乳癌治療における画像診断の役割－術前化学療法と画像診断－

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Current Status and Future of Diagnostic Breast Imaging Before and After Primary Chemotherapy

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Summary

Circumstances concerning the diagnosis and treatment of breast cancer have gone through considerable changes over the last few year. Surprising progress in diagnostic technique has been made, and various modalities have been put to effective use in actual clinical settings. In addition, treatment has gone from a time when only surgical management was performed to one which multiple therapies, like pre-and postoperative chemotherapy, hormone therapy, therapy with molecular targeted agents are performed; techniques like sentinel node biopsy has also become firmly established.

As treatment protocols for breast cancer patients have advanced, the purposes of breast imaging have changed from simply diagnostic use to evaluation of cancer spread and predicting the effect of primary therapy.

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はじめに

近年の乳癌診療における画像診断と薬物療法の進歩は目ざましいものがある。それに伴い乳癌の局所療法も変化してきている。乳癌の手術の縮小化には、詳細な術前の画像診断が不可欠である。乳房温存療法における病変の拡がり診断やセンチネルリンパ節生検の適応を決める際の腋窩リンパ節の転移診断などである。また一方、術前薬物の導入により乳房温存療法などの縮小手術の適応が早期乳癌ばかりでなく、術前薬物療法の効果が認められた症例にまで広がりつつある。画像診断も術前薬物療法の抗腫瘍効果判定や効果予測にまで、その用途が広がりつつある。乳癌治療における術前薬物療法の主な目的は、① 使用薬剤の感受性の把握、② 予後の予測(pCR、n0症例)、③ 乳房温存率の向上が挙げられる。さらにpCRに到達した症例に関しては、非手術の可能性が出てくる。そこで術前の画像診断にて原発巣の腫瘍量および分布を把握しておくことと、その治療中における経時的変化を客観的に評価しておくことが重要である。自身の研究課題でもある術前化学療法後のセンチネルリンパ節生検の適応に関する研究においても、治療前の画像診断にて転移したリンパ節の所在やリンパ流を正確に把握しておくことが重要である。

術前薬物療法と画像診断による効果判定における諸問題

従来、術前化学療法は切除不能な局所進行性乳癌に対して行われ、切除可能にすることを主目的としてきた。その後、術前化学療法を手術可能な乳癌に対してまで適応を広げるにあたり、最も重要なエビデンスを生み出した臨床試験はNSABP B-18である。癌細胞の発生から増殖、進展という経過において、手術の前後どちらかにAC(アドリアマイシン + シクロフォスファミド)4コースの化学療法が行われれば、健存率、生存率ともに変わりがなかったというデータが報告された[1,2]。以後、① 使用薬剤の感受性の把握、② 予後の予測(pCR、n0症例)、③ 乳房温存率の向上を目指して手術可能な乳癌にまで術前薬物療法が標準的に使用されるようになる。ここで留意しなけらばならないのが、この試験の対象に比較的早期の乳癌も含まれており、乳房温存率は術後化学

日獨医報　第54巻 第2号 136-142 (2009)

表1　当院における術前化学療法レジメンの変遷

Regimen	Treatment period	Number of patients
ADM (50mg/m²), DTX (60mg/m²) × 4 (AT)	1998.5-2002.2	144
ADM (50mg/m²), DTX (60mg/m²) × 2, PTX (80mg/m²) ×12 (ATT)	2002.3-2002.8	24
PTX (80mg/m²) × 12 (wPTX)	2002.7-2006.2	18
ADM (50mg/m²), CPA (600mg/m²) × 4 PTX (80mg/m²) ×12 (ACT)	2002.9-2006.2	75
5FU (500mg/m²), EPI (100mg/m²), CPA (500mg/m²) × 4, PTX (80mg/m²) ×12 (CEF/PTX)	2003.1-2006.2	106

表2　術前化学療法施行患者の背景因子

- Number of patients　367
- Age　50 (26-78) y/o
- Menopausal status　Pre 187 (51%)　Post 180 (49%)
- Clinical tumor size before NAC　5.2 (2.5-12)cm
- Stage IIA/ IIB/ IIIA/ IIIB/ IIIC　123/ 113/ 68/ 58/ 5
- Tumor type : IDC/ ILC/ special type　333/ 15/ 19

療法群60%に対して術前化学療法群では68%と有意差は認めるものの大きな違いはない。術前化学療法により触診上計測が不能になったcCRは36%であったが、病理組織学的検査にて浸潤癌が消失したpCRはその1/4の9%にすぎなかった。すなわち、術前治療によってわかりづらい形態にて遺残する癌細胞の評価がより困難になってくる可能性がある。言い換えると、縮小手術の適応とする際には、治療前後の画像診断をもとに、かなり慎重に実施すべきである。実際、NSABP B-18の8年経過観察のデータでは術前化療群と術後化療群では局所再発率に有意差はなかったものの、9.9 vs 7.1%であり、術前化療群では癌細胞の遺残により十分に注意するような治療計画が必要とされている。さらにNSABP B-27では、術前AC4コースに続き、ドセタキセルを4コースを加えた場合、cCRは63.6%とさらに向上し、pCRは18.9%となり、ますます術前化学療法に伴う画像診断が重要となってきている。

