Table 6. Ages at onset of participants with breast and/or ovarian cancer

	All	Breast cancer (female)	Breast cancer (male)	Ovarian cancer
Number of subjects	135	122	4	18
Age at diagnosis				
Overall	46.5 ± 12.1	46.2 ± 12.1	64.5 ± 3.7	50.2 ± 11.8
No deleterious mutations	47.7 ± 12.1 (n = 99)	47.3 ± 12.0 (n = 86)	64.0 ± 4.4 (n = 3)	49.4 ± 13.1 (n = 13)
Deleterious mutations in *BRCA*1 or *BRCA*2	43.1 ± 11.3 (n = 36)	42.4 ± 11.0 (n = 34)	66 (n = 1)	52.2 ± 8.6 (n = 5)
P-values	0.052	0.0272	0.7295	0.6647
Deleterious mutations in *BRCA*1	42.0 ± 11.9 (n = 17)	41.8 ± 9.6 (n = 16)	–	52.2 ± 8.6 (n = 5)
Deleterious mutations in *BRCA*2	44.2 ± 13.1 (n = 19)	42.9 ± 12.3 (n = 18)	66 (n = 1)	–
P-values	0.574	0.757	–	–

statistical significance was observed in clinicopathological indices such as tumor size, nodal status, and stage by *BRCA*1 mutational status.

In 122 subjects with female breast cancer, cumulative incidences were analyzed by Kaplan–Meier plot and log-rank test (Fig. 2). In subjects with deleterious *BRCA*1/2 mutations, median ages at onset were 42.5 years (*BRCA*1/2), 42 years (*BRCA*1), and 42.5 years (*BRCA*2), respectively, indicating that breast cancer developed at a significantly younger age than in non-carriers (P = 0.0144 between *BRCA*1/2-positive and -negative subjects, P = 0.0338 between *BRCA*1-positive, *BRCA*2-positive, and -negative subjects) (Fig. 2). Similar analysis was extended to relatives and it was shown that the age at onset of breast cancer could be a significant predictor of *BRCA*1/2 mutational status (Table 8). Breast cancer developing before age 40 within second-degree relatives indicated a significantly higher prevalence of *BRCA*1/2 mutations (P = 0.0265). Of the 122 pedigrees among which index patients suffered from female breast cancer, 26 pedigrees (21.3%) fulfilled this condition and the frequency of deleterious *BRCA*1/2 mutations was significantly higher than in the controls (46.2% [12/26] *vs* 22.9% [22/96], OR 2.833, 95% CI 1.165–7.136). This feature was further emphasized when the disease history of cousins was included in the family history, in which 29 of 122 pedigrees (23.8%) fulfilled the criteria and the prevalence of *BRCA*1/2 mutations showed a significant increase compared to the controls (48.3% [14/29] *vs* 21.5% [20/93], OR 3.407, 95% CI 1.412–8.217). When the index patient suffered from breast cancer, the presence of ovarian cancer and/or bilateral breast cancer within second-degree relatives was shown to be a strong indicator of *BRCA*1/2 mutations. Half of the enrolled subjects (49.2% [60/122]) fulfilled this condition and the prevalence of *BRCA*1/2 mutations in this group was considerably high (38.3% [23/60] *vs* 17.7% [11/62], OR 2.882, 95% CI 1.252–6.637).

Discussion

A total of 135 subjects were enrolled in the study, 131 women and four men, all of whom had a history of breast and/or ovarian cancers (Table 1). All patients were selected and enrolled in the study from genetic counseling clinics of the corresponding hospitals and the average number of sessions of genetic counseling was 3.36 ± 0.82. Patients usually underwent one or two sessions before and one session after gene testing when test results were negative. For patients with deleterious mutations, additional sessions were performed as follow-up because of the risk of developing psychosocial issues; hence, the number of sessions for mutation carriers was significantly more than for non-carriers (3.75 ± 1.20 *vs* 3.22 ± 0.56, P = 0.0007). In all subjects, the course was uneventful until the end of the study. Genealogical information was obtained in counseling sessions and the numbers of relatives greater than second-degree were significantly more in mutation carriers than non-carriers

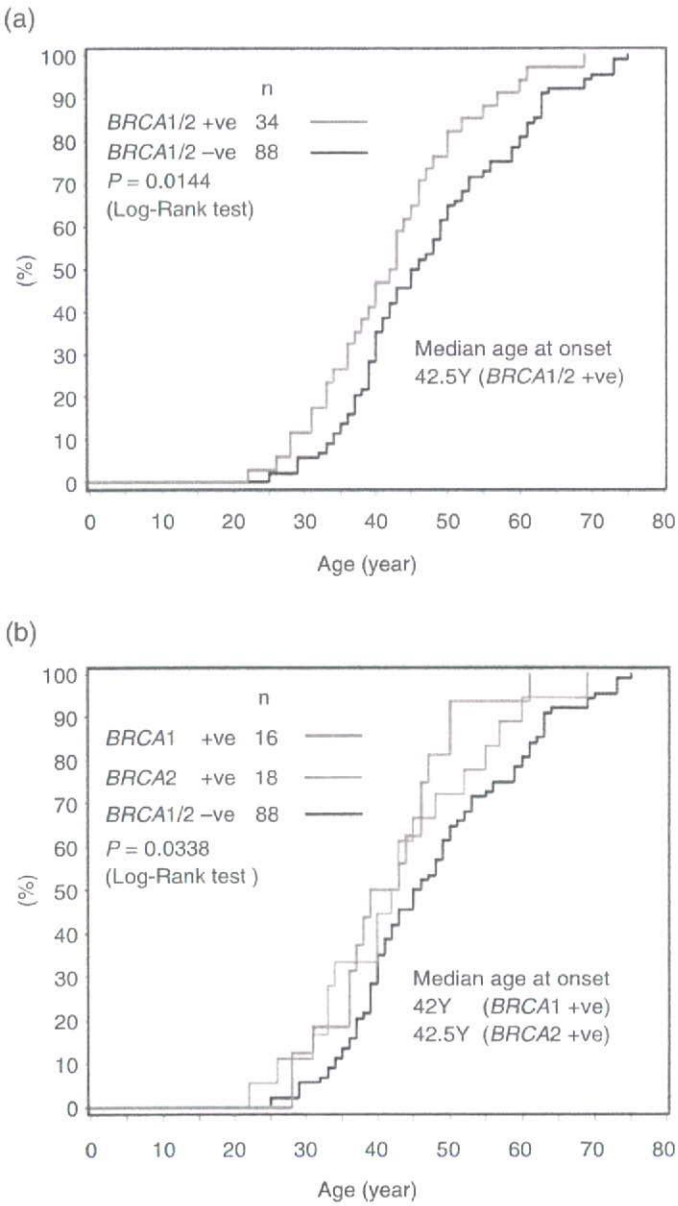

Fig. 2. Kaplan–Meier plot of the cumulative incidence of breast cancer in female index patients examined for germline *BRCA*1/2 mutations. (a) Grouped in *BRCA*1/2 positive (n = 34) or negative cases (n = 88), (b) grouped in *BRCA*1 positive (n = 16), *BRCA*2 positive (n = 18) and *BRCA*1/2 negative cases (n = 88).

Table 7. Clinicopathological characteristics of the breast or ovarian cancers by *BRCA*1/2 mutational status

Variables		Breast cancer					Ovarian cancer		
		Non-carrier*	Deleterious mutations in			*P*-values*	Non-carrier	Deleterious mutations in	*P*-values
			*BRCA*1/2	*BRCA*1*	*BRCA*2*			*BRCA*1	
	No. of subjects	91	35	16	19		13	5	
Tumor size (T)	Tis	2	0	0	0	0.3884	–	–	0.8338
	T1	50	16	7	9		8	3	
	T2	35	14	7	7		1	0	
	T3	1	3	1	2		3	1	
	Missing (No.)	(3)	(2)	(1)	(1)		(1)	(1)	
Nodal status (N)	Negative	70	25	11	14	0.7859	7	3	1.000
	Positive	17	7	4	3		4	1	
	Missing (No.)	(4)	(3)	(1)	(2)		(2)	(1)	
Stage	0	2	0	0	0	0.026	–	–	0.9875
	I	56	15	6	9		6	3	
	II	25	13	6	7		1	0	
	III	1	3	3	0		3	1	
	IV	1	0	0	0		1	0	
	Missing (No.)	(6)	(4)	(1)	(3)		(2)	(1)	
ER status	Positive	57	15	2	13	0.0002			
	Negative	22	15	11	4				
	Missing (No.)	(12)	(5)	(3)	(2)				
PgR status	Positive	53	11	2	9	0.0020			
	Negative	26	18	11	7				
	Missing (No.)	(12)	(6)	(3)	(3)				
Histological grade	Grade 1	22	2	0	2	0.0386			
	Grade 2	28	9	2	7				
	Grade 3	14	10	5	5				
	Missing (No.)	(27)	(14)	(9)	(5)				
Laterality	Unilateral	75	29	13	16	0.9711			
	Bilateral	16	6	3	3				

*χ^2-test was performed between non-carriers, subjects with *BRCA*1 mutations, and *BRCA*2 mutations. ER, estrogen receptor; PgR, progesterone receptor.

