厚生労働科学研究委託費

革新的がん医療実現化研究事業

StageIV 乳癌に対する標準治療の確立に関する研究

平成 26 年度　委託業務成果報告書

業務主任者　枝園　忠彦

平成 27（2015）年　3 月

本報告書は、厚生労働省の革新的がん医療実用化委託事業による委託業務として、枝園忠彦　が実施した　平成 26 年度「StageIV 乳癌に対する標準治療の確立に関する研究」の成果を取りまとめたものです。

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厚生労働科学研究委託費（革新的がん医療実現化研究事業）
委託業務成果報告（総括）

StageIV 乳癌に対する標準治療の確立に関する研究

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本研究は多施設共同の臨床試験であり、個々の分担研究者固有の研究ではないため、本総括研究報告書がすべてを代表するものとする

研究要旨：StageIV 乳癌に対する治療の目標は症状の緩和が主であり、効果の期待される薬物を順次投与する。本研究ではこれまで標準とされていた薬剤のみの治療に、原発巣切除術を組み合わせることで予後改善が得られるかどうかを検証することを目的として多施設共同第 III 相試験を開始した。登録は順調に進んでいる。平成 28 年末までに 410 例を集積しランダム化比較し、その後 4 年の経過観察の後に最終結果を得る予定である。

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A．研究目的

診断時に既に遠隔転移を伴う乳癌（StageIV 乳癌）は、治癒が期待できない状態であり、症状緩和を目的に薬物を順次投与することが標準治療である。

近年、StageIV 乳癌に対して薬物療法に抵抗性を持つがん幹細胞を多く含む原発巣切除が予後を改善する可能性があることが後向き研究で報告され始めた。本研究は、この仮説を前向きに検証し、StageIV 乳癌に対する標準治療を確立することを目的とする。

乳がん標準治療の確立は、年間 6 万人の女性が国内で罹患する現状において、安定した健全な社会環境を保つため優先されるべき事項である。他方、確実に上昇する新規薬剤費用に対し、本試験は安価な 1 回の手術により半年間の生存期間延長を確認することで、今後の薬剤の費用対効果の見直し

にも影響を及ぼすものと考える。

B. 研究方法

本試験はJCOG乳がんグループによる、初期薬物療法の効果が見られたStageIV乳癌患者に対する原発巣切除の有用性を確立する多施設共同第III相試験（優越性試験）である（JCOG1017）。

未治療の患者を一次登録し、薬剤の感受性を考慮した最適な薬物療法を行った後、増悪がない患者に対して「薬物療法継続群」と「原発巣切除を行った後に薬物療法を再開継続する群」にランダム割付を行う。

Primary endpointは全生存期間、secondary endpointsは、遠隔転移無増悪割合、年次無局所再発生存割合等である。登録期間5年。予定登録数は二次登録ランダム化例として410例。

試験が安全かつ適切に実施され、データが正確に収集されている事を確認するため年2回の定期モニタリングが行われ、施設訪問監査が参加施設に対して行われる。

（倫理面への配慮）

乳癌薬物療法および手術療法両者に関する十分な経験を持つ基幹病院のみで本試験を実施。「臨床研究に関する倫理指針」およびヘルシンキ宣言などの国際的倫理原則を遵守し、患者本人から文書で自発的同意を得、個人情報保護を徹底する。

C．研究結果

本試験は2011年5月に患者登録が開始され、2014年12月末までに276例が登録されている。

附随研究として「Stage IV乳癌に対する原発巣切除が血中循環乳癌細胞に及ぼす影響に関する研究」を検討するにプロトコール（JCOG1017-A1）を作成し2015年4月より開始予定である。

また本試験に類似した試験で、現在アメリカを中心に患者登録が行われているECOG2108試験との統合解析について情報交換および会議を行い、準備を進めている。

D．考察

診断時に既に遠隔転移を伴う乳癌（StageIV乳癌）は、治癒が期待できない状態であり、症状緩和を目的に薬物を順次投与することが標準治療である。

近年明確に示されるようになったがん幹細胞理論によると、既存の薬物によりがんを死滅できない理由として、がん幹細胞が薬剤抵抗性を持ちさらに自己複製能と分化能をもつことが挙げられる。そしてその多くは、StageIV乳癌の状態においても原発巣に多く含まれている。また原発巣は全身にがん細胞を散布する元であるとともに、放出したがん細胞を活性化する化学物質を放出することも基礎的研究により報告されている。これらの理論から、原発巣を外科的に切除することが有用である可能性が示唆された。

他方、薬物療法は、癌の性質をより細かく分類しそれぞれの特徴に応じたホルモン剤や分子標的治療剤を患者に合わせて個別に投与することで、効果的な治療を行えるようになった。

効果予測に基づく選択に応じて薬剤治療を開始し、その効果を得たうえで残されたがん幹細胞を含む原発巣切除を行う治療戦

略を確立するには、薬物治療と外科治療の両者に十分な経験を持つ施設による質の高い第 III 相試験が必須である。

平成 26 年より、JCOG 乳癌グループは登録の少ない施設を活発な施設に入れ替え、関連施設を増やしながら、全体で 36 施設となった。登録は順調に進んでおり、価値のある成果を世界に発信する予定である。

E．結論

薬物療法を行いながら、効果的に手術療法を組み合わせることの意義を問う本研究は、主に外科医が診断から再発後の薬物療法までトータルに治療を行っている我が国でのみ行うことのできる集学的治療の検証である。

StageIV 乳癌患者に対し、原発巣切除が有用であることが確認できれば、新規の高額な薬剤が次々と開発使用されているこの領域において患者予後を向上することに留まらず、費用対効果基準の見直しや、今後の治療開発に影響を与えることになるだろう。

