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Honors Thesis:

The feasibility of conducting manual image segmentation of 3D sonographic images of axillary lymph nodes

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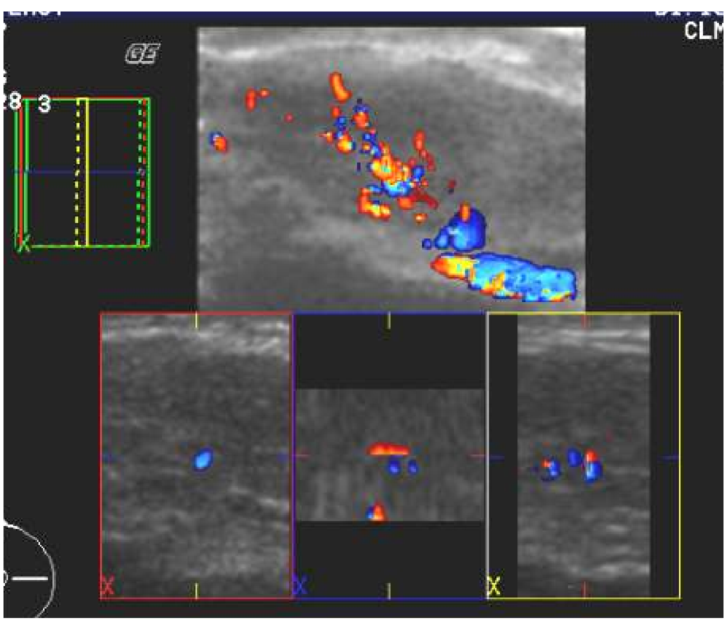
Problem Statement

Breast cancer is one of the most common causes of death in women in the United States (Centers for Disease Control and Prevention, 2007). Not only is it hard to detect, but once diagnosed the treatment is usually a long and difficult process. In the human body, cancer cells are disseminated throughout by the lymphatic and vascular systems, potentially forming metastases in surrounding tissues or organs. Many studies have shown that the most common cause of death in cancer patients is this distribution of primary tumor cells aided by the lymphatic system (Qatarneh, et. al., 2006). Because most primary malignancies spread systematically in this way, the investigation of axillary lymph node metastases is extremely important in detecting patient mortality. Discovery of the affected lymph nodes predicts a much shorter disease-free survival (Harisinhani, et. al., 2004). In fact, 70% of patients with negative lymph nodes survive more than ten years after cancer diagnosis, while in those patients with metastatic nodes; the statistics are associated with a higher mortality rate (Nori, et. al., 2005).

Therefore, clinical detection of normal or malignant lymph nodes is extremely beneficial to cancer diagnosis and treatment. Currently, however, this is a challenge due to the huge variability of lymph node characteristics and the variations in imaging. In typical modalities such as computed tomography (CT), malignancies must have a short axis of greater than 10 mm to be detected, but this has been commonly shown to be unreliable and results in missing smaller tumors (Harisinghani, et. al., 2004). It is also important to consider the increased patient dose associated with the radiation from a CT scan. The risk of repeated radiation exposure is not yet fully understood, but in a study of women with scoliosis who were exposed to multiple diagnostic x-rays there was a statistically significant increased risk for breast cancer making this an important factor in the consideration of x-ray modalities for screening potential disease (Brenner, et. al., 2003).

Invasive or surgical procedures remain the most reliable and common for predicting nodal metastases in patients. These procedures include axillary lymph node dissection (ALD), biopsy, or lymphadenectomy, all of which have significant morbidity and cost (Harisinghani, et. al., 2004). Most invasive diagnostic procedures are ultimately combined with surgery in the attempt to treat breast cancer. The current gold standard for the diagnosis of lymph node metastasis is ALD. Despite the prognostic importance of diagnosing metastasis in 60-70% of breast cancers, nodal pathology is not always obtained, therefore, this diagnostic step is underutilized due to cost and the invasive nature (Nori, et. al., 2005).

Therefore, a procedure which would allow for consistently successful and accurate lymph node screening is necessary. Recently, the use of 3D sonography has proven to be a successful and noninvasive method of visualizing and modeling tumors, both small and large, in breast cancer patients before surgery (Sato, et. al., 1998). This idea can also be extended to the modeling of axillary lymph nodes without surgery or biopsy in order to examine them based on volume and in comparison to other



lymph nodes. By examining the volume and voxel counts of sonographic generated 3D axillary nodes, it is possible that significant diagnostic information could be obtained. However, as previously stated the wide dispersion of lymph nodes and the difficultly in obtaining sonographic lymph nodes makes this imaging technique in need of further exploration (Evans, et. al., 2007). If successful, this technique could decrease the need for invasive and or ionizing radiation to obtain this screening information.

Related Research

The use of sonography in the segmentation of images has not been attempted until very recently and the extension of this to lymph node assessment represents an innovation for the field. Lymph node segmentation has been experimented with in other imaging modalities, either directly or in conjunction with the segmentation of other anatomical structures, but only on a very small scale. A 2006 study of the CT evaluation of neck masses, explored imaging tumors of the oral, nasal, and throat cavities. These tumors often metastasize quickly into the lymph nodes of the neck. The need for surgery in these cases was common and difficult. The surgeon had to remove both the primary tumor and the affected nodes without damaging the major blood vessels and spinal cord located in the adjacent area. The researchers found that most surgeries were planned using CT axial images of the neck to determine tumor size and location, the ultimate determination of whether surgery was possible. However, in their practice, the limit of 2D images led to misinterpretations and errors which often led to the cancelation of surgery (Cordes, et. al., 2006).

