The Stiffness of Lymph Nodes Containing Lung Carcinoma Metastases

A New Diagnostic Parameter Measured by a Tactile Sensor

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BACKGROUND. It is believed that the stiffness or hardness of a lymph node containing a metastasis differs from that of lymph node without a metastasis because of the difference in tissue density, which is derived from the lymph node's histopathologic features. Prior to this study, however, there had been no attempts to quantify the hardness or stiffness of lymph nodes. The authors developed a new tactile sensor and system for measuring the stiffness (g/cm) of lymph nodes accurately, and they studied its utility as a tool for diagnosing lymph node metastases.
METHODS. Clinical specimens were obtained from 14 patients who underwent lobectomy or pneumonectomy with hilar and mediastinal lymph node dissection for nonsmall cell lung carcinoma at the University of Tokyo between January and July 1996. With the tactile sensor developed by the authors, 212 resected lymph nodes were measured for their stiffness.
RESULTS. Among these 212 resected lymph nodes, 57 were diagnosed as containing metastases (38 from adenocarcinomas and 19 from squamous cell carcinomas). The mean stiffness of the lymph nodes that contained metastases was 3.35 ± 1.57 g/cm, and that of lymph nodes without metastases was 1.23 ± 0.50 g/cm ($P < 0.001$). Receiver operating characteristic analysis revealed that the area under the curve was 0.93, indicating excellent accuracy of the method. When the cutoff was 1.5 g/cm, the sensitivity was 91.2% and the specificity was 78.1% for detection of lymph node metastases.
CONCLUSIONS. Measurement of the stiffness of resected lymph nodes was confirmed as an accurate approach to diagnosing lymph node metastases without knowledge of other factors, such as lymph node size or color. ***Cancer* 1997; 80:1920–5.** *© 1997 American Cancer Society.*

KEYWORDS: tactile sensor, nonsmall cell lung carcinoma, lymph node metastasis, stiffness.

It is thought that the stiffness or hardness of a lymph node containing a cancer metastasis differs from that of a lymph node without a metastasis because of the differences in tissue density and cellular composition, which are derived from the lymph node's histopathologic features. In fact, it is well known that some lymph nodes containing cancer metastases appear as hard and swollen masses. So far, however, there have been no attempts to quantify the hardness or stiffness of lymph nodes.

We have begun to apply a tactile sensor in thoracoscopic surgery for detecting small and invisible pulmonary nodules.[1] We have improved this tactile sensor and its ancillary systems for measuring the stiffness (g/cm) of lymph nodes accurately, and in this study we inves-

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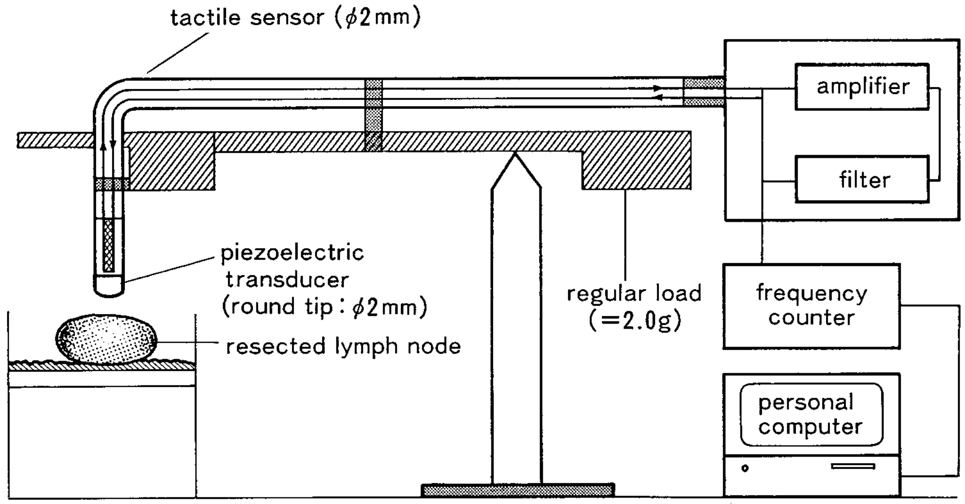

FIGURE 1. The tactile sensor measurement system, which consists of a catheter-type sensor probe, an amplifier, a filter, and a frequency counter, is shown. The sensor probe measures the delta-f of the resected lymph nodes, touching the central area of the lymph node set on a gauze soaked in saline with a regular load (2.0 g). The delta-f values are processed sequentially by a personal computer.

tigated its utility in the diagnosis of lymph nodes containing lung carcinoma metastases.

