Significance of measurement of tumor marker in primary breast cancer

Tousei Ohmura[1)], Tomoko Fujikane[1)], Noriko Nishikawa[1)], Keisuke Ohno[1)], Tomomi Ueki[1)], Hidekazu Kameshima[1)], Akiko Yajima[1)], Rika Fukui[1)], Nobuhiko Toyoda[1)], Goro Kutomi[1)], Toshio Honma[2)], Toshihiko Mikami[3)], Yasuyo Suzuki[1)], Koichi Hirata[1)]

[1)]*Department of Surgery, Sapporo Medical University. S-1, W-16, Chuo-ku, Sapporo* 060-8556, *Japan*
[2)]*Central Women's Clinic, Odori* 18, *Sapporo* 060-8556, *Japan*
[3)]*Surgery, Higashi Sapporo Hospital, Shiroishi-ku, Sapporo, Japan*

ABSTRACT

We investigated a prognosis in the presence or absence of preoperative marker abnormality for 371 cases with primary breast cancer that we experienced in our department this time. 60 (16%) of 371 cases showed the abnormality of the tumor marker and 25 (41.7%) of 60 patients had a recurrence. The positive rate of the marker was 8.1% in CA 15-3, 6.7% in CEA, 4.1% in NCC-ST-439, and each rate of recurrence was 56.7%, 48.0%, 33.3%. Rate of recurrence in the negative cases was 12.7%, 13.9, 15.0% respectively and recognized a significant difference statistically ($p < 0.001$) . Of 11 cases (3.8%) shown CA 15-3 abnormal high level, 3 cases (27.2%) had recurrence when we examined in 0-3 metastases to lymph nodes according to markers. 281 cases (96.2%) was normal range in CA15-3. Only 15 cases (5%) had recurrence. It showed a significant difference statistically ($p < 0.05$) . For the cases shown abnormality of the preoperative CA 15-3, careful serial observations are necessary.

Key words : Breast cancer, Tumor marker, CA15-3, CEA, NCC-ST-439

INTRODUCTION

The main purpose of the tumor marker measurement is palindromic early detection, a monitor of the supporting clinical course for the effect of treatment judgment. In addition, prognostic predictions, a diagnostic aid of the early cancer and progress of the primary carcinoma are done.

"The guide of the effect of treatment judgment using a marker" was shown by a Japanese breast cancer society squad study in 2001. It evaluated that the change of the marker level reflected condition for progress / the recurrent breast cancer cases of the marker positive.

On the other hand, comparing high specificity, sensitivity of prostate-specific antigen in the

CORRESPONDENCE TO:Tousei Ohmura, Department of Surgery, Sapporo Medical University, S-1, W-16, Chuo-ku, Sapporo. 060-8556, Japan

prostatic carcinoma detection, superior marker in breast cancer about the diagnosis of the early cancer is absent.

A prognosis seems to be poor for cases shown the abnormal high level of the marker when we compare a prognosis in the abnormal presence of the marker about the prognostic prediction with the tumor marker in the primary breast cancer cases according to a clinical stage.

We investigated a prognosis in the presence or absence of preoperative marker abnormality for the primary breast cancer cases that we experienced in our department this time.

OBJECTIVES

It is widely admitted as common practice that the tumor marker of the breast cancer is measured for postoperative palindromic early detection, a judgment of the effect of treatment, monitoring of the progress. Also, it is general to measure tumor markers before initial treatment for a primary breast cancer, but there are few reports that reviewed the significance.

We studied whether we produced a difference as for the rate of recurrence by having aberrant high level or not of the tumor marker in the patient with primary breast cancer.

MATERIALS AND METHODS

We intended for 371 patients with primary breast cancer which we experienced in our department for from January, 2001 to November, 2006.

The average age of patients was 56 (25–86 years old) and the average observation period was 3.5 (1.0–6, 8 years) .

When distribute cases according to stage, 27cases (7%) was in stage0, 87 (23.5%) in stage Ⅰ, 113 (30.5%) in stage Ⅱ A, 39 (10.6%) in stage Ⅱ B, 22 (6%) in stage Ⅲ A, 50 (13.5%) in stage Ⅲ B, 5 (1.3%) in stage Ⅲ C, 28 (7.6%) in stage Ⅳ. Also, 223 cases (60.1%) don't have any lymph node metastasis, 69 cases (18.6%) have 1–3 lymph node metastases, 32 cases (8.6%) have 4–9 lymph node metastases, and 47 cases (12.7%) have over ten lymph node metastasis by metastases to lymph nodes number distinction.

