その後の報告もあわせ、2剤（ACなど）ではCMFとの差はないが、3剤(CAFなど)においてはCMF療法よりも勝っているとされている。これが5-FUの効果なのかは不明である（表2）。

また、Adriamycinの投与量は60mg/m²以上の増量でもさらなる効果発現はないとされているが（CALGB 9344)、Epirubicinにおいては FEC50とFEC 100の比較からFEC100が健存率および生存率において有意に良好な結果をもたらしており、dose responseが認められた（FASG Trial)。この点については術前化学療法におけるFEC 50とFEC100の比較で、HER2陰性においては奏効率に有意差はなかったが、HER2陽性例においては両者の差は明らかでFEC100投与例において良好な奏効率を示していた（Clin C Research. 7：1577-81, 2001)。このことはHER2陽性例に対してはEpirubicin投与量の増量（60mgから90-100mg/m²へ）が必要であることを意味している。

表2. 早期乳癌における2剤および3剤でのAnthracyclineレジメンとCMFとの比較

Author		症例数	Regimens	健存率, %
2剤 Anthracycline				
Fisher, 2001	*N-*	*2008*	*AC vs CMF*	*88 vs 88*
Fisher, 1990	N+	1557	AC vs CMF	62 vs 63
Piccart, 2001	N+	777	EC/HEC vs CMF	72/80 vs 78
Galligioni, 2000	N+	207	EC vs CMF	5.5 vs 4.2 yrs (median)
≥3剤 Anthracycline				
Misset	N+	248	AVCF vs CMF	53 vs 36*
Carpenter	N+	528	CAF vs CMF	NR**
Hutchins	N-	2691	CAF vs CMF	85 vs 82*
Mouridsen	N-/N+	1195	CEF vs CMF	63 vs 58*
Levine	N+	710	CEF vs CMF	63 vs 53*

*P < .05; **P > .05 for overall survival.

3）補助療法におけるTaxanesの役割

リンパ節転移陽性乳癌に対するCALGB 9344 Intergroup TrialにおけるACx4サイクル後のPaclitaxelx4サイクルの有無での結果をみると、Paclitaxel投与群において健存率および生存率は良好な結果を示していた。さらに2003年ASCOにおいて発表されたリンパ節転移例に対するACx4サイクルとさらにPaclitaxelx4サイクルを追加する治療とのNSABP B28の結果（Mamounasら）をみると、術後の健存率において有意にPaclitaxel追加群が良好であった。この効果はホルモンレセプター陽性例やTamoxifen内服例においても認められ、注目されている。

Docetaxelについてみると、2002年のASCOで発表されたBCIRG 001 trialで、リンパ節転移陽性例に対するFAC療法とTAC療法の比較を行い、術後3年目時点ではあるがTAC群の健存率が良好であった。とくに興味がもたれたのはリンパ節転移個数が1－3個と少ない群でよりその差は明らかで、4個以上群では逆に全く差は認められなかった点である。このことは病期の進んでいない症例では強力な治療が有効であるが、進行した症例ではそれ程治療の意味がないということを示唆している。しかし、さらなるfollow-upと検討が必要である。そして、TACの効果はER陽・陰性に関わらず出現していたが、HER2状況でみると、HER2陽性例においてFAC療法との差が有意となっていた。

このように、Taxanesを含んだ治療法の検討がおこなわれているが、表3に示すようにPaclitaxel、Docetaxelともに追加した治療群が良好な成績を示していた。ただ、Paclitaxelは4サイクルでいいのか、またDocetaxelとどちらが有用性が高いのかなど解決されていない点も多い。

表3. Taxanes vs non-Taxanes adjuvant/neoadjuvant 臨床試験の成績

Study	Adj/neo	Results
CALGB9344	Adj	AC<AC+P, 再発17%↓
MD Anderson	Adj	FAC<FAC+P,再発26%↓
BCIRG 001	Adj	FAC≦TAC, DFS 74% vs 82% OS NS
MD Anderson	Neo	Tri-weekly<weekly, pCR 15% vs 29%
Aberdeen	Neo	pCR; CVAP < CVAP+D,
NSABP B27	Neo	AC<AC+D, pCR 13.7% vs 25.6%

4）投与量・間隔の問題：Dose Dense療法がいいのか

Dose Intensive Chemotherapyとは単位期間（週）あたりの投与量を多くする方法であるのに対し、Dose Dense Chemotherapyとは間隔を短く投与する方法である。CALGB 9741 trialではdoxorubicin、cyclophosphamide、paclitaxelを用いて、標準的な3週間投与とこれを2週間に短縮したdose denseの比較、さらには逐次投与がよいのか、同時投与がよいのかについても検討された。結果をみると同時か逐次かには差がなく、dose dense投与が標準投与よりも健存率、生存率ともに有意に優れていた。また、

有害事象についてもGCSF投与により問題なく行われていた。しかし、GCSF投与が必ず必要であるし、わが国での採用は現時点では困難である。

このdose dense投与を術前化学療法の面でみると、Geparduo Study（ASCO, 2002）において、adriamycinおよびdocetaxelの同時dose dense投与とAC-docetaxelの遂次投与を比較している。臨床的および組織学的CR率はともにdose dense投与が劣っていた。一方、Epirubicinを用いた試験で、CEF（60mg/m²x2/4W）とdose dense EC（120mg/m²/2W）の比較を行い、CR率はCEF群がやや良好であり、健存率も同等であった（J. Clin. Oncol., Vol.21, No.5, 2003)。このように、術後補助療法における場合と違い、術前療法においてはdose　dense投与のbenefitはないという結果であった。

5）化学療法と内分泌療法の投与時期・順序

Breast INT 0100 trialにて化学療法のCAF療法と内分泌療法であるTamoxifenを同時投与する場合と遂次投与の比較試験が行われた。8年での結果、CAFからTAMへと遂次投与された群の健存率はCAFT（同時投与）群よりも良好であった（18%の再発リスク低下)。もちろんTAM単独群に対しても良好な結果を示していた。これの機序として、CAF療法などの化学療法がcell　cycle中にある増殖細胞に有効であるのに対し、TAMにはG0/G1の増加およびS期細胞の減少を引き起こすことが認められており、この作用点の相違によりもたらされたものと考えられる。この発表より、化学療法とTAMの同時投与は行われなくなった。ただし、アロマターゼ阻害剤の化学療法との関連性については不明である。

6）術後補助化学療法の施行基準など

補助療法としての化学療法を行う基準はSt.Gallenのrecommendationにより、リンパ節転移陽性例およびハイリスクのn0乳癌とされている。ハイリスクの捉え方に多少の相違はあるものの、大方の理解は得られている。これまでの考え方では化学療法はより進行した症例、例えばn（+）高度例に対して行われていたが、近年のデータをみるにリンパ節転移に関わりなく行われるようになったし、ましてやn（+）軽度例に有効とも言われている。また、化学療法はER（−）のみでなく、ER（+）例に対しても有効とする報告もあり、ER状況は適応基準から除外されそうである。

投与量については標準とされる量を下回る投与での有効性は確認されておらず、GCSFをも使用すべきであると云われている。一方、標準を大きく上回る投与もまた有効性は確認されていない。

現時点でのまとめとすれば、

・術後補助療法（化学療法、ホルモン療法）をすることで明らかな生存の延長が認められる。
・Anthracyclineが含まれたレジメンは、Anthracyclineが含まれないものより明らかに優れている。
・Taxanesが含まれたレジメンは、含まれないレジメンより優れている（未確証だが)。

3.術前化学療法について

1）利点と欠点

まず利点として、以下のことが考えられる。

・早期に全身治療を始められる
・手術後の急速増殖を防ぐことができる
・手術や放射線で障害されていない血管系から薬剤をゆきわたらせることができる
・化学療法の効果を病理学的に確認できる
・原発巣およびリンパ節転移の縮小により、down stagingができる
・局所療法の軽減、さらに乳房温存手術が可能となる

次に欠点としては以下のことが懸念される。

・Non responderにとっては局所療法開始が遅れる
・薬剤耐性を誘発する

・臨床病期以外の予後因子の判定が不可能、不正確になる
・手術，放射線療法のリスクが高くなる
・Overtreatment になる case（非浸潤癌）がある

2）Epirubicin を用いた熊本市民病院のデータ

CEF および EC 療法による Primary chemotherapy の効果についてみると、臨床的奏効率は31/53（58.5%）であり、組織学的奏効率は Grade 2 以上を有効とすると11/42（26.1%）であった。とくに問題となるのは臨床的に有効であっても組織学的にはほとんど効果なしと判定された症例が存在することである。今回の対象では臨床的 PR：23例中組織学的に有効であったのはわずか 7 例（30.4%）であった。臨床的に効果が高かったのは高増殖能例であり、組織学的な効果に最も関連していたのは EIC であった（Nishimura ら：Breast Cancer, 2003)。

現在は Taxanes を含んだレジメン（ET 療法）を用いている。

3）術前化学療法の trial から学ぶ

これまでに行われた術前化学療法の成績から、（1）術前化学療法と術後療法において生存率の差異はない。（2）術前化学療法により乳房温存手術の機会を増やすことができる。（3）治療効果の予測因子はまだ確定していない。また、乳房温存手術を目指した化学療法も今後増加するものと思われるが、Rouzier らは化学療法後に温存手術を行った症例の乳房内再発率は 5 年：16%、10年：21.5%と高率であったと述べている（J Clin Oncol 2001)。この点は NSABP B18の結果からも臨床的 CR 例の再発率は低いが、非CR例では高率と報告されている（Fisherら)。この点は前述したように、縮小しても組織学的には viable な細胞が多く残っていることも多く、効果発現の predictive factor と広がり診断がさらに重要となる。