F．健康危険情報

本研究では該当する危険情報はなかった。

G．研究発表

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3. Tadahiko Shien, Yuko Abe, Ayako Watanabe, Yuichiro Miyoshi, Taeko Mizoo, Tomohiro Nogami, Satoko Watanabe, Naruto Taira, Hiroyoshi Doihara. The evaluation of safety of skin-sparing mastectomy and nipple sparring mastectomy with reconstruction after neoadjuvant chemotherapy for locally advanced breast cancer. 14th St. Gallen International Breast Cancer Conference. 2015 年 3 月 Wine

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H．知的財産権の出願・登録状況

特に予定していない。

II. 学 会 等 発 表 実 績

委託業務題目「StageIV乳癌に対する標準治療の確立に関する研究」

1．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
A randomized controlled trial comparing primary tumor resection plus systemic therapy with systemic therapy alone in metastatic breast cancer [PRIM-BC]: Japan Clinical Oncology Group Study JCOG1017.（ポスター）	Shien T, Iwata H, Nakamura K, Kinoshita T, Hara F, Fujisawa T, Masuda N, Inoue K, Shibata T, Fukuda H.	37th San Antonio Breast Cancer Symposium.	2014年12月	国外
StageIV乳癌に対する効果的な原発巣切除術とは～手術の目的とタイミングの検討（口演）.	枝園忠彦、土井原博義、安部優子、三好雄一郎、原　暁生、溝尾妙子、岩本高行、野上智弘、元木崇行、平　成人.	第76回日本臨床外科学会	2014年11月	国内
The evaluation of safety of skin-sparing mastectomy and nipple sparring mastectomy with reconstruction after neoadjuvant chemotherapy for locally advanced breast cancer.（ポスター）	Tadahiko Shien, Yuko Abe, Ayako Watanabe, Yuichiro Miyoshi, Taeko Mizoo, Tomohiro Nogami, Satoko Watanabe, Naruto Taira, Hiroyoshi Doihara.	14th St. Gallen International Breast Cancer Conference.	2015年3月	国外
Influence of immediate breast reconstruction (IBR) on adjuvant therapy for breast cancer patients.（ポスター）	Tomohiro Nogami, Naruto Taira, Satoko Watanabe, Yuuko Abe, Taeko Mizoo, Takayuki Iwamoto, Takayuki Motoki, Tadahiko Shien, Yoshihiro Kimata, Hiroyoshi Doihara.	14th St. Gallen International Breast Cancer Conference.	2015年3月	国外
cStageIIIc BC patients diagnosed by PET/CT can get good prognosis with intensive treatment.（ポスター）	Ayako Watanabe, Tadahiko Shien, Yuko Abe, Akio Hara, Yuichiro Miyoshi, Taeko Mizoo, Tomohiro Nogami, Takayuki Iwamoto, Takayuki Motoki, Naruto Taira, Hiroyoshi Doihara.	14th St. Gallen International Breast Cancer Conference.	2015年3月	国外
The evaluation of safety of postmastectomy radiation therapy after immediate breast reconstruction.（ポスター）	Yuko Abe, Tadahiko Shien, Satoko Watanabe, Hidejiro Tokuyama, Taeko Mizoo, Takayuki Iwamoto, Tomohiro Nogami, Takayuki Motoki, Naruto Taira, Hiroyoshi Doihara, Keisuke Kimata.	14th St. Gallen International Breast Cancer Conference.	2015年3月	国外
Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer: A multicenter cohort analysis(ポスター)	Masuda N, Niikura N, Hayashi N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Tokuda Y, Saji S, Iwata H	European Society For Medical Oncology	2014年9月	国外
Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: A multicenter retrospective analysis(ポスター)	Hayashi N, Niikura N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Yamauchi H, Saji S, Iwata H	San Antonio Breast Cancer Symposium	2014年12月	国外

The long-term prognosis of sentinel lymph node-positive breast cancer patients without axillary dissection(ポスター)	Taguchi Y, Yasojima H, Masuda H, Mizutani M, Masuda N, Mori K, Kodama Y, Manou M, Nakamori S, Sekimoto M	European Society of Surgical Oncology	2014年10月	国外

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Tamoxifen versus tamoxifen plus doxorubicin and cyclophosphamide as adjuvant therapy for node-positive postmenopausal breast cancer: results of a Japan Clinical Oncology Group Study (JCOG9401).	Shien T, Iwata H, Aogi K, Fukutomi T, Inoue K, Kinoshita T, Takahashi M, Matsui A, Shibata T, Fukuda H.	International Journal of Clinical Oncology	2014	国外
Resection of the primary tumor in stage IV breast cancer.	Shien T, Doihara H.	World Journal of Clinical Oncology	2014	国外
Tamoxifen plus tegafur-uracil (TUFT) versus tamoxifen plus Adriamycin (doxorubicin) and cyclophosphamide (ACT) as adjuvant therapy to treat node-positive premenopausal breast cancer (PreMBC): results of Japan Clinical Oncology Group Study 9404.	Shien T, Iwata H, Fukutomi T, Inoue K, Aogi K, Kinoshita T, Ando J, Takashima S, Nakamura K, Shibata T, Fukuda H.	Cancer Chemotherapy and Pharmacology.	2014	国外
Clinicopathological features of young patients (<35 years of age) with breast cancer in Japanese Breast Cancer Society supported study	Kataoka A, Tokunaga E, Masuda N, Shien T, Kawabata K, Miyashita M	Breast Cancer	2014	国外
Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer of each subtype:a multicenter retrospective analysis	Niikura N, Hayashi N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Tokuda Y, Saji S, Iwata H	Breast Cancer Res Treat	2014	国外
A phase II study of metronomic paclitaxel/cyclophosphamide/capecitabine followed by 5-fluorouracil/epirubicin/cyclophosphamide as preoperative chemotherapy for triple-negative or low hormone receptor expressing/HER2-negative primary breast cancer.	Masuda N, Higaki K, Takano T, Matsunami N, Morimoto T, Ohtani S, Mizutani M, Miyamoto T, Kuroi K, Ohno S, Morita S, Toi M.	Cancer Chemotherapy and Pharmacology	2014	国外
Prognostic factors of HER2-positive breast cancer patients who develop brain metastasis: a multicenter retrospective analysis	Hayashi N, Niikura N, Masuda N, Takashima S, Nakamura R, Watanabe K, Kanbayashi C, Ishida M, Hozumi Y, Tsuneizumi M, Kondo N, Naito Y, Honda Y, Matsui A, Fujisawa T, Oshitanai R, Yasojima H, Yamauchi H, Saji S, Iwata H	Breast Cancer Res Treat	2015	国外