MATERIALS AND METHODS

Tactile Sensor

Our tactile sensor was described previously.[2,3] The principles behind it are as follows: Each material has its own resonance frequency; and when the material touches an object vibrating at this frequency, a shift in the resonance frequency is observed. This difference in frequency (delta-f) depends on the stiffness of the object. The tactile sensor system consists of a sensor probe, an amplifier, and a filter. When the sensor probe touches an object and the resonance frequency shifts, a vibration detector picks up the delta-f and sends a signal to the amplifier that keeps a piezoelectric transducer vibrating at the changed frequency. In this study, we used a new sensor with a small tip, 2 mm in diameter, which is a 6 F catheter type 165 cm in length (Fig. 1).

Calibration of Stiffness

The relationship between stiffness and delta-f for our tactile sensor can be determined using the counterweight-and-depression method employing bovine gelatin, the stiffness of which is known.[4] The stiffness (g/cm) was calculated using the following calibration formula for our sensor (Fig. 2):

delta-f (Hz)

= 3742.415 Log (stiffness [g/cm]) − 4834.946,

that is:

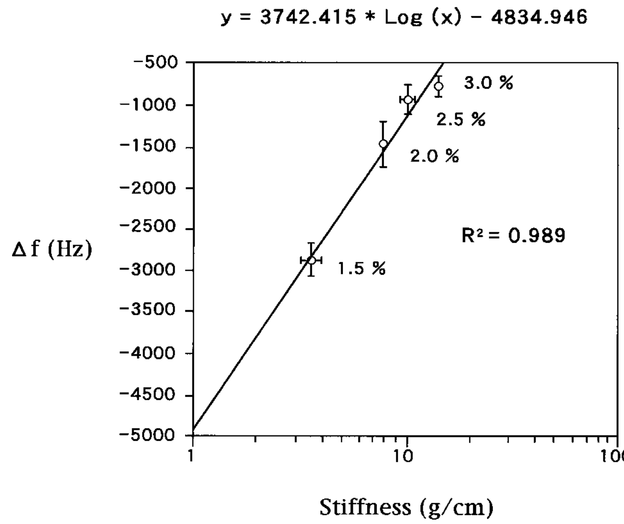

FIGURE 2. The good correlation between stiffness and delta-f of the tactile sensor (R^2 = 0.989) is shown. The plots represent the stiffness and delta-f derived from bovine gelatin.

stiffness (g/cm)

= 10^{(delta-f + 4834.946)/3742.415}.

Measurement of Lymph Node Stiffness

A catheter-type sensor was used to measure the stiffness of resected lymph nodes, touching the central area of each lymph node placed on gauze soaked in saline using a regular load (2.0 g). The lymph nodes were obtained from 14 patients (10 with adenocarcinoma and 4 with squamous cell carcinoma) who underwent lobectomy or pneumonectomy with hilar and mediastinal lymph node dissection for nonsmall cell lung carcinoma at our institution between January and July 1996. The mean age of these patients was 64.6 ± 8.4 years. There were 10 men and 4 women, and the total number of resected lymph nodes was 212. In this study, calcified lymph nodes were excluded, although there was only one such lymph node among the total. The 212 lymph nodes measured 11.7 ± 5.0 mm in long axis diameter and 8.1 ± 3.5 mm in short axis diameter. After measurement of lymph node size and stiffness, histopathologic examination was performed. All specimens were fixed in 10% formaldehyde solution, embedded in paraffin, and sectioned and stained with hematoxylin and eosin.