当院での術前化学療法の成績と画像診断

当院では、1998年5月より腫瘍径(T)3cm以上あるいは、腋窩リンパ節転移を認める(N1以上)乳癌患者に対して、術前化学療法を院内臨床試験として実施してきた。化学療法のレジメンの変遷を表1に示す。現在のプロトコールは65歳未満の症例には、AC(FEC)×4サイクルとweekly PTX × 12サイクル、65歳以上の症例にはweekly PTXのみ12サイクル施行してしている。HER2陽性症例には、最近ではtrastuzumabを追加している。

2006年2月までの時点で367人に対して術前化学療法を施行してきたが、その成績について述べる。対象患者は表2に示すように、平均年齢が50歳、平均腫瘍径は5.2cmとなっている。腫瘍径に関しては、乳房温存療法ガイドラインを参考に、原則として温存療法の適応がない症例を術前化学療法の対象にしている。

術前化学療法の原発巣に対する効果を、術前化学療法導入前の1995年の臨床的腫瘍径3cm以上の症例と1998年

表3　病理学的腫瘍径より推測した術前化学療法による原発巣に対する効果
化学療法は腫瘍の分布を平均約3/4程度に縮小させる.

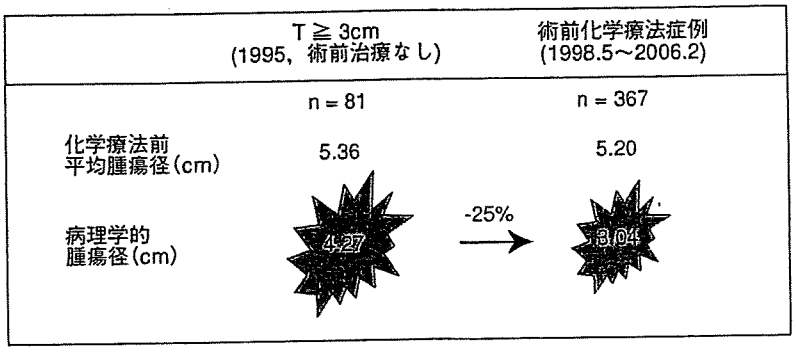


表4　術前化学療法レジメン別の治療効果

Regimen	cCR (%)	Grade 3(%)	pCR(%)
AT (n = 144)	15.3	5.5	8.3
ATT (n = 24)	16.7	12.5	20.8
wPTX (n = 18)	27.8	11.1	22.2
ACT (n = 75)	40	12	20
CEF/PTX (n = 106)	41.5	13.2	19.8
Total (n = 367)	28.6	9.8	15.5

表5　化学療法前後の各種画像診断による病変サイズ

	pPR	pCR
MMG		
(before NAC) (cm)	3.7	3.6
(after NAC)	1.5	1.5
US		
(before NAC) (cm)	3.8	3.5
(after NAC)	1.0	1.2
CT		
(before NAC) (cm)	4.5	4.2
(after NAC)	1.4	1.6
Pathology (cm)	2.2	0.0

5月以後の術前化学療法が施行された3cm以上の症例で比較したものを表3に示す。平均腫瘍径はほぼ同じだが、切除標本における病理学的腫瘍径は平均4.27cmから3.04cmに縮小している。平均して約25%、腫瘍径を減少させていることになる。当院では、時代、レジメンの変遷とともに、術前化学療法の効果も向上してきている。最近のレジメンでは、cCRが約40%、pCRが約20%、癌細胞が完全に消失しているGrade 3が12～13%となっている(表4)。このように、術前化学療法の効果とともに乳房温存療法の適応となりうる症例も増えるわけであるが、表5に示すようにpCRは各種画像診断を用いても判定することは不可能である。対象病変が、微小あるいは散在性に残るためPET-CTを用いても評価が不能である。当院の経験では、治療前の画像診断にて限局型であった症例は、求心性に縮小し、非限局型の症例は、散在性に癌細胞の遺残を認めることが多いことを報告してきた(図1)。当然のごとく、乳房温存療法における断端陽性率も非限局型の方が高い結果となる(表6)。

