Results

Tumor and patient characteristics in the neo TAM and neo ANZ groups are shown in Table 1. The clinical response rates (cCR+cPR) for the neo TAM and neo ANZ groups were 46.4 and 76.5%, respectively. Of the neo ANZ group, only four patients underwent breast-conserving surgery, because some patients with good clinical responses chose mastectomies and refused postoperative radiotherapy. Patients treated with neo ANZ showed a statistically significantly higher rate of pathological

Table 2 Tumor characteristics and responses to NAET stratified by patients with events and those without events.

	Non-response group ($n = 11$)	Pathological response group ($n = 34$)	
Age	57 (51–73)	61 (52–87)	
Tumor before NAET			
T2	9	20	
T3	1	10	
T4	1	4	NS
Histological grade before NAET			
Grade 1	1	8	
Grade 2	6	15	
Grade 3	4	9	NS
Not available	0	2	
HER2 status before NAET			
Negative	11	34	
Positive	0	1	NS
NAET			
Tamoxifen	10	18	
Anastrozole	1	16	NS
Clinical response			
CR	0	4	
PR	4	18	
NC	7	12	NS
PD	0	0	
Ki-67 index before NAET			
High	6	17	
Low	5	17	NS
Residual Ki-67 index			
High	7	16	
Low	4	18	NS
Proportional reduction of Ki-67 index			
Median(Q_1–Q_3)	−0.05 (−0.67–0.37)	−0.46 (−0.85–0.83)	NS
Lymphovascular invasion			
Negative	9	28	
Positive	2	6	NS
Axillary nodal status			
Negative	2	11	
1–3	6	13	
4–9	1	9	
>10	2	1	NS
Adjuvant therapy			
Endocrine only	5	20	
Chemotherapy added	6	14	NS

Q_1: first quartile; Q_3: third quartile.

response (Grades 1+2) than those treated with neo TAM ($p = 0.02$).

Tumor characteristics stratified by patients with pathological response or non-response are shown in Table 2. There were no statistically significant differences in tumor size, histological grade, HER2 status, clinical response, lymphovascular invasion, pathological nodal status, or addition of adjuvant chemotherapy between these groups. Reduction of Ki-67 was not significantly associated with either pathological or clinical response.

The median follow-up time after NAET was 44.7 months. There were 11 locoregional and/or metastatic events during this time. No ipsilateral breast tumor recurrence was observed after breast-conserving surgery. Patients with pathological non-response (25.5%, vs. response group 85.9%, $p = 0.002$; Fig. 1), axillary node positivity (58.4% vs. node negative 100%, $p = 0.045$), addition of adjuvant chemotherapy (41.2% vs. only endocrine therapy 77.5%, $p = 0.01$), and high pretreatment Ki-67 index (41.4% vs. low Ki-67 index 87.1%, $p = 0.03$; Fig. 2) were significantly associated with poor 5-year RFS. Initial T category, histological grade, clinical response, type of endocrine therapy, presence of reduction in Ki-67 values, and lymphovascular invasion was not associated with survival.

The median follow-up time for the neo TAM group was 65.8 months. In this group, patients with pathological non-response (28.0%, vs. response group 88.2%, $p = 0.006$; Fig. 3), axillary node positivity (59.9% vs. node-negative 100%), addition of adjuvant chemotherapy (43.2%, vs. only endocrine therapy 77.8%, $p = 0.03$), and high residual Ki-67 index (44.0%, vs. low Ki-67 index 100%, $p = 0.01$) were significantly associated with poor 5-year RFS.

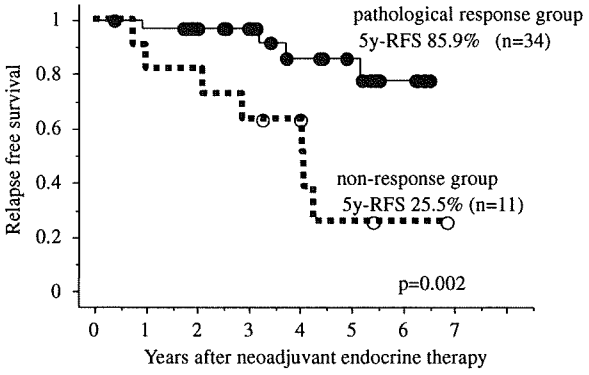

Figure 1 Relapse-free survival curves following neoadjuvant endocrine therapy stratified into a pathological response group (—) and a non-response group (- - -). A statistically significant difference was observed between the groups ($p = 0.002$).

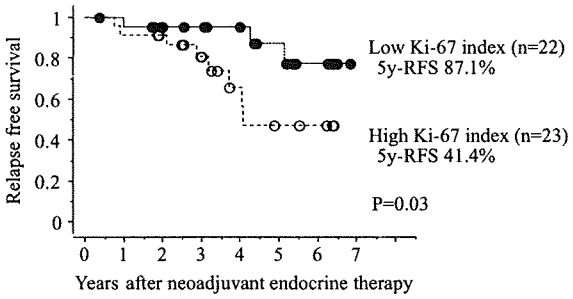

Figure 2 Relapse-free survival curves following neoadjuvant endocrine therapy stratified into a low pretreatment Ki-67 index group (—) and a high Ki-67 index group (- - -). A statistically significant difference was observed between the groups ($p = 0.03$).

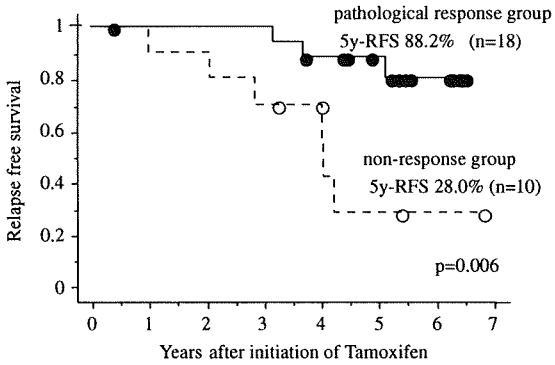

Figure 3 Relapse-free survival curves following neoadjuvant endocrine therapy using tamoxifen stratified into a pathological response group (—) and a non-response group (- - -). A statistically significant difference was observed between the groups ($p = 0.006$).

The median follow-up time for the neo ANZ group was 30.0 months. The pathological response group achieved statistically better 3-year RFS than the non-response group (93.3% vs. 0%, $p < 0.0001$).

Multivariate regression analyses using a logistic regression model were conducted to identify independent prognostic factors for RFS (Table 3). These analyses indicated that pathological response ($p = 0.007$) was significantly related to RFS.

Discussion

Although the sample sizes in this study are small, the pathological response group showed significantly more favorable outcomes than the non-pathological response group following NAET. This result is supported by all of the analyses conducted in this study and suggests that the pathological therapeutic response may be a prognostic factor for

Table 3 Multivariate analysis for RFS after NAET.

		Hazard ratio (95%CI)	*p*-value
Pathological response	Non-response/response	6.3 (1.6–23.8)	0.0067
Pretreatment Ki-67	Low/high	0.26 (0.055–1.17)	0.079
Residual Ki-67	Low/high	0.65 (0.14–2.98)	0.58

RFS: relapse-free survival; CI: confidence interval.

long-term outcome following NAET. The response necessary for a favorable prognosis seems to differ between neoadjuvant chemotherapy and NAET. In the neoadjuvant cytotoxic chemotherapy setting, where response (pCR or not) is a clinically significant predictor of outcome[12], long-term outcome following treatment with cytostatic agents can be predicted based on the achievement of minimal pathological change. Using chemotherapy, total killing of cancer cells is necessary to improve prognosis; therefore, physicians should pursue regimens that will reach the highest pCR rates possible. On the other hand, only a few patients have been reported to achieve pCR following NAET[3]. This is one reason for hesitation in using endocrine agents in a neoadjuvant setting. However, with endocrine therapy, minimal pathological changes may have the same power to improve prognosis.

In this study, low Ki-67 index before NAET in all cases and low residual Ki-67 index in the neo TAM group were significant favorable prognostic factors. Ki-67 has been reported to carry modest prognostic significance and the residual (after treatment) level of Ki-67 may be a better predictor of response and/or absolute long-term outcome than the proportional reduction in Ki-67 because it is more likely to relate to the growth rate of the persistent disease[13]. The results of this study are concordant with these results. The results of the IMPACT trial supported the hypothesis that a reduction of Ki-67 in NAET might be predictive of long-term outcome, but this was not demonstrated in this study. As Urruticoechea has reported that a change in Ki-67 score of at least 32–50% between two determinations using core needle biopsies is required to consider the difference statistically different for an individual patient and attributable to treatment effects[13], the problem with the reproducibility of Ki-67 measurements must be overcome.

Patients who underwent additional adjuvant chemotherapy showed a statistically significant reduction in RFS compared with those who underwent only endocrine therapy. Selection bias must be considered, as most of the patients with positive lymph nodes were treated with chemotherapy. However, whether or not the chemotherapy was efficacious remains controversial because hormone-sensitive breast cancer is less responsive to chemotherapy[14,15]. Further investigations are required to determine the best treatment plan for such cases.