III. 研究成果の刊行物・別刷

Int J Clin Oncol (2014) 19:982–988
DOI 10.1007/s10147-013-0657-z

ORIGINAL ARTICLE

Tamoxifen versus tamoxifen plus doxorubicin and cyclophosphamide as adjuvant therapy for node-positive postmenopausal breast cancer: results of a Japan Clinical Oncology Group Study (JCOG9401)

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Received: 28 October 2013 / Accepted: 5 December 2013 / Published online: 7 January 2014

Abstract

Background Cancer subtype has recently become an increasingly important consideration when deciding the treatment strategy for breast cancer. For the estrogen receptor positive (ER+) subtype, the efficacy of adjuvant endocrine therapy is definitive, but that of adjuvant chemotherapy is controversial.

Methods In order to evaluate the effect of adding doxorubicin (A) and cyclophosphamide (C) to tamoxifen (TAM) (ACT) on the overall survival (OS) of node-positive postmenopausal breast cancer (PMBC) patients, we conducted a randomized trial. Eligibility criteria included pathologically node-positive (n = 1–9) PMBC, stage I–IIIA disease. Patients were randomized to receive either TAM (20 mg daily) for 2 years or A (40 mg/m^2) and C (500 mg/m^2) plus TAM (ACT) as adjuvant therapy following surgery.

Results One hundred twenty-nine patients were recruited (TAM 64, ACT 65) between October 1994 and July 1999. The hazard ratios for OS and relapse-free survival (RFS) were 0.58 (95 % CI 0.24–1.39; log-rank p = 0.22) and 0.45 (95 %CI 0.24–0.86; log-rank p = 0.013), respectively, in favor of ACT. The 5-year OS and RFS were 76.9 % (ER+ 87.1 %, ER− 53.3 %) and 54.9 % (ER+ 59.3 %, ER− 42.9 %) for TAM and 85.0 % (ER+ 90.0 %, ER− 77.1 %) and 76.7 % (ER+ 76.9 %, ER− 76.0 %) for ACT. A higher proportion of the patients receiving ACT than those receiving TAM experienced grade 3 decreased white blood cell count and grade 2–3 nausea.

Conclusion The efficacy of adding AC to TAM was not high for ER+, node-positive PMBC. However, adjuvant ACT therapy was considered to be effective for ER−, node-positive PMBC.

Keywords Breast cancer · Adjuvant treatment · Node-positive · Postmenopausal women

On behalf of the JCOG Breast Cancer Study Group. The 22 institutions that belong to the JCOG Breast Cancer Study Group are listed in Appendix.

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Introduction

Tamoxifen (TAM) is an effective drug used as adjuvant therapy for postmenopausal breast cancer (PMBC) patients. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found, through a meta-analysis, that adjuvant TAM produced better disease-free survival (DFS) and overall survival (OS) in 1990, regardless of the patient's hormone receptor status [1]. Adjuvant chemotherapy for PMBC patients has otherwise been regarded as effective for improving prognosis. The EBCTCG suggested that an anthracycline-containing regimen could improve the breast cancer death ratio and recurrence rate ratio by 16 and 11 %, respectively, compared to a cyclophosphamide, methotrexate, and fluorouracil regimen [2]. At a National Institutes of Health conference, it was proposed that an anthracycline-containing regimen should be the standard adjuvant therapy for resected breast cancer [3]; therefore, an anthracycline-containing regimen has since become the standard adjuvant therapy for node-positive breast cancer patients. However, the efficacy of TAM plus chemotherapy for PMBC was not evaluated in the 1990s.

At a conference at St. Gallen in 1992, chemotherapy was recommended for postmenopausal, node-negative, estrogen receptor (ER) negative (ER−) patients [4]. Fisher et al. [5] reported that TAM plus chemotherapy was more effective than TAM alone for node-positive PMBC in a subgroup analysis of data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-16 trial. Meanwhile, the EBCTCG meta-analysis also showed that chemotherapy alone contributed little to the prolongation of the survival of breast cancer patients over 50 years of age [2]. Thus, TAM plus chemotherapy was expected to be promising as an adjuvant therapy for postmenopausal, node-positive breast cancer patients.

In 1994, to elucidate the efficacy of adding an anthracycline-containing chemotherapy to TAM used as an adjuvant therapy for PMBC, the Breast Cancer Study Group of the Japanese Clinical Oncology Group (JCOG) designed a prospective randomized clinical trial of a regimen of doxorubicin (A) and cyclophosphamide (C) plus TAM (ACT) compared to TAM alone.

Patients and methods

Patients

Postmenopausal female patients who were younger than 70 years and had clinical stage I–IIIa breast cancer were eligible for this study. All patients had to have undergone curative mastectomy with axillary node dissection, and the involvement of 1–9 axillary nodes had to have been detected upon histological examination. Additional eligibility criteria were a World Health Organization performance status of 0–1 and adequate bone marrow, liver, and kidney function. Patients who received previous treatment for breast cancer were excluded. Informed consent was obtained from each patient before study participation.

Planned treatment schedules

All patients were randomly assigned to either of the following two regimens: the TAM arm (only TAM was administered at 20 mg/day until relapse or for a maximum of 2 years), and the ACT arm (A was administered at 40 mg/m^2 intravenously and C was administered at 500 mg/m^2 intravenously on day 1 every 28 days for 6 cycles, while TAM was administered at 20 mg/day for a maximum of 2 years in the absence of relapse, regardless of hormone receptor status).

