Improvement of breast cancer irradiation techniques
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Chapter 3

Accuracy of internal mammary lymph node localisation using lymphoscintigraphy, sonography and CT

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Abstract

Purpose. An accurate IM lymph node localisation technique is required for proper irradiation of the internal mammary (IM) lymph nodes in breast cancer patients. Three techniques for direct or indirect localisation of the IM nodes were compared.

Methods and materials. In 40 patients the IM node depth and lateral distance from the patient midline were measured with lymphoscintigraphy and the corresponding position of an IM vessel was measured with sonography and CT. The vessel measurements were compared to determine the accuracy of sonography. The node and vessel data were inserted into a mathematical model to determine the measurement accuracy of lymphoscintigraphy and CT for node detection in one intercostal space.

Results. Vessel depths measured by sonography were systematically too shallow and the lateral vessel position could not be accurately determined. The mathematical model showed that the node depth and laterisation can be measured directly (and indirectly) by lymphoscintigraphy (CT) within an accuracy (1 SD) of 5 mm (6 mm) in depth and 6 mm (7 mm) in the lateral direction.

Conclusions. Sonography is not a suitable technique for measuring the IM vessel or node position. Lymphoscintigraphy and CT have measurement accuracies for node detection that are acceptable for radiotherapy.
Introduction

In approximately 20% of breast cancer patients the internal mammary (IM) lymph nodes show metastatic invasion [1,2]. Some oncology centres include the IM lymph nodes in the irradiation fields for mediially located tumours or when axillary nodes are involved [3,4]. Irradiation of the locoregional nodes has shown benefits [5-7] but also an increase in irradiation-induced morbidity and mortality [8,9]. To reduce these negative side effects, it is necessary to use an irradiation technique that properly covers the lymph nodes and the breast target volume, while irradiating as little heart and lung tissue as possible [10-12]. The lateralisation and depth of the IM lymph nodes vary between individuals [13,14]. Standard field sizes are not always applicable and the lymph nodes have to be localized individually to determine the correct field borders [15-19].

With the development of accurate IM lymph node irradiation techniques [17,20] it is important that the position of the lymph nodes is determined with sufficient accuracy. Inaccurate localisation of the lymph nodes can result in a systematic positioning error in the irradiation of the nodes. If this error is larger than the patient systematic set-up error at the treatment unit, it can be the most dominant source for insufficient irradiation coverage of the nodes. With careful positioning of the patient for irradiation, a systematic set-up error of 2-5 mm (1 SD) can be reached [21]. If the accuracy for IM lymph node localisation is approximately 5 mm or smaller it will not dominate over this set-up error. The random set-up error is about 5 mm or smaller [21] but has less influence on the dose distribution compared to the systematic errors [22].

In this study three techniques, lymphoscintigraphy, sonography and CT, for direct or indirect localisation of the IM lymph nodes were evaluated. Lymphoscintigraphy is a standard technique for visualisation of the IM lymph nodes [23-25] and has the advantage of visualising the nodes directly. Disadvantages are that not all the nodes are visualized and that the technique requires an intramuscular injection and is time consuming for the patient since at least 2 hours have to pass between the injection and the localisation scan. Sonography and CT do not have these practical disadvantages, but the position of the IM lymph nodes can only be determined indirectly. The IM lymph nodes are situated close to the internal mammary artery and vein between the ribs and the pleura. If sonography or CT is used, it has to be assumed that the nodes are situated close to these vessels.

With Doppler sonography the depth from the skin to the IM vessels and the pleura can be measured in the intercostal spaces (ICSS) [26,27]. The depth to the pleura can be used as an estimation of the maximum depth of
the lymph nodes. The advantage of this technique is that it is a non-invasive procedure that takes only about 10 minutes to perform. On a CT scan the IM vessels are clearly visualized without the use of a contrast agent and the position of the vessels is easy to determine. The disadvantage is that it is a time-consuming and costly procedure that is often not standard for these patients.

In this study three questions were investigated:

1. How accurately does sonography determine the vessel position?
   In this part of the study the sonography and CT measurements were compared to determine whether sonography is a reliable tool for determining the vessel position, and thereby indirectly the node position. Here it was assumed that the vessel position determined on the CT scan was the most accurate and could be used as a reference.

2. How accurately does lymphoscintigraphy determine the node position?
   Since no golden standard to determine the node position is available for comparison with the lymphoscintigraphy measurements, a more complicated approach was used for the analysis of the lymphoscintigraphy data. The lymphoscintigraphy node measurements were compared to the vessel measurements on CT. The correlation between the node and vessel data and the variance of the measured data were inserted into a mathematical model, based on a simplified structural Equation model (28). In contrast to the investigation of question 1, the measurement error to determine the vessel position on CT was here taken into account. Unknown parameters in this analysis were the size of the distribution of the distance between the node and the vessel and the accuracy of CT to measure vessel positions. By varying these unknown parameters, a range for the lymphoscintigraphy measurement accuracy could be determined.

3. How accurately can a node position be estimated using the visible vessel position on CT?
   Using the mathematical model, the CT measurement accuracy for indirect node detection was defined as the sum of the accuracy to determine a vessel position and the size of the node distribution around the vessel. Different combinations of these parameters were used to estimate the CT measurement accuracy range for node localisation.