Table 8. Univariate analysis of family-based clinical variables associated with germline *BRCA*1/2 mutations in 122 pedigrees with female probands affected with breast cancers

Variables		*BRCA*1/2 deleterious mutations		*P*-values (χ^2-test)	Odds ratio (95% confidence interval)
		Yes	No		
Breast cancer before age 40 Within second-degree relatives	Yes No	12 22	14 74	0.0265	2.833 (1.165–7.136)
Breast cancer before age 40 Within second-degree relatives and cousins	Yes No	14 20	15 73	0.0084	3.407 (1.412–8.219)
Ovarian cancer and/or bilateral breast cancer within second-degree relatives	Yes No	23 11	37 51	0.0151	2.882 (1.252–6.637)

($P < 0.0001$). Patient accrual was decided by family history within second-degree relatives, and in greater than second-degree relatives, family history might be investigated more precisely in subjects with deleterious *BRCA*1/2 mutations after disclosure of test results; therefore, genealogical information on relatives greater than second-degree may be biased in carriers.

Among mutations detected in *BRCA*1, L63X (c.188T > A), Q934X (c.288C > T), and K503X (c.1507 A > G) were previously reported in Japanese.[7,9–11] Sekine *et al.* reported L63X and Q934X as the two common founder mutations in Japanese.[11] L63X was detected in five subjects and Q934X in only one subject in this study. In a search of the BIC database, five mutational types were previously unreported, of which K503X (c.1507 A > G) was detected in one Japanese subject,[10] and the other four mutational types were considered to be previously unreported deleterious mutations. Genetic variants of unknown significance were detected in nine subjects; all were missense mutations and three types were thus far unreported in the BIC database (Table 3).

In the analysis of *BRCA*2, 5804del4 (c.5576_5579delTTAA), Q3026X (c.9076C > T), and R3128X (c.9382C > T) were previously reported in Japanese people (Table 4).[9–11] As for genetic variants of uncertain significance, two mutational types (G2044V [c.6131G > T] and V2109I [c.6325G > A]) were reported in Japanese, and G2044V was found in at least one of 28 Japanese healthy volunteers.[12] M524I (c.1572G > C), K610Q (c.1828 A > C), I770V (c.2308 A > G), and S2616F (c.7847C > T) were previously unreported mutational types.

The prevalence of *BRCA*1/2 mutations in Japanese subjects classified to each subgroup was compared with that of non-

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Ashkenazi individuals, and statistical difference was observed in subgroup I-1, in which two mutational types were detected in three subjects in Japanese. They were 314delTT in exon 3 of *BRCA*2 and two subjects with c.5576_5579delTTAA or 5804delTTAA in exon 11 of *BRCA*2. Two cases with 5804delTTAA have been reported so far in Japanese.[9,11] Ikeda *et al.* reported seven cases of 5802del AATT,[10] which is the same mutational type as 5804delTTAA as there is a repeated sequence in this region; therefore, this mutational type seems to be rather common in Japanese. In this study, c.5576_5579delTTAA were detected in two subjects. In the former, breast cancer developed in identical twins at 57 and 58 years of age, respectively. Reportedly, statistically significant effects of heritable factors were observed for breast cancers coincidentally developing in identical twins, some of which would be attributed to polygenic inheritance.[26] In the latter case, lt-breast cancer developed at 52 years of age in the proband and her aunt developed lt-breast cancer at 63 years. No other relatives suffered from breast and/or ovarian cancer in these pedigrees and we strongly suspected that c.5576_5579delTTAA might be a relatively common mutation with low penetrance in Japanese. If these two subjects were excluded, no statistical significance was observed between Japanese subjects and non-Ashkenazi individuals in the subgroup I-1. Further studies are required to elucidate the prevalence of this particular mutational type in a Japanese healthy cohort.

A significantly higher frequency of mutation was found in patients with breast cancer older than 50 years of age who had a family history of breast cancer at older than 50 years within second-degree relatives (Subgroup I-1) compared to the corresponding non-Ashkenazi individuals (Table 5). This may imply that Japanese carriers of *BRCA*1/2 mutation suffer from breast cancer with later onset than non-Ashkenazi carriers. As for non-Ashkenazi individuals, the clinical backgrounds of the enrolled subjects, such as age at onset, were not available except for the data so far reported;[6] therefore, it is hard to produce a Kaplan–Meier plot of cumulative incidences in non-Ashkenazi individuals. Likewise, few reports have shown the prevalence of *BRCA*1/2 mutations analyzed by full sequencing in non-Ashkenazi individuals as a population-based study or cross-sectional study. Recently, John *et al.* estimated the prevalence of *BRCA*1 mutations in white, non-Hispanic breast cancer patients without Ashkenazi ancestry younger than 65 years at diagnosis. They analyzed 508 breast cancer patients enrolled in the Breast Cancer Family Registry and pathogenic mutations of *BRCA*1 were found in 14 subjects, of which six subjects (42.8%) and 11 (78.6%) developed breast cancer before age 35 and age 50, respectively.[27] Not exclusive to non-Ashkenazi individuals, Metcalfe *et al.* analyzed 927 women with unilateral breast cancer and with positive *BRCA*1/2 mutations from eight countries (Austria, Canada, France, Israel, Italy, Norway, Poland, and the US) and their average age at diagnosis of the first breast cancer was 42.2 years.[28] In our study, average age at onset of breast cancer in *BRCA*1/2 carriers was 42.4 years and these data look similar to those reported in Western countries.

The numbers of subjects classified into each group were 42 in Group I, 75 in Group II, one in Group III, seven in Group IV, and 10 in Group V (Table 5). Originally, we assumed that more subjects would be enrolled into Group I than Group II, as the first recruitment of all eligible patients was made by the attending doctors, and a considerable number of the breast cancer patients fulfilling the eligibility criteria had a modest family history. It seemed likely that patients with a higher risk wished to be enrolled in the study and those with a modest risk did not visit the clinic for genetic counseling. This may be why fewer subjects were enrolled in Group I than in Group II. We designed the study as an unbiased hospital-based, cross-sectional study in which all subjects with a family history of breast and/or ovarian cancer were enrolled, but the results seemed closer to a family-based study rather than a hospital-based study. This trend was similar to the subjects enrolled in the study through press advertising.

The results of the Mantel-Haenszel test showed that the prevalence of *BRCA*1/2 mutations in Japanese was significantly higher than those reported in non-Ashkenazi individuals. As the sample size was too small to reach a conclusion, one reason may be that all gene tests were carried out in genetic counseling clinics, where clients were more likely to be prone to hereditary cancers. It should be noted that the prevalence of *BRCA*1/2 mutations in Japanese was as high or even higher than that of non-Ashkenazi individuals reported in the US.

Ikeda *et al.* examined 113 Japanese breast cancer patients showing a modest to minimal familial risk, i.e. those with at least one breast cancer or one ovarian cancer patient within their first-degree relatives.[10] They reported that families with early onset patients diagnosed at younger than 40 years of age showed a higher frequency (38%, 19/50 subjects) of *BRCA*1/2 mutations than those without early onset patients, and families with bilateral breast cancer patients showed a higher frequency (40%, 6/15 subjects) than those with only unilateral breast cancer patients, but all these differences were statistically insignificant.[10] In the present study, we found statistical significance in families with breast cancer before age 40 within second-degree relatives (46.2%, 12/26 subjects) and within second-degree relatives and cousins (48.3%, 14/29 subjects). Families with ovarian cancer and/or bilateral breast cancer within second-degree relatives exhibited statistically significant *BRCA*1/2 mutation frequency (38.3%, 23/60 subjects). Predisposition to breast cancer in cousins seems informative for assessing familial risk, particularly in cases where the responsible genes are likely to be transmitted from the paternal side. In genetic counseling, precise family history is a key point in assessing genetic risk and the inclusion of familial risk within second-degree relatives or cousins would be helpful for proper risk assessment.

In conclusion, this is the first cross-sectional study elucidating the prevalence of *BRCA*1/2 mutations among Japanese people with varying genetic susceptibility. Genetic counseling performed prior to gene testing in genetic counseling clinics is an effective approach to assess the risk for cancer predisposition and subsequent indication for gene testing. Full sequencing analysis of *BRCA*1/2 genes would be a useful modality for diagnosing HBOC and the results of the present study provide a basis for the clinical application of a cancer prevention strategy targeted to *BRCA*1/2 mutation carriers in Japanese.