The target recruitment for each study arm was 110 patients. Randomization was conducted using the minimization method, and the arms were balanced in terms of ER and progesterone receptor (PR) status (positive, i.e., >10 %, versus negative or unknown), HER2 status (positive versus negative or unknown), number of metastatic nodes (1–3 versus 4–9), age (≤60 versus 61–70 years), and institution.

Patient assessment

Initial workup included medical history, tumor assessment, physical examination, routine hematology and chemistry analyses, chest radiography, liver ultrasonography, and bone scan. Hematology and chemistry analyses, tumor marker measurements, and urinalysis were repeated monthly. To check for distant metastasis, chest radiography and liver ultrasonography were performed every 6 months, a bone scan was performed every year, and bilateral mammography was performed every 2 years. Hematological disorders and toxicity were evaluated according to the toxicity grading criteria of the Japan Clinical Oncology Group [6], and were recorded in case report forms.

Endpoint

As per the study design, the primary endpoint was OS and the secondary endpoint was RFS. OS was defined as the time from randomization to death from any cause, and it was censored at the final follow-up date. RFS was defined as the time from randomization to either the first event of recurrence or death from any cause, and it was censored on the date that recurrence-free status was verified. OS and RFS were evaluated according to hormone receptor status (either ER+ or PR+ versus both ER− and PR− or unknown) in subgroup analyses. In addition, the safety of the treatment was evaluated.

Statistical analysis

If the OS of the patients treated with ACT was significantly longer than that of the patients treated with TAM, ACT would be recommended as the new standard treatment. The estimated 5-year OS of these patients is commonly 64–88 % [7–9]. The initial sample size was calculated as 280 patients to detect a prolongation of 5-year OS from 75 % in the TAM arm to 87 % in the ACT arm with 80 % power and a two-sided alpha of 5 %. The planned study period was originally 2 years for accrual and an additional 5 years for follow-up. Due to the slow accrual, the protocol was revised to prolong the accrual period, and the sample size was revised to 220 patients with an accrual period of 5 years. OS and RFS were estimated using Kaplan–Meier method, and curves were compared by using a log-rank test. Hazard ratios of treatment effects were estimated through a Cox regression model. All analyses were based on intention to treat. All statistical analyses were performed using the SAS software package, release 8.2.

Interim analysis and monitoring

It was planned that an interim analysis would be performed when half of the total number of patients had been enrolled. The Data and Safety Monitoring Committee (DSMC) of the JCOG independently reviewed the interim analysis report, and premature termination of the trial was considered at that stage. In-house interim monitoring was performed by the Data Center to ensure data submission, patient eligibility, protocol compliance, safety, and on-schedule study progress. The monitoring reports were submitted to and reviewed by the DSMC every 6 months.

Results

Patient population

This study was initially implemented in 1994. After approximately 110 patients had been enrolled, the protocol was revised to prolong patient recruitment until December 1999. At the interim analysis on June 1999, patient accrual was so slow that DSMC recommended that patient accrual should be terminated or continued with the primary endpoint changed to RFS. Furthermore, at a consensus meeting in St. Gallen in 1997, it was established that the administration of TAM to hormone receptor-negative patients was ethically unacceptable. Therefore, the recruitment of patients was terminated based on suggestions from the DSMC of JCOG.

In total, 131 patients were recruited. Two patients were registered twice. Thus, 129 patients were randomized

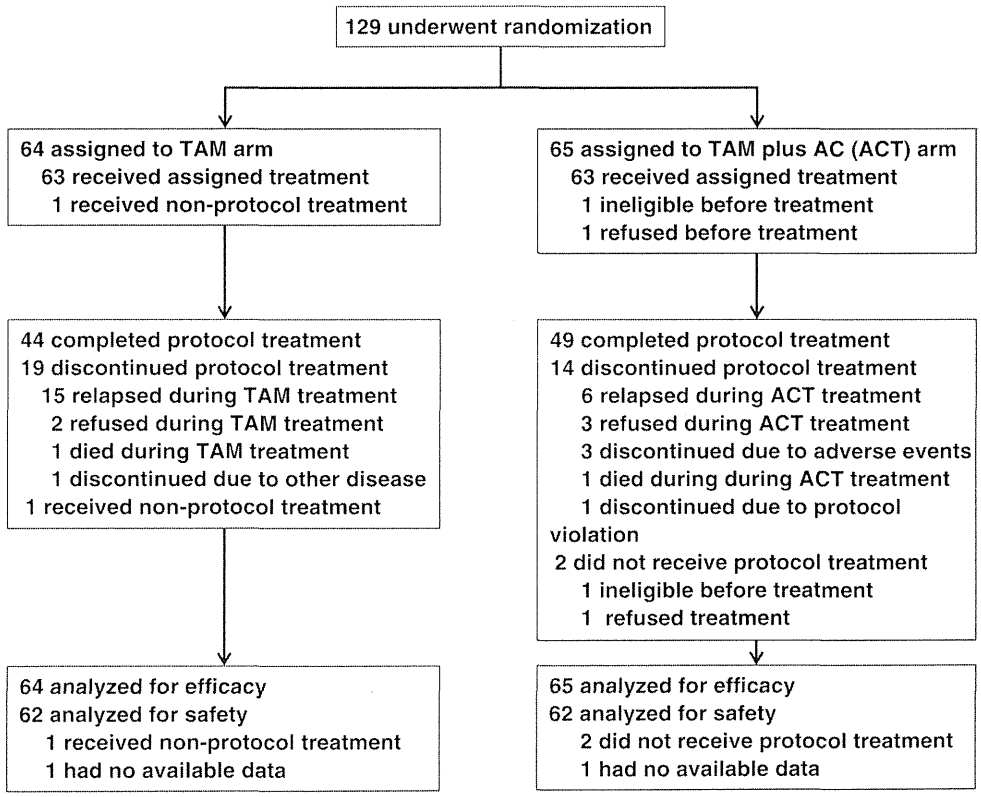

Fig. 1 Trial profile of the Japan Clinical Oncology Group study JCOG 9401

Table 1 Patient characteristics

	TAM ($n = 64$)	ACT ($n = 65$)
Age (years)		
Median	58	59
Range	47–70	46–70
No. of positive axillary nodes		
1–3	46	46
4–9	18	19
ER and/or PgR		
Negative/unknown	18	19
Positive	46	46
HER2		
Negative/unknown	53	57
Positive	11	8
Stage		
I	10	12
II	44	43
IIIA	10	10
Operation		
Radical mastectomy	3	6
Total mastectomy	59	55
Partial resection	2	4