To summarize, the goal of the study was to investigate whether lymphoscintigraphy, sonography and CT determine the position of the IM lymph nodes directly or indirectly with sufficient accuracy for use in radiotherapy.
Methods and materials

Selection of patients

Forty patients to be treated with irradiation of the left or right side IM lymph nodes participated in the study after written informed consent. The study was approved by the medical ethical committee of the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam. The study included patients receiving irradiation of the IM lymph nodes only or in combination with irradiation of the breast or the thoracic wall after a modified radical mastectomy. Nineteen patients had a mastectomy, while 21 patients underwent breast-conserving therapy. In 21 patients the left side was treated and in 19 patients the right side.

In all examinations, the patients were positioned similarly. For patients who had received a mastectomy the arm was placed along the side of the body, as during irradiation. During the breast conserving treatment the patients are irradiated with the ipsilateral arm abducted and placed in an armrest. In this position it is not possible to enter the CT scanner and therefore those patients kept the arms placed along the body and the hands under the buttocks with the palm of the hand towards the Table.

Placement of reference marks

In most patients the lymphoscintigraphic examination took place first, followed by sonography and thereafter a CT scan. Usually the three examinations were performed within one week. Before the first examination, reference marks were painted with ink on the sternal notch and the xiphoid. These marks were used during all examinations to determine the cranial-caudal positions of the intercostal spaces and the lymph nodes. A straight line connecting the marks through the middle of the sternum on the skin was used for measurements of lateralisation of lymph nodes or vessels.

Node and vessel localisation procedures
Lymphoscintigraphy

The routine protocol for a lymphoscintigraphic examination was extended to include, apart from an anterior scan, a lateral scan. The patients were injected at the subcostal level in the m. rectus abdominis to just above the deep fascia with 60 MBq Technetium-99m nanocolloid on the affected side 2 hours prior to the scans. To visualize the position of the ICSs, Cobalt sources were placed on the reference marks on the sternum.
notch, the xiphoid and on the sternum at the insertion of the 2nd, 3rd and 4th ribs. Anterior and lateral scans were made with a 15% $^{99m}$Tc window at 141 keV and a 5% $^{57}$Co window at 120 keV. The window width of the Co channel was chosen such that the source brightness corresponded to typical node brightness. Anterior and lateral Tc, Co and combined Tc+Co images were printed. A physicist measured the cranial-caudal distance from the sternal notch and lateral distance and depth of the lymph nodes on the images. As in the routine hospital protocol, the lymph node positions in ICSs 2, 3 and 4 were measured. To determine the intercostal space of a lymph node, the cranial-caudal distance, compared to the position of the intercostal spaces determined on CT, and the Co sources on the ribs were used.

**Sonography**

The positions of the first four intercostal spaces were found using a 6-9 MHz transducer and were marked on the skin. With a transversal measurement in each intercostal space the IM vessels were located. The examination was part of the daily workload and performed by the radiologist assigned to the sonography for that day. In total seven radiologists participated in the study. In order to ensure that the protocol for this project was followed, one or two physicists were present during the examination. For this project the radiologist was instructed to keep the transducer as perpendicular to the Table as possible and to minimize the pressure of the transducer onto the skin. The depth to the middle of the most lateral IM vessel (artery or vein) was measured and images were printed of each intercostal space. The physicist marked the position of the transducer on the skin with a pen. After the measurements a flexible ruler was placed along the middle of the sternum between the reference marks on the sternal notch and xiphoid. The cranial-caudal distance from the sternal notch to each intercostal space and the lateral distance from the middle of the sternum to the middle of the transducer were measured. The middle of the transducer indicated an approximate lateral position of the vessel. In combination with this measurement, the vessel position on the printed images gave the lateralization of the mammary vessel in each intercostal space.

**CT scan**

Radio opaque markers were placed on the reference marks on the sternal notch and the xiphoid and a radio opaque catheter was placed between them along the sternum midline. The thorax was scanned with 5 mm slice thickness and slice separation without administration of a contrast agent. A physicist and a radiation oncologist identified the most lateral IM
vessel by marking it in images of the first four intercostal spaces. The cranial-caudal distance, the depth from the skin and the lateral distance from the catheter to the vessel were measured. Only the vessels that could clearly be seen on the CT images were used in the analysis.

**Data analysis**

1. **Accuracy of sonography to determine the vessel position.**
   The correlation between the vessel positions measured with sonography and CT was determined. All available data from ICSs 1-4 were used.

2. **Accuracy of lymphoscintigraphy to determine the node position.**
   With the mathematical model, described in the Appendix, we wanted to find an expression for the accuracy of lymphoscintigraphy for lymph node detection using our measured node and vessel data. The final expression was (Equation 12 in the appendix):

\[
\sigma_{NS}^2 = \text{SD}_{NS}^2 + \text{SD}_{VC}^2 - 2\text{Cov}_{VC,NS} - \sigma_{VC}^2 - \sigma_{DNV}^2 .
\]  

(1)

The subscripts are abbreviations of the following expressions: 'Node-Scintigraphy' (NS), 'Vessel-CT' (VC) and 'Distance Node-Vessel' (DNV).