今後の問題としては
・術前化学療法の対象患者はどのような患者か
・どのようなレジメンを用いるのが良いか
・術前化学療法の効果予測は可能か？
・乳房温存手術の適応基準は？

以上の問題はあるものの、術後化学療法の対象症例に対して、まず化学療法を術前に施行し、その効果を確認し、その後の治療法を決定するという考えも出てくる。今後はさらに術前化学療法は乳癌治療において重要な位置を占めることになるであろう。化学療法を行うにあたっては、患者サイドと十分な Informed Consent のもとに治療法を決定すべきであることは云うまでもない。

原著

2004.9.21受付

術後補助療法は乳房温存手術後の乳房内再発抑制に寄与しているか？

西村令喜[*1]　松田正和[*1]　岡崎伸治[*1]　甲斐千晴[*1]　日吉幸晴[*1]

Does Adjuvant Systemic Therapy Contribute to Decrease of Breast Recurrence after Breast-conserving Surgery?：Nishimura R, Matsuda M, Okazaki S, Kai K, Hiyoshi Y(Department of Surgery, Kumamoto City Hospital)

Preventing breast recurrence after breast-conserving surgery is an important issue. The main factors contributing to breast recurrences are positive margins and absence of radiotherapy. In late years a standard adjuvant treatment is widely used in Japan. We examined whether these standard treatments contributed to reduction of a breast recurrence. By March 2003, 845 patients were treated by breast-conserving surgery, and the cases were divided into two groups by operation period; 426 cases until 1998(the first half group) and 202 patients with follow-up periods more than 2 years (the latter group). There were much positive margins and patients with radiotherapy in a latter group in background factor. An endocrine therapy for ER positive was performed in 68.1% in first half period, and in contrast 94.2% in the latter period, and chemotherapy was performed in 87% (mainly Epirubicin) for ER negative in the latter period, and 77%(mainly oral agent) in the first half period. There was a significant difference of breast recurrence-free survival between 2 groups; an early recurrence was seen in 19 cases (4.5%) in the first half period and 2 cases(1.0%) in the latter group. In particular the difference was significant in patients with absence of radiotherapy or negative ER. Multivariate analysis revealed that the operation time was a significant factor for breast recurrence. In conclusion, an apparent reduction of breast recurrence may be brought by a standard adjuvant therapy.

Key words：Breast cancer, Breast conserving surgery, Breast recurrence, Adjuvant therapy
Jpn J Breast Cancer **19**(6)：568～574, 2004

はじめに

1980年代に始まったわが国の乳房温存療法の施行率はすでに40%を超え，さらに適応拡大もあいまって，今後も増加が予想されている．この乳房温存療法において最も重要なことは乳房内再発の回避であり，放射線治療の非施行と切除断端陽性が乳房内再発の重要な因子であるとされ[1,2]，さらに，若年者，ER(エストロゲンレセプター)陰性なども有意なリスク因子と報告されている[3,4]．適応拡大により，再発リスクを持つ症例が増加する可能性もあり，適応拡大とともに再発防止への対策も必要である．そのためには全例において断端を陰性にし，放射線治療を行うことが求められるが，それでも再発例は存在すると思われるし，適応拡大とは逆に症例は限定されてくる．さらなる再発を抑制する手段として考えられるのは術後の補助療法である．これまでの報告で術後化学療法およ

*1 熊本市民病院外科

表1　対象症例および乳房内再発

1．対象症例　(術前化学療法例を除く)
1989.4月～2004.3月　乳房温存手術施行：845例
術式変更　45例　↓
最終的な施行例：800例
うち術後2年以上経過した例：628例
前期：1989年4月～1998年　426例（温存率：37.3%）
後期：1999年～2002年5月　202例（温存率：42.6%）

2．再発例　乳房内再発：51例(6.4%)

再発部位	症例数	乳腺内	乳腺外*
Breast	31(3.9%)	17	14
Breast+Distant	20(2.5%)	8	12
Distant	45(5.6%)		

*乳腺外再発の内訳
炎症性乳癌型：　8例
リンパ節：　2例
筋肉内：　6例
皮膚，皮下：　10例

びTamoxifenにより乳房温存手術後における局所再発率の減少が報告されている[5,6]．

一方，近年，術後の補助療法はSt.Gallen国際会議などにより標準的な治療が推奨され，わが国においても標準治療が浸透し，多くの施設で施行されている．当院においても1999年よりAnthracycline系薬剤(Epirubicin)を含む化学療法を積極的に施行している．これらの標準的治療が乳房内再発の抑制に寄与しているのかについてretrospectiveに検討した．特に悪性度が高い症例は2年以内の早期に再発が見られる場合が多いことより，今回はこの早期再発について検討を行った．

対象および方法

1989年4月より2004年3月までに当科にて施行した乳房温存手術例は845例である(術前化学療法例を除く)．このうち最終的に乳房温存手術を施行し，術後2年以上経過した例は628例である．この症例を1998年までの前期と1999年以降の後期に分けると，各々の症例数は426例，202例となった．また，同期間の全手術例に対する温存手術率は37.3%，42.6%であった．これまでの乳房内再発例は**表1**に示すように51例であり，うち乳腺内再発が25例，炎症性乳癌型再発も含めた乳腺外再発が26例であった．

手術法は腫瘤縁より2cm以上離し，乳頭方向へやや長くしたwide excisionで，リンパ節郭清は原則としてLevel IIまで施行した．術後の放射線治療は線源Tele-Co^{60}をTotal：46～50Gy(なお，断端陽性にはブーストとして電子線8-10Gyを追加)施行した．検討項目は断端状況(全割による病理検索により5mm以内を陽性)，腫瘍径，リンパ節転移およびリンパ管侵襲(ly)の程度，ホルモンレセプター(estrogen receptor(ER)：EIA法およびIHC法にて評価)である．

今回，比較検討の対象とした前期および後期の乳房温存手術症例の背景因子を見ると(**表2**)，年齢，リンパ節転移の程度，ly，ER状況に全く差を認めなかった．腫瘍の大きさを見ると，後期にやや大きい症例が多かったが有意差はなかった．しかし，切除断端状況，術後照射で両者間に有意差を認めた．すなわち，後期例に断端陽性例および照射例が多くなっていた．また，術後照射非施行例について見ると，後期にER陽性，断端陽性例が有意に多くなっていたが，年齢，リンパ節転移，腫瘍径およびlyに有意差は認められなかった．

術後補助療法について見ると，1999年からはSt.Gallen国際会議の推奨に基づき行っているが，化学療法としてAnthracycline系含有の治療(CEFまたはEC療法：Cyclophophamide 600 mg/m^2, Epirubicin 60-75mg/m^2, (5-FU 500mg/m^2))を中心に行っている．これに対し，1998年までは一部CMF療法(Cyclophosphamide, Metothorexate, 5-FU)を含むが，ほとんどの症例ではFU系の経口抗がん剤の投与がなされていた．また，内分泌療法は以前からTamoxifenを投与していたが，その投与期間において相違が見られ，前期では2年であるのに対し，後期では5年である．

統計処理として，**表2～4**における群間の比較に

表2　対象症例の背景因子

1)全症例

		前期	後期	計	p値
年齢					
～35		25(5.9)	10(5.0)	35	
36～50		205	86	291	0.32
51～		196	106	302	
リンパ節転移					
0		305(73.1)	147(75.9)	452	
1～3		73	32	105	0.38
4～		39	17	56	
腫瘍の大きさ					
～2cm		351(81.9)	154(74.8)	505	
2.1～3		64	39	103	0.22
3.1～		11	8	19	
ER	+	257(69.5)	139(72.0)	396	0.59
	−	113	54	167	
断端	+	62(14.6)	48(23.8)	110	0.006
	−	364	154	518	
リンパ管侵襲(ly)					
	−	189(44.7)	85(42.1)	274	
	+	181	94	275	0.67
	++	53	23	76	
照射	+	87(20.4)	87(43.1)	174	<0.0001
	−	339	115	454	

2)非照射例

	前期	後期	p値
	17(5.0)	2(107)	
	158	47	0.12
	164	66	
	256(77.6)	91(82.7)	
	51	15	0.61
	18	4	
	281(82.9)	91(79.1)	
	50	21	0.65
	8	3	
	200(69.0)	87(81.3)	0.02
	90	20	
	11(3.2)	13(11.38)	0.002
	328	102	
	171(50.9)	62(53.9)	
	131	47	0.28
	24	6	

はχ²検定，Fisher's exact testを用い，予後(累積健存率)はKaplan-Meier法にて算出し，logrank法にて検定を行った．また，乳房内再発に関わる因子の単・多変量解析にはCoxの比例ハザードモデルを用いた(SPSS)．

結　果

1) 対象症例における補助療法の実際

対象症例における補助療法の状況を見ると(表3)，前期では治療なし例がやや多かったが，多くの症例において補助療法が施行されていた．さらに，ER状況で見ると，ER陽性に対する内分泌療法の施行率は前期：68.1%，後期：94.2%と有意に後期で高率であった．また，ER陰性に対しての化学療法施行率は前期：77.0%，後期：87.0%と有意差はないものの後期で高率であった．