Neoadjuvant chemotherapy has now been established as one of the standard treatments for operable breast cancer. On the other hand, there is less evidence on NAET than on neoadjuvant chemotherapy, including long-term outcome. In this situation, NAET should be used to treat selected patients who will obtain great benefit from endocrine therapy and will not respond to chemotherapy and/or do not need chemotherapy. Without a doubt, hormone receptor status is the first eligibility criterion. Many studies on neoadjuvant chemotherapy have confirmed that hormone-sensitive tumors show worse responses to chemotherapy than hormone-resistant tumors[14,15]. However, not all hormone-sensitive tumors respond to endocrine therapy, underscoring the need for additional predictive tests. Gene analysis can be used as a second eligibility criterion. A multigene assay (Oncotype DX)™ succeeded in predicting that approximately half of the women with node-negative, hormone receptor-positive breast cancer who were treated with local therapy and tamoxifen have an excellent prognosis, with more than 90% having 10-year relapse-free survival; these patients are unlikely to benefit from chemotherapy[16,17]. A more favorable response and long-term outcome without severe adverse events may be achieved with only hormone therapy using gene expression profiles to select patients who are good candidates for NAET.

This study suggests that pathological response is a favorable prognostic factor following NAET. We await validation of these results in large studies such as the IMPACT trial or Letrozole P024 to establish the surrogate markers that predict the risk of recurrence.

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原著

2007.3.5受付

Intracystic papillary carcinoma (ICPC) の診断と臨床的特徴
—自験例14例からの検討—

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Clinical and Pathological Features of Intracystic Papillary Carcinoma (ICPC) of The Breast：Akagi T*1, Kinoshita T*1, Shien T*1, Hojo T*1 and Akashi S*1 (*1Breast surgery division, National cancer center hospital)

Background：Intracystic papillary carcinoma (ICPC) of the breast is rare and preoperative diagnosis is difficult. Materials and Methods：This study investigated the clinical and pathological features of ICPC. Fourteen ICPC were included in this study. We reviewed their clinicopathological findings and treatments. Results：In 9 cases, diagnoses of ICPC were obtained using fine needle aspiration and core needle biopsy. In 5 cases, a diagnosis could not be obtained preoperatively. MRI in addition to sonography helped to establish the differential diagnosis from benign tumor and maintain disease-free surgical margins. Conclusion：Preoperative diagnosis of ICPC is difficult and excisoinal biopsy was necessary unless fine needle aspiration and core needle biopsy can obtain the diagnosis. MRI is available to diagnose the invasiveness of this disease.

Key words：Intracystic papillary carcinoma, Preoperative diagnosis
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はじめに

Intracystic papillary carcinoma (ICPC) は乳癌全体の約2％弱[1]とまれな疾患である．現在の乳癌取扱い規約では非浸潤性乳管癌ductal carcinoma *in situ* (DCIS) に含まれ，線維性の壁に囲まれた内腔へ乳頭状に突出し発育する乳癌で，通常周囲間質に高度の浸潤を伴わないとされる[2]．しかし，組織学的に嚢胞壁外や乳管内での高度の進展を示す例[3]や，同時性肝転移例[4]などの報告もある．また良性嚢胞腫瘍との鑑別が困難である．今回われわれは，ICPCの14例を経験したので臨床病理学的検討とともに若干の文献的考察を加えて報告する．

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1．対象と方法

2000年10月から2006年12月まで当科で経験した原発性乳癌は約2,700症例，そのうちICPCと診断されたのは14例0.51％であった．この14例において臨床病理学的特徴，予後を検討し，さらに免疫組織染色によりホルモンレセプター，HER2，p53を評価した．

2．結　果

1) 臨床的特徴（表1）

年齢は中央値72.5歳（36～82歳）で，14人のうち1人が男性，女性13人のうち3例が閉経前，10例は閉経後であった．主訴は全例乳房腫瘤で，自己発見が13例，検診発見が1例で，腫瘍径の中央値は25.5mm（11～220mm）であった．占拠部位はA領域に7例，B領域に1例，C領域に2例，D

表1　Intracystic papillary carcinomaの臨床的特徴および診断

症例	年齢・性	病悩期間(月)	部位	US 最大径(嚢胞mm)	US 最大径(充実内腫瘤mm)	US 充実腫瘤形状	MMG 腫瘤陰影	MMG 石灰化	MRI	FNA	CNB	術前病理診断
1	84・F	2	右A	22	5	不整型	辺縁不整	なし	／	／	／	なし
2	83・F	2	左D	11	6	整型	辺縁平滑	なし	／	class 5	／	DC
3	75・F	3	右A	22	7	不整型	辺縁不整	A	／	class 3	＋	なし
4	60・F	4	右B	36	10	整型	辺縁平滑	なし	／	class 2	＋	なし
5	43・F	3	左A	15	3	整型	辺縁平滑	なし	／	／	＋	なし
6	36・F	9	左C	34	17	不整型	はっきりせず	なし	／	／	＋	ICPC
7	57・F	4	左E	10	4	整型	辺縁平滑	なし	／	class 5	／	DC
8	70・M	6	左E	50	15	不整型	辺縁不整	なし	／	／	＋	ICPC
9	75・F	2	右A	28	20	整型	辺縁平滑	A	／	class 5	／	DC
10	48・F	3	左A	23	5	整型	辺縁平滑	P	／	class 2	＋	なし
11	74・F	8	左A	14	14	整型	／	／	／	／	＋	ICPC
12	82・F	24	右C	200	30	整型	／	／	BCP	class 2	＋	ICPC
13	81・F	2	右A	170	52	不整型	辺縁不整	なし	BCP	class 2	＋	ICPC
14	71・F	2	左E	60	21	不整型	辺縁平滑	なし	BCP	／	＋	ICPC

＊US：乳腺超音波検査．A：amorphous集簇．P：pleomrphic集簇．BCP：乳癌造影パターン
FNA：Fine needle aspiration．CNB：Core needle biopsy．DC：ductal carcinoma．

表2　手術・病理所見

症例	術式	嚢胞壁外浸潤	周囲DCIS	リンパ節転移	各種レセプター	p53	G	NG
1	Bp	なし	なし	郭清なし	ER 2 PgR 2 HER 2＋	－	1	1
2	Bp	なし	なし	郭清なし	ER 2 PgR 0 HER 2－	－	1	1
3	Bt＋sampling	なし	なし	0/2	ER 2 PgR 2 HER 2－	＋	2	2
4	Bq	なし	なし	郭清なし	ER 2 PgR 1 HER 2－	－	2	2
5	Bp＋Ax	なし	なし	0/11	ER 2 PgR 2 HER 2－	－	2	2
6	Bp＋Ax	なし	あり	0/22	ER 2 PgR 2 HER 2－	－	1	1
7	Bt＋Ax	なし	なし	0/20	ER 2 PgR 2 HER 2＋	－	2	2
8	Bp	なし	なし	郭清なし	ER 2 PgR 2 HER 2＋	2＋	2	2
9	Bt＋Ax	なし	なし	0/18	ER 1 PgR 1 HER 2－	－	2	3
10	Bq＋SLN	なし	なし	0/4	ER 1 PgR 2 HER 2－	－	1	1
11	Bp	あり	なし	郭清なし	ER 2 PgR 2 HER 2－	－	1	1
12	Bt＋SLN	なし	なし	1/5	ER 3 PgR 3 HER 2－	－	1	1
13	Bt＋SLN	なし	あり	0/5	ER 3 PgR 3 HER 2－	－	1	1
14	Bt＋SLN	あり	あり	0/3	ER 3 PgR 2 HER 2－	－	1	1

領域に1例で，E領域に3例に存在した．病悩期間は中央値5.2カ月（2～24カ月）であった．

2) 診断

超音波検査では1例は多房性の嚢胞であったが，他13例はすべて単房性の嚢胞であり，いずれの症例も内部に充実性成分を認めた．腫瘍径は中央値25.5mm（11～220mm）で，充実成分径は中央値12mm（3～52mm）であった．内部の充実成分の形状は整，不整とさまざまであった．

マンモグラフィー（MMG）は12例に施行，7例が辺縁平滑で，4例は辺縁不整の腫瘤陰影として描出され，1例はMMG上腫瘤陰影を認めなかった．amorphousおよびpleomorphicな集簇する石灰化を3例にみとめた．MRIは3例に施行，嚢胞内容液はいずれも血性所見を呈した．ダイナミックスタディーでは3例（100%）ともに乳癌の造影パターンを示した．また嚢胞壁外進展を1例（症例14）に認めた．8例にFine needle aspiration施行，class5が3例，class3が1例，class2が4例であった．class5であった3例はいずれもductal carcinoma疑いという結果であった．Fine needle aspirationの細胞診陽性率は8例中3例（37.5%）であった．class3以下の5例にはCore needle biopsy 追加施行した．また5例はFine needle biopsy施行せずに，はじめからCore needle biopsyを施行．計10例のCore needle biopsyを施行，