- \(\sigma_{NS}\) = measurement accuracy (SD) of lymphoscintigraphy to determine a node position
- \(\text{SD}_{NS}\) = standard deviation of the measured node positions by lymphoscintigraphy with respect to the patient midline or the depth from the skin surface
- \(\text{SD}_{VC}\) = standard deviation of the measured vessel positions by CT with respect to the patient midline or the depth from the skin surface
- \(\text{Cov}_{VC,NS}\) = covariance between the measured vessel positions by CT and the measured node positions by lymphoscintigraphy
- \(\sigma_{VC}\) = measurement accuracy (SD) of CT to determine a vessel position
- \(\sigma_{DNV}\) = standard deviation of the distance between node and vessel

The sigmas denote the unknown quantities such as the measurement accuracy of a technique or the standard deviation of the distance between the node and the vessel. The values of these quantities have to be assumed to solve Equation 1. The model has constraints regarding the assumed value of \(\sigma_{DNV}\) (Equations 16-18 in the appendix). The denotations 'SD' and 'Cov' express the standard deviation and covariance of the measured data.
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To calculate the covariance (Cov_{VC,NS}), the correlation between the node positions determined from lymphoscintigraphy and the vessel positions measured on the CT scan must be determined. This can be done using corresponding vessel and node positions for each intercostal space in each patient. Node (or vessel) position data without a corresponding vessel (node) position was not used in the analysis.

3. Accuracy of CT to estimate a node position using the visible vessel position.

The measurement accuracy for indirect node detection using CT is the sum of the CT accuracy for vessel detection and the width of the node distribution around the vessel (Equation 14 in the appendix). The subscript ‘NC’ can be read as ‘Node-CT’:

$$\sigma_{NC}^2 = \sigma_{VC}^2 + \sigma_{DNV}^2$$

(2)

where

$$\sigma_{NC}$$ = measurement accuracy (SD) of CT to determine a node position

By combining Equations 1 and 2, the sum of $$\sigma_{NS}^2$$ and $$\sigma_{NC}^2$$ is a constant derived from the measurements (Equation 15 in the appendix):

$$\sigma_{NS}^2 + \sigma_{NC}^2 = SD_{NS}^2 + SD_{VC}^2 - 2Cov_{VC,NS}. \quad (3)$$

Results

1. Accuracy of sonography to determine the vessel position.

In five patients the sonographic examination was not performed according to the project protocol and CT scans were not obtained of two patients. In a total of 34 patients, 104 corresponding vessel depths in ICSs 1-4 were measured by sonography and CT. In Figure 1 the vessel depth measured by sonography is plotted against the vessel depth found by CT. Up to about 40 mm depth on the CT scale there is a good correlation between the data found by sonography and CT, $$r = 0.83$$, but the sonography measurements show a systematic deviation towards shallower depths. The difference between depths measured by sonography and CT increases with increasing vessel depth. On the average the vessel depth below 40 mm was 5 mm deeper measured with the CT scan compared to the sonography measurements. At depths larger than 40 mm there is a poor negative correlation between the depths found by sonography and CT and a large spread in the data.
No correlation ($r = -0.05$) can be found between vessel lateralisation measured by sonography and CT (Figure 2). The figure shows 96 vessel positions in ICSs 1-4 measured in 33 patients. The mean difference in lateralisation found by sonography and CT is 2 mm but the spread in data is large with a SD in difference of about 10 mm.

![Figure 1. Vessel depth measured by sonography in the first four intercostal spaces plotted against the corresponding vessel depth measured by CT. The line $y=x$ is shown.](image)

2. Accuracy of lymphoscintigraphy to determine the node position.

In one patient the lymphoscintigraphic examination was not performed according to the project protocol and in five patients the lymph nodes were not visualized. In one patient, only the lymph nodes on the contralateral side were visualized.

We separated the data into two independent groups representing measurements in the depth direction and the lateral direction, respectively. In order to collect as much data as possible in each group, a measurement of a node or vessel position in the depth direction was included even if the measurement in the lateral direction was not available, and vice versa. The analysis with the mathematical model was performed separately for each group. Further, the mathematical model required corresponding node and vessel data from each patient and intercostal space. This meant that vessel positions without corresponding measured node positions, and vice versa, were excluded from the analysis. After this exclusion, the remaining data was unbiased only in ICS 2 and therefore we chose to perform the analysis using the data from this intercostal space only.

The depth of the lymph node and the corresponding vessel depth from
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the CT scan in ICS 2 could be determined of 25 lymph nodes in 25 patients. In Figure 3 the depth of the lymph nodes, determined by lymphoscintigraphy, is plotted against the vessel depth determined by the CT scan. There is a positive correlation, \( r = 0.78 \), between the measured node depth and the vessel depth. The mean vessel and node depths agree within 1 mm (Table 1).

![Figure 2](image)

**Figure 2.** Vessel lateralisation measured by sonography in the first four intercostal spaces plotted against the corresponding vessel lateralisation measured by CT. The line \( y=x \) is shown.

