Immunohistochemical studies were performed using the antigen retrieval method on the avidin–biotin–peroxidase method or Ventana automated (BenchMark™) stainer according to the manufacturer's instructions.

The panel of antibodies included human immunoglobulin light chains (kappa and lambda) (Dako A/S, Glostrup, Denmark), IgG (Novocastra, Newcastle, UK), IgA (Novocastra), IgM (Novocastra), MCO011 (IgG4;Binding Site, Birmingham, UK), PS-1 (CD3; Immunotech, Marseille, France), 4C7 (CD5; Novocastra), L26 (CD20; Dako), a cocktail of 2G9 (CD21; Novocastra) and RB L25 (CD35; Novocastra), 1B12 (CD 23; Novocastra), DFT-1 (CD43; Dako), 1B16 (CD56; Novocastra), PGM-1(CD68; Dako), 5A4 (CD246 [anaplastic lymphoma kinase, ALK]; Novocastra), SP4 (Cyclin D1; Nichirei Co., Tokyo, Japan), AE1/3 (Dako), V9 (vimentin; Dako), D33 (desmin; Dako), HHF35 (muscle-specific actin; Nichirei Co.), S-100 (Dako), and 137B1 (human herpes virus type-8, Novocastra). Sections with known reactivity for antibodies assayed served as positive controls, and sections treated with normal rabbit- and mouse serum served as negative controls.

In situ hybridization (ISH) with Epstein-Barr virus (EBV)-encoded small RNA (EBER) oligonucleotides was performed to test for the presence of EBV small RNA in formalin-fixed, paraffin-embedded sections using a Ventana automated (BenchMark™) stainer.

DNA was extracted from the paraffin-embedded section. The variable region (CDR2 and FW3) and VDJ region (CDR3) of the immunoglobulin heavy chain (IgH) gene were amplified by semi-nested PCR, using primers of FR2B, LJH, and VLJH, according to a previously described method [14]. Primers were as follows: 5′-CCGG(A/G)AA(A/G)(A/G) GTCTGGAGTGG-3′, as up-stream consensus V region primer (FR2B); 5′-TGAGGAGACGGTGACC-3′, as a consensus J region primer (LJH); 5′-GTGACCAGGGT [A/C/G/T] CCTTGGCCCCAG-3′, as a consensus J region primer (VLJH). PCR products were estimated to be about 200–300 bps in length.

The API2-MALT1 fusion transcript was examined using formalin-fixed and paraffin-embedded tissue according to the method recently described by us [11].

Results

Clinical findings

The clinical histories of PCG are summarized in Table 1. Only one (no.1) of three cases showed bloody sputum. The remaining two cases (nos. 2 and 3) were asymptomatic but had shown abnormal shadows on chest radiograph during a medical check-up. Chest radiographs and computed tomography demonstrated a solitary nodule in the peripheral pulmonary field in two cases (nos. 1 and 3) and four nodules on the peripheral pulmonary field of the bilateral lobes in the remaining one case (no. 2). One patient (no. 3) had a history of rectal cancer before the episode of PCG. Two cases (nos. 2 and 3) showed mediastinal lymphadenopathy. There was no other evidence of disease in any of the three cases.

Elevated serum IgG level had been recorded in one (no. 2) of the three cases. Antinuclear antibody was detected in Case 2. Serum IgG4 level was within the normal range in of two cases (nos. 1 and 3) examined.

Clinically, two cases (nos. 1 and 2) were suspected of having primary lung cancer and Case 3 was suspected of having metastatic rectal cancer. Two cases (nos. 2 and 3) showed hilar lymphadenopathy. However, lymph node biopsies were not performed.

Pathological findings

Macroscopically, two lesions (nos. 1 and 3) were solitary tan and firm and were relatively well circumscribed without fibrosis (Fig. 1a). The remaining case comprised four nodules in the bilateral lungs.

Histologically, the lesions were characterized by a relatively well-demarcated mass composed of a few lymphoid follicles and chronic inflammatory process intermixed with irregular fibrosis (Fig. 1b). The lesions demonstrated severe infiltration of mature plasma cells, plasmacytoid cells, and small lymphocytes (Fig. 1c). Scattered Russell bodies (intracytoplasmic inclusions) and a few immature plasma cells, large transformed lymphocytes, including immunoblasts and histiocytes, were present in all three cases (Fig. 1c), but there were no Dutcher bodies (intranuclear inclusions), centrocyte-like (CCL) cells, or amyloid deposition. There was no remarkable eosinophilic infiltration in any of the three lesions. Three lesions contained scattered multinucleated giant cells. At the boundaries of the nodules, the inflammatory process extended into the adjacent parenchyma, showing fibrous endings of the alveolar septa with lymphoplasmacytic infiltration (interstitial pneumonia pattern) in all three cases (Fig. 1b). EVG staining demonstrated prominent obliterative phlebitis and arteritis in one case (no. 3) (Fig. 1d). However, there was no necrotic area in Case 3.

Staining for CD20, CD3, and CD5 showed the mixed nature of the small lymphocytes. The majority of large transformed lymphocytes, including immunoblasts, expressed B-cell antigen. Immunohistochemical studies of light chain determinants for plasma cells, plasmacytoid cells, and B-immunoblasts have demonstrated a polyclonal pattern (Figs. 1e and f). There were numerous IgG-positive plasma cells with scattered IgA- or IgM-positive plasma cells. However, IgG4-positive cells comprised only 5–10% of the IgG-positive plasma cells. There were no $CD20^+$, $CD5^+$, $CD43^+$, or cyclin $D1^+$ medium-sized lymphocytes in any of the three lesions. Staining with monoclonal antibody, a cocktail of CD21 and CD35 and CD23 highlighted the meshwork of follicular dendritic cells (FDCs). The FDC networks usually showed a normal/reactive pattern. There were no lymphoepithelial lesions

Table 1
Summary of clinical findings.

	Age/ gender	Symptom	Location (number)	Size (cm)	Hilar LA	Autoantibody	IgG4 (mg/ dl)	Treatment	Outcome
1	58/M	Bloody sputum	Right lower lobe, peripheral (1)	4	–	NE	18.1	Video-associated thoracoscopic surgery	4 m alive (–)
2	68/M	–	Bilateral lobe, peripheral (4)	7	+	ANA	NE	Video-associated thoracoscopic surgery	56m alive (+)
3	72/M	–	Left lower lobe (1)	2.5	+	NE	52	Partial lobectomy	4 m alive (–)

Abbreviations: LA, lymphadenopathy; NE, not examined; ANA, antinuclear antibody; m, months;(—), without disease; (+), with disease.
Normal range of IgG4 < 135 mg/dl (Ref [16]).