2) 手術後の乳房内再発について

乳房温存手術後の乳房内再発について見ると，図1に示すように後期例の予後は良好で，前期例に比して有意差を認めた．これを再発率で検討してみたのが表4である．今回の主要な検討項目である術後2年での再発率は前期：4.5%であるのに対し，後期では1.0%と明らかに低くなっていた(P=0.03)．また，予後不良な炎症性乳癌型再発例も前期の8例に対し，後期には現在までに経験していない(p=0.06)．このように後期例は前期に比し乳房内再発例は明らかに少なかった．

3) 術後照射およびER状況より見た術後乳房内無再発生存率

術後照射の有無で乳房内再発を検討すると，照射施行群では前期および後期とも同様な健存率であったが，照射なし群では後期例に現在までに再発例はなく，前期例に対し有意差を認めた．また，ER状況で見ると，ER陽性では両者間に明らかな差は認められなかったが，ER陰性においては後期例において有意に良好な成績であった(図2)．

4) 乳房内再発危険因子の単・多変量解析

表5に示すように，乳房内再発に関わる因子の検討を多変量解析にて行うと，手術時期は年齢，ERとともに有意の因子であった．

表3　手術時期より見た術後補助療法についての検討

1)術後補助療法の内訳

術後補助療法	前期	後期
なし	56(13.1)	13(6.4)
化学療法	139(32.6)	46(22.8)
内分泌療法	140(32.9)	102(50.5)
化学＋内分泌	91(21.4)	41(20.3)

2)ER状況別に見た化学/内分泌療法施行率

ER陽性に対し内分泌療法施行	TAM：2年 175/257(68.1)	TAM/AI：5年 131/139(94.2)
	p<0.0001	
ER陰性に対し化学療法施行	経口FU,一部CMF 87/113(77.0)	CE(F)/Taxanes 47/54(87.0)
	p=0.19	

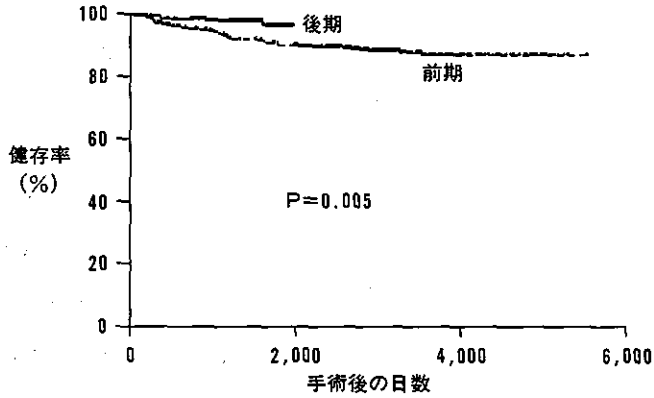

図1　手術時期と乳房内再発―術後乳房内無再発生存率―
後期例の術後乳房内無再発生存率は良好で，前期例に比して有意差を認めた(P=0.005)．

表4　手術時期より見た乳房内再発率,特に2年以内での検討

	症例数	再発	2年以内	炎症性乳癌型
前期	426	47	19(4.5)	8
後期	202	4	2(1.0)*	0**

*P=0.03　**P=0.06

考　察

乳房温存療法はわが国においても早期乳癌に対する標準治療となって久しい．近年では新聞や雑誌における乳房温存療法の記事などから，とにかく乳房温存療法を希望するケースもある．インフォームド・コンセントにて最終的に手術法が決定されるが，その説明でいかに正確な情報を与えるかが重要で，時には適応外で乳房切除を推奨することも必要である．現在，日本乳癌学会の乳房温存療法ガイドラインを多くの施設が参考にしていると思われるが，そのガイドラインに沿ったとしても当然再発例は存在する．断端陰性と照射施行にて多くの再発を回避できると思われるが，新

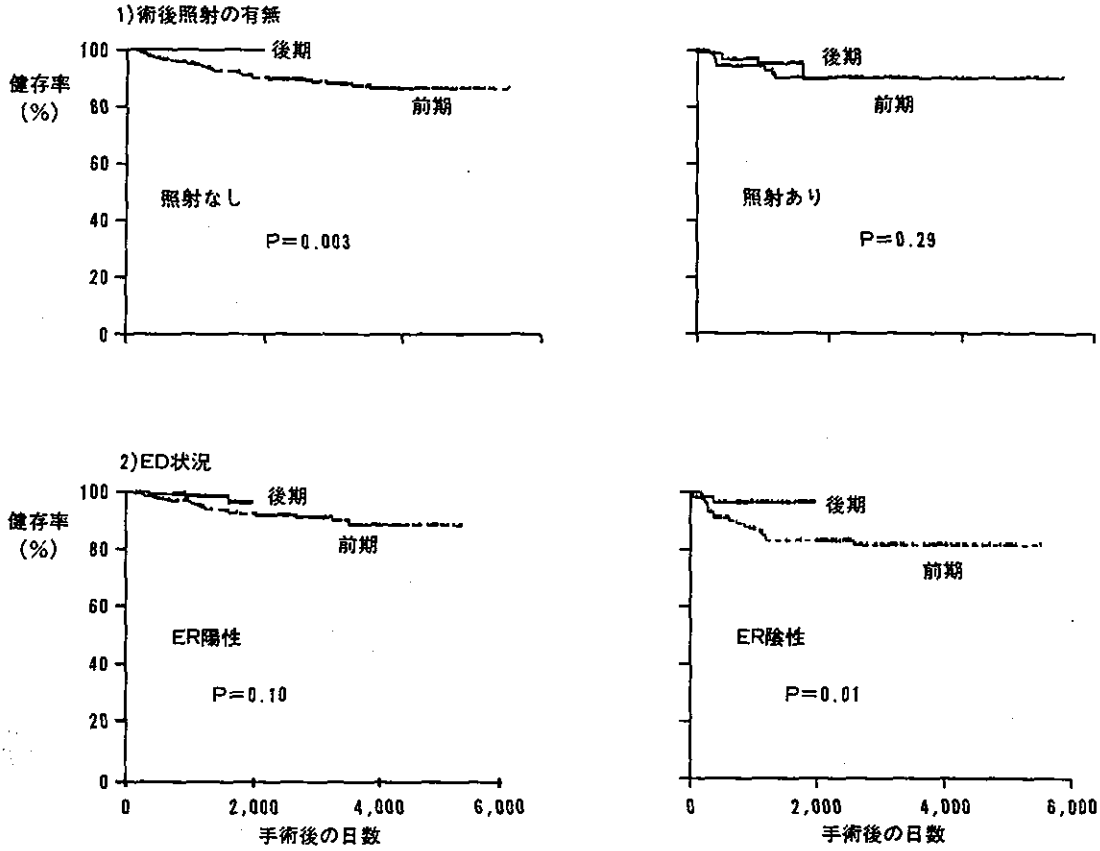

図2　術後照射の有無およびER状況と手術時期から見た乳房内再発

術後照射の有無で乳房内再発を検討すると(1)，照射施行群では前期および後期とも同様な健存率であったが，照射なし群では後期例に現在までに再発例はなく，前期例に対し有意差を認めた(P=0.003)．

また，ER状況で見ると(2)，ER陽性では両者間に明らかな差は認められなかったが，ER陰性においては後期例において有意に良好な成績であった(P=0.01)．

表5　乳房温存手術後の乳房内再発に関わるリスクファクターの検討(単・多変量解析)

因子	Category	Relative Risk	P-value (単変量)	P-value (多変量)
切除断端	+/−	2.28	0.007	0.11
放射線治療	Yes/No	0.95	0.88	
年齢(歳)	36～50/～35	0.28	0.0002	0.0004
	51～/～35	0.07	<0.0001	<0.001
腫瘍径	21～30/～20	0.78	0.57	0.64
(mm)	31～/～20	2.54	0.08	0.18
リンパ節転移	+/−	2.13	0.008	0.11
リンパ管侵襲	+/−	1.86	0.04	0.46
ER	+/−	0.47	0.01	0.002
手術時期	後期/前期	0.26	0.011	0.004

病変も含めると，少なくない症例において温存乳房内の病変出現の可能性は高い．果たして，再発を防止するためには，断端を陰性し，照射を行ったあとに何をなすべきなのか．今回は術後の全身療法の効果について検討を行った．

乳癌術後の補助療法は乳房切除術に対してのみ

ならず，乳房温存療法においても再発率低下の効果を認め，特に乳房内再発の抑制についても報告されている[5,6]．術後の内分泌療法について見ると，閉経後ER陽性乳癌に対して行われた乳房温存手術＋放射線照射にTAMを加えることにより，局所再発を有意に抑制することが報告されている[6,7]．また，非浸潤癌の場合にも放射線治療にTAMを追加することで，同側および対側の乳癌発生に対して抑制効果を示すとしているが[8]，一方，Houghtonら[9]はTAMによる乳房内再発の抑制効果は有意ではなく，対側乳癌の発生抑制に関しては効果があったとしている．今回の検討で見ると，ER陽性においては後期例の再発率は少なかったが($p=0.10$)，これにはER陽性に対しての内分泌療法施行率が有意に高かったことが関与していると思われた．また，投与期間も前期と後期では2年と5年と相違が見られたが，これによる効果も十分に期待できるわけで，さらなる経過観察により明らかになるものと思われる．