図1　画像診断上のタイプ(限局型／非限局型)と術前化学療法による原発巣の縮小のパターン
限局型は限局型に縮小し，非限局型は非限局型に縮小することが多い．

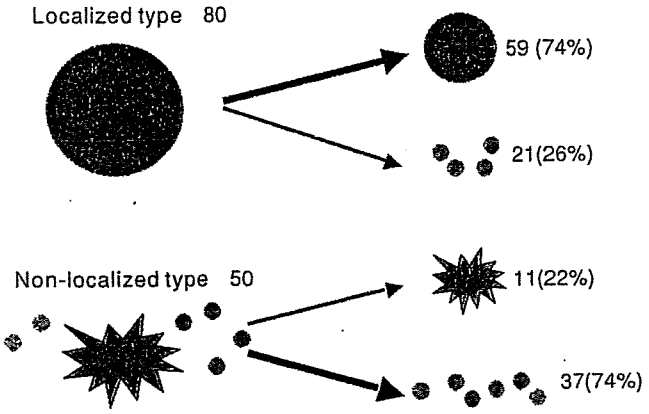


表6　画像診断病型と切除断端の状況

	Marginal status	
	Positive	Negative
Localized	3	30
Non-localized	7	3

表7　臨床的効果と病理学的効果の関係

	Clinical response	
Pathological response	cPR	cCR
0	6	0
1a/1b	141	37
2	42	44
3	11	24
Total	201	105

表8　臨床的効果別、乳房温存手術の成績

Clinical response	No. of pts.	BCT (%)	Positive margin (%)
NC/PD	61	18	36
PR	201	35	33
CR	105	56	15
Total	367	38	26

化学療法後に縮小効果を認めた症例が、乳房温存療法の適応になるわけであるが、画像診断も含めて本当にcCRなのか、cPRでよいのかの判定が重要である。表7に示すようにcCRと判定された症例は、2/3が病理診断にても効果が認められているが、cPR症例では、病理診断にて十分な効果が認められた症例は1/4にすぎない。したがって、化学療法効果の過大評価が、局所治療の失敗につながる危険性がある。表8に示すように術前化学療法後症例の当院の乳房温存率は全体で38%と決して高いものではないが、治療効果がPR以下の症例では、断端陽性率もPRで33%、NC/PDで36%と比較的高い結果となっている。一方、CRと判定された症例では、乳房温存率が56%であるにもかかわらず断端陽性率は15%と良好な治療成績となっている。術前化学療法後症例の乳房温存療法適応決定の際に画像診断上、① 治療前の腫瘍の分布にタイプ、② 治療後の効果判定においてnear pCRなのかどうかの判定(十分に化学療法が効果を示しているのかどうか？)が大切である。

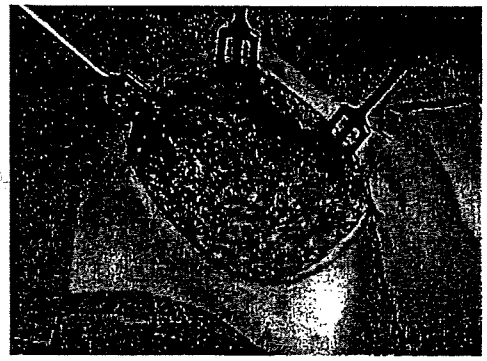
当院では、図2、3に示すように化学療法前の腫瘍の局在を化療前3D-CTや仰臥位3D-MRIの情報を手術中に投影して適切な切除部位の決定し乳房部分切除術を実施している。

術前化学療法後センチネルリンパ節生検法と画像診断

術前化学療法の導入により多くの症例でダウンステージ効果により乳房温存療法が可能になってきた。術前化学療法は従来、病期IIIB以上のいわゆる局所進行癌を対象に非切除例を切除可能にする目的で実施されてきたが、近年は病期IIAからIIIAの症例も術前化学療法の対

図2　術前化学療法著効例への工夫
A　化学療法前の3D-CTイメージ
B　術前に化学療法前3D-CTイメージを再現
術前化学療法後に乳房温存療法を予定する際には，化学療法前の画像情報も重要である．

A | B



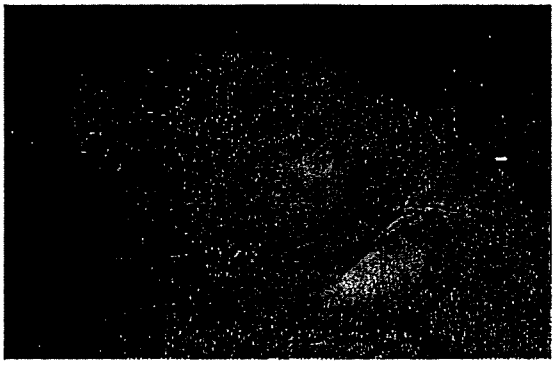


図3　術前化学療法後乳房温存手術の流れ
A　化学療法前の腫瘍のイメージを術野に再現
B　皮弁形成
C　乳房温存手術後イメージ
本症例は画像診断上もCRとなり，化学療法前のCTの情報をもとに乳房温存手術を実施した．

