＜乳腺腋窩の解剖＞

岡山大学病院乳腺・内分泌外科　教授
土井原　博義

乳がんは現在本邦では年間約54,000人の女性が罹患し、12,000人が死亡すると報告されており、罹患率は1990年代前半より女性の癌罹患率で第１位、死亡率は第5位でいずれも年々増加している疾患である。その診断に関しては集団検診や診断方法、診断機器の進歩により、早期乳がんは増加しているものの依然として進行癌として発見される症例も少なくない。治療法には手術療法、薬物療法、放射線療法などがあるが、単一の治療が施行されることは少なく、2つあるいはすべてを組み合わせた集学的治療が中心である。

今回、乳がん手術における腋窩の解剖を知る上で腋窩リンパ節郭清の意義、センチネルリンパ節生検について概説した後、腋窩の解剖について説明する。

1．乳がんにおける腋窩リンパ節郭清の意義

腋窩リンパ節郭清の意義は、①病期の決定　②治療方針の決定　③腋窩リンパ節再発の予防（局所コントロール）と考えられている。Fisherら[1]により根治的乳房切除（乳房切除＋腋窩リンパ節郭清）、乳房切除のみ、乳房切除＋腋窩放射線治療の3群比較の25年フォローアップデータが発表されており、術式による無再発生存率、全生存率において各群に有意差はみられなかった。ただ、リンパ節転移の有無による生存率の差は明らかであり、予後の指標、治療の指標としての腋窩リンパ節郭清は大きな意義があり、その手技を会得することは重要である。

2．センチネルリンパ節生検

腋窩郭清により上肢の浮腫、疼痛、知覚鈍麻や挙上障害などの合併症が少なからず起こり得る。従って不要なリンパ節郭清を省略するために考えられたのがセンチネルリンパ節生検でセンチネルリンパ節とは「がんからのリンパ流を最初に受けるリンパ節：見張りリンパ節」のことである。実際の同定方法は色素法とラジオアイソトープ法があり、「臨床的腋窩リンパ節転移陰性の原発性乳癌に対するセンチネルリンパ節生検の安全性に関する多施設共同臨床試験」（主任研究者：中村清吾）[2]によれば11,489例の登録例の内、色素法単独の同定率は97.6%、ＲＩ法97.1%、色素＋ＲＩ法　99.0%といずれも良好な同定率を示している。本術式はすでに保険認可されており、臨床的に腋窩リンパ節転移を認めない症例に対しては必須になっている。

3．腋窩の解剖

乳がんにおける腋窩リンパ節郭清の範囲はレベルⅠ～Ⅲまであり、レベルⅠは小胸筋外側縁より外側、レベルⅡは小胸筋背側および胸筋間リンパ節、レベルⅢは小胸筋内縁より内側のリンパ節と定義

されている。通常はレベルⅠ～Ⅱまでで十分であり、レベルⅢの郭清意義は見出されていない。腋窩リンパ節郭清において重要な解剖には**神経**：大小胸筋の運動を司る胸筋神経（上胸筋神経、中間胸筋神経、下胸筋神経）、肋間上腕神経（上腕内側の知覚）、長胸神経（前鋸筋の運動）、胸背神経（広背筋の運動）、**動脈**：胸肩峰動脈（胸筋枝）、外側胸動脈、肩甲下動脈～胸背動脈、肩甲回旋動脈、**静脈**：腋窩静脈、外側胸静脈、胸背静脈などがあり、その走行を熟知することは手術をする上で必須である。

以下手術手順に沿って解説する。まず内側神経束の側枝で（C8,T1）で腋窩動静脈間を下降して小胸筋外側縁から大胸筋に達する下胸筋神経（内側胸筋神経）と小胸筋を貫いて大胸筋に達する中間胸筋神経を確認、温存する。肋間上腕神経は第2、3肋間神経の外側皮枝で肋間隙から前鋸筋を貫いて腋窩、上腕へ達する知覚神経である。長胸神経（C5,C6）は腕神経叢C8,T1の背面を走行して前鋸筋に達する。前鋸筋が麻痺すると翼状肩甲骨になる。胸背神経は後神経側の側枝（C6,7,8）で腋窩後壁に沿って下外側を走行し、広背筋上部に達する。胸背神経は胸背動静脈と共に束を作って走行しており、容易に確認できる。次に動脈系であるが、腋窩動脈は鎖骨下動脈の続きとして第1肋骨の外側縁から始まり、大円筋の下縁で終わり、以遠は上腕動脈となる。腋窩動脈の第一部は第1肋骨外側縁から小胸筋内側縁までで最上胸動脈が分枝する。ここは郭清リンパ節のレベルⅢの範囲である。

第二部は小胸筋の背側で胸肩峰動脈と外側胸動脈が分枝する。第三部は小胸筋外側縁から大円筋下縁まででここから分枝するのが肩甲下動脈で肩甲回旋動脈と胸背動脈に分かれる。静脈系も動脈系と同様に3部からなり、動脈とほぼ同様の走行をするが、非常に変異に富み，吻合も多い。

以上、乳がんにおける腋窩リンパ節郭清の意義及び解剖を中心とした手技について解説した。腋窩リンパ節郭清はがんのリンパ節郭清の基本とも言われており、外科医にとって習得すべき必須の術式と考える。また近年内視鏡下手術や小切開手術が行われるようになり、直視下に解剖を見る機会が減ってきている。従って今回の3D映像による解剖の供覧は研修医、若手外科医にとって手術手技の習得、解剖の理解に非常に有用なツールになると考える。

参考文献

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2) 「臨床的腋窩リンパ節転移陰性の原発性乳癌に対するセンチネルリンパ節生検の安全性に関する多施設共同臨床試験」（主任研究者　中村清吾）：厚生労働科学研究費補助金　医療技術実用化総合研究事業（H19－がん臨床－一般－023）総括・分担研究報告書，2010

TOPICS 第20回日本乳癌学会学術総会より

女性乳腺医師の抱える問題 —アンケート調査報告—

田中眞紀*1 徳永えり子*1 岩瀬弘敬*1 大野真司*1
田村和夫*1 丹黒 章*1 土井原博義*1 西村令喜*1
光山昌珠*1

はじめに

国家試験合格者に占める女性医師の割合は3割を超え，女性医師の活躍の場は拡がっている．とくに乳腺診療においては患者からのニーズも高く，専門医を目指す女性医師は年々増加している．一方女性医師全体をみると妊娠・出産・育児を契機に離職する医師が多いのも事実である．そこで女性乳腺医師支援のため現在抱えている諸問題・課題の抽出および教育啓発活動やさまざまな提言などから解決策を図ることと，女性乳腺医師のみならず乳癌診療に携わるすべての医療関係者の地位向上とライフワークバランス向上により医学界および社会に貢献することを目的としてWomen Breast Cancer Consortium（以下WBCC）を設立した．

今回はおもに九州地区に在住する乳腺診療を行っている女性医師を対象に，現在の勤務状況や問題点につきアンケート調査（**表1**）を行ったので報告する．

方 法

2011年の第1回WBCCに参加した女性乳腺医師41名を対象に無記名のアンケート形式で調査した．

結果と考察

女性乳腺医師が勤務を継続する上で出産・育児は最大の障壁であり，多くの者が家庭と仕事の両立は困難と感じた経験を持っていた（**図1**）．女性医師支援として出産・育児期間中の当直やオンコール免除，フレックス制導入などの勤務時間短縮を望む回答は多く，また病児保育や院内保育園の設置・充実については今でも十分な環境整備ができていないようであった．女性乳腺医師の勤務状況満足度をみると61%が満足しており，その理由は満足していない理由と対照的に，やりがい，適正な仕事量，上司の理解と回答しこれらはモチベーションにつながる重要な要素であると思われた（**図2**）．女性乳腺医師の勤務継続は医師不足の解消につながり，女性医師支援だけでなく男性医師の勤務状況も改善するべきと思う女性医師は多かった（**表1**）．

