the breast was discovered by physical examination. The localization of the tumour in the lateral quadrant was about 50%. The surgery performed was modified radical mastectomy (40%), modified radical mastectomy after diagnostic lumpectomy (17%), lumpectomy and ALND (29%), or ALND alone after diagnostic lumpectomy (14%). In 88% of the patients the operation was on the same day as the injection of the

Table 1. Characteristics of the SN procedure

	University	Cancer centre	General	Total
No. of surgeons	6	5	1	12
No. of patients	63	107	62	232
Positive FNAB primary tumour	10	17	6	33
% after lumpectomy	19%	36%	32%	31%
% 1 day procedure	87%	97%	79%	89%
Probe	RMD	RMD	C-trac	
Amount of radioactivity	40 MBq	30 MBq	30 MBq	

Table 2. Characteristics of the patients

	University	Cancer centre	General	Total
%SN positive scan	100%	85%	89%	89%
No. of parasternal SNs	6	5	3	14
% ≥1 identified SN	92.5%	91.6%	95.2%	92.5%
% ≥1 SN with lump	95%	94%	100%	96%
Mean no. of SNs	1.6	1.3	1.5	1.5
% N^+ T1a+b:T1c:T2:T3	22%:29%:57%:100%	22%:30%:58%:100%	22%:38%:53%:100%	22%:31%:56%:100%
No. of false negative SNs	2	2	1	5

radioactive tracer. The mean time between injection and operation was 4.5 hours (1.5–7). In the patients who underwent surgery the next day the mean time between injection and operation was 19 hours (15–26).

Table 2 summarizes the characteristics of the patients treated in the participating hospitals. In this table the heterogeneity of the patient groups and hospitals is indicated.

Lymphoscintigraphy identified one or more hot spots in the axilla in 89% of patients, and in 14 patients there was a hot-spot parasternally besides axillary activity. We tried to localize and remove this hot spot in two patients; in one patient this procedure was associated with bleeding. In the other 12 patients no attempt was made to remove the parasternal nodes.

In 15 patients no SN could be identified either by radioactive tracer or by blue dye. In 10 of these patients a diagnostic lumpectomy was performed a few weeks before SN biopsy. These 15 patients were distributed equally among the three hospitals and 14 (including all 10 patients with preceding lumpectomy) occurred in the first year of the study. After more careful palpation of the lumpectomy cavity and placing the radioactive depots 1–1.5 cm outside this area in normal breast tissue there was no difference in identification rate between patients after lumpectomy or with tumour *in situ.* However, in most patients with a preceding lumpectomy no metastases were found on histological examination, so there is no absolute assurance that the correct SN was identified and removed. The average number of retrieved lymph nodes was 14.6 (5–37). The mean number of sentinel nodes was 1.5 (0–3). In Fig. 1 the traceability of the SN is shown calculated as the results of the last 25 patients. The first 10 patients of the study were left out because the SN was detected in the ALND specimen outside the patient. There was a learning curve of less than 50 patients in our study.

The identified SN, traced with both methods, was

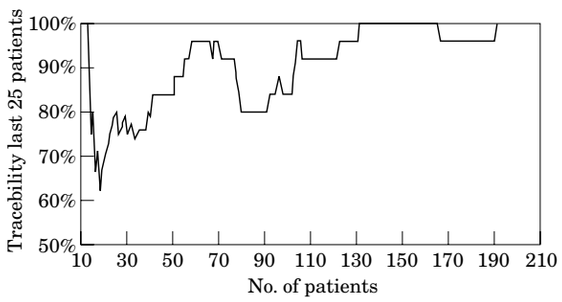

Fig. 1. The learning curve of the sentinel node. The detection rate calculated over the preceding 25 patients.

All patients	PA+	PA−
SN+	93	0
SN−	5	119

University	PA+	PA−
SN+	28	0
SN−	2	30

Cancer centre	PA+	PA−
SN+	39	0
SN−	2	57

General	PA+	PA−
SN+	26	0
SN−	1	32

	All patients	University	Cancer centre	General
Sensitivity	95%	93.3%	95.1%	96.3%
Specificity	100%	100%	100%	100%
PPV	100%	100%	100%	100%
NPV	95.9%	93.8%	96.7%	97.0%
Accuracy	97.7%	96.7%	97.1 %	98.3%

Fig. 2. Pathological and statistical results.

radioactive and blue in 77%, only radioactive in 18% and only blue in 4%. In one patient the SN, blue only, was found to be falsely negative. Histological examination of the SN with multiple sections and H&E staining identified metastases in 52 patients. IHC found a (micro)metastasis in an additional eight patients. The SN was negative in 124 patients, but in five of them a metastasis was found in one of the non-sentinel LN. In 32 patients the SN was the only positive node.

The sensitivity of the procedure (ultrasound and sentinel node) defined as the percentage of a correct prediction of the axilla in node positive patients is 95%, with an accuracy of 97.7%. For the participating hospitals A, B and C the sensitivity is 93.3%, 95.1% and 96.7%, respectively (Fig. 2).

Discussion

Recently, considerations were discussed as to whether or not the sentinel node should be introduced as the standard treatment; it was concluded that the time is not yet ready.[16]

The first argument is that a SN biopsy must be proved to be as accurate as full ALND or it must be decided that a less accurate staging procedure will be acceptable because of its low morbidity. These arguments can be met if losses and gains of the new procedure can be calculated. Serial sectioning and immunohistochemical staining will increase the number of positive lymph nodes[17–19] and false-negative outcomes will reduce the profit. Comparison of the two numbers will show the overall loss or gain of the procedure. In our study the additional profit of the multiple sectioning is not known but the IHC reveals metastases in an additional 7%, the loss is 5% so there is an overall profit of at least 2%.

In the Netherlands a multi-disciplinary group consisting of surgeons, pathologists and nuclear medicine specialists was installed to coordinate the introduction of the SN procedure in the Netherlands.[20] It was suggested that a false-negative rate of 5% is acceptable provided that the profit of multiple sectioning and IHC will exceed this rate. The 5% false-negative rate results in the following calculation; 95% positive predictive value, the sentinel node in 19 of 20 patients with lymph node metastases predicts the axillary status correct. A metastases rate of 40% combined with a positive predictive value of 95% results in (at least) 50 SN 'double' procedures (a combined procedure of both the SN procedure and a full ALND).

A suggestion was made to determine such an acceptable percentage for every T-subgroup. To do so, very large subgroups are needed, especially in T1a and b, because the rate of lymph-node positive patients is low. The T1a and b patients are exactly those who would benefit from a correct staging of the axilla, the false-negative rate should be as low as possible. However, one false-negative rate for all patients is reported in all studies. Another problem is that the pT is not 100% in concordance with the cT.

An important point is the lack of a standard procedure. No two reported studies used the same method, dose and type of colloid or dye. This is mainly due to the availability of the material and the preference of the study group. We used the same type and dose of the radiocolloid in the participating hospitals but there was still a difference in detection rate of the sentinel node. When a hospital starts performing the SN procedure they have to follow a standard protocol but gradually they may have to adjust the procedure in order to develop the optimal procedure for that particular hospital. In our study we adjusted the concentration of the colloid in the radioactive solution, we started to inject the blue dye intracutaneously after disappointing results of the peritumoral injection and, in cases of a preceding lumpectomy, we only injected cranially to the scar because of failure of the caudal injections. With these corrections the results became excellent.

Can this procedure be extended to other hospitals? A few surgeons with extensive experience performed most of the procedures. In case of introduction of the SN biopsy as a standard procedure the biopsy will also be performed by inexperienced surgeons. The greatest concern is quality control during and after the learning period. As mentioned earlier, one person who observed almost every SN biopsy and reported experiences and pitfalls of surgeons coordinated our study, and we think this greatly influenced the results. However, this influence can not be calculated precisely. In our region the introduction of the SN procedure will be centrally coordinated as recommended by the aforementioned study group. Our experience regarding the organizational aspects of introducing the sentinel node procedure in a multi-centre setting now serves as a model to organize its application in a much wider number of hospitals. In the first period of introduction there will be one coordinator visiting all regional hospitals (23 hospitals, 1200 patients with breast cancer yearly) and develop the optimal procedure for each hospital. After that period there will be meetings analysing reasons to learn from mistakes made. Because there are no studies with a follow-up of 5 or more years of the node-negative patients treated with a SN biopsy, we will also regionally register all patients undergoing an SN biopsy. After the learning curve the breast cancer patients will be treated with removal of the tumour and a sentinel node biopsy. The axilla of SN negative patients will be examined by an ultrasound once a year in order to control the axillary lymph nodes left behind. With this examination we hope to maintain the present high level of local control.

After many publications regarding the value of the sentinel node procedure in breast cancer patients, all with positive results, we conclude that there is no doubt about the SN concept for breast cancer; the SN is as accurate as a staging procedure as a complete ALND. Based on our experience we recommend a double procedure (SN + ALND) during the learning curve of 50 patients. If the above standard of less than 5% false-negative results is met, a hospital can proceed with SN biopsy only, provided that there is a central registration point and adequate follow-up. Regular ultrasound of the axilla during follow-up is recommended.[21]

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Accepted for publication 19 May 2000

CHAPTER 2

Multicentre study of ultrasonographically guided axillary node biopsy in patients with breast cancer.

A.Y. de Kanter, C.H.J. van Eijck, A.N. van Geel, R.H. Kruyt, S.C. Henzen-Logmans, M.A. Paul, A.M.M. Eggermont, T. Wiggers

British Journal of Surgery 1999, 86, 1459-1462

Multicentre study of ultrasonographically guided axillary node biopsy in patients with breast cancer

A. Y. de Kanter, C. H. J. van Eijck‡, A. N. van Geel, R. H. Kruijt*, S. C. Henzen†, M. A. Paul§, A. M. M. Eggermont and T. Wiggers

Departments of Surgery, *Radiology and †Pathology, University Hospital Rotterdam/Daniel den Hoed Cancer Center, ‡Department of Surgery, University Hospital Rotterdam/Dijkzigt Hospital and §Department of Surgery, Zuiderziekenhuis Rotterdam, Rotterdam, The Netherlands
Correspondence to: Dr T. Wiggers, Department of Surgery, University Hospital Rotterdam/Daniel den Hoed Cancer Center, PO Box 5201, 3008 AE Rotterdam, The Netherlands

Background: **Axillary lymph node dissection is still performed as a staging procedure since lymph node status is the most important prognostic factor in patients with breast cancer. Sentinel node biopsy may replace routine axillary lymphadenectomy, especially in patients with small breast cancers. This study investigated whether ultrasonographically guided fine-needle aspiration cytology (FNAC) of the axillary lymph nodes in clinically node-negative patients was an accurate staging procedure to select patients for sentinel node biopsy.**

Methods: **One hundred and eighty-five consecutive patients were included. All had axillary ultrasonography and detected nodes were categorized according to their dimensions and echo patterns. Ultrasonographically guided FNAC was carried out if technically possible. These results were compared with the results of the sentinel node biopsy and subsequent axillary dissection.**

Results: **In 116 patients no lymph nodes were detected by ultrasonographic imaging. Of 69 patients with visible nodes, 31 had malignant cells on FNAC. There were no false-positive results. Some 87 of 185 patients had axillary metastases on definitive histological examination. Ultrasonography was sensitive in patients with extensive nodal involvement. Failure of the examination was caused by problems learning the method, difficulty in puncturing small lymph nodes and sampling error.**

Conclusion: **In patients without palpable axillary nodes, a sentinel node biopsy could be avoided in 17 per cent since ultrasonography combined with FNAC had already diagnosed axillary metastases. The method is particularly valuable in larger breast cancers.**

Paper accepted 7 June 1999 British Journal of Surgery 1999, **86**, 1459–1462

Introduction

The treatment of operable breast cancer consists of radical excision of the tumour or mastectomy combined with complete axillary lymph node dissection. Axillary node status remains the most important prognostic factor in breast cancer. Complete axillary clearance provides the most accurate information about node status but is mostly considered a diagnostic intervention[1–3]. However, it has a significant associated morbidity including lymphoedema, pain, stiffness and weakness of the shoulder[4,5]. In breast cancer it has been demonstrated that a negative sentinel node (the first lymph node draining the primary tumour) indicates that there is no spread to any of the axillary lymph nodes[6–9]. Full axillary lymph node dissection is redundant as a staging procedure for patients with a negative sentinel node.

The disadvantages of sentinel node biopsy are that it is time consuming, the sentinel node cannot always be found (especially in patients with extensive lymph node metastases), there are occasional false-negative results, radioisotopes are needed and frozen-section histological analysis is required. It would be valuable if sentinel node biopsy could be replaced by easier methods.

Bonnema *et al.*[10] evaluated the accuracy of ultrasonography alone and in combination with cytology for detection of axillary metastases in patients with breast cancer and non-palpable lymph nodes. Lymph node metastases were detected by preoperative ultrasonography in combination with cytology in 26 per cent of patients (63 per cent of all node-positive patients).

Because of these results and because it is less invasive and unpleasant for the patient, ultrasonographically guided

axillary cytology has been included in the present multicentre sentinel node study. The aim was to determine the sensitivity and specificity of sentinel node biopsy in patients thought to have negative axillary nodes following ultrasonographically guided aspiration cytology. A multicentre study was undertaken to increase recruitment.

Patients and methods

From December 1996 to July 1998, 185 consecutive patients with a clinically axillary node-negative, operable breast carcinoma were treated in the participating hospitals, Zuiderziekenhuis Rotterdam, University Hospital Rotterdam locations Dijkzigt Hospital and Daniel den Hoed Cancer Centre. Mean age of the patients was 54 (range 24–87) years. The pathological size of the breast tumours was less than 10 mm ($T_{1a,b}$) in 36 patients, 11–20 mm (T_{1c}) in 52 patients, 20–50 mm (T_2) in 87 patients and greater than 50 mm (T_3) in ten patients. The location of the tumour was in the lateral upper quadrant in half of the women. Histological examination showed that the tumour was invasive ductal carcinoma in 71 per cent, invasive lobular carcinoma in 17 per cent and other types of invasive breast cancer in 12 per cent. Informed consent was obtained from all patients.

Ultrasonographic evaluation of the axilla was done with an Acuson XP128 (Acuson; Mountain View, California, USA) or Siemens Elegra (Siemens, The Hague, The Netherlands) machine using a 7–10 MHz linear array transducer. The length and width of any identified nodes were measured and the echo pattern was classified as inhomogeneous, homogeneous or node with an echo-rich centre. The first two classifications were considered malignant and the last benign.

If technically possible, ultrasonographically guided aspiration cytology was performed with a 21-G needle. Where two or more nodes were visible in the axilla, only the largest or most suspicious were aspirated up to a maximum of two. The aspiration biopsies were examined after standard Giemsa and Papanicolaou staining. Cytology was classified as benign, malignant or not possible to evaluate. Malignant cytology was based on clusters of epithelial cells with nuclear enlargement, prominent nucleoli and nuclear irregularity.

Patients with cytologically malignant cells in the axillary nodes were spared sentinel node biopsy. In the remainder, identification of the sentinel node was done by peritumoural injection of 30–40 MBq ^{99m}Tc-radiolabelled nanocolloid at least 2·5 h before surgery and intradermal injection of 0·5 ml patent blue dye during operation. The sentinel node was identified with guidance of the RMD-CTC4 probe (Radiation Monitoring Devices, Watertown, Maine, USA) and the blue-stained lymph vessel.

Under general anaesthesia, sentinel node biopsy was performed before definitive surgery, preferably through the planned incision. After sentinel node biopsy a routine complete axillary lymph node dissection was performed. All axillary specimens were processed for histological examination using haematoxylin and eosin staining. The sentinel node was examined in multiple sections (between two and eight, depending on lymph node diameter) and by immunohistochemical staining with a monoclonal cytokeratin antibody against low molecular weight cytokeratin (CAM 5.2).

Results

In all 31 patients with positive cytology from axillary nodes detected by ultrasonographic imaging, subsequent histological examination of axillary clearance specimens confirmed the presence of lymph node metastases (there were no false-positive results). The other 154 patients had either no nodes detected ultrasonographically ($n = 116$) or negative cytology of detected nodes ($n = 38$). In 44 of these 154 patients, metastases were found in the sentinel node on histological analysis with standard haematoxylin and eosin staining. In eight patients a (micro)metastasis was detected using immunohistochemical staining. There were four patients with one or more metastatic nodes in the axillary clearance specimen despite a negative sentinel node (all in the first year).

The overall incidence of metastatic disease in the axilla was 87 (47 per cent) of 185. In 31 (36 per cent) of these 87 patients the lymph node metastases were detected by ultrasonography and cytology (17 per cent of all 185 patients with operable breast cancer). The sensitivity of ultrasonographic detection was low. There was no correlation between the site of the breast tumour and the ultrasonographic detection rate. The more axillary lymph nodes detected by ultrasonography the higher was the percentage of metastases (*Fig. 1*). This suggested that the greatest improvement in the detection of metastases could be obtained by trying to visualize lymph nodes.

Classification of nodes into inhomogeneous or homogeneous as suggesting malignancy seemed to be correct (*Fig. 2*). However, 30 per cent of nodes thought benign, as classified according to an echo-rich centre, were in fact malignant.

As expected, the incidence of lymph node involvement increased with increasing size of the primary breast tumour (*Fig. 3*). Also the rate of detection of lymph nodes by ultrasonography increased with increasing tumour size.

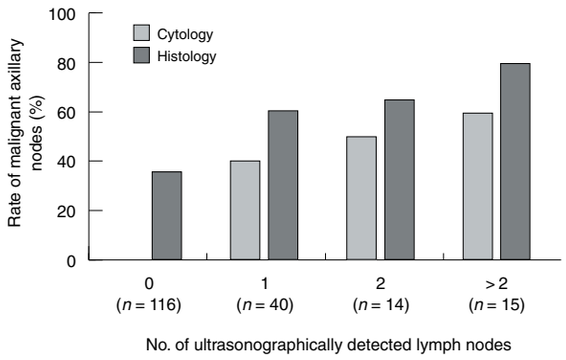

Fig. 1 Relation between the number of lymph nodes detected by ultrasonography and the rate of lymph node malignancy

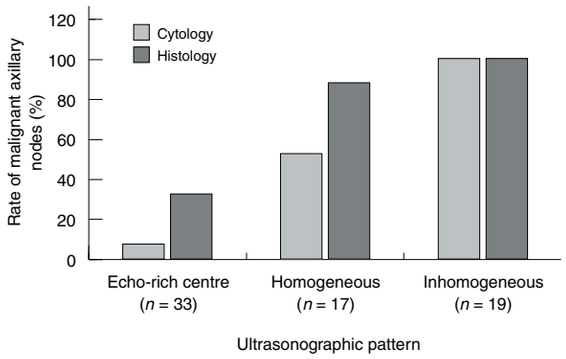

Fig. 2 Relation between ultrasonographic pattern and lymph node malignancy

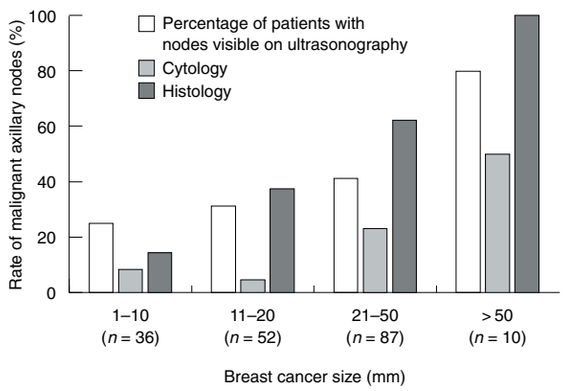

Fig. 3 Relation between tumour diameter and lymph node malignancy

At the start of the study the first hospital had no experience in examining the axilla but was experienced in examining lymph nodes in the neck. The second hospital had 5 years of experience in examining axillary lymph nodes, but after 2 months the most experienced radiologist left. The third hospital had no previous experience. After the initial 50 patients the first hospital had a detection rate of 45 per cent compared with 25 per cent for the second and third hospitals.

Discussion

Removal and histological examination of the axillary lymph nodes is standard for determining whether metastases are present. Besides its role in deciding upon adjuvant treatment, it also prevents axillary node recurrence. The reported incidence of axillary lymph node involvement in breast cancer varies between 30 and 50 per cent. Differences in the number of lymph nodes examined and the techniques of the pathologist account for this variation. If sentinel node biopsy replaced axillary dissection as a staging procedure this should make staging the axilla more accurate because examination of the sentinel node is standard, involving multiple sections and immunohistochemical staining.

The role of ultrasonography of the axilla in breast cancer has been evaluated by a number of investigators. The sensitivity and specificity for axillary involvement is in the range 56–73 per cent and 70–100 per cent, respectively[10–17]. Reports about ultrasonography in combination with cytology are rare[18]. In other tumours, combined ultrasonographic imaging and cytology is common, especially in head and neck cancer[19–21]. Bonnema *et al.*[10] introduced ultrasonography in combination with cytology for the detection of lymph node metastases in patients with breast cancer.