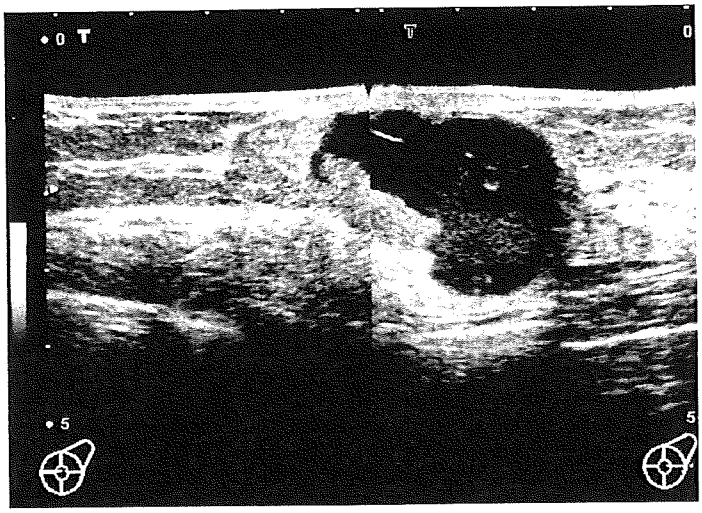

図1　超音波所見

後方エコーの増強を伴った50×43×26 mmの嚢胞と，嚢胞壁の一部から内腔に突出する21×18×7 mm大の乳頭状腫瘍を認めた．

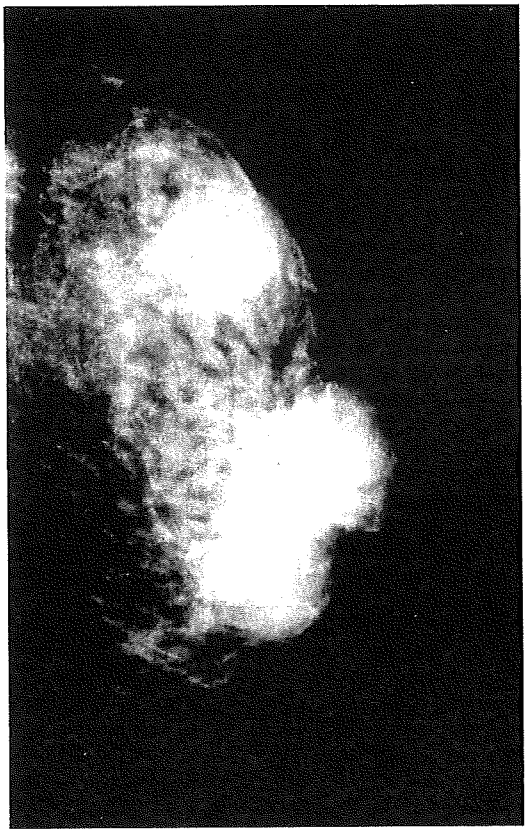

図2　マンモグラフィー所見

medio-lateral viewでE領域に辺縁平滑で，ほぼ均一な腫瘤陰影を認めた．石灰化は認めなかった．

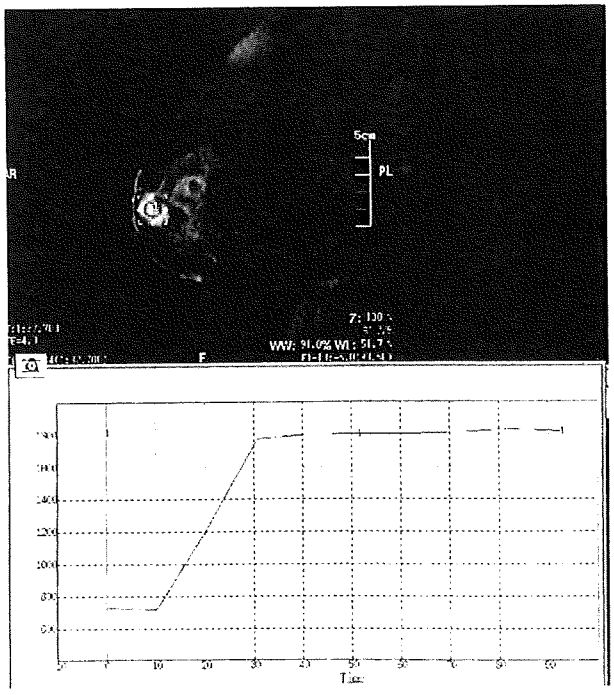

図3　MRI

ダイナミックスタディーにて乳癌の造影パターンを示した．

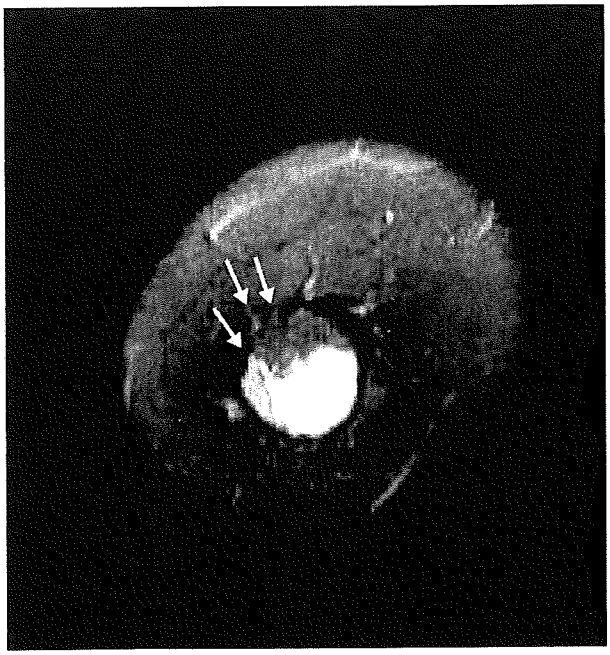

図4　MRI

T2W1において嚢胞壁と考えられる低信号域の断裂が認められ，MRI上，腫瘍の嚢胞壁外進展がみられた．

ICPCの術前病理学的診断を得た症例は計6例(60%)であり，残りの4例はCore needle biopsyでも確定できず切除生検にて乳癌の診断を得た．なお1例はFine needle aspirationおよびCore needle biopsyをともに施行せずに切除生検を行った．

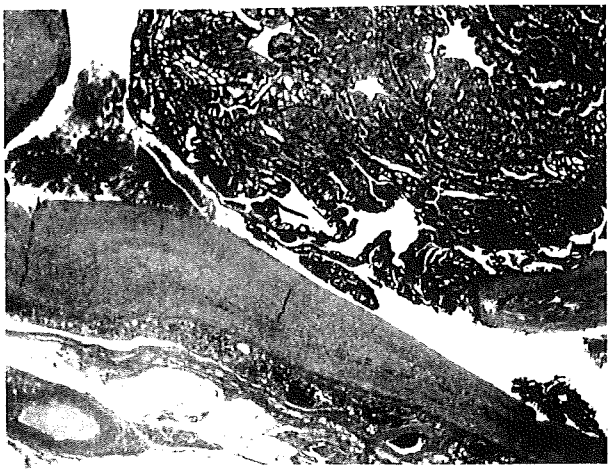

図5　病理組織所見
径5cm大の嚢胞内に2cm大の乳頭状隆起性病変を認め，嚢胞液は暗赤色であった．この隆起性病変は中等度の核異型，核分裂像を有する腫瘍細胞が乳頭状，cribriform patternを呈して増殖．

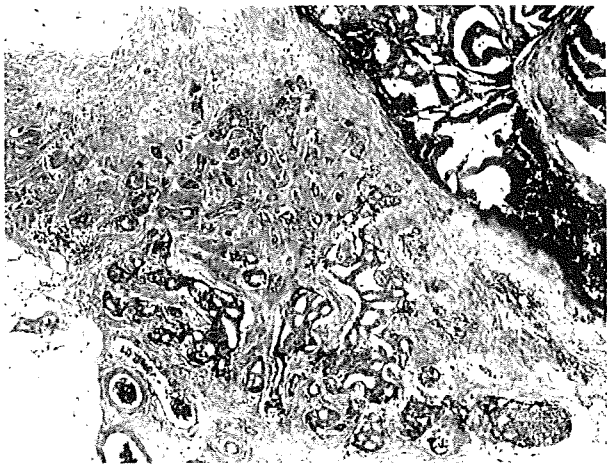

図6　病理組織所見
腫瘍細胞の間質への浸潤が認められた．

3) 手術・病理（表2）

5例に腋窩郭清を伴う乳房切除術および乳房部分切除術を施行，4例は腋窩郭清を伴わない乳房部分切除術を施行した．さらに2004年以降の4例はセンチネルリンパ節生検を伴う乳房切除術および乳房部分切除術を施行した．嚢胞内容液の性状はいずれもきわめて淡い血性から濃い暗赤色を呈し，14例のうち2例（14.2%）に間質浸潤を認めた．また3例に嚢胞壁外にDCISを認め，1例に腋窩リンパ節転移を認めた．G1とG2がそれぞれ8例（57%）6例（43%），NG1とNG2とNG3がそれぞれ8例（57%）5例（36%）1例（7%）であった．またホルモンレセプターはERが全例（100%），PgRは13例が陽性（92.8%）で，HER2は3例（21.4%），p53は2例（14.2%）が陽性であった．