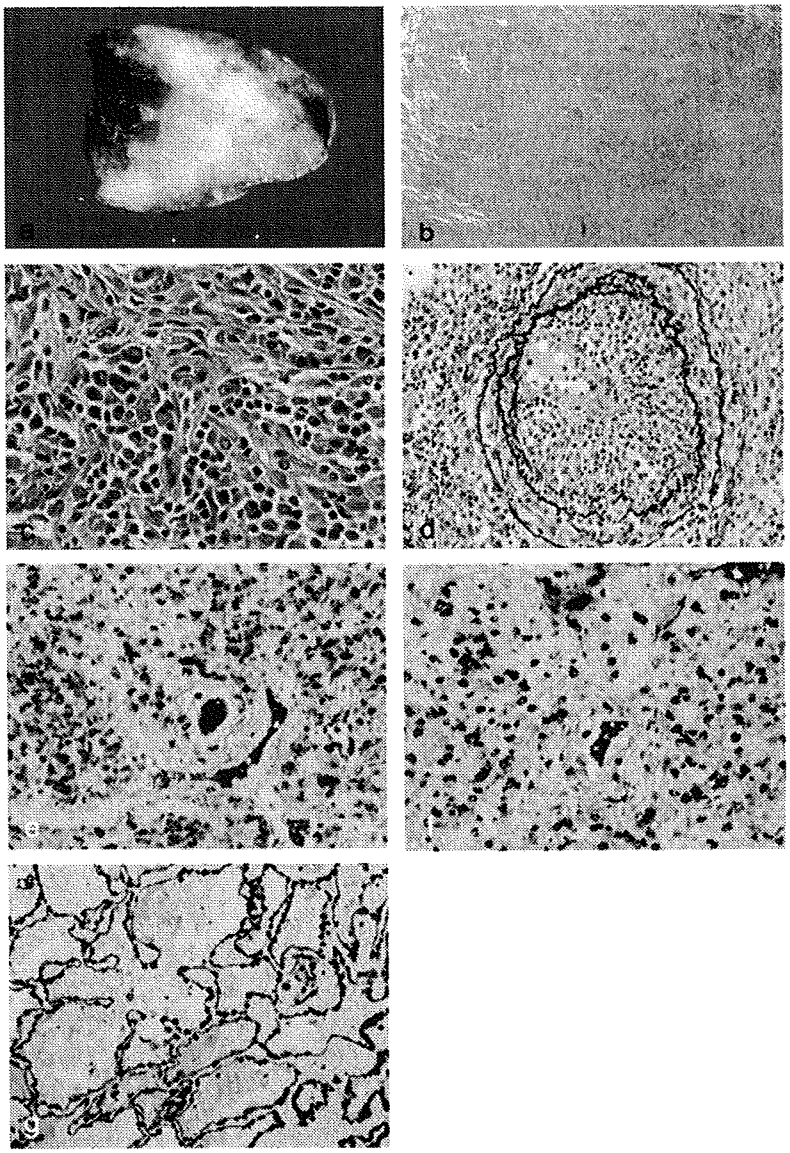

Fig. 1. (a) Cut surface of the resected specimen demonstrated a solitary tan and firm mass that was relatively well circumscribed without fibrosis. Case 3. (b) Low-power field of the lesion. The lesion was a relatively well-demarcated mass composed of a few reactive germinal centers with well-preserved mantle zones and a chronic inflammatory process intermixed with irregular fibrosis. At the boundaries of the nodules, the lesion showed an interstitial pneumonia pattern. Case 3. HE × 10. (c) High-power field of Fig. 1b. The lesion demonstrated severe infiltration of mature plasma cells, plasmacytoid cells, and small lymphocytes. Scattered Russell bodies (intracytoplasmic inclusions) and a few immature plasma cells, large transformed lymphocytes, and histiocytes were present in all three cases. Case 3. HE × 100. (d) EVG staining demonstrated obliterative arteritis. Case 3. × 50. Immunostaining for light chain determinant of the immunoglobulin demonstrated the polytypic nature of mature plasma cells. (e) Kappa and (f) Lambda Case 3. × 50. (g) There were no lymphoepithelial lesions on immunostaining of cytokeratin. Case 1. × 50

(LELs) detected even by immunostaining for cytokeratin in any of the three lesions (Fig. 1g).

There were no CD68+, vimentin+, desmin+, muscle-specific actin+, ALK+, S-100+ spindle cell proliferation cells in any of the three lesions. Moreover, there were no cocktails of CD21 and CD35+, CD23+, EBER+ FDCs in any of the three lesions.

There were no HHV-8 or EBER-positive cells in any of the three cases.

Genotypic findings

A discrete band of amplified IgH gene was found in one case (no. 3) (Fig. 2), respectively. In the remaining two cases (nos. 1 and 2), only germ line bands were detected.

Discussion

IPTs of the lung appear to comprise a set of heterogeneous disease entities [20] that include true neoplastic proliferation of mesenchymal cells, post viral infection state, and autoimmune disease (IgG4-related sclerosing disease) [8,16,21,22]. Histologically, in the present three cases, plasmacytic infiltration was the most conspicuous histological finding compared to myofibroblastic proliferation or collagenous stroma, and all of the present three lesions were diagnosed as PCG [21].

A portion of pulmonary IPTs demonstrated anaplastic lymphoma kinase (ALK) and ALK expression on immunohistochemistry [1,4–6]. At present, these cases are recognized as neoplasms with intermediate biologic potential, namely "inflammatory myofibroblastic tumor" [21]. Immunohistochemical cytoplasmic positivity

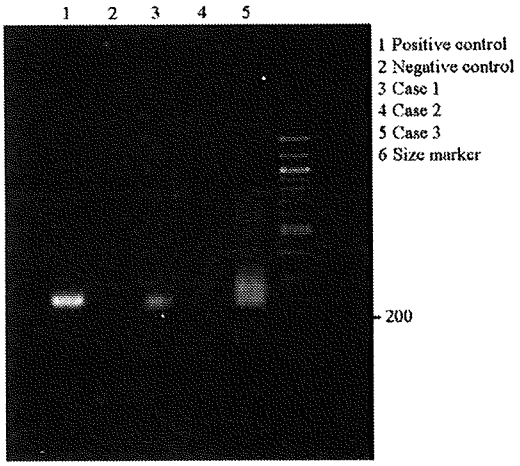

Fig. 2. PCR analysis of three cases for clonal Ig heavy chain rearrangement.

for ALK correlates well with the presence of ALK rearrangements detectable by fluorescent in situ hybridization [4]. However, there were no ALK+ cells in any of the three lesions [21]. Expression of ALK was noted in 40% of the pulmonary inflammatory myofibroblastic tumor [21]. However, there were no CD68+, vimentin+, desmin+, muscle-specific actin+, ALK+, S-100+ spindle cells in any of the three lesions [21]. EBV+ FDC sarcoma appears to be another differential diagnostic problem [3]. However, there were no EBV+ atypical FDCs among the cocktail of CD21 and CD35+ and CD23+FDCs in any of the three lesions [3].

The present three lesions contained numerous IgG+ plasma cells. However, IgG4-positive cells comprised only 5–10% of the IgG-positive plasma cells [16]. Moreover, the serum IgG4-level was within the normal range in two cases examined [16].

Approximately, 70–90% of the primary pulmonary lymphomas are marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type [18]. Various degrees of plasma cell differentiation have been noted in MALT type lymphoma, and plasma cells may occasionally obscure the CCL cells, which are the tumor cells of MALT type lymphoma [18]. Hussong et al. [10] reported five cases of extramedullary plasmacytoma that showed characteristic histological findings of MZBL, including the presence of a marginal zone distribution pattern, CCL cells, reactive lymphoid follicles with or without follicular colonization, and LEL at sites where epithelium was present. Based on these observations, they suggested that a portion of extramedullary plasmacytoma can be regarded as an extreme plasmacytic differentiation of MZBCL [10].

The present three cases should be differentiated from MZBL extreme plasmacytic differentiation. Immunohistochemical studies of light chain determinants demonstrated the polytypic nature of the plasma cells and plasmacytoid cells. There were no CD43+ B-lymphocytes in any of the three lesions [15]. Moreover, there were no LELs detected in any of the three lesions even by immunostaining for cytokeratin. However, PCR assay for IgH gene demonstrated a clonal band in one of the three cases, whereas there was no API2-MALT1 fusion transcript detected in any of the three lesions, although it is detected in approximately 40% of pulmonary MALT type lymphoma [7].

Histologically, vasculitis was observed in numerous arteries and veins in one case (no. 3). Moreover, PCR assay for IgH gene demonstrated a clonal band in Case 3 only. Histological findings of Case 3 were somewhat similar to those of lymphomatoid granulomatosis grade 1 [9,18]. Case 3 should also be differentiated from lymphomatoid granulomatosis grade 1. However, there was no necrotic area in Case 3. Moreover, there were no EBER+ large lymphoid cells in this lesion [9,19].

Recently, Nam-Cha et al. [17] analyzed six florid RFH specimens using immunohistochemistry, IgH-PCR, and microdissected PCR. They found that some germinal centers contained a population of plasma cells and plasmacytoid germinal center cells showing immunoglobulin light chain restriction [17]. In three cases, the monotypic germinal center cells also showed distinct bcl-2 expression [17]. Two cases demonstrated a predominant IgH rearrangement on a florid polyclonal background, and one showed an IgH monoclonal rearrangement on PCR [17]. Nam-Cha et al. [17] reported that only one of the six cases developed follicular lymphoma. As suggested by Nam-Cha et al. in the previous series, it remains unclear whether Case 3, demonstrating IgH gene rearrangement in the present series, could be a sign of prelymphomatous stage (incipient MALT lymphoma) or merely represents an exaggeration of normal B-cell clonal response. However, Case 3 has only undergone a short follow up to date. To clarify this issue, further study is needed.