Therefore, their study was dedicated to finding the best methods for imaging and segmenting tumors and lymph nodes pre-operatively. They used four different methods of CT segmentation: automatic, conventional or region-growing, interactive, and live-wire. Manually, parameters of the areas of interest were drawn by an operator every four axial slices and a 3D model was then rendered. They found the results of live-wire segmentation to be promising. However, the success of their work was inconsistent between different anatomical parts and especially more difficult in low contrast regions, such as those found in the axillary lymph node areas. Another problem with their work was the significant amount of time involved, as well as the major radiation dose to patients associated with CT (Cordes, et. al., 2006).

Magnetic resonance imaging (MRI) has also been used to examine lymph nodes in cancer staging. A 2004 study suggested that MRI could be another noninvasive method of determining lymph node metastatic status. The researchers measured magnetic tissue parameters of cancer metastases and normal unmatched lymph nodes using lymphotropic nanoparticle enhanced magnetic resonance imaging (LMRI). They found that after comparing these differing nodes' unique magnetic tissue parameters, they could accurately distinguish metastatic from normal nodes 98% of the time (Harisinghani, et. al., 2004). Not only that, but the process could be semi-automated and used for three-dimensional reconstruction of the complete nodal anatomy of patients with different primary cancers. This was a significant finding for breast cancer staging because it allowed for cancer staging without invasive procedures and even an earlier start to chemotherapy prior to a surgical lymph node assessment. However, like CT, MRI requires that patients spend a great deal of time waiting for images to be acquired.

While CT and MRI have made great contributions to cancer staging through the 3D imaging and segmentation of lymph nodes the easiest and non-ionizing imaging modality would be sonography. While its use in the same capacity has yet to be fully explored there is a great deal of encouraging research about its relevance to this field. A 1998 review of the literature presented the major problems with utilizing sonography for segmentation and also a method for overcoming these issues (Wang, et. al., 1998). The main problem with the segmentation of sonograms was the identification of ultrasound speckle, otherwise known as an imaging artifact. This is a result of the fact that speckle artifacts are inherent in the ultrasound signal and are directly proportional to the magnitude of the ultrasound signal strength. This multiplicative artifact results in very bright regions where significant noise makes the defining boundary edges difficult for automated segmentation. The edge detector seeks sharp intensity changes to define, however, because speckle causes boundary edges to be erroneous, this leads to incorrectly defined boundaries. Furthermore, the different ultrasound attenuations by varied tissues in the body, make the image boundaries even more complicated and difficult to distinguish.

This study proposed a new method, a saliency model, which they found could resolve the image edges by correcting for both the multiplicative artifact and the uneven tissue attenuations. Using this newly corrected image they used a segmentation model called a systolic snake to automatically define parameters of their regions of interest. However, the saliency model alone made manual definition of edges of interest much easier (Wang, et. al., 1998). Subsequent research has adopted similar models or gradients which are used in this way to make manual and automatic sonography segmentation easier and more accurate. Consequently, evidence continues to mount that sonography could be a very plausible contender as the best clinical practice for 3D image segmentation.

This method of using segmented sonography images in three dimensions was employed early in Japan (Sato, et. al., 1998). Japanese researchers described several case studies that have been conducted utilizing sonographic images for segmentation. The researchers used ultrasound to obtain three-dimensional models of breast tumors. This was actually performed in the operating room prior to surgical resection in order to define the exact position and shape of the tumors. The goal was to allow surgeons to both accurately remove the tumor as well as maximize breast conservation. After capturing sonographic images of the breast, a filter was used in order to reduce the troublesome speckle artifact. Then, low-intensity regions, suspected to be tumor regions, were extracted. A 3D model was created by the technology and slice by slice an operator specified the breast tissue. The tumor volume was then generated and a special video camera used to superimpose the tumor onto the video images for the surgeon (Sato, et. al., 1998).

While this research succeeded in its aims to use sonography to create and project a three dimensional image of the tumor for surgery, the efficiency and reliability of this process was not convincing. The process was relatively time-consuming, taking around fifteen minutes to complete. Additionally, each model had to be checked by several experts to assure that the operator had not mistakenly missed tumor volume or included normal breast tissue (Sato, et. al., 1998). Therefore, the fact that this procedure was performed in the operating room was inconvenient and would be more feasible pre-operatively. A major benefit of this imaging procedure was that, although CT and MRI can provide similar models, ultrasound provided a lower cost and non-ionizing result.

A similar study was performed prior to the surgery of forty women undergoing breast cancer resection. Again, sonography was performed and three dimensional models were created and superimposed on a video image of the patient. These researchers even took the process a step further and measured the difference in sizes between the 3D sonographic images and the pathological examination. The results were remarkable with very high correlation ($r = 0.89$) and statistical significance between the images and pathologic result. This indicated that the 3D sonographic models were reliable and quite comparable to the actual anatomical structures within the body (Inoue, et. al., 2004).