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症　例

破骨細胞様巨細胞の出現を伴う乳癌の9例

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1999年から2007年の9年間における破骨細胞様巨細胞（OCGC）の出現を伴う乳癌（OCGC乳癌）の自験例につき臨床病理学的，免疫組織化学的特徴を検討した．OCGC乳癌は9症例であり，全乳癌における頻度は0.3%であった．臨床病期はStage Ⅰ：4例，Stage ⅡA：3例，Stage ⅡB：2例であった．最大腫瘍径は1.5cm—6.0cm（平均3.1cm），リンパ節転移を4例（44%）に認めた．腫瘍組織型は全例浸潤性乳管癌，組織学的異型度は全例grade2であった．estrogen receptorは5例（56%），progesteron receptorは6例（67%）で陽性，HER2は7例で検討し，1例（14%）で陽性であった．予後は原病死1例を認めた以外は無再発生存中（平均観察期間4年10カ月）である．OCGC乳癌は臨床病期，組織学的異型度，リンパ節転移，ホルモン受容体発現状況等から悪性度は中等度，あるいは比較的良好の可能性があることが示唆された．

索引用語：乳癌，破骨細胞様巨細胞

緒　言

破骨細胞様巨細胞（Osteoclast-like giant cell，以下OCGC）の出現をみる乳癌（以下OCGC乳癌）は0.5～1.2%と極めて稀であり，OCGC出現機序は生物学的，臨床病理学的側面からも興味深い．今回われわれは1999年から2007年の間に当院で経験したOCGC乳癌9症例についてその臨床病理学，免疫組織化学的特徴について検討したので若干の文献的考察を加えて報告する．

対象および方法

1999～2007年の9年間に当院で手術した乳癌3546症例のうち，摘出標本にてOCGC乳癌と診断された9症例（0.3%）を対象とした．OCGC乳癌は組織学的に腫瘍胞巣内あるいは腫瘍間質内にOCGCの出現を認めるもの，と定義した（図1，2）．臨床病理学的検討は「乳癌取扱い規約」[1]に準拠した．さらにestrogen receptor（以下ER），progesteron receptor（以下PgR），HER2，p53の免疫組織化学的検討を行った．これらの結果を1999年～2006年に当院で手術された全浸潤性乳管癌症例（対照群）と比較検討した．

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成　績

年齢は38～72歳（平均50歳）で女性8例，男性1例であった（表1）．発生部位は右側7例，左側2例と右側に多く，C領域が6例で最も多かった．臨床病期はStage Ⅰ：4例（44%），Stage ⅡA：3例（33%），Stage ⅡB：2例（22%）であった．対照群ではStage Ⅰ：33.4%，Stage Ⅱ：57.6%，Stage Ⅲ：8.9%で両群間に差異を認めなかった．施行術式は乳房温存部分切除術＋腋窩リンパ節郭清術：5例，両胸筋温存乳房切除術＋腋窩リンパ節郭清術：3例，乳房温存部分切除術＋センチネルリンパ節生検術：1例であった．リンパ節転移を4例（44%）に認め，1例に5個以上の転移を認めた．リンパ節転移の頻度は対照群（44%）と同等であった．手術摘出標本の肉眼所見では腫瘍割面は赤褐色調を含むものが多く，通常経験される乳腺浸潤癌の肉眼像と異なっていた．病理学的最大腫瘍径は1.5cm～6.0cm（平均3.1cm），組織学的には全例浸潤性乳管癌であり，優位な組織像は乳頭腺管癌が8例，硬癌が1例であった（表2）．腫瘍胞巣内および腫瘍間質内にOCGCを瀰慢性に認めた．OCGC乳癌は組織学的に①腫瘍成分が未分化な肉腫様パターンを示し，高率に骨や軟骨化生を伴うmetaplastic carcinoma with OCGC，②比較的分化型の腺癌に伴うもので肉腫様成分や骨，軟骨化生のないcarcinoma with reactive

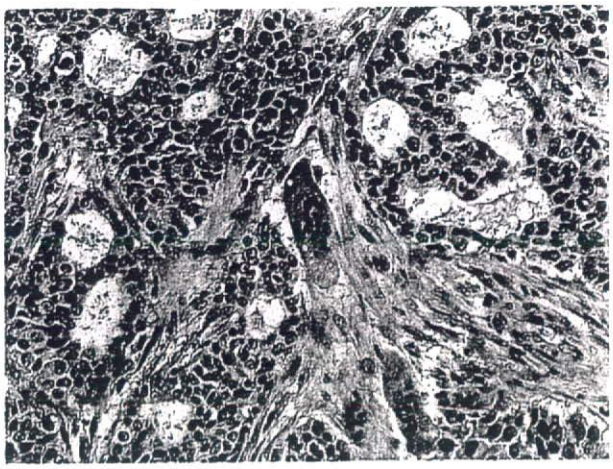

図1　病理組織所見：腫瘍は浸潤性乳管癌（乳頭腺管癌）であり，腫瘍間質にはOCGCの浸潤を散在性に認める（症例1，HE染色，対物20倍）．

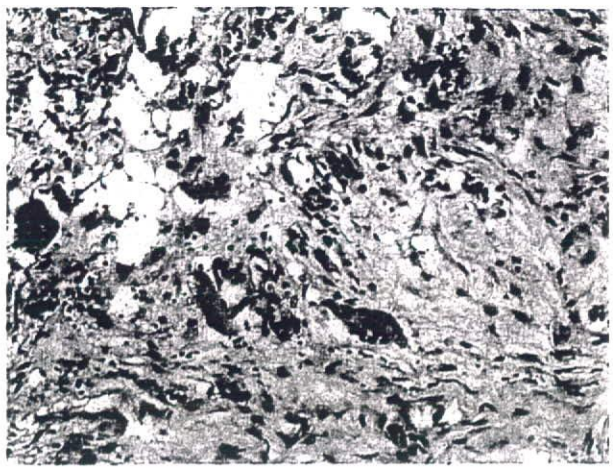

図2　病理組織所見：腫瘍周囲間質に出現した多数のOCGC（症例3，HE染色，対物20倍）．

stromal giant cells，③上皮性成分がなく，骨の巨細胞腫に類似性が求められるextraskeletal osteoclastomaに分類可能とされる[2]が，自験例は全て②に相当するものであった．OCGCの出現数には各症例間でばらつきがみられたが，その形態には違いがみられなかった．組織学的異型度（modified Bloom-Richardson分類）は全例grade2，リンパ管侵襲を3例に認めたものの，静脈侵襲は全例陰性であった．7例で脂肪浸潤を，1例で真皮への浸潤をきたしていた．高度乳管内進展を3例に認めた．いずれの症例においても扁平上皮化生や間質の骨・軟骨化生は認められなかった．対照群では組織学的異型度はgrade1：10%，grade2：48%，grade3：42%であり，対照群のほうが異型度が高い傾向にあった．免疫組織化学的検査ではERが5例（56%），PgRが6例（67%）で陽性であり，検討した7例中1例（14%）でHER2蛋白の過剰発現を認めた．またER，PgRがいずれも陽性であったのは3例（33%）であった．なおER，PgRは免疫染色で10%以上の腫瘍細胞が染まるものを陽性とした．p53は2例で陽性，5例で弱陽性であった．対照群ではERが72%，PgRが67%の症例で陽性，HER2の過剰発現を20%の症例で認めた．ER，PgRがいずれも陽性であったのは60%であった．OCGC乳癌症例では対照群と比較するとER陽性率が低い傾向にあった．術前穿刺吸引細胞診を施行された6例のうち当院で検討されたのは4例で，異型上皮細胞と多核巨細胞をともに認めたものは2例であった．予後は1例が術後5年10カ月で多発骨転移，多臓器転移にて死亡したものの，他症例は無再発生存中（平均観察期間4年10カ月）である．

考　察

OCGCの出現を伴う癌の報告はさまざまな臓器でみられるが極めて稀であり，乳癌においても同様でその頻度は0.5～1.2%[3)~5)]といわれている．1931年にLeroux[6]が初めて報告して以来約100例の報告があるのみである．臨床的特徴として，通常型乳癌と比較して若年齢，閉経前の症例が多いとの報告が散見される[4)7)]が，自験例では平均50歳，閉経前が6例，自然閉経後と子宮卵巣摘出術後がそれぞれ1例ずつであり，通常型乳癌との差異を認めなかった．

男性に発症したOCGC乳癌の報告はなく，自験例が初めての症例であった．当症例は組織像においても，嚢胞内にポリープ状に発育し乳頭状～一部胞巣状に増殖した乳頭腺管癌で，本邦で従来報告されたOCGC乳癌はすべて充実性の発育を示している点からも極めて稀な症例と考えられる．本症例は術後2年で胸骨転移を，5年10カ月で上腕骨転移，多臓器転移をきたし死亡した．

腫瘍の組織型として1995年のViacavaらは多彩な組織型を報告している[8]が，とりわけ本邦においては大多数が浸潤性乳管癌である[9)~12)]．自験例でも全症例が浸潤性乳管癌であった．

免疫組織化学的検討について，OCGC乳癌がER陽性，HER2陰性の傾向があることを示した報告[10]や，それとは異なりER陰性，PgR陽性症例が多いとする報告[4)13)]もある．予後についても通常型乳癌と比較し良好とするもの[11)14)]や，差異がないとするもの[15]，一方で比較的進行した症例が多いとするもの[4]まで様々で一

表1　OCGC 乳癌症例の臨床所見

症例	年齢（歳）	性別	TNM	術式	術後経過（術後観察期間）
1	41	女	T1cN0M0	Bp+SLN	no rec.（3M）
2	45	女	T2N0M0	Bt+Ax	no rec.（37M）
3	45	女	T1cN0M0	Bp+Ax	no rec.（42M）
4	57	女	T1cN0M0	Bp+Ax	no rec.（71M）
5	38	女	T2N0M0	Bp+Ax	no rec.（69M）
6	41	女	T2N0M0	Bp+Ax	no rec.（99M）
7	72	男	T2N1M0	Bt+Ax	胸骨転移（70M）
8	44	女	T1bN0M0	Bp+Ax	no rec.（51M）
9	64	女	T2N1M0	Bt+Ax	no rec.（81M）

Bp+SLN：乳房温存部分切除術＋センチネルリンパ節生検術，Bt+Ax：両胸筋温存乳房切除術＋腋窩リンパ節郭清術，Bp+Ax：乳房温存部分切除術＋腋窩リンパ節郭清術，no rec.：無再発生存中