(Fig. 1). One patient was ineligible because of the previous administration of TAM, but was still included in the analysis. The baseline characteristics were well balanced between the two groups (Table 1). The median age was 59 years (46–70 years). The number of patients with node metastases involving 1–3 nodes was 92 (71.3 %) and the number with 4–9 involved nodes was 37 (28.7 %). The number of patients with both ER− and PR− tumors, including patients with unknown hormone status, was 37 (28.7 %). Most patients (95.3 %) underwent total mastectomy. Sixty-four cases were assigned to the ACT arm and 65 cases were assigned to the TAM arm. The data from an immunohistochemistry assay of HER2 protein were missing for 2 cases in the ACT arm and for 1 case in the TAM arm; the data from a cytosol assay of HER2 protein were missing for 2 cases in each group. However, this did not influence the results of this study.

Treatment completion

The protocol treatment in the TAM arm was completed in 44 of the 64 cases (68.8 %). The protocol treatment in the ACT arm was completed in 49 of the 65 cases (75.4 %) (Fig. 1).

Survival

Sixty-four and 65 patients were enrolled and analyzed in the TAM and ACT arms, respectively, with no significant

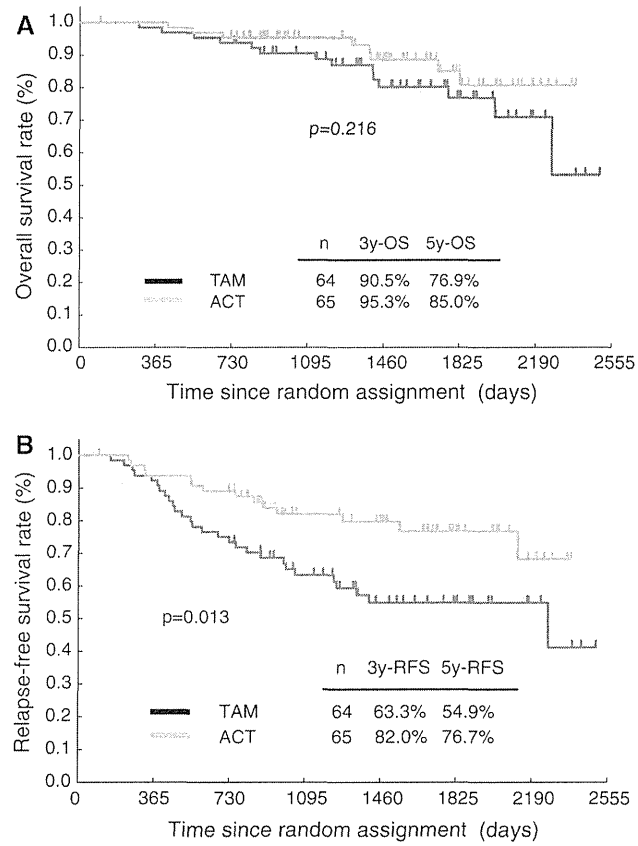

Fig. 2 Kaplan–Meier curves of overall survival (**a**) and relapse-free survival (**b**) for node-positive breast cancer patients treated with tamoxifen or tamoxifen with anthracycline and cyclophosphamide

difference in overall survival between them [$p = 0.216$, hazard ratio 0.58, 95 % confidence interval (CI) 0.24–1.39] (Fig. 2a). The 3- and 5-year OS were 90.5 and 76.9 % for the TAM arm and 95.3 and 85.0 % for the ACT arm, respectively. The RFS in the ACT arm was significantly longer than that in the TAM arm ($p = 0.013$, hazard ratio 0.45, 95 % CI 0.24–0.86) (Fig. 2b). The 3- and 5-year RFS were 63.3 and 54.9 % in the TAM arm and 82.0 and 76.7 % in the ACT arm, respectively.

Subgroup analysis was performed according to hormone receptor status. The numbers of ER+ and/or PR+ patients in the TAM and ACT arms were 46 (71.9 %) and 46 (70.8 %), respectively. The OS is shown in Fig. 3a. ER− patients included in the TAM arm had a worse prognosis than those in the other three groups. ER− patients on ACT showed a better overall survival than those on TAM alone. The OSs of the ER+ and/or PR+ groups were good, regardless of the arm considered. RFS in the ER+ and/or PR+ patients in the TAM arm was worse than those in the ACT arm (Fig. 3b). The ER− and PR− patients included in the TAM arm had the worst prognosis.