結 語

女性乳腺医師の課題を男性医師にも共有し，各施設での具体的な対策，改善に向け継続的に取り組んで行く予定である．

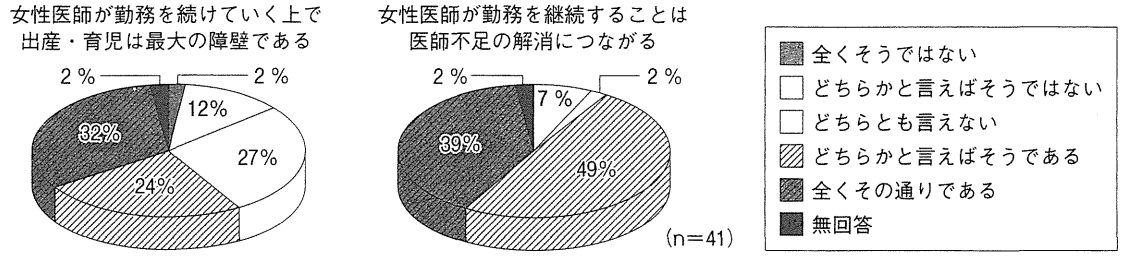

図1 最近の医療問題と女性医師について

*1 Women Breast Cancer Consortium（WBCC）

表1　Women Breast Consortium アンケート（n＝41）

年齢	30歳未満：7　30～39歳：24　40～49歳：9　50歳以上：1
診療科	初期臨床研修医：5　外科：11　乳腺外科：24　放射線科：1
現在の勤務状況の満足度は自分が女性であることと関係があると思う	全くそうではない：9　どちらかといえばそうではない：8 どちらとも言えない：11　どちらかといえばそうである：4 全くその通りである：4　無回答　2
現在結婚していますか	している：18　していない：20　その他：4
お子様はおられますか	無：22　有：15　無回答：4
育児サポートとして特に役に立ったのは　以下のいずれでしょうか（3つまで複数回答可）	配偶者：7　自分の母：10　配偶者の母：5　院内保育園：5 院外保育園：2　24時間保育：1　延長保育：2　病児保育：3 幼稚園：2　学童保育：1　ベビーシッター：3
今までに家庭と仕事の両立が困難だと感じたことがある	無：2　有：11　無回答：1
家庭と仕事の両立に悩んで仕事を辞めようと思ったことがある	無：10　有：5
今後女性医師支援として病院に特に求めたいものは以下のいずれでしょうか（主なもの5つまで）	フレックス制：15　時短制：10　勤務日短縮：10　院内保育園の設備：16 病児保育の充実：20　当直・オンコール免除：20　復職支援プログラム：8 周囲の医師の意識改革：8　産休・育休休暇の充実：7　ポストの確保：4 早朝・夕方のカンファレンス廃止：4　事務処理など雑務の軽減：3 育児などを考慮した業績評価：2　男性の育児休暇取得促進：3 X線被爆の回避：0　その他：1　特になし：7
医療崩壊について最大の原因と思われるものはどれでしょうか	訴訟リスク：7　医師の絶対数不足：1　医師の地域的偏在：8 医師の診察科の偏在：8　医師の劣悪な勤務状況：11　医療費削減：1 医療情報の氾濫：0　社会・患者の要望の変化：4 女性医師の増加：0　その他：0
女性医師が医療崩壊に対して何らかの役割を果たし，日本の医療に貢献できることはあると思う	はい：31　いいえ：1　どちらともいえない：7　無回答：2
現在勤務している病院でも今後積極的に女性医師支援を行っていくべきである	全くそうではない：0　どちらかといえばそうではない：2 どちらとも言えない：0　どちらかといえばそうである：15 全くその通りである：23　無回答：1
女性医師支援とともに男性医師の勤務状況を改善すべきである	全くそうではない：0　どちらかといえばそうではない：0 どちらとも言えない：6　どちらかといえばそうである：13 全くその通りである：21　無回答：1

（単位：人）

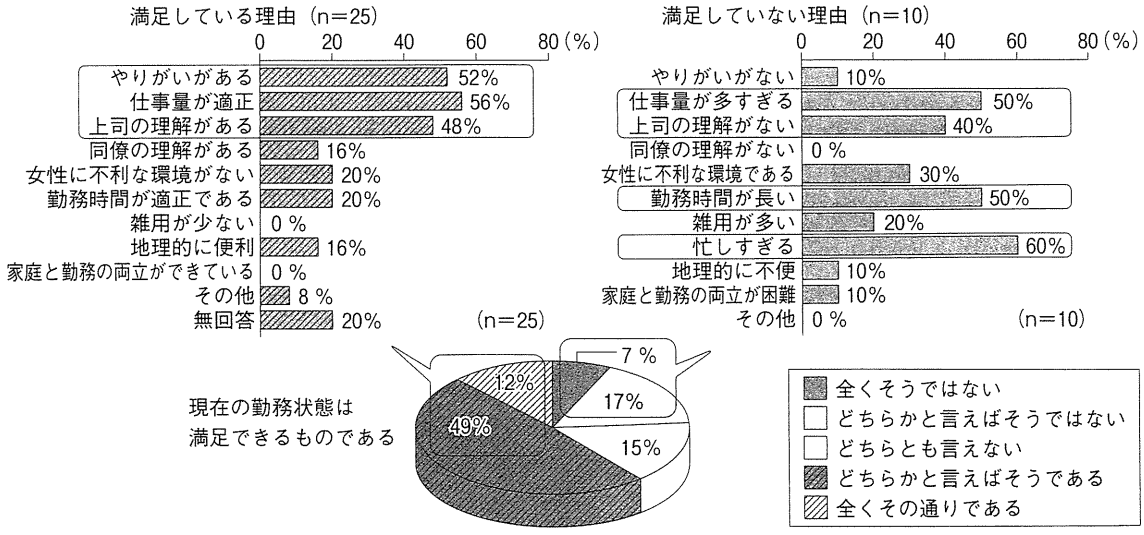

図2　現在の勤務状態について

TOPICS

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CLINICAL TRIAL

Efficacy of zoledronic acid in postmenopausal Japanese women with early breast cancer receiving adjuvant letrozole: 12-month results

Shunji Takahashi · Takuji Iwase · Norio Kohno · Takashi Ishikawa · Tetsuya Taguchi · Masato Takahashi · Jun Horiguchi · Seigo Nakamura · Yasuo Hozumi · Masao Fukunaga · Shinzaburo Noguchi

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Abstract Aromatase inhibitor-associated bone loss has not been proved in the Japanese or Asian women. The aim of this study was to evaluate an upfront or delayed strategy of bone protection therapy with zoledronic acid administered at 4 mg every 6 months in postmenopausal Japanese women with early breast cancer to compare with results of the Z-FAST and ZO-FAST studies in western countries. Postmenopausal women with hormone receptor positive early breast cancer receiving adjuvant letrozole were randomly assigned to receive either upfront or delayed-start zoledronic acid (4 mg intravenously every 6 months). The delayed group received zoledronic acid when lumbar spine (L_2–L_4) bone mineral density (BMD) decreased to less than young adult mean −2.0SD or when a nontraumatic fracture occurred. The primary endpoint of this study was to compare the percent change in L_1–L_4 BMD at 12 months between the groups. Secondary endpoints included percent changes in L_2–L_4 and total hip (TH) BMD. The upfront and delayed groups included 94 and 95 patients, respectively. At 12 months, L_1–L_4, L_2–L_4, and TH BMD significantly decreased by 2.0, 2.4, and 2.4%, respectively, in the delayed group. L_1–L_4 BMD was 4.9% higher in the upfront group than in the delayed group (95% CI 3.9–5.8%; $p < 0.001$). L_2–L_4 BMD was 5.6% higher (95% CI 4.5–6.6%; $p < 0.001$), and TH BMD was 4.4% higher (95% CI 3.3–5.4%; $p < 0.001$). At 12 months, upfront zoledronic acid therapy prevented bone loss in postmenopausal Japanese women who were receiving adjuvant letrozole, confirming the Z-/ZO-FAST study results in western populations.