Sonography proved a successful imaging modality for segmentation and cancer diagnosis in two dimensions as well as three. In 2001, researchers reviewed 400 mammograms and associated breast sonograms, which had already been diagnosed through biopsy or aspiration, to assess the accuracy of computer-aided diagnosis (CAD) detection method (Horsch, et. al., 2001). They used either a manual, partially automatic, or fully automatic segmentation technique which was based on the gray-value thresholding of pre-identified breast lesions. Each lesion was manually outlined by a mammographer or physicist and then placed into an automatic segmentation algorithm. The algorithm first used gray-value thresholding to determine the potential lesion margins. Then the four main characteristics used to examine breast lesions were quantified by the system and examined by radiologists to determine a diagnosis.

The study found that this method of sonographic segmentation was highly successful at distinguishing between malignant and benign lesions (Horsch, et. al., 2001). This is significant because it proves that the use of sonography was not hindered by noise or artifact due to the expanding technology and smoothing filtrations available. Sonography has the potential to allow for the consistent image creation of small masses, such as tumors and possibly lymph nodes, and also to allow segmentation, which provides significant diagnostic information.

Finally, a quasi-experimental Italian study focused on the preoperative assessment of patients selected for sentinel node biopsy (Nori, et. al., 2005). The axillary nodes of 117 women diagnosed with breast cancer were imaged using conventional sonography. In only nine of these women were less than four nodes found, and in the remaining participants the sonographic information was tested for its diagnostic significance. They found that sonography correctly identified normal lymph nodes which agreed with histology, or 72.7% were true negatives. Unfortunately, this imaging technique missed many of the smaller micro-metastasis, on the order of 0.1-0.5 mm in size. The false negative rate was 27.3% of cases and the false positive to true positive rate was very similar (Nori, et. al., 2005).

Therefore, while sonography is a promising screening option and may facilitate image segmentation, more research is needed to replace the gold standard of ALD. One of the conclusions of this study was that increased operator training could probably decrease the number of false negatives and positives with sonography. Furthermore, the technology is innovative and with increased training, may provide better results upon replication of this study (Nori, et. al., 2005).

A gap in the literature existed because a there is a paucity of research that utilizes three dimensions instead of two to image a lymph node with sonography. This was an unexplored imaging technique. With the constant improvement of the inherent quality of ultrasound transducers and the reliability of image segmentation, it was extremely plausible that non-ionizing and non-invasive evaluation of lymph nodes could be conducted. Prior to the completion of this research no studies existed which utilized 3D sonography to assess lymph nodes or tumors with image segmentation. Therefore, a feasibility study was the next logical step in advancing this line of scientific inquiry.

Objectives of the study

The objective of the study was to conduct a feasibility study of the use of manual image segmentation using sonographic images of axillary lymph nodes to create 3D models. Since aging changes could have made this evaluation difficult, it was much less complicated to only image nodes that were normal in configuration and then segment them using the "snake" to create the 3D model. Once the computer software manipulation was completed, the 3D volume model could be created. This is a significant step forward in staging a clinical research project that includes abnormal lymph nodes. The research question for this step of the research was as follows: *Can manual image segmentation create consistent sonographic 3D models of normal lymph nodes regardless of the experience of the operator?*

Procedures

Population and Sample

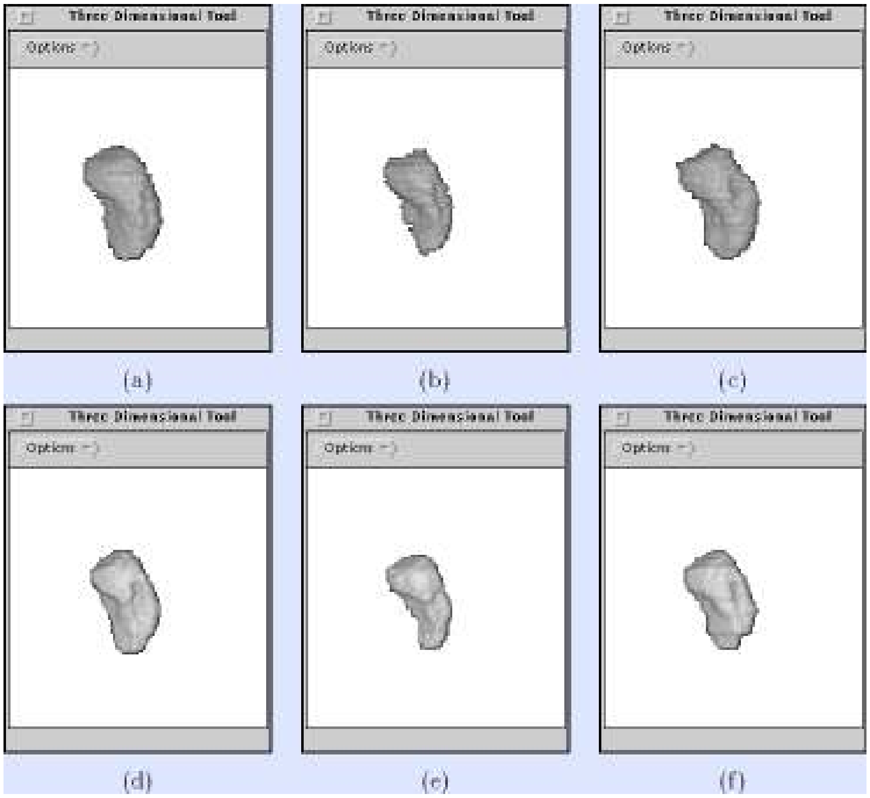
A flyer was posted in Atwell Hall with contact and study details to recruit a convenient sample of women, ages 18-40, to provide sonographic images of their lymph nodes. The proposed sample was 40 volunteers, to obtain a statistical power of 0.59, a moderate effect size of 0.5, with an alpha of 0.5. Dr. Evans' graduate research assistant scheduled all the volunteers and confirmed their ages and that they were not under any kind of treatment that would affect their lymph nodes. Verbal assent was obtained from all participants.