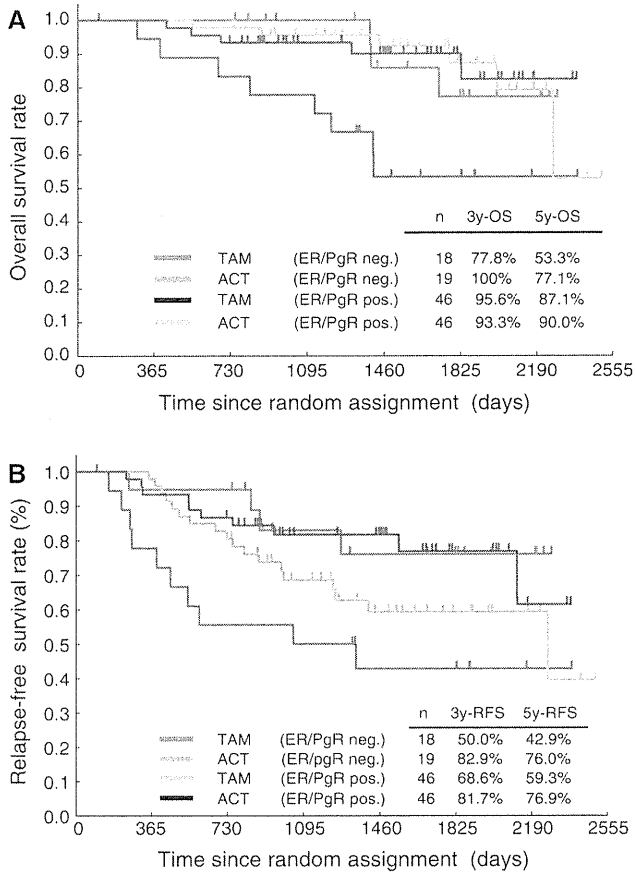

Fig. 3 Kaplan–Meier curves of overall survival (**a**) and relapse-free survival (**b**) for node-positive breast cancer patients treated with tamoxifen or tamoxifen with anthracycline and cyclophosphamide, according to estrogen receptor (ER) and progesteron receptor (PgR) status

Table 2 Hematological (A) and nonhematological (B) toxicities

Toxicities	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
(A) Hematological toxicities (n = 62)			
TAM			
WBC	0 (0)	0 (0)	0 (0)
Hb	1 (2)	0 (0)	0 (0)
T-Bil	2 (3)	0 (0)	0 (0)
GOT	3 (5)	0 (0)	0 (0)
GPT	4 (6)	0 (0)	0 (0)
ACT			
WBC	9 (15)	3 (5)	0 (0)
Hb	2 (3)	0 (0)	–
T-Bil	7 (11)	0 (0)	0 (0)
GOT	7 (11)	0 (0)	0 (0)
GPT	7 (11)	0 (0)	0 (0)
(B) Non-hematological toxicities (n = 62)			
TAM			
Infection	0 (0)	0 (0)	0 (0)
Nausea/vomiting	0 (0)	0 (0)	–
Thrombosis	0 (0)	0 (0)	0 (0)
Alopecia	0 (0)	–	–
ACT			
Infection	1 (2)	0 (0)	0 (0)
Nausea/vomiting	20 (32)	1 (2)	–
Thrombosis	1 (2)	0 (0)	0 (0)
Alopecia	29 (42)	–	–

Safety

Toxicities detected are listed in Table 2. No grade 4 events were noted. Higher proportions of the patients in the ACT arm experienced grade 3 decreased white blood cell count (TAM 0 %, ACT 4.8 %), grade 2–3 nausea (TAM 0.0 %, ACT 33.9 %), and grade 2 alopecia (TAM 0.0 %, ACT 46.8 %) than the corresponding patients in the TAM arm. Higher proportions of the patients in the TAM arm had grade 2 increased GOT and GPT (TAM 11.3 and 11.3 %, ACT 4.8 and 6.5 %).

Discussion

It is uncertain whether adjuvant chemotherapy is required in the treatment of postmenopausal breast cancer with hormone-responsive and intermediate risk. There have been few clinical trials to compare hormone therapy alone with chemotherapy plus hormone therapy [10, 11]. These studies suggested that the efficacy of chemoendocrine therapy as an adjuvant therapy for improving the prognosis of highly ER-positive patients was limited [11]. A meta-analysis of metastatic breast cancer cases indicated that chemoendocrine therapy did not lead to an improved prognosis compared to monotherapy [12]. We reanalyzed and reported this old study starting from 1994, because we thought that this would provide a valuable source of information when attempting to answer this clinical question and determine the optimal adjuvant treatment strategy for those patients. This study was designed to demonstrate the superiority of our anthracycline-containing regimen, ACT, over TAM alone (regardless of ER and PR status), which was the most common adjuvant treatment for postmenopausal patients in the early 1990s. The planned recruitment for each study arm was 110 patients at the beginning of the study and patient recruitment was started in December 1994. This trial was terminated in July 1999 because patient accrual was slow and TAM was contraindicated for ER− PMBC during the course of this trial [13]. The NSABP B-23 reported no improvement in the prognosis of ER− patients receiving adjuvant TAM. A meta-analysis conducted by the EBCTCG showed that the risk

reduction for recurrence on using TAM in ER− patients was 6 %; however, these results were biased by the error associated with ER- and PR-like enzyme immunoassay methods [14]. After those reports, TAM was not used for ER− patents. In this study, ER− patients (28.7 %) who received only TAM had the worst prognosis, as shown in the subgroup analysis. These patients may include both completely negative ER and 1–9 % positive patients for whom adjuvant hormone therapy has recently been indicated. The prognosis for the patients with completely negative ER was probably similar to that of the patients who did not receive adjuvant treatment, and the efficacy of TAM for the patients with slightly positive ER was unclear based on these results.

Overall, the analysis showed that there was no significant prognostic effect of adjuvant chemotherapy on OS in spite of the inclusion of ER− patients. The effect on the prognosis was greater for ER− patients than for ER+ patients, and TAM is not effective for ER− patients. Currently, the common duration of TAM treatment for ER+ patients is 5 years. Two years of adjuvant TAM might not have maximized the prognosis for these patients. However, these factors could not have influenced the superiority of additional chemotherapy in this study. Rather, the inclusion of ER− patients and the insufficient number of enrolled patients may have influenced this result. In addition, we believe that the insignificant effect of chemotherapy in ER+ rather than in ER− patients is important.