In one of the participating hospitals, ultrasonographically guided cytology of the axilla had been a standard examination for several years, with a sensitivity of 39 per cent and specificity of 100 per cent determined retrospectively. In the present multicentre study, the sensitivity of ultrasonographically guided cytology was 36 per cent. There are some suggestions that could improve the sensitivity of the this technique. First, the place where the sentinel node is most commonly located should carefully be palpated and examined by ultrasonography. This is just behind the pectoralis major muscle at the crossing of the cranial edge of breast tissue and the pectoralis major muscle. Second, cytological examination of a homogeneous or inhomogeneous node could be repeated if the first result is benign. Similarly, the cytological analysis should be repeated in smears with a non-evaluable result. Another advantage of ultrasonography is in the false-negative biopsies of the sentinel node procedure. The commonest cause of a false-

negative sentinel node procedure is extensive nodal involvement. If a node is replaced by tumour there is poor uptake of radioactivity. Ultrasonography and cytology is, however, particularly sensitive in patients with extensive axillary node involvement.

Whereas sentinel node biopsy may become standard treatment for patients with small (T_1) breast cancers, the incidence of lymph node metastases in bigger (T_{2-3}) tumours was 58 per cent in the present series. To reduce the number of sentinel node procedures, ultrasonographic examination with cytology is a useful selection procedure. With this examination 17 per cent of the patients will not need sentinel node biopsy since ultrasonographically guided cytology will already have detected metastases and complete axillary node dissection can be performed as a primary procedure.

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CHAPTER 3

Ultrasound-guided fine needle aspiration cytology of axillary lymph nodes in breast cancer patients. A preoperative staging procedure.

V. Kuenen-Boumeester, M.B.E. Menke-Pluymers, A.Y. de Kanter, I-M.A. Obdeijn, D. Urich, T.H. van der Kwast

European Journal of Cancer 2003, 39, 170-174

Ultrasound-guided fine needle aspiration cytology of axillary lymph nodes in breast cancer patients. A preoperative staging procedure

V. Kuenen-Boumeester[a,*], M. Menke-Pluymers[b], A.Y. de Kanter[b], I.-M.A. Obdeijn[c], D. Urich[c], T.H. Van Der Kwast[a]

[a]*Department of Pathology, Daniel den Hoed Cancer Center/ Erasmus Medical Center Rotterdam, PO Box 5201, 3008 AE Rotterdam, the Netherlands*
[b]*Department of Surgical Oncology, Daniel den Hoed Cancer Center/ Erasmus Medical Center Rotterdam, PO Box 5201, 3008 AE Rotterdam, the Netherlands*
[c]*Department of Radiology, Daniel den Hoed Cancer Center/ Erasmus Medical Center Rotterdam, PO Box 5201, 3008 AE Rotterdam, the Netherlands*

Received 8 October 2001; received in revised form 5 August 2002; accepted 11 September 2002

Abstract

Currently, axillary lymph node dissection is increasingly being replaced by the sentinel node procedure. This method is time-consuming and the full immunohistochemical evaluation is usually only first known postoperatively. This study was designed to evaluate the accuracy of preoperative ultrasound-guided fine needle aspirations (FNAs) for the detection of non-palpable lymph node metastases in primary breast cancer patients. We evaluated the material of 183 ultrasound-guided FNAs of non-palpable axillary lymph nodes of primary breast cancer patients. The cytological results were compared with the final histological diagnosis. Ultrasound-guided FNA detected metastases in 44% (37/85) of histologically node-positive patients, in 20% of the total patient population studied. These pecentages are likely to be higher when women with palpable nodes are included. Cytologically false-negative and false-positive nodes were seen in 28 (15%) and three cases (1.6%), respectively. Interestingly 25% ($n=7$) of the false-negative nodes, revealed micrometastases on postoperative histology. The sensitivity was 57%, the specificity 96%. We conclude that ultrasound-guided FNA of the axillary lymph nodes is an effective procedure that should be included in the preoperative staging of all primary breast cancer patients. Whether lymph nodes are palpable or not, it will save considerable operating time by selecting those who need a complete axillary lymph node dissection at primary surgery and would save a significant number of sentinel lymph node dissections (SLNDs).

Keywords: Breast cancer; Ultrasound; FNA; Lymph node; Axilla

1. Introduction

Lymph node status has long been the golden standard in determining the prognosis of breast cancer patients. Lately, the need for complete axillary dissection as a common staging procedure for all breast cancer patients has been questioned, because of the high morbidity of the procedure caused by lymphoedema and neuropathy of the involved arm. For this reason, regional lymph node staging by histological examination of the so-called sentinel node, defined as the first node draining the primary tumour in the regional lymphatic basin, has been introduced. Various studies [1–3] have now shown that histopathological examination of the sentinel node is reliable in predicting axillary lymph node status in breast cancer. Consequently, this procedure can replace routine axillary lymphadenectomy when the sentinel node is found to be negative. However, the procedure is time-consuming and the full histological and immunohistochemical evaluation is often only first known postoperatively. It would therefore be of great interest for

* Corresponding author. Tel.: +31-10-439-1362; fax: +31-10-439-1033.
E-mail address: kuenen-boumeester@padh.azr.nl (V. Kuenen-Boumeester).

the patient and surgeon to find an accurate technique for identifying lymph node metastases preoperatively.

Bonnema and colleagues [4] have studied the accuracy of ultrasonographically-guided fine needle aspiration (FNA) of non-palpable axillary lymph nodes in detecting breast cancer metastases. They found that ultrasound-guided FNA of the axilla could be performed in 62% of patients with primary breast cancer and that 63% of all node-positive patients could be detected preoperatively by this method. In a multicentre study of the sentinel node staging procedure, the preoperatively performed ultrasound-guided cytology showed a 36% detection rate of the lymph node metastases [5]. These results were promising and in our institute FNA cytology of non-palpable axillary lymph node under ultrasound guidance before primary surgery has become the standard procedure in the preoperative staging of primary breast cancer patients. Here, we present the outcome of our analysis of the cytology of axillary lymph nodes of breast cancer patients collected between January 1998 and July 2000.

2. Patients and methods

2.1. Patient material

Axillary lymph node material from 180 patients with a primary diagnosis of breast cancer was collected from January 1998 until July 2000. 3 patients had bilateral breast carcinomas and therefore FNAs of both left and right axillary nodes were performed. Thus, the final study consisted of material from 183 lymph nodes of 180 patients. Ultrasonographic evaluation of the axilla was carried out with an Acuson XP 128 (Acuson, Mountain View, CA, USA) using a 7.5-MHz linear array transducer. When lymph nodes were visible an ultrasound-guided FNA was performed with a 21-G needle, regardless of the benign/malignant ultrasound pattern. When more nodes were seen, either the sonographically most malignant looking, or the one closest to the breast and therefore most likely to be the sentinel node, was aspirated. The slides were Giemsa stained and evaluated according to the following three criteria: none or only few lymphocytes: inadequate; many lymphocytes, but no epithelial cells: benign; atypical epithelial cells in combination with lymphocytes: malignant. When atypical epithelial cells, but no lymphocytes were found and it was not apparent that an actual lymph node was aspirated, it was mentioned in the conclusion.

When the cytological diagnosis of the lymph node was positive, a complete axillary lymph node dissection was performed at primary surgery. In all other cases, a routine sentinel node procedure was applied as described in Ref. [5]. In short, the identification of the sentinel node was realised by peritumoral injection of 30–40 MBq ^{99m}Tc-radiolabelled nanocolloid at least 2.5 h before surgery and intradermal injection of 0.5 ml patent blue dye during the operation. The sentinel node was identified with the guidance of the RMD-CTC4 probe (Radiation Monitoring Devices, Watertown, ME, USA) and the blue- stained lymph vessel. Frozen sections of the sentinel node were examined and when negative, multiple at 250-μ intervals stepwise, sectioned paraffin slides were studied—following standard histological and immunohistochemical staining procedures using a monoclonal antibody against low molecular weight cytokeratin (CAM 5.2, Dako, Denmark) [6]. Histological features of the tumour were recorded. Typing was performed following the World Health Organization (WHO) classification, grading was done according to Bloom and Richardson [7].

The results were analysed with descriptive statistical methods. Sensitivity, specificity, overall accuracy, and positive and negative predictive values were calculated by comparing the results of FNAB and histological findings.

3. Results

The clinicopathological features of the primary breast cancers are listed in Table 1. The histological subtypes included 155 ductal, 12 lobular, 5 mixed and 11 other type carcinomas. Most tumours were grade II ($n=77$, 42%), pT1 ($n=131$, 72%) and N0 ($n=98$, 54%). There was only one pT3 tumour.

Table 2 gives the correlation between the cytological and histological diagnosis of the axillary nodes. In

Table 1
Pathological characteristics of 183 breast cancer specimens

	n	%
Type		
Ductal	155	(85)
Lobular	12	(7)
Mixed	5	(3)
Other	11	(6)
Grade		
I	43	(23)
II	77	(42)
III	60	(33)
Unknown	3	(2)
Size		
T1	131	(72)
T2	51	(28)
T3	1	(0.5)
N		
N0	98	(54)
N1–3	58	(32)
N > 3	24	(13)
Unknown	3	(2)

Table 2
Correlation between cytological and histological diagnoses

Cytology	Histology		
	n	Benign	Malignant
Inadequate	49	29	20
Benign	94	66	28
Malignant	40	3	37
Total	183	98	85

49/183 (27%) cases, insufficient material was aspirated, 20 of which were histologically-positive. In 103/183 (56%), the cytology and histology was concordant, i.e. 37/103 were both positive for malignancy and 66/103 were both negative for malignancy. In 31/183 (17%) lymph nodes, the cytological and histological results did not correspond: in 28 cytologically-negative cases, histologically-positive lymph nodes were seen. However, histology of three cytologically-positive nodes (1.6%) did not reveal cancer metastases. Reviewing the cytology of the latter lymph nodes, we found that the material presented as lymph node aspiration in one case did show tumour cells against a background of lymphocytes and was in our opinion therefore rightly considered to be a metastasis. However, histology showed that the primary tumour was multifocal and the more laterally located small tumour area in particular was surrounded by lymphocytes. This lateral tumour extension was considered a likely explanation for the positive cytology result. In the next case at second look, the aspirated cell groups, misread as metastatic groups, were interpreted as mesothelial cells. Apparently, the radiologist had aspirated material from the pleural cavity. In the last case, tumour groups but no lymphocytes were seen in the cytological specimen, but since the consulted radiologist confirmed that an axillary lesion was aspirated, it was considered to be a lymph node metastasis. Nevertheless, no positive nodes were found in the surgical specimen.

Most inadequate and false-negative aspirations were found in the group with one positive node, 13 and 17, respectively (Table 3). Of these 17 false-negative aspirations, seven contained micrometastases only, i.e. 25% (7/28) of the total number of cytologically false-negative nodes.

Of the total group with one histologically-positive node, 25% was cytologically-detected, compared with 83% in the group with more than three positive nodes. Three patients with a positive sentinel node refused further surgery and, consequently, no axillary dissection was performed and the number of positive nodes is unknown. In those cases, regular ultrasound examinations of the axilla were included in the follow-up.

The relationship between the size of the tumour, the number of histologically-positive nodes and cytological detection, is shown in Table 4. In 29% (14/49) of T1 tumours and and in 64% (23/36) of T2 tumours histologically-positive nodes were cytologically-detected, in 57% (13/23) of T2 tumours with more than three positive nodes.

In 20% of the total patient population studied, lymph node metastases were cytologically-detected. This is 44% (37/85) of the group of patients with histologically-proven positive lymph nodes.

The sensitivity (the aspirations with inadequate material not included) was 57%, the specificity 96%, overall accuracy 76% and positive and negative predictive values 92%, and 70%, respectively.

4. Discussion

A simple reliable preoperative assessment of the axillary lymph node status of primary breast cancer patients would be of great value for the patient and surgeon, especially since the introduction of the sentinel node procedure. It would save time and costs by avoiding this procedure when metastases are found. Non-palpable axillary lymph nodes can be detected by ultrasound. Unfortunately, the accuracy of ultrasonography is too low to rely on this technique for the selection of

Table 3
Correlation between cytological diagnosis and lymph node status

	Number of histologically-positive lymph nodes					
Cyt	*n* = 1	*n* = 2–3	*n* = > 3	Unknown	Total (%)	
Inadequate	13 (5[a])	4	1	2 (1[a])	20	(24)
Benign	17 (7[a])	7	3	1	28	(33)
Malignant	10	7	20	–	37	(44)
Total	40	18	24	3	85	

[a] Number of lymph nodes with only micrometastases.

Table 4
Correlation between tumour size and number of histologically-positive lymph nodes (number of cytologically-detected nodes between parentheses)

	N = 1	*N* = 2–3	*N* = > 3	*N*?	Total (%)
T1					
1a	1	–	1	–	2
1b	8 (1)	1 (1)	–	–	9 (2)
1c	20 (3)	7 (2)	9 (7)	2[a]	38 (12)
T2	11 (6)	10 (4)	14 (13)	1[a]	36 (23)
Total	40 (10)	18 (7)	24 (20)	3	85 (37)

[a] 3 patients with a positive sentinel node, refused further surgery and therefore the number of positive nodes is not known.

node-negative/positive patients, the sensitivity being 36–73% and the specificity between 70 and 100% [4,5,8–10]. A combined approach of ultrasound and FNA cytology is rarely applied [4,5,11], but the results are promising. Bonnema and colleagues [4] found that in 87% of ultrasound-guided FNA of axillary lymph nodes, adequate material was aspirated, with a sensitivity and specificity of 63 and 100%, respectively. In the study of Kanter and colleagues [5], the sensitivity was 36% and the specificity 100%. We found that 73% of lymph node aspirations contained adequate material with a sensitivity of 57% and a specificity of 96%. These variations in the detection of metastases may be explained by the fact that in Bonnema's study two experienced radiologists were involved whereas in the other two studies, several radiologists did the aspirations and some of them had little experience with this technique. However, after a learning phase, the identification and aspiration of lymph nodes improved and so did the results (data not shown). It underlines the importance of good communication between the radiologist, pathologist and surgeon to maintain high standards with regard to the quality of the proceedings.

Unfortunately, 3 cases of positive cytology proved to be negative in histology. In 1 case this could be explained by the multifocality of the tumour, associated with a dense lymphocytic infiltrate. It is known that in multifocal breast cancer, a negative sentinel node does not exclude axillary metastases [12]. Therefore, a complete axillary lymph node dissection has to be performed. The second false-positive case was caused by cytological misreading of the cell groups. Here, a complete lymph node dissection was an overtreatment. Awareness of the rare possibility that the pleural cavity is aspirated may help to avoid this pitfall. The third case remains unexplained.

Cytologically false-negative and inadequate findings were in general restricted to the group of patients with one or 2–3 positive nodes. That so few lymph nodes are positive may explain why aspiration is more difficult and the chance of sampling errors is enhanced. What is even more important, 25% of the cytologically false-negative lymph nodes, were found histologically to contain micrometastases only. Although the biological significance of these micrometastases is still being discussed, it is clear that neither ultrasound nor cytology can replace histology in the detection of these metastases, but it partly explains the relative low sensitivity (57%) found in this study.

Screening programmes have led to an earlier diagnosis of breast cancer and therefore smaller invasive cancers [13]. Moreover, the size of the tumour is related to the number of nodes involved [14–16]. Consistent with these findings, we observed that 131/183 (72%) of the tumours were T1. However, the percentage of T1 tumours with positive nodes was relatively high (37%) compared with other studies [16–18]. Most likely a selection bias has occurred. After all, patients were selected upon the sonographical visibility of the axillary lymph nodes and since metastic lymph nodes are in principal visible, the chance of nodes being positive was much higher in this group than in a population of primary breast cancer patients with no visible nodes.

In this study, ultrasound-guided FNA could identify 44% of histologically-proven axillary metastases in primary breast cancer patients with pT1 and pT2 tumours, 20% of the total patient population. Consequently, the sentinel node procedure could be avoided, saving considerable operating time as the surgeon can proceed to axillary dissection without waiting for frozen sections and avoiding a second operation later.

Both ultrasound and FNA are non-aggressive, patient-friendly and reliable methods, relatively easy to apply when in experienced hands. We conclude that ultrasound-guided FNA of the axilla should be included in the preoperative staging procedure of all primary breast cancer patients. It it will save a significant number of SLNDs, by selecting those patients who need a total axillary lymph node dissection at primary surgery.

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CHAPTER 4

Non-sentinel lymph node involvement in patients with breast cancer and sentinel node micrometastasis; too early to abandon axillary clearance

M.A. den Bakker, A. Van Weeszenberg, A.Y. de Kanter, F.H. Beverdam, C. Pritchard, T.H. van der Kwast, M.B.E. Menke-Pluymers

Journal of Clinical Pathology 2002; 55: 932-935

Non-sentinel lymph node involvement in patients with breast cancer and sentinel node micrometastasis; too early to abandon axillary clearance

M A den Bakker, A van Weeszenberg, A Y de Kanter, F H Beverdam, C Pritchard, Th H van der Kwast, M Menke-Pluymers

J Clin Pathol 2002;**55**:932–935

See end of article for authors' affiliations

Correspondence to: Dr M A den Bakker, Department of Pathology, Erasmus Medical Centre Rotterdam, Daniel den Hoed Location, Groene Hilledijk 301, PO Box 5201, 3008 AE, Rotterdam, Netherlands; michael@dbakker.demon.nl

Accepted for publication 12 July 2002

Aims: It has been suggested that patients with T1–2 breast tumours and sentinel node (SLN) micrometastases, defined as foci of tumour cells smaller than 2 mm, may be spared completion axillary lymph node dissection because of the low incidence of further metastatic disease. To gain insight into the extent of non-sentinel lymph node (n-SLN) involvement, SLNs and complementary axillary clearance specimens in patients with SLN micrometastases were examined.

Methods: A set of 32 patients with SLN micrometastases was selected on the basis of pathology reports and review of SLNs. Five hundred and thirteen n-SLNs from the axillary clearance specimens were serially sectioned and analysed by means of immunohistochemistry for metastatic disease. Lymph node metastases were grouped as macrometastases (> 2 mm), and micrometastases (< 2 mm), and further subdivided as isolated tumour cells (ITCs) or clusters.

Results: In 11 of 32 patients, one or more n-SLN was involved. Grade 3 tumours and tumours > 2 cm (T2–3 *v* T1) were significantly associated with n-SLN micrometastases as clusters (grade: odds ratio (OR), 8.3; 95% confidence interval (CI), 1.4 to 50.0; size: T2–3 tumours *v* T1: OR, 15; 95% CI, 2.18 to 103.0). However, no subgroup of tumours with regard to size and grade was identified that did not have n-SLN metastases.

Conclusions: In patients with breast cancer and SLN micrometastases, n-SLN involvement is relatively common. The incidence of metastatic clusters in n-SLN is greatly increased in patients with T2–3 tumours and grade 3 tumours. Therefore, axillary lymph node dissection is especially warranted in these patients. However, because n-SLN metastases also occur in T1 and low grade tumours, even these should be subjected to routine axillary dissection to achieve local control.

The sentinel node procedure was pioneered for penile carcinoma.[1] In recent years, it has been introduced for breast cancer, where its main purpose is to gain insight into the status of the axillary basin for the presence of metastatic disease.[2 3] Axillary clearance with its associated morbidity can be avoided if metastatic disease in the SLN cannot be proved. To rely on the SLN procedure in guiding patient management, it is essential that it be thoroughly investigated. Many studies have clearly shown that more sensitive techniques such as serial sectioning, the use of immunohistochemistry, and molecular techniques (such as reverse transcription polymerase chain reaction) dramatically increase the detection rate of metastatic disease in lymph nodes.[4–10] A direct consequence of this enhanced sensitivity is the observed increased incidence of micrometastatic and "occult" disease. Although not all studies agree on this, several papers showed a survival disadvantage for patients with micrometastatic disease.[6 11–13]

In addition to its application as a staging procedure in guiding further treatment, it has been suggested that the SLN procedure may in certain circumstances serve a secondary function as a means of local disease control by removing metastatic disease.[14 15] In this setting, it is assumed that the SLN has effectively filtered out early metastatic disease before tumour microemboli have had the chance to spread beyond the initial lymph node. Furthermore, it is assumed by some that certain forms of micrometastatic disease, such as isolated tumour cells, may not have the potential for outgrowth.[4 16] Accepting these hypotheses implies that metastatic disease in n-SLNs should only rarely be found in cases with SLN micrometastases. To test these assumptions we examined the n-SLNs of patients with micrometastatic SLN disease.