The relationship between lymph node stiffness and pathological features and the efficiency of stiffness as a diagnostic parameter for lymph node metastasis were studied.

Statistical Analysis

Statistical analysis was done with the SAS program (SAS Institute, Cary, NC). All results are given as mean ± standard deviation. The two-tailed Student's t test was used to compare continuous data, such as the stiffness and size of lymph nodes with and without metastases. Differences were regarded as statistically significant at $P < 0.05$. A logistic procedure was employed to construct a logistic model for stiffness and metastasis of lymph nodes. Receiver operating characteristic (ROC) analysis was used to examine the efficiency of this diagnostic method. The ROC curve is usually employed to evaluate and compare diagnostic tests and explore the trade-offs between their sensitivity and specificity. Tests that discriminate well will show crowding of the curve toward the upper left corner. The overall accuracy of a test can be described as the area under the curve (from 0 to 1); a larger area under the curve indicates a better test because it optimizes sensitivity and specificity.

RESULTS

In 6 of 14 patients, resected lymph nodes were diagnosed as containing metastases (from adenocarcinoma in 3 patients and from squamous cell carcinoma in 3 patients). No patient with a solitary metastatic lymph node was found in this examination; those in whom metastatic lymph nodes were detected had two or more (Table 1). Among 212 lymph nodes, 57 were diagnosed as containing metastases (from adenocarcinoma in 38 lymph nodes and from squamous cell carcinoma in 19). Among these 57 lymph nodes, 6 had microscopic metastases (from adenocarcinoma in 4 and from squamous cell carcinoma in 2).

The frequency distribution for the stiffness of metastasis positive and negative lymph nodes is shown in Figure 3. The stiffness of lymph nodes with metastases was 3.35 ± 1.57 g/cm and that of lymph nodes without metastases was 1.23 ± 0.50 g/cm. The difference between the two lymph node types was regarded as highly significant ($P < 0.0001$). The stiffness of lymph nodes with adenocarcinoma metastases was 3.16 ± 1.56 g/cm and that of lymph nodes with squamous cell carcinoma metastases was 3.71 ± 1.56 g/cm. The difference in stiffness between lymph nodes containing adenocarcinoma metastases and those containing squamous cell carcinoma metastases was not significant ($P = 0.21$).

The logistic model revealed the predictive probability of lymph node metastasis versus lymph node stiffness, as shown in Figure 4. The predictive probability of lymph node metastasis (p) was

$$p = e^{(2.54*\text{stiffness (g/cm)} - 5.75)} / (1 + e^{((2.54*\text{stiffness (g/cm)} - 5.75)}) \quad (P < 0.0001).$$

This logistic model represents well the correlation between lymph node metastasis and stiffness ($P < 0.0001$). In this logistic model, the predictive probability of lymph node metastasis was 0.336 when lymph node stiffness was 2.0 g/cm and 0.865 at 3.0 g/cm.

The ROC analysis of lymph node stiffness revealed that the area under the curve was 0.93 (Fig. 5). When the cutoff value was 1.5 g/cm, the diagnostic sensitivity was 91.2%, the specificity 78.1%, and the accuracy 82%. The corresponding values for a cutoff of 2.0 g/cm were 78.9%, 92.9%, and 89%, respectively.

The mean long axis diameter of lymph nodes containing metastases was 12.5 ± 6.8 mm and that of lymph nodes without metastases was 11.4 ± 4.1 mm; the difference was not significant ($P = 0.23$). The frequency distribution for the short axis diameter of metastasis positive and negative lymph nodes is shown in Figure 6. The short axis diameter of lymph nodes containing metastases was 9.2 ± 4.5 mm and that of lymph nodes without metastases was 7.7 ± 2.8 mm; the difference was statistically significant ($P < 0.05$). ROC analysis of the short axis of lymph nodes revealed that the area under the curve was 0.57. The mean stiffness of lymph nodes containing microscopic metastases was 1.61 ± 0.63 g/cm (n = 6), and that of the remaining lymph nodes was 3.55 ± 1.52 g/cm (n = 51); the difference was statistically significant ($P < 0.01$).