The effect of adjuvant chemotherapy on the prognosis for ER+ patients may be less than that for ER− patients, and the additional effect on top of that of endocrine therapy is relatively small. A meta-analysis by the EBCTCG showed that the reduction in the risk for recurrence from the use of adjuvant chemotherapy in postmenopausal ER− breast cancer patients was twice that in ER+ patients [2]. Based on the drug effects predicted from tumor biology, the new treatment strategy was recommended at the St. Gallen consensus meeting of 2011 [15]. ER+ patients have a low Ki67 labeling index, which is correlated with the efficacy of chemotherapy, and HER2-negative breast cancer patients have a low sensitivity to chemotherapy and a high sensitivity to endocrine therapy. In this study, no significant effect on OS was noted upon the addition of chemotherapy to endocrine therapy in node-positive patients with a high risk for recurrence. The ER− subgroup showed improved prognosis with additional chemotherapy, but the ER+ subgroup did not. The chemotherapy dose was lower than recently recommended, because the standard AC regimen was not established at the beginning of this study in Japan. Thus, the maximum effect of the adjuvant chemotherapy was not fully elicited in this study. However, we believe that one of the reasons for this negative result is that some ER+ subgroups can be treated adequately with endocrine therapy. In addition, we need extra information to judge the indication for adding chemotherapy to endocrine therapy in ER+ breast cancer patients. The degree of ER expression is one of them. It is reported that the efficacy of adjuvant chemotherapy in highly ER+ breast cancer cases is limited [11]. The most promising methods to use to identify these subgroups are the multigene assay and the Ki67 labeling index. Oncotype DX, which is a multigene assay to predict the efficacy of adjuvant chemotherapy against ER+ breast cancer, has been evaluated in prospective studies in which it showed demonstrable utility [16, 17]. However, these assays are not commonly performed because of the cost and inconvenience involved. The Ki67 labeling index is reported to be a prognostic factor. Moreover, it may be a predictive factor for chemotherapy [18, 19] and is especially meaningful in ER+ patients [20]. However, the limitations of this method include a lack of measurement clarity and thresholds [21]. Our study was started in 1994, and the surgical specimens were very old, so we cannot reanalyze these factors. We need to plan a study to establish a strategy for appropriate adjuvant treatment of ER+ patients using these new indices.

TAM alone was less toxic than ACT. No grade 3 toxicities were noted in patients treated with TAM alone, and the frequency of all toxicities was less in the TAM arm than in the ACT arm. A previous study reported an increased rate of thromboembolic complications with chemoendocrine combination adjuvant therapy [10]. There was only one G2 thrombosis in the patients with ACT.

In this study, there was no significant improvement in PMBC patient prognosis upon adding chemotherapy. Both benefits and risks need to be considered when choosing whether to implement adjuvant treatment. Many chemotherapy-associated toxicities are harmful and sometimes fatal. In the absence of an effect on the prognosis to offset the risks associated with additional chemotherapy, adjuvant chemotherapy should not be administered to all ER+ patients. More detailed analysis and definitive prospective trials are warranted to validate our findings.

Acknowledgments We thank Ms. Kyoko Minamoto and Kazumi Kubota for data management, Dr. Naoki Ishizuka and Mr. Junki Mizusawa for statistical analyses, and Dr. Kenichi Nakamura for the preparation of the manuscript. This study was supported by a National Cancer Center Research and Development Fund (23-A-16 and 23-A-17) and Grants-in-Aid for Cancer Research (5S-1, 8S-1, 11S-1, 11S-4, 14S-1, 14S-4, 17S-1, 17S-5, 20S-1 and 20S-6) from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest Hiroji Iwata received honoraria for speaking events from Chugai Pharmaceutical Co., Ltd. Tadahiko Shien, Kenjiro Aogi, Takashi Fukutomi, Kenichi Inoue, Takayuki Kinoshita, Masato Takahashi, Akira Matsui, Taro Shibata, Haruhiko Fukuda had no conflicts of interest.

Appendix: Participating institutions (from north to south)

The 22 institutions that belonged to the JCOG Breast Cancer Study Group and participated in this trial are as follows: National Sapporo Hospital, International Medical Center of Japan, Tochigi Cancer Center, Metropolitan Komagome Hospital, National Cancer Center, National Cancer Center East, Tokai University Hospital, National Atami Hospital, Hamamatsu Medical Center, Aichi Cancer Center, Osaka National Hospital, Kinki University Hospital, National Shikoku Cancer Center, National Kure Medical Center, National Nagasaki Medical Center, Saitama Cancer Center, St Luke's International Hospital, Hyogo Medical Center, Shizuoka Cancer Center, Niigata Cancer Center Hospital, Kawasaki Medical School Hospital, and Kitakyushu Municipal Medical Center.

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World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5306/wjco.v5.i2.82

World J Clin Oncol 2014 May 10; 5(2): 82-85
ISSN 2218-4333 (online)

TOPIC HIGHLIGHT

WJCO 5th Anniversary Special Issues (2): Breast cancer

Resection of the primary tumor in stage Ⅳ breast cancer

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Received: December 28, 2013 Revised: January 23, 2014
Accepted: March 11, 2014
Published online: May 10, 2014

Abstract

Stage Ⅳ breast cancer refers to breast cancer that has already metastasized to distant regions when initially diagnosed. Treatment for stage Ⅳ is intended to "prolong survival and palliate symptoms". Resection of a primary tumor is considered to be "effective only at alleviating chest symptoms and providing local control" in spite of the advances of imaging examination and medication for breast cancer. Molecular target and endocrine drugs are very effective and useful to tailor-make a treatment strategy according to breast cancer subtypes. Positron emission tomography-computed tomography can detect and diagnose the very small metastases and recurrences which can potentially be cured even if they are distant metastases. Recently, many retrospective studies have reported the survival benefit of surgery for breast cancer patients with metastases and some clinical trials which confirm the surgical prognostic benefit for them have started to enrol patients. The goal of treatment has to be clearly identified: increase the patient's survival time, provide local control or perform histology to determine the cancer's properties. The best evidence is absolutely essential to treat patients who need surgery at the right time. We need to evaluate the treatment strategy, including primary resection for stage Ⅳ breast cancer particularly, and find new evidence by prospective analysis.