> "It has been suggested that the sentinel lymph node procedure may in certain circumstances serve a secondary function as a means of local disease control by removing metastatic disease"

METHODS

Identification of the sentinel node was performed by peritumoral injection of 40 MBq (99m)Tc radiolabelled nanocolloid at least 2.5 hours before surgery and intradermal injection of 0.5 ml patent blue dye during surgery. The sentinel node was identified with the guidance of the RMD-CTC4 probe (Radiation Monitoring Devices, Watertown, Maine, USA), aided by visual identification of the blue stained vessel, and was removed under general anaesthesia. After frozen section analysis (superficial level of one half of a bisected lymph node), the remaining SLN tissue was formalin fixed and paraffin wax embedded. Large nodes were trimmed down into smaller pieces and submitted in toto for histology. Sections were cut at four 250 μm intervals with parallel haematoxylin and eosin (H&E) and immunohistochemical (IHC) staining with anticytokeratin antibodies.

Abbreviations: CI, confidence interval; H&E, haematoxylin and eosin; IHC, immunohistochemistry; ITC, isolated tumour cell; LN, lymph node; n-SLN, non-sentinel lymph node; OR, odds ratio; SLN, sentinel lymph node

Table 1 Tumour characteristics of patient set

	Positive n-SLN	Negative n-SLN
No. of patients (%)	11 (34)	21 (66)
Primary tumour		
Ductal	10	17
Lobular	1	4
Size (mm)	26.1 (median, 21)	14.7 (median, 12)
T1	3	19
T2	6	2
T3	2	0
Grade (Bloom and Richardson)		
I	2	5
II	4	12
III	5	4

n-SLN, non-sentinel lymph node.

On the basis of pathology reports, 40 patients were identified who had an SLN micrometastasis. The SLNs and primary tumours of these patients were reviewed. Grading of the primary tumours was performed according to the modified Bloom and Richardson criteria.[17] The sizes of the SLN and n-SLN micrometastases were measured on the microscope stage using the Vernier scale; in equivocal cases, a digital image was acquired and measurements were made using an image analysis application (AutoCyte Link; TriPath Imaging Inc, Burlington, North Carolina, USA). Metastases were divided into three groups, namely: metastases larger than 2 mm (macrometastases); micrometastases (< 2 mm) consisting of groups of four or more cells in close approximation, termed clusters; and micrometastases consisting of isolated single tumour cells or small collections of up to three tumour cells together, designated as isolated tumour cells (ITCs).[16] When multiple micrometastases were present in a single node, the largest metastasis was measured. The sizes of individual metastases were not added together. After reviewing the SLNs, eight patients were excluded from our study (in seven patients the metastasis was over 2 mm in size, one patient did not proceed to axillary node dissection). The remaining 32 patients formed the basis of our study. From these patients, all n-SLNs were cut at 250 µm intervals through the paraffin wax block, resulting in three to 10 additional sections for each block. The sections were immunostained with anticytokeratin antibody CAM 5.2 (Becton Dickinson, Mountain View, California, USA) using a standard peroxidase–anti-peroxidase procedure in an automated immunostainer (Mark V; DPC, Los Angeles, California, USA). Appropriate positive and negative controls were incorporated in each run of the immunostainer. In equivocal cases, H&E stained sections were prepared from retained ribbons for comparison. The presence of micrometastases was scored and compared with the tumour parameters size and grade using the statistical package SPSS for Windows release 10.05 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Thirty two patients with breast cancer were identified with a SLN micrometastasis. Forty five SLNs were derived from these patients, ranging from one to four lymph nodes (LNs)/patient (median, one). The primary tumours were 27 ductal type adenocarcinomas "not otherwise specified" and five lobular carcinomas (table 1). Mean tumour size was 19 mm (range, 6–55 mm). The axillary clearances yielded 513 LNs (range, 3–28; median, 14). Because of the poor clinical condition of one patient, only a limited (level 1) LN dissection was performed, yielding four LNs. Metastases in n-SLNs were identified in 24 of 513 LNs (4.7%) from the axilla of 11 of 32 patients, five of whom had initially been diagnosed as not having n-SLN metastases ("occult metastases") (table 2). In addition to eight identified involved n-SLNs in the original reports, 16 extra involved n-SLNs were documented after serial sectioning and IHC. In two patients a macrometastasis was found. Three patients had ITCs only, two patients only had clusters (including one patient with a macrometastasis), and six patients had ITCs and clusters (including one patient with a macrometastasis). The number of involved n-SLNs ranged from one to four (median, two). Within the group of 11 patients with n-SLN micrometastases, 10 carcinomas were of the ductal type and the 11th case was a lobular carcinoma. The mean tumour size in this group was 26.1 mm (range, 12–55). Two of the carcinomas in this group were multifocal (multiple non-continuous foci of invasive carcinoma, not necessarily confined to one quadrant). In the group of 21 patients without n-SLN micrometastases, the mean tumour size was 14.7 mm (range, 6–35), 17 carcinomas were of the ductal type and four tumours were lobular carcinomas. In this group of patients, two patients had only ITCs in the SLN, two patients had ITCs and clusters, and the remaining 17 patients had clusters.

The average tumour size was significantly larger in patients with involved n-SLNs than in those without n-SLN metastases (26.1 mm (SD, 14.3) *v* 14.7 mm (SD, 7.2); *t* test, t = 2.474 (unequal variance); p = 0.028). The presence and type of metastasis (ITC *v* cluster) of n-SLN metastases was analysed with respect to tumour size and grade by calculating relative odds (odds ratio; OR). A significantly greater risk of positive n-SLNs with clusters was found for high grade tumours (OR, 8.3; 95% confidence interval (CI), 1. 4 to 50.0). The odds of n-SLN metastases as clusters were significantly greater for carcinomas > 2 cm (OR, 15; 95% CI, 2.18 to 103.0).

Table 2 Characteristics of tumours and results in 11 patients with n-SLN involvement

Patient	No. of SLNs (pattern of involvement)	No. of n-SLNs	Pattern of n-SLN involvement (n)	Tumour type	Size (mm)	Grade (B&R)
1	2 (SLN1 and SLN2 ITC)	19	ITC+ cluster (4)‡	Ductal	25	3
2	2 (SLN1 ITC+ cluster, SLN2–)	13	ITC (1)	Lobular	50	1
3	1 (cluster)	8	Cluster* (3)‡	Ductal	12	1
4	1 (cluster)	22	Cluster (1)	Ductal	21	3
5	1 (cluster)	10	ITC (1)‡	Ductal	17	2
6	1 (cluster)	11	Cluster* (2)	Ductal	26	2
7	1 (cluster)	15	Cluster† + ITC (4)	Ductal	30	3
8	3 (SLN1 cluster, SLN2 and SLN3–)	4	Cluster (2)	Ductal	20	3
9	1 (cluster)	22	Cluster† (3)	Ductal	21	2
10	1 (cluster)	10	ITC (1)‡	Ductal	55	2
11	1 (ITC+ cluster)	28	Cluster (2)‡	Ductal	10	3

*n-SLN micrometastasis larger than SLN metastasis; †n-SLN macrometastasis; ‡negative n-SLN status in original report.
B&R, Bloom and Richardson; ITC, isolated tumour cell; nSLN, non-sentinel lymph node; SLN, sentinel lymph node.

DISCUSSION

The question arises whether the presence of microscopic tumour deposits in the SLN justifies complete axillary clearance and adjuvant treatment. It may be argued that for staging purposes the object has been achieved by finding metastatic disease in the SLN and that further involved nodes are unlikely to be found. Moreover, the view may be taken that removing an SLN with micrometastatic disease constitutes adequate local control and that axillary clearance is not justified in these cases. Accepting this perspective implies that either metastatic deposits in n-SLNs are highly unlikely or that even if further micrometastatic deposits in n-SLNs are present these will not result in locoregional disease.

To gain insight into possible metastatic disease in the remaining (non-sentinel) axillary LNs we performed serial sectioning with IHC on the n-SLNs of 32 patients with SLN micrometastases. Metastases were grouped as macrometastases (> 2 mm) and as micrometastases (< 2 mm). Micrometastases were further subdivided into "clusters" (four or more cells together) and isolated tumour cells (single cells and groups of up to three cells together). We found that in 11 of 32 patients metastatic disease was present in non-sentinel nodes from the axilla, whereas in seven patients more than one node was involved and in four patients the n-SLN metastasis was larger than the SLN metastasis (including two patients with n-SLN macrometastases). It is possible that erroneous SLN identification had occurred in the patients with macrometastases. Nevertheless, excluding these two patients does not significantly detract from our observation that n-SLN involvement is not uncommon when sensitive techniques are used. Large n-SLN metastases in micrometastatic SLN involvement have been noted previously, including n-SLN metastasis in cases with single cells in the SLN.[7]

> "On the basis of our findings and the literature data, we find it premature to conclude that axillary dissection may be avoided in patients with T1–2 tumours and sentinel lymph node micrometastases, as suggested by Chu *et al* and Reynolds *et al*"

In our study, LNs with radioactive tracer uptake were designated as SLNs, the blue dye served only as a visual aid in identification. Other workers have in some instances included blue, non-radioactive nodes as SLNs, a practice that has been challenged.[18 19] From a conceptual viewpoint it could be argued that there can only be a single "true" SLN and that all other nodes are non-sentinel nodes. If this line of reasoning is pursued, two of seven patients from our group without n-SLN involvement would have to be considered as having n-SLN involvement. Conversely, it has been shown that more than one first echelon node (SLN) may be present. In accordance with these observations we chose to accept multiple SLNs.

We found that n-SLN metastases as clusters were associated with tumours > 2 cm in size and with high grade tumours. Other groups have not found tumour grade to be an independent risk factor for n-SLN metastasis.[18 20 21] This is surprising, because grade has been shown to be associated with an increased risk for nodal metastases in small tumours.[22 23]

The term micrometastasis has only been defined arbitrarily, and its definition varies between studies. A cut off point of 2 mm has been used in many studies and is included in the TNM classification.[16 24 25] Alternatives, such as the area of lymph node involved by tumour and the particular pattern of lymph node involvement, have been suggested.[19 26–28] The importance of micrometastatic disease and the implications for treatment when it is demonstrated hinge upon delineating the biological behaviour of small tumour deposits and small numbers of isolated tumour cells.[12] Experimental studies suggest that most isolated (circulating) tumour cells are not viable and will not result in metastatic disease. Thus, in the strictest sense, a micrometastasis requires the arrest of tumour cells in the tissue and proliferation.[4 16] Biological characteristics such as viability, angiogenic capacity, and avoidance of the host immune reaction may be equally important factors.[29 30] In addition, it may be necessary to look at the host lymph node response, because this may also influence the ability of a micrometastasis to expand.[26] In this setting, it is interesting to note that Colpaert *et al* found a survival advantage for patients with SLN micrometastases and hypothesised that this may result from an enhanced host immune response.[31]

Take home messages

- Non-sentinel lymph node (n-SLN) involvement is relatively common in patients with breast cancer and sentinel lymph node micrometastases
- Metastatic clusters in n-SLN are found more frequently in patients with T2–3 tumours and grade 3 tumours
- Thus, axillary lymph node dissection is especially warranted in these patients, but because n-SLN metastases occur even in T1 and low grade tumours, these tumours should be subjected to routine axillary dissection to achieve local control
- Further studies are needed with larger series and patient follow up to assess the clinical relevance of these findings

Whatever the outcome of single tumour cells in the circulation or in organs may be, it should be appreciated that the very fact that they are detected implies that access to the lymphatics or blood vessels has been gained, and that a line of defence has been breached in the metastatic pathway.

The incidence of n-SLN involvement varies in reports and this is in part a result of the sensitivity of the detection method used. Naturally, more intensive analysis of LNs with serial sectioning and immunohistochemistry will reveal more metastatic disease, as has been shown in SLN research.[9 10] Reynolds *et al* did not observe n-SLN metastases in 18 patients with T1 tumours and micrometastases in the SLN. They propose that axillary lymph node dissection may not be necessary in patients with T1 breast tumours and SLN micrometastases.[21] Likewise, Chu *et al* found that less than 5% of patients with T1 tumours and only 6% of patients with T1–2 tumours and micrometastatic SLN disease had n-SLN involvement, and they also suggest that axillary lymph node dissection may not be necessary in these patients.[18 20] However, the methods used in their study, with one or two sections for each n-SLN and without IHC, probably underestimated the extent of n-SLN disease.[20] The same investigators in Giuliano's group later found that 24% of patients with T1–2 tumours and micrometastases in the SLN (either detected by H&E staining or IHC) harboured n-SLN metastases. In that study, two level IHC was used, which may have increased the sensitivity. However, they did find that when lymphatic vascular invasion and extranodal hilar tissue invasion were taken into account only one of 58 patients with T1–2 tumours had an n-SLN metastasis.[32] Another study, examining n-SLN involvement in patients with positive SLNs, found n-SLN involvement in 27% of patients with a single SLN harbouring a metastasis < 1 mm.[28] In our series, three of 21 patients with T1 tumours and an SLN micrometastasis had n-SLN metastases detected by serial sectioning and IHC. On the basis of our findings and the literature data,[28] we find it premature to conclude that axillary dissection may be avoided in patients with T1–2 tumours and SLN micrometastases, as suggested by Chu *et al* and Reynolds *et al*.[18 20 21] Indeed, if n-SLN metastases are relatively common in patients with micrometastatic SLN disease and are likely to be followed by axillary node dissection, then it is imperative that the SLN is meticulously investigated. Therefore, the question that must be answered is how thoroughly this must be done and at what cost.[33] The ultimate test of the importance of

SLN micrometastatic disease and its treatment implications will be disease recurrence and disease related survival. For this issue to be resolved, further studies are needed with larger series and patient follow up. A trial incorporating these aspects organised by the oncology group of the American College of Surgeons is under way.[34]

Authors' affiliations
M A den Bakker, A van Weeszenberg, Th H van der Kwast, Department of Pathology, Erasmus Medical Centre Rotterdam, Daniel den Hoed Location, Groene Hilledijk 301, PO Box 5201, 3008 AE, Rotterdam, Netherlands
A Y de Kanter, Department of Radiotherapy, Erasmus Medical Centre Rotterdam
M Menke-Pluymers, Department of Surgery, Erasmus Medical Centre Rotterdam
C Pritchard, Department of Research and Development Support Unit, Royal Cornwall Hospitals Trust, Treliske Hospital, Truro, Cornwall, TR1 3LJ, UK
F H Beverdam, Department of Surgery, Medisch Centrum Rijnmond Zuid, Location Zuider, 3075 EA Rotterdam, Netherlands

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CHAPTER 5

Reasons for failure to identify positive sentinel nodes in breast cancer patients with significant nodal involvement.

A.Y. de Kanter, M.B.E. Menke-Pluymers, S.C. Henzen-Logmans, A.N. van Geel,
C.H.J van Eijck, T. Wiggers, A.M.M. Eggermont

European Journal of Surgical Oncology 2006

Reasons for failure to identify positive sentinel nodes in breast cancer patients with significant nodal involvement

A.Y. de Kanter[a], M.B.E. Menke-Pluijmers[a], S.C. Henzen-Logmans[d,e], A.N. van Geel[a], C.J.H. van Eijck[b], T. Wiggers[a,c], A.M.M. Eggermont[a,*]

[a]*Department of Surgery, Erasmus University Medical Centre-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands*
[b]*Department of Surgery, Erasmus University Medical Centre, Central Hospital, Rotterdam, The Netherlands*
[c]*Department of Surgery, University Medical Centre Groningen, Groningen, The Netherlands*
[d]*Department of Pathology, Erasmus University Medical Centre-Daniel den Hoed Cancer Centre, Rotterdam, The Netherlands*
[e]*Department of Pathology, Zuiderziekenhuis, Rotterdam, The Netherlands*

Accepted 17 February 2006

Abstract

Aim: To analyse causes of failure of sentinel node (SN) procedures in breast cancer patients and assess the role of pre-operative ultrasound examination of the axilla.

Methods: In 138 consecutive clinically node negative breast cancer patients with the primary tumour in situ a SN procedure with radiolabeled colloid and blue dye was performed. Radioactivity in the SN was scored as inadequate or adequate. The axillary lymph node dissection scored for number of involved nodes and presence of extranodal growth.

Results: In 53/138 patients, the SN was positive for tumour. Full axillary node dissection revealed that 58/138 were node positive. So in five patients the SN failed to predict true nodal status. In 3/5, the radioactive ratio (SN vs background) was inadequate. All were found to have extensive nodal involvement. The radioactivity ratio was inadequate in 37/138 patients. This ratio was inadequate in 10 of 15 patients with ≥ 4 positive nodes and 27 of 123 in patients with 0–3 positive nodes ($p < 0.001$). If extranodal growth was present the radioactive ratio was inadequate in 13 of 18 patients, whilst this was only the case in 24 of 120 patients without extranodal growth or metastases ($p < 0.001$). Ultrasound (US) examination and US-guided FNAC was able to pre-operatively identify 16 of the 26 patients with four or more metastases in the axilla.

Conclusions: Extensive nodal involvement is an important cause of failure of the sentinel node biopsy. Pre-operative ultrasound examination of the axilla can avoid this in almost two thirds of these patients.

Keywords: Breast cancer; Sentinel node; Failure; Extra nodal growth; Extensive nodal involvement

Introduction

After the initial publication of the sentinel node (SN) in penile carcinoma by Cabanas this hypothesis was tested for other tumours.[1] The SN is by definition the first draining lymph node of the tumour site and histologic examination of this node reflects regional lymph node status. This staging procedure identifies the most significant prognostic factor in breast cancer, melanoma and other solid tumours. In melanoma and breast cancer, the SN biopsy has already proven to be as accurate as a full lymph node dissection.[2–6] At this moment SN procedure is standard of care in breast cancer patients with acceptance of a false-negative rate of 5%. Failure of the procedure can be defined: (1) removal of the wrong (non-sentinel) node or; (2) as failure to trace, identify and remove the sentinel node. Failure can be caused by anatomic factors[7,8] and by technical inadequacies in any of the three disciplines involved in the SN-procedure: nuclear medicine, surgery and pathology. Most failures are due to little or no experience with the various aspects and intricacies of the procedure. Inadequacies in the nuclear medicine part of the procedure are a result of the radioactive dose, the amount of injected fluid and the injection technique. Surgical causes are the technique used to trace sentinel nodes during surgery, the time between injection

* Corresponding author. Address: Department of Surgical Oncology, University Hospital Rotterdam-Daniel den Hoed Cancer Centre, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands. Tel.: +31 10 439 1911; fax: +31 10 439 1011.

E-mail address: a.m.m.eggermont@erasmusmc.nl (A.M.M. Eggermont).

0748-7983/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.ejso.2006.02.012

Table 1
Detection and false-negative rate of other groups investigating the value of the SN procedure

	N	Traceable SN (%)	False-negative rate (%)
Krag[15]	443	91	11
O'Hea[16]	60	92	15
Sato[14]	186	98.4	2.1
Tafra[13]	535	87	13
Cox[11]	466	94	1
Roumen[17]	83	69	3
Veronesi[18]	163	98	5
Flett[19]	68	82	17
Giuliano[20]	107	93	0
Albertini[21]	62	92	0
Borgstein[9,a]	112	93	2
Van der Ent[22]	70	100	4
de Kanter[12]	232	90	5

[a] Number of patients corrected, all 112 patients had a malignant tumour and known results of the SN and ALND.

and operation, whether lumpectomy was performed shortly before SN biopsy and the presence of multifocal tumour.[9–11] False-negatives may be due to inadequate histopathological inadequate work-up method of the sentinel node to detect (micro) metastases. In the literature, percentages of failure range from 0 to 31% (Table 1). We evaluated the false-negative procedures in our institutions and looked for factors that might be responsible for removal of a non-sentinel node. Ultrasound with fine needle aspiration cytology (FNAC) of the axilla is part of the routine pre-operative investigation. We have previously reported that when US and FNAC demonstrate metastatic lymph node(s) no SN procedure is performed and a full axillary lymph node dissection is performed.[12] However, initially we have performed a SN procedure in ten of these patients. In one of them the SN was negative while four other nodes contained tumour. In another one the SN happened to be the only tumour-free node.

We hypothesized that the following mechanism might be operative: when the inflow of lymph into the SN is completely blocked by tumour, it will be directed towards another node. If a SN procedure is carried out in such patients, both the radioactive tracer and the blue dye will accumulate in the non-sentinel node, causing a false-negative result. The aim of our study is to investigate the role of this phenomenon in a consecutive series of patients with both the SN procedure and a full axillary lymph node dissection.

Patients and material

Patients

Between December 1996 and September 1998, 161 consecutive clinically node negative breast cancer patients with the primary tumour in situ underwent ultrasound examination and FNAC of the axilla. Cytological examination showed tumour cells in 33 patients (no false-positive results), in 23 of them no SN biopsy was performed, so 138 patients were scheduled for SN biopsy.