4) リンパ節転移症例

ICPC14例のうち1例に腋窩リンパ節転移を認めた．本症例は82歳女性，病悩期間が24カ月，腫瘍径が20cmであった．Core needle biopsyでICPCの診断を得，乳房切除術およびセンチネルリンパ節生検を施行，術中迅速病理診断にてセンチネルリンパ節転移はなかったが，永久標本にてリンパ節1個にmicrometastasisを認めた．ER，PgRはともに陽性，HER2，p53はいずれも発現していなかった．作成標本上，嚢胞壁外への浸潤はみとめていない．

5) 補助療法・予後

13例にTAM投与，温存術8例中3例に残存乳房に対する術後照射を行った．男性症例の1例の他因死を除き，13例すべて再発の所見なく生存中である．次に代表的な1例（症例14）を提示する．

症　例：71歳，女性．

家族歴：特記事項なし．

既往歴：特記事項なし．

現病歴：2006年10月，左乳房腫瘤に気づき前医受診し，当科紹介となる．

入院時血液検査所見：末梢血，生化学検査ともに正常範囲内で，腫瘍マーカー（CEA 0.9ng/ml，CA15-3 14U/ml，ST439<1.0）の上昇もみられなかった．

入院時現症：左乳房E領域を中心にBD領域に及ぶ60mm大のやや弾性硬の腫瘤を認めた．胸筋，皮膚への固定は認めなかった．乳頭分泌なく，腋窩リンパ節も触知しなかった．

超音波所見（図1）：後方エコーの増強を伴った60×43×26mmの嚢胞と，嚢胞壁の一部から内腔に突出する21×18×7mm大の乳頭状腫瘍を認めた．

MMG所見（図2）：E領域に辺縁平滑で，ほぼ均一な腫瘤陰影を認めた．石灰化は認めなかった．

MRI：ダイナミックスタディーにて乳癌の造影パターンを示した（図3）．また，T2W1において嚢胞壁と考えられる低信号域の断裂が認められ，

MRI上，腫瘍の嚢胞壁外進展がみられた（図4）．

経　過：以上の所見より，2006年11月Core needle biopsy施行し，ICPCの診断を得て，乳房切除術＋センチネルリンパ節生検を施行した．術中迅速病理診断にてセンチネルリンパ節に転移は認めなかった．

病理組織所見：径5cm大の嚢胞内に2cm大の乳頭状隆起性病変を認め，嚢胞液は暗赤色であった．この隆起性病変は中等度の核異型，核分裂像を有する腫瘍細胞が乳頭状，cribriform patternを呈して増殖（図5），一部間質への浸潤が認められた（図6）．リンパ節転移は認めず(0/3)，G2，NG2および免疫組織学的検索にてER，PgRはともに陽性，HER2，p53はいずれも発現していなかった．

3．考　察

ICPCは嚢胞内腔へ乳頭状に突出し発育する乳癌で，乳癌全体の約2％弱[1]といわれている．一般的にductal carcinoma *in situ*の範疇で浸潤を伴うことはほとんどなく，現在の乳癌取扱い規約によれば，病巣が嚢胞内に限局し，非浸潤性嚢胞内乳癌とすることが記載されている．しかし，組織学的にも嚢胞壁外への浸潤や乳管内で広く進展を示す例[3]や，同時性肝転移例[4]などの報告もあり，定義についてはいまだコンセンサスを得られていない．したがって今回われわれは，浸潤の有無を問わず病理学的検索にて，ICPCと診断された14例を検討した．通常の乳癌と比較すると，平均年齢65歳（範囲34～92歳）[1]と高齢者に多いとされ，今回の14例でも中央値72.5歳（36～82歳）であり通常乳癌より高齢であった．また病悩期間も長いことも報告[2,5]されており，今回も中央値5カ月（1～24カ月）であった．腫瘍の性質として通常乳癌より発育が緩徐で，潰瘍を形成せずにGradeが低いため，放置されやすいと考えられる．良悪性の鑑別として，嚢胞内乳頭腫と鑑別は困難である．鑑別点としては嚢胞内乳頭腫の平均年齢は40.7～47歳で低く，60歳以上の嚢胞内腫瘍では，癌は81％に認めたという報告がある[7,8,9]．また腫瘍径は悪性であれば良性より大きい傾向にあるが，良悪性鑑別において診断的価値は低い[7,8]と報告されている．超音波検査は良悪性の鑑別検査としてあげられるが，嚢胞内腫瘤部分の辺縁など良悪性とも不整なものが多く鑑別にあまり有用でないといわれている[8,9]．通常乳癌における良悪性の鑑別としてMRIは有用であり，MRI所見が乳癌病理組織像を反映するという報告もある[10]．われわれは症例12以降の3例においてMRIを施行しいずれもダイナミックスタディーにて悪性を示す造影パターンを呈した．ICPCにおいても良悪性鑑別のため画像診断の1つとしてMRIは重要であると考えられる．またさらに，症例14においてMRIで腫瘍の嚢胞壁外浸潤を認めたように，MRIは進展度診断にも有用であり，嚢胞壁進展の評価にもきわめて有効である．以上より，少しでも悪性が疑われる場合はFine needle aspirationを行い，さらにCore needle biopsyをエコーガイド下に充実性部分を確実に穿刺することが必要である．しかし本検討症例においてもそうであるが，嚢胞内充実成分への針生検は難しく，Fine needle aspirationおよびCore needle biopsyにても診断の得られない症例では積極的に切除生検を考慮するべきと思われる．治療は原則として非浸潤性乳管癌(DCIS)治療に沿って行うことが可能である．しかし，嚢胞壁外浸潤を示す例[3]や，同時性肝転移例[4]などの報告もあることを把握しておく必要がある．報告によると浸潤癌はまれではなく，乳管内進展についても嚢胞壁より2cm以上超えて乳管内を進展するものも報告されている[6]．今回の14例中2例に浸潤部分を認め，さらに別の1例に作成標本には浸潤部は認めなかったが，リンパ節転移を認め，標本作成外に浸潤部分が存在したことが推察された．このように切除範囲決定には，MRIによる進展度評価を参考にし，広範な腫瘍進展を念頭において断端陰性となることが重要である．術前化学療法，術後化学療法の報告はなく，統一された指針はないが，第一選択治療は切除療法と考える．リンパ節転移に関しては0～25％と報告に幅があるが，通常の乳癌より頻度は低いとされている[8,9]．われわれは2004年以降よりセンチネルリンパ節生検を開始し，4例にセンチネルリンパ節生検を伴う乳房切除，乳房部分切除術を施行した．通常乳癌と同様，郭清省略には慎重であるべきで，センチネルリンパ節生検はよい適応と思われる．

今回14例すべてホルモン感受性を認め，乳房部分切除は8例に施行した．補助療法としては，明確な指針はないがDCIS治療にしたがって，症例を選びホルモン療法，残存乳房放射線照射などを考慮する必要があると思われる．

4. 結　語

ICPCの14例につき臨床病理学的検討を加え報告した．良悪性の鑑別は困難であり，Fine needle aspiration, Core needle biopsyに加え切除生検が必要である．切除範囲決定には，MRIによる進展度評価を参考に，広範な腫瘍進展を念頭において断端陰性となることが重要である．また，腋窩リンパ節の評価は病変の大きさに関わらず必要であり，現在広く施行されているセンチネルリンパ節生検は腋窩リンパ節転移の少ないICPCによい適応と考えられる．

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Original Articles

Feasibility Study of Docetaxel with Cyclophosphamide as Adjuvant Chemotherapy for Japanese Breast Cancer Patients

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Objective: The 7-year follow-up of the US oncology 9735 trial demonstrated the superiority of TC [docetaxel (DTX)/cyclophosphamide (CPA)] to doxorubicin/CPA therapy. To introduce TC therapy in Japan, the verification of the safety and tolerability is essential. We performed a collaborative prospective safety study with Okayama University to introduce TC therapy.
Methods: The subjects were 53 patients aged from 33 to 67 years at intermediate risk based on the St Gallen risk classification who underwent radical surgery for primary breast cancer between August 2007 and December 2008. As post-operative adjuvant chemotherapy, four cycles of TC (DTX 75 mg/m^2 + CPA 600 mg/m^2) were administered at 3-week intervals. Adverse events were evaluated based on National Cancer Institute—Common Terminology Criteria for Adverse Events ver. 3.0. The safety and completion rate were evaluated as the primary and secondary endpoints, respectively.
Results: Regarding hematological toxicity, Grade (G) 4 neutropenia occurred in 71.7% and G3 in 26.4%. G3–4 leukopenia developed in 32.1% and 56.6%, respectively, G4 anemia in 1.9% and G1–2 anemia in 26.4%. Regarding non-hematological toxicity, systemic malaise, skin eruption, edema, myalgia, arthralgia and nausea were noted in most patients. The completion rate was 94.3%, dose reduction was necessary in 7.5% and granulocyte colony-stimulating factor (G-CSF) support was required in 17.0%. On comparison between patients aged 65 years or older and younger than 65 years, the completion rate, dose reduction and incidence of febrile neutropenia (FN) were higher in the elderly patients. G-CSF support was more often needed in this subgroup.
Conclusions: TC therapy is tolerable for Japanese patients, but attention should be paid to the development of FN and neutropenia. The completion rate was lower in the elderly patients, showing that tolerability was not necessarily favorable.

