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■ 特 集 ■ 高齢者乳癌（2）

高齢者乳癌の放射線療法

山内 智香子

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特集 高齢者乳癌（2）

高齢者乳癌の放射線療法

山内 智香子*1

Radiotherapy for Elderly Patients with Breast Cancer：Yamauchi C*1 (*1Department of Radiotherapy, Shiga Medical Center for Adults)

Breast cancer in elderly patients is increasingly encountered in clinical practice. Although it is recognized that radiotherapy after breast-conserving surgery (BCS) for early breast cancer or mastectomy for advanced breast cancer, there are some barriers to treatment for elderly patients. In older women, transport might be particularly problematic for radiotherapy. For elderly patients with early breast cancer, omission of whole breast radiotherapy after BCS might be an option in those 70 years of age or older with estrogen receptor positive, clinically node-negative, T1 tumors who receive adjuvant endocrine therapy. Hypofractionated whole breast irradiation has been shown equivalent therapy to standard schedules in randomized trials. Hypofractionated schedules are useful for elderly patients especially with difficulty of transport. Concerning post-mastectomy patients, chest wall irradiation should be considered for patients with at four positive node or a pT3/4 tumors.

Key words：Breast cancer, Elderly patients, Radiation therapy

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はじめに

わが国では，乳癌の罹患率上昇や高齢化社会の到来により，高齢乳癌患者は増加している．一方，高齢者乳癌に関するランダム化比較試験やレベルの高いエビデンスは乏しいのが実情である．また，「高齢者」といっても，その身体的・精神的な状態は非常に個人差が多く，ひとくくりにできない面がある．緩和的放射線療法については，年齢にかかわらず積極的に行われるべきであるが，実臨床で問題になるのは初期治療における術後放射線療法である．本稿では日本乳癌学会の乳癌診療ガイドライン2011年版[1]，NCCN（National Comprehensive Cancer Network）ガイドライン[2]，SIOG（International Society of Geriatric Oncology）・EUSOMA（European Society of Breast Cancer Specialists）のガイドライン[3]などを踏まえ，高齢者乳癌に対する乳房温存術後放射線療法ならびに乳房切除術後放射線療法について，私見を含めて概説する．

1．高齢者乳癌に対する治療の問題点

高齢者においては，治療法の選択においてさまざまな問題点を考慮する必要がある．医学的な見地からは，若年者に比べて身体的・精神的な問題を抱えていることが多い．身体的な面では，他の悪性疾患を含む余病の存在の有無がきわめて重要である．乳癌の術後放射線療法において，その恩恵を被るのは治療から数年後である．余病により余命が限られていると予測される場合には，放射線療法の省略を

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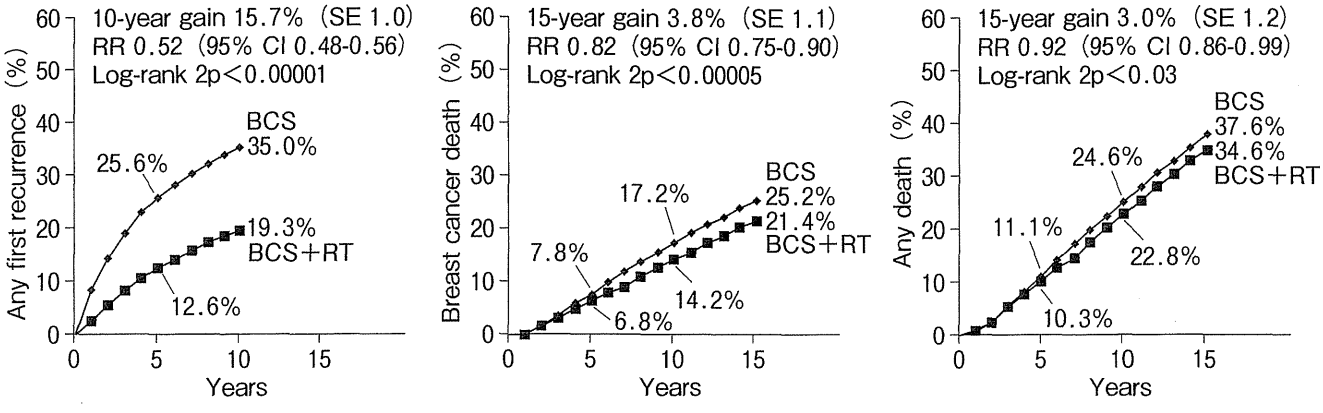


（文献5より引用）

図1　17のメタアナリシスにおける再発率・乳癌死亡率・全死亡率

a：再発率（局所＋遠隔）
b：乳癌死亡率
c：全死亡率
放射線治療は10年で再発率を15.7%，15年乳癌死亡率を3.8%，全死亡率を3％低下させた．

考慮してよいと思われる．一方，認知機能の低下や老年期うつ病，過度な不安なども治療の妨げとなる．放射線療法は患者の協力なしでは実施できない治療であり，治療選択においては重要である．医学的な面だけでなく，社会的な背景も治療の妨げとなる場合がある．もっとも問題となるのが放射線治療施設への通院手段である．わが国の放射線治療施設の数や配置については十分とはいえず，患者の居住地によっては施設までの通院に長時間を要することがある．また，たとえ近隣に治療施設があっても身体的・経済的な理由などで自力での通院が困難な場合がある．通常の術後放射線療法においては，5～6週間にわたり週5日の通院が必要であるので，高齢乳癌患者においては大きな支障となることがある．

2．乳房温存療法における放射線療法

乳房温存療法は乳房温存手術後に放射線療法を行う治療法であり，基本的には乳房温存術後のすべての症例に行われるべきである．近年，欧米のランダム化比較試験の結果やガイドラインなどにより，放射線療法の重要性が認識され，その施行率は増加している[4]．一方，一部の高齢者においては放射線療法を省略しても問題ないとの考えもある．この項では，乳房温存療法における放射線療法の役割について，浸潤性乳癌と非浸潤性乳癌にわけて概説する．

1）浸潤性乳癌

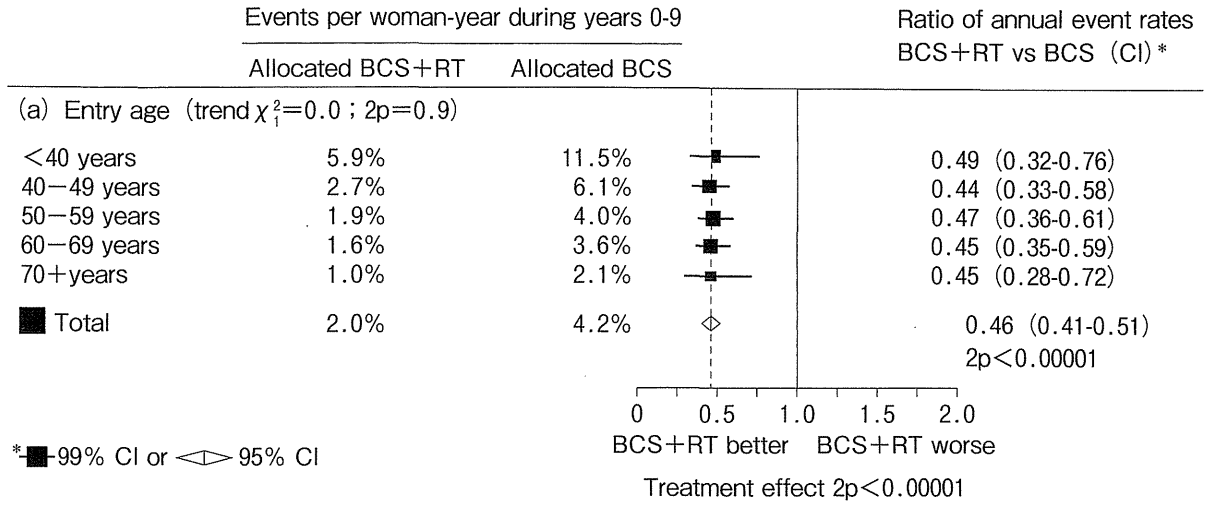
（1）放射線療法の適応

乳房温存手術を受けた患者では，基本的に全例が適応となる．放射線治療を実施できない患者では乳房温存手術そのものを避けるべきである．放射線治療を避けるべき状態は以下の通りである．