A | B
C

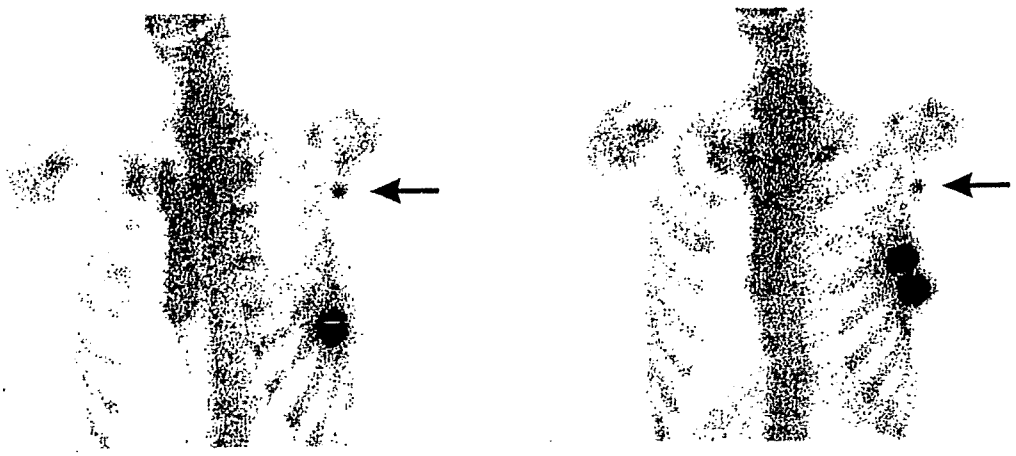


図4　化学療法前後のリンフォシンチグラム
A　化学療法前
B　化学療法後
化学療法の効果にかかわらず腋窩にセンチネルリンパ節が描出される.

象とし、原発が巣縮小した結果、多くの症例で乳房温存療法が可能となっている。これらの効果は、原発巣ばかりではなく当然、腋窩リンパ節転移巣にも確認されている。アンスラサイクリン系を含む術前化学療法では、腋窩リンパ節転移を約30％減じ[2]、さらにタキサン系を加えたレジメンでは約40％減ずると報告されている[3,4]。当院では1998～2005年まで約360例の乳癌症例に術前化学療法を実施してきた。術前化学療法の原発巣における効果は、約85％以上の症例がPRであった。約25％の症例は原発巣がCRとなったが、これらの症例の腋窩リンパ節転移陽性率は25％で、早期乳癌のそれとほぼ同程度まで低下していることが確認された。このような術前化学療法が著効した症例に対して早期乳癌と同様にセンチネルリンパ節生検を実施し、腋窩郭清を省略することが可能かどうかを明らかにすることは非常に重要な課題である。

術前化学療法後のセンチネルリンパ節生検に関してはいまだ十分なエビデンスは得られていない。これまでの報告例はいずれも単一施設で少数例の結果であり大規模な臨床試験は行われていない。早期乳癌症例に対するセンチネルリンパ節生検と比較すると、術前化学療法後の症例の問題点は、①腫瘍径の大きな症例が対象になる。②腋窩リンパ節転移の存在する、または存在した症例がより多く含まれる、③術前化学療法が腫瘍－リンパ管－リンパ節の流れに影響を与える可能性がある、④術前化学療法は転移陽性だったセンチネルリンパ節とノンセンチネルリンパ節に同程度の効果があるのか、⑤術前化学療法後のn0の意義がまだ明らかになっていない、などが挙げられる。これらの要因が術前化学療法のセンチネルリンパ節生検の妥当性を検証するうえで問題点となってきた。

一方、術前化学療法後の腋窩リンパ節の画像診断による転移診断は、さらに困難であると容易に察せられる。必然的に侵襲的な手法であるセンチネルリンパ節生検法の介入が必要となってくる。しかし、③の問題が解決されないかぎり手技としてその安全性は担保されないことになる。センチネルリンパ節生検前に実施されるリンフォシンチグラムでは、化療前後でも、多くの症例が腋窩のホットスポットとしてセンチネルリンパ節を同定することができる(図4)。これに同時に撮像したCT画像を一致させ解剖学的な局在を明らかにする研究を実施した(図5)。

化学療法前後の3D SPECT-CTにて描出されるセンチネルリンパ節の局在が一致することを補助にセンチネルリンパ節生検を実施することにより、安全性の高い試験が可能となっている。

おわりに

今後、術前薬物療法は進化していくとともに、その適応はさらに拡大していくと考えられ、適切な画像診断と病理学的判定を相互に照らし合わせて解析したうえで、

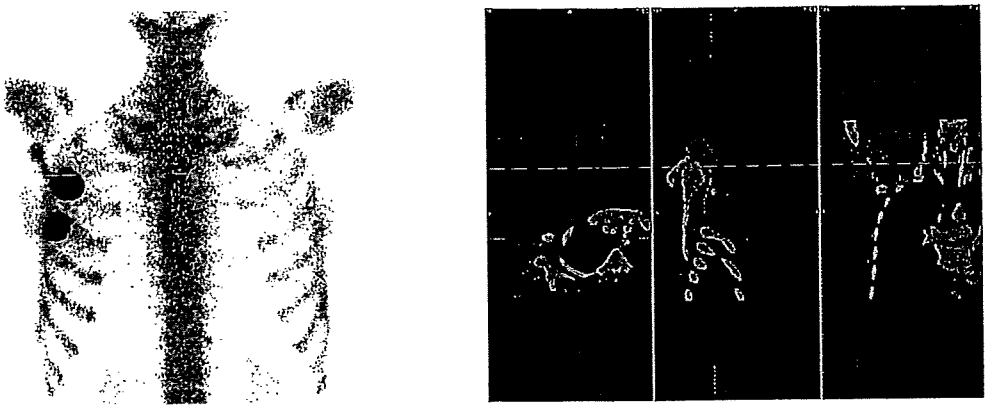


図5　センチネルリンパ節の解剖学的局在診断
リンフォシンチグラムとCTフュージョン画像を得ることによりセンチネルリンパ節の解剖学的局在はより明らかになる.