Sentinel node identification

The sentinel node was identified with radiocolloid and blue dye. On the day of the operation 3–4 ml 30–40 MBq 99m-Technetium nanocolloid was injected around the tumour in healthy breast tissue. When the operation was planned for the next morning, the amount of radioactivity was doubled and injected in the afternoon. Two hours after injection a lymphoscintigraphy was made to identify location and number of the sentinel node(s). Visible nodes were marked on the patient's skin. After making the incision in the axilla, the sentinel node was identified with guidance of the RMD-CTC4 or C-trac probe and/or the blue stained lymph vessels. The SN was identified and removed before a routine complete axillary lymph node dissection (ALND) was performed. The radioactivity ratio (SN vs background) was measured by the probe in counts per second (cps).

Levels of activity

We distinguished two levels of activity: inadequate (0–45 cps) and adequate ratio (>50 cps). This classification is not based on any study but is raised by analysing the counts per second. If a patient had adequate radioactivity ratio, i.e. >50 cps, this was in all patients at least 80 cps.

Pathology

All axillary specimens were processed for histologic examination using hematoxylin and eosin (H & E) staining and examined by the pathologist. The sentinel node was examined with multiple sections, 4–8 sections, and immunohistochemical staining (IHC) using cytokeratine antibody (CAM 5.2) in order to improve the detection of (micro) metastases. On pathological examination the number of involved nodes were counted and the presence of extranodal growth (ENG) was recorded. Discrimination between 1–3 and ≥ 4 positive nodes was made based on the Dutch guidelines for adjuvant treatment.

Results

General

The mean age of the patients was 56 years (25–88). Mean pathological size of the tumour was 20 mm (4–80 mm). Half of the tumours were situated in the lateral upper quadrant.

In 53 of the 138 patients, the SN was positive for tumour. Examination of the preceding full axillary lymph node dissection revealed another five node positive patients.

Table 2
Influence of the number of positive nodes on the radioactivity in the axilla

	0	1–3+	≥4	Total
Inadequate (0–45 cps)	14	13	10	37
Adequate (>80 cps)	66	30	5	101
Total	80	43	15	138

Radioactive ratio

Adequate radioactive ratio was present in 101/138 patients. In 37/138 patients, the radioactive ratio in the axilla was inadequate, 23 of these 37 patients were node positive. No radioactivity was found in 11 patients, in five of them there was a blue SN identified.

Both the presence of positive lymph nodes and presence of extranodal growth were recorded. The influence of the number of positive nodes and extranodal growth on level of radioactivity in the axilla is shown in Tables 2 and 3.

Influence of the number of positive nodes

In Table 2, the influence of the number of positive nodes on the amount of radioactivity is shown. In 10 of the 15 patients with four or more positive axillary lymph nodes there was inadequate radioactivity. In the patient groups with 1–3 or no metastases the ratio was inadequate in 27 of 123 patients, this is a significant difference ($p<0.001$). The difference between 1–3 metastases and ≥4 is also significant ($p<0.025$), the difference between 0 and 1–3 metastases is not significant.

Influence of the presence of extranodal growth

In Table 3, the influence of the presence of ENG on the radioactivity in the axilla is shown. In 13 of the 18 patients with ENG in one or more axillary lymph nodes there was inadequate radioactivity. In the patient groups without ENG or no metastases, the ratio was inadequate in 24 of 120 patients. Again, ENG vs no ENG and ENG vs no metastases/no ENG is a significant difference.

US and FNAC

In Table 4, the results of the FNAC vs the number of positive nodes is shown. This concerns the 161 patients without a previous lumpectomy. Ultrasound examination and FNAC can pre-operatively identify 16 of the 26 patients with four or more metastases in the axilla.

Table 3
Influence of the presents of extranodal growth (ENG) on the radioactivity in the axilla

	ENG	No ENG	No metastases	Total
Inadequate (0–45 cps)	13	10	14	37
Adequate (80 cps)	5	30	66	101
Total	18	40	80	138

Table 4
Result of the FNAC vs the number of metastases in the axilla

	No metastases	1–3+	≥4	Total
Malignant	0	15	16	31
Not malignant	82	38	10	116
Total	82	53	26	161

False-negative sentinel nodes

As mentioned above, five patients had a false-negative SN, i.e. the radioactive node was tumour-free while metastases were found in one or more of the other axillary lymph nodes. In 3/5, the radioactive ratio was inadequate, all found to have extensive node involvement. In the two patients with normal radioactivity, the failure was due to the surgical procedure. In these patients lymphoscintigraphy showed several nodes and at operation not all hot nodes were removed and after the sentinel node biopsy the axilla was not checked whether there was any activity left.

Discussion

Our postulated hypothesis seems to be correct. There is a significant relationship between extend of nodal involvement in terms of ENG and/or total number of positive nodes and failure of the SN detection. The radioactivity is bound to colloid and the colloid is phagocytosed by macrophages. However, if the SN is completely replaced by tumour-cells there is no healthy lymph tissue left to phagocytose the colloid and radioactivity. The colloid will skip the SN and be phagocytosed by another non-sentinel lymph node or will not be phagocytosed at all. This will result in false-negative sentinel nodes or non-detectable sentinel lymph nodes. An example of this phenomenon is our observation in one of our patients with a positive pre-operative ultrasound examination of the axilla and FNAC. The node identified by blue staining whilst being not radioactive, was almost the only tumour free node in the axilla. Another example is a patient also with positive ultrasound and FNAC. In this patient, we only injected the blue dye and again the found blue SN was tumour free while four non-sentinel nodes contained metastases. Alternatively, a SN replaced by tumour may also lead to blockage of lymph flow and thus redirected lymph flow away from SN towards another node. In a recent case, not part of this series of consecutive patients, we found blockage of lymph vessels by two small extranodally intralymphatically located ‘in-transit’ tumour metastases that lead to false-negative SN procedure.

To increase the accuracy of the SN procedure in the patients with lymph node metastases injecting more radiolabelled colloid will not solve the problem. Our suggestion is to perform in clinically node negative patients

an ultrasound examination of the axilla in combination with fine needle aspiration cytology.

Tafra et al. reported their identification and false-negative results in 529 patients were due to varies of factors, the total number of positive lymph nodes <5 vs ≥ 5 did not reach statistical significance possibly due to the small number of patients with ≥ 5 positive nodes.[13] Sato et al. studied the factors associated with the uptake of radiocolloid by the sentinel node. Only age ≥ 65 years and large SN of ≥ 8 mm was significant. Node positive vs node negative did not reach statistical significance, however, there was no discrimination between the number of positive nodes.[14] According to Sener et al. the reasons for mapping failure are multifactorial, and it appeared that mechanical obstruction of parenchymal breast lymphatics was associated with mapping failure in 40% of patients with more than 10 positive nodes.[7]

We reported previously on the results of ultrasound examination of the axilla in patients with breast cancer.[12] Non-metastatic lymph nodes are hard to detect; they have an echo-rich, fatty centre, which is difficult to distinguish from surrounding axillary fat tissue. Lymph nodes containing tumour have an inhomogeneous structural aspect on ultrasound. The more tumour is present the more inhomogeneous the aspect. An inhomogeneous aspect is even easier to detect with ultrasound if extranodal growth is present. In most patients with extensive node involvement there was extranodal growth. This combination reveals a high ultrasound detection rate for patients with extensive node involvement. In this study, ultrasound and FNAC was able to pre-operatively identify 16 of 26 patients with four or more metastases in the axilla.

In conclusion, failure of the sentinel node procedure; non-detectable and false-negative sentinel nodes should be as low as possible. Advanced nodal involvement (≥ 4 nodes or ENG) causes failure of the sentinel node biopsy in a majority of patients. Changes in the procedure will decrease only one parameter of failure. Both failure parameters will decrease if the sentinel node procedure will be combined with a pre-operative ultrasound examination of the axilla.

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CHAPTER 6

Radiation protection for the sentinel node procedure in breast cancer

A.Y. de Kanter, P.P.A.M. Arends, A.M.M. Eggermont, T. Wiggers

European Journal of Surgical Oncology 2003; 29: 396-399

Radiation protection for the sentinel node procedure in breast cancer

A. Y. de Kanter*, P. P. A. M. Arends†, A. M. M. Eggermont* and T. Wiggers*

*Department of Surgical Oncology and †Division of Radiation Protection, University Hospital Rotterdam/Daniel den Hoed Cancer Center, The Netherlands

Aims: The purpose of our study was to determine the radiation dose for those who are involved in the sentinel node procedure in breast cancer patients and testing of a theoretical model.
Methods: We studied 12 consecutive breast cancer patients undergoing breast surgery, and a sentinel node dissection including an axillary lymph node dissection (ALND). We performed measurements on the surgeon, the assistant, the theatre nurse, the pathologist and his assistant.
Results: The measurements on the theatre nurse and both pathologist as his assistant are beneath the detection limit of 10 μSv. The highest measured doses are the hands of the surgeon and his assistant (17–61 μSv), however the dose limits for hands are higher than for other parts of the body. Taking the dose limits into account the abdominal wall of the surgeon relatively receives the highest dose, with an average of 8.2 μSv per procedure.
Conclusion: Radiation dose levels are less than the established dose limits for (nonexposed) workers if the number of procedures is restricted to about 100/person/year.

Key words: sentinel node, radiation protection, surgeon, pathologist, breast cancer, safety.

INTRODUCTION

Sentinel node (SN) biopsy identifies the most significant prognostic factor in breast cancer, melanoma and other solid tumours. It has become a standard procedure in the management of breast cancer and melanoma patients.[1–3] As it involves the injection of radiolabeled colloid and the volume of especially breast cancer cases is very high, questions have been raised about safety issues regarding this procedure. Exposure to ionising radiation can be harmful and working with radioactivity has rigid rules. Some protection measures are enforced. Only qualified persons are allowed to administer radioactivity to the patient. Radioactivity must be given in a dedicated area. Statutory dose limits for exposure to ionising radiation must be observed.

Dose limits are determined for three groups, exposed workers, workers and members of the public. The radiation dose of exposed workers in 2 or 4 weeks is measured with dosimeters and quantified in effective dose. The special S.I.-unit of effective dose is the sievert (Sv); 1 sievert is equal to $1\,J \cdot kg^{-1}$. Ionising radiation has its origins in natural and artificial sources. The average dose of natural radiation, is 1.4 mSv/year. The artificial radiation (such as from Chernobyl, nuclear tests and medical investigations) is 0.7 mSv/year.[4]

Dose limits are prepared to prevent deterministic effects, such as, erythema, and stochastic effects such as cancer. Dose limits for deterministic effects are expressed in dose limits for hands, feet, ankles, forearms, skin and the eye lens. The maximum hand-dose for workers and exposed workers are 50 and 500 mSv/year respectively. Dose limits for stochastic effects are expressed in effective dose limits. The maximum effective dose for workers and exposed workers is 1 and 20 mSv/year respectively.

The maximum effective dose of 1 mSv/year can be compared with 20 X-rays of the chest or 10 roundtrips London–New York on an aeroplane.

Radioactivity creates a 'fear-factor', and the exposure to it should be as low as possible.

The sentinel node can be identified with a radioactive tracer injected around the tumour in the breast. Surgeons and pathologists working with the radioactive breast are usually (non-exposed) workers. Studies all show that the exposure rate is very low.[5–10] The purpose of our study was to determine the radiation dose for people involved

Correspondence to: Prof. Alexander M. M. Eggermont, MD, PhD, University Hospital Rotterdam/Daniel den Hoed Cancer Center, Department of Surgical Oncology, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands. E-mail: Eggermont@chih.azr.nl

in the sentinel node procedure in breast cancer patients and testing of the theoretical model.

PATIENTS AND MATERIAL

We studied 12 consecutive breast cancer patients undergoing breast surgery, a sentinel node dissection including an axillary lymph node dissection (ALND).

We identified and removed the SN before a full ALND was performed. Seven patients underwent a mastectomy and five a breast sparing operation. On the day of operation 3 ml of 30 MBq 99m-Technetium nanocolloid was injected subcutaneously around the tumour or the lumpectomy site. The patients underwent a lymphoscintigraphy and 2 h hereafter the patient was ready for operation. During the operation the radiation dose to which the surgeon, his assistant and the theatre nurse were exposed was measured. In order to get a proper insight in the exposure to the radiation, the dose of the thoracic wall, the dose on abdominal wall and both the dose on the hands of the surgeon and her assistant were measured with small thermoluminoscent-dosemeters (TLD100 LiF) ($3 \times 3 \times 0.9$ mm). Only the chest wall dose of the theatre nurse was measured. After the operation the breast tissue and all lymph nodes were passed on for histologic examination. The radiation exposure of the pathologist was measured by thoracic, abdominal and fingers dosimeters. The chest exposure of the pathologist's assistant was measured.

The exposure dose was calculated in mSv corrected by the background dose measured in the operation room and pathology department at 3 m from the patient and breast tissue respectively.

RESULTS

Calculated results

Before the measurements we also made calculations to get insight about the absorbed dose we could expect. To make those calculations there were some starting points (Table 1). These calculations have been made with the assistance of formulas mentioned in the addendum. The results for the pathologist-assistant are calculated by the assumption that he stays 2.5 h at a distance of 2 m of the radioactive tissue and in the two following days 2 h at 50 cm and 14 h at 3 m of the radioactive tissue.

Table 2 shows the calculated results for one procedure.

Measured results

The average operation time was 1.56 h $\pm$ 0.38 h, there was a small difference in time between mastectomy (1.65 h) and breast conservative therapy (1.48 h). There was no difference between measured radiation of the thoracic wall if lumpectomy and ALND were performed in the same time as mastectomy. Therefore the radiation dose of the thoracic wall is averaged over all 12 patients. The average activity at the start of the operation was 16.95 MBq $\pm$ 2.63 MBq. Table 3 shows the results of the measured dose of radiation. To estimate the effective dose we used the exposure to the abdominal wall.

Table 1 Most important starting points

Injected activity 99m-Tc	30 MBq
Half-life time 99m-Tc	6.02 h
Time between injection and operation	4 h
Operation time	2 h
Distance hand-radioactive tissue	5 cm
Distance for determination of the effective dose	50 cm
Internal contamination	0.1% of the activity present at the beginning of the procedure
Time between injection and pathology department	7 h
Proces time in the pathology department	30 min

The results of the measurements on the theatre nurse and both pathologist as his assistant are beneath the detection limit of 10 μSv. The detection limit depends on the used measuring device; we used TLD-100 chips with a detection limit of 10 μSv. Figure 1 shows the 'hand-exposure dose of the surgeon'. First, the longer the operation time the higher the hand-dose. Secondly, the non-dominant hand is exposed to a higher radiation dose in contrast with the dominant hand. Figure 1 also shows that a breast-conserving operation takes less time and the difference between non-dominant and dominant hand is less than in case of a mastectomy.

In this study on exposure to radioactivity by the key personnel involved in Sentinel Node Procedures we found that the results of the calculated and measured numbers are similar. The radiation exposure of the abdominal wall of the surgeon (effective dose) is somewhat higher than the calculated results mostly because of the distance between abdomen and radio-active breast. In the calculated results we used a distance of 50 cm while at the operation table the distance is half for the surgeon and his assistant. The measured hand dose for both surgeon and his assistant is less than the calculated dose. The distinction for the surgeon between left and right hand is the same as dominant hand and non-dominant hand because all surgeons were right handed. The difference between the dominant hand and the non-dominant hand is caused by the operating technique. The non-dominant hand presents the tissue to be removed by the dominant hand. This results in a shorter distance between non-dominant

Table 2 Calculated results for one procedure

	Surgeon (μSv)	Assistant-surgeon (μSv)	Pathologist (μSv)	Pathologist-assistant (μSv)
Effective dose by external exposure	2.1	2.1	0.38	0.63
Effective dose by internal exposure	0.4	0.4	0.28	0.32
Total effective dose	2.5	2.5	0.66	0.95
Hand dose	85	85	5	3.8

Table 3 Measured results

	Surgeon (μSv)	Assistant-surgeon (μSv)	Theatre nurse (μSv)	Pathologist (μSv)	Assistant pathologist (μSv)
Thoracal wall	3.7 (0–9.8)	0.9 (0–7.5)	1.9 (0–6.3)	0.4 (0–8.5)	2.0 (0–8.0)
Abdominal wall	8.2 (0–32.7)	2.1 (0–8.7)		1.0 (0–6.8)	
Left hand	61 (22.2–152.8)	21 (3.2–51.8)		3 (0–6.4)	
Right hand	18 (1.8–42)	17 (0–30.4)		2 (0–12.2)	

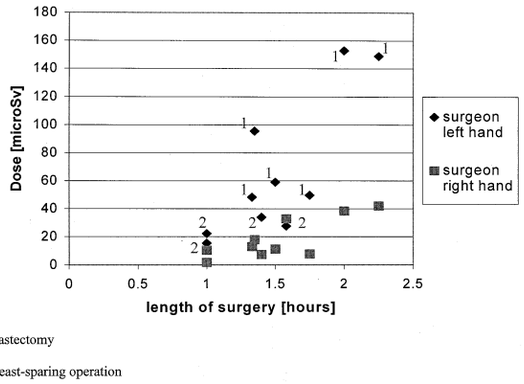

Figure 1 Hand-dose surgeon; left vs right hand.

hand and radioactive tissue in comparison with the dominant hand.

The radiation dose depends on some factors, first the time between injection and operation; the longer this time the less activity at the beginning the operation and the less exposure. Secondly, the radiation dose depends on the duration of the operation; the longer the operation the more exposure time.

DISCUSSION

We have shown that most people involved in the sentinel node procedure are effectively non-exposed workers, with a dose limit of 1 mSv/year. The highest measured dose is at the abdominal wall of the surgeon. This is the worst case effective dose, with an average of 8.2 μSv per procedure. One surgeon could thus perform 100 sentinel node procedures a year if he performed a one-day procedure with 30 MBq 99m-Technetium, within Dutch statutory limits.

In the United States the annual allowable radiation exposure limits are set by the Occupational Safety and Health Administration (OSHA).[11] For the general population the allowed dose for the whole body is 5 mSv.

Miner *et al.*[6] studied the radiation exposure in breast cancer and melanoma patients who underwent sentinel node biopsy. Radiation exposure based on the relative activity using a Geiger–Mueller counter revealed a mean dose of 98 μSv to the hands of the surgeon. Stratmann *et al.*[7] studied in 20 breast cancer patients who underwent a sentinel node biopsy the radiation exposure with a hand-held Geiger counter. The exposure to the surgeon's hands was 342.5 μSv/h and to the surgeon's torso 13.3 μSv/h. In this study we found a much lower exposure. The figures of Stratmann *et al.*[7] are higher because they performed dose-rate measurements at shorter distance from the place of injection. This seems not very representative for the real position of the surgeon's hands. In general, dose-rate measurements are more difficult to interpret and translate to exposure conditions in the daily practice of the surgeon. Therefore dose measurements seem to be more suitable. This can explain the difference between the two studies.

CONCLUSION

Instruction of all involved people is essential to make them understand safety of the procedure and avoid unnecessary fear. Normal hygiene measures should be

taken. Radiation dose levels are less than the established dose limits for (nonexposed) workers if the number of procedures is restricted to about 100/person/year.

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ADDENDUM

Effective dose for external exposure:

$$E_e = \dot{E}_{op50cm}(0) \cdot e^{-\ln 2((t_1 - t_0)/T_{1/2})} \cdot t$$

Effective dose for internal exposure:

$$E_{50} = e_{50,volwassen,ingestie} \cdot b \cdot A \cdot t$$

Total effective dose:

$$E_{tot} = E_e + E_{50}$$

Hand-dose:

$$H_{hand} = \dot{H}(0) \cdot e^{-\ln 2((t_1 - t_0)/T_{1/2})} \cdot t$$

$H(0) =$ equivalent dose rate at $t = 0$

$\dot{E}_{op50cm}(0) =$ effective dose rate at a distance of 50 cm at $t = 0$

$H_{hand} =$ equivalent dose on the hands

$t =$ time in hours

$t_0 =$ time of injection

$t_1 =$ time starting external exposure

$T_{1/2} =$ half-life in hours

$b =$ fraction of the present activity coming into the body by oral intake or inhalation

$A =$ 99m-Tc activity during the action with internal exposure (Bq)

Accepted for publication 9 December 2002

CHAPTER 7

Is internal mammary chain sentinel node biopsy worth while?
Outcome in 90 consecutive non-biopsied patients with a positive IMC scintigraphy.

M.W.J.M. Wouters, M.B.E. Menke-Pluijmers, A.Y. de Kanter, H.G. de Bruin, L. Verhoog, A.M.M. Eggermont, A.N.van Geel.