**Table 1.** Mean, standard deviation and correlation coefficient of the data measured in intercostal space 2.

<table>
<thead>
<tr>
<th></th>
<th>Depth</th>
<th>Lateralisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>†meanvc (mm)</td>
<td>25.6</td>
<td>26.6</td>
</tr>
<tr>
<td>†meanNS (mm)</td>
<td>26.3</td>
<td>22.2</td>
</tr>
<tr>
<td>‡SDvc (mm)</td>
<td>8.7</td>
<td>5.7</td>
</tr>
<tr>
<td>§SDNS (mm)</td>
<td>7.8</td>
<td>6.4</td>
</tr>
<tr>
<td>‡²VC,NS (mm²)</td>
<td>0.78</td>
<td>0.33</td>
</tr>
</tbody>
</table>

† Mean of the vessel positions measured by CT.
‡ Mean of the lymph node positions measured by lymphoscintigraphy.
§ Standard deviation (SD) of the vessel positions measured by CT.
§ SD of the lymph node positions measured by lymphoscintigraphy.
² Correlation coefficient between measured vessel and node positions.
The laterisation of the lymph node and the corresponding vessel position in ICS 2 could be determined in 27 lymph nodes in 27 patients. Figure 4 shows the laterisation of lymph nodes measured by lymphoscintigraphy plotted against the corresponding vessel laterisation.

**Figure 3.** Lymph node depth in intercostal space 2 measured by lymphoscintigraphy plotted against the corresponding vessel depth measured by CT.

**Figure 4.** Lymph node laterisation measured by lymphoscintigraphy in intercostal space 2 plotted against the corresponding vessel laterisation measured by CT.
measured on the CT scan. The lateral spread of the lymph nodes around the vessels is larger than the spread in the depth direction. There is hardly a correlation between the measured lateral node position and lateral vessel position, \( r = 0.33 \). The mean lateral node position was 4.4 mm medial to the mean vessel position (Table 1).

### Table 2a. The value of \( \sigma_{NS} \) and \( \sigma_{NC} \) in the depth direction for different combinations of \( \sigma_{VC} \) and \( \sigma_{DNV} \).

<table>
<thead>
<tr>
<th>( \sigma_{DNV} ) (mm)</th>
<th>( \sigma_{NS} ) (mm)</th>
<th>( \sigma_{NC} ) (mm)</th>
<th>( \sigma_{DNV} ) (mm)</th>
<th>( \sigma_{NS} ) (mm)</th>
<th>( \sigma_{NC} ) (mm)</th>
<th>( \sigma_{DNV} ) (mm)</th>
<th>( \sigma_{NS} ) (mm)</th>
<th>( \sigma_{NC} ) (mm)</th>
</tr>
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<tbody>
<tr>
<td>2.5</td>
<td>4.8</td>
<td>2.7</td>
<td>1.7</td>
<td>4.4</td>
<td>3.4</td>
<td>0.3</td>
<td>2.4</td>
<td>5.0</td>
</tr>
<tr>
<td>3</td>
<td>4.6</td>
<td>3.2</td>
<td>2</td>
<td>4.2</td>
<td>3.6</td>
<td>1</td>
<td>2.2</td>
<td>5.1</td>
</tr>
<tr>
<td>4</td>
<td>3.7</td>
<td>4.1</td>
<td>3</td>
<td>3.6</td>
<td>4.2</td>
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<td>5.1</td>
<td>4</td>
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<td>2.4</td>
<td>0</td>
<td>5.5</td>
</tr>
<tr>
<td>5.5</td>
<td>0</td>
<td>5.6</td>
<td>4.7</td>
<td>0</td>
<td>5.6</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The highest and lowest values of \( \sigma_{DNV} \) to determine the range of \( \sigma_{NS} \), have been found according to Equations 16-18.

\[
\sigma_{NS} = \sigma_{VC}^2 + \sigma_{DNV}^2 - 2 \sigma_{VC} \sigma_{DNV} \\
\sigma_{NC} = \sigma_{VC}^2 + \sigma_{DNV}^2
\]

### Table 2b. The value of \( \sigma_{NS} \) and \( \sigma_{NC} \) in the lateral direction for different combinations of \( \sigma_{VC} \) and \( \sigma_{DNV} \).

<table>
<thead>
<tr>
<th>( \sigma_{DNV} ) (mm)</th>
<th>( \sigma_{NS} ) (mm)</th>
<th>( \sigma_{NC} ) (mm)</th>
<th>( \sigma_{DNV} ) (mm)</th>
<th>( \sigma_{NS} ) (mm)</th>
<th>( \sigma_{NC} ) (mm)</th>
<th>( \sigma_{DNV} ) (mm)</th>
<th>( \sigma_{NS} ) (mm)</th>
<th>( \sigma_{NC} ) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
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<td>5.9</td>
<td>3.8</td>
<td>1.6</td>
<td>4.7</td>
<td>5.2</td>
</tr>
<tr>
<td>4</td>
<td>5.7</td>
<td>4.1</td>
<td>3</td>
<td>5.6</td>
<td>4.2</td>
<td>2</td>
<td>4.5</td>
<td>5.4</td>
</tr>
<tr>
<td>5</td>
<td>4.8</td>
<td>5.1</td>
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<td>4.9</td>
<td>5.0</td>
<td>3</td>
<td>3.9</td>
<td>5.8</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>6.1</td>
<td>5</td>
<td>3.9</td>
<td>5.8</td>
<td>4</td>
<td>2.9</td>
<td>6.4</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>7.1</td>
<td>6.4</td>
<td>0</td>
<td>7.1</td>
<td>5</td>
<td>0</td>
<td>7.1</td>
</tr>
</tbody>
</table>