Design

Once volunteers were consented, they were scheduled for a twenty minute screening sonogram of the axillary region using a 4D16L transducer from GE Healthcare, Ultrasound (Waukee, WI) which is specifically built to make volume measurements after scanning. GE Medical provided all the hardware and software for this project to be conducted. GE Medical provided Dr. Evans with a TRU 3D and Vocal software, which is commercially available in limited areas. These exams were conducted in Dr. Evans' Atwell Hall lab. The goal was to attempt to image at least three lymph nodes from each volunteer in volume sets for 3D reconstruction. Once the volunteers were imaged they were not recalled for future imaging.

The TRU 3D and Vocal probe technology was used to generate a 3D reconstruction of the node image. Using the deformable model "snake", the 3D lymph node images were manually segmented using the software and a mouse. To manually segment the lymph node images they were divided by the system into six slices, 30 degree rotations apart, and an ROI (region of interest) manual snake used. The operator looked at each of the six sliced images of each lymph node and drew a line around the outer margin of the node. This was performed by three operators with a standardizing precaution and inter-rater reliability was calculated.

Once this manual technique was performed the operator then allowed the system to



create a 3D model of the manually segmented lymph node based on the operator's defined parameters and a cubic volume was given in cm^3. From this a voxel count could be calculated mathematically and recorded for future reference and comparisons between lymph nodes. Finally, images were de-identified and retained on a flash drive kept in a locked office to be deleted at the end of the study if not used for publication.

The timetable to complete the manual segmentation began when the first volunteer was consented on Tuesday, April 1, 2008 and was completed by June 1, 2008. All the manual segmentation was completed by August, 2008 and data analysis was conducted during summer 2008.

Data Analysis

The cubic volumes of the segmented 3D model nodes are reported. The inter-rater reliability is reported as a correlation between the sonographers. The Pearson product correlation was conducted to insure stability of the segmented node measurements between sonographers. A correlation of r = 0.6 or higher was anticipated as a measure of reasonable to high correlation between sonographers.

Facilities and Resources

This study was a subset of an OSU IRB approved study (2007H0235) titled: *Image segmentation for evaluating axillary lymph nodes: A feasibility study*. The study was conducted by Dr. Kevin Evans, PhD, Principle Investigator and Dr. Steffen Sammet, MD, PhD, co-PI. Their project included both the manual segmentation technique and also the automated segmentation technique that was conducted by Dr. Sammet in his Means Hall computer lab. This subset of the study demonstrated the ability of a student to conduct manual segmentation of each volunteer's lymph node.

Results

Results were concluded based on 14 patients who provided 36 total nodes for evaluation. Manual segmentation was conducted on all of these axillary lymph nodes captured with 3D ultrasound. These nodes, along with several others, were also segmented independently by Dr. Kevin Evans and Yvette Ramos, registered sonographers both trained on segmentation technology.

One of the most important elements to the segmentation of these nodes was the quality of reproducibility. Thus, it was imperative that inter-rater reliability between Dr. Evans (Sonographer A), Yvette (Sonographer B), and the student was high. After the manual image segmentation of each node was converted to a 3D model and the cubic volume of that model recorded, a comparison was made for each individual node. The Pearson correlation coefficient was then used to determine the statistical correlation between the group. These measurements are included below (Table 1).

Between the two registered sonographers for node 1 in each series, the correlation coefficient was r = 0.91 (see Figure 1.a), which indicates an extremely high positive correlation between their measurements (Harris, et. al., 2004). The statistical significance of this agreement was $p \leq 0.00$ at the 0.01 alpha level. For node 2 of each series, the correlation was r = 0.97 (Figure 1.b) and for node 3 it was r = 0.99 (Figure 1.c) both of which also indicated the same level of high statistical significance.

Between the student and each of the sonographers there was also a somewhat high degree of correlation and significance. For node 1, the student's correlation with Sonographer A's data was r = 0.56 (Figure 1.d) which indicates a fairly reasonable correlation (Harris, et. al., 2004). The statistical significance of this correlation was $p \leq 0.00$ at the 0.05 alpha level. When compared with Sonographer B on node 1, the correlation was 0.50 (Figure 1.g), however, no statistically significant relationship was determined. For nodes 2 and 3, however, the reliability dramatically increased. When compared with Sonographer A on nodes 2 and 3, a correlation of r = 0.94 and r = 0.96 (Figures 1.e and 1.f), respectively, were determined. Sonographer B and the student on nodes 2 and 3 had correlations of r = 0.92 and r = 0.95 (Figures 1.g and 1.i) respectively. These correlations with both operators for nodes 2 and 3 were also significant at the 0.01 alpha level.