Is Internal Mammary Chain Sentinel Node Biopsy worth while?

Outcome in 90 consecutive non-biopsied patients
with a positive IMC scintigraphy

M.W.J.M. Wouters[1], M.B.E. Menke-Pluijmers[1], A.Y. de Kanter [1], H.G. de Bruin [2],

L. Verhoog [3], A.M.M. Eggermont [1,] A.N.van Geel [1].

From the departments of Surgical Oncology [1], Radiology [2], Pathology [3] of the Erasmus Medical Center/ Daniel den Hoed, Rotterdam, the Netherlands

Abstract

Background: Although the status of the regional lymph nodes is the most important determinant of prognosis in breast cancer, harvesting sentinel nodes (SNs) detected in the internal mammary chain (IMC) is still controversial.
Aims: The aim of this study was to determine in how many patients the identification of a positive IMC SN might change the systemic or locoregional therapy, with a possible benefit in outcome.
Patients and methods: In a 6½ years period, data of all patients with T1-2 breast cancer, who had a SN procedure, were prospectively collected. In this period our policy was *not* to explore the parasternal region even if the IMC was the only localisation of a SN.
Results: Of 571 patients scintigraphy indicated in 86 a hot spot in the IMC. In 64 of these patients the axillary SN was negative. Of these only 25 did *not* have an indication for adjuvant systemic treatment based on their tumour characteristics. From the literature is known that in axillary negative patients IMC metastasis are found in 0-10% of the cases. Therefore, routine IMC SN biopsies would only in 2 to 3 of our patients have resulted in the identification of an indication for adjuvant systemic therapy. During a median follow-up of 36 months no parasternal recurrences were found.
Conclusions: Routine performance of an IMC SN procedure is not necessary, because parasternal recurrences are very rare and only very few patients benefit in the sense that an indication for adjuvant systemic therapy is identified.

Keywords: breast cancer, sentinel node biopsy, internal mammary lymph nodes, staging

Introduction

In breast cancer sentinel node (SN) biopsy of the axilla is a widely accepted procedure for staging purposes [1 2]. The axillary lymph node status is one of the most important prognostic factors on which decisions about adjuvant treatments are based. However, dissemination of tumour cells through the lymph system is not only taking place to the axillary lymph nodes but also to the supraclavicular and internal mammary lymph nodes [3]. Although studies of lymphatic drainage patterns report internal mammary chain (IMC) involvement in 13 to 35%, the value of a SN procedure for IMC is still controversial [4-8].
A survival benefit has not been observed after complete dissection of the IMC region [9-14]. Although adjuvant locoregional radiation therapy has proven to be beneficial after mastectomy [15-17], the contribution of radiation to the IMC to improve survival and recurrence rates, is still unclear. A tumour-positive IMC node could be a reason for selective IMC radiation. Several articles addressed this subject. Although IMC radiation might decrease loco-regional recurrence, there is no evidence for a beneficial effect on survival, while the risk of complications like pneumonitis and cardiac toxicity increase [18-22].

Despite the lack of impact of surgical and radiation therapy for tumour-positive IMC nodes, the identification of these node-metastasis might be important for an other reason [11 23]. The tumour status of IMC nodes does have a prognostic value, which is comparable to that of the status of the axillary lymph nodes [10 24 25] . Especially for axillary node negative patients, with SNs in the IMC on lymfoscintigraphy, stage migration could be the result of harvesting these nodes [26 27]. Upstaging is seen in 7–17 percent of the patients in who an IMC SN is found [8, 27].

So, an IMC SN procedure might promote accurate staging. However, we must take account of the shortcomings of the procedure. Although it is possible to identify and selectively remove IMC SNs with minimal morbidity, complications are reported in 2.2% to 8% of the cases [8 27 28 46]. Only a therapeutical benefit justifies such extra morbidity.

Because of the failure of studies to demonstrate any significant survival benefit, in the past our policy was not to remove IMC SNs visualized on the lymphoscintigraphy, even when axillary nodes were negative.
The purpose of this study was to determine in how many patients the identification of a positive IMC SN would have changed the systemic or locoregional therapy, which might have resulted in a benefit in outcome.

Patients and Methods

Since July 1997 an axillary SN biopsy is the standard staging procedure for patients with T1 or T2 breast cancer in our hospital. Prior to surgery ultrasound of the axilla is routinely performed with additional fine needle aspiration if suspicious lymph nodes are seen [29]. When this reveals an axillary lymph node metastasis, the SN procedure is abandoned and an axillary lymph node dissection (ALND) is performed. All patients *without* FNA proven lymph node metastasis get a SN procedure. On the day of the operation 39 MBq Technetium-99M is administered in 3 peritumoral injections. In case of nonpalpable breast cancer the peritumoral injection is guided by ultrasound or stereotaxis. After 2 hours a lymphoscintigraphy is made to identify the routing of the colloid and the subsequent SN (Figure I). The anterior and lateral images are preoperatively shown and described to the surgeon by the nuclear specialist. Also, the locations of SNs are marked on the skin with indelible ink and during surgery confirmed with a hand-held gamma-probe. Just before surgery, 1.0 mL of Patent Blue is injected intradermal above the tumour. The SN biopsy of the axilla is performed before surgery of the breast, with a frozen section of the SN, that if found tumour-positive, leads to an ALND. Post-

operative, the frozen-section is followed by further pathologic evaluation, cutting the node at a minimum of six levels and hematoxylin-eosin and immunohistochemical staining. Secondary found SN metastasis also lead to ALND.

All patients with a SN procedure in the period July 1997 to November 2003 were included in a prospective database. In this period our policy was *not* to explore the parasternal region even when the IMC was the only localisation with a hot spot on lymphoscintigraphy. To evaluate this policy we selected all patients with an IMC SN on the lymphoscintigraphy from our prospective database. For these patients the following data were collected; date of birth, date of the SN surgery, pathological N status, pathological characteristics of the primary tumour (tumour size in mm, differentiation according to Bloom and Richardson I, II and III, Mitotic Activity Index, Estrogen and Progesterone receptor status), radiotherapy and adjuvant systemic therapy (yes or no), clinical signs of IMC node recurrence and if performed date and results of CT scans of the chest and bone scans. If any of these data could not be found in the pathology or radiology reports, the histological material was reviewed by a pathologist and the images were reviewed by a radiologist.

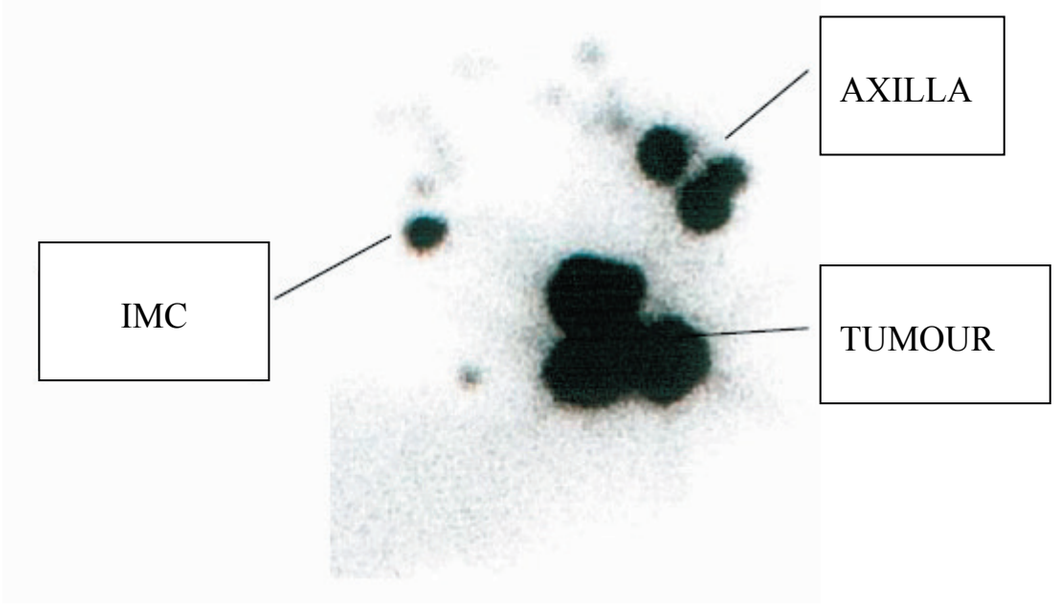


Figure I
Lymphoscintigraphy in a breast cancer patient showing the axillary and the internal mammary chain lymph nodes

The pathology reports of all patients with an IMC SN on the lymphoscintigraphy were reviewed and the indication for adjuvant systemic therapy was reconsidered based on the most recent guidelines in the Netherlands [30]. These guidelines (Figure II) are a result of a multidisciplinary consensus derived from the evidence-based literature.

Results

From 1 July 1997 to 1 November 2003, a SN procedure was performed in 571 consecutive patients. In 481 of these patients there was only an axillary lymph node visualized on the nucleotide scan. In 89 patients both an axillary and an IMC SN were detected. In 1 patient

only an IMC SN was seen and this patient was also included in the study. All but one of these 90 patients were female. The age at the time of SN biopsy was 31-85 (mean 50) years.
In 4 of 90 patients the definitive pathological diagnosis showed no invasive breast cancer (2 patients with severe sclerosis, 1 patient requested a prophylactic mastectomy and SN biopsy, and 1 other patient had DCIS with a positive SN). These patients were excluded, leaving 86 patients in the study.

Figure II
Current Dutch Guidelines for the treatment of breast cancer [34]

Adjuvant systemic treatment in node negative breast cancer and age >35 years

Tumour size	Differentiation (SBR) and age		
	BR I	BR II	BR III
≤ 1 cm	-	-	-
1-2 cm	- (≤ 35y see N+)	- (≤ 35y see N+)	See N+
2-3 cm	- (≤ 35y see N+)	See N+	See N+
> 3 cm	See N+	See N+	See N+

Adjuvant systemic treatment in node positive breast cancer (all ages) and N0 (≤ 35years)

Receptor status	Menopausal status			
	Premenopausal	Postmenopausal		
		50-59 years	60-69 years	≥70 years
ER+ and/or PgR+	**N ≥ 1:** CT and HT	**N ≥ 1:** CT and HT	**N 1-3:** HT **N ≥ 4:** CT and HT	**N ≥ 1:** HT
ER- and PgR-	**N ≥ 1:** CT	**N ≥ 1:** CT	CT	**N ≥ 1:** no advice possible

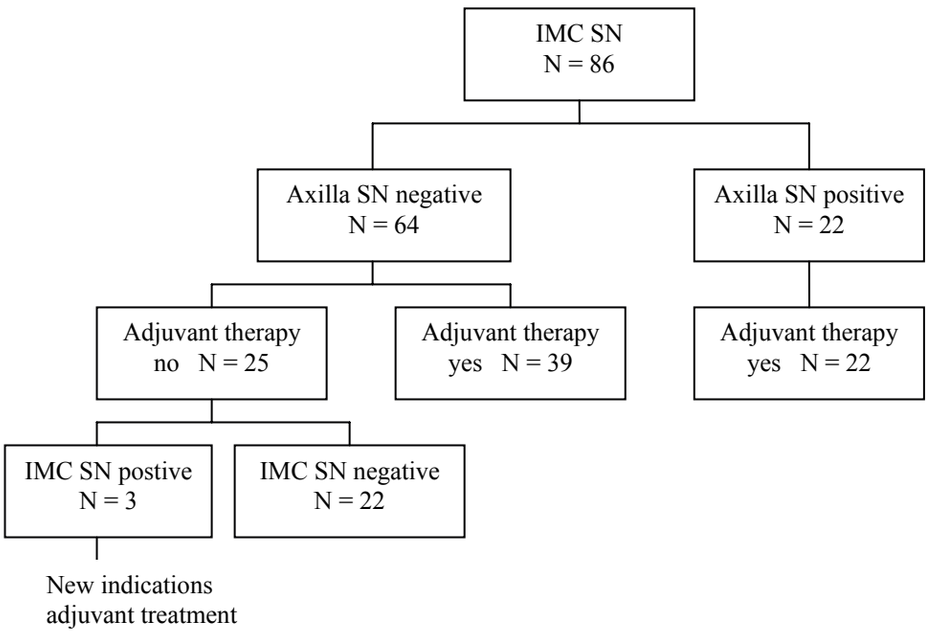
Legend; BR=differentiation according to Bloom and Richardson (I, II and II); N=Nodal stage; ER=Estrogen Receptor; PgR=Progesterone Receptor; CT=Chemotherapy; HT=Hormone Therapy

In 64 of 86 patients (74%) the axillary SN was negative. The other 22 patients (26%) had a tumour positive axillary SN and consequently they underwent an ALND and received adjuvant systemic treatment. Another 27 patients received adjuvant systemic treatment on the basis of the characteristics of the primary tumour, in line with the national guidelines *at that time*. Therefore, 37 patients (43%) did *not* have an indication for adjuvant systemic therapy. Under the *current* guidelines, last revised in 2004 (Figure II), this number would be reduced to 25 (29%). These are of special interest because information about the IMC status could change the management of these patients. Upstaging from N0 to N+ status could mean an indication for adjuvant systemic treatment (Figure III).

In the absence of information about the IMC status, none of the patients received selective parasternal radiotherapy. Neither was the IMC irradiated as part of regional radiotherapy. For various reasons 3 patients received postoperative chest wall irradiation, and 24 patients underwent radiotherapy as part of breast-conserving therapy.

The median follow-up time was 36 months (range 3-89 months). According to the national guidelines patients had a physical examination every 3 months and radiological imaging of the breasts every year. Further imaging was only performed on indication, such as pain, swelling and various other reasons. A CT-scan of the chest was performed at any time during follow-up in 35 cases. No IMC recurrences were found. We did find one patient with *clinical* signs of a possible parasternal recurrence, but in this case a sternal metastasis with pathological fracture was diagnosed, as a part of wide-spreaded bone metastasis. There were no signs of IMC metastasis on this patient's CT scan. The other CT scans, which were revised especially for this study, did not show enlarged IMC nodes, both in their primary and secondary assessment.

Figure III
Break down of the number of Internal Mammary Chain Sentinel Nodes of 86 patients according to the indication for adjuvant systemic therapy.



Abbreviations; AX=axillary, IMC=internal mammary chain, SN=sentinel node, *present indication according to the national guidelines published in 2004.

Discussion

In our series of 571 patients the lymphoscintigraphy showed an IMC SN in 90 cases (16%). We did not see a single case with clinical signs of IMC metastasis at a mean follow up of 41 months. Not a single parasternal metastasis was diagnosed in spite of the fact that none of our patients received radiotherapy to the IMC, after surgery. Though, the status of the IMC SNs could be relevant in another way. Exploration of the IMC could improve staging, which is especially important when upstaging leads to a change in management of the patient.

From the literature is known that treatment of the IMC, either by surgery or by radiotherapy, does *not* improve survival. Veronesi et al. reported 56 patients with positive

axillary nodes who had undergone either quadrantectomy with axillary node dissection or Halsted's mastectomy. Patients were randomized to receive either postoperative radiation therapy to the supraclavicular and IMC nodes or no further treatment. Survival curves at ten years showed no advantage with adjuvant radiation therapy to these sites [31]. Palmer and Ribeiro reported a much larger prospective randomized trial for postoperative radiation to the axilla, supraclavicular and parasternal region, which also failed to show a difference in survival even after 30 years follow-up [32]. Host et al. confirmed the absence of a survival benefit in the long-term results of the Oslo study, but found a lower incidence of loco-regional recurrence [22].

Also, in more recent literature, authors state that an IMC SN procedure leads to a better selection of patients who *might* benefit from postoperative radiotherapy to the parasternal region [8 27 46].

In our series, we looked into the 90 cases of hot spots in the IMC. Since patients did not receive parasternal radiotherapy, possible microscopic disease in the IMC nodes was left untreated. Although the IMC could have received some irradiation dose in breast conserving treated patients, we did expect some cases of parasternal recurrence during follow-up. Based on the literature we can assume that 9 to 30 percent of our patients had metastasis in the IMC nodes shown on the lymphoscintigraphy [8 10 24 36 44]. But, calculating with these percentages we must take into account that the technique for detecting and harvesting IMC SNs differs greatly. In our series of 571 patients the lymphoscintigraphy was suggestive for an IMC SN in 16% of the cases. This was the result of the use of 39 MBq injected peritumorally. Others report a detection rate of 25% using a ten times higher dose of technetium-99m [6]. The subsequent biopsies have different success rates, ranging from 63 to 97 percent [6 8 27 45]. Variations in technique give different procedure outcomes. But, because most series report a visualization rate between 5 and 20%, we may conclude that above mentioned percentages are applicable to our series [9]. Untreated, one expects this metastasis to grow and lead to locoregional symptoms. In subsequent imaging it could be difficult to differentiate a sternal erosion or solitary bone metastasis from a lymph node recurrence. But, in our series we had only 3 patients with a sternal lesion, and all had widespread bone or visceral metastases. According to the definition used in the literature, these patients are *not* considered to have a lymph node recurrence in the IMC [33,34]. Other reports confirm that only a fraction of (micro)metastasis in the IMC become clinically evident [35].

Just like the nodes in the axilla, IMC nodes *do* have a prognostic value. Veronesi et al. found in their analysis of 1119 patients that survival was significantly affected by the presence of positive IMC nodes. 10-year survival varied from 80% in patients with axillary *and* IMC negative nodes, 55% in axillary positive *and* IMC negative nodes, 53% in IMC positive *and* axillary negative patients and 30% in patients with both axillary and IMC positive nodes [36].

Therefore, the failure of recognizing an IMC positive node, *could* lead to under-staging. In Veronesi's series 9% of the patients had negative axillary and positive IMC nodes. Other articles report slightly lower percentages of 2 to 8 % [8 10 28 37]. In this group under-staging could lead to under-treatment, because a node positive status is one of the main indications for adjuvant systemic treatment.

In our series of 86 patients with breast cancer and an IMC SN on the lymphoscintigraphy, there were 64 patients (74%) with a tumour negative SN in the axilla. Without information about the IMC status, 39 of these patients would have had an indication for adjuvant systemic treatment, based on most recent Dutch guidelines (Figure I) [30]. So, 25 patients would not receive adjuvant treatment. In the literature cases with no axillary metastases in which IMC metastasis changed the N0 to a N+ status, were found in 0% to 10% of these patients (Figure IV). So, if in one tenth of the 25 patients the N status turns positive, 2 to 3 of the original 64

axillary negative patients *could* benefit from the IMC SN procedure (5%). They are the ones who 'gain' an indication for adjuvant systemic treatment. The other 61 biopsies will be without any therapeutic consequence.

The possibility to define a subgroup of patients which can be selected to perform an IMC SN procedure on the basis of localisation, size, grade or other characteristics of the tumour is still questionable [5 10 38-40].

Figure IV
Results of lymph node biopsies of the Internal Mammary Chain in the literature

Article	SN procedures	IMN on lympho scintigraphy	IMN biopsies	IMN positive	IMN pos axilla neg
Goyal, 2005 [51]	1139	120	58	8	5
Farrús, 2004 [52]	225	20	14	2	0
Lawson, 2004 [53]	175	10	6	0	0
Estourgie, 2003 [8]	691	150	130	22	9
Galimberti, 2002 [29]	n.r.	182	160	14	4
Ent v.d., 2001 [6]	256	65	41	11	3
Dupont, 2001 [54]	1273	n.r.	30	5	3
Dupont, 2001 [22]	1470	n.r.	36	5	2
Johnson, 2000 [55]	80	10	10	3	0
Noguchi, 2000 [56]	41	5	5	0	0
Winchester, 1999 [58]	180	20	20	3	0
				(0-30%)	(0-10%)

Abbreviations: IMN = Internal Mammary Node, SN = Sentinel Node,
lymphosc. = lymphoscintigraphy, n.r. = not reported

Non palpable medial tumours might drain more often to the IMC nodes independent of tumour size [6,41]. There are three reports on the influence of tumour location on IMC metastases in axillary node-negative patients [42-44]. Two of them show no difference in the incidence of IMC metastases between medial and lateral primary tumours. The other one, from Li in 1984, showed from 1242 cases of extended radical mastectomy for medial tumours 8 percent IMC positive nodes versus 2 percent for lateral tumours.
In addition, if size, grade and receptor status are known prior to the SN procedure, harvesting an IMC SN can be abandoned when an indication for adjuvant systemic treatment is already present. Accurate imaging and a histological biopsy is needed to obtain this information preoperatively. If such a biopsy would be successful in 100% of the cases, the number of SN biopsies, relevant for the management of the patient, could be reduced significantly. If we *could* have selected the 25 patients in our series, for whom the tumour characteristics where *no* indication for adjuvant systemic therapy, we could have restricted the IMC SN biopsies to these patients. With a tumour positive IMC SN in 2 to 3 patients, we would still have performed 10 biopsies to find 1 tumour positive SN.