In Table 1 the standard deviation of the measured vessel data by CT, \( SD_{VC} \), the measured node data by lymphoscintigraphy, \( SD_{NS} \), and the correlation coefficient between the vessel and node data, \( r_{VC,NS} \), are given for ICS 2. The accuracy of lymphoscintigraphy for node detection, \( \sigma_{NS} \), was estimated according to Equation 1. In this Equation, \( \sigma_{VC} \) and \( \sigma_{DNV} \) are unknown values. We inserted the values of \( \sigma_{VC} = 1, 3 \) and 5 mm into Equation 1, and calculated \( \sigma_{NS} \) for a range of values of \( \sigma_{DNV} \). The final paragraph of the Appendix describes how the lowest and highest values of \( \sigma_{DNV} \) were determined. Table 2 gives the results for the depth direction (Table 2a) and lateral direction (Table 2b). In accordance with Equations 2
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and 3 the sum of $\sigma_{VC}^2$, $\sigma_{DNV}^2$ and $\sigma_{NS}^2$ is constant. The maximum value of $\sigma_{NS}$ is 4.8 mm in the depth direction and 6.0 mm in the lateral direction.

The value of $\sigma_{DNV}$ gives the width of the node distribution around the vessel. As can be derived from Equation 1, an increase in this value gives a decrease in the value of $\sigma_{NS}$. This can be interpreted as the larger the spread of nodes around the vessel, the more accurate lymphoscintigraphy is for node detection, using this model to determine the measurement accuracy. Also according to the model, the greater the value of $\sigma_{VC}$, the smaller the value of $\sigma_{NS}$. This means that the more inaccurately the vessel position is measured by CT, the more accurately the node position is determined by lymphoscintigraphy.

3. Accuracy of CT to estimate a node position using the visible vessel position.

In Table 2 the accuracy of CT for indirect node localisation, $\sigma_{NC}$, can be found for different combinations of $\sigma_{VC}$ and $\sigma_{DNV}$ according to Equation 2. In accordance with Equation 3 the sum of $\sigma_{NS}^2$ and $\sigma_{NC}^2$ is constant. With an increasing value of $\sigma_{DNV}$ or $\sigma_{VC}$ the value of $\sigma_{NC}$ increases. This means that if either the node distribution around the vessel or the inaccuracy for vessel detection increase, the inaccuracy for node detection also increases. In the depth direction there is a theoretical maximum value of $\sigma_{NC}$ of 5.6 mm and in the lateral direction of 7.1 mm.

Discussion

1. Accuracy of sonography to determine the vessel position.

The lateral vessel positions measured by sonography do not correlate with the CT measurements. Under ideal circumstances for the sonography measurements, the transducer was held perpendicular to the sternum midline, parallel to the Table and with no pressure onto the skin. In practice this was difficult to accomplish since the anatomy of the patient determined the angle at which the transducer could be held. Best correlation between sonography and CT was found in those patients that underwent breast-conserving therapy and had small breasts, i.e. the breast did not rise at an angle above the ribs when the patient lay on her back.

The sonography depth measurements showed a systematic error that increased with increasing vessel depth. For depths less than 40 mm it seemed like the systematic error was related to the thickness of the tissue above the vessel, which was estimated on the CT images. This indicates that the transducer is pushed harder against the skin for patients with a thick
fat layer compared to those with a thin layer. If the vessel is situated deeper, the sonography error is even larger and the measurements are almost uncorrelated with the CT measurements. All these deep data points were obtained with patients with large breasts. For these patients it seems particularly difficult to measure without placing the transducer at an angle and without pressure.

If electron fields are used for irradiation of the IM lymph nodes, the systematic underestimation of the vessel depth may lead to a systematically too low choice of electron beam energy and an underdosage of the IM lymph nodes. The systematic error at vessel depths below 40 mm can possibly be corrected for by adding the mean difference, about 5 mm, between CT and sonography to all depth measurements or by fitting a line through the data. Although such a correction seems an option, it is likely that the accuracy of the sonography measurement under routine conditions would be even worse. According to the project protocol the radiologist was constantly aware to hold the transducer perpendicular to the Table and without pressure to the skin. Correction of sonography depth measurements can therefore only be recommended if similar data would be collected under routine clinical conditions. It must also be taken into account that the measurement result might be operator dependent.

The systematic error in depth and the uncorrelated data in lateralisation show that sonography does not accurately determine the vessel position and therefore it is not a reliable technique for indirect lymph node localisation.

2. Accuracy of lymphoscintigraphy to determine the node position.

A reasonable correlation between the node depth found by lymphoscintigraphy and the vessel depth found by CT (r = 0.78) was present. In the depth direction, the intercostal muscle and the endo thoracic fascia limit the space for the lymph nodes. The nodes and the vessels should therefore have approximately the same depth. The data confirmed this assumption since the mean vessel and node positions in depth agreed within 1 mm in ICS 2.