新たな薬物療法後の乳癌画像診断基準が必要である。そのうえで、より精度の高い治療効果判定がなされ、さらなる低侵襲治療、非外科治療が可能になるものと考える。

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手術症例報告

若年男性乳癌の1例

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はじめに

男性に発生する乳癌は，全乳癌の1%以下で比較的まれな疾患である。女性に比べて平均年齢は高い，予後は不良であることが多い，ホルモンレセプターの陽性率が高いなどとされている。今回若年の男性乳癌を経験したので文献的考察を加えて報告する。

I. 症　例

患　者：31歳，男性

既往歴：特記すべきことなし。

家族歴：父が肺癌

現病歴：2〜3年前より右乳房腫瘤を自覚。増大傾向にあるため，近医受診。右乳房E領域に腫瘤を認め，FNA施行し，class Vと診断された。2008年3月19日当院紹介受診となった。

現　症：右乳房E領域に3.5×3.0 cm大の硬い腫瘤を触知。乳頭分泌（-），乳頭変化（-），皮膚変化（-），女性化乳房（-），腋窩リンパ節（-）。

血液検査所見：血算・生化学検査で異常数値はなかった E2<10.0（19.0〜51.0 pg/ml）。

腫瘍マーカー：CEA 1.0 ng/dl（<5.0 ng/ml），CA15-3 10 U/ml（<28 U/ml），ST439 <1.0 U/ml（<4.5 U/ml）。

画像所見：

マンモグラフィ：右乳房CD〜E領域に4.2×2.8 cm大の高濃度腫瘤を認める。不整形〜分葉状で，境界は一部で明瞭であるがほぼ不明瞭，石灰化は認めなかった（図1）。

乳腺超音波：右E領域乳頭直下に4.1×2.7×2.6 cm大の不整形〜分葉状，境界明瞭粗造な低エコー腫瘤を認めた。皮膚直下から大胸筋直上まで存在する。8 mm大の腋窩リンパ節を認めたが，反応性腫大を疑った（図2a）。