DISCUSSION

Stiffness of Lymph Nodes

For nonsmall cell carcinomas of the lung, radical surgery involving hilar and mediastinal lymph node dissections are widely performed. Surgeons have carried

TABLE 1
Patient Data

Patient no.	Age	Gender	Histology	Surgery	Measured LNs	LNs with metastasis
1	75	M	ADC	Lt. PN	17	2
2	59	M	SCC	Rt. UL	20	11
3	63	F	SCC	Rt. UL	9	0
4	61	F	ADC	Lt. UL	6	0
5	73	F	ADC	Rt. UL	22	0
6	67	M	SCC	Rt. UL	12	2
7	67	M	ADC	Lt. UL	12	0
8	67	M	ADC	Rt. UL	29	19
9	70	M	ADC	Rt. ML	16	0
10	68	F	ADC	Rt. UL	17	0
11	60	M	ADC	Lt. UL	12	0
12	54	M	ADC	Rt. UL	19	17
13	45	M	ADC	Lt. UL	9	0
14	75	M	SCC	Rt. LL	12	6
				Total	212	57

LN: lymph node; ADC: adenocarcinoma; SCC: squamous cell carcinoma; PN: pneumonectomy; UL: upper lobectomy; ML: middle lobectomy; LL: lower lobectomy.

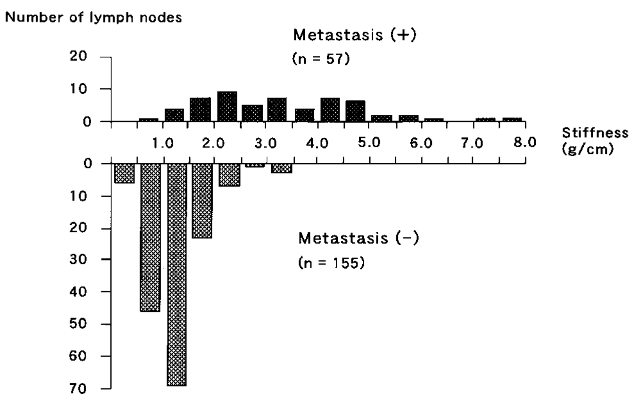

FIGURE 3. This figure shows the frequency distribution of the stiffness of lymph nodes with and without metastases, obtained by measuring stiffness with a tactile sensor. Solid bar: metastasis positive; hatched bar: metastasis negative.

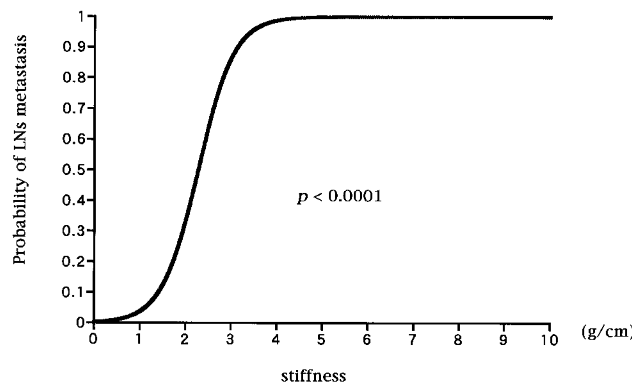

FIGURE 4. The predictive probability of lymph node metastasis versus lymph node stiffness is shown. The predictive probability of lymph nodes metastasis (p) is

$$p = e^{(2.54*\text{stiffness (g/cm)} - 5.75)}/(1 + e^{(2.54*\text{stiffness (g/cm)} - 5.75)})$$

The predictive probability of lymph node metastasis is 0.336 when the lymph node stiffness is 2.0 g/cm. The value is 0.865 at 3.0 g/cm and 0.988 at 4.0 g/cm. LNs: lymph nodes.