In the lateral direction the correlation between the node and the vessel position was not so good (r = 0.33). In this direction there is more space for the node distribution around the vessel, which could explain the weak correlation with the vessel positions. No data concerning the width of the node distribution could be found in the literature.

To determine the accuracy of lymphoscintigraphy for node detection (σNS) using the mathematical model and the measured data, the width of the node distribution around the vessel (σDV), as well as the measurement accuracy of CT to determine the vessel position (σVC), had to be assumed (Equation 1). The vessel is clearly visible on the CT images and therefore a
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good accuracy in the determination of the vessel position ($\sigma_{VC}$) can be expected. Still, measurement errors can be caused by inaccuracies in placement of the wire along the sternum midline and in measuring the lateral and depth distance to the vessel.

Table 2 shows the relation in the model between $\sigma_{NS}$, $\sigma_{VC}$ and $\sigma_{DNV}$. The data in the columns show that a higher assumed $\sigma_{DNV}$ results in a lower estimated value of $\sigma_{NS}$ and thus a better measurement accuracy of lymphoscintigraphy. The assumed value of $\sigma_{VC}$, as well as having an independent effect on the estimated $\sigma_{NS}$, also determines the possible range for $\sigma_{DNV}$ (see Equations 16-18 in the appendix).

Comparing Tables 2a and 2b we observe that the model gives allowable values of $\sigma_{DNV}$ that are smaller in the depth than in the lateral direction. This is in accordance with the limitation in space for the nodes in the depth direction by the intercostal muscle and the endothoracic fascia. From Table 2 we can determine $\sigma_{NS}$ for what we believe are reasonable values for $\sigma_{VC}$ and $\sigma_{DNV}$. In a 'worst case' scenario for the lymphoscintigraphy accuracy where the value of $\sigma_{NS}$ in Table 2 has the highest allowable value, the measurement accuracy of the CT scan, $\sigma_{VC}$, is 1 mm (1 SD), and the width of the node distribution has the smallest possible value. According to Table 2, the value of $\sigma_{NS}$ is then 4.8 mm in depth and 6.0 mm in the lateral direction. In reality, the wire placement is rather difficult and the value of $\sigma_{VC}$ is probably slightly higher than 1 mm. We may then conclude that the accuracy of lymphoscintigraphy for node localisation is 6 mm or better in the lateral direction and better than 5 mm in the depth direction.

The analysis in depth and lateral direction was only performed in ICS 2, but the results can be applied to the other ICSs if the data and the assumptions made in the mathematical model can be assumed to be equal to ICS 2. Adding the data of ICS 3 to the analysis did not change the values of $\sigma_{NS}$ significantly.

3. Accuracy of CT to estimate a node position using the visible vessel position.

The calculation of the accuracy of the CT scan for lymph node detection ($\sigma_{NC}$) as the sum of two estimated parameters, $\sigma_{VC}$ (the accuracy for vessel detection) and $\sigma_{DNV}$ (the standard deviation of the distance between node and vessel), suggests that it is not possible to exactly determine $\sigma_{NC}$. However, Equation 3 shows the relation between $\sigma_{NS}$, $\sigma_{NC}$ and the measured data. To test the values of $\sigma_{NC}$ determined in Table 2, a phantom experiment was performed with lymphoscintigraphy, mimicking the in vivo situation. The $\sigma_{NS}$ found in this experiment was about 3 mm in depth and 1 mm in the lateral direction. Inserting these values for $\sigma_{NS}$ into Equation 3,
gives values for $\sigma_{NC}$ of 4.7 mm (1 SD) in depth and 7.0 mm in the lateral direction. These values might seem high, but it has to be kept in mind that this accuracy is the sum of the accuracy of CT for vessel detection and the width of the node distribution around the vessel (Equation 2). Moreover, the \textit{in vivo} accuracy of lymphoscintigraphy is probably worse than that measured \textit{in vitro} with a phantom. According to Table 2, the data allows values of $\sigma_{NS}$ up to 4.8 mm for depth and 6.0 mm for lateralisation. Therefore, looking at more realistic values of 3-5 mm of $\sigma_{NS}$ in Table 2, the value of the accuracy of CT for node localisation ($\sigma_{NC}$) is probably about 5 mm in depth and 6 mm in lateralisation.

The difference in the mean lateral node and vessel positions in ICS 2 was 4.4 mm. This might be a systematic difference introduced by our measurements, since we always measured the most lateral of the IM vessels. This difference in mean vessel and node position did not influence the analysis of the random measurement errors, but it does have consequences in the clinical practice. If a vessel position found by CT is used as a reference to determine the field borders for irradiation of the lymph nodes, it is important to know any systematic differences in the position between the vessel and the node. Systematic measurement errors must also be known to determine a correct field border. To determine the systematic measurement errors a more extended statistical analysis is required with more data than were available in this study.