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●原 著●

腋窩リンパ節転移陰性乳がんに対する術後補助化学療法としてのDocetaxelとCyclophosphamideの忍容性および安全性
—JECBC04試験—

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柳田 康弘[*2] 藤澤 知巳[*2] 藤井 博文[*2] 佐伯 俊昭[*2] 黒住 昌史[*2]

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Tolerability and Safety of Docetaxel Plus Cyclophosphamide as Adjuvant Chemotherapy for Axillary Lymph Node-Negative Breast Cancer—JECBC04 Trial: Naohito Yamamoto[*1,2], Toshio Tabei[*2], Kenichi Inoue[*2], Hiroyuki Takei[*2], Nobuaki Sato[*2], Yasuhiro Yanagita[*2], Tomomi Fujisawa[*2], Hirofumi Fujii[*2], Toshiaki Saeki[*2] and Masafumi Kurosumi[*2] (*[1]*Chiba Cancer Center, Division of Breast Surgery,* *[2]*Japan East Cancer Center Breast Cancer Consortium*)

Summary

A recent foreign clinical trial showed that the combination of docetaxel plus cyclophosphamide (TC) is associated with a superior disease-free survival compared with doxorubicin plus cyclophosphamide as adjuvant chemotherapy for breast cancer. To assess the tolerability and safety of TC in a Japanese patient population, we conducted a multicenter, open-labeled clinical trial. Eligible patients were women who had axillary lymph node-negative breast cancer with surgical excision of the primary tumor. Patients were treated with 4 courses of TC (75 and 600 mg/m^2, respectively), administered intravenously every 3 weeks. The primary endpoint was feasibility, which was defined as the proportion of patients who completed 4 courses of the chemotherapy. From October 2006 to November 2007, 39 patients were enrolled and 32 were evaluable. Seven patients were excluded because of the inadequate treatment schedule. Feasibility was 96.9% (31/32). One patient did not complete treatment because of the hypersensitivity. The mean administered dose was 73.2 mg/m^2 for docetaxel and 588.3 mg/m^2 for cyclophosphamide, respectively. The mean relative dose intensity was 96.1% and 95.7%, respectively. The grade 3/4 toxicity including leukopenia, neutropenia, and febrile neutropenia was manageable. From these results, we consider that TC might become a standard non-anthracycline adjuvant regimen for operable breast cancer. **Key words**: Breast cancer, Docetaxel, Cyclophosphamide, Adjuvant therapy (*Received Apr. 6, 2009/Accepted Jun. 8, 2009*)

要旨 海外の臨床試験成績から，docetaxel＋cyclophosphamide（TC）の4コース投与は乳がんの術後補助化学療法として有効と考えられるが，国内での使用経験は十分ではない。このためTCの忍容性および安全性を評価する目的で多施設共同臨床試験を実施した。対象は原発乳がんの根治術が施行され，腋窩リンパ節転移陰性の女性とした。docetaxelおよびcyclophosphamideの用量はそれぞれ75および600 mg/m^2（いずれも点滴静注）とし，3週間隔で4コース投与した。主要評価項目は試験治療を4コース完遂した患者の割合とした。2006年10月～2007年11月にかけて本試験には39名の患者が組み入れられ32名を評価した。7名は試験治療が手順どおりに投与されなかったため除外した。試験治療の完遂割合は96.9%（31/32）で，1名は過敏性反応のために試験治療を中止した。実投与量の平均値はdocetaxelが73.2 mg/m^2，cyclophosphamideが588.3 mg/m^{2}で，計画した投与量のそれぞれ96.1，95.7%であった。grade 3/4の有害事象は白血球，好中球/顆粒球，発熱性好中球減少などで，投与中止を必要としたものはなかった。以上から，non-anthracyclineレジメンのTCは乳がんの術後標準治療の一つになり得ると考えられた。

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はじめに

原発乳がんの手術後薬物療法は，腋窩リンパ節転移個数，腫瘍径，ホルモン感受性の有無，HER2発現の有無，年齢といった因子に基づいて選択される[1]。これまで手術後の補助化学療法としては，cyclophosphamide＋methotrexate＋fluorouracil（CMF），doxorubicin＋cyclophosphamide（AC）などが標準的に使用されてきた[2-4]が，その後，taxane系薬剤がレジメンに取り入れられるようになった[5-7]。最近では長期生存者の増加に伴いanthracycline系薬剤による心毒性が懸念されるようになり，non-anthracyclineレジメンの開発が期待されている。

このような観点からUS Oncology 9735試験では，Ⅰ・Ⅱ期および手術可能なⅢ期の原発乳がんを対象として，ACの4コース投与とdocetaxel＋cyclophosphamide（TC）の4コース投与を比較した結果，TC群の無病生存期間はAC群よりも有意に長いことが確認された[8]。年齢，ホルモン感受性の有無，腋窩リンパ節転移の有無といった因子によるサブグループ解析でもこの傾向は一貫していたことから，TCは早期乳がんの術後補助化学療法の標準治療になり得ると結論された。しかし，この試験は海外の患者を対象としたもので，国内の患者集団でのTCの忍容性および安全性は十分に評価されていない。

こうしたことから，US Oncology 9735試験と同一の用法・用量で国内の乳がん患者にTCを投与した時の忍容性および安全性を評価する目的で，多施設共同オープン試験を実施した。

Ⅰ．対象および試験方法

本臨床試験は2006年10月～2007年11月にかけて国内の6施設（新潟県立がんセンター，群馬県立がんセンター，埼玉県立がんセンター，神奈川県立がんセンター，栃木県立がんセンター，千葉県がんセンター）で実施された。試験の実施に際してはヘルシンキ宣言[9]および臨床研究に関する倫理指針[10]を遵守し，各施設の倫理審査委員会で事前に試験実施の承認を得るとともに，試験に参加した全患者から文書による同意を取得した。

1．対象集団

本試験の対象は，組織学的に診断された原発乳がん女性で，根治術が施行され，腋窩リンパ節郭清またはセンチネルリンパ節生検によって腋窩リンパ節転移が陰性であることが確認された患者とした。またSt. Gallen分類の中等度のリスクに相当するよう年齢は20歳以上34歳以下であるか，あるいは35歳以上70歳以下で，「原発巣の腫瘍最大径＞2 cm」「分化度がgrade 2または3」「腫瘍組織周囲への脈管侵襲」「human epidermal growth factor receptor-2（HER2）の過剰発現（immunohistochemistryが3＋，またはfluorescence *in situ* hybridization（FISH）が陽性）」のいずれかを満たすこととした。

その他，①Eastern Cooperative Oncology Groupのperformance status（PS）：0または1，②臓器機能が良好（ヘモグロビン：9 g/dL以上，白血球数：4,000/mm^{3}以上12,000/mm^{3}以下，好中球数：2,000/mm^{3}以上，血小板数：10×10^4/mm^{3}以上，血清総ビリルビン値：施設基準値の上限以下，ASTおよびALT：100 IU/L未満，血清クレアチニン値：施設基準値上限の1.5倍以下）などを選択基準とした。

また，①術前，術後補助療法として放射線療法，内分泌療法，化学療法の施行歴がある，②感染症など試験治療に支障を来す可能性がある患者は本試験の対象から除外した。

2．試験治療

試験治療はdocetaxel（タキソテール，サノフィ・アベンティス株式会社，東京）＋cyclophosphamide（注射用エンドキサン，塩野義製薬株式会社，大阪）の併用療法とし，これを3週間隔で合計4コース投与することとした。docetaxelの用量は75 mg/m^2，cyclophosphamideの用量は600 mg/m^{2}とし，両薬剤とも各コースの第1日目に投与した。docetaxelの副作用であるアレルギーおよび浮腫を予防する目的でのステロイドを使用するかどうかは各施設の判断に任せた。各コース第1日目の標準的な投与手順を以下に示す。

手順1：生理食塩液100 mL＋dexamethasoneまたはbetamethasone 8 mgを急速点滴静注

手順2：生理食塩液250 mL＋docetaxelを1時間かけて点滴静注

手順3：生理食塩液250 mL＋cyclophosphamideを30分かけて点滴静注

手順4：生理食塩液100 mLを急速点滴静注

ただし，以下の条件に1項目でも抵触する場合は，すべての項目が回復するまで投与を延期することとした。投与の延期は投与予定日から最大3週までとした。①白血球数＜3,000/mm^3，かつ好中球数＜1,500/mm^3，②grade 2以上の神経障害，③grade 2以上の浮腫，④grade 2以上の肝・腎機能障害，⑤その他，担当医師が必要と判断した場合。

また，以下に示す有害事象が認められた場合には以降の投与量を1段階減量し（docetaxelは75 mg/m^{2}から60 mg/m^2，cyclophosphamideは600 mg/m^{2}から500

Table 1 Baseline characteristics of 32 evaluable patients with operable breast cancer

Characteristic		Category	n	%
Age		30-34	1	3.1
		35-70	31	96.9
Performance status		0	32	100.0
		1	0	0.0
Post menopause		Yes	11	34.4
		No	21	65.6
Hormone receptor	ER	+	8	25.0
		−	24	75.0
	PgR	+	6	18.8
		−	26	81.3
HER2	IHC	3+	5	15.6
		2+	7	21.9
		1+	14	43.8
		−	6	18.8
	FISH	+*	2	6.3
		−	2	6.3
		Not tested	13	40.6
		Unknown	15	46.9
Primary lesion		Right breast	15	46.9
		Left breast	17	53.1
TNM	T	Tis, T0, T1	16	50.0
		T2, T3, T4	16	50.0
	N	N0	32	100.0
	M	M0	32	100.0
Stage		I	16	50.0
		IIa, IIb, IIIb	16	50.0
Histological type	Invasive	Papillo tubular Ca.	6	18.8
		Solid tubular Ca.	11	34.4
		Scirrhous Ca.	11	34.4
		Other	3	9.4
		Unknown	1	3.1
Surgery		Lumpectomy	24	75.0
		Mastectomy	8	25.0
Allergy predisposition		Yes	30	93.8
		No	2	6.3
Anamnesis of hypersensitive drug reaction		No	32	100.0
		Yes	0	0.0
Complications		No	26	81.3
		Yes	6	18.8