S. Takahashi (✉)
Department of Medical Oncology and Hematology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: stakahas@jfcr.or.jp

T. Iwase
Department of Breast Surgery, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

N. Kohno
Department of Breast Oncology, Tokyo Medical University Hospital, Tokyo, Japan

T. Ishikawa
Department of Breast and Thyroid Surgery, Yokohama City University Medical Center, Yokohama, Japan

T. Taguchi · S. Noguchi
Department of Breast and Endocrine Surgery, Osaka University Hospital, Osaka, Japan

M. Takahashi
First Department of Surgery, Hokkaido University Hospital, Sapporo, Japan

J. Horiguchi
Department of Breast and Endocrine Surgery, Gunma University Hospital, Gunma, Japan

S. Nakamura
Department of Breast Surgery, St Luke's International Hospital, Tokyo, Japan

Y. Hozumi
Department of Breast and General Surgery, Jichi Medical University Hospital, Tochigi, Japan

M. Fukunaga
Kawasaki Medical School, Okayama, Japan

Keywords Bone mineral density (BMD) · Aromatase inhibitor-associated bone loss · Letrozole · Zoledronic acid · Lumbar spine (LS) · Total hip (TH)

Introduction

Third-generation aromatase inhibitors such as letrozole, anastrozole, and exemestane have shown to improve disease-free survival of postmenopausal endocrine-sensitive breast cancer patients compared with tamoxifen in several large clinical studies such as ATAC [1], BIG1-98 [2], or IES [3].

Adjuvant endocrine therapy with aromatase inhibitors causes complete depletion of estrogen, and increases bone metabolism suddenly and continuously, so may cause bone loss. In the large clinical studies, patients treated with aromatase inhibitors showed higher bone fracture rates than those treated with tamoxifen [4, 5, 6], and marked bone loss with aromatase inhibitor treatment has been shown in bone sub-studies of those large studies [7].

Oral bisphosphonates such as alendronate [8], ibandronate [9], or risedronate [10] have shown to prevent or improve postmenopausal osteoporosis. Some studies have also shown that those oral bisphosphonates prevent aromatase inhibitor-associated bone loss [11, 12]. However, oral bisphosphonates have some weak points such as low bioavailability due to low absorption, gastrointestinal adverse events (AEs), and low compliance [13].

In a clinical study for postmenopausal osteoporosis patients, once a year intravenous infusion of zoledronic acid 4 mg significantly increased bone mineral density (BMD) of lumbar spine (LS) and femoral bone [14]. Then a large clinical study comparing once a year intravenous infusion of zoledronic acid 5 mg versus placebo in postmenopausal osteoporosis patients showed that zoledronic acid significantly decreased spinal and femoral fracture rates for 3 years [15].

Clinical studies were performed to show whether zoledronic acid could inhibit bone loss with adjuvant aromatase inhibitor for early breast cancer patients in Northern America and Europe (Z-FAST and ZO-FAST) [16, 17]. Those studies compared BMD between upfront group who are treated with zoledronic acid every 6 months from the start of letrozole, and delayed group who are treated with zoledronic acid when BMD decreases to less than −2.0SD or fragility fracture occurs, in letrozole-treated breast cancer patients. Both the studies showed that upfront treatment with zoledronic acid significantly improved BMD of LS and femoral bone, and suppressed letrozole treatment-associated bone loss.

But in the Japanese or Asian women, aromatase inhibitor-associated bone loss has not been proved in the prospective study. In retrospective studies, Yoneda et al [18] reported no significant bone loss with 1-year treatment with anastrozole in Japanese women, and they speculated that Japanese women are less fat, and effects of aromatase inhibitors on bone mass might be less in lean women. In the Japanese subgroup study of TEAM (tamoxifen vs. exemestane), BMD of patients with tamoxifen and exemestane were not significantly different [19]. Furthermore, phase III study comparing tamoxifen versus switch from tamoxifen to anastrozole in Japanese postmenopausal breast cancer patients (N-SAS BC03) showed that fracture rate was not significantly different between two groups [20].

This study is designed to compare BMD of LS and femoral bone in upfront group who are treated with zoledronic acid every 6 months and delayed group who are treated with zoledronic acid after decrease of LS (L_2–L_4) BMD to less than −2.0SD of young adult mean (YAM) or occurrence of nontraumatic clinical fracture in hormone receptor-positive, clinical grade I–IIIA, postoperative postmenopausal breast cancer patients, who are planned to be treated with letrozole 2.5 mg per day as adjuvant endocrine therapy. This study will investigate whether letrozole decrease the BMD in Japanese women as the same level as the western women, and whether zoledronic acid can improve BMD and prognosis of letrozole-treated early breast cancer patients.

Patients and methods

Study patients

Inclusion criteria were as follows; (1) adequately diagnosed and treated invasive breast cancer defined as: 1. clinical stage I, II, or IIIA, 2. primary tumor was removed by an appropriate surgical procedure such as mastectomy or breast conserving surgery; (2) estrogen receptor (ER) and/or progesterone receptor (PgR) positive defined with immuno-histochemical staining; (3) postmenopausal status defined by one of the followings: 1. women >54 years with cessation of menses, 2. spontaneous cessation of menses within the past 1 year, and are amenorrheic in women <55 years, and according to the definition of "postmenopausal range" for FSH and estradiol level, 3. bilateral oophorectomy; (4) patients with a baseline LS: L_2–L_4 BMD of YAM −2.0SD or more; (5) patients who have no LS or total hip (TH) fracture; (6) ECOG performance status of ≤2; (7) adequate organ function; (8) the date of randomization must be within 12 weeks from completion of surgery or from completion of adjuvant chemotherapy (completion of chemotherapy is defined as completion of the last full course including recovery time); (9) patients

who have discontinued the following drugs known as affecting the skeleton more than 4 weeks: oral bisphosphonates, estrogen, raloxifene, calcitonin, vitamin K, activated vitamin D, ipriflavone, (10) a written informed consent is obtained.

Exclusion criteria were as follows: (1) patients with any clinical or radiological evidence of distant spread of their disease at any point before randomization, (2) patients with invasive bilateral breast cancer, (3) patients who have started adjuvant endocrine therapy, (4) patients who have received any endocrine therapy within the past 12 months, (5) patients who have received prior treatment with intravenous bisphosphonates within the past 12 months, (6) patients with the following diseases which may interfere with dual-energy X-ray absorptiometry (DXA) scan: severe scoliosis, hyperostosis, or sclerotic changes at the LS, other vertebral diseases, and calcification of abdominal aorta, (7) patients with previous or concomitant malignancy (not breast cancer) within the past 5 years, (8) current active dental problems including infection of the teeth or jaw, and recent (within 6 weeks) or planned dental or jaw surgery (e.g., extraction, implants), (9) other conditions judged as inappropriate for the study by the investigator.