Table 1. Patient Nodal Volumes

Patient #1	Node 1(cm^3)	Node 2(cm^3)
KE	0.08	0.40
YR	0.11	0.39

SV	0.11	0.10

Patient #2	Node 1(cm^3)	Node 2(cm^3)
KE	0.44	0.25
YR	0.31	0.39
SV	0.20	0.29

Patient #3	Node 1(cm^3)
KE	0.14
YR	0.17
SV	0.08

Patient #4	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.16	0.12	0.13
YR	0.17	0.12	0.17
SV	0.07	0.09	0.19

Patient #5	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.16	0.21	0.13
YR	0.17	0.34	0.17
SV	0.16	0.23	0.11

Patient #6	Node 1(cm^3)	Node 2(cm^3)
KE	0.15	0.11
YR	0.11	0.12
SV	0.10	0.15

Patient #7	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.14	0.10	0.21
YR	0.13	0.11	0.22
SV	0.23	0.22	0.23

Patient #8	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.36	1.09	0.95
YR	0.36	1.17	0.98
SV	0.33	1.16	0.66

Patient #9	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.12	0.20	0.12
YR	0.15	0.14	0.20
SV	0.19	0.17	0.10

Patient #10	Node 1(cm^3)	Node 2(cm^3)
KE	0.21	0.21

YR	0.19	0.21
SV	0.18	0.18

Patient #11	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.31	0.06	0.34
YR	0.21	0.20	0.49
SV	0.39	0.07	0.40

Patient #12	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.44	0.12	0.14
YR	0.46	0.12	0.13
SV	0.35	0.06	0.23

Patient #13	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.40	0.44	0.82
YR	0.43	0.43	0.87
SV	0.13	0.40	0.76

Patient #14	Node 1(cm^3)	Node 2(cm^3)	Node 3(cm^3)
KE	0.20	0.62	0.54
YR	0.11	0.56	0.57
SV	0.12	0.82	0.56