表2　OCGC 乳癌症例の病理組織所見と免疫組織化学所見

症例	腫瘍径（cm）	リンパ節転移	組織型（優位組織像）	G/NG	ly/v	ER/PgR	HER2	p53
1	5.1	n0(0/2)	IDC(pap)	2/3	(−)/(−)	(+)/(+)	(−)	…
2	3.5	n1(4/24)	IDC(pap)	2/1	(+)/(−)	(+)/(+)	(−)	(±)
3	1.5	n1(1/12)	IDC(pap)	2/2	(−)/(−)	(−)/(+)	(−)	(±)
4	2.0	n0(0/23)	IDC(pap)	2/3	(−)/(−)	(+)/(−)	(−)	(−)
5	2.1	n0(0/14)	IDC(pap)	2/2	(−)/(−)	(−)/(+)	(−)	(±)
6	2.3	n0(0/31)	IDC(pap)	2/2	(−)/(−)	(+)/(+)	…	(+)
7	5.0	n1(7/24)	IDC(pap)	2/2	(+)/(−)	(−)/(−)	…	(+)
8	0.8	n0(0/15)	IDC(sci)	2/2	(−)/(−)	(−)/(+)	(−)	(±)
9	6.0	n1(3/21)	IDC(pap)	2/2	(+)/(−)	(+)/(−)	(+)	(±)

IDC：浸潤性乳管癌，pap：乳頭腺管癌，sci：硬癌，G：組織学的異型度（modified Bloom-Richardson 分類），NG：組織学的核異型度，ly：リンパ管侵襲，v：静脈侵襲，ER：estrogen receptor，PgR：progesteron receptor

定の見解が得られていない．自験例では ER 陽性率が対照群より低い傾向にあった．津田[16]はリンパ節転移の程度と組織学的異型度（modified Bloom-Richardson 分類）を最も重要な独立した予後因子としているが，今回の臨床病期，リンパ節転移の程度，ホルモン受容体発現状況の検討からはその悪性度は通常型乳癌とほぼ同等であるものと考えられる一方，臨床病期 Stage IIB であった1例が術後5年10カ月後に原病死した以外全例無再発生存中であること，組織学的異型度が OCGC 乳癌症例のほうが低い傾向にあったことは，OCGC 乳癌の予後が比較的良好であることを示唆している．

術前画像診断について OCGC 乳癌は境界明瞭な腫瘤を形成する頻度が高いため，マンモグラフィにて良悪性の鑑別が困難であることが多く，そのことが予後を悪くしている可能性があるとの報告がある[4]．自験例では1症例がマンモグラフィ，超音波検査にて良悪性鑑別困難な嚢胞性腫瘤と診断され1年間経過観察となっている．他の1症例はマンモグラフィにて異常所見を認めず，超音波検査でも質的診断困難な低エコー腫瘤との診断であったが，造影 MRI での腫瘤の形状，造影パターンにて浸潤性乳管癌を疑われ，穿刺針生検にて浸潤性乳管癌と診断された．他の7症例ではマンモグラフィにて辺縁不整な，spicula あるいは石灰化を伴う腫瘤等の所見により，乳癌あるいはその疑いと指摘された．自験例からは良悪性の鑑別が困難な傾向は認められなかった．

術前穿刺吸引細胞診について OCGC 乳癌の診断に有用であるとの報告があるが[17]，今回細胞診を検討した4例中，異型上皮細胞と OCGC をともに認め，OCGC 乳癌が疑われたのは2例であった．OCGC の出現数に各症例間でばらつきがあったことがその原因と

考えられる．

OCGCの発生起源として過去の報告では間質系の組織球由来とする見解でほぼ一致している[9)~12)17)]．1症例のみの検討であるが，自験例でも免疫染色で単球・マクロファージ系に特異的なCD68が陽性となっておりその見解と矛盾しない．

OCGCの出現機序としては不明な点が多い．OCGCは腫瘍部位にのみ認められ，電子顕微鏡による検討では組織球の融合にて形成されるとの報告もみられる[11)]．またマウスを用いた実験でinterleukin-1(IL-1)が破骨細胞の多核細胞化と骨吸収活性の誘導を促したという報告があり[18)]，癌細胞と関連してサイトカインが放出されOCGCが誘導されるとも考えられる．in-vitroでOCGCがparathormoneからの刺激にて溶骨能を持つことから，骨転移との関連を指摘する報告もある[19)]．因果関係は不明であるが，自験例での死亡症例も骨転移をきたした．今後更なる研究によりその出現機序が解明されればOCGC乳癌の生物学的特性，予後等が明らかになっていくものと考えられる．

結　語

OCGCの出現を伴う乳癌は稀な特殊型である．今回の検討ではその悪性度は中等度，あるいは比較的低い可能性があることが示唆された．OCGCの出現機序はまだ不明な点が多いが，その解明は腫瘍の生物学的特性を考える上で役立つものと考えられる．

稿を終えるにあたり，病理学のご指導をいただきました当院病理部長谷部孝裕先生に深く感謝いたします．

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NINE CASES OF MAMMARY CARCINOMA CHARACTERIZED BY THE PRESENCE OF OSTEOCLAST-LIKE GIANT CELLS

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Mammary carcinoma containing osteoclast-like giant cells (OCGC) is an extremely rare tumor. We have encountered nine additional cases of this tumor, so we investigated is clinico-pathological and immunohistochemical characteristics. Four cases were in Stage I, three were in Stage II A, and two were in Stage II B. The tumor size varied from 1.5cm to 6.0cm. Lymph node metastasis was observed in four cases (44%). In all cases, histopathological examination revealed invasive ductal carcinoma containing OCGC among the tumor cell nests. The tumors were grade 2 in all cases, according to the modified Bloom-Richardson classification. Immunohistochemically, estrogen receptor, progesterone receptor and HER2 receptor were positive in five cases, six cases, and one case, respectively. One patient died of the disease five years and ten months after surgery while no signs of recurrence have been seen in the other cases. According to these results, it is possible that the prognosis of mammary carcinoma charaeterized by the piaeuce of OCGC is better than that of ordinary mammary carcinoma.

原著

2007.11.11受付

原発性乳がんに対するPrimary systemic therapy (PST)の適応—PST抵抗性乳がんを治療前に判定可能か？

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Clinicopathologic Features of Primary Breast Cancer Resisting Primary Systemic Therapy：Shien T[*1], Yoshida M[*1], Hojo T[*1], Shimizu C[*2], Kouno T[*2], Ando M[*2], Akashi-Tanaka S[*1], Seki K[*3], Katsumata N[*2], Fujiwara Y[*2] and Kinoshita T[*1] ([*1]Department of Surgery, [*2]Breast and Medical Oncology Division, [*3]Department of Pathology, National Cancer Center Hospital)

We evaluated the clinicopathologic and radiological features of patients with primary breast cancer resistant to PST to demonstrate the predictive factors of PST. Between 1998 and 2007, 443 PBC underwent curative surgical treatment after PST (anthracycline and/or taxane) at National Cancer Center Hospital (NCCH). We could evaluate 8 (2%) primary breast cancer patients who clearly judged clinical progressive disease (PD) with radiological examinations. Histological classifications were metaplastic carcinomas in 5 (63%) patients, but 2 of these patients were not correctly diagnosed before PST by core needle biopsy. All patients were triple negative (ER, PgR and HER2) by immunopathological examinations. On radiological examinations, the tumors were visualized as localized, round and non homogeneus masses. The clinicopathological and radiological features of PBC resistant PST were clear in this study. However, these features were similar to PBC with high sensitivity to PST. Another predictor is needed to accurately judge sensitivity to PST.

Key words：Breast cancer, Primary systemic therapy, Predictive features
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はじめに

現在乳がんに有効な抗がん剤の進歩に伴い，局所進行乳がんのみならず比較的早期の乳がんに対しても広くPrimary systemic therapy (PST) が行われるようになった．その，目的は[1]PSTにより原発腫瘍の完全消失（pCR）を得て予後を改善する．[2]原発腫瘍をできるだけ縮小させて切除範囲のできるだけ小さな乳房温存療法を可能にする．[3]原発腫瘍に対する抗がん剤の感受性を確認する．とされている[1]．しかし，治療前にPSTの効果を予測し効果にあわせたPSTの適応はいまだ議論されている最中である．

今回われわれは，PSTに抵抗性であった症例の臨床病理学的および画像的特徴を分類し，これらの症例を治療前に判定可能か検討した．

1.　対象と方法

1998年5月から2007年9月までに国立がんセンター中央病院（NCCH）においてanthracyclineまたはtaxaneを含むPrimary systemic therapy (PST)を行った後治癒切除を行った原発性乳がん

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表1　患者背景および予後

症例	年齢	病期	PST	手術	再発・転移	DFS	死亡	OS
1	62	IIIB	AT	Bt+Ax	骨・肝	24	D	25
2	26	IIA	FECT	Bt+Ax	肺	14	D	21
3	42	IIIA	FECT	Bt+Ax	胸水	11	D	12
4	56	IIIB	ACT	Bt+Ax	局所	14	A	38
5	57	IIA	ACT	Bt+Ax	骨・肺	13	A	17
6	37	IIB	ACT	Bt+Ax	—	12	A	12
7	37	IIIB	ACT	Bt+Ax	肺	5	A	7
8	48	IIB	FECT	Bt+Ax	肺	6	D	9

AT：doxorubicin+Docetaxel. FECT：fluorouracil+epirubicin+cyclophosphamide followed by paclitaxel. ACT：doxorubicin+cyclophosphamide followed by paclitaxel. Bt：total mastectomy. Ax：axillary disection (level II). D：dead. A：alive

表3　画像所見

症例	組織型	画像所見
1	sq	限局性，境界明瞭，内部不均一
2	MPC	限局性，境界明瞭，内部不均一
3	sc	spiculaを伴う腫瘤
4	so	乳頭部に限局，境界明瞭
5	sq+sp	限局性，境界明瞭，内部不均一
6	so	限局性，境界明瞭，内部不均一
7	sp	限局性，境界明瞭，内部不均一
8	mix	限局性，境界明瞭，内部不均一

sq：squamous cell carcinoma. MPC：matrix producing carcinoma. so：solid tubular carcinoma
sc：scirrhous carcinoma. sp：adenocarcinoma with spindle cell metaplasia. mix：mixed epitherial metaplastic carcinoma.