Study design (Fig. 1)

In this open-label, multicenter, randomized study, all patients received letrozole 2.5 mg orally daily for 5 years or until relapse. Patients were randomly assigned to upfront or delayed zoledronic acid 4 mg or an adjusted dose based on renal function intravenous injection over 15 min every 6 months for 5 years. The upfront group received zoledronic acid after random assignment, whereas the delayed group received zoledronic acid when either post baseline LS (L_2–L_4) BMD decreases to YAM −2.0SD or less, or a nontraumatic clinical fracture occurred.

Patients were stratified according to adjuvant chemotherapy (yes or no) and baseline LS (L_2–L_4) BMD (normal: less than YAM −1.0SD or mild to moderate osteopenia: BMD between YAM −1.0SD, and YAM −2.0SD).

Primary endpoint of this study was the percent change in LS BMD (L_1–L_4) at 12 months in patients receiving upfront compared with delayed-start zoledronic acid. The secondary endpoints were the percent change in LS BMD (L_2–L_4), TH BMD and changes in serum N-telopeptide (NTx) and bone-specific alkaline phosphatase (BSAP) concentrations at 12 months. Additional secondary endpoints, including percent change in LS and TH BMD at 2, 3, 4, and 5 years; incidence of any clinical fracture at 3 years; time to disease progression, will be reported as these results become available.

BMDs of the LS and TH were evaluated at baseline and at 6, 12, 24, 36, and 48 months and at the final visit using either Hologic or Lunar DXA devices. All DXA devices were standardized and cross-calibrated using 4 Bio-Imaging Bona Fide Phamtoms.

Serum NTx and BSAP concentrations were evaluated at baseline and every 6 months during years 1–2, once at 36 and 48 months, and at the final visit.

AEs and disease progression were evaluated every 6 months. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

The institutional review board or the ethics committee of the participating institutions approved the study. Informed consent was obtained from each patient before enrollment.

Statistical analysis

The study design used a 2-sample Student's t test, with power 80% and a significance level of $P = .05$ to detect a 4% difference in percent change in LS (L_1–L_4) BMD from baseline to 12 months between the groups. A sample size of 74 patients per treatment arm was required. To allow 20% dropout rate, at least 90 patients in each treatment are required.

The primary efficacy analysis was performed after all patients had passed the 12-month visit. An analysis of covariance model was used to compare differences

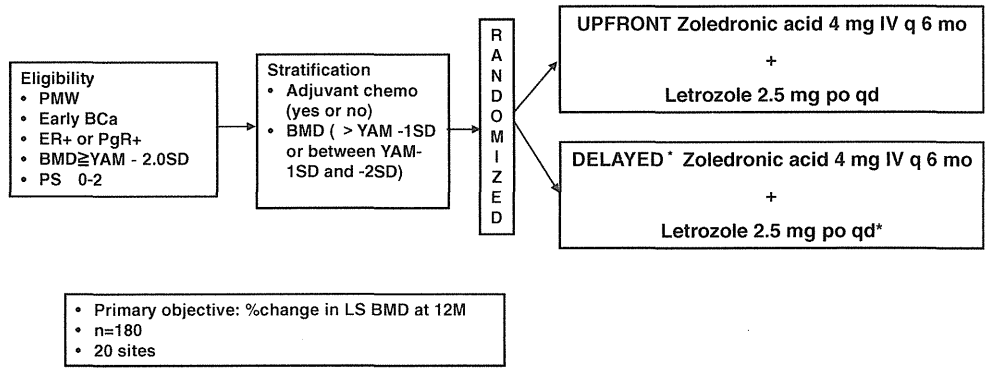

Fig. 1 Study design. *Received ZA when L_2–L_4 BMD decreased to <YAM −2.0SD or when a nontraumatic fracture occurred. *PMW* postmenopausal women, *Bca* breast cancer, *BMD* bone mineral density, *YAM* young adult mean, *Chemo* chemotherapy, *ER* estrogen receptor, *PgR* progesterone receptor

between groups; paired t test was used to compare differences within treatment groups in LS and TH BMD and serum NTx and BSAP concentrations from baseline to month 12.

The study was not powered to detect a difference in the incidence of clinical fractures or breast cancer relapse. The frequency of AEs was reported for both groups.

Results

Study population

Between May 2008 and April 2009, 204 patients were randomized in 18 Japanese centers to receive either upfront or delayed zoledronic acid. The baseline characteristics of the two groups were similar except for body mass index (BMI; Table 1).

Five patients (5.2%) and 7 patients (7.2%) in the delayed group received zoledronic acid therapy by months 6 and 12, respectively. For these patients, the mean time to initiation of zoledronic acid was 7.6 months (range 5.9–12.3 months). Of these, 4 patients were started based on the LS (L_2–L_4) BMD falling to less than YAM −2.0SD. Three patients were started because of misunderstanding of the protocol at the site level.

BMD

At month 12, the mean percent difference in BMD between the groups was 4.9% for L_1–L_4 (95% CI 3.9–5.8%; $p < 0.0001$), 5.6% for L_2–L_4 (95% CI 4.4–6.6%; $p < 0.0001$), and 4.4% for TH (95% CI 3.3–5.3%; $p < 0.0001$) (Fig. 2).

At baseline, 115 (59.3%) patients had normal LS (L_2–L_4) BMD (57 patients, 58.8% in the upfront group; 58 patients, 59.8% in the delayed group). At 12 months, a higher percentage of patients in the delayed group with normal baseline BMD developed mild to moderate osteopenia (between YAM −1.0SD and YAM −2.0SD) compared with patients in the upfront group (24.1 vs. 0%). The difference in distributions was statistically significant ($p = 0.0001$). At baseline, 79 (40.7%) patients had already had mild to moderate osteopenia at the LS (L_2–L_4) BMD (40 patients, 41.2% patients in the upfront group, and 39 patients, 40.2% patients in the delayed group). In the upfront group, BMD improved to normal (more than YAM −1.0SD) in 22.2% of patients, and there were no patients with severe osteopenia (less than YAM −2.0) at 12 months. In the delayed group, BMD improved to normal in 5.1% of the patients, but worsened to severe osteopenia in 5.1% of the patients. The difference in distributions was statistically significant ($p = 0.00435$) (Table 2). In the patients with baseline TH BMD between YAM −1.0SD and YAM −2.0SD, BMD improved to normal in 21.1% and none worsened to severe osteopenia in upfront group, but none improved to normal and 16% worsened to severe osteopenia in delayed group (Fig. 3).

Markers of Bone Turnover

In the upfront group, the levels of serum NTx decreased by 6.5% at 6 months and by 23.6% at 12 months from baseline significantly ($p = 0.0026$ and $p < 0.0001$, respectively). Serum BSAP also decreased by 33.6% at 6 months and by 39.4% at 12 months from baseline significantly ($p < 0.0001$ and $p < 0.0001$, respectively). On the other hand, in the delayed group, serum NTx and BSAP increased by 21.8% at 6 months and by 9.4% at 12 months ($p = 0.0563$ and $p = 0.2619$, respectively) and by 14.9% at 6 months and by 10.2% at 12 months ($p = 0.0291$ and $p = 0.4694$, respectively), with no significance (Fig. 4).

Fractures

At month 12, no nontraumatic clinical fracture occurred in patients receiving upfront and delayed-start zoledronic acid.