Key words: Breast cancer; Metastasis; Surgery; Survival; Stage Ⅳ; Clinical trial

Core tip: Resection of a primary tumor of stage Ⅳ breast cancer was considered to be "effective only at alleviating chest symptoms and providing local control" in spite of the advances of imaging examination and medication for breast cancer. Recently, many retrospective studies have reported the survival benefit of surgery for breast cancer patients with metastases and some clinical trials which confirm the surgical prognostic benefit for them have started to enrol patients. We need to evaluate the treatment strategy, including primary resection for stage Ⅳ breast cancer particularly, and find new evidence by prospective analysis.

Shien T, Doihara H. Resection of the primary tumor in stage Ⅳ breast cancer. *World J Clin Oncol* 2014; 5(2): 82-85 Available from: URL: http://www.wjgnet.com/2218-4333/full/v5/i2/82.htm DOI: http://dx.doi.org/10.5306/wjco.v5.i2.82

INTRODUCTION

Stage Ⅳ breast cancer refers to breast cancer that has already metastasized to distant regions when initially diagnosed. Even if such cancer were to be treated, complete cure would not be expected. Treatment is intended to "prolong survival and palliate symptoms". Medication has made advances and treatments that are anticipated to be efficacious are administered. This situation has changed little as new drugs are coming out every year. In an increasing number of patients, appropriate use of

those drugs allows long-term control of symptoms and a longer life with disease.

In addition, marked advances in diagnostic imaging equipment have been made. Over the past few years, the prevalence of positron emission tomography-computed tomography has led to the early diagnosis of extremely small metastases that were not previously noted[1]. Stage IV breast cancer with these small metastases is referred to as "minimal stage IV disease[2]" and patients with this more limited form are expected to have a better prognosis than patients with full-blown stage IV breast cancer. Although it has yet to be precisely defined, the concept of "oligometastasis" is being debated[3]. According to this concept, metastases can potentially be cured, even if they are distant metastases, depending on their location and number.

Resection of a primary tumor was previously considered to be "effective only at alleviating chest symptoms and providing local control", but some studies have reported that resection increases survival time[4,5]. Breast-conserving surgery is a widely used form of surgery for breast cancer. Anesthesia has also made advances and is safe. At the current point in time, surgery for breast cancer is extremely simple, depending on tumor size, and minimally invasive. A longer survival time seldom results from drug administration but it can result from surgery. Surgery for stage IV breast cancer is an important topic that may substantially alter future treatment strategies.

SIGNIFIC-NCE OF RESECTION OF THE PRI-.-R. TUM.OR IN ST-GE I. BRE-ST C-NCER: STUDIES REPORTING INCRE-SED SUR.I.-L TIM.ES -ND REL-TED ISSUES

As mentioned earlier, a number of recent studies have reported that surgery for stage IV breast cancer affects a patient's survival time. Many of these retrospective studies indicated that surgery prolonged survival time. Several systematic reviews have reported significant differences in survival time (HR of about 0.6)[4,5]. A look at subgroups indicates that factors facilitating surgery include "complete excision of the primary tumor", "metastasis only to bone and/or soft tissue", "few metastases" and "being younger"[6,7]. A study reported differences in the effectiveness of surgery for different subtypes of tumors[8]. However, all of the findings cited were the result of retrospective analysis so they are presumed to be highly biased. "Patients who undergo surgery" are invariably "patients in good enough condition to undergo surgery" while "patients who do not undergo surgery" are possibly "patients who are unable to undergo surgery because of their worsening condition". In addition, medication has not been studied in detail and patients who undergo surgery are likely to include a number of patients whose condition could have been satisfactorily controlled with medication. The timing of surgery is also unclear. There is no clear answer as to whether surgery should be done during initial treatment or whether it should be a final option that is used after medication proves inefficacious.

-H. DOES RESECTION OF ONL. THE PRI-.-R. TUM.OR HELP -HEN C-NCER CELLS H- .E SPRE-D THROUGHOUT THE BOD.?

According to the seed and soil theory by Paget[9], the distant metastasis is not local disease. Cancer cells have already spread to whole body circulation. So, local therapies do not affect overall survival, whereas there are several theories on the basic rationale for resection of the primary tumor increasing the survival time for patients with stage IV breast cancer. The first is a "reduction in total tumor volume". Circulating tumor cells (CTCs) are a major indicator of tumor volume. A reduction in CTCs is reported to be correlated with prognosis[10]. Resection of the primary tumor reduces the tumor volume and thus reactivates autoimmunity and increases the efficacy of medication[11]. A study prospectively demonstrated that resection of the primary tumor is useful when kidney cancer is in stage IV (this is the only other solid tumor besides breast cancer for which this holds true)[12]. According to the study, resection of the primary tumor is a theoretical basis for the effectiveness of surgery.

Another theory as to why resection of the primary tumor increases the survival time concerns the particular action of the primary tumor. "Cancer stem cells" that are prevalent in the primary tumor are resistant to medication[13]. In addition, the concept of "cell seeding" indicates that cells released into the blood by the primary tumor return to the primary tumor, so the primary tumor activates those cancer cells[14]. Both of these mechanisms are based on results of basic experiments and no studies have described results from actual patients. If, however, they are true, then they are sure to be key to devising cancer treatment strategies in the future. These mechanisms should be verified in the future.

LOC-L CONTROL

As mentioned at the very beginning, resection of the primary tumor has been useful in alleviating chest symptoms, such as bleeding and ulceration as well as pain due to invasion of the chest wall. However, no studies or prospective trials have determined whether or not earlier surgery is useful to achieve local control. At the current time, there are absolutely no data corroborating the contention that "earlier surgery is useful since it improves local control, even if it does not increase survival time". When local control alone was envisioned, radiation therapy was considered in addition to surgery. Although sample sizes are small, studies have described an improvement in the prognosis for the primary tumor in stage IV breast cancer as a result of radiation therapy (like the improvement in