患者は443名であった．そのうち，PSTに抵抗性で触診および画像上明らかに腫瘍の増大をみとめた症例8例（2％）について，病理学的特徴として治療前core needle biopsy (CNB) 検体および術後組織標本における，組織型，悪性度，リンパ節転移および免疫染色にてER, PgR, HER2, p53を比較検討した．また，治療前および術前画像結果から画像的特徴を検討した．

2. 結　果

表1に8例の臨床的特徴を示す．年齢中央値は45歳（26～62歳）．臨床病期はStage IIA 2名，Stage IIB 2名，Stage IIIA 1名およびStage IIIB 3名であった．PSTのレジメンはいずれもanthracyclineおよびtaxaneをともに含むもで，AT (doxorubicin；50mg/m²/docetaxel；60mg/m²) 1名，FEC followed by paclitaxel (fluorouracil；500mg/m²，epirubicin；100mg/m²，cyclophosphamide；500mg/m²，paclitaxel；80mg/m²) 3名およびAC followed by paclitaxel (doxorubicin；60mg/m²，cyclophosphamide；600mg/m²，paclitaxel；80mg/m²) 4名であった．Trastuzumabを投与された症例はなかった．手術は全例レベル2郭清を伴う乳房切除術が行われていた．予後についても同様に**表1**に示す．8例中7例で2年以内に再発を認めそのうち6例は遠隔臓器転移で1例は局所再発であった．また，再発した7例中3例は再発後1年以内に死亡していた．

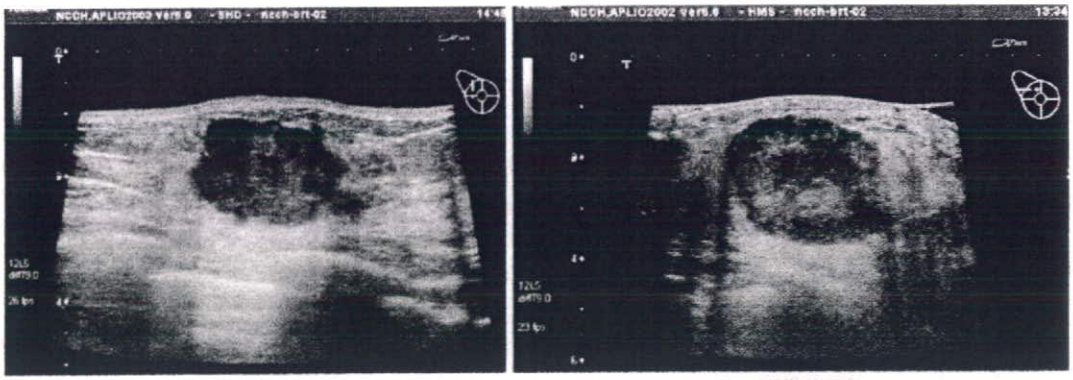
表2　免疫病理学的検査結果

症例	組織型(治療前CNB)	ER	PgR	HER2	G	p53	n
1	sq (sq)	0	0	0	3	2	21
2	MPC (so)	0	0	0	3	3	0
3	sc (sc)	0	0	0	3	3	19
4	so (so)	0	0	2+(0)	3	3	7
5	sq+sp (sq)	0	0	0	3	3	0
6	so (so)	0	0	0	3	3	2
7	sp (IDC)	0	0	0	3	3	1
8	mix (so)	0	0	0	3	3	3

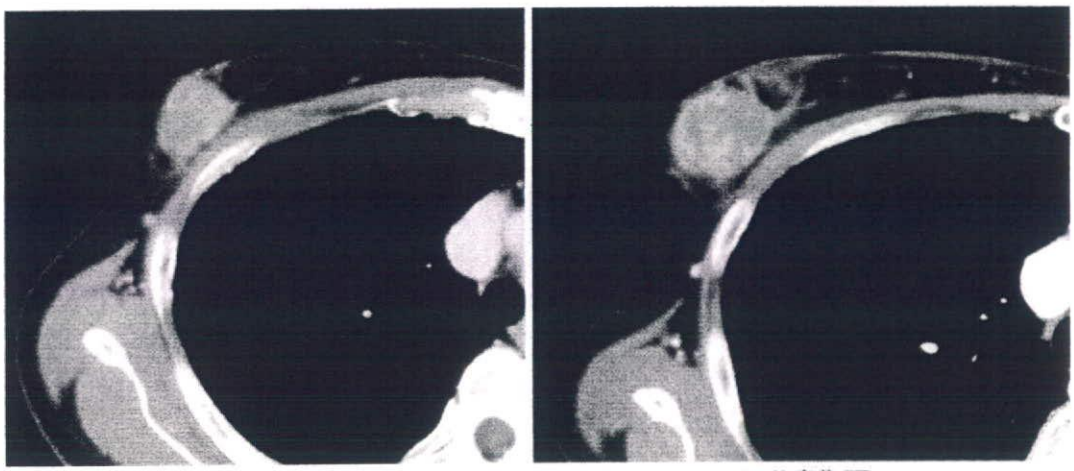
sq：squamous cell carcinoma. MPC：matrix producing carcinoma. so：solid tubular carcinoma
sc：scirrhous carcinoma. sp：adenocarcinoma with spindle cell metaplasia. IDC：invasive ductal carcinoma. mix：mixed epitherial metaplastic carcinoma.
G：grade.
n：pathologically lymph node metastases

つづいて免疫病理学的検査結果を**表2**に示す．腫瘍の組織型は術後病理結果にて8例中5例（63％）でmetaplastic carcinomaの診断だった．しかし，そのうち2例は治療前CNBによる診断では浸潤性乳管癌であった．免疫組織学的検査結果ではホルモンレセプターはいずれも陰性でありHER2の発現は1例で2＋の結果であったもののFISH法にて陰性と判定されており，こちらも全例陰性の結果であった．つまり，8例ともtriple negativeであった．加えてp53は免疫染色にていずれも強陽性であり，組織学的悪性度はいずれもgrade 3（高悪性度）であった．リンパ節転移は8例中3例において7個以上（7～21個）の多数個認めたのに対してその他5例では3個以下（0～3個）と比較的転移個数は少なかった．

乳腺超音波またはCTによる画像検査結果を**表3**に示す．比較的リンパ節転移が多く組織型が硬癌の診断であった1例を除いていずれも比較的限局



a：治療前US　b：治療後US



c：治療前CT　d：治療後CT

図1　画像所見

症例5　57歳女性　AC 4コースでclinical CR後，paclitaxel 3週にて再増大組織型はSquamous cell and spindle cell metaplasia. USおよびCTにて限局性，境界明瞭および内部不均一な腫瘤を認める．

性，境界明瞭で内部は不均一なものであった（図1）．

3. 考　察

近年抗がん剤治療の進歩および乳がん手術の縮小化に伴い，Primary systemic therapy (PST) は広く行われるようになった．当院においても，現在PST適応症例として治療前腫瘍径3 cm以上または治療前に明らかに腋窩リンパ節転移が疑われる症例としている．この理由は，腫瘍径3 cmにおいては乳房温存療法のガイドラインにおける温存療法の適応が腫瘍径3 cm以内である[2]ため，PSTを行って温存療法を可能にするためである．また，明らかに腋窩リンパ節転移陽性の症例については現在術後補助療法の指標とされているSt. Gallenのリスク分類[3]に従えば，術後必ず抗がん剤治療が行われることとなるために，PSTとして先に抗がん剤投与を行っても良いと考えられるためである．予後に関しては，基本的に同じ抗がん剤を手術前に行っても手術後に行っても腫瘍が完全消失するpCR症例以外予後は変わらないことが報告されている[4,5]．しかし，リンパ節転移に関しては近年PST後のリンパ節転移の個数がその後の予後を左右することが報告されており[6]，こういった面からも治療前にリンパ節転移陽性の症例がPSTにより転移個数が減少または消失した場合は良好な予後を得られる可能性があり，PSTの適応とされている．しかし，こういった適応を決める際に，腫瘍に対してPSTが予想しているような効果を挙げるかどうかは判定しておらず，PSTに