That these results are not theoretical is confirmed by earlier studies [23,45]. In the UK ALMANAC multicenter trial, in which 1139 patients had a SN biopsy for T1-T3 breast cancer, there was IMC node drainage in 120 (10.5%) of the patients, of which 60 where biopsied. Only 4 (7%) of these patients had a change in management, meaning a 'new' indication for systemic therapy.

Conclusion

Based on our series and a review of the literature we conclude that the indication for an IMC SN procedure is very limited. For only 2 to 3 of our 571 patients (0,5%) harvesting an IMC SN could have been beneficial. If tumour characteristics are known prior to the procedure, a further selection of patients might be possible. But even then, of the patients in whom an IMC SN is successfully biopsied only 7 to 10% *might* benefit as a result of adjuvant therapy. On top of the futile therapeutic contribution one should be aware of introducing a procedure which, like any other procedure has complications.

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CHAPTER 8

5-Year follow-up of sentinel node negative breast cancer patients:
few axillary recurrences, futility of ultrasound of the axilla

A.Y. de Kanter, M.B.E. Menke-Pluymers, M.W.J.M. Wouters, J.P.J. Burgmans,
A.N. van Geel, A.M.M. Eggermont

European Journal of Surgical Oncology 2006; 32: 282-286

5-Year follow-up of sentinel node negative breast cancer patients

A.Y. de Kanter, M.M. Menke-Pluymers, M.W.J.M. Wouters, I. Burgmans, A.N. van Geel, A.M.M. Eggermont*

Department of Surgical Oncology, Erasmus MC-Daniel den Hoed Cancer Center, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands

Accepted 28 November 2005
Available online 24 January 2006

Abstract

Aim: To report the long-term results of sentinel node negative breast cancer patients treated without axillary lymph node dissection and the 5-year follow-up results of 149 patients.

Methods: The incidence of axillary—and local recurrences and second ipsilateral primary tumours was evaluated. The added value of annual ultrasound of the treated axilla, being part of the standard follow-up, was also evaluated.

Results: After a mean follow-up of 65 months (50–79) axillary recurrences were observed in four patients, local recurrences or ipsilateral second primary tumours were diagnosed in another seven patients. All axillary recurrences were diagnosed because of a palpable axillary mass; ultrasound in combination with fine needle aspiration cytology did not have an added value.

Conclusion: It can be concluded that the incidence of axillary recurrences after negative SN is much lower than expected. There is no added value of US and FNAC of the axilla in the routine follow-up of SN negative patients.

Keywords: Sentinel node; Breast cancer; Follow-up; Ultrasound; Recurrence

Introduction

Since, the introduction of the SN in breast cancer patients by Giuliano and Krag in the early 1990s,[1,2] the SN has proven to be a valuable tool in predicting the status of the axilla.[3–5]

After a validation period many institutes abandoned standard ALND as a staging procedure. Only in those patients with a positive SN ALND is performed. The SN biopsy became routine practice despite lack of long-term follow-up results concerning local control and overall survival. The meaning of isolated tumour cells and even micrometastases in the SN is still uncertain and topical subject in many discussions. Future studies should define the management of these metastases. Up until now there is no standard treatment of axillary- and local recurrences. For instance, in case of a local recurrence in the breast the necessity of ALND is still discussed.

Our study reviews all clinical data and follow-up collected in 149 patients with SN negative invasive breast cancer.

Because of our positive experience with ultrasound (US) examination of the axilla combined with fine needle aspiration cytology (FNAC) in the pre-operative detection of axillary lymph-node metastases,[6] we incorporated this procedure in our follow-up routine.

The purpose of our study was to evaluate the value of US combined with FNAC in the follow-up and our axillary recurrence rate.

Patients and methods

Between November 1998 and May 2001 160 clinically node negative, operable breast cancer patients underwent SN biopsy that revealed a negative histological status. No further ALND was performed. Part of the work up was US examination of the axilla and in case of visible nodes FNAC was performed. In case of pre-operative positive US-FNAC patients were scheduled for ALND. In all other cases SN biopsy was part of the operation. Eleven patients were followed-up in other hospitals; leaving 149 patients for evaluation.

* Corresponding author. Tel.: +31 10 4391506; fax: +31 10 4391011.
E-mail address: a.m.m.eggermont@erasmusmc.nl (A.M.M. Eggermont).

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doi:10.1016/j.ejso.2005.11.014

Technique

Our SN biopsy technique is described in detail before.[5] In short the procedure included peritumorally injection of 39 MBq 99m-Technetium nanocolloid (Solconanacoll) at least 2.5 h before the operation. Two hours post-injection a static lymphoscintygraphy was made. Prior to the operation 1 ml Patent Blue was injected intradermally above the tumour. Subsequently, the SN was identified with guidance of a Europrobe and the blue-stained lymphvessels. In case of internal mammary chain hotspots, no attempt was made to trace and remove these lymph nodes. The SN biopsy of the axilla is performed before surgery of the breast, with a frozen section of the sentinel node, that if found tumour-positive, leads to a level I and II axillary lymph node dissection. In case of negative frozen-sections, further pathologic evaluation, cutting the node at a minimum of six levels and hematoxylin-, eosin and immunohistochemical staining is followed. Patients with secondary found (micro-) metastasis were offered ALND in a separate operation session.

Adjuvant treatment and follow-up

The decision for adjuvant systemic therapy was individualized and made by the medical oncologist and the patient. External beam radiation was part of breast conserving therapy. Patients received 50 Gy to the whole breast with tangential fields, with a boost to the tumour bed to a total of 65 Gy.

The follow-up consisted of taking history and physical examination every 3 months during the first 2 years and subsequently every 6 months, combined with an annual US examination of the axilla and mammography. In case of US visible lymph nodes FNAC was performed.

Results

Mean age of the 149 patients was 55 years (29–82). The median tumour size was 1.2 cm, 56% were T1c tumours. Eighty-four patients (56%) choose breast-conserving therapy. Histopathological examination showed ductal carcinoma in 122 patients, the Bloom–Richardson was mostly grade II. Only 20 patients (13%) received adjuvant systemic treatment mostly because of tumour characteristics. The mean follow-up was 65 months (50–79).

Axillary recurrences

During follow-up axillary recurrences were observed in four patients. In three patients, the initial treatment was ablation. All initial tumours were small (10, 15, 16 and 17 mm), Bloom–Richardson grade I or II and the ER was positive in all four cases. All patients were analysed because of a palpable lymph node in the axilla. Time to axillary recurrence was 10, 12, 14 and 56 months. After positive cytology, all patients underwent ALND. In all patients there were at least two positive lymph nodes. Decisions for adjuvant treatment depended on the pathological results, three patients received chemo-, hormonal- and radiotherapy and the fourth patient received only hormonal therapy. Unfortunately, one patient developed brain- and bone metastases 27 months after her axillary recurrence. Up until now the other three patients are free of disease 6, 45 and 49 months after their delayed axillary treatment.

Local recurrences

Local recurrences or ipsilateral second primary tumours were diagnosed in seven patients. Ablation was in three patients the initial treatment. The initial tumour ranged from 10 to 25 mm with all but one positive ER. The recurrences were detected due to a palpable mass (five patients), ultrasonographically metastatic axillary lymph nodes ($N=1$) or screening mammography ($N=1$). Time to local recurrence was 18, 26, 33, 38, 39, 53 and 59 months. Treatment consisted of ablation of the breast including ALND in case of primary breast conserving therapy. In case of primary ablation local resection and ALND was performed followed by radiotherapy of the chest wall. In one patient no ALND was performed in dialogue with the patient because of indistinction about the necessity. Pathological examination of the ALND showed in four patients metastases. Decisions for adjuvant treatment (chemo-, hormone and/or radiation of the axilla and supraclavicular region) depended on the pathological results. One patient, primary treated with ablation and SN, developed sternal pain a few months after resection of her medial located recurrence. Cytology revealed sternal metastatic cells and because screening for distant metastases was negative she was treated with 50 Gy to the sternal bone. No adjuvant hormonal treatment was given because of negative receptors, patient refused adjuvant chemotherapy. One year after ending radiation treatment she developed supraclavicular metastases and started treatment with Herceptin.

Screening for distant metastases after the surgical treatment of the recurrence, was positive (lung and liver metastases) for another patient and she was treated with systemic therapy. Up until now the other five patients are free of disease 16, 17, 25, 38 and 60 months after their recurrence treatment.

Annual ultrasound examination of the axilla

In order to detect axillary recurrences as soon as possible, annual US examination of the treated axilla was part of the follow-up. Unfortunately, this examination was not performed in 48 patients due to several reasons. The US combined with FNAC was only once positive in only one of 101 patients. This patient had axillary lymph-node metastases of a pathologically proven second primary

breast tumour. In three of the four axillary recurrences patients detection of the palpable lymph nodes was before the scheduled annually ultrasound. The fourth axillary recurrence patient had three US examinations and once there was a visible node with benign characteristics and negative FNAC, a few months after her last US examination there was a palpable axillary lymph node. Subsequent ALND revealed two metastatic lymph nodes. In all other 100 patients the more than 200 US examinations and 43 FNAC yielded no positive cytology.

Discussion

The sentinel node concept, firstly described by Cabanas in 1977,[7] is extensively studied in breast cancer. Because of the results the SN procedure replaced ALND as standard axillary staging procedure with acceptance of 5% axillary recurrences. Since, this replacement attention was focussed on the incidence of axillary recurrences in SN negative patients treated without further ALND. As we know from the literature, the incidence of node positive patients is about 40%. However, the incidence of axillary recurrences in breast cancer patients without treatment of the axilla is 7–18% after a median of 14.7–31 months at a follow-up of 63–126 months.[8,9] Apparently, not all tumour cells found with pathological examination are potentially metastatic. Although ALND is performed to reduce the number of axillary recurrences, the incidence is still 0–2.1% at follow-up of 40–180 months. The influence of surgical- and adjuvant treatment on overall survival is unclear because of the small numbers of patients and change of single- towards multimodality treatment approach.[8,10–16]

At best the incidence of axillary recurrences after negative SN biopsy is as low as after ALND. Up until now, the reported studies concerning follow-up after negative SN show comparable good results (Table 1). Although our incidence is 2.7%, compared with the other reported results it is at least doubled but clearly lower than the expected 5%. This is partially explicable by our long follow-up and less adjuvant systemic treatment. Since January 2005, the indications for adjuvant systemic treatment are extended.

On the basis of the reported data it can be concluded that the incidence of axillary recurrences after negative SN is much lower than expected. Possible explanations are: a lower incidence of false-negative SN procedures than the 5% during the validation period, partially irradiated axilla in patients treated with breast conserving therapy due to tangential radiation fields, extending the possibilities of chemo- and/hormonal adjuvant therapy and the lower than expected capacity of tumour cells to develop into metastases.

Besides the sensitivity and the incidence of axillary recurrences the outcome of those patients who have developed an axillary recurrence was of great concern during and after the validation period. To date the follow-up of SN negative patients is too short to give an answer. However, the reported incidence is as low as after ALND

Table 1
Reported axillary recurrences

Author	Number of SN negative	Number axillary recurrence (initial treatment)	%	Time to axillary recurrence (months)	LR	DM	Mean FU (months)
Badgwell[20]	159	0	0	–	1	4	32 (24–43)
Blanchard[21]	685	1 (abl)	0.14	41	5	8	28 (7–46)
Chung[22]	208	3 (bct, 2×n.m.)	1.44	4, 11, 40	0	3	26
Jeruss[23]	592	1 (abl, CT, HT)	0.17	22	n.m.	n.m.	27.4 (1–98)
Kokke[24]	113	1 (abl, CT)	0.88	29	1	0	37 (24–53)
Langer[25]	122	1 (bct, CT, HT)	0.82	14	6	3	42 (12–64)
Naik[26]	2340	3 (3×bct, 1×HT)	0.13	18, 29, 38	n.m.	n.m.	31 (1–75)
Reitsamer[27]	200	0	0	–	0	n.m.	36 (22–56)
Roumen[28]	100	1 (abl)	1	14	1	1	24 (16–40)
Sanjuan[29]	159	1 (bct, CT)	0.63	19	n.m.	n.m.	21 (4–45)
Schrenk[30]	83	0	0	–	0	0	22 (4–48)
Smidt[31]	439	2 (2×abl, 1×HT)	0.46	4, 27	n.m.	n.m.	26 (1–90)
Torrenga[32]	104	1 (bct, syst)	0.96	24	n.m.	3	57 (48–83)
van der Vegt[33]	107	1 (bct)	0.93	26	n.m.	n.m.	35 (17–59)
Veronesi[34]	953	3 (abl, 2×bct, 1×HT, 1×CT)	0.3	26, 29, 37	12	22	38
Zavagno[18]	479	0	0	–	n.m.	n.m.	36 (12–68)
De Kanter	149	4 (3×abl, 1×bct)	2.68	10,12,14, 56	7	9	65 (50–79)

Abbreviations: LR, local recurrence; DM, distant metastases; FU, follow-up; abl, ablation; bct, breast conserving therapy; CT, chemotherapy; HT, hormonal therapy; syst, systemic therapy; n.m., not mentioned.

and the influence on overall survival of axillary recurrences after ALND is still unknown.

Because of our pre-treatment US results (sensitivity 57%)[17] and our false-negative percentage during the validation period (5%),[5] part of the follow-up of SN negative patients was US examination of the axilla combined with FNAC in case of visible lymph nodes, as mentioned above. With this procedure we hoped to detect axillary recurrences before they were clinically present in order to prevent simultaneous distant metastases and worse prognosis. However, none of the patients with axillary recurrences were detected with US. Moreover, the patients with visible nodes were anxious about the results that were in all cases benign. These disappointing results combined with the reported low incidence of axillary recurrences and the fact that treatment is still of curative intent, we decided that US and FNAC was no longer part of the standard follow-up. Only two other studies after the incidence of axillary recurrences used US of the axilla is in the follow-up. However, both studies had no axillary recurrences.[18,19]

An other unsolved issue is the management of the axilla in SN negative breast cancer patients with a local recurrence in the breast or on the abdominal wall.

Should re-SN or ALND be considered? In our study, in four out of six patients lymph-node metastases were found after ALND. This might suggest a possible role for re-SN staging, but in the one patient where we tried no SN could be identified.

In conclusion, the incidence of axillary recurrences after negative SN without proceeding ALND is lower than expected, in case of an axillary recurrence this can usually be treated by routine ALND. Whether one can determine its potential impact on survival is uncertain in view of the scarcity of these axillary recurrences. There is no added value of US and FNAC of the axilla in the routine follow-up of SN negative patients.

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SUMMARY

In the recent years the surgical treatment of breast cancer has changed towards a less invasive and less mutilating procedure. Breast conserving therapy and the introduction of the sentinel node (SN) procedure are the two most important changes. The introduction of a new technique is a time consuming procedure. First it should be developed and evaluated in a local situation. If the new technique is believed to be better than the standard treatment, the technique should be come available if possible after a randomised controlled trial for all patients concerned. In **CHAPTER 2** the introduction of the SN procedure in three participating hospitals (a large teaching hospital, a cancer centre and a university hospital) is described. Special attention was made on the role of a co-ordinator to assure standardisation and quality control in this multicenter study. The role of the co-ordinator was two folded; firstly the supervision of the implementation in the several involved departments and secondly to refine the procedure upon the collected data. During our study we adjusted several aspects of the procedure: the concentration of the colloid in the radioactive solution, the injection of the blue dye intracutaneously after disappointing results of the peritumoral injection and, in cases of a preceding lumpectomy, a cranial injection to the scar because of failure of the caudal injections. With these corrections the results became excellent.
In the end the results of the procedure (sensitivity and false negativity) were the same for the three participating hospitals.

Based on this experience an implementation project was started with the support of the Comprehensive Cancer Centre Rotterdam. The regional hospitals implementing the SN procedure were recommended to perform during the learning curve a double procedure (SN + axillary lymph node dissection (ALND)) of 50 patients. The hospital could proceed with SN biopsy only if less than 5% false-negative results were obtained, all patients were registered centrally and were able to be followed adequately.
Special recommendation was made towards ultrasound of the axilla during follow-up with the expectation to detect a regional recurrence in an earlier phase.

The SN procedure is complex and time consuming. It has several disadvantages such as low identification rate in extensive axillary lymph node metastases, false negative results, need for radioisotopes and requirement of frozen-section histological analysis. For this reason it would be valuable if SN biopsy could be replaced by easier methods. In a study before the era of SN biopsy preoperative ultrasound of the axilla in combination with fine needle aspiration cytology (FNAC) had proven to be a method with a low sensitivity but with a specificity of 100 per cent. Therefore this examination was part of the SN procedure in the multicenter study after the value of the SN biopsy in clinically node negative operable breast cancer patients. When metastases in the axilla were demonstrated, the SN biopsy was not relevant any more for the clinical decision making.

In **CHAPTER 3** the results of the ultrasound and FNAC were evaluated. The echo pattern was classified as inhomogeneous, homogeneous or node with an echo-rich centre. The first two classifications were considered potentially malignant and the last potentially benign. Subsequent histological examination of the axillary clearance specimens confirmed no false-positive results. The more axillary lymph nodes detected by ultrasonography the higher the percentage of metastases. The incidence of lymph node involvement and the rate of detection of lymph nodes increased with increasing tumour size.

In 36 per cent of all node positive operable breast cancer patients lymph node metastases were detected by ultrasonography and cytology. With this technique 17 percent of the patients do not need SN biopsy since ultrasonographically guided FNAC did already have detect

metastases and complete ALND can be performed as a primary procedure. These percentages are rather low probably due to a learning curve in recognising and aspirating lymph nodes with a suspicious image on ultrasound.

Keeping the learning curve in mind it was reasonable to predict an increased sensitivity of the ultrasound and FNAC after the initial study. Since a full ALND continued to be the standard treatment in node positive breast cancer patients the sensitivity and specificity of the combined procedure could be evaluated even after the implementation of the SN procedure. In **CHAPTER 4** the results of this succeeding study is shown. Lymph node aspiration contained adequate material in 73 percent with a sensitivity of 57 percent and a specificity of 96 percent in detecting metastases. Ultrasound-guided FNAC could identify 44 percent of histologically proven axillary metastases in primary breast cancer patients, 20 percent of the total patient population. In contrast of earlier results there were 3 false-positive results, explained by multifocality of the tumour associated with a dense lymphocytic infiltration, cytological misreading of cell groups and one is still unknown.

Ultrasound and FNAC was able to identify 83 percent of the patients with 4 or more axillary lymph node metastases. Twenty-five percent of the patients with 1-3 positive axillary lymph nodes were found to contain micrometastases only. It is clear that neither ultrasound nor cytology can replace histology in the detection of these metastases, but it partly explains the relative low sensitivity in both the initial multicenter and the single institution succeeding study. It seems unlikely that with the present technique the sensitivity will increase further.

Naturally, more intensive analysis of lymph nodes with serial sectioning and immunohistochemistry will reveal more metastatic disease. Up until now the biological relevance of micrometastases detected by immunohistochemical staining only is unclear. It has been suggested that the SN may, in certain circumstances, be capable of controlling local disease by removing metastatic tumour cells. It is also speculated that isolated tumour cells may not have potential for outgrowth. This could explain that metastatic disease in non-sentinel nodes only rarely occur in cases with micrometastasis. The term micrometastasis has only been defined arbitrarily, and its definition varies between studies. A cut off point of 2mm has been used in many studies and is included in the TNM classification. In **CHAPTER 5** the incidence of metastases in non-SNs is described in case of a detected micrometastasis. The non-SNs were investigated like the SN; cut at 250 μm intervals, immunostained with anticytokeratin antibody CAM 5.2 using a standard peroxidase procedure in an automated immunostainer. Metastases in non-SNs were identified in 11 of 32 patients, five of whom had initially been diagnosed as not having non-SN metastases. In seven patients more than one node was involved and in four patients the non-SN metastasis was larger than the SN metastasis (including two patients with non-SN macrometastases). It was observed that non-SN metastases as clusters were associated with tumours > 2cm in size and with high-grade tumours. The question arises whether the presence of microscopic tumour deposits in the SN justifies complete axillary clearance and adjuvant treatment. The answer hinge upon delineating the biological behaviour of small tumour deposits and small numbers of isolated tumour cells. A micrometastasis requires the arrest of tumour cells in the tissue and proliferation. Biological characteristics such as viability, angiogenic capacity, and avoidance of the host-immune reaction may be equally important factors. Whatever the outcome of single tumour cells in the circulation or in organs may be, it should be appreciated that the very fact that they are detected implies that access to the lymphatic or blood vessels has been gained, and that a line of defence has been breached in the metastatic pathway. On the basis of our findings we find it premature to conclude that ALND may be avoided in patients with T1-2 tumours and SN micrometastases.