We measured tumor marker CA 15–3, CEA (carcino embryonic antigen) , NCC–ST–439 for 371 breast cancer cases before the preoperation or chemoendocrinetherapy. The cutoff limit was established at 30.0U/ml, 5.5 U/ml, 7 U/ml respectively. We measured markers after an operation and/or chemoendocrinetherapy every 3–6 months.

We investigated the rate of recurrence of the breast cancer case shown aberrant high level before treatment according to stage of disease and the metastases to lymph nodes number.

The statistics were assessed using Wald method by Proportional Hazard Model.

RESULTS

After the diagnosis the average follow-up time was 3.5 years (range1–6.8years) . CA15–3, CEA, NCC–ST–439 were assessed from 371 breast cancer patients before operation or chemoendocrinetherapy.

60 (16%) of 371 patients with primary breast cancer had the abnormality of the tumor marker. 25 patients (41.7%) of those had recurrence.

On the other hand, of 311 (84%) marker negative cases, 35 patients (11.3%) had a recurrence (Table1) . The positive rate of the markers were 8.1% in CA 15–3, 6.7% in CEA, 4.1% in NCC–ST–439. Also, each rate of recurrence was 56.7%, 48.0%, 33.3%. Rate of recurrence of the negative cases were 12.7%, 13.9, 15.0% respectively. It recognized a significant difference statistically ($p < 0.001$) (Table2) .

We studied recurrence rate of marker positive cases and the negative cases according to Stage. The results did not show a significant difference statistically (Table3) . Also, we examined recurrence rate of marker positive cases and the negative cases in 0, 1–3, 4–9, over ten lymph nodes metastasis according to the number of the metastases to lymph nodes equally. As the results, it did not recognize a significant

difference statistically (Table4) . However, rate of recurrence tended to be high for a marker positive case in 0 metastases to lymph nodes and also 1-3 metastases.

As for 11 cases (3.8%) shown CA 15-3 abnormal high level, 3 patients (27.2%) of those showed a recurrence when we examined in 0-3 metastases to lymph nodes according to a marker (Table5) . On the other hand, of 281 cases (96.2%) shown CA 15-3 normal level, only 15 cases (5%) had recurrence. It showed a significant difference statistically ($p < 0.05$) .

Table 1 Results of Tumor Marker (TM) analysis

	Number of cases	Number of recurrent cases	
Total	371	60 (16.2%)	
TM (+ve)	60 (16.2%)	25 (41.7%)	P<0.001
TM (-ve)	311 (83.3%)	35 (11.3%)	

Table 2 Results of Each TM analysis

Tumor marker	Number of cases	Number of TM(+ve) Cases	Number of reccurent cases	Number of TM(-ve) cases	Number of recurrent cases	P-value
CA15-3	371	30(8.1)	17(56.7)	341(91.9)	43(12.7)	P<0.001
CEA	371	25(6.7)	12(48.0)	346(93.3)	48(13.9)	P<0.001
NCC-ST-439	371	24(4.1)	8(33.3)	347(95.9)	52(15.0)	P<0.001

Table 3 Results of TM analysis in Stage

Stage	Number of cases	Number of TM(+ve) cases	Number of recurrent cases	Number of TM(-ve) cases	Number of recurrent cases	P-value
0	27	0(0.0)	0(0.0)	26(96.3)	0(0.0)	NS
Ⅰ	87	4(4.6)	0(0.0)	83(95.4)	1(1.2)	NS
ⅡA	113	12(10.6)	1(8.3)	101(89.4)	4(4.0)	NS
ⅡB	39	5(12.8)	1(20.0)	34(87.2)	1(2.9)	NS
ⅢA	22	3(13.0)	0(0.0)	19(82.6)	4(21.1)	NS
ⅢB	50	18(36.0)	8(44.4)	32(64.0)	12(37.8)	NS
ⅢC	5	2(40.0)	1(50.0)	3(60.0)	2(66.7)	NS
Ⅳ	28	15(53.6)	14(93.3)	13(46.4)	11(84.6)	NS