Safety

Safety analysis was evaluated in 194 cases that were treated with the investigating drugs. AEs of occurrence with 5% or more are shown in Table 3. Fever occurred significantly more in the upfront group (23.2 vs. 3.1%, $p < 0.001$). The fever is the acute phase response to bisphosphonates, and usually occurs only at the first treatment with zoledronic acid. There was no significant increase of fever with zoledronic acid at the second or the third treatment. There was no significant difference of AEs other than fever between the two groups. Arthralgia occurred in about 50% of both groups, but almost all were grade 1 and controllable with NSAIDs. Two patients withdrew from the study due to arthralgia. If the patient was diagnosed or was suspected to have osteonecrosis of the jaw (ONJ), the patients should be withdrawn from the study, but no one was diagnosed or suspected to have ONJ.

Discussion

Letrozole is a non-steroidal, reversible aromatase inhibitor similar to anastrozole, but is reported to be more effective in inhibiting aromatase and decreasing estrogen levels in vitro and in vivo [21, 22]. The randomized comparative study of letrozole and anastrozole for postmenopausal early breast cancer patients (FACE study) is ongoing [23]. On

Table 1 Basal patient characteristics

Characteristic	Upfront group	Delayed group	*p*
Patients in safety population	97	97	
Age (years)			
Mean ± SD	61.47 ± 6.80	60.45 ± 6.56	0.4052
Median (range)	60.0 (48.0–82.0)	60.0 (46.0–79.0)	
BMI			
Mean ± SD	24.26 ± 3.87	23.08 ± 3.16	0.0329
Median (range)	24.2 (15.6–43.6)	22.5 (15.6–33.3)	
ECOG PS			
0	97	97	
1	0	0	
2	0	0	
Menopausal status			
Bilateral oophorectomy	1	1	0.9787
≥55 years with cessation of menses	83	82	
Amenorrheic in women <55 years	13	14	
Bone mineral density (g/cm^2)			
Lumbar spine(L_1–L_4), mean ± SD	0.9791 ± 0.1242	0.9714 ± 0.1370	0.6854
Total hip, mean ± SD	0.8547 ± 0.1195	0.8318 ± 0.1061	0.1641
Clinical stage			
I	48	52	0.2950
IIA	31	26	
IIB	10	15	
IIIA	8	3	
Unknown	0	1	
ER status			
−	0	0	
+	97	97	
PgR status			
−	26	25	0.7088
+	69	71	
Unknown	2	1	
Nodal status			
−	74	65	0.1843
+	23	32	
Surgery			
Breast conserving	68	65	0.6389
Mastectomy	28	31	
Unknown	1	1	
Stratification factors			
Prior adjuvant chemotherapy	38	39	0.8833
Normal BMD	57	58	0.8838
Osteopenia BMD	40	39	

Normal BMD: less than YAM −1.0SD

Osteopenia BMD: between YAM −1SD and YAM −2SD

the other hand, letrozole may cause aromatase inhibitor-associated bone loss (AIBL) more severely with stronger inhibitory activity, but bone marker changes, severity of bone loss or increase of fracture rate seem similar to anastrozole in clinical studies so far [24, 25].

In Japanese patients, AIBL may be less severe from some studies. Yoneda et al. [18] reported that there were no significant changes in BMD and bone metabolic markers in Japanese women treated with anastrozole for 1 year. Okisiro et al. [26] also showed that bone loss of Japanese women induced by anastrozole was less compared that of ATAC bone study (1.3 vs. 2.2% at 1 year and 2.8 vs. 4.0% at 2 years). In the Japanese subgroup bone study of TEAM, BMDs of patients treated with tamoxifen versus

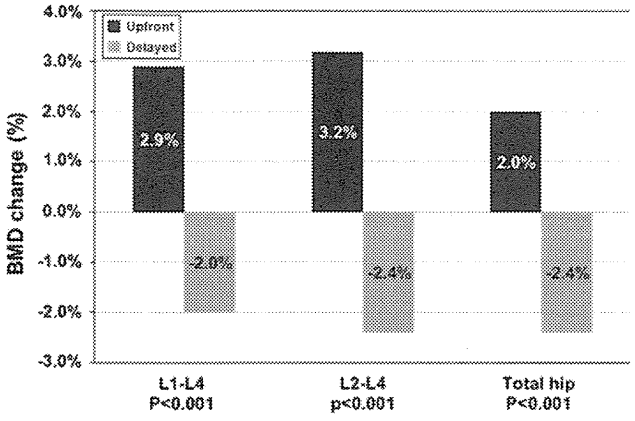

Fig. 2 Mean percent change in BMD of LS (L_1–L_4 and L_2–L_4) and TH at 12 month. p value was calculated by t test

Table 2 LS BMD measurements at month 12

Baseline and month 12 BMD	Upfront group		Delayed group	
	No.	%	No.	%
Normal baseline BMD, month 12 BMD	54		58	
Normal	54	100	44	75.9
Mild osteopenia	0		14	24.1
Osteopenia at baseline BMD, month 12 BMD	36		39	
Normal	8	22.2	2	5.1
Mild osteopenia	28	77.8	35	89.7
Severe osteopenia	0		2	5.1

Normal BMD: **YAM −1SD

Mild osteopenia BMD: between YAM −1SD and YAM −2SD

Severe osteopenia BMD: <YAM −2SD

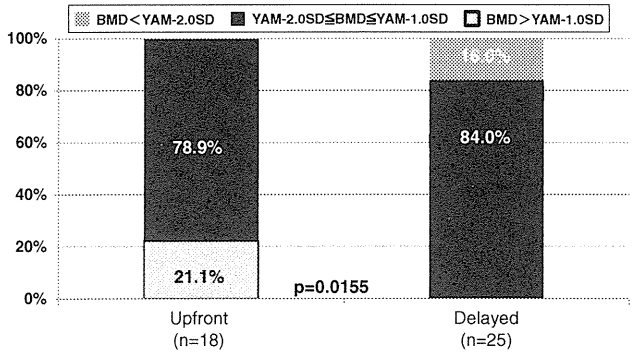

Fig. 3 Shift in TH BMD distribution at 12 months in patients with baseline BMD between YAM −2SD and YAM −1SD. p value was calculated by χ^2 test

exemestane after 1 and 2 years were 88.1 and 87.8% versus 87.5 and 86.8%, although bone metabolic markers (urine NTx and BSAP) were significantly high in exemestane

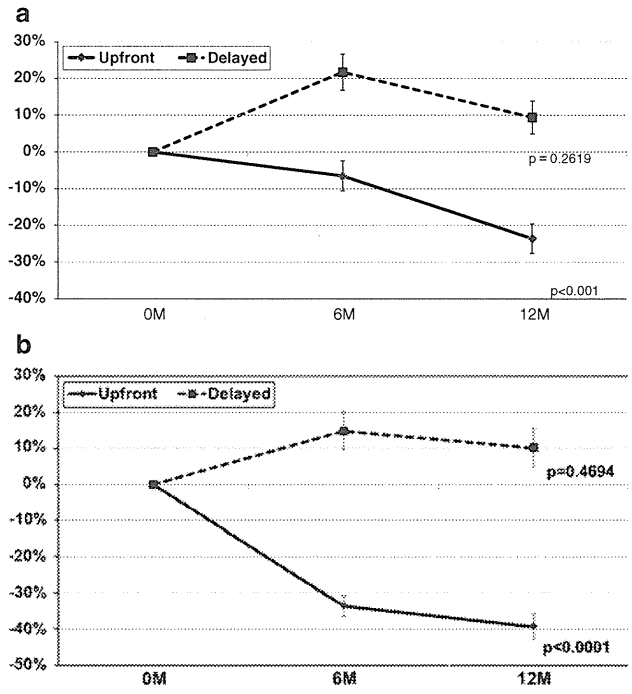

Fig. 4 Mean % change in serum **a** NTx and **b** BSAP from baseline. p value was calculated by t test