Key words: breast cancer – docetaxel – cyclophosphamide – adjuvant therapy – safety

INTRODUCTION

The standard regimen most widely adopted for post-operative adjuvant chemotherapy for breast cancer is combination chemotherapy with drugs including anthracycline. Taxanes are also key drugs of post-operative adjuvant chemotherapy for breast cancer, and the efficacy of taxanes administered in addition to anthracycline regimens has been demonstrated by many randomized control trials (RCTs) (3). The US oncology 9735 trial (USON9735) was the first RCT in which anthracycline and taxane were directly compared as post-operative adjuvant chemotherapies for breast cancer, and the analytical results of a 7-year median follow-up have been reported (1,2). AC [doxorubicin 60 mg/m^2 i.v. on day 1; cyclophosphamide (CPA) 600 mg/m^2 i.v. on day 1; every 21 days × 4 cycles] and TC [docetaxel (DTX) 75 mg/m^2 i.v. on day 1; CPA 600 mg/m^2 i.v. on day 1; every 21 days × 4 cycles] were compared as post-operative adjuvant chemotherapies for Stages I, II and III resectable invasive breast cancer. The primary endpoints were disease-free survival (DFS) and overall survival (OS). The lymph node metastasis

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positivity rate was 50% in the patients, and 16% of the patients were 65 years of age or older. DFS was 81% in the TC group and 75% in the AC group ($P = 0.033$), and OS was 87% in the former and 82% in the latter ($P = 0.032$), showing that TC therapy was significantly superior regarding the two parameters. Concerning the safety profile, the incidence of febrile neutropenia (FN) was slightly higher in the TC than in the AC group, but long-term bone marrow toxicity and cardiotoxicity were low, showing that the therapy was feasible. It was also reported that the tolerability of elderly patients at 65 years of age or older was favorable, showing the superiority of TC therapy. Based on these, the standard post-operative adjuvant chemotherapy for early-stage breast cancer may change from the current regimens including anthracyclines to taxane-based regimens without anthracycline.

There are racial differences in the effects and adverse effects of chemotherapy. The standard regimens to administer many therapeutic drugs for breast cancer employed in Western countries are also applicable for Japanese, but the recommended doses of some drugs established by Phase II dose-setting studies conducted in Japan are lower than those in Western countries. The standard dose of DTX for every 3-week administration in monotherapy is 100 mg/m^2 in Western countries, but 70 mg/m^2 in Japan. Moreover, there is no safety data concerning the combination of DTX and CPA in Japan. To introduce the TC regimen (75/600) adopted in the USON9735 into Japan, the confirmation of its safety in Japanese is essential. Based on this background, we performed a study to confirm the safety of the TC regimen (75/600) of the USON9735.

PATIENTS AND METHODS

Of patients who underwent radical surgery for primary breast cancer at the Shikoku Cancer Center and Okayama University Hospital, those who met the following inclusion criteria were selected: an age between 20 and 70 years, and a risk category of intermediate or higher employing the 10th St Gallen risk classification assessed based on the clinical background and post-operative pathological diagnosis, i.e. hormone receptor-negative cases, lymph node metastasis-positive cases and lymph node metastasis-negative cases, hormone receptor-positive cases meeting one of the following conditions: a 2 cm or greater diameter of tissue invasion, histological grade of 2–3, 35 years of age or younger, the presence of severe vascular invasion and HER2-positivity. Estrogen (ER) and progesterone receptors were assessed by immunostaining, and a positive cell rate of 10% or higher was regarded as positive. HER2 was assessed by the Hercep test, and scores of 0 and 1+ were regarded as negative, and 3+ as positive. In cases graded 2+, the HER2/neu amplification rate was determined, and a 2.2 or higher rate was regarded as positive. Other inclusion criteria were the absence of distant metastasis and severe complications with a performance status of 0 or 1 and sufficient bone marrow, liver and renal functions. Written informed consent was obtained from all patients. Patients with pre-operative chemotherapy, a past medical history of drug allergy which may interfere with the therapy, inflammatory and bilateral breast cancers, double cancer and a past medical history of psychiatric diseases were excluded.

In the administration, after pre-treatment with 8 mg dexamethasone and 5-hydroxytryptamine $(HT)_3$ receptor blockade, 75 mg/m^2 DTX was administered by drip infusion for 60 min, followed by the administration of 600 mg/m^2 CPA for 30 min on day 1. From 12 h later, oral dexamethasone 4 mg was administrated twice daily for 2 days. These were administered every 21 days four times (four cycles). Blood testing was performed on the day of administration in each cycle to decide on the next administration. The criteria for initiating administration were as follows, and administration was postponed until all items recovered: WBC $\geq$3000/mm^2, neutrophil count $\geq$1500/mm^2, neuropathy $\leq$Grade (G) 2, edema $\leq$G2, liver dysfunction $\leq$G1 and renal dysfunction $\leq$G1. When these did not recover for 21 days from the scheduled administration day, the protocol was discontinued. When the following adverse reactions were noted in the previous cycle, the first dose reduction was performed based on the dose reduction criteria: (i) G3 or severer non-hematological toxicity, (ii) G4 or severer hematological toxicity excluding leukopenia and neutropenia and (iii) G4 leukopenia and neutropenia persisting for 7 days or longer. The level of first dose reduction was as follows: DTX, 60 mg/m^2 and CPA, 500 mg/m^2. When these adverse reactions were present after the dose reduction, the protocol was discontinued. Regarding supportive therapy, preventive antibiotic administration was prohibited, but administration for FN decided on by the attending physician was accepted. The preventive administration of granulocyte colony-stimulating factor (G-CSF) was also prohibited based on the ASCO 2006 guidelines, but according to the decision by the attending physician, the following administration criteria were accepted: (i) fever ($\geq$38°C) development with a neutrophil count of $<$1000/mm^2 or a neutrophil count of 500/mm^2 after the completion of drug administration, (ii) when an identical chemotherapy is employed after meeting the condition (i), the subsequent administration starts when the neutrophil count reaches 1000/mm^2.

The primary endpoint was set as the safety. The types and grades of adverse reactions were identified following the National Cancer Institute (NCI)—Common Terminology Criteria for Adverse Events (CTCAE) ver. 3.0, and the incidences of G3 or severer adverse reactions were evaluated. The secondary endpoint was set as the protocol treatment completion rate. During the protocol treatment period, the body weight and temperature were measured, and blood testing was performed to investigate adverse reactions once a week at the outpatient clinic. Expecting of the number of patients in our institutions for a year who correspond to inclusion criteria, the target number of enrollments was set

to 50. This study was approved by the Institutional Review Board.

The standard treatment arm in the USON9735 was AC (60/600), and the tolerability against this regimen has been reported and widely adopted in Japan. The dose of TC superior to AC shown by this trial should be accepted from a dose density viewpoint. Although a dose-setting study is necessary for the safety confirmation of translational combination therapy, the initial dose was set to TC (75/600). To ensure the safety of patients, an early stopping rule was established, in which enrollment was suspended after five early cases were enrolled until the completion of the protocol treatment in all five cases, and adverse reactions were evaluated. When the following adverse reactions were noted in two or more of the five cases, the study protocol was reviewed: (i) G3 or severer edema, (ii) G3 or severer peripheral neuropathy, (iii) FN, (iv) other G4 hematological toxicity and (iv) discontinuation of the protocol treatment due to an adverse reaction. The adverse event profiles of the five cases were submitted to the Effect/Safety Evaluation Committee to examine the feasibility of study continuation.

RESULTS

Enrollment was initiated in May 2007, and the five early cases were enrolled by July 2007. The protocol treatment was completed in four of the five cases, clearing the early stopping rule. Continuation of the study without protocol revision was approved by the Effect/Safety Evaluation Committee. Enrollment was re-started in September 2007, 53 were registered by October 2008 and the protocol treatment of the 53 cases was completed by January 2009. Adverse events could be adequately assessed in all patients.

The clinicopathological background factors of the patients are shown in Table 1. The median age was 54 years (33–67 years) and five patients (9.4%) were 65 years of age or older. Thirty-eight cases (71.7%) were ER-positive, 12 (22.6%) were HER2-positive, the mean tumor size was 1.94 cm (0.7–11.5 cm), and 22 cases (41.5%) were lymph node metastasis-positive, with a mean number of lymph node metastases of 1.4 (1–3).