①絶対的禁忌：妊娠中，患側乳房や胸壁に照射歴あり

②相対的禁忌：背臥位にて患側上肢の挙上が困難，活動性の強皮症やSLEの合併，色素性乾皮症

若年～壮年乳癌患者と比べ，高齢者で問題となる場合があるのが「患側乳房や胸壁への照射歴」と「患側上肢挙上困難である」．他癌のために照射歴を有する患者，関節炎や脳血管系疾患の後遺症などで上肢挙上が困難な患者に遭遇することがある．そのような場合，基本的には乳房切除術が勧められるが，後述する一部の症例においては放射線療法の省略も許容されるので，患者の希望に応じて乳房温存術も



（文献5より改変）

図2　年齢層別の年間再発率と相対リスク

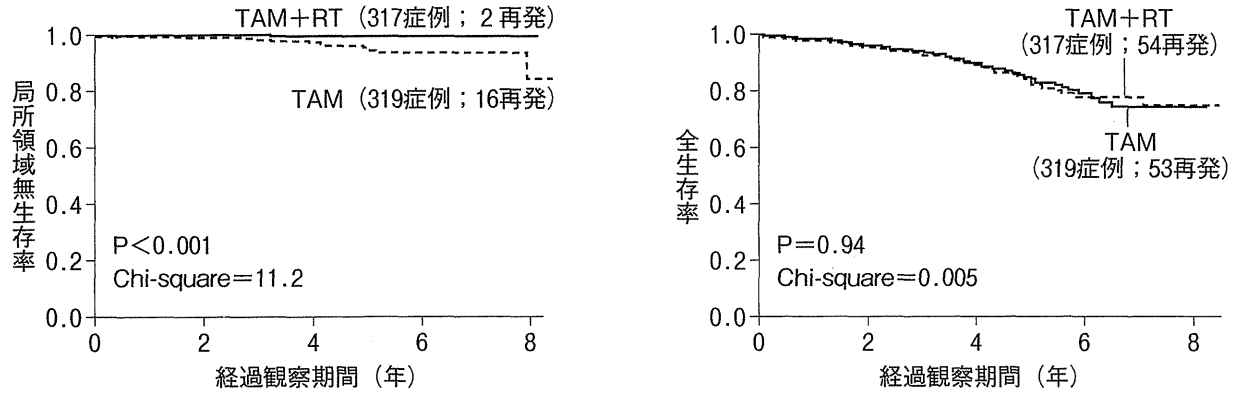
選択肢となる．

（2）放射線療法の意義

欧米では放射線治療の必要性を検証するランダム化比較試験が行われ，いずれのトライアルにおいても照射群は非照射群に比し有意な乳房内再発の低下が認められた．最新の Early Breast Cancer Trialists' Collaborative Group（EBCTG）によるメタアナリシスでは，17のランダム化比較試験における10,801例の個々のデータを用いて解析を行っている[5]．この報告では，局所-領域リンパ節再発あるいは遠隔再発を含む初再発は照射により全体として35.0%から19.3%（絶対差15.7%，95%信頼区間13.7-17.7，2p<0.00001）に減少し，15年目の乳癌死は25.2%から17.2%（絶対差3.8%，95%信頼区間1.6-6.0，2p<0.00005）に減少した（**図1**）．さらに再発リスクの因子にかかわらず，4例の10年再発（局所-領域再発と遠隔再発）を防ぐと15年乳癌死を1例防ぐと結論づけている．これらをふまえ，乳房温存術後には温存乳房に放射線治療を施行することが推奨されている．一方，年齢層別のサブ解析において，放射線照射群は非照射群に対して年間再発率を0.45倍（信頼区間0.28-0.72）に減少させるが，絶対値は1.0%と2.1%でありその差は小さい（**図2**）．

（3）高齢者乳癌における放射線療法のランダム化比較試験

高齢者乳癌に関する放射線療法の省略に関してこれまでに2つのランダム化比較試験が行われた．いずれも高齢早期乳癌に対してタモキシフェン（TAM）を投与した場合に放射線療法（RT）が省略可能かどうかを見極めるために行われ，乳房温存術後の TAM 単独治療と，TAM＋放射線治療（TAM＋RT）を比較した．Fyles らカナダのトライアル[6]では，年齢が50歳以上，病理学的に腫瘍径が5 cm 以下で断端陰性の症例が対象である．65歳未満では病理学的にリンパ節陰性患者が対象であるが，65歳以上では臨床的にリンパ節陰性か病理学的に陰性であれば対象としている．全乳房に40 Gy/2.5 Gy/4週と腫瘍床へ12.5 Gy/2.5 Gy/1週を照射し，TAM は20 mg/日を5年間投与した．Hughes ら CALGB/RTOG/ECOG のトライアル[7]では年齢が70歳以上，臨床病期 stage I（T1N0M0）でエストロゲンレセプター（ER）陽性または不明例が対象である．切除断端は陰性で臨床的にリンパ節陰性患者が対象である．全乳房に45 Gy/1.8 Gy/5週と腫瘍床へ14 Gy/2 Gy/1.5週を照射し，TAM は20 mg/日を5年間投与した．カナダのトライアルでは，769例がエントリーされ，TAM＋RT 群386例と TAM 単独群383例に割り付けられた．観察期間の中央値は5.6年で，5年局所再発率は TAM 単独群が7.7%に比し，TAM＋RT 群では0.6%であった（hazard ratio, 8.3；95% CI, 3.3〜21.2；p<0.001）．サブグループ解析では，T1か



（文献7より引用）

図3　高齢でホルモンレセプターにおける放射線療法の意義

a：局所領域無生存率

b：全生存率

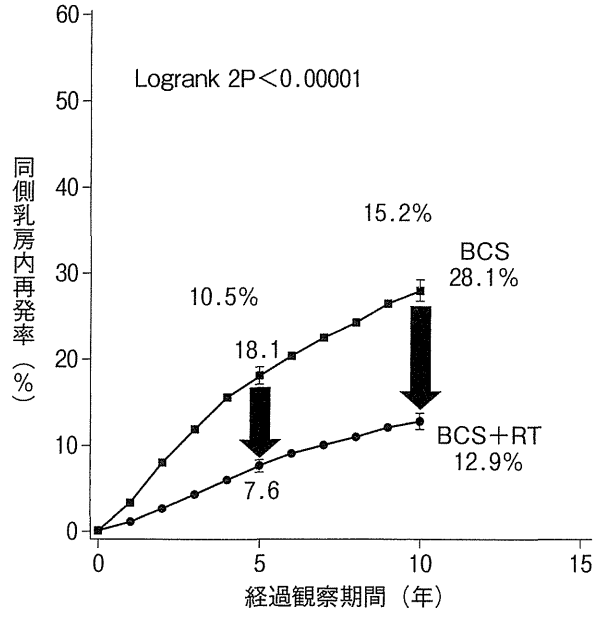
放射線療法は局所領域再発を有意に低下させるがその差は小さく，生存率には寄与しない．

つホルモンレセプター陽性患者611例においても5年局所再発率はそれぞれ5.9%と0.4%（p<0.001）で有意差を認めた（p<0.001）．5年無病再発率はそれぞれ84%と91%であった（p=0.004）が，遠隔再発・全生存率には有意差はなかった．CALGB/RTOG/ECOGのトライアルでは，636例がエントリーされ，TAM+RT群317例とTAM単独群319例に割り付けられた．観察期間の中央値は5年で5年局所領域（乳房+腋窩）再発はTAM単独群が4%に比し，TAM+RT群では1%であった（p<0.001%）．局所再発による乳房切除術の施行率，遠隔転移率には有意差はなく，また全生存率にも有意差はなかった（p=0.94）．対象が50歳以上という設定では局所再発率の差も大きく，さらに，腫瘍径が1cm以下でホルモンレセプター陽性というサブグループにおいても5年局所再発率に有意差を認めている（p=0.02）．一方，70歳以上を対象とした後者のトライアルでは，有意差はあるものの両群間で局所再発率の差は小さく，乳房切除率にも有意差はなかった（**図3**）．以上の結果より，閉経後でホルモンレセプター陽性であってもTAMに放射線治療を併用することにより局所領域再発を低下させるが，70歳以上の患者においてはTAM単独療法も選択肢の1つと考えられる．しかし，全生存率に有意差はなくても温存療法後の乳癌患者にとって，局所再発の経験やそれによる温存乳房の喪失は大きな精神的ダメージを与えるものと思われる．放射線治療による有害事象やコスト，わが国の放射線治療をとりまく社会的環境を考えると高齢者に対する照射省略の可否を見極めることは重要な課題である．65歳以上を対象とした同様のランダム化比較試験（PRIME II, http://homepages.ed.ac.uk/prime/prime2.html）が行われ，その結果が待たれるところである．NCCNのガイドライン[2]では，70歳以上でエストロゲンレセプター陽性，臨床的に腋窩リンパ節転移陰性のT1症例で，補助内分泌療法を施行される患者では放射線療法を省略可能としている（カテゴリー1）．一方，2007年のSIOGガイドラインではNCCNのガイドラインと同様の記載であったが，2012年のSIOG・EUSOMAのガイドラインでは高齢者であっても全乳房照射を行うべきであるとしている[3]．