Table 3 AEs >5% of patients

AE	Upfront (N = 95)	Delayed (N = 97)	Fisher, p
Fever	22 (23.2)	3 (3.1)	<0.001
Fatigue	9 (9.6)	11 (11.3)	0.805
Hot flashes	13 (13.7)	9 (9.3)	0.397
Sweating	5 (5.3)	3 (3.1)	0.580
Arthralgia	49 (51.6)	47 (48.5)	0.925
Myalgia	6 (6.4)	6 (6.2)	0.602
Nausea	5 (5.3)	2 (2.1)	0.324
Pruritus	5 (5.3)	3 (3.1)	0.276
Rash	5 (5.3)	2 (2.1)	0.324

No cases of ONJ have been reported

group compared with tamoxifen group [19]. In the phase III study, comparing tamoxifen for 5 years versus switch from tamoxifen for 1–4 years to anastrozole for 1–4 years in Japanese postmenopausal breast cancer patients (N-SAS BC03), fracture rate was not significantly different between two groups (tamoxifen 2.6%, tamoxifen to anastrozole 1.4%) [20]. AIBL has not been proved clinically significant in Japan yet. This is the first study that prospectively investigated AIBL with BMD as the primary endpoint in multi-institutions of Japan.

Bisphosphonates have been reported to be effective for inhibiting AIBL. Some studies have shown that those oral bisphosphonates prevent aromatase inhibitor-induced bone

loss [11, 27]. Weekly 35 mg risedronate treatment for 2 years improved BMD by 4.0% at LS and 2.9% at femoral bone in anastrozole-treated breast cancer patients. Monthly 150 mg oral ibandronate treatment for 12 months also improved BMD by 5.45% at LS and 3.3% at femoral bone in anastrozole-treated breast cancer patients with osteopenia. For letrozole-associated bone loss, treatments with zoledronic acid 4 mg every 6 months inhibit bone loss at 1 year in three randomized studies in western countries, Z-FAST [16], ZO-FAST [17], and E-ZO-FAST [28].

To investigate whether letrozole causes bone loss in Japanese women at the same level as in Caucasian women and whether zoledronic acid can inhibit AIBL similarly, we performed prospective randomized study to compare changes of L_1–L_4 BMD in upfront group who are treated by zoledronic acid every 6 months or delayed group who are treated with zoledronic acid after occurrence of bone loss in Japanese postmenopausal breast cancer patients treated with adjuvant letrozole therapy, as the same way as those in Z-FAST or ZO-FAST study, and compare those data.

In the western countries, WHO reported the diagnostic categories of osteoporosis at 2004 [29], which use *T* score to evaluate BMD. In Japan, BMD was evaluated as percentage of YAM of L_2–L_4 according to diagnostic guideline for primary osteoporosis of Japanese Society of Bone Mineral Metabolism [30]. In this study, eligible patients had BMD of more than YAM −2.0SD in L_2–L_4, although eligible patients had BMD of T score −2.0SD in L_1–L_4 and TH.

In the delayed group, BMDs after 12 months of L_1–L_4, L_2–L_4, and TH decreased by 2.0, 2.4, and 2.4% compared with baseline. These data are comparable to BMD decrease of L_1–L_4 and TH (3.5 and 2.4%) in the delayed group of ZO-FAST study, so letrozole-induced bone loss is almost similar to Caucasian women in Japanese women. Furthermore, BMD worsened to mild osteopenia in 25% of patients with normal baseline BMD, and to severe osteopenia in 5.1% of the patients with mild baseline osteopenia at 12 months. In Z-FAST study, 12.6% of patients with normal baseline BMD changed to mild osteopenia, and 14.8% of patient with mild baseline osteopenia changed to severe osteopenia at 12 months. Our data about transition are also comparable to those of western country studies. Therefore, AIBL is clinically significant also in Japan.

Upfront treatment with zoledronic acid 4 mg every 6 months increased BMD of L_1–L_4, L_2–L_4, and TH at 12 months by 2.9, 3.2, and 2.0% from baseline. Differences between upfront group and delayed group were significant ($p < 0.001$). The improvement of BMD (4.9, 5.6, and 4.4%) with zoledronic acid was also comparable to ZO-FAST study (5.7% at L_1–L_4, and 3.6% at TH). So, zoledronic acid is also effective for preventing AIBL in Japanese women.

Bone metabolic markers, serum NTx and BSAP concentrations decreased significantly from baseline in upfront group, which suggested that zoledronic acid suppresses the letrozole-associated bone resorption rapidly and maintains normal bone metabolism at least for 12 months. The rates of decrease were also comparable to those of Z-FAST study. On the other hand, both serum NTx and BSAP tended to increase from the baseline in the delayed group and suggested letrozole-induced bone resorption, although those were not significant. The number of actual measurement of serum bone marker in the delayed group was 60% of the scheduled measurement, and it might cause the insignificance.

Decrease of BMD is a strong surrogate for fracture events in postmenopausal women, although fracture risk is influenced by many factors such as age, body weight, smoking, prior fracture, exercise. In BIG1-98 study, fracture rate in the first year of letrozole-treated patients was 2.2% [31, 32]. In out study, adjuvant letrozole therapy decreased BMD of LS and TH similarly to western studies, but no non-traumatic fracture occurred at 12 months. We will investigate occurrence of fracture after 2, 3, and 5 years.

In the combined analysis of Z-FAST and ZO-FAST study, significant decrease of breast cancer relapse was shown in the upfront group [33]. Recently, the results of the adjuvant randomized phase IIII study of zoledronic acid (AZURE) were reported [34]. Adjuvant zoledronic acid (4 mg div monthly for 6 months, 3-monthly for 1.5 years, then 6-monthly for 3 years) with standard therapy decreased breast cancer relapse in postmenopausal patients. In our study, only one patient in the upfront group had a relapse of breast cancer. We will also investigate occurrence of relapse at after 2, 3, and 5 years.

This study is ongoing, and will continue treatment and follow-up for 5 years. At the 12-month data, upfront 4 mg zoledronic acid treatment every 6 months was effective for inhibition of bone loss with adjuvant letrozole treatment. Especially, the patients with bone loss (between YAM −1.0SD and YAM −2.0SD) at the start of aromatase inhibitor therapy have high risk of osteoporosis without appropriate therapy such as bisphosphonates.

In conclusion, AIBL occurs in Japanese women just the same way with Caucasian women, and upfront zoledronic acid therapy prevented bone loss in postmenopausal Japanese women who were receiving adjuvant letrozole, confirming the Z-/ZO-FAST study results in western populations.