化学療法について見ると，EBCTCGのデータからも乳房内再発の抑制が示されている[5]．今回のデータで見ると，ER陰性において後期例の再発は明らかに低かったが，この要因としての化学療法施行率は後期例で高く，かつ化学療法の内容における相違が考えられた．後期例においてはAnthracycline系薬剤を中心に補助療法を行い，前期ではFU系による治療を行ってきた．FU系治療の効果がないわけではないが，今回の検討項目である術後2年での再発率という点から見ると，Anthracycline系等による化学療法がより奏効する可能性は高いと考えられる．EORTCのデータで手術単独に比して，1コースのCAF療法により乳房内再発の有意な減少が示されている[10]．乳房内再発を抑制するということは温存乳房内に術後残存している癌細胞の増殖を抑え，時には癌細胞の消失を意味している．この乳房内腫瘤に対する化学療法の効果を最もよく反映し，確認できるものは術前化学療法である．

腫瘍径の大きな乳癌に対して，術前化学療法を導入することによって，生存率を落とすことなく温存手術を施行することが期待できる[11]．また，抗癌剤の感受性を知ることができ，組織学的な腫瘍の完全消失は良好な予後の指標となりうるなど有用な点も多く，腫瘍径の大きな乳癌に対して術前化学療法は推奨される治療法である．今回と同じEpirubicinを用いたレジメンの検討で(50例)，奏効率は56%で，組織学的な完全消失が7%に認められた．さらに，predictive factorの検討で高増殖能例に奏効率は高く，EICを認める症例では組織学的効果が少なかった[12]．これらのことより，乳房内腫瘤に対する化学療法の効果は高いが，すべての症例に効果があるわけではないことがわかる．高増殖能例においては再発率も高く，再発までの期間も短いことが示されており[13]，乳房内再発においても同様であった．このような早期再発例に対し，Epirubicinを含むレジメンは効果を発揮している可能性がある．

乳房内再発は乳房温存手術において最も回避すべきことであるが，今回の検討より，術後の補助療法が再発防止に寄与していることが示された．ただし，今回は2年時点での評価であり，ER陽性に対しての内分泌療法(TAM)，およびER陰性に対しての化学療法(CE(F))の効果をさらに検討するには長期の経過観察による評価も必要である．しかし，標準的な補助療法は遠隔転移ばかりでなく，乳房内再発をも抑制することの意味は大きい．今後は症例に応じた標準治療の実施が求められるが，乳房温存療法においても補助療法に関する情報提供は必要と思われる．

文　献

1) Komoike Y, Motomura K, Inaji H, et al: Long-term results of breast conserving surgery for stages I and II breast cancer: experiences at Osaka Medical Center for Cancer and Cardiovascular Diseases. *Breast Cancer* 9: 248-253, 2002

2) Ohsumi S, Sakamoto G, Takashima S, et al: Long-term results of breast-conserving treatment for early-stage breast cancer in Japanese women from multicenter investigation. *Jpn J Clin Oncol* 33: 61-67, 2003

3) Jobsen JJ, van der Palen J, et al: The impact of age on local control in women with pT1 breast cancer treated with conservative surgery and radiation therapy. *Eur J Cancer* 37: 1820-1827, 2001

4) 西村令喜, 松田正和, 宮山東彦, 他：若年者になぜ乳房温存手術後の乳房内再発が多いのか？ 乳癌の臨 18：523-529, 2003
5) Early Breast Cancer Trialists' Collaborative Group：Polychemotherapy for early breast cancer：an overview of the randomised trials. *Lancet* 352：930-942, 1998
6) Dalberg K, Johansson H, Johansson U, et al：A randomized trial of long term adjuvant tamoxifen plus postoperative radiation therapy versus radiation therapy alone for patients with early stage breast carcinoma treated with breast-conserving surgery. Stockholm Breast Cancer Study Group. *Cancer* 82：2204-2211, 1998
7) Fisher B, Bryant J, Dignam JJ, et al：Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol* 20：4141-4149, 2002
8) Fisher B, Dignam J, Wolmark N, Wickerham DL, Fisher ER, Mamounas E, Smith R, Begovic M, Dimitrov NV, Margolese RG, Kardinal CG, Kavanah MT, Fehrenbacher L, Oishi RH：Tamoxifen in treatment of intraductal breast cancer：National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. *Lancet* 353：1993-2000, 1999
9) Houghton J, George WD, Cuzick J, et al：Ductal Carcinoma in situ Working Party：DCIS trialists in the UK, Australia, and New Zealand. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand：randomised controlled trial. *Lancet* 362：95-102, 2003
10) Elkhuizen PH, van Slooten HJ, Clahsen PC, et al：High local recurrence risk after breast-conserving therapy in node-negative premenopausal breast cancer patients is greatly reduced by one course of perioperative chemotherapy：A European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group Study. *J Clin Oncol* 18：1075-1083, 2000
11) Fisher B, Brown A, Mamounas E, et al：Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer：findings from National Surgical Adjuvant Breast and Bowel Project B-18. *J Clin Oncol* 15：2483-2493, 1997
12) Nishimura R, Nagao K, Miyayama H, et al：An evaluation of predictive factors involved in clinical or pathological response to primary chemotherapy in advanced breast cancer. *Breast Cancer* 9：145-152, 2002
13) Nishimura R, Matsuda M, Miyayama H：Proliferative activity evaluated by MIB-1 predicts the time and type of recurrence in breast cancer. *Breast Cancer Res Treat* 82(Suppl 1)：S165, 2003

Combination Chemotherapy with Docetaxel and Doxifluridine showed a Beneficial Outcome in Advanced or Recurrent Breast Cancer Patients with Longer Disease-free Interval

REIKI NISHIMURA[1], TAKESHI TOMINAGA[2], SHOSHU MITSUYAMA[3], HIDEAKI AOYAMA[4], TARO ASAGA[5], SHINJI OHNO[6], NOBUO OKUYAMA[7], MORIHIKO KIMURA[8], HIROTAKA IWASE[9], KAZUHIRO KANDA[10], TOSHIHIRO KOGA[11], EIICHI SHIBA[12] and TADASHI IKEDA[13]

[1]Department of Surgery, Kumamoto City Hospital, 1-1-60 Kotoh, Kumamoto 862-8505;
[2]Breast Cancer Center, Toyosu Hospital, Showa University School of Medicine, 4-1-18 Toyosu, Koto-ku, Tokyo 135-8577;
[3]Department of Surgery, Kitakyushu Municipal Medical Center, 2-1-1 Bashaku, Kokura-kita-ku, Kitakyushu, Fukuoka 802-0077;
[4]Department of Surgery, National Nagoya Hospital, 4-1-1 San-nomaru, Naka-ku, Nagoya 460-0001;
[5]Department of Surgery, Breast and Thyroid Division, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815;
[6]Department of Breast Surgery, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395;
[7]Department of Thoracic-Cardiovascular Surgery, Toho University School of Medicine, 6-11-1 Omori-nishi, Ota-ku, Tokyo 143-8541;
[8]Department of Surgery, Gunma Cancer Center, 617-1 Takabayashi-nishi-cho, Ota-shi, Gunma 373-8550;
[9]Second Department of Surgery, Nagoya City University Medical School, Kawasumi 1, Mizuho-ku, Nagoya 467-8601;
[10]Department of Surgery, Hamamatsu Medical Center, 328 Tomitsuka-cho, Hamamatsu 432-8580, (currently: Kanda Clinic);
[11]Department of Surgery, Kurume University School of Medicine, 67 Asahi-cho, Kurume, Fukuoka 830-0011 (currently: Hirose Hospital);
[12]Department of Breast and Endocrine Surgery, Osaka Kosei-Nenkin Hospital, 4-2-78 Fukushima, Osaka 553-0003;
[13]Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Abstract. *Fundamental studies have confirmed that combination chemotherapy with docetaxel and doxifluridine (a capecitabine metabolite) is very useful in the treatment of breast cancer. This study investigated the usefulness and tolerability of a combination chemotherapy consisting of docetaxel administration on day 8 of doxifluridine therapy in 40 advanced/recurrent breast cancer patients. The overall response rate was 41.0% in 39 eligible patients. The median time to progression (TTP) for all patients was 295 days. Many responders had lung metastasis, soft tissue metastasis or a good performance status, whereas the clinical response showed no correlations with the estrogen receptor status or prior treatment with an anthracycline. The most common hematological toxicities were leukopenia and neutropenia, but dose reduction or delay of administration of either drug was unnecessary. Conclusion: The good response rate and long TTP of this doxifluridine plus docetaxel regimen indicate its potential as a first- or second-line treatment for advanced/recurrent breast cancer patients.*

Even when patients with advanced/recurrent breast cancer respond to drug treatment, achieving cure is often impossible. Nevertheless, chemotherapies are being established as standard therapies which play important roles in alleviating the disease symptoms and improving the patients' quality of life (QOL) (1). The response rate of advanced/recurrent breast cancer to chemotherapy is comparatively high, and combination chemotherapy regimens being currently carried out as standard chemotherapies include CMF [cyclophosphamide (CPA), methotrexate, 5-FU], CAF [CPA, adriamycin (ADM), 5-FU], AC (CPA, ADM) and the recently approved taxanes (paclitaxel, docetaxel), *etc.* (2). In recent years, the US FDA has approved the use of an oral fluorouracil (FU) agent (capecitabine) (3) in the treatment of taxane-refractory breast cancer. In Japan, doxifluridine, an intermediate metabolite of capecitabine, has been approved for use, and Niitani *et al.* found

Correspondence to: Reiki Nishimura, Department of Surgery, Kumamoto City Hospital, 1-1-60 Kotoh, Kumamoto 862-8505, Japan. Tel: +81-96-365-1711, Fax: +81-96-365-1712, e-mail: j_nishimura2002@yahoo.co.jp

Key Words: Recurrent, docetaxel, doxifluridine.