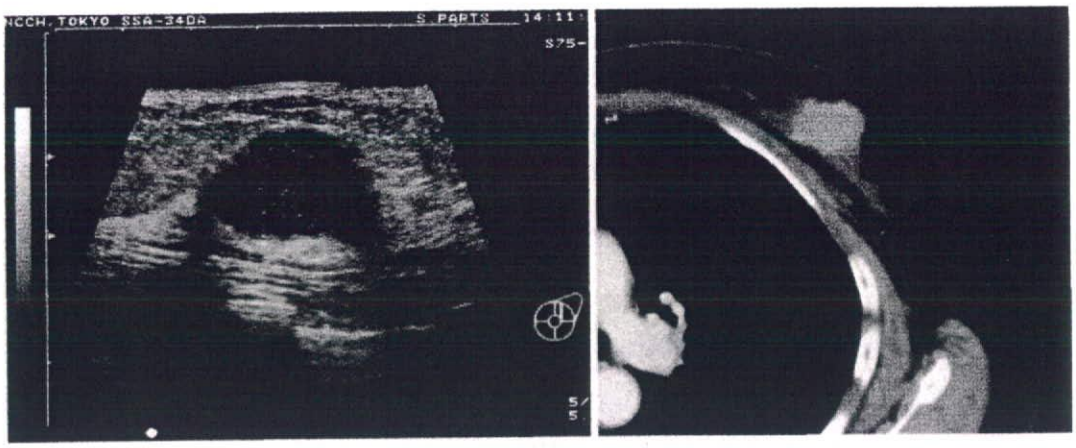


図2　pCR症例の画像所見

症例57歳女性．組織型は充実腺管癌．治療前CNBによる免疫組織学的検査結果はTriple negativeおよび組織学的悪性度grage 3
ACTによるPST効果はpCR（腫瘍の完全消失）．治療前画像所見では限局性，境界明瞭な腫瘤を認めた．

対する感受性は投与後に判定するのが現状である．

PSTの効果予測についてはさまざまな報告がある[7~10]が，いずれも決定的なものではなく，臨床に応用されているものは少ない．なかでもとくに有用とされ，コンセンサスを得られ始めているのは，PSTに非常に感受性があるとされるpCR症例の予測因子としてのホルモン陰性および組織学的高悪性度である．画像所見では，比較的限局性のものがびまん性に広がるものと比べて縮小効果が高いとされている[11,12]．ただし，これらの特徴のみでは適応を決めるまでにはいたっていない．

今回われわれは，当院において経験したPST症例のうち明らかにPSTに対して抵抗性で腫瘍の増大を認めた8例に絞って検討を行った．組織学的にはmetaplastic carcinoma症例が多かった．これまでにも，metaplastic carcinomaが治療抵抗性であり予後が悪いことは当院からも報告している[13,14]．しかし，今回の症例においても示されているとおり，CNB検体にて組織診断が必ず可能かどうかは不明である．これにはCNBの精度も関係するが，腫瘍内部の細胞が均一ではないことが考えられ，PSTによりPSTの効果のある腫瘍細胞は死滅するが，抵抗性の腫瘍は増大し最終的に残存する可能性も考えられるためである．とくに，これらの症例においてはこれまでの報告によりEGFRの発現や筋上皮への分化が示されているものもあり[15]，こういった症例を治療前に判定する上で新たな因子を検討する必要があると考える．

免疫学検査結果では全例ホルモンレセプター陰性およびHER2陰性であるいわゆるTriple negativeの症例であった．さらに組織学的悪性度も全例grade 3であった．さらに画像検査所見では，限局性，境界明瞭なものがほとんどであった．これらの因子は，上記のこれまでの報告や実臨床においてにおいても比較的PSTが良く効くと考えられている特徴とほぼ同一である（**図2**）．

Triple negativeに関しては抗がん剤に対する感受性が特殊であることから近年注目を集めている．それは，今回提示した症例のように抗がん剤に対して非常に抵抗性であるものと，逆に抗がん剤に対して著効を示すものがあるためである．当院における術前化学療法403例の検討においても，Triple negative症例のpCR達成率は15%であり，それ以外の症例の7%に比べて非常に高かった．Triple negative症例の中で今回提示したような症例が，Basal like typeといわれる治療抵抗性の症例分類と同一かどうかは今回の検討では明らかではないが，現在日常的に行われている組織学的検査およびホルモンレセプターとHER2といった免疫学的検査だけではPSTの適応を決定することは非常に困難であり，これらとは別の因子の検討が必要と考えた．

今回PSTの適応を検討するため，とくにPSTに抵抗性である症例を除外することが可能かどうか検討した．結果いくつかの因子の中で，とくに有用な因子としてMetaplastic carcinomaの組織型が明らかとなった．しかし，治療前に確実にこの組織型を判定することは困難と考えられ，今後更なる症例の集積と新たな因子の検討が必要と考えた．

結　語

PSTに対してPDであった症例は，metaplastic carcinomaの組織型を持つものが多く，免疫染色でtriple negativeおよび画像所見では限局性，境界明瞭で内部不均一といった特徴があった．こういった症例はPSTの適応外と考えられたが，これらの特徴はPSTに非常に感受性のある症例と類似しており，治療前に全て診断するためには更なる検討および新しい予測因子が必要と考えた．

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CLINICAL INVESTIGATION **Lung**

CHANGES IN PATTERNS OF CARE FOR LIMITED-STAGE SMALL-CELL LUNG CANCER: RESULTS OF THE 99-01 PATTERNS OF CARE STUDY—A NATIONWIDE SURVEY IN JAPAN

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Background: This study was undertaken to analyze the practice process of thoracic radiotherapy (TRT) and evaluate changes in patterns of care for patients with limited-stage small-cell lung cancer (LS-SCLC) in Japan.
Methods and Materials: The Patterns of Care Study (PCS) conducted the second nationwide survey of care process for patients with LS-SCLC treated by using TRT between 1999 and 2001.
Results: The PCS collected data for 139 patients with LS-SCLC (man-woman ratio, 5:1; median age, 69 years; age > 70 years, 43%; Karnofsky Performance Status > 70, 73%; and Stage III, 88%). Median total dose was 50 Gy. Twice-daily TRT was used in 44% of patients. Median field size was 12 × 14 cm. The most commonly used photon energy was 10 MV (77%), whereas obsolete techniques using ^{60}Co or X-ray energy less than 6 MV comprised 12%. Three-dimensional conformal therapy was used with 12% of patients. Computed tomography simulation was performed in 40% of cases. Only 12 patients (8.6%) received prophylactic cranial irradiation (PCI). Concurrent chemotherapy and TRT (CCRT) was used for 94 patients (68%). Only 6 patients (4.4%) entered clinical trials. Compared with the previous PCS 95-97, significant increases in the use of CCRT (34–68%; $p < 0.0001$), twice-daily TRT (15–44%; $p < 0.0001$), and PCI (1.7–8.6%; $p = 0.0045$) were observed, although the absolute number of patients receiving PCI was still extremely low.
Conclusions: Evidence-based CCRT and twice-daily TRT has penetrated into clinical practice. However, PCI is not yet widely accepted in Japan. © **2008 Elsevier Inc.**

Patterns of Care Study, Small-cell lung cancer, Thoracic radiation therapy, Nationwide survey, Practice process.

INTRODUCTION

The Patterns of Care Study (PCS) is a retrospective study designed to investigate the national practice processes for selected malignancies during a specific period (1). In addition to documenting practice processes, the PCS is important in developing and spreading national guidelines for cancer treatment. In Sept 1998, the Japanese PCS conducted the first nationwide survey for patients with lung cancer treated using thoracic radiotherapy (TRT) between 1995 and 1997 (PCS 95-97). The main findings from the PCS 95-97 are summarized as follows. First, the use of TRT for patients with limited-stage small-cell lung cancer (LS-SCLC) in Japan is predominantly influenced by institutional characteristics, rather than age group. Second, patient age significantly influenced the use of chemotherapeutic modality, such as etoposide and cisplatin for patients with LS-SCLC (2, 3).

Because results of several key clinical studies of patients with LS-SCLC were reported between 1997 and 1999, it seems meaningful to evaluate whether practice processes in Japan were changed accordingly. The second PCS for lung cancer investigated patient characteristics, workup studies, the process of TRT, and use of chemotherapy in patients with LS-SCLC treated by using TRT between 1999 and

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2001. The objectives of the present study are as follows. First, compile processes in TRT for patients with LS-SCLC treated between 1999 and 2001, and second, compare patient characteristics and treatment modalities between the PCS 95-97 and PCS 99-01 in Japan.

METHODS AND MATERIALS

Between July 2002 and August 2004, the PCS conducted a second national survey of radiation therapy for patients with lung cancer in Japan. The Japanese PCS developed an original data format for patients with lung cancer. The PCS performed an extramural audit survey for 73 (38 academic and 35 nonacademic institutions) of 556 institutions by using stratified two-stage cluster sampling and collected data for 768 eligible patients with lung cancer. Data collection consisted of two steps of random sampling. Before random sampling, all institutions were classified into one of four groups. Criteria for stratification were described elsewhere (2, 4). Briefly, the PCS stratified Japanese institutions as follows: A1, such academic institutions as university hospitals or national/regional cancer center hospitals treating 430 or more patients per year; A2, academic institutions treating fewer than 430 patients; B1, nonacademic institutions treating 130 or more patients per year; and B2, those treating fewer than 130 patients per year. Cutoff values for numbers of patients treated per year between A1 and A2 institutions and B1 and B2 institutions were increased from those used in the previous PCS because of the increase in number of patients treated using radiation therapy in Japan (4).

Eligible patients included those with 1997 International Union Against Cancer Stages I–III lung cancer treated by using TRT between 1999 and 2001, with Karnofsky Performance Status (KPS) greater than 50 before the start of treatment and no evidence of other malignancies within 5 years. The International Union Against Cancer staging system was used because the PCS comprehensively surveyed patients with non-SCLC and those with SCLC. As mentioned, Stages I–III SCLC do not precisely match the definition of LS-SCLC by Mountain (5). However, no definition of this term has been universally accepted. The PCS survey of TRT charts showed that for patients with SCLC, the tumor could be encompassed within the TRT field. Thus, in the present study, all patients were regarded as having LS-SCLC.