Figure 1. Scatterplots of Segmented Data

Figure 1.a

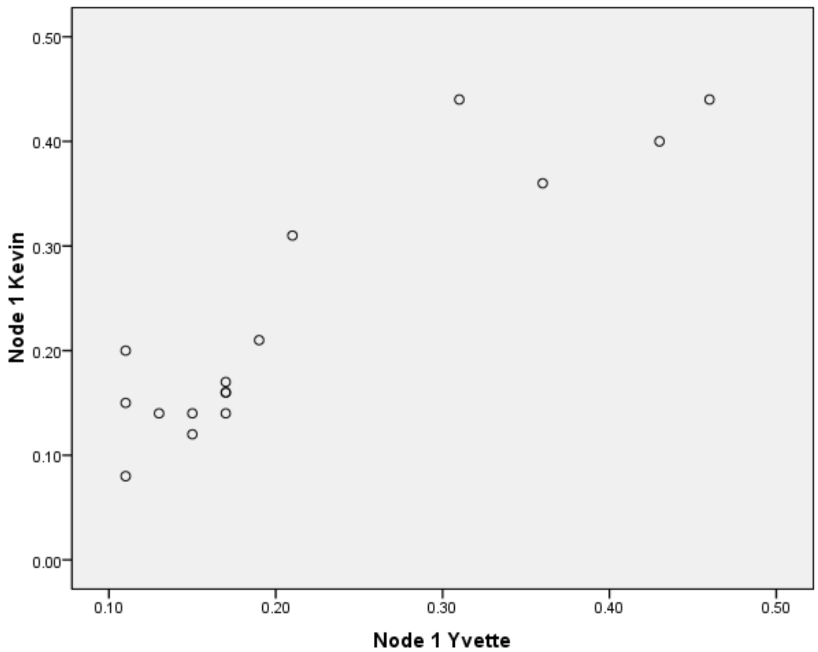


Figure 1.b

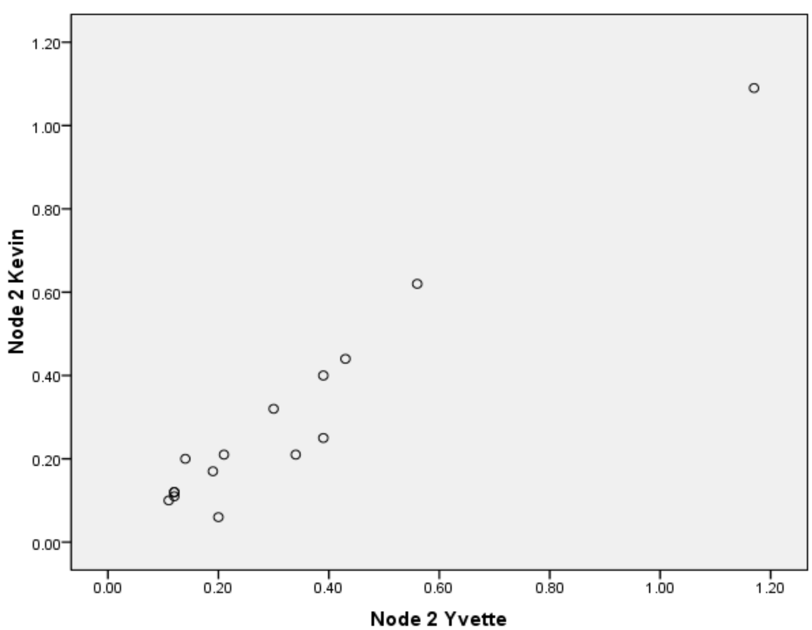


Figure 1.c

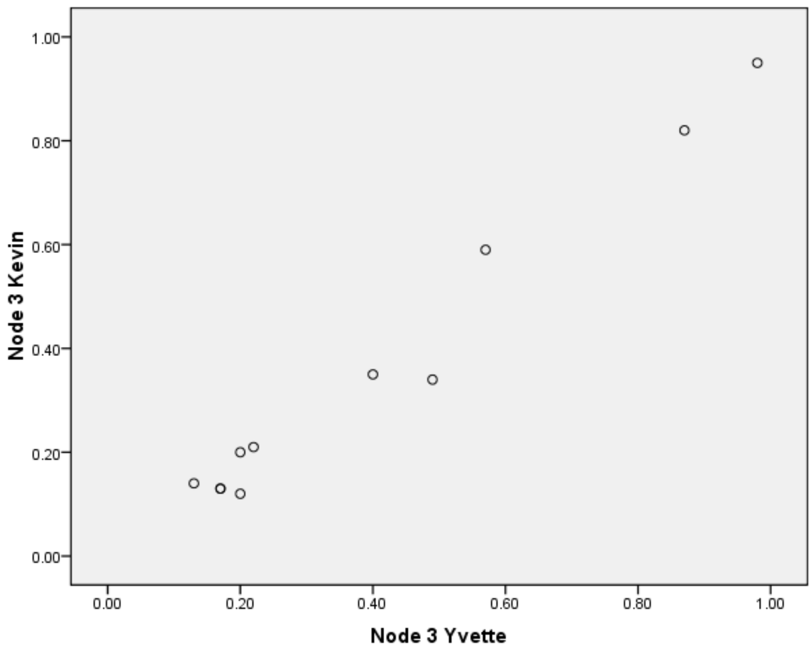


Figure 1.d

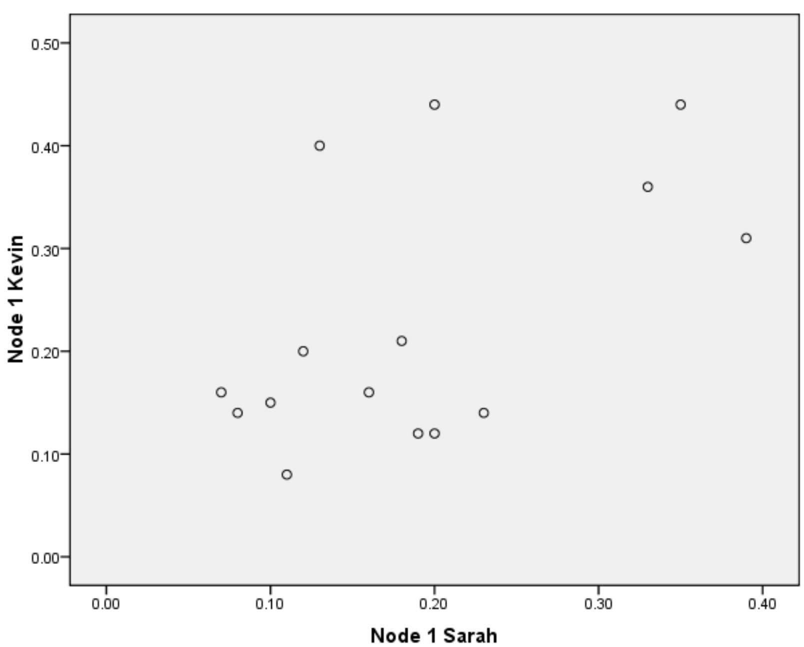


Figure 1.e

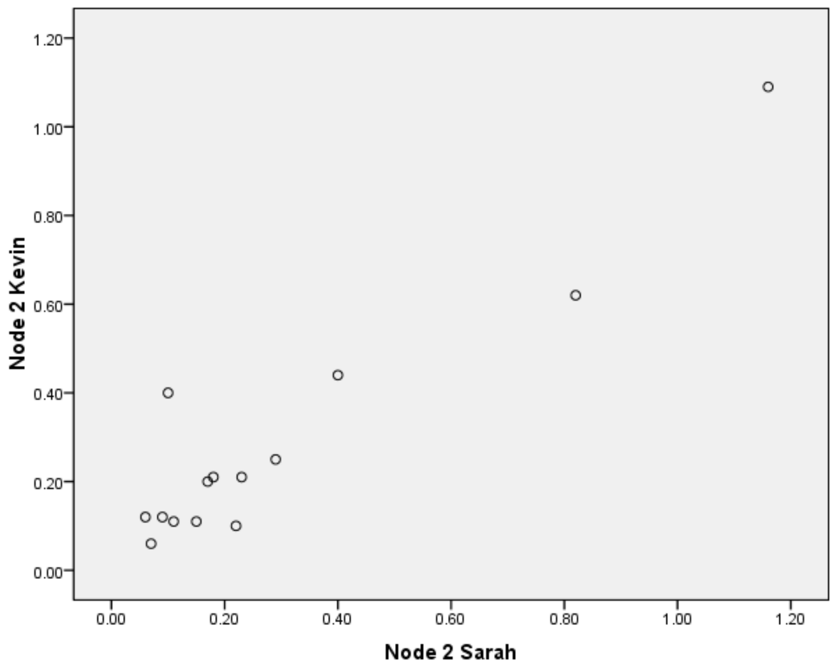


Figure 1.f

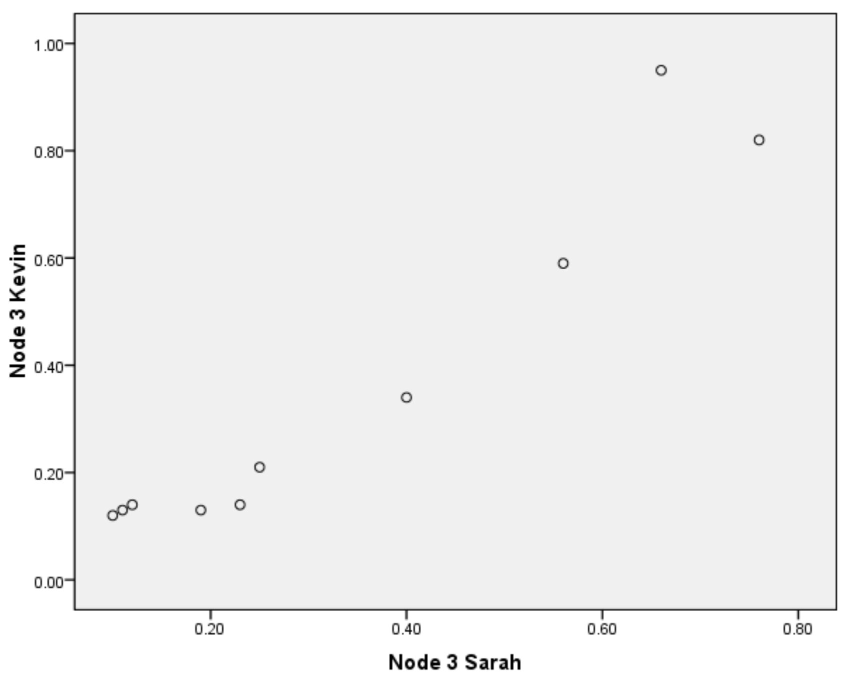


Figure 1.g

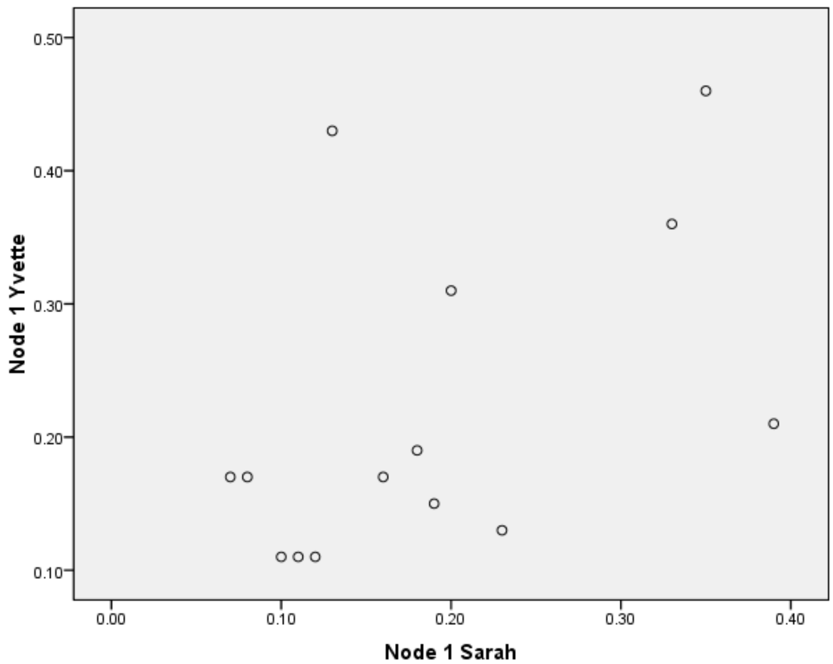


Figure 1.h

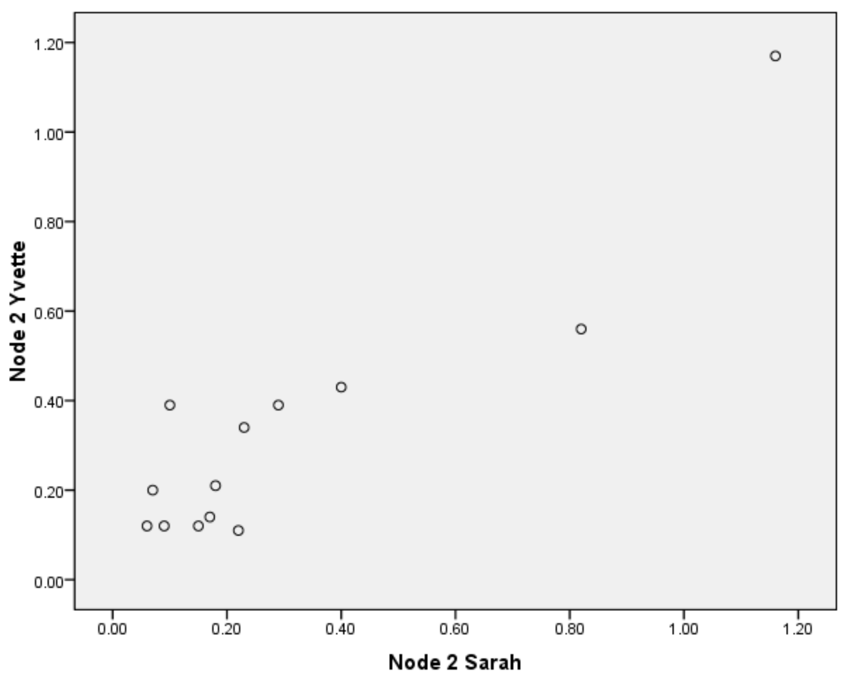
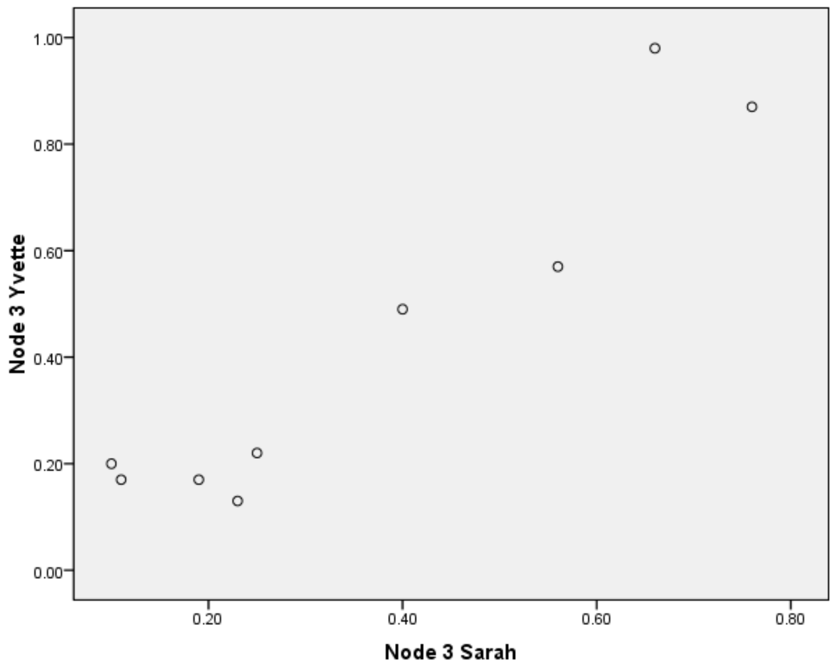


Figure 1.i



Discussion

One of the deterrents to utilizing manual image segmentation has been the variability of the models based on the operators. In the field of sonography this is especially true, since these images have often been deemed the most challenging to read, even with prior training. However, the data from this project has demonstrated a rejection of these concerns. The very high correlation between the sonographers' measurements for determining the cubic volume of axillary lymph nodes is an extremely promising result for this research. The correlations and statistical significance were impressively high. Furthermore, even