**Summary and conclusions**

Although sonography is a simple, fast and cheap technique its use cannot be recommended. In the lateral direction it is not possible to determine the vessel position with sonography. In the depth direction, systematic errors that are patient and probably operator dependent hamper the use of sonography. If sonography must be used to determine the depth of the nodes because CT and lymphoscintigraphy are not available, a study of the systematic error under true clinical conditions is necessary for correction.

Despite the lack of a golden standard to determine the exact node position, it was possible to determine the measurement accuracy of lymphoscintigraphy and CT for node detection in one intercostal space with a mathematical model. Systematic measurement errors were not taken into account in the analysis. A requirement for the positioning accuracy of about 5 mm (1 SD) or better was recommended for accurate irradiation. Under the
assumptions used in the model it was shown that lymphoscintigraphy can determine node positions within an accuracy of 5 mm (1 SD) in the depth direction and 6 mm in the lateral direction, which is acceptable for radiotherapy. Using CT the node positions can be determined within an accuracy of 6 mm in the depth direction and 7 mm in the lateral direction.

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Appendix

Model for the CT and lymphoscintigraphy measurements in one ICS

The population average of the vessel position (distance to the midline or depth from the skin surface) is denoted $D^v$ and the random deviation from $D^v$ in patient $i$ is denoted $D^v_i$. The (signed) distance between the lymph node and the vessel has a population average $D^l_{NV}$. The random deviation in this distance between the node and the vessel in patient $i$ is denoted $D^l_{NV}$. According to this model, the vessel position in patient $i$ is

$$D^v_i = D^v + D^v_i$$  \hspace{1cm} (4)

and the lymph node position in patient $i$ is

$$D^l_i = D^l + D^l_{NV} + D^l_{NV} + D^l_{NV}$$  \hspace{1cm} (5)

The CT and lymphoscintigraphy measurements were assumed to have random and systematic measurement errors. The vessel position in patient $i$ measured by CT, $D^l_{VC}$, and the node position measured by lymphoscintigraphy, $D^l_{NS}$, could then be described in the following way:

$$D^l_{VC} = (D^v + D^l_i) + E^{Sys}_{VC} + E^{i}_{VC}$$  \hspace{1cm} (6)

$$D^l_{NS} = (D^v + D^l_i + D^l_{NV} + D^l_{NV} + D^l_{NV}) + E^{Sys}_{NS} + E^{i}_{NS}$$  \hspace{1cm} (7)
where

\[ E_{\text{VC}}^S, E_{\text{VC}}^i = \text{systematic and random measurement error, respectively, of CT (of a vessel)}, \]

\[ E_{\text{NS}}^S, E_{\text{NS}}^i = \text{systematic and random measurement error, respectively, of lymphoscintigraphy (of a node)}. \]

**Estimation of the random measurement errors**

Equation 6 and 7 contain four systematic components: \( D^S_{\text{VC}}, E_{\text{VC}}^S, D^S_{\text{NS}} \)

and \( E_{\text{NS}}^S \). Since we only have two measurements (lymphoscintigraphy and CT), it is impossible to solve the Equations for the systematic components. However, by making some reasonable assumptions it is possible to estimate the random measurement errors. It was assumed that \( D^i_{\text{VC}}, D^i_{\text{NS}}, E^i_{\text{VC}} \)

and \( E^i_{\text{NS}} \) were normally distributed with variances \( \sigma^2_{\text{DV}}, \sigma^2_{\text{DNV}}, \sigma^2_{\text{VC}} \)

and \( \sigma^2_{\text{NS}} \). These variables were assumed to be independent, except \( D^i_{\text{VC}} \) and \( D^i_{\text{NS}} \) which had the covariance \( \text{cov}_{\text{DV,DNV}} \). This covariance was introduced since it could not be excluded that the width of the distribution of nodes around the vessel depended on the lateralisation or the depth of the vessel. Further it was assumed that there existed a covariance between the vessel position as measured by CT and the node position measured by lymphoscintigraphy. Calculating all variances and covariances from Equations 6 and 7 with these assumptions we obtained the following Equations for the random errors:

\[ \sigma^2_{\text{DVC}} = \sigma^2_{\text{DV}} + \sigma^2_{\text{VC}} \]  

(8)

\[ \sigma^2_{\text{DNS}} = \sigma^2_{\text{DV}} + \sigma^2_{\text{DNV}} + \sigma^2_{\text{NS}} + 2 \text{cov}_{\text{DV,DNV}} \]  

(9)

\[ \text{cov}_{\text{DVC,DNS}} = \sigma^2_{\text{DV}} + \text{cov}_{\text{DV,DNV}} \]  

(10)

where

\[ \sigma_{\text{DVC}} = \text{standard deviation around the population mean of the vessel positions measured by CT} \]

\[ \sigma_{\text{DV}} = \text{standard deviation of the vessel distribution} \]

\[ \sigma_{\text{VC}} = \text{measurement accuracy (SD) of CT to determine a vessel position} \]

\[ \sigma_{\text{DNS}} = \text{standard deviation around the population mean of the node positions measured by lymphoscintigraphy} \]

\[ \sigma_{\text{DNV}} = \text{standard deviation of the distance between node and vessel} \]

\[ \sigma_{\text{NS}} = \text{measurement accuracy (SD) of lymphoscintigraphy to determine a node position} \]

\[ \text{cov}_{\text{DV,DNV}} = \text{covariance between the vessel position and the distance} \]
between the node and vessel

\[ \text{COV}_{\text{DVC,DNS}} = \text{covariance between the vessel position measured by CT and node position measured by lymphoscintigraphy} \]