2）非浸潤性乳管癌（ductal carcinoma in situ：DCIS）

（1）放射線療法の適応と意義

非浸潤性乳管癌（ductal carcinoma in situ：DCIS）における照射の有用性を検証するランダム化比較試験は4つあり[8~11]，いずれのトライアルにおいても放射線治療の有用性が示された．これら4つの



（文献12より引用）

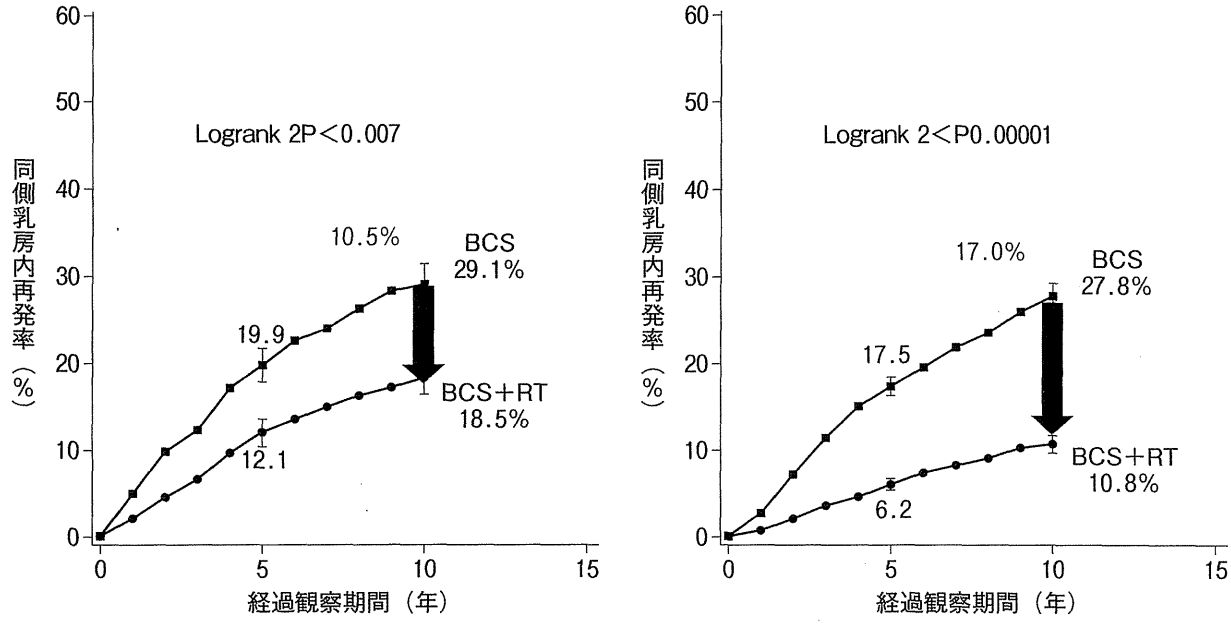
図4　DCISにおける放射線療法の意義
DCISにおいて乳房温存術後の照射線療法は同側乳房内再発を低下させる．

トライアルについてEBCTCGが行ったメタアナリシスでは，5年同側乳房内再発率を10.5%，10年同側乳房内再発率を15.2%低下させた[12]（**図4**）．Cochrane Databaseにおけるシステマティック・レビュー[13]でも温存術後放射線療法は同側乳房再発率を有意に低下させることが示された（HR：0.49，p<0.0001）．また，このシステマティック・レビューでは，完全切除できたかどうか，年齢（50歳以下/50歳超），comedo型壊死の有無，腫瘍径（1 cm未満/1 cm以上）などにかかわらず，放射線療法が有効であることも示されている．NCCNガイドラインにおいては，局所再発のリスク因子として触知可能腫瘤・大きな腫瘍径・高グレード・切除断端近接/陽性・年齢<50歳としている．NCCNのガイドラインではリスクが低い患者においては放射線療法の省略も可能（カテゴリー2B）とされており，高齢でかつその他のリスク因子がなければ照射省略も選択肢である．年齢については若年者で乳房内再発が高いことが知られているが，一方でEBCTCGのシステマティック・レビューでは，50歳以上の症例の方が放射線療法による乳房内再発の減少が大きいことが示されている（**図5**）[12]．基本的には照射が勧められるが，患者の身体的・社会的背景と腫瘍状態によって照射省略も考慮してよいと思われる．

3）放射線治療方法

乳房温存手術後の放射線療法では温存乳房全体を照射する．近年，腫瘍床のみに放射線照射する加速乳房部分照射（APBI：Accelerated Partial Breast Irradiation）も行われているが，まだ臨床試験でのみ行われるべきであり，現段階では温存乳房全体を照射するのが標準治療である．

線量は，総線量45-50.4 Gy/1回線量1.8-2.0 Gy/4.5-5.5週が標準となっている．一方，近年では寡分割照射の安全性についても報告されている．カナダで行われたランダム化比較試験では42.5 Gy/16回/22日と50 Gy/25回/35日が比較され，両者の10年局所再発率，全生存率，整容性に差を認めなかった[14]（**図6**）．イギリスでも寡分割照射に関するいくつかのランダム化比較試験が行われ，そのうちの1つであるSTART-Bトライアルでは40 Gy/15回/3週と50 Gy/25回/35日が比較された[15]．このトライアルでも5年局所再発率は両者で有意差を認めなかった．また，整容性については寡分割照射でむしろ良