*: IHC=2+

mg/m^2)，有害事象が回復しても投与量をもとに戻さないこととした。① grade 3 以上の非血液学的毒性（悪心・嘔吐，全身倦怠感を除く），② grade 4 以上の血液学的毒性（白血球減少，好中球減少を除く），③ grade 3 以上の発熱性好中球減少，④ grade 4 の好中球減少，白血球減少が7日間以上継続。なお，1段階を超える減量が必要な場合は試験を中止することとし，さらなる減量は認めなかった。

3．併用療法に関する規定

試験治療の評価に影響を及ぼすと考えられる化学療法，ホルモン療法，biologic response modifier，放射線療法，手術療法の併用は禁止した。granulocyte colony-stimulating factor（G-CSF）製剤は grade 4 または 38℃以上の発熱があり，かつ grade 3 以上の好中球減少または白血球減少が認められた場合に投与してよいこととし，予防目的での投与は禁止した。G-CSF 製剤を投与

Table 2 Reasons of dose reduction and dose delay

Reasons of dose reduction	Course			Total
	2	3	4	
Non-hematological toxicity greater than grade 3*	0	0	0	0
Hematological toxicity greater than grade 4†	0	0	0	0
Febrile neutropenia greater than grade 3	2	1	0	3
Grade 4 leukocytes and neutrophils for 7 days or more	0	0	0	0
Judgement of investigator	2‡	0	1§	3

*: Except nausea, vomiting and fatigue
†: Except leukocytes and neutrophils
‡: Two were due to grade 4 leukocytes and neutrophils for 6 days or less.
§: One was due to rash grade 2 and the patient's wish.

Reasons of dose delay	Course			Total
	2	3	4	
Leukocytes $<3,000/mm^3$ and neutrophils $<1,500/mm^3$	0	1	0	1
Neuropathy greater than grade 2	0	0	0	0
Edema greater than grade 2	0	0	0	0
Liver or renal disorders greater than grade 2	0	0	0	0
Judgement of investigator	1‖	0	1¶	2
Social factor	2	1	2	5

‖: One was due to the dental treatment.
¶: One was due to rash grade 2 and the patient's wish.

した場合は，白血球数が $10,000/mm^3$ 以上または好中球数が $5,000/mm^3$ 以上に回復した時点で投与を中止することとした。

4．評価項目

主要評価項目は試験治療を4コース完遂した患者の割合とした。副次評価項目は安全性，dose intensity（1コース当たりの実際の投与量），relative dose intensity（1コース当たりの実際の投与量/計画した投与量）とした。有害事象は National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 の日本語訳[11]に基づいて評価した。

5．目標とする患者数

目標とする患者数は4コースの完遂割合の推定値に基づいて設定した。具体的には完遂割合の期待値を80%，閾値を60%とし，有意水準片側5%，検出力90%で，十分な完遂割合が達成されたかどうかを検証できる患者数を正規分布近似によって計算すると必要な患者数は44名となり，これに脱落などの影響を考慮し50名とした。

Ⅱ．結　果

本試験には2006年10月～2007年11月の間に39名の患者が組み入れられた。予定症例集積期間1年間に対し予定された50名に満たなかったが，効果安全性評価委員および運営委員にて協議した結果，32名を評価に採用し忍容性の評価は可能と考え，症例集積を終了した。残る7名は試験治療が手順どおりに投与されなかったため評価から除外した。

評価可能であった32名の患者背景をTable 1に示す。35歳未満の患者は1名のみで，残る患者の年齢はすべて35～70歳であった。PSは良好で全患者が0に分類された。閉経後の患者は11名（34.4%）で，エストロゲンおよびプロゲステロン受容体に感受性のある患者はそれぞれ8名（25.0%），6名（18.8%）であった。

4コースの試験治療を完了したのは32名中31名で完遂割合は96.9%であった。1名はgrade 2の過敏性反応が出現し，処置後に試験治療を再開したが再度同様の症状が出現したため試験治療を中止した。1コース当たりの実際の投与量（dose intensity）の平均値はdocetaxelが73.2（SD 3.9）mg/m^2，cyclophosphamideが588.3（SD 26.2）mg/m^2で，relative dose intensityはdocetaxelが96.1%，cyclophosphamideが95.7%であった。コースごとの減量および投与延期の内訳をTable 2に示す。減量理由で多かったものは，「発熱性好中球減少」および「担当医師の判断」であった。

非血液毒性の有害事象をTable 3に示す。発現の多かった有害事象は悪心，食欲不振，脱毛，粘膜炎（咽頭），味覚変化，便秘，爪の変化，疲労，浮腫，皮疹/落屑，色素沈着，神経障害，筋肉痛および関節痛であった。ほとんどの有害事象はgrade 1または2で，grade 3に該当したのは疲労，筋肉痛，関節痛，腹部痛が各1名（3.1%），

Table 3　Non-hematological toxicity

Adverse event	grade					
	1		2		3	
	n	%	n	%	n	%
Fatigue	19	59.4	8	25.0	1	3.1
Pain-muscle	8	25.0	5	15.6	1	3.1
Pain-joint	9	28.1	7	21.9	1	3.1
Pain-abdomen	0	0.0	0	0.0	1	3.1
Alopecia	6	18.8	26	81.3	0	0.0
Rash/desquamation	4	12.5	17	53.1	0	0.0
Nail changes	20	62.5	3	9.4	0	0.0
Hyperpigmentation	15	46.9	1	3.1	0	0.0
Mucositis-pharynx	18	56.3	4	12.5	0	0.0
Taste alteration	21	65.6	1	3.1	0	0.0
Nausea	18	56.3	1	3.1	0	0.0
Anorexia	16	50.0	2	6.3	0	0.0
Constipation	15	46.9	2	6.3	0	0.0
Diarrhea	8	25.0	3	9.4	0	0.0
Vomiting	4	12.5	0	0.0	0	0.0
Edema: limb	10	31.3	5	15.6	0	0.0
Edema: head and neck	1	3.1	1	3.1	0	0.0
Watery eye	7	21.9	1	3.1	0	0.0
Neuropathy-sensory	15	46.9	3	9.4	0	0.0
Neuropathy-motor	2	6.3	0	0.0	0	0.0
Allergic reaction/hypersensitivity	2	6.3	2	6.3	0	0.0
Cystitis	1	3.1	2	6.3	0	0.0
Phlebitis	0	0.0	1	3.1	0	0.0
Albumin, serum-low	9	28.1	0	0.0	0	0.0
AST, SGOT	9	28.1	0	0.0	0	0.0
ALT, SGPT	9	28.1	0	0.0	0	0.0
Alkaline phosphatase	3	9.4	0	0.0	0	0.0
Bilirubin	1	3.1	0	0.0	0	0.0
Creatinine	4	12.5	0	0.0	0	0.0
Calcium, serum-low	15	46.9	1	3.1	0	0.0
Sodium, serum-high	3	9.4	0	0.0	0	0.0
Potassium, serum-high	1	3.1	0	0.0	0	0.0
Potassium, serum-low	1	3.1	0	0.0	0	0.0
Others	9	28.1	4	12.5	0	0.0

grade 4/5 adverse events were not observed.

Table 4　Hematological toxicity

Laboratory event	grade							
	1		2		3		4	
	n	%	n	%	n	%	n	%
Leukocytes	1	3.1	1	3.1	15	46.9	7	21.9
Neutrophils/granulocytes	1	3.1	1	3.1	1	3.1	19	59.4
Febrile neutropenia	0	0.0	0	0.0	5	15.6	0	0.0
Fever	1	3.1	1	3.1	0	0.0	0	0.0
Hemoglobin	17	53.1	6	18.8	0	0.0	0	0.0
Platelets	5	15.6	0	0.0	0	0.0	0	0.0

grade 5 adverse events were not observed.