0250-7005/2004 $2.00+.40

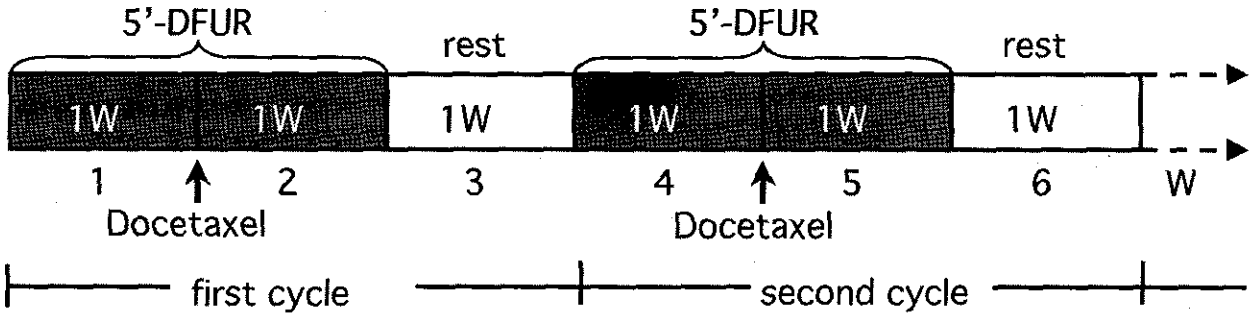

Figure 1. *Administration schedule for combination chemotherapy using doxifluridine plus docetaxel. Doxifluridine was administered po at 800 mg/day on days 1-14. Docetaxel was administered at 60 mg/m^2 on day 8 by intravenous infusion over 1 hour. One course lasted 3 weeks and the regimen was repeated for as many cycles as possible.*

it to be useful in the treatment of solid tumors, including breast cancer (4). Doxifluridine is a prodrug that is converted to 5-FU as a result of activation by dThdPase (5). It is known that dThdPase is more abundant in tumor tissues than in normal tissues. Several years ago, Sawada *et al.* reported fundamental studies which demonstrated the specific induction of dThdPase activity in tumor tissues by administration of various anticancer agents, including docetaxel (6). In addition, Cook *et al.* had reported earlier that, in relation to tumors showing specific induction of dThdPase, the combination of docetaxel and doxifluridine showed strong synergistic activity not seen with other drugs (7). It is anticipated that these two agents will also show a combined effect in the clinical setting. On the other hand, a recent report by O'Shaughnessy *et al.* found that the combined use of capecitabine and docetaxel showed statistically significant prolongation of the duration of survival and the time to progression (TTP) in comparison with docetaxel alone (8).

An *in vitro* study was carried out by Fujimoto-Ouchi *et al.* (9) to examine the timing of drug administration in the case of combination therapy of breast cancer using docetaxel and doxifluridine. Treatment was started with doxifluridine and docetaxel was administered on day 1, day 8 or day 15. The results showed that the greatest synergistic effect was obtained when docetaxel was administered on day 8 (9). Based on the results of that study, the present authors carried out a phase I study to investigate the tolerability of a combination therapy schedule in which doxifluridine was administered to breast cancer patients on days 1-14 and docetaxel was administered on day 8. We found that the optimal dosages were 800 mg/day for doxifluridine and 60 mg/m^2 for docetaxel (10).

The present study was designed to investigate the efficacy and safety of that schedule for combined administration of doxifluridine and docetaxel in the treatment of advanced or recurrent breast cancer patients. The usefulness and clinical significance of this combination chemotherapy for breast cancer are discussed.

Patients and Methods

Patients. The patients enrolled in this study had advanced/recurrent breast cancer, for which the primary lesion was histologically or cytologically proven to be breast cancer. In addition, the patients satisfied the following inclusion criteria: (i) In the case of patients who had received previous treatment, in principle at least 4 weeks had passed since discontinuing that treatment. However, a washout period of at least 2 weeks was sufficient in the case of prior treatment with a biological response modifier, hormonal preparation, *etc.* (ii) In the case of previous treatment consisting of postoperative adjuvant chemotherapy, in principle the washout period was at least 4 weeks. (iii) The performance status (PS) was 0-1. (iv) The patient could be expected to survive for at least 3 months. (v) The patient had adequate hematological, hepatic, renal and cardiac functions (WBC: 4,000-10,000/mm^3; neutrophil count: ≥ 2,000/mm^3; platelet count: ≥ 100,000/mm^3; Hb: ≥ 9.5 g/dL; AST and ALT: ≤ 1.5 times the upper normal limit; Al-P: ≤ 2.5 times the upper normal limit; total bilirubin: ≤ 1.5 mg/dL; serum creatinine: ≤ 1.2 mg/dL; ECG: within the normal range). (vi) The patient was at least 20 years old and less than 70 years old. (vii) The patient gave informed consent. (viii) The patient had measurable or evaluable lesions.

Patients were excluded from the study if they had any of the following: a history of previous treatment with a taxane (paclitaxel or docetaxel); a history of drug allergic reaction; serious complications; a fever, with suspicion of an infection; peripheral neuropathy; brain metastasis with symptoms; an active double-cancer; inflammatory breast cancer; male breast cancer; pregnancy or the possibility thereof, or currently breastfeeding; interstitial pneumonia; pulmonary fibrosis; edema; pleural effusion or pericardial fluid retention requiring treatment; diabetes requiring insulin therapy; a requirement for treatment with a steroid; severe psychosis; psychiatric disorder; or any other condition on the basis of which the investigator judged the patient to be unsuited for inclusion in the study.

Study methods. Forty patients with advanced/recurrent breast cancer satisfied the inclusion criteria and were centrally enrolled in the study by facsimile transmission during the period from August 1999 to December 2001. These patients were treated with a combination chemotherapy regimen, one course of which was as

Table I. *Patient characteristics.*

Characteristics	Patients n (%)
No. of enrolled patients	40
No. of eligible patients	39
Ineligible patient*	1
Age (years)	
Median (range)	53 (36-73)
Performance status	
0	32 (82)
1	7 (18)
Prior therapy	
Yes	34 (87)
No	5 (13)
Prior anthracycline therapy (including as adjuvant therapy)	
Yes	12 (31)
No	27 (69)
Metastatic site †	
Soft tissue metastasis	19 (49)
Bone metastasis	14 (36)
Lung metastasis	10 (26)
Liver metastasis	14 (36)
No. of metastasized organs	
1	24 (62)
2	10 (26)
3≤	5 (13)
Estrogen receptor status	
positive	21 (54)
negative	18 (46)
Disease-free interval (DFI)	
≤ 3 years	20 (51)
> 3 years	14 (36)

*: prior paclitaxel therapy; †: overlapping count

Table II. *Clinical efficacy of combination chemotherapy using doxifluridine plus docetaxel.*

	No. of patients (%)		
Complete response	5	(12.8)	RR (%)
Partial response	11	(28.2)	16/39 (41.0)
No change/stable disease	13	(33.3)	
Progressive disease	6	(15.3)	
Non-evaluable	4	(10.3)	

95% confidence interval: 25.6%-56.5%

Table III. *Results of multivariate analysis of patient background factors for correlation with the clinical effect of combination chemotherapy using doxifluridine plus docetaxel.*

Factor	Variable	Odds ratio	95% CI§			*P*
a) Total patients (39)						
PS*	0 / 1	17.461	0.606	~	502.941	0.095
ER†	- / +	0.673	0.123	~	3.681	0.648
Organ No.	1/2/3	7.403	0.938	~	58.435	0.058
Bone meta.	- / +	0.772	0.091	~	6.545	0.813
Liver meta.	- / +	0.627	0.074	~	5.334	0.669
Soft tissue	- / +	0.139	0.017	~	1.116	0.063
Lung meta.	- / +	0.032	0.001	~	0.734	0.031
b) Recurrent patients (34)						
PS	0 / 1	6.916	0.277	~	172.429	0.239
ER	- / +	0.385	0.037	~	4.025	0.425
Bone meta.	- / +	4.177	0.335	~	52.110	0.267
Liver meta.	- / +	6.953	0.369	~	131.106	0.196
Soft tissue	- / +	0.420	0.056	~	3.126	0.397
Lung meta.	- / +	0.236	0.017	~	3.303	0.284
DFI **	-3y/3y-	0.022	0.001	~	0.455	0.014

*: performance status; †: estrogen receptor; **: disease-free interval; §: confidence interval

follows: doxifluridine was administered po at 800 mg/day for 2 weeks on days 1-14, followed by a one-week rest period. Docetaxel was administered at 60 mg/m^2 on day 8 by *i.v.* infusion over 1 hour. One course lasted 3 weeks and the regimen was repeated for as many cycles as possible (Figure 1).

The primary efficacy assessment endpoint was reduction in the size of the tumor, while the secondary endpoints were the time to progression (TTP), survival and safety. Evaluation of the clinical effect was performed in accordance with the "General Rules for Clinical and Pathological Recording of Breast Cancer" (in "Guideline for Treatment of Breast Cancer". 13th Edition; edited by the Japanese Breast Cancer Society). Measurement of measurable lesions and evaluation of evaluable lesions were performed objectively on the basis of image findings using X rays, CT scans, MRI *etc.*, and extracorporeal measurements. Whenever possible, the same methods were used for carrying out the measurements and evaluations in the same patient. The TTP was defined as the time period from the start of therapy until the first evidence of progression of the disease. The safety of the combination chemotherapy was assessed on the basis of the Japanese Clinical Oncology Group (JCOG) version of the NCI-Common Toxicity Criteria.