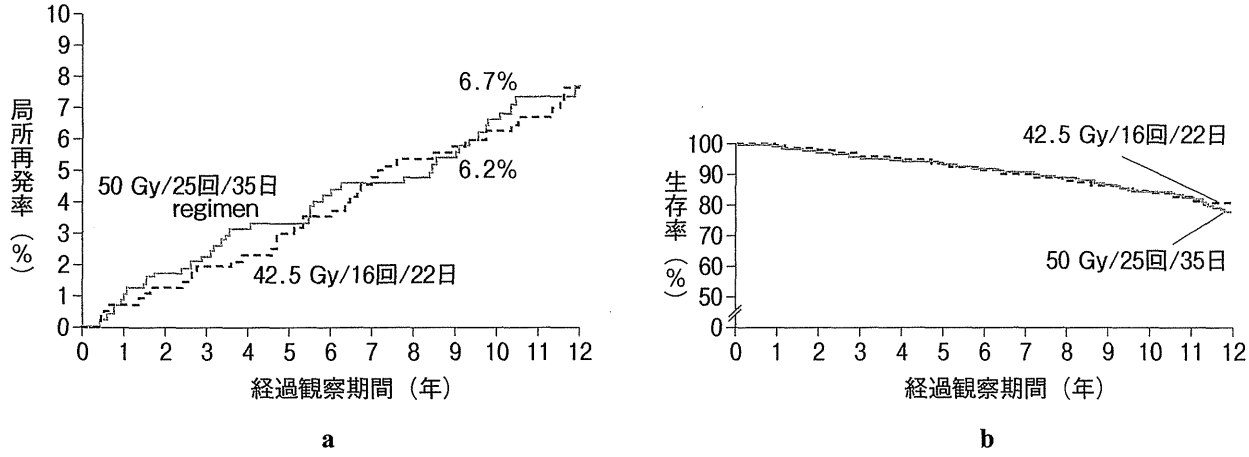
（文献12より引用）

図5　DCISにおける年齢による放射線治療の意義の差

a：年齢<50，911例

b：年齢≧50，2,818例

DCISにおける温存乳房への放射線療法では，50歳未満より50歳以上で乳房内再発の抑止率が高い．



（文献14より引用）

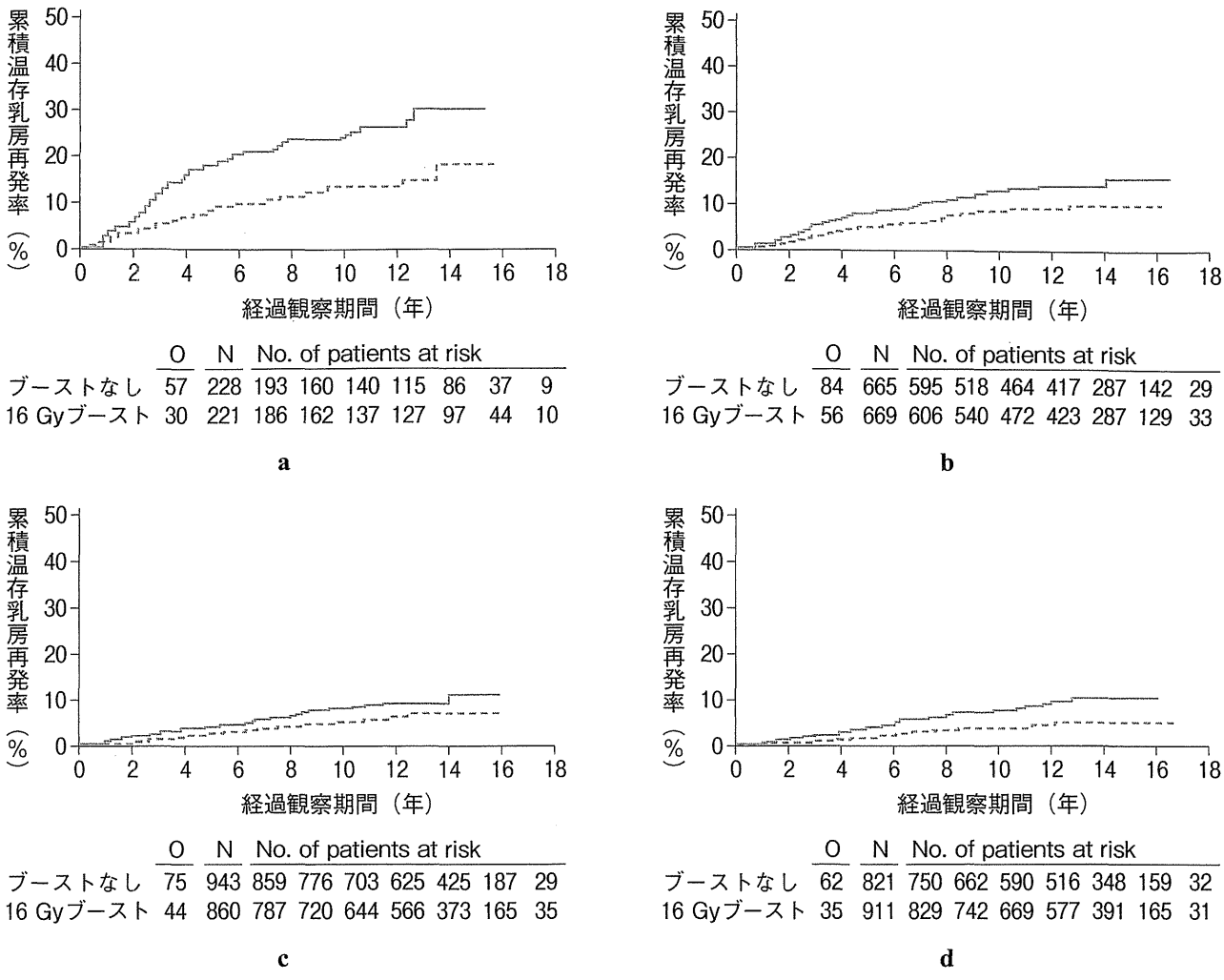
図6　標準的分割照射と寡分割照射のランダム化比較試験

a：局所再発率

b：生存率

全乳房照射は42.5 Gy/16回 /22日と50 Gy/25回 /35日で局所再発率と全生存率には有意差なし

好であった．これらの結果をうけ，米国放射線腫瘍学会（American Society for Therapeutic Radiology and Oncology；ASTRO）では，50歳以上，温存手術後のpT1-2N0，全身化学療法を必要としないなどの規準を満たす症例については，寡分割照射も従来の照射と同等であるとのガイドラインを発表している[16]．わが国では欧米との体格の差などがあり，寡分割照射による有害事象の増強などが懸念される．そのため「乳房温存療法の術後照射における短期全乳房照射法の安全性に関する多施設共同試験



（文献19より引用）

図7　断端陰性症例での腫瘍床ブースト（16 Gy）の意義

a：40歳以下（p＝0.014）
b：41-50歳（p＝0.02）
c：51-60歳（p＝0.012）
d：60歳以上（p＝0.008）
全年齢層で温存乳房再発を低下させたが，その絶対値は若年で大きい．

（JCOG0906）」を実施中でありその結果が待たれる．高齢乳癌患者においては通院が問題となることが多く，その点でも症例選択や心臓等への線量に留意すれば行うことを考慮しても良いと考えられる．

4）腫瘍床ブースト照射

腫瘍床に対するブースト照射は乳房内再発のリスクを減少させる．わが国でも原則として全例に行うことが推奨されているが[17]，手術の切除範囲が欧米より大きいことや線量増加が美容結果に及ぼす影響への懸念から，断端近接あるいは陽性例に限ってブースト照射を追加している施設が多い．しかし，断端陰性でも腫瘍床に対するブースト照射が温存乳房内再発のリスクを減少させることが2つのランダム化比較試験で証明されている[18, 19]（**図7**）．これらのトライアルではわが国と比べて切除範囲が小さく，病理学的断端陽性の基準も異なることから，わが国でも全例にブースト照射を行うかどうかについてはまだ議論の余地がある．しかし，若年者（とくに50歳未満）に比し，ブースト照射による局所再発抑制効果が小さいので，高齢者の断端陰性症例に関しては必ずしも必要ないと考えられる．

3．進行乳癌に対する乳房切除術後放射線療法

局所進行乳癌に対する乳房切除後症例，とくに腋窩リンパ節転移陽性症例においては，乳房切除後放射線療法（Postmastectomy Radiation Therapy：PMRT）が行われている．近年，腋窩リンパ節陽性例などの局所進行期例で，PMRTが胸壁再発を軽減させるだけでなく，生存率を向上させることが示された．PMRTが，腋窩リンパ節4個以上陽性例において適切な全身療法との併用により生存率を向上させることはコンセンサスが得られているが，腋窩リンパ節転移1～3個の患者に関してはまだ異論のあるところである．

適応と意義

New England Journal of Medicineに掲載された2つの第III相臨床試験の結果を契機に，PMRTは進行乳癌における重要性が認識された．デンマークとカナダでの大規模なランダム化比較試験の結果，閉経前のリンパ節陽性患者において局所制御のみならず生存率も有意に向上したのである[20, 21]．その後，閉経後のハイリスク患者に対するランダム化比較試験でも生存率の向上が示された[22]．これらをふまえ，2001年にASCO（American Society of Clinical Oncology）から出されたClinical Practice Guidelinesでは，術後照射の適応，放射線治療を行うべき領域等について勧告がなされている[23]．後者の研究は，乳房切除術後閉経後乳癌患者で，TAM＋RT群（686例）とTAM単独群（689例）を比較したものである．年齢のうちわけは，60歳以上が67％であったが，70歳以上は含まれていない．局所領域再発率はそれぞれ8％と35％（$p<0.001$）であり，無病生存率・全生存率においてもTAM＋RT群で良好であった．60歳以上に限って見てみると，10年無病生存率は37％と23％，10年生存率は46％と37％であったASCOのガイドラインでの適応は腋窩リンパ節転移が4個以上，T3またはT4症例とされており，腋窩リンパ節転移1～3個の症例についてはPMRTを推奨するだけの根拠がないとされていた．

一方，腋窩リンパ節転移1～3個の患者に関してはDanish 82bトライアルと82cトライアルをあわせた解析の結果，4個以上転移があった症例と同等に，15年局所領域制御率（96％ vs 73％，$p<0.001$）と生存率の向上（57％ vs 48％，$p=0.03$）が示された[24]．リンパ節転移1～3個の全症例にPMRTをするべきかどうかについてはまだ議論のあるところであるが，高齢乳癌患者においては，少なくとも腋窩リンパ節転移4個以上，またはT3/T4症例で行うべきと考えられる．