発熱性好中球減少が5名（15.6%）であった。grade 4以上に該当する有害事象はなかった。試験治療の中止を必要としたのは先に記載した過敏性反応の1名のみで，1段階の減量を必要としたのは発熱性好中球減少の3名であった。

血液毒性に関する有害事象をTable 4に示す。発現が

多かったのはヘモグロビン，白血球，好中球/顆粒球で，このうち白血球減少はgrade 3～4が22名（68.8%），好中球減少はgrade 3～4が20名（62.5%）であった。投与延期を必要としたのは白血球および好中球が減少した1名であった。なお，grade 4の好中球減少症19例中7例とgrade 3の発熱性好中球減少症5例中2例にG-CSFが使用された。

Ⅲ. 考　察

腋窩リンパ節転移陰性の乳がん術後補助化学療法としては，これまでCMFやACが使用されてきた[3,4]。その後，報告されるようになったtaxane系薬剤[5-7]のうち，docetaxelはcyclophosphamideとの併用ではヒト腫瘍移植マウスでの研究で相乗的な効果を示すことが報告されていた[12]。この組み合わせを用いたTCは近年，ACよりも再発抑制効果が優れることが示された[8]。TCの再発抑制効果は部分集団でも検討され，年齢，ホルモン受容体あるいはリンパ節転移の有無の状況にかかわらず，TCがACより優れる傾向が示された。

一方，国内でのTCの報告は，US Oncology 9735試験における投与量とは異なり，その使用経験は十分とはいえない[13-15]。このためわれわれは，特に腋窩リンパ節転移陰性の中間リスク例に対する有用性に着目し，国内の患者にTCが投与可能かどうかを評価する目的で本試験を実施した。docetaxelとcyclophosphamideの投与順序に関してはUS Oncology 9735試験[8]において特別の記載がなかったため，本試験実施開始時にはdocetaxelとcyclophosphamideの投与手順は厳密に規定しなかった。しかし，初期登録例のうち7例でdocetaxelの前にcyclophosphamideが投与され，その7例中5例にgrade 2以上のアレルギー反応が起こったため効果安全評価委員会の判断で投与手順をdocetaxel，cyclophosphamideの順と規定し，それ以外の投与手順で投与された7例は評価から除外した。その後，規定どおり投与された32例を評価可能症例とした。評価可能であった32名中31名（96.9%）が4コースの投与を完了することができ，TCの忍容性は良好であった。また，relative dose intensityは両薬剤とも約96%で，減量を必要とした患者は少なかった。US Oncology 9735試験でのTC群の完遂割合は93%で，2剤のrelative dose intensityは99.8%であり[8]，欧米と日本でほぼ同等の忍容性であると考えられた。

本試験でみられた有害事象のうちgrade 3～4に該当したのは白血球，好中球減少，発熱性好中球減少などであった。US Oncology 9735試験ではgrade 3～4として61%の好中球減少，8%未満の感染症および5%の発熱を報告されている[8]。今回の試験ではgrade 3～4の好中球減少は同程度（62.5%）であり，感染症は認めなかった。これらの多くでは試験治療の継続が可能であり，投与延期を必要としたのは白血球および好中球減少の1名のみであった。しかし5名（15.6%）の発熱性好中球減少が出現しており，うち3名が1段階の減量を必要とした。9名では試験中にG-CSFが投与された。白血球数や好中球数の変化を監視しながら必要に応じて減量，投与延期またはG-CSF投与で対処することによってTCの安全性は確保できるものと考えられた。またgrade 1～2ではあるものの，US Oncology 9735試験では言及されていない皮疹/落屑（65.6%）や過敏反応（12.5%）も認めたこと，中止の1例は過敏反応によるものであったことを念頭に置き治療を行うことも重要である。

以上から，TCは海外と同一の用法・用量で国内の患者に投与可能で，白血球や好中球が減少した場合でも減量，投与延期またはG-CSF投与によって対処可能と考えられた。現在，ACは乳がんの術後補助化学療法として広く使用されているが，doxorubicinを含むanthracycline系薬剤には心毒性があり，心筋障害，心不全などの重大な副作用が報告されている[16-18]。このため，特に長期生存が期待される早期乳がんの術後補助化学療法では，anthracycline系薬剤を含まないレジメンを確立することは重要な課題である。

これらを考慮すると，TCは術後補助化学療法の標準治療になり得るものと期待することができる。US Oncologyでは，さらにTCとdocetaxel＋doxorubicin＋cyclophosphamide（TAC）を比較する臨床試験が進行中である（NCT00493870: Clinical Trial. gov）。今後はさらに使用経験を積んでTCの安全性プロファイルを確認するとともに，有効性についても評価することが望ましい。

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CLINICAL TRIAL

Study of time-course changes in annual recurrence rates for breast cancer: data analysis of 2,209 patients for 10 years post-surgery

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Abstract Annual recurrence rates (ARR) are used to assess changes in the risk of breast cancer recurrence following surgery. In this retrospective study, ARR were calculated from the clinical records of 2,209 breast cancer patients who had undergone surgery. The time-course changes of ARR associated with prognostic/predictive factors were calculated. Overall, ARR decreased for 5 years following surgery and then remained almost constant. In hormone receptor (HR)-negative patients, ARR peaked after 2 years and peaked again at 6–7 years. In HR-positive patients, ARR peaked at 2 years. ARR increased in relation to the number of lymph-node metastases for 5 years, and peaked after 2 years in the absence and presence of venous invasion. The log-rank test demonstrated significant differences in recurrence between HR-negative and HR-positive cancer up to 5 years post-surgery. The presence of venous invasion had a significant effect on recurrence in the first 5 years, and the presence of lymph-node metastasis had a significant effect on recurrence up to and after 5 years. In conclusion, prognostic/predictive factors affected breast cancer recurrence in the first 5 years but had a lesser effect on recurrence more than 5 years post-surgery.

Keywords Aromatase inhibitor · Breast cancer · Chemotherapy · Hormone receptor · Hormone therapy · Lymph node · Risk · Recurrence · Surgery · Venous invasion

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Introduction

A number of comparative studies of post-operative adjuvant therapy for breast cancer have been reported. Meta-analyses of these studies have served as the basis for therapeutic guidelines for patients with breast cancer [1], so that all patients are treated under the principle of evidence-based medicine.

The purpose of post-operative adjuvant therapy is to reduce the risk of breast cancer recurrence. Annual recurrence rates (ARR) are used to assess changes in the risk of recurrence. ARR are defined as the 'percentage of patients developing recurrent cancer in 1 year among those without recurrence, at a certain time after surgery'. This definition is based on the hypothesis that ARR are constant, regardless of the time elapsed after surgery. ARR are widely used as an index for simulation of recurrence-free survival curves and to calculate the risk reduction: the odds of non-recurrence X years after surgery in patients with ARR of 15% are calculated as $(1–0.15)^X$. For evaluation of the therapeutic effect, reduction of ARR is also used to assess decreases in risk of recurrence after post-operative adjuvant therapy.

However, it is questionable whether the above hypothesis is realistic. A total of 70% of recurrences occur within 3 years post-surgery [2], and based on an integral analysis of data from the Eastern Cooperative Oncology Group (ECOG), it has been reported that the risk for breast cancer recurrence reaches a peak 1–2 years after surgery and then decreases [3]. According to the results of a meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), the optimal administration period for tamoxifen is 5 years [4, 5]; however, there is insufficient evidence available to determine the optimal treatment period of other hormone therapies. Moreover, chemotherapy is generally recommended for short periods in patients with hormone receptor (HR)-negative breast cancer. In the present study, we investigate time-course changes of ARR associated with HR-expression status, number of lymph-node metastases and the presence or absence of venous invasion. These prognostic/predictive factors are considered to be key determinants affecting recurrence after surgery. We also discuss therapeutic strategies, including post-operative adjuvant therapy, taking ARR into consideration.

Methods

This was an exploratory retrospective study. The study was approved by the ethics committee of Gumma Cancer Centre, and performed in accordance with the Declaration of Helsinki. ARR were calculated from the clinical records of breast cancer patients who had undergone surgery between April 1972 and March 2003 at the Gunma Cancer Centre. Time-course changes of ARR and differences in time-course changes in ARR between patients with different prognostic/predictive factors were investigated.

ARR were defined as 'the percentage of patients with recurrence between X years after surgery and $X + 1$ years after surgery among patients without recurrence X years after surgery'. ARR were calculated for the whole study population and were assessed according to HR-expression status, number of lymph-node metastases and the presence or absence of venous invasion. The specific time when ARR tended to change was also determined. Recurrence rates before and after that time were compared using 95% confidence intervals and log-rank tests. Since the study was exploratory, no adjustment was made for multiplicity, and the level of statistical significance was set at 5%.

Results

Patient characteristics

The ARR of 2,209 patients were calculated. The clinical characteristics of the study population, including prognostic/predictive factors, are summarised in Table 1.

Changes in ARR

The overall ARR peaked at 2 years post-surgery, gradually decreased up to 5 years post-surgery and then remained relatively constant (Fig. 1).

Time-course changes in ARR differed according to HR-expression status. In HR-negative patients, ARR peaked within 2 years post-surgery and then reached another peak 6–7 years post-surgery. In HR-positive patients, ARR peaked 2 years post-surgery and then remained almost constant (Fig. 2). ARR increased in relation to the number of lymph-node metastases up to 5 years post-surgery, peaking at 2 years, but remained relatively constant between 5 and 10 years (Fig. 3). ARR varied greatly depending on the presence or absence of venous invasion up to 5 years post-surgery with a peak at 2 years, and thereafter remained almost constant (Fig. 4).