The aims of this study are to provide patterns of practice concerning: (*1*) patient background; (*2*) workup studies; (*3*) TRT, including photon energies, total dose, spinal cord dose, field arrangements, prescription point, and use of prophylactic cranial irradiation (PCI); and (*4*) chemotherapy, including agents, number of chemotherapy cycles, sequence of chemotherapy, and TRT. Patient background included demographics and medical status, such as KPS, comorbidities, stage, and whether treated on an outpatient basis. In addition, practice patterns of the PCS 99-01 were compared with those of the PCS 95-97.

To validate the quality of collected data, the PCS used the Internet mailing list among all the surveyors. *In situ* real-time check and adjustment of the data input were available between each surveyor and the PCS committee. In tables, "missing" indicates that the item in the data format was left empty, whereas "unknown" means that the item in the format was completed with data unknown. We combined missing and unknown in tables because their meanings were the same in most cases; no valid data were obtained in the given resources. Cases with unknown values were included when both percentage and significance values were calculated. Statistical significance was tested by using chi-square test. A $p < 0.05$ was considered statistically significant. Overall survival, assessed from the first day of radiation therapy, was estimated by using the Kaplan-Meier product-limit method, and differences were evaluated using log-rank test.

RESULTS

Patient backgrounds

There were 141 patients with SCLC, which constituted 18% of all patients with lung cancer surveyed. Of those, 2 patients underwent initial surgical resection and adjuvant postoperative irradiation. Thus, in the present study, the PCS analyzed the remaining 139 patients who did not undergo surgery (Table 1).

There were 116 men and 23 women with an age range of 36–85 years (median, 69 years). Patients older than 70 years constituted 43% of the patient population. For that elderly patient pool, the institutional breakdown was as follows: 31% in A1, 39% in A2, 50% in B1, and 50% in B2 ($p = 0.037$). For comorbidities, the most frequent adverse medical conditions were cardiovascular disease (34%) and diabetes (14%). Seventy-three percent had KPS of 80% or greater. Comparison of four institutional groups failed to show differences in terms of patient background other than patient age and KPS. Patients with KPS of 80 or greater comprised 89% of A1, 55% of A2, 74% of B1, and 65% of B2 strata ($p = 0.0071$). A majority of patients (88%) had Stage III disease. There were no significant differences in distributions of T and N classifications or clinical stages between institutional groups. Only 5% of all patients were treated on an outpatient basis.

Workup studies

Workup studies are listed in Table 2. Pretreatment workup included chest computed tomography (CT) in 96%, bronchoscopy in 93%, brain CT or magnetic resonance imaging in 86%, and bone scan in 79% of surveyed patients. Chest/abdominal CT and bone scan were used for a majority of patients, whereas positron emission tomography (PET) was used for an extremely small number of patients. Comparison of four institutional groups failed to show differences in terms of workup studies.

Practice process of TRT

Thoracic radiotherapy methods are listed in Table 3. Median total dose of TRT was 50 Gy, and median field size was 12 × 14 cm. Median dose to the spinal cord was 42 Gy. A CT simulator was used for planning in 40% of patients. Three-dimensional conformal therapy was used in 12%. The planning target volume included the ipsilateral hilus in 96%, ipsilateral mediastinum in 96%, contralateral mediastinum in 84%, contralateral hilus in 17%, ipsilateral supraclavicular region in 25%, and contralateral supraclavicular region in 15%. Field reduction during the course of TRT was done for 61%. Twice-daily radiotherapy was used for 44%. Photon energy generally was 10 MV (77%), whereas obsolete techniques using ^{60}Co or X-ray energy less than 6 MV were used for 12%. Only 12 patients (8.6%) received PCI. Median dose of PCI was 25 Gy. Only 6 patients (4.4%) entered clinical trials.

Table 1. Patient and tumor characteristics

Characteristics	Stratification of institutions					*p*-value
	A1	A2	B1	B2	Total	
No. of patients	36	23	54	26	139	
Age (y)						0.037
Range	44–85	36–81	40–81	54–85	36–85	
Median	69	68	71	71	69	
>70 (%)	31	39	50	50	43	
Sex						0.780
Men	30	18	47	21	116	
Women	6	5	7	5	23	
Karnofsky performance status						0.013
≥80 (%)	89	55	74	65	73	
Clinical stage/UICC 1997						0.475
I	0	1	2	2	5	
IIA, IIB	3	3	4	1	11	
IIIA	10	6	19	10	45	
IIIB	23	13	28	13	77	
Unknown/missing	0	0	1	0	1	
T classification						0.569
T1–2	14	11	25	14	64	
T3–4	22	12	28	12	74	
Unknown/missing	0	0	1	0	1	
N classification						0.551
N0–1	7	4	9	6	26	
N2–3	29	19	44	20	112	
Unknown/missing	0	0	1	0	1	

Abbreviation: UICC = International Union Against Cancer.

Institutional stratification influenced several radiotherapeutic parameters (Table 4). Photon energy of 6 MV or greater was used for 97% of patients in A1, 96% in A2, 87% in B1, and 69% in B2 institutions ($p = 0.0006$). The ^{60}Co machines were not used in any A1 to B1 institutions. Twice-daily radiotherapy was used for 57 of 113 patients in A1 to B1 institutions, but only 4 of 26 patients in B2 institutions were treated in that manner ($p = 0.0012$). The PCI was used for 7 of 36 patients (19%) in A1 institutions, but only 5 patients (4.9%) in the remaining institutions ($p = 0.0073$). Use of a CT simulator was more frequent in A1 (52%) and A2 (65%) compared with B1 (34%) and B2 (17%) institutions ($p = 0.011$).

One hundred twenty-nine patients (93%) received systemic chemotherapy. Of those, platinum-based chemotherapy constituted 98%. Concurrent chemotherapy and TRT (CCRT) was used for 68% (73% of patients who received systemic chemotherapy). Median number of chemotherapy cycles was four. Median times from the first day of systemic chemotherapy to the first date and last date of TRT were 3 and 44 days, respectively. Proportions of patients who received chemotherapy were 97% in A1, 96% in A2, 91% in B1, and 89% in B2 institutions ($p = 0.49$).

Comparison between two PCS studies

Patient backgrounds and practice patterns in PCS 99-01 were compared with those in PCS 95-97. Differences between the two studies are listed in Table 5. Based on two-stage cluster sampling, the ratios of academic to nonacademic institutions were almost equal in the two surveys. Although median age in PCS 99-01 was slightly older than that in PCS 95-97, patients' backgrounds were similar in the studies. Use of obsolete treatment equipment (photon energy < 6 MV and ^{60}Co) decreased from 20% in PCS 95-97 to 12% in PCS 99-01 ($p = 0.06$). The greatest differences were seen in the use of twice-daily TRT and CCRT. Twice-daily TRT increased from 15% in PCS 95-97 to 44% in PCS 99-01 ($p < 0.0001$). Use of CCRT in PCS 99-01 was twice as high as in PCS 95-97 (68% vs. 34%; $p < 0.0001$). Although a significant increase in the use of PCI was observed (1.7–8.6%; p = 0.0045), the rate was still extremely low in Japanese practice.

Table 2. Percentage of patients examined by using each diagnostic technique in the course of staging

Chest CT	96%
Chest MRI	7%
Bronchoscope	93%
Bone scan	79%
Abdominal CT	88%
Positron emission tomography	2%
Brain CT or MRI	86%

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging.

Table 3. Process of thoracic radiation therapy for patients with limited-stage small-cell lung cancer

Median total dose (Gy)	50
Median spinal cord dose (Gy)	42
Use of CT simulator (%)	40
Three-dimensional conformal therapy (%)	12
Beam energy (%)	
^{60}Co	1.4
<6 MV	10.8
≥6 MV	88
Median field size (cm)	12 × 14
Field reduction during treatment (%)	61
IRB-approved protocol treatment (%)	4.4
Twice-daily radiotherapy (%)	44
Prophylactic cranial irradiation (%)	8.6
Area included in planning target volume (%)	
Ipsilateral hilus	96
Ipsilateral mediastinum	96
Contralateral mediastinum	84
Contralateral hilus	17
Ipsilateral supraclavicula	25
Contralateral supraclavicula	15
Systemic chemotherapy (%)	93
Concurrent chemotherapy and thoracic radiotherapy (%)	68

Abbreviations: CT = computed tomography; IRB = institutional review board.

Comparison of preliminary outcomes between studies

There are known limitations in survival analyses in this type of retrospective survey study. Still, preliminary outcome data in the two studies could be compared. Overall survival rates of the entire patient pool in each study are shown in Fig. 1. Two-year survival rates in PCS 95-97 and PCS 99-01 were 34% and 45%, with a median follow-up of only 11 months in both studies, respectively. Median survival times of the patient pools in PCS 95-97 and PCS 99-01 were 14 and 17 months, respectively. These differences did not reach a statistically significant level.