The protocol treatment was completed in 50 of the 53 cases, with a completion rate of 94.3%. The protocol was discontinued in three due to fatigue, skin eruption, G4 leukopenia and neutropenia based on the judgment by the attending physician or patient's request. One was a 62-year-old female in whom G4 leukopenia and neutropenia occurred after the first cycle, and the dose was reduced following the dose reduction criteria in the second cycle, but her attending physician decided on discontinuation due to G4 hematological toxicity. The second case was a 67-year-old female in whom G4 leukopenia and neutropenia and G2 fatigue developed following the first cycle, and the treatment was discontinued based on the patient's request. The third case was a 61-year-old female in whom G4 leukopenia and neutropenia

Table 1. Patients characteristics

Category	*n*	%
Age		
<65	48	90.6
≥65	5	9.4
Median age	54 (33–67)	
Menopause		
Pre	24	45.3
Post	29	54.7
ER		
+	38	71.7
–	15	28.3
PgR		
+	32	60.4
–	21	39.6
HER2		
Positive	12	22.6
Negative	41	77.4
T		
T1	25	47.2
T2	27	50.9
T3	1	1.9
N		
0	31	58.5
1	22	41.5
Nuclear grade		
1	12	23.1
2	20	38.5
3	20	38.5
Number of pN		
0	31	58.5
1	16	30.2
2	3	5.7
3	3	5.7
Risk category		
Intermediate	49	92.5
High	4	7.5
Surgery		
Bp	32	60.4
Bt	21	39.6

ER, estrogen receptor; PgR, progesterone receptor; pN, pathological N; Bp, breast conserving; Bt, mastectomy.

Table 2. Hematologic toxicity

	Grade							
	1		2		3		4	
	n	%	*n*	%	*n*	%	*n*	%
Neutropenia	1	1.9	0	0	14	25	38	71.7
Leucopenia	0	0	5	9.4	30	56.7	17	32.1
Febrile neutropenia	0	0	0	0	15	28.3	0	0
Anemia	10	18.9	4	7.5	0	0	1	1.9

Table 3. Non-hematologic toxicity

	Grade					
	1		2		3	
	n	%	*n*	%	*n*	%
Fatigue	22	41.5	20	37.7	0	0
Aiopeicia	1	1.9	51	98.1	0	0
Arthralgia	18	34	2	3.8	0	0
Myalgia	18	34	3	5.7	0	0
Nausea	17	32.1	2	3.8	0	0
Vomiting	4	7.5	0	0	0	0
Constipation	11	20.8	2	3.8	0	0
Diarrhea	8	15.1	1	1.9	0	0
Edema	13	24.5	0	0	0	0
GOT, GPT	5	9.4	0	0	0	0
Nail change	15	28.3	0	0	0	0
Rash	18	34	10	18.9	1	1.9
Stomatitis	8	15.1	2	3.8	0	0
Watery eye	1	1.9	0	0	0	0
Neuropathy	10	18.9	2	3.8	0	0
Cystitis	2	3.8	0	0	0	0

GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

and G3 systemic skin eruption developed following the first cycle, and her attending physician decided on the discontinuation. Dose reduction conflicting with the dose reduction criteria was necessary in four cases (7.5%).

On hematological toxicity evaluation following the NCI-CTCAE, G3–4 leukopenia developed in 47 (88.7%), G3–4 neutropenia in 52 (98.1%) and FN in 15 (28.3%). G-CSF was administered to nine (17.0%). G4 anemia occurred in one (1.9%) (Table 2).

Regarding non-hematological toxicity, hair loss occurred in most patients, and G2 or milder fatigue in 42 (79.2%). Edema occurred in 13 (24.5%), but all were G1, and could be resolved by diuretic treatment. G2 or milder arthralgia and myalgia occurred in 20 (37.8%) and 21 (39.7%), respectively. Peripheral neuropathy developed in 12 (22.7%), but the severity was G2 or milder (Table 3).

As another non-hematological toxicity, skin eruption accompanied by pruritus appeared at a high incidence. In one case (1.9%), systemic skin eruption developed and was graded G3.

As subgroup analysis by age, the patients were divided into those aged 65 years or older and those younger than 65 years, as in the USON9735. Dose reduction was necessary in 2 of 48 patients younger than 65 years (4.2%), and 2 of 5 patients aged 65 years or older (40%). All patients in the younger group completed the protocol treatment, whereas only two of the five patients (40%) completed the treatment in the elderly group, with higher dose reduction rate, decreasing the completion rate. FN developed in 11 (22.9%) in the younger group and 4 (80%) in the elderly group, showing that the incidence of FN was also higher, and G-CSF support was more often needed in the elderly patients (Table 4).

Table 4. Summary by age group

	≥65 ($n = 5$)	<65 ($n = 48$)
Completion rate	40%	100%
Dose reduction	40%	4.2%
G-CSF support	40%	14.6%
Febrile neutropenia	80%	22.9%

G-CSF, granulocyte colony-stimulating factor.

DISCUSSION

Although the importance of systemic drug therapy to improve the prognosis of breast cancer is widely recognized, combination chemotherapy including anthracycline has been employed as the standard post-operative adjuvant chemotherapy after initial cyclophosphamide, methotrexate, 5-FU therapy (4–6). Many clinical studies have since been performed, and the efficacy of additional taxane administration for lymph node metastasis-positive and -negative high-risk cases was demonstrated, which attracted attention to taxanes for post-operative adjuvant therapy (7,8). Although the efficacy of anthracyclines was established, the development of cardiotoxicity and myelodysplasia as late adverse effects was often problematic. An increase in the incidence of cardiotoxicity to 4–18% in a cumulative dose-dependent manner has been reported (9). Three fatal cases due to heart disease and osteomyelodysplasia syndrome were also reported in the USON9735, for which the involvement of adriamycin could not be ruled out because of the administration of the AC arm alone (1). As HER2 and Topo IIα gene aberrations attract attention as anthracycline efficacy predicting factors, the

individualized administration of anthracycline in consideration of these predictive factors may also progress in the future (10,11). In addition, a recurrence-inhibitory effect of trastuzumab in HER2-overexpressing patients has been demonstrated, and the frequency of combining trastuzumab with cytotoxic drugs or consecutive administration has increased, with which the usefulness of taxanes with lower-level cardiotoxic adverse effects has been increasing (12,13). As the superiority of TC to AC therapy was demonstrated in the USON9735 (1,2), taxane regimens not including anthracycline may become a major trend in the future, and this trend may not be ignored in Japan. Regarding the safety, although the 9735 trial reported favorable tolerability (1), it is well known that there exists ethnic or racial difference in pharmacokinetics and pharmacodynamics. These have been attributed to the distinctions in the genetics, physiological and pathological factors. Moreover, these differences are also known to be influenced by several extrinsic factors such as socioeconomic backgrounds, culture, diet and environments (14,15). Therefore, the verification of tolerability and adverse effects is an important clinical task to introduce TC therapy into Japan. This is the first report on the safety of TC therapy in Japanese patients.

The overall completion rate was 94.3%, similar to that (93%) in the USON9735. The protocol treatment was discontinued in three cases (5.7%). Dose reduction was necessary in 7.5%. The dose intensities of DTX and CPA were 98.5% and 98.7%, respectively. The completion rate was mostly favorable, and fewer cases required dose reduction, but hematological toxicity: G3–4 leucopenia and neutropenia occurred in almost all cases. In the USON9735, the incidence of G3–4 neutropenia was 61%, slightly lower than that in the present study, but this difference may have been due to variation in the observation interval: every 3 weeks in the 9735 trial, whereas weekly in our study to closely observe adverse effects. Since the safety of TC therapy in Japanese was confirmed by this study, observation every 3 weeks and on the administration days may be sufficient for actual clinical practice. The incidence of FN in all cases was reported to be 5% in the USON9735, but attention should be paid to the fact that the administration of prophylactic antibiotics was accepted in the USON9735. No prophylactic administration was performed in our study, and the incidence was 28.3%. FN could be controlled by oral antibiotics in most cases, but G-CSF administration was necessary in 17%. Regarding hematological toxicity in AC therapy (60/600 mg/m^2), Tsutani et al. (16) reported that G3–4 neutropenia occurred in 24.3% and FN in 3.8% in Japanese. Based on these findings, the incidences of hematological toxicity and FN are apparently higher in TC than in AC therapy, to which closer attention should be paid. For actual clinical cases, prophylactic antibiotics administration may be considered. Regarding non-hematological toxicity, G2 or milder edema developed in 34% in the USON9735, whereas the grade was G1 or milder, and the incidence was only 24.5% in our study. Diuretics were administered to some cases, but most cases remitted under course observation alone. The incidences of nausea and vomiting were 35.9% and 7.5%, respectively, lower than those in the USON9735 (53% and 14%, respectively). Another non-hematological toxicity mentioned was skin eruption. The incidences of G1, G2 and G3 skin eruption were 34%, 18.9% and 1.9%, respectively, ~55% in total. Skin eruption persisted after the completion of four cycles in some cases. The establishment of effective countermeasures against skin eruption in TC therapy is necessary. Regarding DTX-induced skin eruption, although several cases have been reported, no therapy has been established, and only symptomatic therapy is available (17–19). The incidence in DTX monotherapy is reported to be 20–48%, suggesting that the combination with CPA increases the rate of development (20).