まとめ

高齢乳癌患者においても，放射線療法は浸潤癌に対して局所領域再発を抑え，生存率を向上させる．非浸潤癌でも局所再発を抑え，その抑止率は若年者より大きい．一方，放射線療法においては，治療の毒性が年齢に大きく左右されないにもかかわらず，通院などの点が妨げになることがある．高齢者であっても重大な併存症などを認めず，長期の余命が見込まれる患者においては可能な限り放射線療法を受けられるよう，サポートする必要がある．また，再発した場合，高齢であるが故に強力な救済治療が適応できないこともあるので，放射線療法を省略した際には局所領域再発を早期に発見するような計画的経過観察も必要と思われる．

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Patterns of Practice in Intensity-modulated Radiation Therapy and Image-guided Radiation Therapy for Prostate Cancer in Japan

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Background: The purpose of this study was to compare the prevalence of treatment techniques including intensity-modulated radiation therapy and image-guided radiation therapy in external-beam radiation therapy for prostate cancer in Japan.
Methods: A national survey on the current status of external-beam radiation therapy for prostate cancer was performed in 2010. We sent questionnaires to 139 major radiotherapy facilities in Japan, of which 115 (82.7%) were returned.
Results: Intensity-modulated radiation therapy was conducted at 67 facilities (58.3%), while image-guided radiation therapy was conducted at 70 facilities (60.9%). Simulations and treatments were performed in the supine position at most facilities. In two-thirds of the facilities, a filling bladder was requested. Approximately 80% of the facilities inserted a tube or encouraged defecation when the rectum was dilated. Some kind of fixation method was used at 102 facilities (88.7%). Magnetic resonance imaging was routinely performed for treatment planning at 32 facilities (27.8%). The median total dose was 76 Gy with intensity-modulated radiation therapy and 70 Gy with three-dimensional radiation therapy. The doses were prescribed at the isocenter at the facilities that conducted three-dimensional radiation therapy. In contrast, the dose prescription varied at the facilities that conducted intensity-modulated radiation therapy. Of the 70 facilities that could perform image-guided radiation therapy, 33 (47.1%) conducted bone matching, 28 (40.0%) conducted prostate matching and 9 (12.9%) used metal markers. Prostate or metal marker matching tended to produce a smaller margin than bone matching.
Conclusions: The results of the survey identified current patterns in the treatment planning and delivery processes of external-beam radiation therapy for prostate cancer in Japan.

Key words: radiation therapy – urologic-radoncol – radiation oncology

INTRODUCTION

External beam radiation therapy (EBRT) has developed rapidly in recent years (1,2) and treatment equipment with which intensity-modulated radiation therapy (IMRT) and/or image-guided radiation therapy (IGRT) can be conducted are being introduced into Japan (3). IMRT and IGRT are particularly useful in EBRT for prostate cancer and are routinely used in the USA (4) and recommended in worldwide guidelines (5,6).

In Japan, IMRT and IGRT were listed as eligible for insurance reimbursement in 2008 and 2010, respectively. However, the present situation regarding the use of these techniques in EBRT for prostate cancer remains unclear (7,8). Therefore, we conducted a survey that would clarify the operational situation, treatment planning and treatment processes of IMRT and/or IGRT when used in EBRT for prostate cancer.

PATIENTS AND METHODS

In February 2010, we sent a questionnaire on EBRT for prostate cancer to 139 major facilities including university hospitals, cancer centers and designated prefectural cancer centers and hospitals. The questionnaire was also sent to the hospitals which had treatment machines with IGRT functions, including Novalis (BrainLAB, Heimstetten, Germany), Tomotherapy (Accuray Inc., Sunnyvale, USA) and MHI-TM2000 (Mitsubishi Heavy Industries, Ltd., Nagoya, Japan).

The survey was composed of categories regarding treatment planning, dose fractionation and methods of implementation of EBRT for prostate cancer. If methods differed according to the type of radiation techniques used such as three-dimensional radiation therapy (3DCRT) or IMRT, we required responses regarding the most precise radiation method presently used. Among the 139 facilities to which we sent the survey, 115 (82.7%) gave responses, which were then analyzed. The high response rate allowed an extensive and representative data analysis.

RESULTS

General Information

Figure 1 shows the distribution of the number of patients with prostate cancer treated with EBRT at facilities in 2009 over the course of 1 year. There were 30 facilities (26.1%) at which over 50 patients were treated in 1 year. Of the 115 total facilities, 67 (58.3%) conducted IMRT, 70 (60.9%) conducted IGRT and 58 (50.4%) conducted both.

Treatment Planning

Figure 2 shows the condition of the bladder at the treatment planning stage and during the treatment. In approximately two-thirds of the facilities, a filling bladder was requested. The time spent pooling urine was 1 h at 56 facilities (48.7%), 1–2 h at 8 facilities (7.0%) and 30 min at 7 facilities (6.1%). Seven facilities (6.1%) also asked patients to drink water prior to treatment.

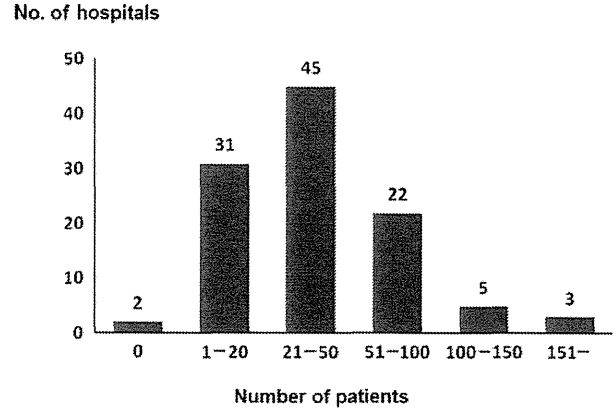

Figure 1. Total number of patients with prostate cancer treated with external-beam radiation therapy at facilities in 2009. Because some data were missing, the total numbers of patients were less than the actual number.

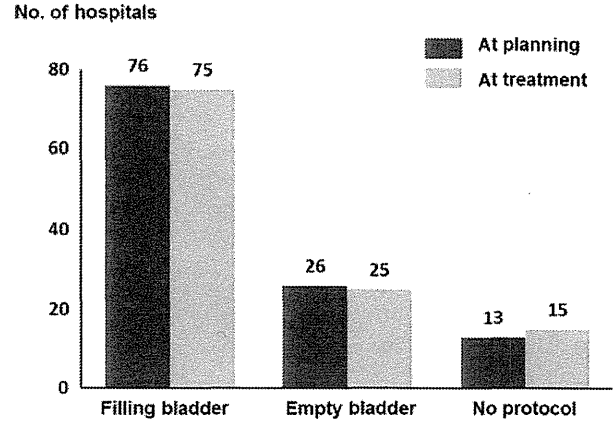

Figure 2. Condition of the bladder at the treatment planning stage and during treatment.

Figure 3 shows the condition of the rectum. Approximately 80% of the facilities inserted a tube or encouraged defecation when the rectum was dilated. Laxative medication was used at one-quarter of the facilities.

Simulations and treatments were performed in the supine position at 105 facilities (91.3%) and the prone position at 10 facilities (8.7%). Figure 4 shows methods of patient fixation. Some kind of fixation method was used at 102 facilities (88.7%). Although various methods were reported, a vacuum cushion, thermoplastic shell and foot support were used most frequently.

Magnetic resonance imaging (MRI) was routinely performed for treatment planning at 32 facilities (27.8%). Of these, 15 facilities (13.0%) performed computed tomography

(CT)-MRI image fusion with treatment planning software. MRI taken at the time of diagnosis was used as a reference at 66 facilities (57.4%), while 17 facilities (14.8%) did not use MRI for treatment planning.

Treatment

Radiation therapy was carried out with 2 Gy per fraction at 100 facilities (86.9%), 2.1–3 Gy at 14 facilities (12.2%) and 1.8 Gy at 1 facility (0.9%). Most facilities conducted treatment five times a week. Treatment was conducted three times a week at five facilities (4.3%) and four times a week at three facilities (2.6%).

Figure 5 shows the distributions of radiation doses delivered to the prostate at facilities using a fraction dose of 2 Gy. The median total dose was 76 Gy with IMRT and 70 Gy with 3DCRT. The doses were prescribed at the isocenter at the facilities that conducted 3DCRT. In contrast, the dose prescription varied greatly at the facilities that conducted IMRT. Of the 67 facilities that conducted IMRT, D95, which is the minimum absorbed dose that covers 95% of the planning target volume (PTV), was used as a dose prescription at 24 facilities (35.8%). A dose prescription requiring that 95% of the prescribed isodose line cover 95% of the PTV was used at 4 facilities (6.0%), the mean PTV dose was used at 13 facilities (19.4%) and other methods at 26 facilities (38.8%).