Comparison of recurrence up to 5 years post-surgery with more than 5 years post-surgery

There were differences in time-course changes of recurrence rates between up to 5 years post-surgery and after more than 5 years post-surgery. Table 2 shows recurrence rates and confidence intervals in the first 5 years post-surgery and after more than 5 years post-surgery, according to prognostic/predictive factors. Confidence intervals for recurrence rates up to 5 years post-surgery in patients distributed by HR-expression status, number of lymph-node metastases and the presence or absence of venous invasion, did not overlap, whereas confidence intervals for recurrence rates 5–10 years post-surgery did overlap.

When evaluated using the log-rank test, there were significant differences in recurrence between patients with HR-negative cancer and those with HR-positive cancer for up to 5 years post-surgery (Table 3). There were also significant differences in recurrence depending on the presence or absence of venous invasion in the first 5 years. When assessed by HR-expression status and the presence or absence of venous invasion, there were no significant differences in recurrence 5–10 years post-surgery. The presence of

Table 1 Clinical characteristics of the study population

Total number of patients (*N*)	2,209
Age, years	
Median	51
Range	20–92
Menopause status, *n*	
Premenopause	961
Postmenopause	1,084
Unknown	164
Hormone receptor-expression status, *n*	
Positive	1,211 (54.8%)
Negative	526 (23.8%)
Unknown	472 (21.4%)
Lymph-node metastasis, *n*	
0	1,237 (56.0%)
1–3	505 (22.9%)
4–6	403 (13.2%)
≥7	63 (2.9%)
Unknown	1 (0.0%)
Venous invasion status, *n*	
Presence	1,105 (50.0%)
Absence	1,009 (45.7%)
Unknown	95 (4.3%)
Histological classification, *n*	
Infiltrating mammary duct carcinoma	1,923 (87.1%)
Infiltrating lobular carcinoma	76 (3.4%)
Other/unknown	210 (9.5%)

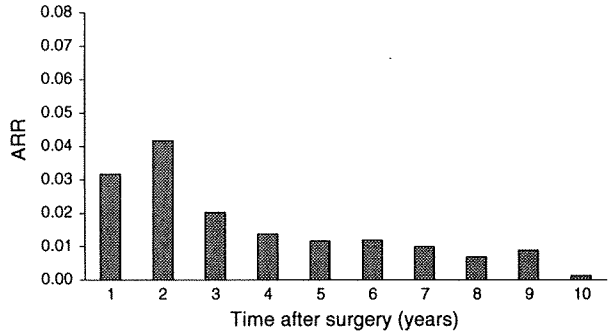

Fig. 1 Time-course changes of the overall annual recurrence rates (ARR)

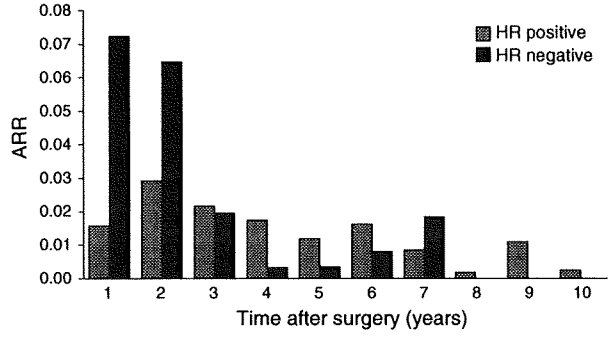

Fig. 2 Time-course changes of annual recurrence rates (ARR) in hormone receptor-positive and -negative patients

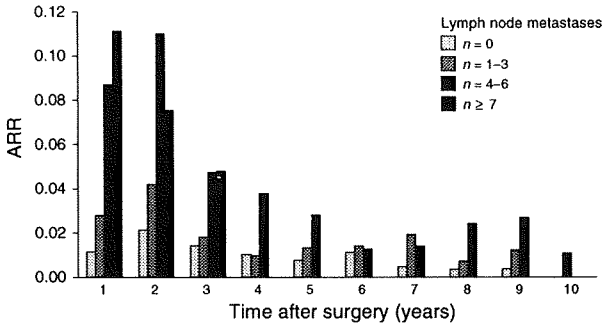

Fig. 3 Time-course changes of annual recurrence rates (ARR) according to number of lymph-node metastases

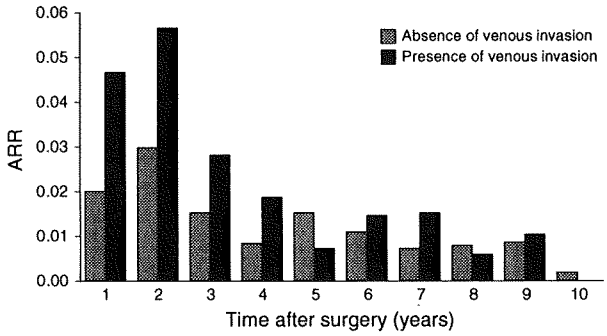

Fig. 4 Time-course changes of annual recurrence rates (ARR) in patients according to the absence or presence of venous invasion

lymph-node metastasis had a significant effect on recurrence up to 5 years post-surgery and 5–10 years post-surgery.

Discussion

In the present study, the ARR up to 5 years post-surgery reached a peak at 2 years and then gradually decreased, while the ARR more than 5 years post-surgery remained almost constant. Time-course changes in ARR in the first 5 years post-surgery were different from those more than 5 years post-surgery. Annual hazard rates of recurrence (AHRR) have been calculated previously based on the results of seven clinical studies carried out by the ECOG [3]. The time-course changes of AHRR in all patients and for patients distributed according to HR-expression status and the presence or absence of lymph-node metastasis tended to be similar to the results of the present study. The results of the meta-analysis done by the EBCTCG also showed that the AHRR more than 5 years post-surgery was lower than in the first 5 years post-surgery

Table 2 Recurrence rates up to 5 years and 5–10 years post-surgery according to prognostic/predictive factors

	Up to 5 years post-surgery		5–10 years post-surgery	
	Recurrence rates	95% CI	Recurrence rates	95% CI
All patients	224/2,209 (10.1%)	8.9–11.5	42/1,247 (3.4%)	2.4–4.5
HR+	96/1,211 (7.9%)	6.5–9.6	23/677 (3.4%)	2.2–5.1
HR-	75/526 (14.3%)	11.4–17.5	6/251 (2.4%)	0.9–5.1
Absence of lymph-node metastasis	67/1,237 (5.4%)	4.2–6.8	15/723 (2.1%)	1.2–3.4
Presence of lymph-node metastasis	157/971 (16.2%)	13.9–18.6	27/523 (5.2%)	3.4–7.4
No. of lymph-node metastases (1–3)	51/505 (10.1%)	7.6–13.1	16/357 (4.5%)	2.6–7.2
No. of lymph-node metastases (4–6)	95/403 (23.6%)	19.5–28.0	11/158 (7.0%)	3.5–12.1
No. of lymph-node metastases (≥7)	11/63 (17.5%)	9.1–29.1	0/8 (0.0%)	0.0–31.2
Presence of venous invasion	134/1,009 (13.3%)	11.2–15.5	18/482 (3.7%)	2.2–5.8
Absence of venous invasion	85/1,105 (7.7%)	6.2–9.4	24/731 (3.3%)	2.1–4.8

CI, confidence intervals; HR+/–, hormone receptor-positive/-negative

Table 3 Log-rank test for recurrence up to 5 years post-surgery and 5–10 years post-surgery according to prognostic/predictive factors

Prognostic/ predictive factor		Recurrence up to 5 years post-surgery		Log-rank test	Recurrence 5–10 years post-surgery		Log-rank test
		Presence *n*	Absence *n*		Presence *n*	Absence *n*	
HR	HR+	96 (7.9%)	1,115 (92.1%)	$P < 0.0001$	23 (3.4%)	654 (96.6%)	$P = 0.4454$
	HR–	75 (14.3%)	451 (85.7%)		6 (2.4%)	245 (97.6%)	
Lymph-node metastasis	n+	157 (16.2%)	814 (83.8%)	$P < 0.0001$	27 (5.2%)	496 (94.8%)	$P = 0.0025$
	n–	67 (5.4%)	1,170 (94.6%)		15 (2.1%)	708 (97.9%)	
Venous invasion	v+	134 (13.3%)	875 (86.7%)	$P < 0.0001$	18 (3.7%)	464 (96.3%)	$P = 0.3343$
	v–	85 (7.7%)	1,020 (92.3%)		24 (3.3%)	707 (96.7%)	

HR+/–, hormone receptor-positive/-negative; n+/–, presence/absence of lymph-node metastasis; v+/–, presence/absence of venous invasion

[4, 5], suggesting that time-course changes in ARR up to 5 years post-surgery were different from those more than 5 years post-surgery.