Combining Equations 8-10 gives:

\[
\sigma_{\text{VC}}^2 + \sigma_{\text{NS}}^2 + \sigma_{\text{DNV}}^2 = \sigma_{\text{DNS}}^2 + \sigma_{\text{DVC}}^2 - 2 \text{COV}_{\text{DVC,DNS}}. \tag{11}
\]

The standard deviations \( \sigma_{\text{DNS}} \) and \( \sigma_{\text{DVC}} \) and the covariance \( \text{COV}_{\text{DVC,DNS}} \) can be estimated from the standard deviations and the covariance of the measurements. The final Equation for the accuracy of determining the node positions by lymphoscintigraphy is then:

\[
\sigma_{\text{NS}}^2 = \text{SD}_{\text{NS}}^2 + \text{SD}_{\text{VC}}^2 - 2 \text{COV}_{\text{VC,NS}} - \sigma_{\text{VC}}^2 - \sigma_{\text{DNV}}^2 \tag{12}
\]

where

- \( \text{SD}_{\text{NS}} \) = standard deviation of the measured data of the node positions by lymphoscintigraphy
- \( \text{SD}_{\text{VC}} \) = standard deviation of the measured data of the vessel positions by CT
- \( \text{COV}_{\text{VC,NS}} \) = covariance between the measured vessel positions by CT and the measured node positions by lymphoscintigraphy
- \( \text{COV}_{\text{VC,NS}} = \text{SD}_{\text{VC}} \cdot \text{SD}_{\text{NS}} \cdot r_{\text{VC,NS}} \tag{13} \)

\( r_{\text{VC,NS}} \) = the Pearson correlation coefficient between the measured vessel positions by CT and the measured node positions by lymphoscintigraphy.

The measurement accuracy for indirect node detection using CT is the sum of the CT accuracy for vessel detection and the width of the node distribution around the vessel:

\[
\sigma_{\text{NC}}^2 = \sigma_{\text{VC}}^2 + \sigma_{\text{DNV}}^2 \tag{14}
\]

where

- \( \sigma_{\text{NC}} \) = measurement accuracy (SD) of CT to determine a node position.

By combining Equations 12 and 14, the sum of \( \sigma_{\text{NS}}^2 \) and \( \sigma_{\text{NC}}^2 \) is a constant derived from the measurements:

\[
\sigma_{\text{NS}}^2 + \sigma_{\text{NC}}^2 = \text{SD}_{\text{NS}}^2 + \text{SD}_{\text{VC}}^2 - 2 \text{COV}_{\text{VC,NS}}. \tag{15}
\]

**Limits for \( \sigma_{\text{DNV}} \)**

The value of \( \sigma_{\text{NS}} \) was calculated by inserting a value of \( \sigma_{\text{VC}} \) into Equation 12 and thereafter varying the value of \( \sigma_{\text{DNV}} \). One condition for the value of \( \sigma_{\text{DNV}} \) is that \( \sigma_{\text{NS}}^2 \) must be larger or equal 0.

Another condition is determined by the correlation coefficients \( r_{\text{N,V}, r_{\text{V,NV}}} \)
and \( r_{N, NV} \), where \( r_{N,V} \) is the correlation coefficient between the node positions and the vessel positions, \( r_{V, NV} \) between the vessel positions and the distance between the node and vessel and \( r_{N,NV} \) between the node positions and the distance between the node and vessel.

These correlation coefficients can be expressed as:

\[
\begin{align*}
r_{N,V} &= \frac{\sigma_{DV}^2 + \text{cov}_{DV, DNV}}{\sigma_{DV} \sqrt{\sigma_{DV}^2 + \sigma_{DNV}^2 + 2 \text{cov}_{DV, DNV}}} \\
r_{V, NV} &= \frac{\text{cov}_{DV, DNV}}{\sigma_{DV} \sigma_{DNV}} \\
r_{N, NV} &= \frac{\sigma_{DNV}^2 + \text{cov}_{DV, DNV}}{\sigma_{DNV} \sqrt{\sigma_{DV}^2 + \sigma_{DNV}^2 + 2 \text{cov}_{DV, DNV}}}.
\end{align*}
\]

Using Equations 8 and 10 and the measured data, and by assuming a value for \( \sigma_{VC}^2 \), the correlation coefficients \( r_{N,V} \), \( r_{V, NV} \) and \( r_{N, NV} \) can be calculated for different values of \( \sigma_{DNV} \). A value of \( \sigma_{DNV} \) is only valid if it results in \( r_{N,V} \), \( r_{V, NV} \) and \( r_{N, ND} \) between \(-1\) and \(1\) (and \( \sigma_{NS}^2 \) positive or zero).

In the same way, Equations 16-18 can be used to determine the limits of \( \sigma_{DNV} \) to estimate \( \sigma_{VC}^2 \), using an assumed or known value of \( \sigma_{NS}^2 \) and Equations 8, 10 and 12.

References

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