The most popular IGRT methods (54 facilities) involved 2D matching with X-ray fluoroscopy or 3D matching with a flat-panel cone-beam CT. Eight facilities used CT on rail and 4 facilities used ultrasonic devices. Of the 70 facilities that could perform IGRT, 33 (47.1%) conducted bone matching, 28 (40.0%) conducted prostate matching and 9 (12.9%) used metal markers. At the treatment of prostate cancer, 60 facilities (85.7%) always conducted IGRT, while 9 (12.9%) conducted IGRT at regular intervals.

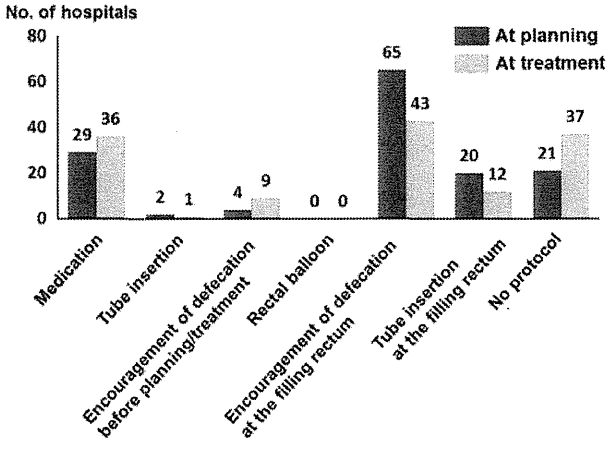

Figure 3. Condition of the rectum at the treatment planning stage and during treatment. Multiple answers allowed.

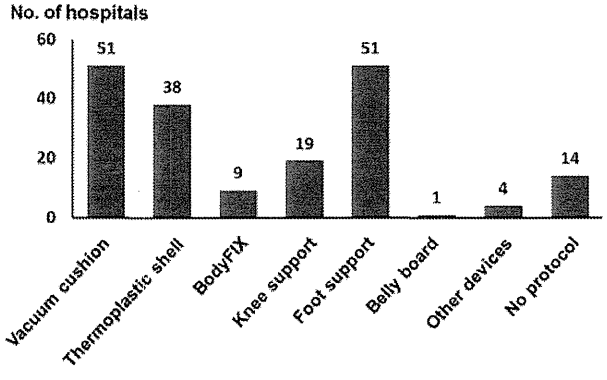

Figure 4. Fixation of the patients at the treatment planning stage and during treatment. Multiple answers allowed.

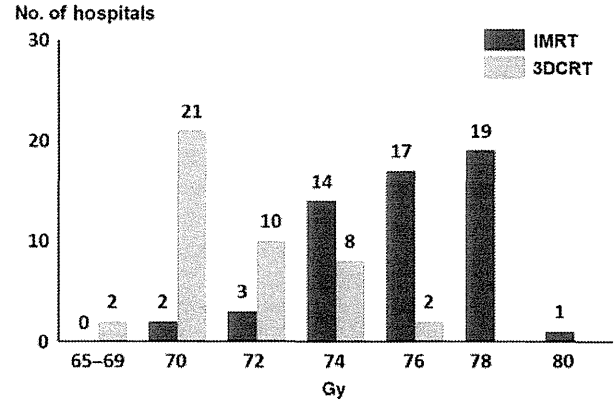

Figure 5. Total dose to the prostate.

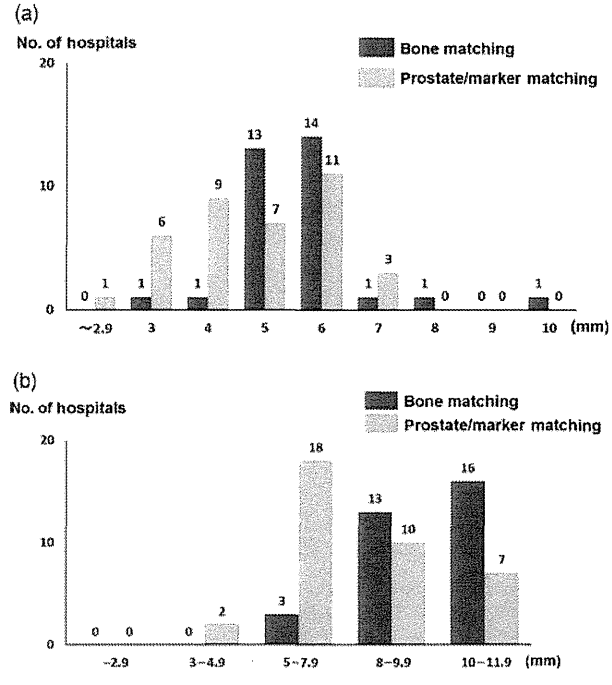

Figure 6. Margins from the prostate to planning target volume for patients with T1–2 tumors treated with IGRT: (a) rectal side and (b) other sides.

Figure 6 show the distribution of the prostate-PTV margins for patients with typical T1–2 tumors treated with IGRT. Prostate or metal marker matching tended to produce slightly smaller margins than bone matching.

DISCUSSION

This study provides a clear picture of present practices of IMRT and/or IGRT for prostate cancer in Japan.

Simulations and treatments were performed in the supine position at most facilities. However, facilities employed various fixation methods. In most facilities, some kind of fixation method was used, although immobilization devices for body malignancies are not covered by health insurance in Japan. In the patterns of care study on prostate cancer patients who were treated with EBRT from 2003 to 2005, immobilization devices were used on only 15% of patients (7). One reason for the high frequency of the usage of patient immobilization devices in this study could be the gradual popularization of fixation methods over time. An additional reason is probably the fact that some sort of fixation method tends to be used in more precise radiation treatment, because patient immobilization can be an important contributor to the reproducibility and accuracy of radiotherapy (9).

The pretreatment condition of the bladder and rectum also varied greatly among facilities. Although fixation of the prostate is frequently conducted with a rectal balloon in Western countries (10), this method has not been used at all in Japan.

In this study, we did not investigate PTV margins when IGRT was not used. Therefore, we were unable to clarify whether IGRT causes decreased margins. However, PTV margins tended to be slightly smaller with prostate or fiducial marker matching than that with bone matching. PTV margins should be determined at each facility taking into account position errors caused not only by the IGRT method, but also by the patient position, fixation method and pretreatment condition of the bladder and rectum. Enmark et al. (11) demonstrated that a margin of 4 mm in all directions was adequate to account for uncertainties including the inter- and intrafraction motions, if IGRT with fiducial markers is performed on a daily basis. Some facilities have chosen prostate-PTV margins of <4 mm. Because of uncertainties such as intrafraction motion or uncertainty of the target delineation, decreases in the PTV margin should be carefully performed even when IGRT is applied.

The radiation dose administered at most facilities was 2 Gy per fraction. The median value of the total radiation dose was 76 Gy with IMRT and 70 Gy with 3DCRT. It is well known that the radiation dose is a strong independent predictor of failure (12), and IMRT can reduce the unwanted doses to nearby organs at risk. Therefore, as IMRT becomes more widespread in Japan, more appropriate higher dosages of radiation should be utilized. However, a significant problem is the fact that the IMRT dose prescription varies. It is necessary to define and develop recommended guidelines for dose prescription and a dose reporting system for IMRT in Japan (13).

IMRT and IGRT were being conducted at approximately half of the facilities in this study. However, our survey targeted large-scale facilities. If all radiation therapy facilities in Japan were to be surveyed, this proportion would probably be smaller (3). At present, high-precision radiation therapy devices such as IMRT and IGRT are being rapidly introduced (3,14), and an increasing number of facilities will surely come to adopt IMRT and IGRT. The results of the survey in this study will provide beneficial information to those facilities as they begin treatment.

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Conflict of interest statement

None declared.

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CLINICAL INVESTIGATION **Thoracic Cancer**

PHASE I STUDY OF CONCURRENT HIGH-DOSE THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY WITH CHEMOTHERAPY USING CISPLATIN AND VINORELBINE FOR UNRESECTABLE STAGE III NON-SMALL-CELL LUNG CANCER

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Purpose: To determine the maximum tolerated dose in concurrent three-dimensional conformal radiotherapy (3D-CRT) with chemotherapy for unresectable Stage III non–small-cell lung cancer (NSCLC).