We found that all the prognostic/predictive factors (HR-expression, lymph-node metastasis and venous invasion) affected the ARR up to 5 years post-surgery, as previously reported. In particular, venous invasion was included in the risk category at the International Consensus Conference on Primary Treatment of Breast Cancer in 2005 [1]. The results of the present study also suggested that venous invasion affected ARR, with a higher ARR in the first 5 years post-surgery than that more than 5 years post-surgery, and the recurrence risk was increased by the occurrence of venous invasion. It is important to discuss therapeutic strategies, including use of post-operative adjuvant therapy, for the prevention of recurrence within 5 years and particularly within 3 years of surgery.

In HR-negative patients, recurrence was observed mainly within 2 years, so it appears reasonable to initiate potent chemotherapy immediately after surgery. Interestingly, ARR again increased 6–7 years after surgery. This suggests that closer observation of HR-negative patients is required, and there should be further discussion about therapeutic strategies, including the possibility of administering extra courses of chemotherapy if necessary.

The pattern of ARR in HR-positive patients was quite different from HR-negative patients. In HR-positive patients, the ARR were almost constant and barely decreased beyond 5 years post-surgery, with a small peak at 2 years. In addition, there was no difference in ARR between premenopausal and postmenopausal patients (data not shown). This correlates with previously published results [3]. The meta-analysis done by the EBCTCG concluded that the optimal treatment period with tamoxifen should be 5 years. Recently, the use of aromatase inhibitors after 2–3 years of tamoxifen has also resulted in improvement in disease-free survival [6, 7]. However, it was reported that aromatase inhibitors, which are becoming first-choice drugs for postmenopausal HR-positive patients with breast cancer, were effective when administered beyond the 5-year treatment period of tamoxifen [8, 9]. This suggests that hormone therapy for more than 5 years post-surgery may be effective. The present study also confirmed that the recurrence rates more than 5 years post-surgery were higher in

HR-positive patients than in HR-negative patients. Further investigation of the usefulness of hormone therapy beyond 5 years post-surgery is required, with a focus on the use of aromatase inhibitors.

As long-term data on ARR accumulate and more clinical studies are conducted, the optimal therapeutic methods for use in breast cancer beyond 5 years post-surgery should become clearer.

Conclusion

In the present study, ARR were not constant and differed between up to 5 years post-surgery and more than 5 years post-surgery. Prognostic/predictive factors affected recurrence up to 5 years post-surgery but had a lesser effect on recurrence more than 5 years post-surgery. The results of this study suggest that recurrence-free survival rates can be improved by preventing recurrence up to 5 years, especially 3 years, after surgery. The use of post-operative adjuvant therapy for more than 5 years after surgery should be considered, depending on the HR-expression status of the patient.

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Computed Radiography-based Mammography with 50-μm Pixel Size:

Intra-individual Comparison with Film-screen Mammography for Diagnosis of Breast Cancers[1]

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Rationale and Objectives. The aim of this study was to evaluate the breast cancer diagnostic capability of "dual-side readout" computed radiography–based mammography (DRCRM) with a 50-μm pixel size compared to that of conventional film-screen mammography (FSM).

Materials and Methods. Thirty patients who were scheduled for surgical treatment for breast cancer and 10 normal volunteers were enrolled. All 30 patients underwent surgical treatment, and breast cancer was proved histopathologically. Twenty-eight patients had 35 invasive carcinomas, and the remaining two had ductal carcinomas in situ. Each of the 40 women underwent both DRCRM and FSM (with double exposure and the same view, without removing compression). Three observers retrospectively interpreted the mammograms independently and evaluated and rated masses and class categories. The accuracy of the detection of masses was evaluated with alternative free-response receiver-operating characteristic analysis. Sensitivity for the detection of masses and of cancers was also evaluated.

Results. The mean areas under the alternative free-response receiver-operating characteristic curves in the detection of the masses were 0.88 for DRCRM and 0.91 for FSM (P = .08). The corresponding values for mean sensitivity for the detection of masses were 0.74 and 0.77 (P = .48) and those for the detection of cancers 0.79 and 0.84 (P = .20).

Conclusion. No significant differences were observed between DRCRM and FSM for diagnosis of breast cancers.

Key Words. Digital mammography; diagnosis; breast cancer; breast radiographic comparative studies.

Over the past decade, various different digital mammographic systems have become available for clinical use (1–3). The main advantage of any digital imaging system is the separation of image acquisition, processing, and display, which allows for the optimization of these steps (1). One such system is a computed radiography (CR)–based mammographic system using photostimulated storage phosphor plates. In recent years, a computed radiographic system dedicated to mammography has been released. This system uses the "dual-side readout" technique, which collects emitted light efficiently from both sides of the storage phosphor plate (1,4). Dual-side readout CR-based mammography (DRCRM) allows for higher detective quantum efficiency, with an image sampling rate of 50 μm (4,5).

The evaluation of microcalcification findings is essential for the detection of breast cancers and to distinguish cancers from other, benign lesions. However, because the spatial

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resolution of 100 μm of most digital mammographic systems is inferior to that of conventional film-screen mammography (FSM), diagnosis with conventional digital mammographic systems has been considered to be at a disadvantage for the evaluation of microcalcification findings. However, DRCRM has twice the spatial resolution of other digital systems, which may help overcome the disadvantage of digital mammography for the evaluation of microcalcification findings.

CR-based mammography has been well accepted in Europe and Japan, because the implementation of the system simply means replacing film-screen cassettes with storage phosphor imaging plate cassettes that can be used in a standard mammographic unit (6). In the United States, the system has been approved by the US Food and Drug Administration in recent years (6). To the best of our knowledge, however, only one study has been performed to compare the diagnostic capability for breast cancer of DRCRM to that of conventional FSM (7). However, saving more data concerning with the diagnostic capability helps the diagnostic performance profile in a clinical setting.

The purpose of this study was thus to evaluate the performance of DRCRM for the diagnosis of breast cancers compared to that of conventional FSM.

MATERIALS AND METHODS

Patients

From January to December 2003, 30 consecutive patients who were scheduled for surgical treatment for breast cancer and 10 normal volunteers aged ≥40 years were enrolled in this study. The mean of age of all subjects was 55.0 ± 13.0 years. This study was approved by the institutional review board of our hospital. Written informed consent was obtained from all women.

All 30 patients underwent surgical treatment, and breast cancer was proved histopathologically. The number and locations of breast cancers were decided by consensus of two radiologists other than three blinded readers on the basis of findings obtained with contrast-enhanced dynamic magnetic resonance imaging, sonography, and definitive surgery. Twenty-eight patients had 35 invasive carcinoma, and the remaining two had ductal carcinomas in situ. The mean diameter of the tumors was 19.8 ± 10.6 mm. For the 10 normal volunteers, no findings suggestive of breast cancer were obtained with mammography, sonography, or palpation.

Mammography

In a CR-based mammographic system, storage phosphor imaging plates are used in place of the traditional film-screen combinations. The storage phosphor imaging plate is contained within a cassette, which can be used in a standard mammographic machine without modification. Each of the 40 women enrolled in our study underwent both DRCRM and FSM using a conventional standard unit (GE DMR; GE Healthcare, Milwaukee, WI). Mammograms of the mediolateral oblique view of the affected sides of the patients' breasts were performed the day before surgical resection of the lesions, and those of the breast on either side were performed for the normal volunteers by experienced technologists certified by the Central Committee on Quality Control of Mammographic Screening. First, an exposure for FSM using a film-screen cassette was performed. After the film-screen cassette had been immediately replaced with a storage phosphor plate cassette, another exposure for DRCRM was performed while maintaining the same breast position, without removing compression. Technique factors (peak kilovoltage, radiation dose, target, and filter) were automatically selected by the unit (using the Automated Optimization Parameters feature). For FSM, the combination of a screen-film system (Kodak Min-R 2000; Eastman Kodak, Rochester, NY) and a room light handling imaging system (Kodak Miniloader 2000P; Eastman Kodak) were used. For DRCRM, combination of a computed radiographic image reader (FCR 5000MA; Fuji Medical Systems, Tokyo, Japan) and a dry-type laser imager (FM-DPM; Fuji Medical Systems) was used. For image processing in DRCRM, the parameters for the gamma function of 1.2 T, 1.4, and +0.12; those for the multifrequency processing of GR 2.0 and EF 0.0; and those for the Pattern Enhancement Processing for Mammography (PEM; Fuji Medical Systems) of BML 2.0 were used. A total of 40 sets of mammograms each were thus acquired with DRCRM and FSM.

Image Assessment

Images from DRCRM and FSM were separately and independently interpreted by three blinded readers retrospectively. These readers were different from the two radiologists who determined the presence or absence of cancers on the basis of certain radiologic and pathologic findings. All three readers were certified by the Central Committee on Quality Control of Mammographic Screening and had interpreted mammograms as part of their daily clinical and research practice. They had no information about the patients' histories.