The subgroup analysis by age in the 9735 trial concluded that the incidence of adverse effects in elderly patients aged 65 years or older was not significantly different, and the tolerability of the elderly patients was favorable (1). In contrast, in our study, because of the small sample size, statistical comparison was not performed, the protocol treatment completion rate was lower in the patients aged 65 years or older than in those younger than 65 years (40% vs. 100%), the dose reduction rate was higher (40% vs. 4.2%) and the incidence of FN was higher (80% vs. 22.9%) (Table 4). Although the number of patients was small, it cannot be concluded that TC therapy is applicable for patients aged 65 years or older. Loibl et al. (21) investigated tolerability against taxane-based adjuvant therapy by age, in which the incidences of leukopenia and neutropenia increased with age, but the incidence of FN was similar. Regarding non-hematological toxicity, there was no age-related difference in the incidence of G1–2 fatigue, but the incidence of G3–4 fatigue was significantly higher in the elderly patients. Regarding skin eruption, there was no age-related difference in the incidence of G1–2, but that of G3 or severer skin eruption was significantly higher in the elderly patients (21). Although simple comparison with TC in the above reports is difficult because the regimen was different, these previous reports may support our study results regarding the feasibility of taxane-containing regimens for elderly patients. No significant difference was noted in non-hematological toxicity between the age groups, which may have been due to the small number of patients.

This study confirmed that TC therapy can be safely performed in Japanese. Regarding hematological toxicity, since FN developed at a relatively high rate (28.3%), the use of prophylactic antibiotics should be considered. Regarding non-hematological toxicity, no severe edema developed, but skin eruption accompanied by pruritus appeared in about half of the patients, for which the establishment of supportive therapy may be necessary. On profiling adverse effects by age, the incidence of hematological toxicity markedly increased in patients aged 65 years or older, decreasing the treatment completion rate. The tolerability of patients aged

65 years or older is not favorable, and administration should be carefully decided upon.

Conflict of interest statement

None declared.

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CASE REPORT

Two cases of occult breast cancer in which PET-CT was helpful in identifying primary tumors

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Abstract We report two cases of occult breast cancer in which masses were completely nonpalpable and positron emission tomography-computed tomography (PET-CT) was extremely helpful in identifying the primary tumor. Case 1 involved a 56-year-old woman with enlarged lymph nodes 3 cm in size in the axilla. Based on excisional biopsy, axillary lymph node metastasis of breast cancer was suspected but an obvious primary tumor in the breast was not identifiable on mammography, contrast-enhanced CT, or ultrasonography. Faint accumulation of fluorodeoxyglucose (FDG) was noted only on PET-CT, so the site was considered to be the primary site, and operation was performed. As a result of postoperative pathological examination, ductal carcinoma in-situ (DCIS) was diagnosed. Case 2 involved a 55-year-old woman with enlarged lymph nodes 3 cm in size in the axilla. Based on the excisional biopsy, axillary lymph node metastasis of breast cancer was suspected. In this case as well, an obvious primary tumor was not identifiable with palpation or mammography. On PET-CT, faint accumulation of FDG was noted in the vicinity of the CD regions, or upper and lower outer quadrants. When contrast-enhanced CT and ultrasonography were performed, a faint nodular opacity less than 1 cm in size corresponding to this site was found and diagnosed as the primary site, operation was subsequently performed. Pathologic diagnosis indicated invasive cancer. PET-CT is a helpful option for the diagnosis of occult breast cancer with primary sites that conventional imaging studies have difficulty identifying.

Keywords PET · Occult cancer · Breast cancer

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Background

The frequency of patients with occult breast cancer with a chief complaint of only enlarged axillary lymph nodes is about 0.3–1% of breast cancers overall [1]. With progress in diagnostic imaging equipment, an increasing number of reports state that contrast-enhanced MRI or CT are able to identify primary tumors, but there are also numerous in which the primary site is unclear on imaging. We discuss two cases of occult breast cancer in which the primary site was nonpalpable and could not be identified on mammography, but it was identified with positron emission tomography-computed tomography (PET-CT).

Case reports

Case 1

The patient was a 56-year-old woman who detected a mass in her left axilla and was seen as an outpatient. On palpation, several enlarged lymph nodes about 2 cm in size were palpated in the axilla. Following excisional biopsy, poorly

differentiated adenocarcinoma was diagnosed. Based on the results of histology and immunostaining (ER 3+, PgR−, and HER2 1+), axillary lymph node metastasis of left breast cancer was suspected, and further examinations were performed. No particular abnormalities were noted on laboratory data, and tumor markers (CEA and CA15-3) were all within normal ranges. A tumor that could be considered an obvious primary tumor was not palpable even with palpation of the left breast. No obvious abnormalities were noted on ultrasonography, and mammography was Category-1. On contrast-enhanced CT, several enlarged lymph nodes with a maximum size of 3 cm were noted at Levels I and II (Fig. 1), but contrast-enhanced regions that could be considered the primary tumor were not detected in the breast. The patient was given a diagnosis occult cancer of unknown primary site, and PET-CT was performed. As shown in Fig. 2, regions displaying faint uptake of fluorodeoxyglucose (FDG) with a standard uptake value (SUV) of 1.06 were noted in the CD regions, or upper and lower outer quadrants. Sites otherwise displaying accumulation of FDG were not present; the same sites were determined to be the primary tumor, and mastectomy and axillary dissection were performed. Results of postoperative histopathological examination indicated DCIS with intraductal spread spanning a maximum area of 4 cm. According to the UICC staging, this was pTis N3a M0 stage III C. In the excised specimens, sites with accumulation of FDG matched sites with the primary tumor.

Case 2

This case involved a 55-year-old woman. She underwent sigmoidectomy for sigmoid colon cancer (well-differentiated adenocarcinoma stage III a) and was followed up

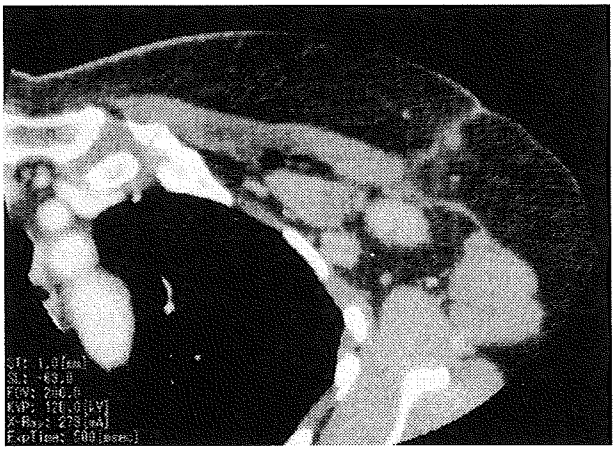

Fig. 1 Contrast-enhanced CT showed several enlarged lymph nodes with a maximum size of 3 cm at Levels I and II

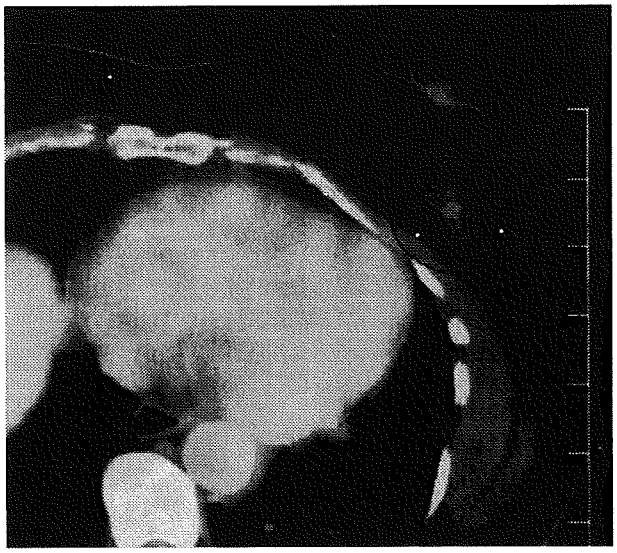

Fig. 2 PET-CT showed faint uptake of fluorodeoxyglucose (*FDG*) with a standard uptake value (*SUV*) of 1.06 in CD regions, or upper and lower outer quadrants (*red circle*)

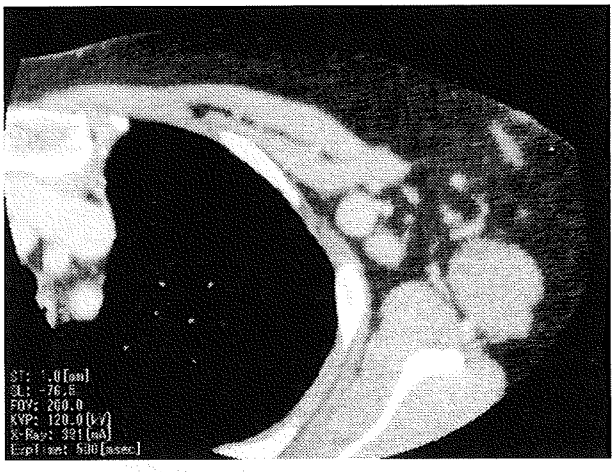

Fig. 3 Contrast–enhanced CT showed enlarged axillary lymph nodes on the left

periodically as an outpatient. In about the second year after surgery, enlarged axillary lymph nodes were noted on the left side (Fig. 3). Fine needle biopsy (FNB) of the site was performed, and ClassV tumor was diagnosed. Excisional biopsy showed poorly differentiated adenocarcinoma. Immunostaining results were keratin 7/20(±), CDX-2(−), ER(−), and PgR(−); axillary lymph node metastasis of sigmoid colon cancer was disproved, and metastasis from breast cancer was diagnosed. Tumor markers were within normal ranges. When PET-CT was performed, faint accumulation of FDG with an SUV of 1.50 was noted in the C region, or upper outer quadrant, of the left breast (Fig. 4).