Table 4. Process of thoracic radiation therapy influenced by institutional stratification

	Stratification of institutions					
Characteristics	A1	A2	B1	B2	Total	*p*-value
Photon energy						0.0006
^{60}Co	0	0	0	2	2	
<6 MV	1	1	7	6	15	
≥6 MV	35	22	47	18	122	
Twice-daily fractionation used						0.0012
Yes	18	11	28	4	61	
No	18	12	26	22	78	
Treatment planning						0.011
Use of CT simulator (%)	52	65	34	17	40	
Prophylactic cranial irradiation used						0.0002*
Yes	7	2	3	0	12	
No	29	17	48	24	118	
Unknown/missing	0	4	3	2	9	

Abbreviation: CT = computed tomography.
* A1 vs. A2–B2; $p = 0.0073$.

Table 5. Comparison of treatment modalities between two studies

Background and treatment process	PCS 95-97 ($n = 174$)	PCS 99-01 ($n = 139$)
SCLC/all lung cancer (%)	16	18
Median age (y)	65	69
KPS > 70 (%)	70	73
Stage III (%)	87	88
Median total dose (Gy)	50	50
Photon energy <6 MV or ^{60}Co (%)	20	12
Use of CT-simulator (%)	NA	40
Twice-daily thoracic radiotherapy (%)*	15	44
Chemotherapy used (%)	92	93
Concurrent chemoradiation (%)†	34	68
Prophylactic cranial irradiation (%)‡	1.9	8.6
Survival at 2-years (%)	34	45

Abbreviations: PCS = Patterns of Care Study; SCLC = small-cell lung cancer; KPS = Karnofsky Performance Status; CT = computed tomography; NA = not available.
* $p < 0.0001$ by chi-square test.
† $p < 0.0001$ by chi-square test.
‡ $p = 0.0045$ by chi-square test.

DISCUSSION

Results of the present PCS reflect national treatment trends for TRT for patients with LS-SCLC in Japan between 1999 and 2001. Through this second nationwide audit survey and data analysis, PCS established the general patterns of care for patients with LS-SCLC in Japan. Results also show the influence of the structure of radiation oncology on the process of TRT and how state-of-the-art cancer care supported by clinical trial results has penetrated into the national practice process during the study period.

During the study period, TRT for LS-SCLC constituted less than one fifth of all radiation therapy for patients with lung cancer. This result was similar to data from the United States (6). Use of such staging studies as chest CT, bone scan, and PET scan for patients with SCLC was in line with guidelines (7) and very similar to the report from the United States (6). A PET scan in clinical use was still scarce. Only a small fraction of patients participated in clinical trials similar to those observed in the United States. In Japan, twice-daily TRT was used more frequently and PCI was used less frequently compared with the United States. However, it should be noted that subjects of the PCS in the United States were treated between 1998 and 1999, preceding the results of key studies that supported the use of twice-daily radiation therapy and PCI.

The study shows that more suitable photon energies were used in TRT at academic institutions. Thirty-one percent of patients in B2 institutions were treated with a linear accelerator with less than 6 MV or a ^{60}Co machine that did not meet the standard of care for equipment to treat patients with lung

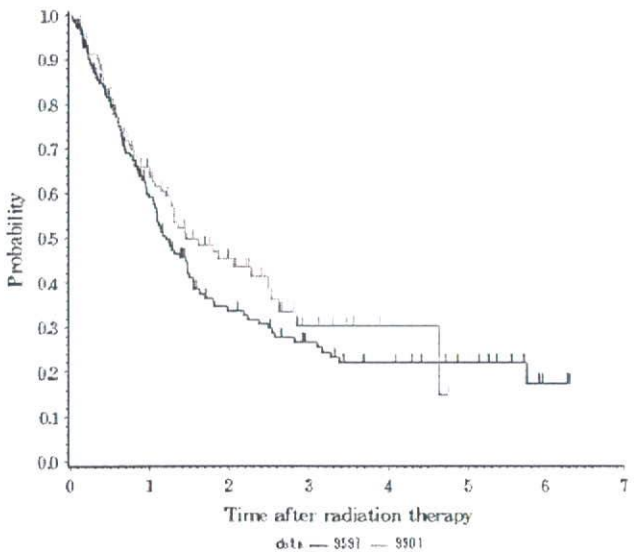

Fig. 1. Kaplan-Meier estimate of overall survival of patients with Stages I–III small-cell lung cancer surveyed in the 1995–1997 (dark line) and 1999–2001 (bright line) Patterns of Care Studies in Japan.

cancer, although this rate decreased from PCS 95-97 (>40% in B2) and was somewhat favorable compared with postoperative radiation therapy for patients with lung cancer in the same period (8). The availability of CT simulators was greater than 50% in academic institutions, but only one third in B1 and even lower in B2 institutions. In modern radiation therapy, CT-based treatment planning is essential for TRT to achieve optimal target coverage while reducing the dose to normal tissue. Twice-daily TRT was used more frequently for patients in A1 to B1 institutions than patients in B2 institutions. The PCI was used for 19% of patients in A1 institutions, but only 4.9% of patients in the remaining institutions. Although the general quality of radiation oncology improved from PCS 95-97, results of the present study show that institutional stratification still influences the structure and process of radiotherapy, such as availability of CT simulators, the flexibility of external beam energy selection, and use of evidence-based cancer care in Japan.

During the past 20 years, survival prolongation in patients with LS-SCLC was attained mainly by clinical trials that studied some aspect of radiation therapy, such as integration of TRT (9, 10), optimization of timing and fractionation of TRT (11), and introduction of PCI (12). The TRT is an essential component of the standard management of patients with LS-SCLC. Two meta-analyses showing the advantage of the addition of TRT to systemic chemotherapy, published in 1992 (9, 10), preceded our first national survey (PCS 95-97). In PCS 99-01, although 43% of all surveyed patients were older than 70 years and 23% of all patients had KPS of 70% or less, 93% of all patients received chemotherapy. This percentage is very similar to that in PCS 95-97 (2, 3).

When interpreting our data, it is important to note that they are limited to patients who received TRT as part of their overall treatment regimen. However, these two surveys showed that use of systemic chemotherapy was reasonably high in Japanese practice. Based on several studies published during the past 10 years, CCRT up front has emerged as a standard of care generating the highest survival rates (11, 13, 14). A landmark study supporting twice-daily TRT was published in 1999 after the previous PCS 95-97 (11). In that study, Turrisi *et al.* (11) showed a significant benefit in 5-year survival rate with the use of twice-daily TRT (45 Gy in 1.5 Gy fractions twice daily) concurrent with chemotherapy compared with once-daily TRT (45 Gy in 1.8 Gy fractions every day). Use of CCRT in PCS 99-01 (68%) was twice as high as in PCS 95-97 (34%). Similarly, there was a notable increase in the use of twice-daily TRT after PCS 95-97. In the present study, 44% of patients received twice-daily TRT, nearly three times as high as in PCS 95-97. Although it is still unclear whether twice-daily TRT to 45 Gy in 3 weeks is superior to a higher total dose of 60–70 Gy delivered by using more standard fractionation, it seems that diffusion of twice-daily TRT to Japanese practitioners was rapid. It seems likely that the marked increase in use of twice-daily TRT with concurrent chemotherapy in Japan contributed to the widespread use (95%) of inpatient treatment in PCS 99-01. In general, once-daily treatment is better accepted for outpatient care, whereas twice-daily scheduling is convenient for the care of inpatients, but at greater cost. Marked increases in the use of CCRT and twice-daily TRT indicates greater acceptance of these treatment modalities by radiation oncologists across Japan.

However, PCI has yet to be systematically adopted in Japanese practice. Despite the 1999 publication of another landmark trial that showed the survival advantage of PCI for complete responders (12), only 8.6% of all patients received this intervention. At the time of PCS 95-97, the role of PCI had not been established and it was used for only 1.9% of all patients (2). Before the present survey, it was expected that the percentage of patients who received PCI would be greater on the basis of the meta-analysis. Although a slight increase in use of PCI was observed, the rate was still extremely low in Japan. Information about the number of complete responders was outside the audit. However, a complete response rate of at least 50% is expected for study subjects (15). Whether this is caused by the small number of radiation oncologists in Japan or the small number of patients who received radiation therapy for cancer treatment is unknown. We reported previously that the number of full-time radiation oncologists is low, especially in nonacademic institutions in Japan (2). According to cancer statistics in Japan, radiation therapy was used for only 11.3% of all patients with cancer in 1999 compared with medical (27.5%) and surgical treatment (69.9%) (16). It is not clear why evidence-based PCI has not yet been widely accepted in Japan as opposed to the rapid diffusion of CCRT and twice-daily TRT in clinical practice. It appears that physicians in Japan hesitate to use PCI, and their patients are reluctant to receive PCI even if it is beneficial. Results of the ongoing third national survey in Japan will be particularly interesting in this regard.

Nonsignificant survival improvement in patient outcome was observed between PCS 95-97 and PCS 99-01. The current PCS has limitations in terms of outcome analysis because of a short follow-up period, significant variations in follow-up information according to institutional stratification (4, 17), and difficulties in outcome survey. One of the ultimate goals of the PCS is to determine how structure and processes of radiation therapy affect patient outcomes, including local control, survival, and quality of life. However, since 2006, personal information is strictly protected by law and outcome surveys are difficult to perform in Japan, even for patients with cancer. Cancer is not yet a reportable disease in Japan. Currently, limitations in data accumulation concerning patient outcomes in this type of survey encouraged us to develop new health care data collection systems and linkages among systems that make systematic recording and analysis of structure/process and outcome data part of routine quality monitoring (Japanese National Cancer Database, funded by the Ministry of Health, Labor, and Welfare Japan).

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