The marginal areas outside of the breast on the film were covered with thick black paper to prevent the readers from knowing whether the acquisition system was DRCRM or FSM. Both film-screen mammograms and hard-copy images from DRCRM were interpreted in a darkened room on a standard mammography alternator with a luminance of ≥3,000 cd/m^2. First, each reader viewed mixed dual-side readout CR-based mammograms of 20 subjects and film-screen mammograms of the remaining 20 subjects that were

arranged in a random order and recorded the presence, location, and diameter of one or more suspected breast mass lesions, including both benign and malignant lesions. The reader then assigned each such mass lesion a confidence rating in determining whether a mass lesion was present or absent on a four-point scale (1 = probably not a lesion, 2 = equivocal, 3 = probable lesion, 4 = definite lesion) according to the conspicuity of the mass lesion. The differentiation between a mass lesion and the focal density caused by any structures other than the mass lesion was comprehensively judged on the basis of the degree of the density of the shadow, the conspicuity of the borderline, and/or the presence or absence of increasing density at the center of the density. On each mammogram, the category classification rating on a five-point scale (1 = negative, 2 = benign, 3 = probably benign, 4 = suspected of malignancy, 5 = highly suggestive of malignancy) was comprehensively obtained on the basis of the overall findings, including the mass findings, the microcalcification findings, and the architectural distortion findings according to the Breast Imaging Reporting and Data System lexicon. More than 2 weeks after the first session, each reader viewed the remaining 20 dual-side readout CR-based mammograms and 20 film-screen mammograms and recorded the ratings in a similar fashion. At the time of scoring, the readers were aware that sensitivity calculations for the mass lesions were made on the basis of only those lesions awarded confidence ratings of 3 or 4.

After the blind reading, the dual-side readout CR-based mammogram for each subject was also compared to the corresponding film-screen mammogram and evaluated as to microcalcification findings, mass findings, and stellate signs.

Statistical Analyses

For the mass lesions, alternative free-response receiver-operating characteristic (AFROC) analysis was performed on a tumor-by-tumor basis. Although the conventional receiver-operating characteristic method allows for only one response per image, the AFROC method allows for multiple responses per image (8). An AFROC curve was fitted to each reader's confidence rating using a maximum-likelihood estimation program (ROCKIT 0.9B; C. E. Metz, University of Chicago, Chicago, IL). The diagnostic performance of both methods and readers was estimated by calculating the area under the AFROC curve (Az). The sensitivity for the diagnosis of the mass lesions for each reader and each method was also determined by using only those mass lesions allocated confidence ratings of 3 or 4. The sensitivity for cancers was also determined by using only those cases allocated category classifications of 3, 4, or 5. In addition to the overall analyses of all breasts, analyses of the subgroup of breasts with dense parenchyma (heterogeneously or extremely dense) and that of breasts with fatty change (fatty or scattered densities) were also performed.

Table 1
Area Under the Alternative Free-response Receiver-operating Characteristic Curves in the Detection of Breast Mass Lesions

Modality	Reader 1	Reader 2	Reader 3	Mean	*P*
All breasts (n = 40)					
DRCRM	0.87	0.88	0.89	0.88	
FSM	0.88	0.90	0.93	0.91	.08
Breasts with dense parenchyma (n = 23)					
DRCRM	0.73	0.87	0.87	0.82	
FSM	0.85	0.90	0.93	0.89	.12
Breasts with fatty change (n = 17)					
DRCRM	0.98	0.87	0.92	0.92	
FSM	DD*	0.91	DD*	0.91	N/A

DD, degenerate data; DRCRM, dual-side readout computed radiography–based mammography; FSM, film-screen mammography.

* Degenerate data were present in the alternative free-response receiver-operating characteristic analysis. In general, degeneracy is found only in very small data sets or in those with many tied values.

For Az values and sensitivities, the statistical significance of any differences between DRCRM and FSM was assessed using a paired t test. A two-tailed P value < .05 was considered significant.

To assess inter-reader and intrareader variability for image interpretation, the unweighted κ statistic was used to measure the extent of agreement among three readers. The extent of disagreement was not factored into the calculation. Kappa values > 0 were considered to indicate positive correlations, values up to 0.40 indicated positive but poor agreement, values of 0.41 to 0.75 indicated good agreement, and values > 0.75 indicated excellent agreement.

RESULTS

Detection of Mass Lesions

The Az values determined for DRCRM and FSM are shown in Table 1. The Az values for breasts with fatty change, for many readers, were degenerated because of a small data set or a data set with many tied values. For each of the three readers, the mean Az values for DRCRM were almost equivalent to those for FSM, without any statistically significant differences. The mean sensitivities for DRCRM were also equivalent to those for FSM (Table 2). Of the 35 mass lesions in all breasts, six were not detected with DRCRM by any of the readers, whereas three were detected with FSM at a confidence level of 3 or 4 by at least one of the readers. With FSM, four mass lesions were not detected by any of the readers, but one was detected with DRCRM at a confidence level of 3 or 4 by at least one of the readers. The

Table 2
Sensitivities in the Detection of Breast Mass Lesions

Modality	Reader 1	Reader 2	Reader 3	Mean	P
All breasts (n = 40)					
DRCRM	0.71	0.77	0.74	0.74	
FSM	0.69	0.86	0.77	0.77	.48
Breasts with dense parenchyma (n = 23)					
DRCRM	0.67	0.81	0.71	0.73	
FSM	0.71	0.81	0.76	0.76	.18
Breasts with fatty change (n = 17)					
DRCRM	0.79	0.71	0.79	0.76	
FSM	0.64	0.93	0.79	0.79	.84

DRCRM, dual-side readout computed radiography–based mammography; FSM, film-screen mammography.

Table 3
Positive Predictive Values in the Detection of Breast Mass Lesions

Modality	Reader 1	Reader 2	Reader 3	Mean	P
All breasts (n = 40)					
DRCRM	0.93	0.82	0.96	0.90	
FSM	0.92	0.81	0.93	0.89	.26
Breasts with dense parenchyma (n = 23)					
DRCRM	0.88	0.81	0.94	0.87	
FSM	0.88	0.81	0.89	0.87	.99
Breasts with fatty change (n = 17)					
DRCRM	1.00	0.83	1.00	0.94	
FSM	1.00	0.77	1.00	0.92	.42

DRCRM, dual-side readout computed radiography–based mammography; FSM, film-screen mammography.

positive predictive values for breast mass lesion detection with DRCRM were thus almost equivalent to those with FSM (Table 3).

Detection of Cancers

The sensitivities for cancer detection of DRCRM and FSM are shown in Table 4. For all breasts, breasts with dense parenchyma, and those with fatty change, the mean sensitivity of FSM was slightly superior to that of DRCRM, although there were no significant differences. Two cases of breast cancer were not detected by any readers with either DRCRM or FSM. Three cancers were not detected with DRCRM by any of the readers, whereas one was detected with FSM and rated as category 3 by one of the readers. However, this case, which was histopathologically proved to be a ductal carcinoma in situ without gross mass formation, was diagnosed by one reader as a cancer on the basis of the false-positive mass lesion. Therefore, none of the three cancers that were not detected with DRCRM should be considered to have been detected with FSM. At the same time, no cancer was detected with DRCRM but not with FSM. Consequently, three cases of cancer were not diagnosed as category 3, 4, or 5 with either DRCRM or FSM by any reader, whereas the remaining 27 cases of cancer were diagnosed as category 3, 4, or 5 with both DRCRM and FSM by at least one of the readers. The positive predictive values for breast cancer detection with DRCRM were thus almost equivalent to those with FSM (Table 5).

Table 4
Sensitivities in the Detection of Breast Cancers

Modality	Reader 1	Reader 2	Reader 3	Mean	P
All breasts (n = 40)					
DRCRM	0.77	0.77	0.83	0.79	
FSM	0.77	0.83	0.93	0.84	.20
Breasts with dense parenchyma (n = 23)					
DRCRM	0.81	0.81	0.81	0.81	
FSM	0.81	0.88	0.94	0.88	.23
Breasts with fatty change (n = 17)					
DRCRM	0.71	0.71	0.86	0.76	
FSM	0.71	0.79	0.93	0.81	.18

DRCRM, dual-side readout computed radiography–based mammography; FSM, film-screen mammography.
Breast cancers were proved histopathologically in 30 patients.

Table 5
Positive Predictive Values in the Detection of Breast Cancers

Modality	Reader 1	Reader 2	Reader 3	Mean	P
All breasts (n = 40)					
DRCRM	0.89	0.89	0.89	0.89	
FSM	0.96	0.89	0.85	0.90	.75
Breasts with dense parenchyma (n = 23)					
DRCRM	0.81	0.81	0.87	0.83	
FSM	0.93	0.88	0.79	0.86	.62
Breasts with fatty change (n = 17)					
DRCRM	1.00	1.00	0.92	0.97	
FSM	1.00	0.92	0.93	0.95	.46

DRCRM, dual-side readout computed radiography–based mammography; FSM, film-screen mammography.
Breast cancers were proved histopathologically in 30 patients.