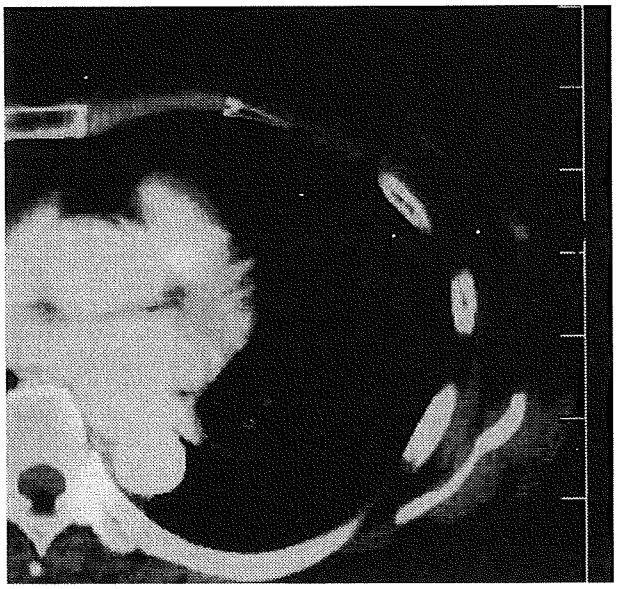

Fig. 4 PET-CT revealed faint accumulation of FDG with a SUV of 1.5 in the C region, or upper outer quadrant, of the left breast (*red circle*)

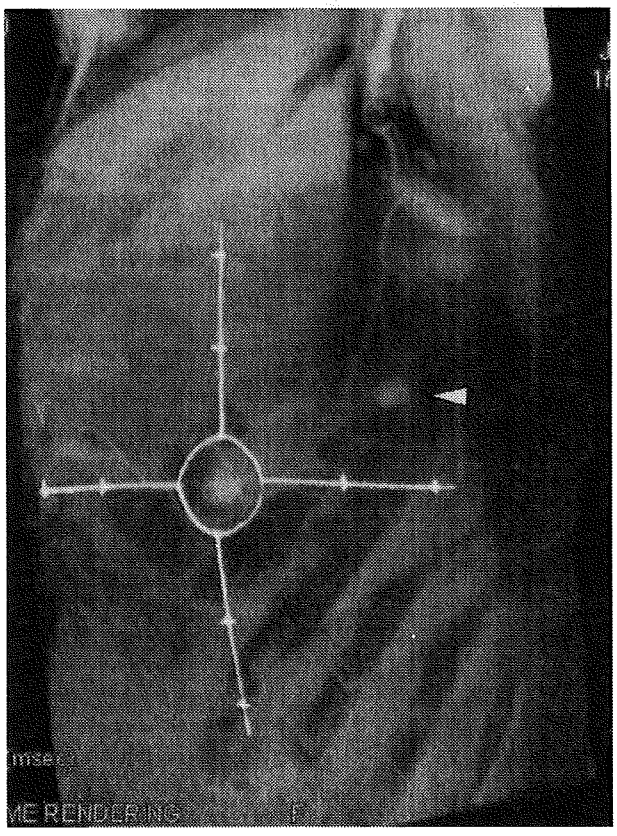

Fig. 5 3D CT revealed the tumor about 1.3 cm in size corresponding to the same site noted on PET-CT (*white arrow*)

A tumor about 1.3 cm in size corresponding to the same site was noted in contrast-enhanced CT and ultrasonography (Fig. 5). This site was determined to be the primary site, but the tumor was nonpalpable and could not be identified with mammography. Ultimately, the axillary lymph node metastasis of breast cancer was diagnosed, and breast-conserving surgery was performed. The postoperative pathologic diagnosis of the primary tumor was invasive ductal carcinoma 1.0 × 0.9 cm in size; solid-tubular carcinoma was diagnosed. According to UICC staging, this was pT1b N2a M0 stage III A.

Discussion

In a limited sense, occult cancer means cancer of unknown primary origin found at a metastatic site, but this term is currently used in a broader sense to include cancer found at a metastatic site. The frequency with which enlarged axillary lymph nodes are found in malignant tumors is highest for malignant lymphoma, followed by breast cancer [2]. Kemeny et al. [3] reported that more than 90% of patients with axillary lymph node metastasis diagnosed with adenocarcinoma had metastasis from breast cancer, and they concluded that there was almost no sense in actively searching for other the primary tumors. While there is metastasis from other sites like thyroid, lung, stomach, pancreas, and colon occur, the frequency of each is only several percent [3]. Tumor markers may serve as a diagnostic reference for these metastases. When metastasis from breast cancer is suspected, if the tumor cannot be palpated then the first examinations should be mammography and ultrasound. Often, though, no abnormalities are noted, as in Case 1. Baron et al. [1] reported that 44% of primary tumors were identified by MMG. With progress in imaging equipment, an increasing number of reports describe cases in which the primary tumor was identified with contrast-enhanced CT or MRI [4–8]. Thus, occult breast cancer that is truly unknown primary site is decreasing. According to a report by Akashi et al. [8], contrast-enhanced CT was able to identify primary tumors as small as about 1 cm. For the detection of DCIS, delayed imaging is sometimes useful, but in Case 1, delayed image could not detect the primary lesion. There are numerous reports on the usefulness of contrast-enhanced MRI [4–7]. Morris et al. reported that contrast-enhanced MRI has an identification rate of 75% [4]. In institutions that does not have PET-CT, it is appropriate to conduct MRI, if the primary lesion is not detected by ultrasonography, MMG, and contrast-enhanced CT scan. However, in our institution, fortunately, PET-CT is readily available. Therefore we conducted PET-CT because it is helpful to examine the whole body as well as the suspected primary site

simultaneously. There have been several reports on the usefulness of PET-CT [9–11], Avril et al. [12] reported that for 12 cases of non invasive breast cancer, the false negative rate of PET-CT was 9%, and the sensitivity was 25%. Owaki et al reported a case of DCIS 0.9 cm in diameter which was detected by PET-CT [13]. Walter et al. [14] reported the sensitivity of MRI and PET-CT for breast disease was 89 and 63%, respectively, the specificity was 74 and 91%, respectively. Problems with contrast-enhanced MRI include its low specificity and potential to produce a certain amount of error in localization because body position during imaging differs from that during surgery. Based on these characteristics, it is important to use different imaging methods according to the case. The major advantages of PET-CT over other examinations are obviously that it allows a search of the entire body in only one examination and that it can almost rule out primary sites besides the breasts. Compared with MRI, PET-CT has low spatial resolution. But in cases of occult cancer, the main purpose is the detection of the primary site. I think low spatial resolution does not matter. In terms of cost-effectiveness, PET-CT is obviously disadvantageous. However for patients, the decrease of repeat examinations and hospital visits is sometimes a great advantage for patients' mental and physical status.

In our report, the tumor in Case 1 might have been identified if MRI had been performed, but PET-CT allows localization to an extent and the results of this case indicate that it may serve as a helpful diagnostic option. In case 1, there was no preoperative histological corroboration, but in the literature there have been reports of breast failure rates reaching close to half when the breast is not treated. After this was explained to the patient, consent for a mastectomy was obtained. Despite a postoperative histologic diagnosis of DCIS, marked axillary lymph node metastasis had occurred, so microinvasion was anticipated in the primary lesion. However, this was not histologically detected. In case 2, contrast-enhanced CT and ultrasound might have eventually detected the primary tumor-like structure, but PET-CT demonstrated superior diagnostic ability.

A problem with PET-CT is that facilities capable of using this technique are limited, so the technique cannot be considered a common one. If PET-CT becomes more widespread in the future, it is sure to demonstrate its power for diagnosing occult breast cancer.

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