Table 4 Results of TM analysis in Lymph nodes status

Metastatic lymph node	Number of cases	Number of TM(+ve) cases	Number of reccurent cases	Number of TM(-ve) cases	Number of recurrent cases	P-value
0	223	19(8.5)	2(10.5)	204(91.5)	6(2.9)	NS
1～3	69	10(14.4)	2(20.0)	59(85.5)	6(10.2)	NS
4～9	32	8(25.0)	5(62.5)	24(75.0)	10(41.7)	NS
10～	47	23(48.9)	16(69.6)	24(51.5)	15(62.5)	NS

Table 5 Results of TM analysis in 0-3Lymph nodes metastasis

Tumor marker	Number of cases	Number of TM(+ve) cases	Number of recurrent cases	Number of TM(-ve) cases	Number of recurrent cases	P-value
CA15-3	292	11(3.8)	3(27.2)	281(96.2)	14(5.0)	P＜0.05
CEA	292	11(3.8)	1(9.0)	281(96.2)	16(5.7)	NS
NCC-ST-439	292	12(4.1)	1(8.3)	280(95.9)	16(5.7)	NS
AllTM	292	29(9.1)	4(13.8)	263(94.1)	13(4.9)	NS

DISCUSSION

CA 15-3 (97%) , CEA (97%) , NCC-ST-439 (68%) were routinely measured in clinical practice as the breast cancer tumor marker in Japan according to the questionary survey of the Japanese breast cancer society squad study in 2001. Also, the measurement of CA 15-3 and CA 27.29 as breast cancer tumor marker were proposed in the guideline of ASCO (American Society of Clinical Oncology) [1] .

An examination for serum HER2 was evaluated with trastuzumab (Herceptin) having been marketed as a therapeutic drug of progress / the recurrent breast cancer in 2001, and it was with insurance adaptation in 2002. It is essential postoperatively to evaluate the HER2 status from breast cancer tissue and as for measuring serum HER2 as a marker for the HER2 positive case postoperatively, it seems with a use now

The measurement of prostate-specific antigen is useful in early detection, a diagnosis of the prostatic carcinoma. On the other hand, specificity, sensitivity equivalent to it are absent in the marker of breast cancer. There are many institutions to measure in order of CA 15-3, CEA, NCC-ST-439, BCA225, TPA as a tumor marker of the breast cancer. The sensitivity before the initial treatment has 5-20% in CA 15-3, 5-24% in CEA, 16-33% in NCC-ST-439, 12% in BCA225 and 12-35% in TPA. In our data, 60 (16%) of 371 patients with primary breast cancer had the abnormality of the tumor marker. Each positive rate of tumor markers was 8.1% in CA 15-3, 6.7% in CEA, 4.1% in NCC-ST-439 and did not recognize a difference compared other reports.

The sensitivity rate of that was 1-5% in Stage Ⅰ, less than 5-10% in Stage Ⅱ. They were low level. Also, it was 4.6% in Stage Ⅰ, 10.6% in Stage Ⅱ A, 12.8% in Stage Ⅱ B in our data and did not recognize a difference compared reported date. On the other hand, CA 15-3 were 54-67%, CEA (27-49%) , NCC-ST-439 (41-55%) , BCA225 (55%) and TPA (62-82%) as for the sensitivity in the recurrent breast cancer [2,3] .They were high level.

The main purpose of the current marker measurement is palindromic early detection, a monitor of the supporting clinical course for the effect of treatment judgment. The marker measurement as the monitoring of the patient with recurrent breast cancer is performed in Europe and America.

The positive rate of the tumor marker at the time of the recurrence discovery varies by recurrence part. In soft tissue, positive rate of CA 15-3 and CEA was 26.7%, 18.1%. In bone, CA 15-3 (50.0%) , CEA (30.2%) . In lung, CA 15-3 (36.6%) , CEA (31.0%) . In liver, CA 15-3 (71.4%) , CEA (59.5%) .

The positive rate of CA 15-3, CEA was 44.0%, 30.5% totally, that was 55.2% when either CA 15-3 or CEA was abnormal high level[4] .