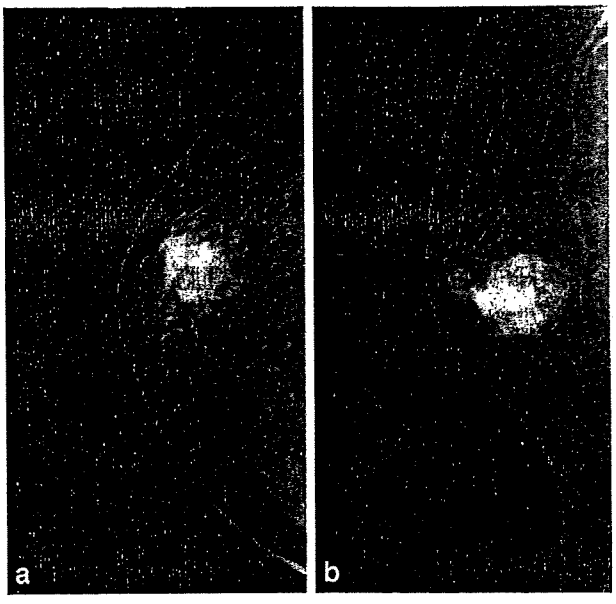

図1　マンモグラフィ
右乳房CD〜E領域に4.2×2.8 cm大の不整形〜分葉状高濃度腫瘤を認めた。
a) R-ML
b) R-CC

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key words：男性乳癌，内分泌療法，予後

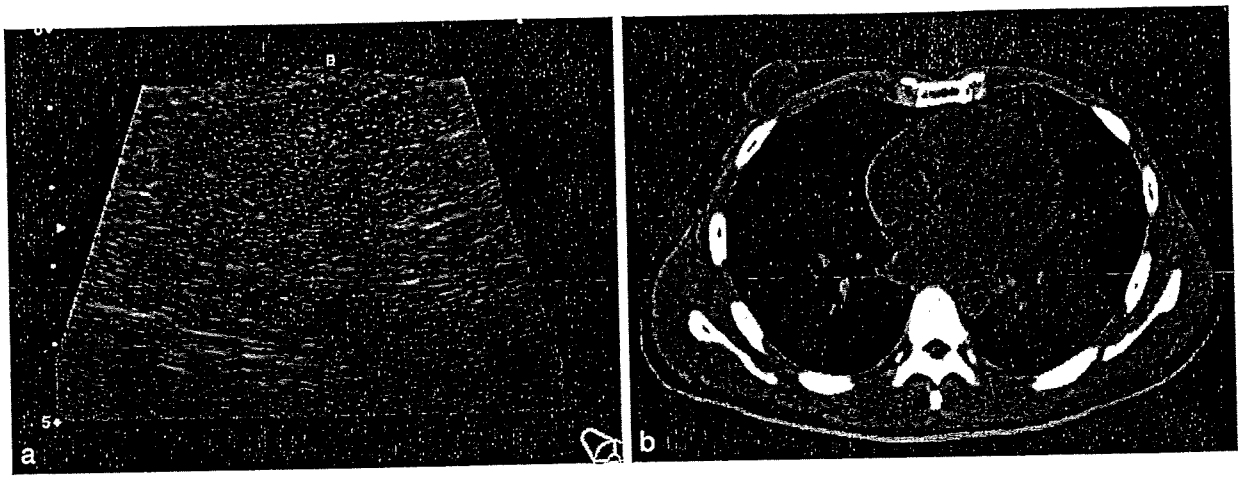

図 2
a）乳房超音波検査：右乳頭直下に 4.1×2.7×2.6 cm 大の不整形～分葉状低エコー腫瘤を認めた。
b）乳腺 CT：右乳頭直下に 3.5 cm 大の境界明瞭な腫瘤を認めた。

CT：右乳頭直下に 3.5 cm 大の境界明瞭で造影効果のある腫瘤を認めた。皮膚と大胸筋に接していた。リンパ節腫大は認めなかった（図 2b）。

針生検：浸潤性乳管癌（充実腺管癌）であり，腫瘍細胞は大小不整形であった。腫瘍内には豊富な繊維性間質も認められた。

手術所見：2008 年 5 月 1 日右乳癌（E, cT2N0M0；stage II A）の診断で乳房全摘＋センチネルリンパ節生検を施行した。術中迅速診断でセンチネルリンパ節陰性であったため，腋窩郭清は省略した。

病理肉眼所見：乳頭直下に 4.0×3.4×2.5 cm の灰白色調，境界明瞭な腫瘤性病変を認めた。

病理組織所見：明瞭な核小体をもつ類円形核と淡好酸性胞体を有する腫瘍細胞が，充実性の癌胞巣を形成し，胞巣間に線維化を伴いながら限局性に増殖していた。胞巣中心部に壊死を散見した。一部では腫瘍が索状に線維性間質に浸潤する硬癌の成分もみられた。腫瘍細胞の核異型度は中等度で，核分裂像を中等度の頻度で認めた（図 3）。ER，PgR は強陽性，HER2 は score 0 であった。

術後診断：浸潤性乳管癌（充実腺管癌），浸潤径 3.0×2.2 cm, G2, NG2, s, ly-, v-,n 0/4, ER 3+, PgR 3+, HER2（0）

術後経過：タモキシフェン投与中である。

II. 考　察

男性乳癌は比較的まれな疾患で，全乳癌に占める割合は 1％以下と報告されている。患者の平均年齢は約 60 歳で，女性乳癌の 40 歳代より高くなっている。伊藤らは本邦の文献的検索では，30 歳代以下の男性乳癌は 15 例と報告している[1]。

遺伝性に関しては，乳癌多発家系内に男性乳癌も発生する家系があることが報告されており，多田らは男性乳癌の発生がみられた 9 家系中 5 家系は第 1 度近親者間であったとしている[2]。

当院の 1962～2008 年 5 月までの全乳癌手術数 11,105 例のうち，男性乳癌は 45 例（0.45％），女性乳癌は 111,060 例であった。男性乳癌症例の年齢の中央値は 64 歳，女性乳癌症例は 55 歳で，男性乳癌の年齢は高い傾向にあった。本症例は当院の男性乳癌症例で最年少であった。乳癌家族歴を有するものは，男性乳癌 5/45 例（11.1％），女性乳癌 1,313/11,060 例（11.9％）で有意差は認めなかった。重複癌に関しては，男性乳癌 11/45 例（24.4％），女性乳癌 402/11,060 例（3.6％）で，統計学的に男性乳癌に多かった（$p < 0.0001$）。重複癌の内訳は，胃癌がもっとも多く，肺癌，前立腺癌の順であった（表 1）。