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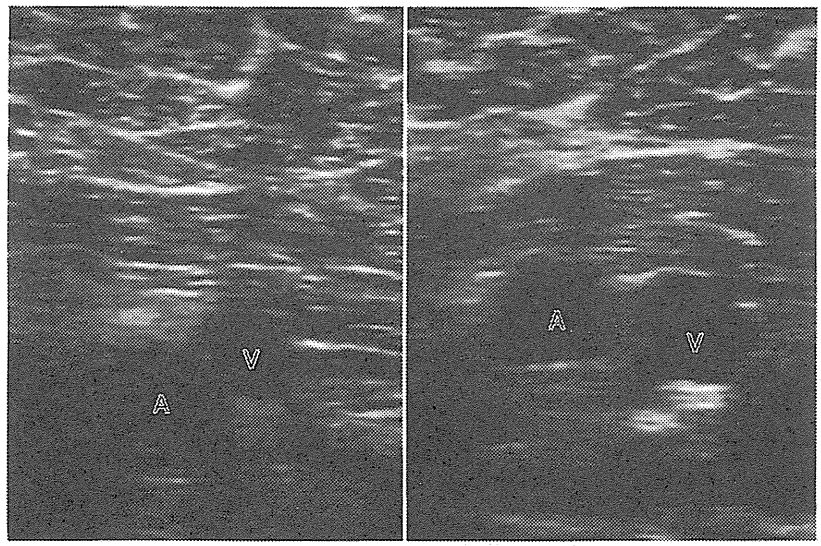
臨床経験

長軸法による超音波ガイド下腋窩静脈穿刺による中心静脈リザーバー留置術の検討*

柴崎　晋　市川伸樹　上徳ひろみ
佐藤雅子　渡邊健一　高橋將人**

はじめに

近年，超音波ガイド下による穿刺法が推奨[1~3]され，鎖骨下静脈のより末梢側である腋窩静脈からのアプローチも増えてきている[4~6]．また，悪性腫瘍に対する抗癌薬治療の発達により，中心静脈（CV）リザーバー留置の頻度も増加している．特に乳癌患者においては，患側を使用できないことが多く，また末梢血管を確保することが困難なことも多く，CVリザーバー留置は非常に重要な手技である．今回，超音波ガイド下腋窩静脈穿刺法によるCVリザーバー留置法の安全性を検討し



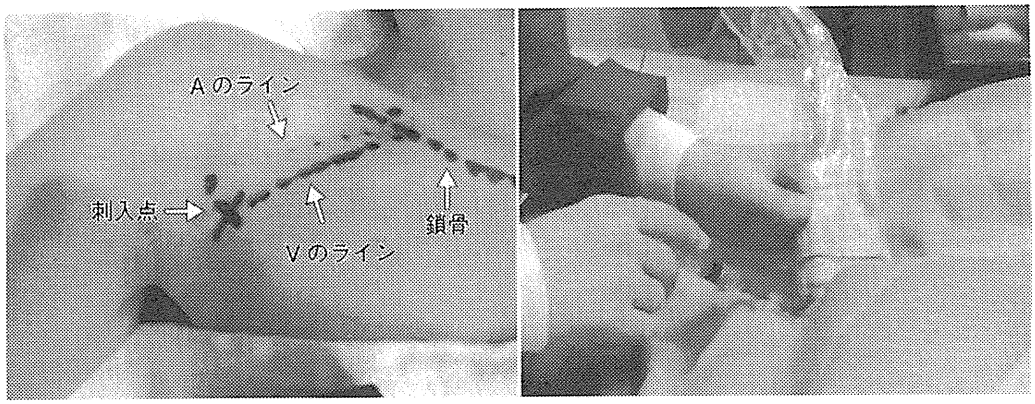
a．内転位　　b．外転位

図1．腋窩部短軸像
上肢を外転位にすることで動脈（A）と静脈（V）が完全に横並びになり，またVも長軸像で直線化しやすくなる．

キーワード：超音波ガイド下，中心静脈穿刺

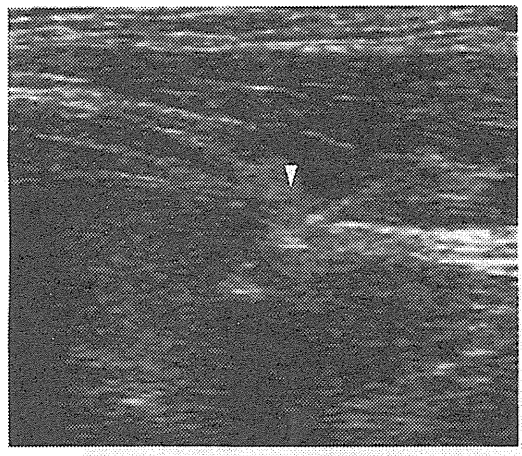
* The axially vein puncture procedure under ultrasonographic guidance

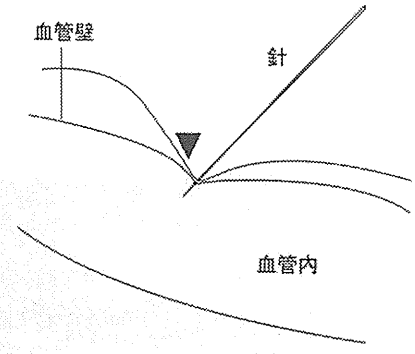
** S. Shibasaki, N. Ichikawa, H. Jotoku, M. Sato, K. Watanabe（医長），M. Takahashi（医長）：北海道がんセンター乳腺外科（〒003-0804　札幌市白石区菊水4条2-3-54）．



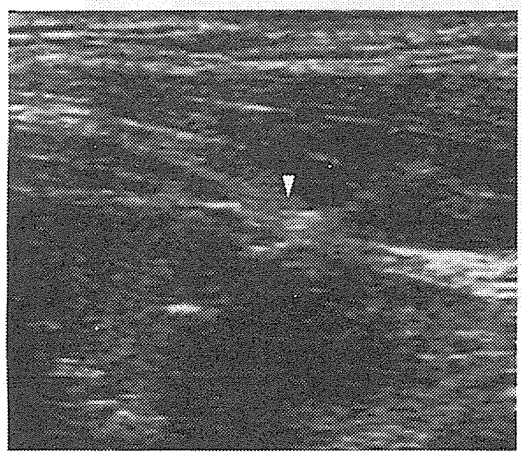
a. 刺入点とメルクマール　　b. 試験穿刺手技の実際

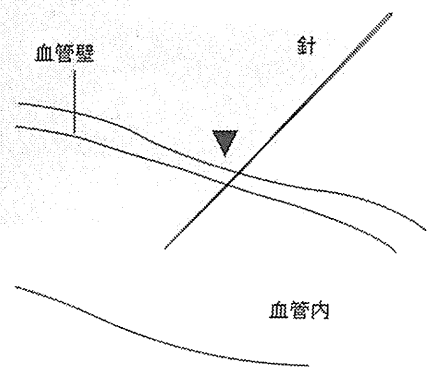
図2. 穿刺部位





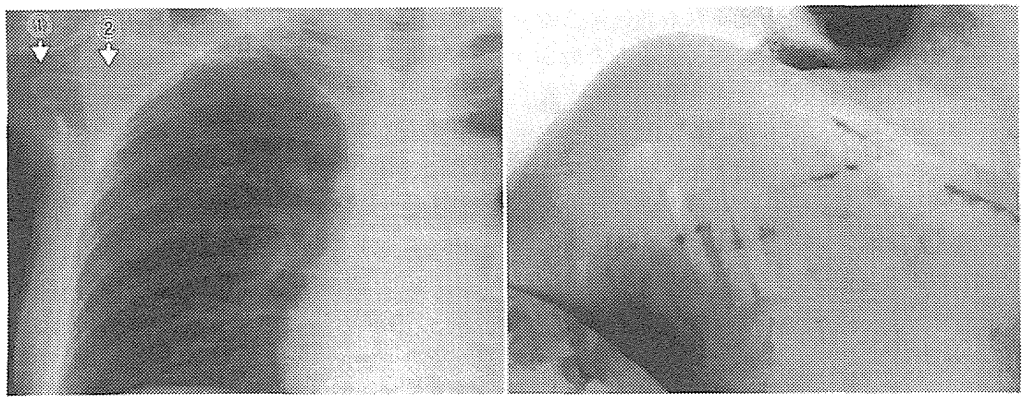
a. 針先が血管を圧排している．血管壁や周囲組織が針に引き込まれて変形している（矢頭）．





b. 血管壁を貫く感触とともに，血管壁の圧排が戻る（矢頭）．針の先端は血管内にある．

図3. 本穿刺時のUS像



a．胸部X線像．①皮膚刺入点，②血管内刺入点．完全に胸郭外である．　　b．手術終了後

図4．挿入後

たので報告する．

Ⅰ．対　　象

2010年7月～2012年2月に女性乳癌患者89例に，超音波（US）ガイド下腋窩静脈穿刺法とX線透視を併用しCVリザーバーを留置した．デバイスはBARD社のGroshongカテーテルを使用した．平均年齢57.6±11.6歳，右側47例，左側42例であった．本法の挿入率，挿入時合併症などを検討した．