Patients and Methods: Eligible patients with unresectable Stage III NSCLC, age ≥20 years, performance status 0–1, percent of volume of normal lung receiving 20 GY or more (V_{20}) ≤30% received three to four cycles of cisplatin (80 mg/m^2 Day 1) and vinorelbine (20 mg/m^2 Days 1 and 8) repeated every 4 weeks. The doses of 3D-CRT were 66 Gy, 72 Gy, and 78 Gy at dose levels 1 to 3, respectively.

Results: Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were enrolled at dose levels 1 to 3, respectively. The main reasons for exclusion were V_{20} >30% (n = 10) and overdose to the esophagus (n = 8) and brachial plexus (n = 2). There were 26 men and 5 women, with a median age of 60 years (range, 41–75). The full planned dose of radiotherapy could be administered to all the patients. Grade 3–4 neutropenia and febrile neutropenia were noted in 24 (77%) and 5 (16%) of the 31 patients, respectively. Grade 4 infection, Grade 3 esophagitis, and Grade 3 pulmonary toxicity were noted in 1 patient, 2 patients, and 1 patient, respectively. The dose-limiting toxicity was noted in 17% of the patients at each dose level. The median survival and 3-year and 4-year survival rates were 41.9 months, 72.3%, and 49.2%, respectively.

Conclusions: 72 Gy was the maximum dose that could be achieved in most patients, given the predetermined normal tissue constraints. © **2012 Elsevier Inc.**

Lung cancer, Chemotherapy, Radiotherapy, High dose, Conformal.

INTRODUCTION

Approximately one third of patients with non–small-cell lung cancer (NSCLC) present with locally advanced Stage III disease at the initial diagnosis (1). Of this category, Stage IIIA disease with bulky N2 and Stage IIIB disease without pleural effusion are characterized by a large primary lesion and/or involvement of the mediastinal or supraclavicular lymph nodes. In addition, the majority of these patients have occult systemic micrometastases. Concurrent thoracic radiotherapy and chemotherapy has been the standard care for these patients with unresectable disease (2, 3). A platinum doublet with a third-generation anticancer agent combined with thoracic radiotherapy was reported to yield a median overall survival time (OS) of more than 2 years and long-term survivors (4–6), but the effect of platinum-based chemotherapy has reached a plateau.

The failure pattern in patients with Stage III NSCLC treated by concurrent chemoradiotherapy was roughly local recurrence alone in one third of the patients, both local and distant recurrence in another third of patients, and distant metastasis without local failure in the remaining third of patients (2, 5).

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Thus, improvement of local control and suppression of distant metastasis are essential for prolongation of patient survival.

The conventional total dose of thoracic radiotherapy in patients with inoperable NSCLC has been 60 Gy administered in 30 fractions. This dose was established in 1987 by randomized Radiation Therapy Oncology Group trials that demonstrated better 3-year survival with a radiation dose of 60 Gy than with lower doses (7). In these trials, two-dimensional treatment planning was used, wherein the tumor volume was defined on kilovoltage radiographs (7). Thereafter, the standard initial target volume included the primary tumor, metastatic lymph nodes, and adjacent uninvolved ipsilateral hilar and mediastinal regions (elective nodal irradiation: ENI). Except for selected patients, excessive toxicity hampered an increase of the total dose to over 60 Gy in patients with locally advanced NSCLC.

It is, however, time now to reconsider the optimal dose of thoracic radiotherapy using new techniques in patients with locally advanced NSCLC, for the following reasons. First, positron emission tomography (PET) provides more accurate diagnosis of mediastinal lymph node metastases (8) and more accurate quantification of the tumor volumes, especially when atelectasis is present (9). Second, three-dimensional conformal radiation therapy (3D-CRT) enables radiation oncologists to delineate the tumor and adjacent normal tissue more sharply and to choose beam angles to maximize tumor coverage with minimum irradiation of normal tissues (10). Third, omission of the ENI resulted in improvement of radiation-associated toxicity without worsening the local control rate of the tumor (11, 12). Thus, by use of these new techniques, the optimal dose of thoracic radiation could exceed the conventional 60 Gy.

Two dose escalation studies in patients with locally advanced NSCLC showed that the total dose of thoracic radiotherapy could be increased up to 90 Gy in concurrent chemoradiotherapy using the 3D-CRT technique combined with weekly carboplatin and paclitaxel chemotherapy (13, 14). In these trials, chemoradiotherapy was administered after induction chemotherapy. However, it remained unclear whether these doses could be delivered safely to the majority of patients with locally advanced NSCLC, because it is not known how many patients were screened for the trials and how many of them were actually registered, and because some of the registered patients were excluded from the chemoradiotherapy phase after induction chemotherapy. The total number of patients evaluated in the two trials was also limited. Furthermore, chemotherapy other than weekly carboplatin and paclitaxel has not been evaluated in the setting of combined chemotherapy with high-dose thoracic radiotherapy, to our knowledge. The objectives of the current study were (1) to evaluate the toxicity of concurrent high-dose 3D-CRT without ENI with cisplatin and vinorelbine for unresectable Stage III NSCLC, (2) to determine the maximum tolerated dose (MTD) of thoracic radiotherapy, and (3) to observe the antitumor effects of this regimen.

PATIENTS AND METHODS

Study design

This study was designed as a Phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center on July 28, 2005. We planned to treat 12 patients at a dose level and follow them up at least 6 months, and then escalate to the next level if 67% of the patients did not experience dose-limiting toxicity (DLT). We followed widely accepted normal tissue dose constraints. Patients with percent volume of the normal lung receiving 20 Gy or more (V_{20}) of greater than 30% were excluded and treated outside the study. Other dosimetric constraints were applied at the discretion of the treating radiation oncologist. Maximum doses exceeding 50 Gy to the spinal cord, 66 Gy to the esophagus, or 66 Gy to the brachial plexus were generally excluded.

Patient selection

Previously untreated patients with locally advanced NSCLC without effusion were screened for entry into this study. The eligibility criteria were (1) histologically or cytologically proven NSCLC, (2) unresectable Stage IIIA or IIIB disease confirmed by both computed tomography (CT) and PET, (3) no previous treatment, (4) measurable disease, (5) $V_{20} \leq 30\%$, (6) age ≥ 20 years, (7) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and (8) adequate bone marrow function (white blood cell [WBC] count $\geq 4.0 \times 10^9$/L, hemoglobin ≥ 9.5 g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ 80 IU/L), renal function (serum creatinine ≤ 1.5 mg/dL), and pulmonary function ($PaO_2 \geq 70$ Torr under room air). Patients were excluded if (1) they had malignant pleural or pericardial effusion or (2) they had a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest x-ray, infection, or other diseases contraindicating chemotherapy or radiotherapy, or (3) they were pregnant or breast feeding. All patients gave their written informed consent.

Pretreatment evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest CT scan, brain CT scan or magnetic resonance imaging, abdominal CT, and PET.

Treatment schedule

Chemotherapy consisted of cisplatin 80 mg/m^2 on Day 1 and vinorelbine 20 mg/m^2 on Days 1 and 8, repeated every 4 weeks for three to four cycles. Cisplatin was administered by intravenous infusion for 60 minutes with 2,500 to 3,000 mL of intravenous fluid for hydration and prophylactic antiemetic therapy consisting of a 5-hydroxytriptamine-3 antagonist on Day 1 and a corticosteroid on Days 1 to 5. Vinorelbine, diluted in 50 mL of normal saline, was administered intravenously.

Radiation therapy started on Day 1 of the first cycle of chemotherapy and was delivered with megavoltage equipment (6–10 MV) once daily for 5 days a week. The total dose was 66 Gy in 33 fractions at level 1, 72 Gy in 36 fractions at level 2, and 78 Gy in 39 fractions at level 3. All patients underwent a 3D treatment planning CT 3 to 7 days before the start of the treatment, and the eligibility was finally confirmed based on evaluation using the

dose–volume histogram (DVH). The gross tumor volume (GTV) was defined as the primary tumor delineated on pulmonary windows of the chest CT or on the diagnostic PET scans. Atelectasis or secondary changes in the peripheral lung region of the primary tumor were not included. Metastatic lymph nodes defined as nodes of 1 cm or larger visualized on mediastinal windows of the CT images or PET-positive lymph nodes were also included in the GTV. The clinical target volume (CTV) was equivalent to the GTV. Uninvolved mediastinum or supraclavicular fossae were not included in the CTV. The planning target volume (PTV) was determined as the CTV plus 1.0 cm for the anterior, posterior, medial, and lateral margins and a 1.0 to 2.0 cm for the superior and inferior margins, taking account of setup variations and internal organ motion. The spinal cord dose was typically limited to 44 Gy, but a maximum of 50 Gy was allowed. The lung V_{20} was limited to 30% in all patients. The maximum dose to the brachial plexus and esophagus did not exceed 66 Gy. The 100% dose was prescribed to the reference point located in the central part of the PTV, and the entire PTV was covered with 95–107% of the prescribed dose principally, but variation of ±10% was allowed. Lung heterogeneity corrections using the equivalent path length algorithm were applied in all patients.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). The lung toxicity grade was defined as the highest grade among cough, dyspnea, obstruction/stenosis of airways, pneumonitis/pulmonary infiltrates, and pulmonary fibrosis in the pulmonary/upper respiratory section (15).