術式は，従来定型的乳房切除術が施行されて

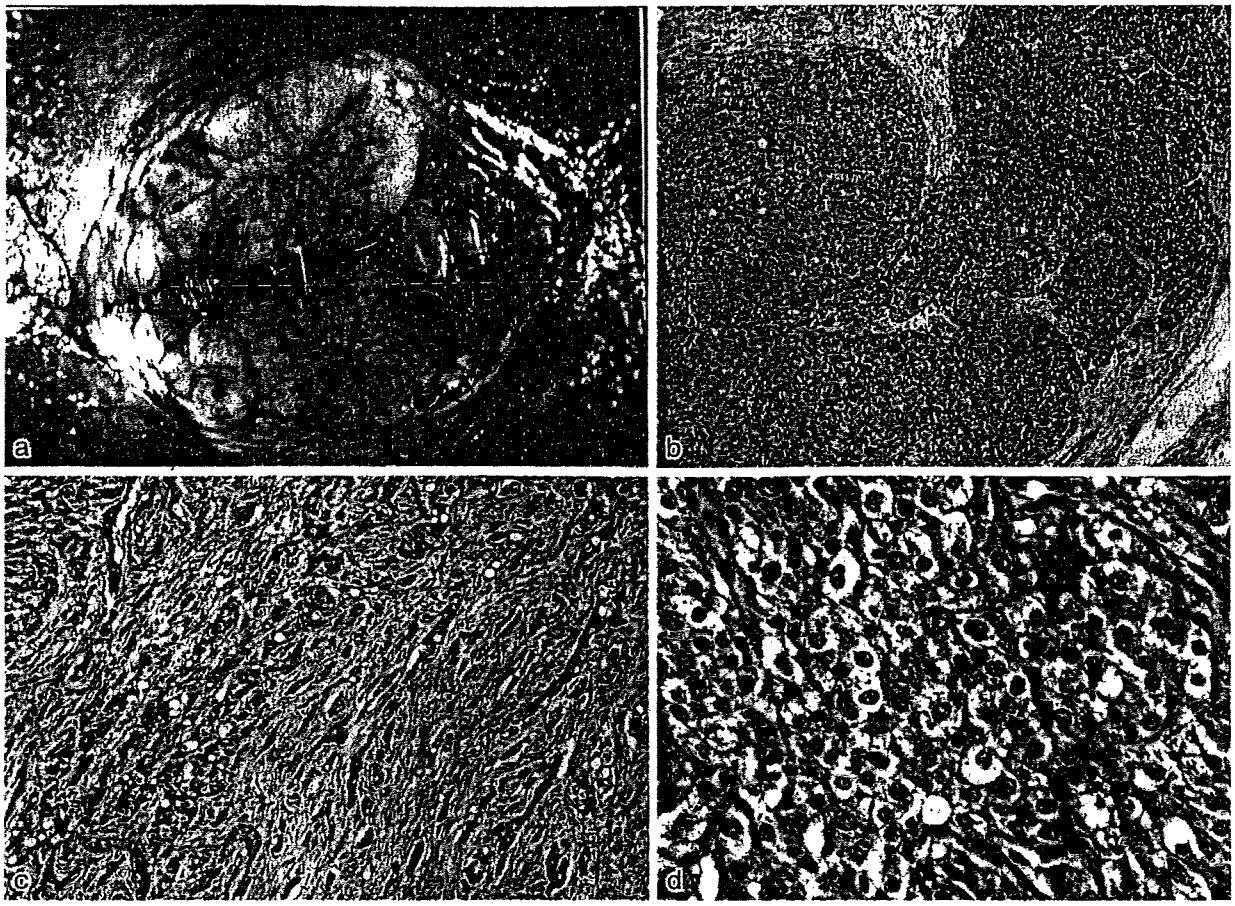

図 3　病理所見
a）4.0×3.4×2.5 cm の灰白色調，境界明瞭な腫瘤性病変を認めた（手術標本）。
b）充実性癌胞巣形成（HE, ×40）。
c）一部硬癌成分も認めた（HE, ×100）。
d）明瞭な核小体をもつ類円形核と淡好酸性胞体を有する腫瘍細胞（HE, ×400）。

表 1

a)

	男　性	女　性	p 値
症例数	45 例（0.4%）	11,060 例	
年齢（中央値）	64 歳	55 歳	
乳癌家族歴	5 例（11.1%）	1,313 例（11.9%）	p＝NS
重複癌	11 例（24.4%）	402 例（3.6%）	p＝＜0.0001

a）1962 ～ 2008 年 5 月までの全乳癌手術数 11,105 例
b）重複癌の内訳

b)

臓　器	延べ数
胃	4
肺	3
前立腺	2
大腸	1
後口蓋	1
不明	3

きたが，1991 年以降は胸筋温存乳房切除が多く，欧米では単純乳房切除も行われている[3)4)]。最近では男性乳癌に対するセンチネルリンパ節生検の有用性も示されてきている[5)]。本症例は臨床的にリンパ節転移を認めず，女性乳癌に準じてセンチネルリンパ節生検を行い，転移陰性であったことから，腋窩郭清は省略した。

男性乳癌の特徴として女性乳癌の ER および PgR 陽性率は各々 40～60%，25～40%であるのと比較し，男性乳癌のホルモンレセプター陽性率は高いとする報告が多い。泉雄らの集計によると，ER 陽性は 30/30 例（83.3%），PgR 陽性は 23/28 例（82.1%）であった[6)]。