Ⅱ．方　　法

仰臥位，上肢外転位としている．外転位とすることで，腋窩静脈と腋窩動脈が横並びになり，またより長軸方向への描出がしやすくなる（図1）．大胸筋の外縁あたりからリニア型プローブで腋窩静脈を長軸に描出し，十分な局所麻酔後，本穿刺を行う（図2）．針の先端を確認しながらゆっくりすすめ，血管の手前にきたら静脈壁がへこむのを確認し，さらに5mm程度針をすすめると，血管壁を貫く感触が伝わるとともに，血管壁のへこみが戻ることが確認できる（図3）．筆者らは感触を得た後で逆血を確認しているが，陰圧をかけながら穿刺してもかまわない．その後ガイドワイヤーを挿入し，透視下で先端が上大静脈にあることを確認後にカテーテルを挿入する．皮弁は穿刺部位よりやや内側とし，閉創は吸収糸で皮下埋没縫合を行った後にステリーテープを貼付している（図4）．

表1．穿刺関連合併症

動脈誤穿刺	1（1.1％）
血　腫	0
血　胸	0
気　胸	0
pinch-off	0
ポート感染	2（2.2％）

Ⅲ．結　　果

本法による穿刺成功率は98.9％であったが，カテーテル挿入成功率は97.8％で，1例は出血傾向があり穿刺自体が困難であり，もう1例は穿刺可能であったがカテーテル挿入ができなかった．逆血は認めていたので，おそらく血管内虚脱が高度でありカテーテルの挿入が困難であったと推測された．平均穿刺回数は1.19±0.4回，挿入時間は38.1±12.9分であった．中止後は十分な圧迫止血により，血腫形成などは認めなかった．主な合併症は表1に示す．

動脈誤穿刺を1例（1.1％）に認めたが，血腫形成はなかった．気胸・血胸は起こさなかった．また，まだ観察期間は中央値が10ヵ月と短いものの，鎖骨と第一肋骨の間に挟まるいわゆるpinch-offの発症も認めていない．ポート感染が2例（2.2％）に発生したが，これは挿入時期や患者の

全身状態に問題があったと考えられる．通常は最低でも抗癌薬治療の前日までに挿入するのであるが，1例は抗癌薬治療後の白血球減少最低値(nadir)の時期に挿入し，もう1例は再発が急激に進行し全身状態が不良な状態で，かつ治療当日に挿入したことが原因と考えられる．いずれも術後1週間以内に感染し，抜去後別部位から再挿入した．その他，留置4ヵ月後にポケット内でポートが反転してしまったのが1例と，カテーテル閉塞例が1例認められた．

Ⅳ．考　　察

USガイド下CV穿刺は，徳嶺は短軸法での描出を基本としている[7]が，われわれは長軸法で施行している．短軸法は，針の先端部を正確に描出するために習熟を要すること，予想よりも気づかないで深く入ってしまうことがあることが問題と思われる．実際，われわれも当初は短軸法で施行していたが，上記のような理由でうまくいかないことや，プローブの軸と針の刺入角度が近くなり，結果として垂直に近い角度で刺さってしまうことなどをたびたび経験したため，長軸法に変更した．長軸法は，針の全長を描出することに若干の技術が必要であるが，いったん慣れると容易に全長を描出させることができ，先端部もしっかりと確認できる．また，刺入角度も水平に近くなり，予想外に深く穿刺する可能性は低くなると思われる．針の全長がしっかりと描出できない場合は，闇雲に先端をすすめたりプローブを動かすのでなく，針の角度を微調整しながら，しっかりと針先を確認しゆっくりすすめることが肝要である．

USガイド下のCVカテーテル留置法の報告としては，渡部ら[5]は鎖骨中線より約3cm外側でアプローチしており，穿刺成功率は97.8％，カテーテル留置成功率は95.6％，挿入時合併症は認めなかった．また棚野ら[6]は，ホルダー付きプローブを用いてのUSガイド下に鎖骨下静脈穿刺を行っており，挿入成功率は99％，穿刺時合併症は0.9％（動脈誤穿刺）と，こちらも非常に良好な成績を報告している．このUSガイド下CVカテーテル挿入法を応用したCVリザーバー留置法は，飯田ら[8]がホルダー付きプローブを用いて鎖骨下穿刺法で挿入成功率98.8％，穿刺時合併症0％を報告している．今回のわれわれの方法では通常のリニア型プローブを用いてフリーハンド下で行っており，特に特殊な器具などは必要とはせず，留置成功率は97.8％，穿刺時合併症が1.1％で，これらの報告と比較しても遜色ない結果であった．通常の鎖骨下静脈穿刺では6.2～10.7％に合併症が起こるといわれ，重篤なものとしては動脈穿刺(3.1～4.9％)，血腫(1.2～2.1％)，血胸(0.4～0.6％)，気胸(1.5～3.1％)と報告されている[9]ため，USガイド下によるカテーテル挿入法を応用したリザーバー留置法は非常に安全に施行可能であると思われる．

今回のわれわれの方法では，渡部ら[5]の穿刺位置よりもさらに外側であり，仮にUSでmisleadingがあったとしても，図4にも示すとおり穿刺部位が胸郭よりもかなり離れているため，胸腔内に穿刺針が到達する可能性は限りなく低いといえ，実際に1例も気胸・血胸の発生はなかった．これこそが本法の最大のメリットと考えられる．ただし，動脈誤穿刺に関しては，残念ながら1例に認めた．これは長軸法の欠点でもあるが，穿刺針の全長をきれいに描出できなければ，先端が他部位に向かっている可能性があるため，手技に習熟する必要がある．しかし，動脈穿刺時であっても穿刺部位が末梢であるので，穿刺部位を容易にかつ確実に圧迫できるため血腫形成の可能性は低く，実際当科で経験した1例も，すみやかな圧迫で血腫形成は起こさなかった．

また，鎖骨下静脈穿刺の場合，鎖骨と第一肋骨の間に挟み込まれ，完全ないしは部分断裂を起こす，いわゆる「pinch-off syndrome」がしばしば問題となる[10]．本邦では神藤らが14例の報告をまとめており，発症時期の中央値は7ヵ月であった[11]が，本検討ではその期間内には1例の発生もなかった．その他の重要な合併症として，ポート感染が2例に発生した．全身状態や挿入時期を十分に考慮すべきと思われた．その他，文献的には右腋窩静脈穿刺時に胸管誤穿刺[12]や出血性ショック[13]にいたった報告もあり，注意が必要と思われる．また，ポート反転例や閉塞例がそれぞれ1例認められたため，今後は症例の蓄積とともに長期経過の観察が必要と思われた．

おわりに

超音波ガイド下腋窩静脈穿刺法によるCVリ

ザーバー留置術は，安全に施行できる手技と思われた．

◆ ◆ ◆ 文献 ◆ ◆ ◆

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