Evaluation of sentinel nodes metastases identified by CT lymphography in patients with primary breast cancer without clinical evidence of lymph node metastases

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Aims and objectives

Sentinel lymph node (SLN) biopsy has replaced axillary lymph node dissection as the standard of care for patients with primary breast cancer without clinical evidences of lymph node metastases. SLNs are commonly marked by the combination of a blue dye and a radioactive tracer. However, in Japan, most hospitals cannot use radioactive tracers because of institutional regulations. At institutions without nuclear medicine departments and gamma probes, SLN biopsies (SLNB) are performed by the dye-staining method alone, which leads to lower identification rates. Therefore, sentinel CT lymphography (CTLG) was adopted at several institutions to improve the accuracy of SLNB. Several authors have previously demonstrated mainly for identification rate of SLN according to CTLG, however, few did so for the correlation with pathological diagnosis and measurements. The aim of this study is to evaluate the identification, findings and the measurements in CT imaging of SLNs using CTLG, and to correlate them with histopathological diagnosis and measurements.
Methods and materials

Patients

From April 2009 through August 2013, 114 patients with primary breast cancer without clinical evidence of lymph node metastases were enrolled in this study. All patients were women with clinically diagnosed as Tis-4N0M0 (stage 0-III) breast cancer, and 3 patients had bilateral breast cancer. Patients with neoadjuvant chemotherapy were excluded.

Computed tomography lymphography (CTLG)

On the day before the surgery, CTLG was performed using 64-row multi-detector CT (CT Aquilion™ 64, Toshiba Medical Systems, Japan). Each patient was placed in the supine position with arms positioned in a cranial direction. Intradermal injection was performed in the periareolar area and skin overlying the tumor, using 2.0 ml of a water-soluble agent (iopamidol; Iopamiron 300, Bayer HealthCare, Japan) after local anesthesia with subcutaneous injection of 1.5 ml of 2% lidocaine hydrochloride. CT scanning with detector of 1mmx32 row was operated at 120kV, 200 to 500 auto-mA, 35cm field of view, 512x512 matrix, pitch factor 0.781, helical pitch 25/0.5sec from the upper thorax to axillary regions, were obtained once before administration of the contrast enhancement agent, and at 90 seconds after the injection preceded by a massage of the area for about 1 min. CT images were reconstructed with a 0.8mm pitch and slice thickness of 1.0mm. 3D CT images were reconstructed from the post-contrast CT images with maximum intensity projection or surface-rendering techniques. The contrasted SLN and lymph flow were identified in reconstructed 3D images. Based on the CT images obtained, CT table was moved to the location so that the horizontal line matches the SLN position, and offset of the SLN from the center of the body was measured on CT image along the skin surface. The corresponding position of the patient's skin was marked with an oil painting pen.

Method of SLNB

During the surgeries, SLN biopsies were performed by the dye-staining methods referring to the lymphatic pathways and nodal anatomy at CTLG. Twenty-five mg of Indocyanine Green (Daiichi-Sankyo, Japan) dissolved in 5ml injection solvent was injected into the intradermal periareolar area. After 300-s of gentle massaging of the area, the surgery was initiated. In the cases of breast-conserving surgery, a skin incision was made at the axilla along the axillary fold by referring to the external marker preoperatively placed on the CTLG, and blue dye-stained lymphatic tract connected to the SLN was pursued.
carefully. In the cases of mastectomy, the SLN biopsy was similarly performed through the skin incision made at the anterior chest wall for the mastectomy. When there was no stained node or stained lymph duct, it was considered that identification of the SLN was not successful, and then axillary lymphnode dissection was performed.

SLNs obtained from biopsies were sliced every 2mm interval along the longitudinal axis and frozen, and were stained with hematoxyline and eosine(H&E) for intraoperative diagnosis. After diagnosis using frozen specimen, all specimens were fixed by 20% buffered formalin, embedded in paraffin and examined by H&E staining. ALND was performed only for patients with metastasis. A pathologist measured metastatic lymph nodes size and the size of metastatic focus in the lymph node.

Indexed lymph nodes in CTLG and evaluation

Two hundred and four nodes were investigated, including lymph nodes that have taken up the contrast enhancement material and confirmed as the primary, secondary and tertiary nodes, as well as non-enhanced lymph nodes with same or larger size than the indexed nodes of the axilla in the same patients. Two radiologists evaluated the imaging of CTLG: lymph duct pattern, shape of lymph node, the pattern of the uptake of the contrast enhancement material of lymph node and duct, size and coefficient of the expansion of LNs after injection, as well as their correlation with pathological diagnosis and the metastatic size, were analyzed.
Results

SLN were identified by preoperative CTLG and intraoperative SLNB using indocyanine green with the identification rates of 96%(110/114) and 98%(112/114), respectively. SLN metastasis was detected in 28 nodes out of 204 indexed nodes.