There is a report that the change of the marker reflects condition for progress, the recurrent breast cancer case of the marker positive in a Japanese breast cancer society squad study in 2001. Furthermore, when tumor marker value after treatment reduced 20% than a tumor marker value at the time of the recurrence, an extension of the time toprogression is obtained, and it was a factor independent of ef-

fect of treatment[5] .

There is the report that a prognosis is poor for cases shown the abnormal high level of the marker when we compare a prognosis in the abnormal presence of the marker about the prognostic prediction with the tumor marker in the primary breast cancer cases according to a clinical stage[6] . It seems that undetectable potential micrometastasis has been already present in the cases that a marker shows aberrant high level. Also, there is a report that various markers are not secreted in breast cancer which differentiation degree is low[7] . The examination in our department showed a recurrence to 25 (42%) of 60 tumor marker abnormality cases, 35 (11%) of 311 tumor marker normal cases. It showed a significant difference statistically ($P<0.001$) . The cases of the metastases to lymph nodes number (0–3) showed connection in rate of recurrence and abnormal having CA 15–3 or not.

It is important to measure tumor marker for a primary breast cancer case.

When taking postoperative chemoendocrinetherapy, it is usual that a recurrence risk classification of the St. Gallen consensus meeting tends to make treatment preferences in reference to evaluating it.

It seems that we need attention in postoperative therapy in the cases with abnormal marker.

When we suspect distant metastasis by the abnormal elevation of the marker, we perform an imaging study and find out an asymptomatic recurrence lesion and then start palindromic early treatment. It is supported by a Japanese breast specialist[4] . On contrary, that is not recommended as for the postoperative periodical marker measurement because there are not data that the time of discovering it controls the prognosis of the patient a recurrence in Europe and America[1] . However, it is significant to measure the markers of cases which tumor cells in the primary breast cancer tissue after an operation develop immunohistologically positive.

CONCLUSION

For the cases shown the abnormality of the preoperative tumor marker, careful serial observations are necessary. When we admitted aberrant high level of the CA 15–3 in particular, rate of recurrence is high in cases of 0–3 metastases to lymph nodes. It is necessary to consider postoperative treatment enough.

REFERENCES

1. Bast RC, Ravdin P, Hayes DF. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19:1865–1878.
2. Tajima T. [Mammary gland disease]. Shindan to Chiryou (Diagnosis and treatment) 2004; 92 Suppl :511–520. (in Japanese)
3. Sonoo H. [Breast cancer and tumor marker]. In: Takayama S, Watanabe H. Eds. Nyugan (Breast Cancer) . (Zusetsu rinshou gan shiri–zu (Progress in cancer clinics) 8) 2nd ed. Tokyo: Medical view ; 1993. p.40–43. (in Japanese)
4. Kurebayashi J, Yamamoto Y, Tanaka K, Sonoo H. Significance of serum carcinoembryonic antigen and CA15–3 in monitoring advanced breast cancer patients treated with systemic therapy: a large–scale retrospective study. Breast Cancer 2003;10:38–44.
5. Kurebayashi J, Nishimura R, Tanaka K, Sonoo H. Significance of serum tumor markers in monitoring advanced breast cancer patients treated with systemic therapy: a prospective study. Breast Cancer 2004; 11: 389–395.
6. Kumpulainen EJ, Keskikuru RF, Johansson RT. Serum tumor marker CA15–3 and stage are the two most powerful predictors of survival in primary breast cancer. Breast Cancer Res Treat 2002; 76:95–102.
7. Nishimura R, Nagano K, Miyayama H. Elevated serum CA15–3 levels correlate with positive estrogen receptor and initial favorable outcome in patients who died fromre-

current breast cancer. Breast Cancer 2003; 10:220–227.

8. Kurebayashi J, Yamamoto Y, Tanaka K, Ogawa Y, Kurosumi M, Kohno N, Taguchi T, Nishimura R, Moriya T. Current status of tumor markers of breast cancer in Japan. A questionnaire survey to the board numbers of the Japanese Breast Cancer Society. Nyugan no Rinsho (Jpn J Breast Cancer) 2002; 17:165–169. (in Japanese)

(Accepted for publication, Jan. 15, 2008)