Analyzed parameters and statistical treatment of data. The background factors, analyzed for the eligible patients were age, performance status (PS), evaluable site (*i.e.*, classified into soft tissue, bone, lung and liver), prior therapy (especially whether or not there had been prior treatment with an anthracycline), the disease-free interval (DFI; classified using a cut-off of 3 years), estrogen receptor (ER) status (assessed by an EIA technique), *etc.* The clinical effect of the therapy was assessed beginning at 4 weeks after the start of therapy and the categories employed were CR (complete response), PR (partial response), NC (no change) and PD (progressive disease).

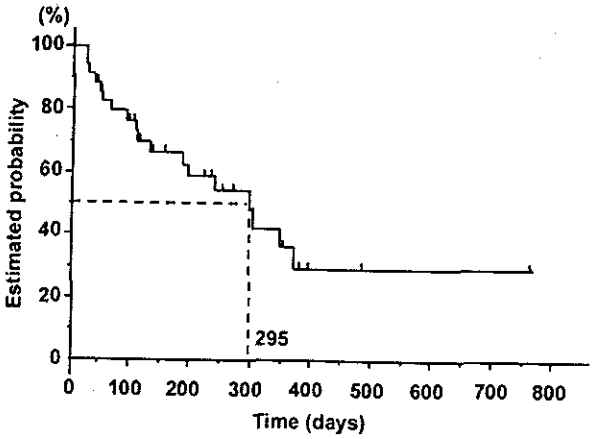

Figure 2. *Time to progression (TTP) in eligible patients (35*) administered the combination chemotherapy using doxifluridine plus docetaxel.*
**: excluding NE cases*
Median value for the TTP, calculated from the start of treatment with the doxifluridine plus docetaxel combination chemotherapy and including patients who were continuing to receive the treatment: 295 days.

Table IV. *Sub-set analysis of combination chemotherapy using doxifluridine plus docetaxel.*

Factor	Variable (n)	TTP * median (days)
Overall	(35)	295
ER†	- (16)	195
	+ (19)	370
DFI**	-3y (16)	185
	3y- (14)	295
Anthracycline Pretreated	yes (10)	768 +
	no (25)	195

*TTP: time to progression; †ER: estrogen receptor;
** DFI: disease-free interval (recurrent cases)

Multivariate analysis of the patient background factors to identify any which might influence the therapeutic effect was carried out by means of logistic regression analysis. The TTP and the duration of survival were calculated by the Kaplan-Meier method.

Results

Patient background factors. Table I compiles the data on the patient background factors. Although 40 patients were enrolled in the study during the period from August 1999 to December 2001, 39 patients were considered eligible, one patient being ineligible due to prior treatment with paclitaxel. The age range of the patients was 36-73 years, with a median age of 53.0 years. Thirty-four patients had undergone prior treatment, while 12 patients had undergone prior treatment with an anthracycline. At the start of this study, 32 patients had a PS of 0. The metastatic site, which was multiple in some patients, was soft tissue in 19 patients, bone in 14 patients, the lung in 10 patients and the liver in 14 patients. In addition, the number of metastasized organs was one in 24 patients, two in 10 patients and three or more in five patients. The ER status was positive in 21 patients. The DFI in the recurrent cases was 3 years or less in 20 patients and greater than 3 years in 14. Five of the patients had advanced breast cancer.

Response rate. Table II compiles the data on the clinical responses of the 39 eligible patients. Five patients achieved CR and 11 patients PR, while 13 patients were assessed as NC and six patients as PD. Four patients were non-evaluable (NE). The response rate was thus 41.0%. The median response duration was 257 days when the calculation included the patients who continued to receive the combination chemotherapy.

Patient background factors influencing clinical effect. The TTP and the duration of survival were calculated on the basis of a study period lasting from August 1999 until July 2002 (median follow-up period: 19 months). Table III presents the results of multivariate analysis (by logistic regression analysis) performed to identify potential responders by detecting patient background factors which influenced the patients' response to the doxifluridine + docetaxel combination chemotherapy. The data for the total 39 patients revealed that the combination chemotherapy was clearly effective in the treatment of lung metastases, while it also showed a tendency to be effective against soft tissue metastases and in patients with PS 0. When the analyzed patient population was the 34 patients with recurrent disease, the past DFI was the only factor which showed a statistically significant correlation with the response. That is, the response rate was significantly higher in the patients with a DFI of greater than 3 years compared with the patients whose DFI was 3 years or less. Accordingly, unlike the total patient group, the site of metastasis and the PS were not statistically background factors in patients with recurrent breast cancer. In addition, neither the ER status nor the number of metastasized organs showed a clear correlation with the clinical response. The presence or absence of prior treatment or a history of treatment with an anthracycline also had no bearing on the clinical response of these patients.

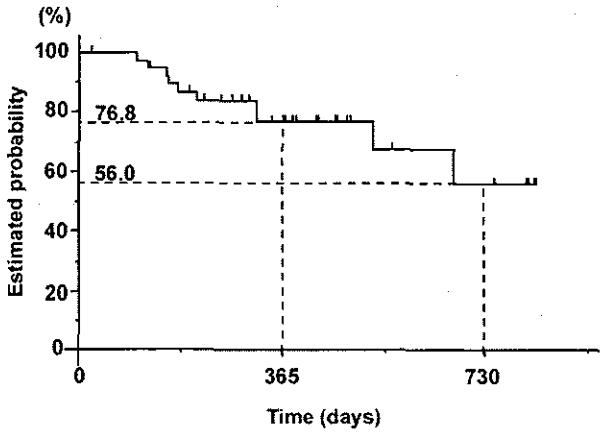

Figure 3. *Overall survival of the total patients (39) after the start of treatment with the combination chemotherapy using doxifluridine plus docetaxel. Survival rate after the start of treatment with the doxifluridine plus docetaxel combination chemotherapy: 76.8% after 1 year and 56.0% after 2 years.*

TTP and survival. As shown in Figure 2, the median value for the TTP in 35 patients was 295 days when the calculation included the patients who continued to receive the combination chemotherapy. Analysis of the TTP for correlations with each of the patient background factors revealed statistically significant differences as a function of the DFI, ER status and the presence or absence of a history of treatment with an anthracycline. That is, the TTP was longer in patients with a longer DFI, patients with a positive ER status and patients with a past treatment with an anthracycline (Table IV).

In addition, Figure 3 shows the plot of the estimated probability of overall survival in the total (39) patients after the start of treatment with the combination chemotherapy. The estimated survival rate after 1 year was 76.8%, while that after 2 years was 56.0%.

Toxicity. Table V compiles the data on the toxicity recorded during the study. The most frequently occurring hematological toxicities were leukopenia and neutropenia, which showed incidences of grade 3 or 4 toxicity of 53.8% and 56.4%, respectively. Ten patients were treated with G-CSF. However, delay of administration and dose reduction were not necessary in any of the patients. As nonhematological toxicities, one patient experienced grade 3 dermatitis, while another patient developed grade 4 facial flush accompanying an anaphylactic-like reaction of dyspnea. Other nonhematological toxicities which occurred at high incidence were anorexia, nausea/vomiting and hair loss, all of which were grade 2 or lower in severity. Only one patient discontinued the treatment because of grade 4 facial flush accompanying an anaphylactic-like reaction of dyspnea. This resolved rapidly after the discontinuation.

Table V. *Toxicity of combination chemotherapy using doxifluridine plus docetaxel.*

a) Hematological toxicity (n=39).

	Grade				Grade 3,4
Toxicity (n)	1	2	3	4	(%)
Leukocytes	4	10	17	4	21 (53.8)
Neutrophils	3	5	7	15	22 (56.4)
Hemoglobin	5	6			
Anemia	3	5			
Platelets	1				

b) Non-hematological toxicity (n=39).

	Grade				Total
Toxicity (n)	1	2	3	4	(%)
Anorexia	16	3			19 (48.7)
Nausea/vomiting	14	2			16 (41.0)
Stomatitis	5	1			6 (15.4)
Diarrhea	9	2			11 (28.2)
Fever	8	2			10 (25.6)
Fatigue	8	1			9 (23.1)
Edema	6	2			8 (20.5)
Skin (rash, HF*)	6	2	1		9 (23.1)
Allergy	2	1		1	4 (10.3)
Neurotoxicity	7				7 (17.9)
Alopecia	12	11			23 (59.0)
Headache	3				3 (7.7)
Other	7	1			8 (20.5)

*: hand-foot skin reaction

Discussion

Chemotherapeutic regimens and endocrine therapy are available for use in the treatment of recurrent breast cancer. The details of the treatment regimen are decided upon taking into consideration the physical condition of the patient, the site(s) of metastasis, the likely response to endocrine therapy (*i.e.*, as a function of the ER status, *etc.*), and whether or not the disease is life-threatening (11). In general, based on the reports published to date, it can be expected that patients with recurrent breast cancer will survive longer when treated with endocrine therapy, whereas there is little expectation of prolonged survival in the case of chemotherapy (12). Accordingly, treatment of recurrent breast cancer patients is usually started with endocrine therapy, this approach also being beneficial in terms of the quality of life of the patient. However, recent years have seen the development of various new therapeutic methods, including the use of taxanes and tratszumab, *etc.*, and the time has come to reconsider the therapeutic approach to this disease.