out intraoperative staging of lung carcinoma by the tumor, metastasis, and lymph node (TMN) classification, according to the *General Rule for Clinical and Pathological Record of Lung Cancer* or *The New International System for Staging Lung Cancer*.[5,6] It is thought that the stiffness of a lymph node containing a metastasis differs from that of a lymph node without a metastasis because of the difference in tissue density and cellular composition. It is well known that some lymph nodes containing metastases appear as hard, swollen masses. Before this study, however, there had been no attempts to quantify the stiffness of lymph nodes. We have introduced a new tactile sensor for detecting small and invisible pulmonary nodules during thoracoscopic surgery.[1] In our previous study, pulmonary nodules were detected by differences in frequency (delta-f) between the nodule and the lung. To compare the stiffness of lymph nodes in different patients, it is necessary to use an absolute value for stiffness (g/cm). In this study, therefore, we converted the delta-f value (Hz) to stiffness (g/cm) using the counterweight-and-depression method.[4] Then we successfully determined the stiffness of resected lymph

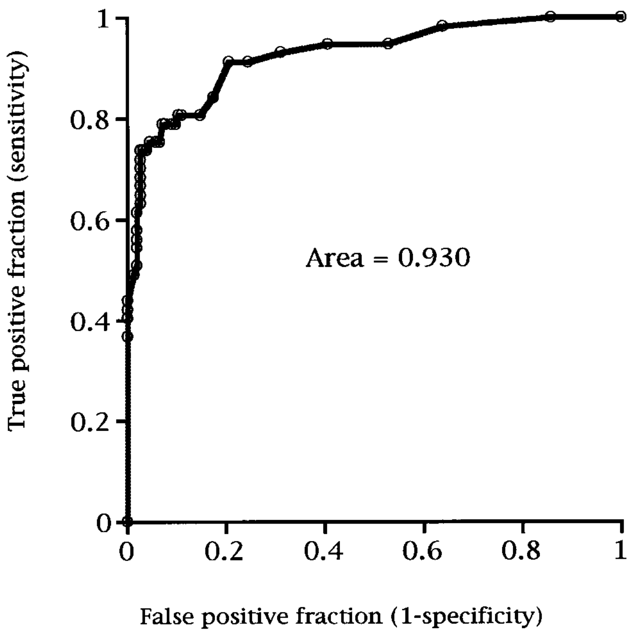

FIGURE 5. Receiver operating characteristic (ROC) analysis of lymph node stiffness is shown. The area under the ROC curve was 0.930. When the cutoff value was 1.5 g/cm, the sensitivity was 91.2%, the specificity 78.1%, and the accuracy 82% for diagnosis of lymph node metastasis. When the cutoff value was 1.6 g/cm, the sensitivity was 91.2%, the specificity 82.0%, and the accuracy 84%. The corresponding values for a cutoff of 2.0 g/cm were 78.9%, 92.9%, and 89%, respectively.

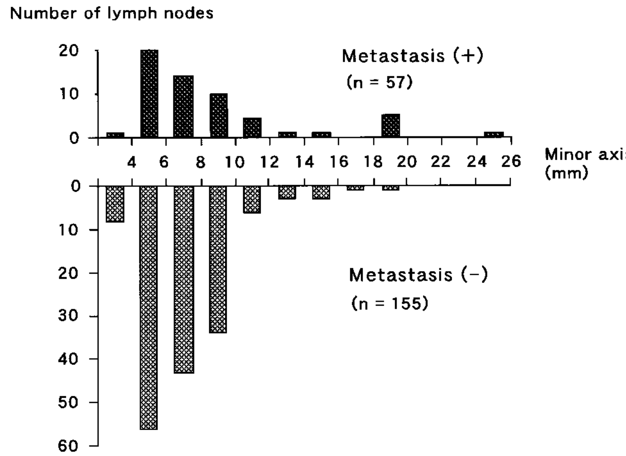

FIGURE 6. Frequency distribution of the short axis diameter of lymph nodes with and without metastasis is shown. Solid bar: metastasis positive; hatched bar: metastasis negative.