As mentioned above the ultrasound guided FNAC is a reliable technique in the primary selection for a successful SN biopsy. However, the tracebility and sensitivity of the SN did not reach 100 percent in the initial multicenter study. In **CHAPTER 6** causes of failure to trace the ("real") SN in clinically node negative breast cancer patients with the primary tumour in situ are evaluated. After injection of 30-40MBq 99m-Technetium nanocolloid the SN was traced with guidance of a probe. The probe measured the radioactivity ratio (SN vs. background) in counts per second. Two levels of activity were distinguished; inadequate and adequate ratio. In case of inadequate ratio the sentinel node was not identified or only after a time consuming search. The number of involved lymph nodes after axillary dissection was classified according to the Dutch guidelines for adjuvant treatment in 1-3 and ≥ 4 positive nodes.

In the normal (non-metastatic) situation the radioactivity is bound to colloid and the colloid is phagocytosed by macrophages. However, if the SN is completely replaced by tumour-cells there is no healthy lymph tissue left to phagocytose the colloid and radioactivity. The colloid will skip the SN and be phagocytosed by another, non-sentinel, lymph node or will not be phagocytosed at all. This will result in a false-negative SN or non-detectable radioactive lymph nodes.

This was the postulated hypothesis for the significant relationship between extend of nodal involvement in terms of extranodal growth (ENG) and/or total number of positive nodes and failure of the SN detection.

There was a significant influence of the number of positive nodes on the radioactive ratio (≥ 4 vs. 0-3 and ≥ 4 vs. 1-3). In case of ≥ 4 positive lymph nodes identification of the "real" SN failed in 67 percent. In 3/5 false negative SN patients the radioactive ratio was inadequate, all found to have ≥ 4 involved nodes. The relation between ENG and the radioactive ratio was also significant (ENG vs. no metastases/no ENG and ENG vs. no ENG). The presence of ENG is in 72 percent responsible for failure of the identification of the "real" SN.

So the postulated hypothesis seems to be correct. In order to avoid failure preoperative ultrasound examination of the axilla in combination with FNAC is recommended. This technique is able to identify at least 62% of the patients with ≥ 4 positive lymph nodes in the axilla.

As mentioned in chapter 2 the co-ordinator was responsible for the implementation in the participating hospitals and involved departments. One of the responsibilities was to inform the involved staff about all aspects of the procedure. Because nuclear medicine was unknown territory for most persons concerned, one of the most frequently asked questions were about safety issues regarding the procedure. In **CHAPTER 7** the results of measurements after the radiation dose are described and discussed.

Exposure to ionising radiation can be harmful and working with radioactivity has rigid rules. Dose limits are determined for three groups; exposed workers, workers and members of the public. Dose limits are prepared to prevent deterministic effects, such as, erythema, and stochastic effects such as cancer. Dose limits for deterministic effects are expressed in dose limits for hands, feet, ankles, forearms, skin and the eye lens. The maximum handdose for workers and exposed workers are 50 and 500 mSv/year respectively. Dose limits for stochastic effects are expressed in effective dose limits. The maximum effective dose for workers and exposed workers is 1 and 20 mSv/year respectively.

During the operation and the histologic examination the radiation dose to which the surgeon, the surgeon-assistant, the theatre nurse, the pathologist and the pathologist-assistant were exposed was measured. Small thermoluminoscentdosemeters were used on the thoracic wall, abdominal wall, left (non-dominant) and right (dominant) hand of the surgeon, the assistant-surgeon and the pathologist. Only the chest wall dose of the theatre nurse and the

pathologist-assistant was measured. The measurements on the theatre-nurse, the pathologist and the pathologist-assistant were beneath the detection level of 10 μSv. The highest measured doses are the hands of the surgeon and his assistant (17±61 mSv), however the dose limits for hands are higher than for other parts of the body.

There was a difference between the exposure of the dominant- and non-dominant had of the surgeon caused by the operating technique. The non-dominant hand presents the tissue to be removed by the dominant hand, resulting in a shorter distance between non-dominant hand and radioactive tissue in comparison with the dominant hand.

Taking the dose limits into account the abdominal wall of the surgeon relatively receives the highest dose, with an average of 8.2 μSv per procedure. Within the Dutch statutory limits a surgeon could perform 100 sentinel node procedures a year (one-day procedure with 30MBq 99m-Technetium). This means that in general there is no need for any concern about the safety of the procedure for health workers.

After the initial study the SN has proven to be a valuable tool in predicting the status of the axilla. The SN biopsy became routine practice despite lack of long-term follow-up results concerning local control and overall survival. In **CHAPTER 8** the follow-up results of breast cancer patients with an internal mammary chain (IMC) hotspot on lymphoscintigraphy are discussed. The axillary lymph node status is one of the most important prognostic factors in predicting prognosis. However, dissemination of tumour cells through the lymph system is not only taking place to the axillary lymph nodes but also to the supraclavicular and internal mammary lymph nodes. In the study period the policy was not to explore the parasternal region even if the IMC hotspot was the only hotspot. This decision was based on studies reporting no survival benefit after complete dissection of the internal mammary lymph nodes [1-3]. In a 6.5 year period lymphoscintigraphy showed in 86 (15%) of 571 patients a hotspot in the IMC, in 64 of them the axillary SN was negative. In the literature the incidence of positive IMC with negative axillary lymph nodes is 0-10%. Based on tumour characteristics, adjuvant systemic therapy was not indicated in 25 of the 86 SN negative patients. Therefore, in case of a 10% incidence of positive IMC with negative axillary lymph nodes, routine IMC SN biopsy would only in 2-3 of the 571 patients have resulted in the single argument for adjuvant systemic therapy. In the follow-up (median 36 months) no parasternal recurrences were found. Because only very few patients would benefit in the sense of indication of systemic therapy and parasternal recurrences are rare, we maintained our policy not to explore the IMC.

Three years after the SN biopsy became routine practice the first reports on axillary recurrences appeared. In **CHAPTER 9** our 5-year follow up results are discussed. We evaluated the value of axillary ultrasound in combination with fine-needle aspiration cytology (FNAC) in the early detection of axillary recurrences and the incidence of axillary- and local recurrences. In the validation period the incidence of false-negative SNs was about 5%. Therefore a recurrence rate of 5% was expected. In a mean follow-up period of 65 months we observed 4 axillary recurrences (2.7 %) and 7 local recurrences in a group of 149 patients. None of the axillary recurrences was detected by ultrasound. Axillary recurrences were treated with full axillary lymph nodes dissection (ALND). Three of the four axillary recurrences were observed within the first 14 months after SN biopsy. Based on reported data on the incidence of axillary recurrences it can be concluded that the incidence after negative SN is much lower than expected. In the group of patients with local recurrence or ipsilateral second primary tumour, part of the treatment was in 6 out of 7 patients ALND. Pathological examination showed in 4 of these 6 patients axillary lymph node metastases. But it remains unclear if the metastases were from the primary tumour or recurrence. We concluded that the

clinical relevant incidence of axillary recurrences after negative SN is much lower than expected. Up until now treatment of axillary recurrences is ALND, the place of re-SN is uncertain. There is no value of axillary ultrasound and FNAC in the routine follow-up and most cases are detected within one and a half-year after the primary procedure.

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SAMENVATTING

In de afgelopen jaren is de behandeling van borstkanker veranderd naar een minder ingrijpende en mutilerende ingreep. Borstbesparende behandeling en de introductie van de schildwachtklier (SWK) procedure zijn de twee belangrijkste veranderingen. De introductie van een nieuwe techniek kost echter tijd. De eerste stap is ontwikkeling en evaluatie. Indien de nieuwe techniek beter lijkt dan de standaard behandeling wordt een gerandomiseerde studie ter bevestiging opgezet en bij positief resultaat komt het ter beschikking van de betrokken patiëntengroep. In **HOOFDSTUK 2** wordt de introductie van de SWK procedure in 3 deelnemende ziekenhuizen beschreven (een groot opleidingsziekenhuis, een oncologie-centrum en een universitair ziekenhuis). Speciale aandacht werd gegeven aan de rol van de coördinatrice ter bewaking van de standaardisatie en kwaliteitscontrole binnen deze multi-centrische studie. De rol van de coördinatrice was tweevoudig: allereerst begeleiding van de betrokken afdelingen bij de invoering en daarna (waarnodig) bijstellen van de procedure. Tijdens de onderzoeksperiode werden enkele aspecten van de procedure bijgesteld: de concentratie van het colloïd in de radioactieve oplossing, intracutane injectie van de blauwe inkt na teleurstellende resultaten van de peritumorale injectietechniek, injectie craniaal van het litteken in plaats van caudaal. Met deze veranderingen werden de resultaten uitstekend. Aan het eind van de studie periode waren de resultaten (sensitiviteit en fout-negativiteit) in de deelnemende ziekenhuizen gelijk.

Naar aanleiding van deze resultaten werd een implementatietraject gestart met hulp van het Integraal Kankercentrum Rotterdam. De regionale ziekenhuizen die de SWK procedure wilden invoeren werd een leerfase van 50 patiënten aangeraden waarbij een “dubbel procedure” werd uitgevoerd (SWK en okselklierdissectie (OKD)). Indien er sprake was van minder dan 5% fout-negativiteit kon volstaan worden met verwijderen van alleen de SWK, alle patiënten werden centraal geregistreerd en adequaat vervolgd. Speciale aandacht werd gegeven aan echografie van de oksel tijdens de follow-up in de hoop regionale recidieven zo spoedig mogelijk op te sporen.

De SWK procedure is gecompliceerd en tijdrovend. Het heeft enkele nadelen zoals een laag identificatiepercentage bij veel uitzaaiingen in de lymfklieren van de oksel, fout-negatieve resultaten, benodigde radioactiviteit en pathologisch onderzoek met behulp van de vriescoupe techniek. Vanwege deze nadelen zou vervanging van de SWK procedure door eenvoudigere methoden nuttig zijn. In een studie voorafgaand aan het SWK tijdperk bleek echografisch onderzoek van de oksel in combinatie met cytologisch punctie een onderzoek te zijn met een lage sensitiviteit maar met een specificiteit van 100%. Vanwege dit resultaat maakte dit onderzoek deel uit van de SWK procedure in een multicentische studie naar de waarde van de SWK biopsie bij klinisch okselklier-negatieve borstkanker patiënten. Indien uitzaaiingen in de oksel werden vastgesteld was de SWK niet meer relevant.

In **HOOFDSTUK 3** worden de resultaten van de echografie en cytologische punctie besproken. Het echopatroon werd beoordeeld als inhomogeen, homogeen of echo-rijk centrum. De eerste twee werden als potentieel maligne beschouwd en de laatste als potentieel benigne. Pathologisch onderzoek van het OKD preparaat toonde geen fout-positieve resultaten. Des te meer lymfklieren echografisch werden geïdentificeerd des te hoger de kans op uitzaaiingen. De incidentie van uitzaaiingen nam ook toe bij toenemende tumorgrootte.
Bij 36% van alle lymfklier-positieve operabele borstkanker patiënten werden uitzaaiingen geconstateerd door middel van echografie gecombineerd met cytologie. Door deze techniek heeft 17% van alle borstkanker patiënten geen SWK procedure nodig en kan een OKD plaatsvinden als initiële behandeling. Deze percentages zijn enigszins laag, vermoedelijk ten

gevolge van de leercurve in de herkenning en aanprikken van lymfklieren met een verdacht echografisch beeld.

Rekening houdend met de leercurve leek het logisch dat de sensitiviteit van de echografie en cytologische punctie zou toenemen na de initiële studie. Aangezien verwijdering van alle lymfklieren in de oksel de standaard behandeling bleef bij lymfklier-positieve borstkanker patiënten kon de sensitiviteit en specificiteit van de gecombineerde procedure ook na de invoering van de schildwachtklier worden geëvalueerd. In **HOOFDSTUK 4** worden de resultaten van de vervolg studie besproken. Bij punctie van een lymfklier was er in 73% voldoende materiaal voor diagnostiek, de sensitiviteit voor het aantonen van uitzaaiingen was 57% met een specificiteit van 96%. Echografie met cytologie was in staat om 44% van de patiënten met een histologisch bewezen uitzaaiing in een lymfklier in de oksel te identificeren, dat is 20% van de gehele patiënten populatie. In tegenstelling tot eerdere resultaten waren er 3 fout-positieve uitslagen, te verklaren door multifocaliteit van de tumor geassocieerd met een dicht lymfogene infiltratie, cytologische misinterpretatie van groepen cellen en een niet-bekende oorzaak. Echografie en cytologie waren in staat om 83% van de vrouwen met 4 of meer uitzaaiingen in de okselklieren aan te tonen. Vijfentwintig procent van de patiënten met 1-3 positieve okselklieren bleken alleen micro-uitzaaiingen te bevatten. Het is duidelijk dat nòg echografie nòg cytologie histologie kan vervangen in de opsporing van deze uitzaaiingen, maar het verklaart deels de relatieve lage sensitiviteit in zowel het initiële multicentrische studie als de vervolg studie die plaatsvond in 1 ziekenhuis. Het lijkt niet aannemelijk dat met de huidige techniek de sensitiviteit verder zal toenemen.

Uiteraard levert meer intensieve onderzoeksmethode van de lymfklieren met sprongserie en immunohistochemie een hoger percentage uitzaaiingen op. Tot op dit moment is het biologische karakter van micro-uitzaaiingen, gevonden met immunohistochemische kleuring, niet duidelijk. Er wordt gesuggereerd dat de SWK soms in staat is lokale ziekte te controleren door verwijdering van uitgezaaide tumorcellen. Er wordt ook gesuggereerd dat geïsoleerde tumorcellen niet de capaciteit zouden hebben om verder uit te groeien. Dit zou kunnen verklaren dat uitgezaaide ziekte in niet-SWKs nauwelijks voorkomt in geval van micro-uitzaaiingen. De definitie van de term micro-uitzaaiing is arbitrair en varieert tussen diverse studies. Een cut-off point van 2mm wordt gebruikt in diverse studies en is geïncludeerd in de TNM classificatie. In **HOOFDSTUK 5** wordt de incidentie van uitzaaiingen in niet-SWKs bij een micro-uitzaaiing in de SWK besproken. De niet-SWKs werden onderzocht conform de SWK; gesneden om de 250µm, immunohistochemische kleuring met anticytokeratine antilichaam CAM 5.2 gebruik makend van een standaard peroxidase procedure in een immunokleurder. Uitzaaiingen in niet-SWKs werden gevonden bij 11 van de 32 patiënten, waarbij 5 patiënten initieel als vrij van uitzaaiingen in de niet-SWKs waren geclassificeerd. Bij 7 patiënten ging het om meer dan 1 lymfklier en in 4 patiënten was de uitzaaiing in de niet-SWK groter dan in de SWK (inclusief 2 patiënten met niet-SWK macro-uitzaaiingen). Er werd gevonden dat uitzaaiingen in de niet-SWK als clusters samen ging met tumoren > 2cm en met hoog-gradige tumoren. De vraag rijst of bij geïsoleerde tumorcellen in de SWK een OKD en adjuvante behandeling noodzakelijk is. Het antwoord hangt af van het biologische gedrag van kleine tumorcelgroepjes en geïsoleerde tumorcellen. Voor de vorming van een micro-uitzaaiing is hechting in weefsel en deling noodzakelijk. Biologische kenmerken zoals levensvatbaarheid, angiogene capaciteit en vermijden van de gastheer immuun respons zouden even belangrijke factoren kunnen zijn. Wat het gevolg van enkele tumorcellen in de circulatie of in organen ook is, het feit dat ze gevonden zijn duidt erop dat er toegang is tot het lymfatisch systeem of bloedvaten en dat een verdedigingslijn doorbroken is. Op basis van

onze resultaten vinden we het te vroeg om te concluderen dat een OKD vermeden kan worden bij patiënten met een T1-2 tumor en een micro-uitzaaiing in de SWK.

Zoals boven vermeldt is de echografie in combinatie met cytologische punctie bij de primaire selectie voor een succesvolle SWK biopsie. Echter, er was geen 100% opsporing en sensitiviteit in de initiële multicentrische studie. In **HOOFDSTUK 6** worden de oorzaken van falen in het opsporen van de "echte" SWK bij klinisch okselklier negatieve borstkanker patiënten met de primaire tumor in situ besproken. Na injectie van 30-40 MBq 99m-Technetium nanocolloid werd de SWK opgespoord met behulp van een probe. De probe meet de radioactiviteits ratio (SWK vs achtergrond) in counts per seconde. Twee activiteitsniveaus werden onderscheiden; onvoldoende en voldoende. In geval van een onvoldoende ratio was de SWK niet geïdentificeerd of slechts na lange tijd. Het aantal uitzaaiingen in de lymfklieren in de oksel werd ingedeeld conform de Nederlandse Richtlijnen voor adjuvante behandeling in 1-3 en ≥ 4 positieve lymfklieren in de oksel. In de normale (niet-uitgezaaide) situatie wordt de radioactiviteit gebonden aan het colloïd en het colloïd wordt opgenomen door macrofagen. Echter, indien de SWK volledig wordt ingenomen door tumorcellen dan is er geen gezond lymfklierweefsel meer om het colloïd en radioactiviteit op te nemen. Het colloïd slaat de SWK over en wordt opgenomen door een andere, niet-SWK, lymfklier of wordt niet opgenomen. Dit resulteert in een fout-negatieve SWK of in niet op te sporen radioactieve lymfklieren.

Dit was onze hypothese voor de significante relatie tussen uitgebreide aantasting van lymfklieren in de oksel, in termen als extranodale groei (ENG) en/of aantal positieve lymfklieren en het falen van de SWK opsporing. Er was een significante invloed van het aantal positieve okselklieren op de radioactiviteits ratio (≥ 4 vs 0-3 en ≥ 4 vs 1-3). In het geval van ≥ 4 positieve lymfklieren in de oksel faalde de identificatie van de SWK opsporing of was de radioactiviteits ratio onvoldoende in 67%. Bij 3 van de 5 fout-negatieve SWKs was de radioactiviteits ratio onvoldoende, allen bleken ≥ 4 aangetaste lymfklieren te hebben. De relatie tussen ENG en de radioactiviteits ratio is eveneens significant (ENG vs geen uitzaaiingen/geen-ENG en ENG vs geen-ENG). De aanwezigheid van ENG is verantwoordelijk voor het falen van de SWK identificatie of onvoldoende ratio in 72%. Het lijkt er dus op dat onze geformuleerde hypothese correct is.

In een poging om falen te vermijden wordt preoperatief uitgevoerde echografie van de oksel in combinatie met cytologische punctie aangeraden. Deze techniek is in staat om tenminste 62% van de vrouwen met ≥ 4 positieve lymfklieren in de oksel te identificeren.

Zoals in hoofdstuk 2 vermeld was de coördinatrice verantwoordelijk voor de implementatie in de deelnemende ziekenhuizen en betrokken afdelingen. Eén van de verantwoordelijkheden was de betrokken personen te informeren over alle aspecten van de procedure. Aangezien nucleaire geneeskunde onbekend terrein was voor de meeste betrokken personen, betrof de meest gestelde vraag het veiligheidsaspect. In **HOOFDSTUK 7** worden de resultaten van de metingen naar de stralingsdosis beschreven en geëvalueerd. Blootstelling aan straling kan schadelijk zijn en het werken ermee gaat gepaard met strenge regels. Dosis limieten zijn vastgesteld voor drie groepen; blootgestelde werknemers, werknemers en de bevolking. Dosis limieten zijn vastgesteld om deterministische effecten, zoals erytheem, en stochastische effecten, zoals kanker, te voorkomen. Dosis limieten voor deterministische effecten worden uitgedrukt in dosis limieten voor handen, voeten, enkels, onderarmen, huid en lenzen. De maximale handdosis voor werknemers en blootgestelde werknemers zijn respectievelijk 50 en 500 mSv/jaar. Dosis limieten voor stochastische effecten worden uitgedrukt in effectieve dosis limieten. De maximale effectieve dosis voor werknemers en blootgestelde werknemers zijn respectievelijk 1 en 20 mSv/jaar. Tijdens de operatie en het

histologisch onderzoek werd de stralingsdosis gemeten waaraan de chirurg, de assistent van de chirurg, de operatiekamerassistente, de patholoog en de assistent van de patholoog werden blootgesteld. Kleine thermoluminiscent dosismeters werden gebruikt op de borst, buik, linker (niet-dominante) en rechter (dominante) hand van de chirurg, de assistent van de chirurg en de patholoog. Van de operatiekamerassistente en de assistent van de patholoog werd alleen de dosis op de borst gemeten. De metingen bij de operatiekamerassistent, de patholoog en diens assistent waren alleen beneden het detectieniveau van 10μSv. De handen van de chirurg en diens assistent kregen de hoogst gemeten dosiswaarden (17 ± 61mSv), de dosislimiet voor handen is echter hoger dan voor andere delen van het lichaam. Er was een verschil in blootstelling van de dominante en niet-dominante hand van de chirurg veroorzaakt door de operatietechniek. De niet-dominante hand presenteert het door de dominante hand te verwijderen weefsel, dit resulteert in een kortere afstand tussen niet-dominante hand en het radioactieve weefsel in vergelijking tot de dominante hand.