The combination chemotherapy consisting of doxifluridine and docetaxel that was investigated in the present clinical trial represents a new drug combination for the treatment of recurrent and advanced breast cancer. Fundamental studies have shown that doxifluridine is a prodrug that is converted to 5-FU as a result of the action of pyrimidine nucleoside phosphorylases (PyNPases), converting enzymes that are strongly expressed in tumor tissues (5). In addition, it was demonstrated that the activity of thymidine phosphorylase (TP), which is one kind of PyNPase, is selectively up-regulated in tumor tissues and that the efficacy of doxifluridine is enhanced by some anticancer agents, such as docetaxel *etc.* (6). In addition, taxanes induce apoptosis *via* phosphorylation of bcl-2 and it is thus thought that apoptosis is readily induced if the level of bcl-2 is low. Moreover, it is thought that induction of apoptosis is inhibited by binding of bcl-2 to BAX, a promoter of apoptosis (13,14). In this regard, it has been reported that doxifluridine inhibits bcl-2 and also reduces the expression ratio of bcl-2/BAX (15) and these findings thus indicate the significance of administering doxifluridine prior to the administration of docetaxel. The present clinical study was carried out in order to investigate the efficacy of the combination chemotherapy regimen of doxifluridine plus docetaxel that was designed to exploit this mechanism of action.

The response rate recorded in this clinical trial of the doxifluridine plus docetaxel combination chemotherapy regimen was 41%, the median duration of response was 257 days and the median TTP for the total patients was 295 days. In reports published to date, the response rate and the TTP when docetaxel was administered alone were reported to be 47% and 29 weeks by Chan *et al.* (16), 47% and 26 weeks by Aapro *et al.* (17), 44.4% and 116 days by Adachi *et al.* (18) and 54.7% and 153 days by Taguchi *et al.* (19). In addition, a 35.9% response rate was reported in the case of treatment with doxifluridine alone (4). On the other hand, when combination chemotherapy with capecitabine and docetaxel was employed, the response rate and the TTP were reported to be 42% and 6.1 months, respectively (8). Comparison of our present results with these data from the published literature shows that the response rates are almost the same, but the TTP of 295 days with our doxifluridine plus docetaxel combination chemotherapy regimen is clearly longer.

Stratification of the data on the basis of whether or not the patients had been previously treated with an anthracycline yielded interesting results. The TTP with doxifluridine + docetaxel combination chemotherapy in the subgroup of patients who had previously been treated with an anthracycline (*i.e.*, anthracycline-resistant cases) was 765 days, which was better than the result in patients who had no history of anthracycline therapy. Analysis of the distribution of the patient background characteristics found no bias as a function of the presence or absence of prior treatment with an anthracycline. Thus, the reason for the good results in the anthracycline-resistant patients remains unclear. In addition, that the result with doxifluridine + docetaxel combination chemotherapy was superior to the result with docetaxel monotherapy in anthracycline-resistant patients indicated that this combination chemotherapy can be expected to be effective even in an anthracycline-resistant patient population. On the other hand, the TTP was 195 days in the patient subgroup with no history of anthracycline therapy, but even this result was not inferior to that with docetaxel monotherapy.

Another interesting finding of the present study is that many of the patients with a long DFI responded to our doxifluridine + docetaxel combination chemotherapy regimen. Also interesting is that there were responders regardless of whether the ER status was positive or negative. Moreover, many of the patients with lung metastasis or soft tissue metastasis responded to this therapy, while the TTP was significantly extended in patients with a long DFI or positive ER status.

An earlier report found that, unlike endocrine therapy, chemotherapy (epirubicin) was highly effective in many patients whose breast cancer showed a short DFI, high proliferative activity and ER-negative status (12). In addition, Airoldi *et al.* reported that docetaxel-epirubicin combination therapy achieved a high response rate in postmenopausal breast cancer patients with a DFI of at least one year and metastasis to less than three organs (20). In our present study, doxifluridine and docetaxel were combined and it is thought that this combination expressed its efficacy as a result of the mechanism of action that was described earlier. However, in earlier reports of responding patients, the patient background characteristics were not thoroughly analyzed for possible correlations with the efficacy. Our present finding that the doxifluridine plus docetaxel combination chemotherapy regimen was effective in patients with a long DFI characterizes this therapy. The therapeutic approach after recurrence of breast cancer is generally decided on the basis of the ER status, the DFI and whether the disease is life-threatening or not, *etc.*. However, the results of the present clinical trial indicate that doxifluridine plus docetaxel combination chemotherapy can be considered as a therapeutic arm for recurrent and advanced breast cancer patients with a long DFI, regardless of their ER status (*i.e.*, negative or positive). Moreover, the response rate was good even in patients who had undergone previous therapy with an anthracycline, showing no difference with patients who had not received such therapy. This finding can be said to indicate that the doxifluridine plus docetaxel combination chemotherapy regimen can serve as a first-line therapy for recurrent and advanced breast cancer patients who had already been treated with an anthracycline as postoperative adjuvant therapy.

In summary, the doxifluridine plus docetaxel combination chemotherapy regimen assessed in the present clinical trial employed a unique schedule of *i.v.* infusion of docetaxel on day 8 of *po* administration of doxifluridine and expressed a high degree of efficacy. The results showed a response rate of 41%, with a median duration of response of 257 days and a median TTP of 295 days. Many of the responders had a long DFI and a long TTP was achieved. In addition, the beneficial effects of this therapy were expressed regardless of whether the ER status was positive or negative. The toxicity was mild to moderate except for one patient who experienced a grade 4 allergic reaction, but who recovered immediately after discontinuation of docetaxel administration. It is anticipated that in the future this regimen will play an important role as a first- or second-line treatment for patients with advanced or recurrent breast cancer.

References

1 Harris JR *et al*: Cancer of breast. *In*: Cancer Principles and Practice of Oncology, 4th ed. (Devita VY, Hellman S, Rosenberg SA, eds). JB Lippincott Co., 1993, pp 1264-1332.

2 Hayes DF and Henderson IC: CAF in metastatic breast cancer: standard therapy or another effective regimen? J Clin Oncol *5*: 1497-1499, 1987.

3 Blum JL, Jones SE, Buzdar AU *et al*: Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol *17*: 485-493, 1999.

4 Niitani H, Kimura K, Sato T *et al*: Phase II study of 5'-deoxy-5-fluorouridine (5'-DFUR) in patients with malignant cancer – a multi-institutional cooperative study. Jpn J Cancer Chemother *12*: 2044-2051, 1985.

5 Miwa M, Nishimura J, Kamiyama T *et al*: Conversion of 5'-deoxy-5-fluorouridine to 5-FU by pyrimidine nucleoside phosphorylases in normal and tumor tissues from rodents bearing tumors and cancer patients. Jpn J Cancer Chemother *14*: 2924-2929, 1987.

6 Sawada N, Ishikawa T, Fukase Y *et al*: Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by Taxol/Taxotere in human cancer xenografts. Clin Cancer Res *4*: 1013-1019, 1998.

7 Cook AF, Holman MJ, Kramer MJ and Trown PW: Fluorinated pyrimidine nucleosides. 3. Synthesis and antitumor activity of a series of 5'-deoxy-5-fluoropyrimidine nucleosides. J Med Chem 22: 1330-1335, 1979.

8 O'Shaughnessy J, Miles D, Vukelja S *et al*: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol *15*: 2812-2823, 2002.

9 Fujimoto-Ouchi K, Tanaka Y and Tominaga T: Schedule dependency of antitumor activity in combination therapy with capecitabine/5'-deoxy-5-fluorouridine and docetaxel in breast cancer models. Clin Cancer Res *7*: 1079-1086, 2001.

10 Tominaga T, Nishimura R, Aoyama H *et al*: A phase I study of docetaxel (TXT) and doxifluridine (5'-DFUR) combination therapy in patients with advanced recurrent breast cancer. Jpn J Cancer Chemother *28*: 965-972, 2001.

11 Hortobagyi GN: Treatment of breast cancer. N Engl J Med *1*: 974-984, 1998.

12 Nishimura R, Nagao K, Miyayama H *et al*: Studies on relationships between the effect and prognosis in chemo-endocrine therapy as a first- or second-line treatment for advanced or recurrent breast cancer. Jpn J Breast Cancer *15*: 309-316, 2000.

13 Srivastava RK, Srivastava AR, Korsmeyer SJ *et al*: Involvement of microtubules in the regulation of Bcl-2 phosphorylation and apoptosis through cyclic AMP-dependent protein kinase. Mol Cell Biol *18*: 3509-3517, 1998.

14 Miyake H, Tolcher A and Gleave ME: Chemosensitization and delayed androgen-independent recurrence of prostate cancer with the use of antisense Bcl-2 oligodeoxynucleotides. J Natl Cancer Inst *92*: 34-41, 2000.

15 Suzuki K, Kazui T, Yoshida M, Uno T *et al*: Drug-induced apoptosis and p53, Bcl-2 and BAX expression in breast cancer tissues *in vivo* and in fibroblast cells *in vitro*. Jpn J Clin Oncol *29*: 323-331, 1999.

16 Chan S: Randomized phase III study: preliminary results. Docetaxel *vs* doxorubicin in metastatic breast cancer resistant to alkylating chemotherapy. Oncology *11 (8, suppl 8)*: 19-24, 1997.

17 Aapro M: Docetaxel *versus* doxorubicin in patients with metastatic breast cancer who have failed alkylating chemotherapy: a preliminary report of the randomized phase III trial. Semin Oncol *25 (5, suppl 12)*: 7-11, 1998.

18 Adachi I, Watanabe T, Takashima S *et al*: A late phase II study of RP56976 (docetaxel) in patients with advanced or recurrent breast cancer. Br J Cancer *73*: 210-216, 1996.