nodes using our new tactile sensor system. However, it is very important to confirm whether or not the measurement of stiffness is really efficient as a diagnostic method. In our study, the stiffness of lymph nodes containing metastases was significantly greater than that of lymph nodes without metastases ($P < 0.0001$). The logistic procedure was performed to construct a logistic model for stiffness and metastasis in lymph nodes, and this model was proven to fit the correlation between lymph node metastasis and stiffness ($P < 0.0001$). ROC analysis also revealed that the area under the curve was 0.93. Thus, our method was proven to be efficient in the diagnosis of resected lymph nodes, even though other factors, such as lymph node size and color, were not taken into consideration.

Calcified Lymph Nodes

Calcified lymph nodes were excluded, although there was only one nonmetastatic calcified lymph node in this series. The stiffness of this calcified lymph node was as high as 20.2 g/cm. The stiffness of lymph nodes containing metastases ranged from 0.95 to 7.74 g/cm, with an average of 3.35 ± 1.57 g/cm. Because the stiffness of calcified lymph nodes is extraordinarily high compared with that of noncalcified lymph nodes with metastases, it is not difficult to distinguish the former from the latter.

Microscopic Metastases

The stiffness of lymph nodes containing microscopic metastases was significantly lower than that of lymph nodes containing advanced metastases. When the cutoff value was 1.5 g/cm, there were 5 false-negative lymph nodes, among which 4 contained microscopic lesions. These results suggest that measurement at only the central area of each lymph node using a sensor equipped with a small tip (2 mm in diameter) may be of limited usefulness for the detection of microscopic lesions. Because the data derived from this study revealed that the stiffness of metastatic lesions was a useful diagnostic parameter, a tactile sensor equipped with larger tip for probing lymph nodes containing microscopic lesions might be able to overcome this problem. With further improvements of the tactile sensor probe and additional experimental studies, we should be able to expand its clinical application.

Short Axis Diameter of Lymph Nodes

In the preoperative evaluation of lymph nodes containing metastases using computed tomography, positron emission tomography, and immunoscintigraphy, lymph node size (especially the short axis diameter) is believed to be a reliable parameter.[7–11] In this series, the difference in short axis diameter between lymph nodes with and without metastases was also regarded as statistically significant ($P < 0.05$), although the difference in long axis diameter was not significant. However, ROC analysis of the short axis diameter revealed that the area under the curve was 0.57. Therefore, the overall diagnostic accuracy of lymph node stiffness seems to be superior to that of short axis diameter.

Possibility of Clinical Application

In this study, we revealed that measurement of lymph node stiffness was a useful parameter for the diagnosis of metastasis in an in vitro setting. We have introduced a tactile sensor for detecting small and invisible pulmonary nodules during thoracoscopic surgery.[1] This type of sensor, which is 350 mm in length and equipped with a tip 3 mm in diameter, is designed for thoracoscopic surgery and can be easily introduced into the chest cavity through a metal trocar 10 mm in diameter. Using this type of tactile sensor, it would be possible to measure the stiffness of mediastinal lymph nodes during thoracoscopic surgery, although it would be necessary to change the tactile sensor tip (3 mm) to a larger one (5 mm) for probing and scanning lymph nodes in order to detect microscopic metastatic lesions in them. Furthermore, it would be necessary to calibrate the stiffness using the counterweight-and-depression method for this type of sensor. We measured the stiffness of lymph nodes containing non-small cell lung carcinoma and confirmed its usefulness as a diagnostic parameter. However, in other kinds of cancers, such as those of the oral cavity, nasopharynx, esophagus and stomach, colon and rectum, pancreas and biliary tract, breast, cervix uteri and ovary, and kidney, the stiffness of lymph nodes containing cancer metastases differs from that of lymph nodes without metastases because of the differences in their tissue density and cellular composition. Therefore, it is possible that the stiffness of lymph nodes measured by the tactile sensor would be an accurate diagnostic parameter in these other types of cancer, although it will first be necessary to study the relation between stiffness and metastasis.

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