in the case of outliers, the scatter plots could be very useful tools in determining what nodes did not contribute to a reliable cubic volume estimate. It would be necessary to review and rework these nodes to determine the cause of this discrepancy. However, overall this was not a problem and the very congruent segmentations have demonstrated the high reliability of this technology when used by this group of trained professionals and a student.

Even in the case of non-ultrasound professionals this research presents promising results. The student, while having been exposed to ultrasound and its principles in the past, had no prior experience identifying structures on ultrasound images. However, while working independently to segment these nodes, the student was able to successfully relate to the volumes determined by the two trained operators. While the correlations were not necessarily as close or as significant as those between Sonographers A and B, there is no doubt the student's measurements were notable. With no significant training in sonography the student was able to provide comparable measurements, but with slightly more practice there is perhaps a chance they may have been equally as analogous.

This is extremely promising for the field in proving that not only is manual segmentation plausible, it can be done consistently. If students and sonographers can both use the technology with relative simplicity then the possible scope is immense. The next step would be to use a greater and more diverse population of both participants and sonographers and to continue to compare this inter-rater reliability to determine how significantly this can be extended.

Ultimately, the possible translational value of this technology is immense. If a non-ionizing and less invasive technique could be standardized for the evaluation of lymph nodes in breast cancer patients, quality of life could be dramatically changed. Consequences such as lymphadema following lymphadenectomy and the incidence of ionizing cancers like leukemia could be significantly decreased, not to mention the possibility of catching metastasis earlier and more often. With increased training and research, this has the potential be a life saving technique.

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