Vinorelbine administration on Day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on Day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level ≥1.6 mg/dL, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. If these toxicities did not recover within 6 weeks from Day 1 of the previous cycle of chemotherapy, subsequent cycles of chemotherapy were stopped. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dL or higher. The dose of vinorelbine was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/L, platelet count $<25 \times 10^9$/L, or Grade 3 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: body temperature ≥38°C, Grade 3 esophagitis, PS of 3, or suspected radiation pneumonitis. Thoracic radiotherapy was terminated if any of the following were noted: Grade 4 esophagitis, Grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 62 days (level 1), 67 days (level 2), or 70 days (level 3). Any protocol-defined treatments were terminated if Grade 4 nonhematologic toxicities other than transient electrolyte disturbances or a PS of 4 was noted.

Dose-limiting toxicity and maximum tolerated dose

The DLT was defined as the following toxicities observed during a 6-month period from the start of treatment: (1) Grade 3 esophagitis, lung toxicity, myelitis, dermatitis associated with radiation, and cardiac toxicity associated with radiation, (2) Grade 4 nonhematologic toxicity, or (3) treatment termination due to prolonged toxicity. Twelve patients were enrolled at each dose level. All patients were followed up for at least 6 months to evaluate DLT. During the period, if none to 4 of the 12 patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. The recommended dose for Phase II trials was defined as the dose preceding the MTD.

Response evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 (16).

Follow-up

Patients who completed the protocol therapy were followed up to monitor toxicity, response, and recurrence. CT of the chest was performed every 2 to 4 months for 1 year, every 6 months for 2 years, and then yearly for 2 years. The relapse pattern was categorized into (1) local alone, including relapse from the primary site or the hilar, mediastinal, or supraclavicular lymph nodes, (2) distant metastasis alone, including pleural dissemination, pleural and pericardial effusions, and distant metastases, and (3) local and distant.

Statistical analyses

Progression-free survival time (PFS) and OS were estimated by the Kaplan-Meier method. The PFS was measured from the date of registration to the date of disease progression or death resulting from any cause or date of last follow-up. The OS was measured from the date of registration to the date of death resulting from any cause or date of last follow-up. Patients who were lost to follow-up without events were censored at the date of their last known follow-up. A confidence interval (CI) for the response rate was calculated by the method used for exact binomial CIs. The Dr. SPSS II 11.0 software package for Windows (SPSS Japan Inc., Tokyo, Japan) was used for the statistical analyses.

RESULTS

Registration and characteristics of the patients

From August 2005 to September 2008, 57 patients were deemed to initially be eligible. Of these, 3 patients were excluded because idiopathic interstitial pneumonitis ($n = 1$) and anemia ($n = 2$) developed. Explanation of the study using the consent form was given to 54 patients, and informed consent was obtained in 51 patients. The 51 patients underwent 3D treatment planning, and eligibility was finally confirmed in 31 patients. Those 31 were enrolled into this study. A total of 20 patients were excluded as a result of the DVH evaluation: because of V_{20} higher than 30% in 10 patients, overdose to the esophagus in 8 patients, and overdose to the brachial plexus in 2 patients. Eventually, of 17 patients assessed as to their eligibility for dose level 1, 16 patients for dose level 2, and 24 patients to dose level 3, 13 (76%), 12 (75%), and 6 (25%) patients were actually enrolled into levels 1 to 3, respectively (Fig. 1).

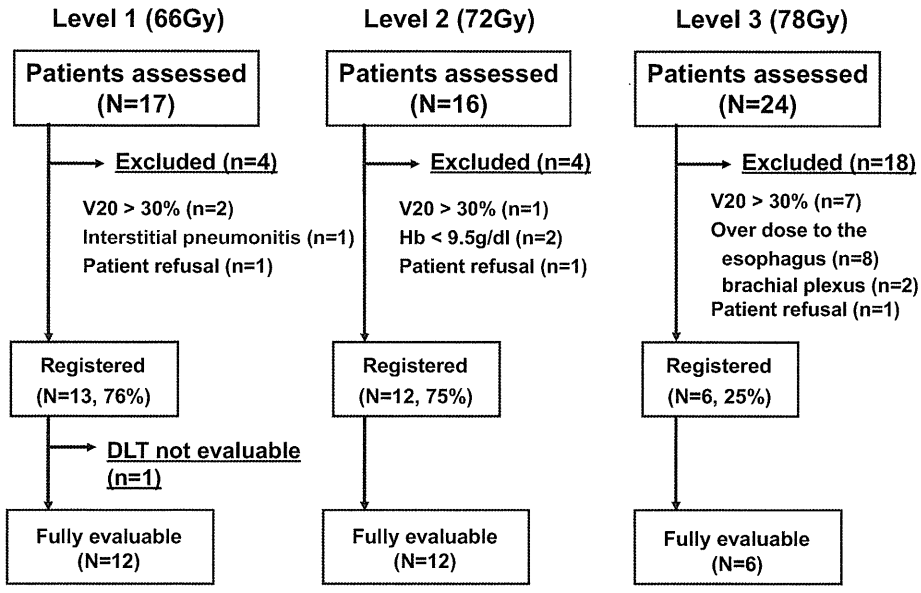

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

The pretreatment characteristics of the patients enrolled in this trial are shown in Table 1. The majority of the patients were in good general condition, with a PS of 0 in 25 (81%) and no weight loss in 26 (84%) patients. Adenocarcinoma was the predominantly encountered histological characteristic, seen in 23 (74%) patients.

Treatment delivery

The treatment delivery to the patients was fairly good (Table 2). The planned dose of radiotherapy was administered to all patients of all the three dose levels. More than 80% of the patients received three to four cycles of chemotherapy without or with only one omission of vinorelbine on Day 8, regardless of the dose levels.

Toxicity and DLTs

The hematologic toxicity was comparable to that of other concurrent chemoradiotherapy (Table 3). Grade 4 septic shock was encountered during the fourth cycle of chemotherapy in 1 patient enrolled at dose level 1, but it was manageable by standard care with antibiotics. Other nonhematologic toxicities were mild and acceptable.

Table 1. Patient characteristics

Characteristic	*n*	(%)
Sex		
M	26	(84)
F	5	(16)
Age (y)		
Median (range)	60	(41–75)
Performance status		
0	25	(81)
1	6	(19)
Body weight loss (%)		
0	26	(84)
0.1–5.0	2	(6)
≤5.0	3	(10)
Histology		
Adenocarcinoma	23	(74)
Squamous cell carcinoma	4	(13)
NSCLC, not otherwise specified	4	(13)
Stage		
IIIA	20	(65)
IIIB	11	(35)

Abbreviation: NSCLC = non–small-cell lung cancer.

Table 2. Treatment delivery

	Level 1 (*n* = 13)	Level 2 (*n* = 12)	Level 3 (*n* = 6)
Radiotherapy			
Total dose (Gy)			
66	13 (100)	–	–
72	–	12 (100)	–
78	–	–	6 (100)
Delay (days)			
≤5	11 (85)	5 (42)	5 (83)
6–10	2 (15)	6 (50)	0
11–15	0	1 (8)	1 (17)
Chemotherapy			
No. of cycles			
4	6 (46)	6 (50)	4 (67)
3	6 (46)	4 (33)	2 (33)
2	0	1 (8)	0
1	1 (8)	1 (8)	0
No. of VNR omissions			
0	10 (77)	7 (58)	2 (33)
1	2 (15)	4 (33)	3 (50)
2	0	0	1 (17)
3	1 (8)	1 (8)	0

Abbreviation: VNR = vinorelbine administered on Day 8.