Size of lymph node

Length of both major and minor axis of lymph node were significantly different between metastatic nodes and non-metastatic nodes (both $p=0.000001$). Area under the curve (AUC) of the length of the major axis of lymph nodes was 0.71 in receiver operating characteristic (ROC). None of lymph nodes whose major axis length was less than 9.4mm turned out to be metastatic($p=0.00029$, Accuracy 72%, sensitivity 64%, specificity 73%, PPV 28%, NPV 92%). AUC of the length of minor axis of lymph nodes was 0.80 in ROC. None of lymph nodes with minor length axis shorter than 3.1mm was found to be metastatic($p=5.518e-07$, accuracy 75%, sensitivity 75%, specificity 75%, PPV 32%, NPV 94%).

Low coefficiency of expansion, calculated by the length of minor axis of the lymph nodes before and after the injection of contrast enhancement material into CTLG, tends to correlate with metastases ($p=0.08$).

Shape of lymph node

Lymph nodes with round or lobulated shape were metastatic ($p=0.0001$). The absence of hilum of lymph node was metastases with the probability of 35% ($p=0.03$).

The absence of hilum of lymph node did not correlate with pathological size of metastatic focus in a lymph node ($p=0.22$).

Range of uptake area in lymph node

Size of the lymph node was compared with the size of the area of the contrast enhancement material update at each lymph node. The size of the area of uptake relative to the size of the lymph node (uptake area) in metastatic lymph nodes was significantly smaller than that in non-metastatic nodes($p=0.0089$). Lymph nodes with high($>75$%) uptake area tend to be non-metastatic at high statistical significance($p=0.0075$, NPV=93%). Fig. 1 shows a case of non-metastatic node with
uptake area more than 75%. Therefore, there is a strong negative correlation between high uptake area of the contrast enhancement material and metastasis.

Further, in the pathologically proven metastatic nodes, nodes with high (>75%) uptake area had a small metastatic focus that occupies a small area (less than 25%) within the lymph nodes (p=0.01, sensitivity=100%, NPV=100%). Fig. 2 shows a case of a metastatic lymph node with a large metastatic focus (occupying more than 75% of the lymph node) with the uptake area smaller than 75%.

Estrogen receptor (ER) status of primary breast cancer

For patients with ER positive breast cancer, lymph nodes showed significantly high probability to be metastatic (p=0.007).

Besides the parameters stated above, no other parameters including ramification pattern of lymph duct, degree of uptake of contrast material of lymph node and duct, show correlations that are statistically significant.
Fig. 1: A case of non-metastatic node with uptake area more than 75%.

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Fig. 2: A case of non-metastatic node with uptake area more than 75%.

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Fig. 3: A case of a metastatic lymph node with a large metastatic focus (occupying more than 75% of the lymph node) with the uptake are smaller than 75%.

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**Fig. 4:** A case of a metastatic lymph node with a large metastatic focus (occupying more than 75% of the lymph node) with the uptake are smaller than 75%.

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Conclusion

We found that size of lymph nodes was most significantly different between metastatic and non-metastatic lymph nodes: Lymph nodes with major axis length less than 9.4mm or with minor axis length less than 3.1mm showed highly significant negative correlation with metastasis. Nevertheless, we discovered that 40% of such small lymph nodes (less than 3.1 mm minor axis length) are metastatic if their uptake area are less than 75% (p=0.04).

Minohara et al. reported that the relative size of the contrast-enhanced part within each node has a correlation with metastases (p<0.0001), which is consistent with our findings. We classified relative area of enhancement in a lymph node: 0-25%, >25<50%, >50<75%, and >75%. And we found that uptake area of metastatic lymph node was smaller than non-metastatic node significantly, and nodes with more than 75% uptake area were significantly non-metastatic nodes. Furthermore, there is a negative relationship between the size of the uptake area and pathological size of metastases in metastatic nodes.

Among 28 metastatic lymph nodes, five did not uptake the contrast enhancement material. We assume that these nodes were tightly filled with tumor cells which prevented the uptake of the material. On the other hand, out of 176 non-metastatic lymph nodes four showed uptake of the contrast enhancement material only to lymph ducts but not to lymph nodes. We do not have an explanation for this.

The ratio of inflation of lymph nodes after injection of the contrast enhancement material tends to be high for non-metastatic nodes, though it was not statistically significant.

Our results demonstrated a high metastasis rate in ER-positive breast cancers. Generally, ER-positive breast cancers are not aggressive, and less prone to be metastatic. We cannot exclude the possibility that there was a bias in the patients due to contraindication of CTLG in case of clinically decided lymph node metastasis.

In conclusion, lymph node size was most significantly different between metastases and non-metastases. Uptake area of metastatic lymph node was smaller than non-metastatic node significantly. Furthermore, among the pathological proven metastatic nodes, there is a negative correlation between metastasis and uptake of the contrast enhancement material into the lymph nodes. Therefore, CTLG is expected to be a useful tool to estimate metastasis of lymph nodes before breast cancer surgeries.
References


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