19 Taguchi T, Mori S, Abe R *et al*: Late phase II clinical study of RP 56976 (docetaxel) in patients with advanced/recurrent breast cancer. Jpn J Cancer Chemother *21*: 2625-2632, 1994.

20 Airoldi M, Cattel L, Pedani F *et al*: Clinical and pharmacokinetic data of a docetaxel-epirubicin combination in metastatic breast cancer. Breast Cancer Res Treat *70*: 185-195, 2001.

Received November 17, 2003
Revised February 9, 2004
Accepted April 5, 2004

2. 原発性乳癌の手術

(2) 乳房温存療法における照射の必要性

京都大学大学院医学研究科腫瘍放射線科学
山内　智香子／光森　通英／平岡　眞寛
Chikako Yamauchi ／ Michihide Mitsumori ／ Masahiro Hiraoka

はじめに

現在わが国においても，乳房温存療法は臨床病期I，II期の乳癌に対する標準的治療法となりつつある。しかし乳房温存術後の放射線照射は日常診療において，約32%で省略されている。本稿では温存乳房に対する照射の必要性について述べる。

照射の必要性に関するランダム化比較試験

現在までに6つのランダム化比較試験により乳房温存術後の乳房照射の必要性が示された(表1)。いずれのトライアルにおいても温存術後の照射の有無で症例を割り付け，照射群では全乳房に50Gy前後，一部の症例では腫瘍床に追加照射を行っている。腫瘍サイズや切除範囲，照射線量に違いはあるものの，これらすべての比較試験において，局所再発は照射群で非照射群に比し有意な減少が認められた[1)~6)]。また，2000年にEarly Breast Cancer Trialists' Group (EBCTG)より報告されたこれらランダム化比較試験のメタアナリシスでは，10年局所再発率は非照射群で27.2%に対し，照射群で8.8%であった[7)]。これらの結果に基づくと，乳房温存術後は乳房照射を行うべきであろう。

照射を省略できる群はあるのか

局所再発のリスクが少なく放射線照射を省略できる群を探る試みが行われている。しかし，上述のランダム化比較試験における解析で，照射省略可能なサブグループは同定されなかった。切除断端・年齢・組織学的悪性度などが局所再発のリスク因子と考えられているが，低リスク群と考えられる症例を対象とし，照射を省略したprospective studyにおいても，局所再発率は高率であった[8)]。また，わが国ではしばしば切除断端陰性例で照射を省略されることがある。確かに，切除断端は評価方法や陽性・近接の定義の違いはあるが，多くの研究で陰性例は陽性・近接例に比し局所再発率が低いことが示されている。しかし，断端陰性例においても局所再発が認められ，また，一概に切除断端陰性といっても一部施設で行われているような，多数切片による詳細な病理学的検討がすべての施設で行われているわけではない。したがって照射の省略は慎重に行われなければならない。放射線照射を安全に省略できるサブグループを

表1　温存手術後の乳房照射に関するランダム化比較試験

Trial	Median FU (m)	Tumor size	Local recurrence (%)		Survival (%)	
			CS	CS + RT	CS	CS + RT
NSABP B-06	144	≦ 4cm	35	10	58	62
Swedish	54	≦ 2cm	18	2	90	91
Ontario	91	≦ 4cm	35	11	76	79
Milan III	52	≦ 2.5cm	18	2	No difference	
Scottish	68	≦ 4cm	25	6	No difference	
English	71	< 5cm	35	13	No difference	

CS：conservative surgery，RT：radiation therapy

同定することは今後の重要な課題であるが，現段階では多くのガイドラインでも，温存手術後の乳房照射は行うよう勧められている。

おわりに

先頃わが国では，Medical Frontierプロジェクトにより乳がん診療ガイドラインが作成され，ここでも乳房温存術後の乳房照射は必要とされた。その裏づけとなる文献のエビデンスレベルから推奨の強さもグレードA(行うよう強く勧められる)にランクされている。欧米に比べて再発率が低いといわれているわが国の乳癌に対して本当に照射は必要かという議論もあるが，日本独自のランダム化比較試験がなく，照射を省略できる群が同定されていない現状ではやはり乳房照射は必要といえる。今後はこれらの問題を解決すべく，日本独自の臨床試験が行われることが望まれる。

文献

1) Fisher B, et al：Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 333：1456～61, 1995.
2) Liljegren G, et al：10-year results after sector resection with or without postoperative radiotherapy for stage I breast cancer：A randomized trial. J Clin Oncol 17：2326～33, 1999.
3) Clark RM, et al：Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer：An update. Ontario Clinical Oncology Group. J Natl Cancer Inst 88：1659～64, 1996.
4) Veronesi U, et al：Breast conservation is a safe method in patients with small cancer of the breast：Long-term results of three randomized trials on 1,973 patients. Eur J Cancer 31A：1574～9, 1999.
5) Forrest AP, et al：Randomized controlled trial of conservation therapy for breast cancer：6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. Lancet 348(9029)：708～13, 1996.
6) Renton SC, et al：The importance of the resection margin in conservative surgery for breast cancer. Eur J Surg Oncol 22：17～22, 1996.
7) Early Breast Cancer Trialists' Collaborative Group：Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer：An overview of the randomized trials. Lancet 355(9217)：1757～70, 2000.
8) Schnitt SJ, et al：A prospective study of conservative surgery alone in the treatment of selected patients with stage I breast cancer. Cancer 77(6)：1094～100, 1996.

Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 1, pp. 146–151, 2004

0360-3016/04/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2003.09.088

CLINICAL INVESTIGATION **Breast**

FEASIBILITY OF BREAST-CONSERVING THERAPY FOR MACROSCOPICALLY MULTIPLE IPSILATERAL BREAST CANCER

SETSUKO OKUMURA, M.D.,* MICHIHIDE MITSUMORI, M.D.,* CHIKAKO YAMAUCHI, M.D.,* SACHIKO KAWAMURA, M.D.,* NATSUO OYA, M.D.,* YASUSHI NAGATA, M.D.,* MASAHIRO HIRAOKA, M.D.,* MASAKI KOKUBO, M.D.,† KEIICHI MISE, M.D.,‡ AND HIROSHI KODAMA, M.D.‡

*Department of Therapeutic Radiology and Oncology, Kyoto University Graduate School of Medicine, Kyoto, Japan; †Department of Image-Based Medicine, Institute of Biomedical Research and Innovation, Kobe, Japan; ‡Kodama Breast Clinic, Kyoto, Japan

Purpose: Macroscopically multiple ipsilateral breast cancer (MMIBC) is generally considered a contraindication for breast-conserving therapy (BCT). The result of BCT for MMIBC is reported and the feasibility discussed.
Methods and Materials: Between July 1993 and February 1999, 34 patients with MMIBC underwent BCT at our clinic. The local control, disease-free survival, and cosmetic results in these patients were compared with those of patients with single disease.
Results: After wide excision, 21 (62%) of 34 patients with MMIBC had a close surgical margin and the rate was significantly greater than that of patients with a single lesion. However, the size of the boost irradiation field was not significantly increased. At a median follow-up of 98 months, no statistically significant difference was noted in local control, disease-free survival, or cosmetic result compared with patients with a single lesion.
Conclusion: Although patients with MMIBC frequently had close surgical margins after BCT, it can be a treatment option for these patients as long as the close surgical margin is accurately detected and treated with an appropriate radiation technique. © **2004 Elsevier Inc.**

Macroscopically multiple ipsilateral breast cancer, Breast-conserving therapy, Surgical margin, Boost irradiation.

INTRODUCTION

Breast-conserving therapy (BCT) was developed to achieve survival equivalent to that after mastectomy, while providing a better quality of life, and this goal has been accomplished in many trials (1–4). However, macroscopically multiple ipsilateral breast cancer (MMIBC) is generally considered a contraindication for BCT (5–8). According to some reports, the local recurrence rate in MMIBC after BCT was significantly greater than that after BCT for a single tumor (9–11). However, other reports have demonstrated good local control for MMIBC treated by BCT, equal to that for single lesions, and concluded that BCT can be considered for MMIBC, as long as negative margins and negative extensive intraductal component was ensured (12, 13).

Since 1993, we have been offering BCT to patients with MMIBC as long as each of the tumors individually meets the criterion for breast-conserving surgery. In this study, we retrospectively compared local control, disease-free survival, and the cosmetic result between the patients with MMIBC and those with single lesions and assessed whether MMIBC can be a candidate for BCT.

METHODS AND MATERIALS

Between July 1993 and February 1999, 34 patients with MMIBC underwent BCT in the Kodama Breast Clinic and Kyoto University Hospital. This corresponded to 5.4% of all patients who underwent BCT (34 of 628) and 49.3% (34 of 69) of all patients with MMIBC in the same period. Their median age was 45 years (range, 29–81 years). The condition of the tumor, as well as patient preference, was considered in making the decision about the extent of surgery. These 34 patients wished to be treated with BCT, did not have absolute contraindications for radiotherapy (RT), such as pregnancy or previous RT to the affected breast, or relative contraindications, such as active collagen disease, and each of their tumors met the criteria for breast-conserving surgery (i.e., neither extensive microcalcification nor nipple invasion was present). The size of the individual

Reprint requests to: Michihide Mitsumori, M.D., Department of Therapeutic Radiology and Oncology, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan. Tel: (+81) 75-751-3762; Fax: (+81) 75-771-9749; E-mail: mitsumo@kuhp.kyoto-u.ac.jp

Received Dec 2, 2002, and in revised form Sep 16, 2003. Accepted for publication Sep 30, 2003.