Rekening houdend met de dosislimieten ontvangt de buik van de chirurg relatief de hoogste dosis met een gemiddelde van 8.2μSv per procedure. Binnen de Nederlandse regelwetgeving mag een chirurg 100 SWK procedures uitvoeren (een-dags procedure met 30MBq 99m-Tc). Dit betekent dat er geen reden is tot ongerustheid betreffende de veiligheid van de procedure voor medewerkers in de zorg.

Na de initiële studie heeft de SWK bewezen van waarde te zijn in het voorspellen van de okselklierstatus. De SWK biopsie werd routine ondanks het ontbreken van follow-up resultaten betreffende lokale controle en overleving. In **HOOFDSTUK 8** worden de follow-up resultaten besproken van borstkanker patiënten met een hotspot op de lymfoscintigrafie ter plaatse van de parasternale klierketen (PSK). De axillaire lymfklier status is een van de meest belangrijke prognostische factoren bij het voorspellen van de prognose. Echter, verspreiding van tumorcellen door het lymfe systeem vindt niet alleen plaats naar de axillaire lymfklieren maar ook naar de supraclaviculaire en parasternale lymfklieren. Tijdens de studieperiode was het beleid dat hotspots ter plaatse van de PSK ongemoeid werden gelaten zelfs als dat de enige hotspot was. Deze beslissing was gebaseerd op studies waarin geen overlevingswinst werd beschreven na complete dissectie van de parasternale lymfklieren [1-3] . In 6.5 jaar toonde de lymfoscintigrafie bij 86 (15%) van de 571 patiënten een hotspot ter plaatse van de PSK. Bij 64 van hen was de axillaire SWK negatief. In de literatuur is de incidentie van positieve PSK met negatieve axillaire lymfklieren 0-10%. Gebaseerd op tumorkenmerken was aanvullende systemische behandeling niet geïndiceerd bij 25 van de 86 SWK negatieve patiënten. In het geval van een incidentie van 10% positieve PSK bij negatieve axillaire lymfklieren, dan zou het standaard verwijderen van de PSK schildwachtklier bij slechts 2-3 van de 571 patiënten hebben geleid tot een argument voor systemische behandeling. Gedurende de follow-up (mediaan 36 maanden) is er bij geen patiënt een parasternaal recidief gevonden. Aangezien slecht een enkele patiënt voordeel zou kunnen hebben, in de zin van een indicatie voor systemische behandeling, en parasternale recidieven slechts sporadisch voorkomen is het beleid gehandhaafd om de PSK ongemoeid te laten.

Drie jaar nadat de SWK procedure standaard behandeling werd, kwamen de eerste artikelen over axillaire recidieven. In **HOOFDSTUK 9** worden onze 5-jaars follow-up resultaten besproken. We bekeken de waarde van echografie van de oksel in combinatie met cytologie in de vroege detectie van axillaire recidieven èn de incidentie van axillaire- en lokale recidieven. Tijdens de validatie periode was de incidentie van een fout-negatieve SWK circa 5%. Daardoor werd een recidief percentage van 5% verwacht. Tijdens de gemiddelde follow-up periode van 65 maanden zagen we in 4 axillaire recidieven (2.7%) en 7 lokale recidieven bij een groep van 149 patiënten. Geen enkel axillair recidief werd gevonden door

de echografie. Axillaire recidieven werd behandeld met een volledig OKD. Drie van de vier recidieven werden binnen de eerste 14 maanden na de SWK procedure ontdekt. Gebaseerd op de gerapporteerde incidentie van axillaire recidieven mag geconcludeerd worden dat de incidentie van axillaire recidieven na een negatieve SWK veel lager is dan verwacht.

In de groep patiënten met een lokaal recidief of ipsilaterale secundaire tumor bestond bij 6 van de 7 patiënten de behandeling onder andere uit een OKD. Pathologisch onderzoek toonde bij 4 van deze 6 patiënten uitzaaiingen in de okselklieren. Maar het blijft onduidelijk of de uitzaaiingen van de primaire tumor of van het recidief zijn.

We concludeerden dat de klinisch relevante incidentie van axillaire recidieven na een negatieve SWK veel lager is dan men verwachtte. Tot op heden is de behandeling een OKD, de plaats van een re-SWK procedure is onduidelijk. In de routine follow-up heeft een echografie van de oksel geen waarde en de meeste gevallen werden binnen anderhalf jaar na de primaire procedure ontdekt.

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DISCUSSION

Our current recommendation for staging clinically node negative breast cancer patients involves sentinel node staging after ultrasound of the axilla as this non-invasive procedure has been demonstrated by us to limit the requirement for SN staging. The histopathologic work up of the SN involves step sectioning and the use of immunohistochemistry for the identification of micrometastases. A full axillary lymph node dissection is recommended for patients with involved sentinel nodes (micrometastases > .2 mm) and is not necessary for patients without sentinel node involvement. We are not of the opinion that sentinel node staging of the internal mammary chain is useful.

We consider this recommendation a recommendation as a temporary one as the management of breast cancer patients is changing every 5-10 years and the impact of molecular staging, gene-profiling of primary tumours, new developments in imaging modalities, new drugs and developments in cancer prevention will change the current recommendations over the years to come.

Several important questions remain for the coming period and will be discussed her within the context of the recent literature:

- What is the relevance of micrometastases? Is size of the micrometastases relevant (isolated tumour cells versus 0,2mm versus 2 mm) in terms of prognosis, need for full axillary lymph node dissection etc.
- What is the need for a full axillary dissection in case of (any) positive (sentinel) lymph nodes.
- Which technique is able to reduce the number of sentinel node procedures? It is clear that even very sophisticated imaging will not be able to detect these smallest metastases. For this purpose the SN procedure will remain the staging procedure of choice. However, the range between macro metastases discovered by US and FNA and these very small metastases is large and every non-invasive technique to identify a higher percentage of these metastases will be worthwhile. Which technique is able to reduce the number of sentinel node procedures?
- What will be the new more powerful prognostic indicators in state lymph node metastases will they make SN-staging redundant?

Clinical relevance of micro-metastases

Traditionally the pathological examination of axillary lymph nodes consisted of hematoxylin and eosin (H&E) staining of only one or a few sections. A false negative result is possible and related to the size of the node, the orientation of the node in the sectioning block, the size and location of any metastases within the node and the number of sections examined[1]. With the introduction of the sentinel node biopsy the pathological examination of the (sentinel) node has become more extensive. The sentinel node was examined with serial or step sectioning and immunohistochemical (IHC) staining in case of negative H&E. This combination is a more sensitive method of detecting tumour cells and therefore results in 9-47% upstaging [2-5]. Many of these metastases detected by immunohistochemistry are micro-metastases or isolated tumour cells. In the new TNM classification a distinction is made

between macro-metastasis (>2mm), micro-metastasis (0.2-2.0mm) and isolated tumour-cells (≤0.2mm) [6].

The clinical relevance of isolated tumour cells or micro-metastases is unclear since we do not know if these cells are capable of further growth and dissemination. The relevance of answering this question is related to the benefit in survival for N0 versus isolated tumour cells (pN0i+) or micro-metastasis (pN1mi), also taking into account tumour characteristics.
Before the sentinel node era, several studies determined the influence of metastases ≤2mm on survival. Especially the latter studies could identify a significance survival difference between patients with metastases ≤2mm and >2mm. Up until now there was no significant difference between N0 and N+ ≤2mm. Again, all studies were based on analysis of axillary lymph node specimens (as opposed to sentinel node specimens) [7-10].

The introduction of the sentinel node technique has created a useful tool for further study of micrometastatic disease. The first studies based in sentinel node specimens show similar to the old studies no significant survival difference between N0 and N0i+ or N1mi [11, 12]. Possible explanations are small numbers of patients, relatively short follow-up and enlargement of adjuvant treatment indications based on tumour characteristics. The American College of Surgeons Oncology Group trial Z0010 and NSABP B-32 study will study the detection of small foci or even single metastatic cells in the sentinel node by the use of serial sectioning, IHC, and molecular techniques, like reverse transcriptase-polymerase chain reaction analysis. This large data set will try to answer the effect on a difference in survival or that there is no real biologic significance of these findings.

In conclusion, identification of isolated tumour cell clusters may not be identifying a group of patients with outcome worse than node-negative patients. The definition before the era of the sentinel node biopsy of 2.0mm for clinically significant metastases may not be far from the new reality. Definitive therapeutic recommendations await the results of ongoing multicentre trials

Preoperative staging of clinically node negative breast cancer patients

CT and MRI

Both CT (computed tomography) and MRI (magnetic resonance imaging) are cross-sectional imaging methods that produce high-quality images of the axilla. Few studies have been published on this subject, but the latest have shown high sensitivity and specificity (CT 93% and 82% respectively and MRI 90% and 82% respectively), although, both CT and MRI are restricted to imaging only. The detection of micro-metastases and small tumour-infiltrated lymph nodes is limited by the currently achievable spatial resolution and make these modalities no superior to sentinel node procedure [13].

PET

Several clinical studies have been carried out to evaluate the accuracy of PET in the axillary staging of operable primary breast cancer. Reported sensitivities range from 20-100% and specificity's from 66-100%. These studies have sometimes provided conflicting results, either supporting the possibility of using PET to select patients who need axillary dissection or questioning whether PET can accurately assess the axillary status in primary breast cancer. The performance of PET depends on primary tumour load and the axillary tumour load so the limitation of PET is in the detection of micro-metastases. The added value offered by PET in comparison with sentinel node biopsy and ultrasound in combination with FNAC lies in the fact that PET is a non-invasive procedure that allows the biological characterisation of breast

cancer and viewing of the entire body. But PET is based on the present literature not superior [14-16].

PET/CT

Combined PET/CT systems have recently been developed and allow functional PET and anatomical CT images to be acquired in one session and rapidly co-registered. The few published studies suggest that PET/CT diagnosis of both primary tumour and axillary lymph node involvement was more accurate than diagnosis using mammography, ultrasound or PET alone. A possible role of PET/CT is in the detection of parasternal metastases [17, 18].

MRI uspio

In the last decade the MRI uspio was developed. Dextran-coated ultrasmall superparamagnetic iron oxide (USPIO) remains after intravenous injection in the intravascular compartment and is eventually incorporated into the reticulo-endothelial system and providing information on lymph node morphology. There is only one published article evaluating the value of uspio-enhanced MRI imaging for preoperative axillary lymph node staging in patients with breast cancer. Michel et al found a sensitivity of 82% with a specificity of 100%. If these preliminary results are confirmed in subsequent studies it could be a valuable pre-operative selecting examination. However, ultrasound in combination with FNAC is much more cost-effective than this new technique [19].

In conclusion, at this time there is no accurate test that can replace sentinel node biopsy. Especially due to the absence of cytology or histology even more than micro-metastases will be missed.

The need for a full axillary dissection in case of positive sentinel lymph nodes.

The immediate risk of leaving residual disease in the axilla when one sentinel node is positive ranges from about 10-40%, depending on the size of the primary tumour and the size of de metastasis in the sentinel node. When the metastasis found in the sentinel node is a cluster no greater than 0.2mm in size, detected only with immunohistochemistry, the risk of finding additional metastatic nodes is exceedingly rare [20, 21]. Isolated tumour cells in the sentinel node with non-sentinel node involvement could be the result of failure to detect the true sentinel node caused by obstruction by metastasis. Preoperative ultrasound with FNA and intra-operative palpation of the axilla may prevent the chance of leaving massive metastatic tumour load in the axilla.

It is important to note that the immediate risk of leaving residual disease in the axilla does not equate to always leaving this disease as untreated. The use of systemic adjuvant treatment and, in case of breast conserving therapy, the use of tangential radiation fields may result in effective treatment of residual (microscopic) axillary nodal disease [22-25]. This hypothesis is currently tested in a randomised EORTC trial. In this “AMAROS” trial breast cancer patients with tumours over 5mm and less than 3cm and a positive sentinel node are randomised between complete axillary lymph node dissection and radiotherapy to the axilla. Next question is whether delayed treatment of residual disease worsens overall survival. The preliminary results of the follow up of sentinel node negative patients with axillary recurrence show no statistically significant differences in local control and survival between initially sentinel node positive patients and secondary node positive patients.

Again, definitive therapeutic recommendations await the results of ongoing multicentre trials.

Prognostic markers in breast cancer patients

The recognition of women who are at risk of relapse later is extremely important. In the near past a positive lymph node status was the most important indication for adjuvant treatment. The beneficial effects of adjuvant systemic treatment in these patients have been repeatedly shown in prospective randomised trials. However, these therapeutic effects have considerable side effects and not all patients benefit from this toxic treatment [26]. But even in lymph node negative patients relapse occurred in 20-30% [27]. It would be of immense clinical value if this high-risk group could be identified by the use of prognostic factors. Most of these factors are determined by identifying certain characteristics of the tumour such as size, grade, histology, receptor status, lymphatic and vascular invasion. Because of the ability of identifying high-risk characteristics, lymph node status was no longer the only adjuvant treatment indication. In the last decade the development of predictive models has accelerated. Her2-neu receptor and gene-expression profiling are the most promising [28-30].

If the development of gene-expression profiling continues the role of the sentinel node biopsy will become more and more less. It is questionable if in node positive patients full axillary lymph node dissection is still necessary for local control and to identify candidates for adjuvant radiotherapy.

It is possible that control of a large axillary tumour load by either surgery or radiotherapy will still be important but non-invasive procedures like ultrasound in combination with fine needle aspiration are able to identify most of these patients. Small metastases will be missed by this procedure but delayed treatment in case of local failure seems to do no harm on overall survival.

In conclusion: the sentinel node plays a significant role in the evolution of breast cancer treatment but is likely that finally its prognostic role will be replaced by combination of primary tumour characteristics and non-invasive staging procedures of the axilla.

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CURRICULUM VITAE

Naam : Antoinette Yda de Kanter

Geboortedatum en –plaats : 29 augustus 1969 te Rotterdam

Burgelijke staat : Gehuwd met Marcel Verbeek
Moeder van Kiki Carolien en Huib Pieter

Mrt ’06 – heden:	Radiotherapeut-Oncoloog Centrale Bestralings Afdeling den Haag
Juli’01 - mrt ’06:	Opleiding tot Radiotherapeut-Oncoloog Erasmus MC, opleider prof. dr. P.C. Levendag
Sept ’00 – juli ’01:	AGNIO Radiotherapie Erasmus MC
Mrt ’99 – sept ’00:	AGNIO Chirurgie St Fransiscus Gasthuis te Rotterdam
Jan – mrt ’99:	Projectmedewerkster van het Integraal Kankercentrum Rotterdam. Projecten: - Implementatie van de sentinel node procedure in de regio Rotterdam - Oorzaken van post operatie mortaliteit bij colorectale tumoren
’96 - ’98:	Studiebegeleidster van het onderzoek naar de sensitiviteit en specificiteit van de sentinel node biopsie bij operabele mammacarcinoompatiënten.
mei ’96:	artsexamen
’94:	Afstudeeronderzoek afdeling Kinderoncologie, Erasmus MC / Sophia Onderwerp: De groei bij kinderen met een rhabdomyosarcoom.
’88 - ’94:	Geneeskunde aan de Erasmus Universiteit Rotterdam Doctoraal examen: mei ’94
’81 - ’88:	Atheneum B aan het Montessori Lyceum te Rotterdam

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DANKWOORD

Het is zover, het boek is af. Bij het tot stand komen ervan hebben velen een belangrijke rol gespeeld. Enkele wil ik in het bijzonder bedanken.

Mijn promotoren, Prof.dr. T. Wiggers en Prof.dr. A.M.M. Eggermont. Theo, met veel plezier denk ik terug aan de brainstorm sessies op de Heemraadsingel. Daar is de basis van dit proefschrift gelegd. Gelukkig bleek het een stevige basis te zijn want er moesten op weg naar deze promotie vele hindernissen worden overwonnen. Dankzij jouw stimulerende gesprekken (waar ook in Nederland) ging ik er weer in geloven en begon vol goede moed aan het volgende traject.

Lex, na de verhuizing van Theo naar het hoge noorden nam je zijn directe begeleidende taak over. Tussen de werkzaamheden door werd er altijd wel een gaatje gevonden om te discussiëren over dit proefschrift en te filosoferen over de toekomst van de schildwachtklier procedure. Bij binnenkomst zei je vaak dat je maar even tijd had. Maar aangezien je jouw snelheid van spreken aanpast aan de hoeveelheid tijd die je hebt was alles gezegd op het moment dat je telefoon ging voor de volgende afspraak en je mij achterliet met fluitende oren.

Mijn opleider Prof.dr. P.C. Levendag. Peter, al bij binnenkomst was de promotiedatum onderwerp van gesprek. Toen deze heel ver weg leek was het te danken aan jouw overredingskracht dat de schouders er toch weer onder werden gezet en de stoptrein de laatste halte kon bereiken. Ik vind het heel bijzonder dat ik veel tijd te besteden kreeg aan het afronden van een onderzoek wat in het geheel niets te maken heeft met Radiotherapie. Aangezien ik in den Haag de hoofd-hals oncologie als een van mijn aandachtgebieden heb hoop ik nog veel met je te kunnen samenwerken en eventueel iets samen te publiceren.

Bert van Geel, het was jouw initiatief om de waarde van de schildwachtklier procedure in Rotterdam te onderzoeken. Bij jou kon ik altijd terecht voor een snelle en kritische beoordeling van de diverse manuscripten. Het mooiste compliment wat je me kon geven was je reactie toen je hoorde dat het onderzoek toch nog afgerond werd met een promotie.

Rick Paul en Casper van Eijck, jullie waren de stimulerende chirurgen in het Zuider en Dijkzigt. Het was altijd erg prettig samenwerken en mede door jullie inzet werd de complexe procedure steeds minder complex.

Marjan Menke, dankzij jouw inzet was het mogelijk een follow-up deel in dit proefschrift te maken. Tijdens de besprekingen heb ik veel bewondering gekregen voor jouw manier van blootleggen van het skelet van een artikel en vervolgens de verbouwing ervan.

De overige leden uit de promotiecommissie Prof.dr. I.H.M. Borel Rinkes, Prof.dr. J.W. Oosterhuis, Prof.dr. G.P. Krestin en Prof.dr. E.P. Krenning dank ik voor de interesse in het manuscript en de snelle beoordeling.

De secretaresses van de afdelingen Radiotherapie en Chirugische oncologie. Natasha, soms voelde ik me wel schuldig als je alles uit je handen liet vallen om mij te helpen. Ook toen ik eenmaal Hagenees was kon ik je altijd bellen om iets voor me op te zoeken en naar me te mailen. Maar eigenlijk is het logisch dat je meer doet voor een Feijenoorder dan voor een Ajacied... Marja, een geboren secretaresse! Afspraken, vergaderruimtes, handtekeningen, adressen; voor alles kon ik je bellen en alles wist je voor me te regelen.

Mijn paranymfen, Annemarie Kragten en Stan de Kanter. Mijn oude “roommate” en voor enkelen mijn alter-ego Annemarie, vol weemoed denk ik aan de kopjes thee op de kamer en de gevoerde gesprekken over alle aspecten van het leven. Je luisterend oor was vaak al genoeg om het juiste spoor (weer) te vinden. Mijn broertje Stan, onovertrefbaar in sms’en en medesupporter van Feijenoord. Vaak zorgde je met een geintje per sms of mail weer voor de nodige ontspanning, al kostte het me een telefoontje naar Buckingham Palace. Volgend jaar op de Coolsingel?

Mijn ouders, altijd vol interesse. Zonder medische achtergrond was het voor jullie niet altijd even gemakkelijk om mij te volgen. Maar de overgave waarmee jullie je verdiepten in de “schildwacht” maakte me trots. Hoewel we binnenkort toch echt Rotterdam gaan verlaten hoop ik dat we nog regelmatig een beroep op jullie mogen doen om op Kiki en Huib te passen.

En tenslotte Marcel, zonder jouw onvoorwaardelijke steun en geduld was het nooit afgekomen. Je vermogen om werk en gezin te combineren is ongekend. Daarbij is je kennis van de computer met alle software erg handig gebleken, vooral als ik weer eens een document “kwijt” was. Graag zou ik eens op jouw vrijdag om het hoekje willen kijken want het is hartverwarmend om je met Kiki en Huib bezig te zien.

Ik ook van jou!