当院の乳癌症例で，ホルモンレセプター，

HER2 scoreが評価されているのは男性乳癌17例，女性乳癌3276例で，ER1＋，PgR1＋，HER2 score 2＋（FISH未施行を含む）を陽性とした。ER陽性率は男性乳癌で14/17例（82.4％），女性乳癌で2,116/3,276例（64.5％），PgR陽性率は男性乳癌11/17例（64.7％），女性乳癌1,738/3,276例（53.1％），HER2陽性率は男性乳癌1/17例（5.9％），女性乳癌607/3,276例（18.5％），triple negativeは男性乳癌2/17例（11.8％），女性乳癌389/3,276例（11.9％）であった。ER陽性率とHER2陽性率は男性乳癌で有意に多かった（それぞれ$p<0.0001$，$p=0.04$）。PgR陽性率は統計学的には男性乳癌と女性乳癌で有意差は認めなかった（表2）。

男性乳癌の術後補助療法に関しては，女性乳癌と男性乳癌で治療反応性が異なるというエビデンスはないため，女性乳癌と同様に推奨されている。ホルモンレセプター陽性率が高いため，内分泌療法に対する奏功率が高い。1980年代までは睾丸摘除術の報告も多いが，現在ではホルモン感受性乳癌に対してはタモキシフェンが多く使用されている[7]。アロマターゼ阻害剤については報告例が少ない。リンパ節転移陽性例やホルモン感受性のない乳癌では化学療法が推奨されている。

男性乳癌は解剖学的に局所進展やリンパ節転移を来しやすいため，進行例が多く，予後不良とされてきた。1970年代までの報告では5年生存率は50％前後とされてきた。しかし，1980年代以降では，5年生存率は80％前後であり[8][9]，10年生存率も60％を超す報告もあり[9]，女性と比べて予後の差はないことが明らかにされてきている。

当院の男性乳癌の10年生存率は女性に比べて有意に予後不良であった（$p=0.03$）（図4a）。予後不良原因として，男性乳癌の平均年齢は63歳で女性より高いことから，死亡数が多い可能性や，2000年以前の症例ではホルモンレセプターを測定していない例も多く，適切な補

表 2　男性乳癌と女性乳癌の免疫染色の比較

	男性 n=17	女性 n=3276	p値
ER陽性	14例 (82.4％)	2,116例 (64.5％)	$p<0.0001$
PgR陽性	11例 (64.7％)	1,738例 (53.1％)	$p=0.3369$
HER2陽性	1例 (5.9％)	607例 (18.5％)	$p=0.0406$
Triple negative	2例 (11.8％)	389例 (11.9％)	$p=0.905$

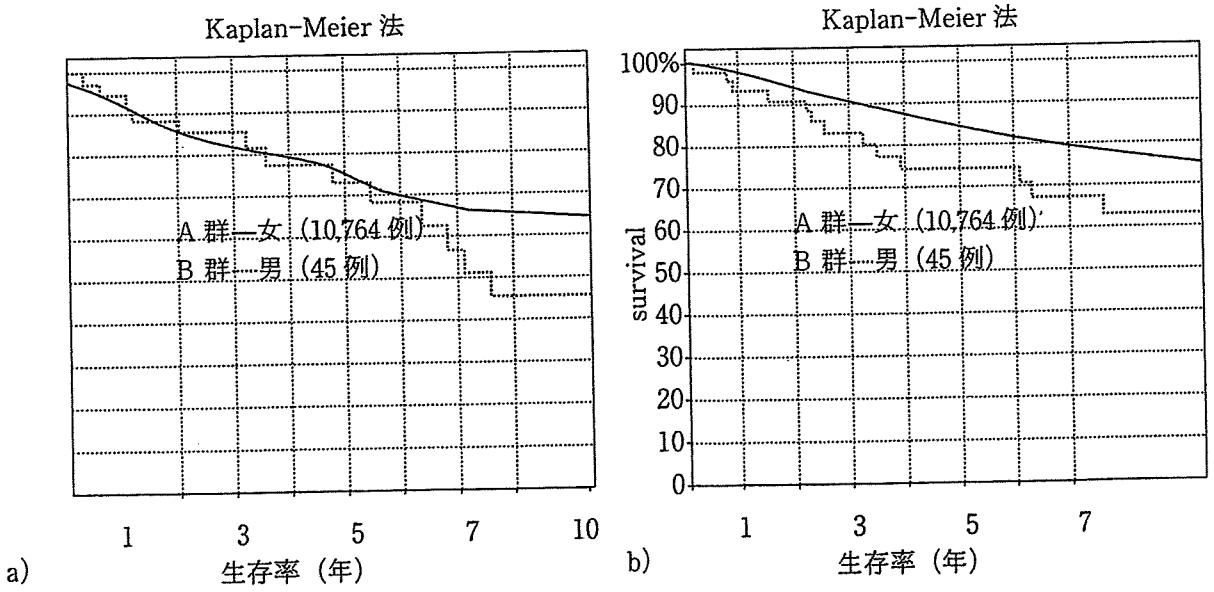

図 4

a）10年生存率：男性乳癌は女性乳癌に比べて統計学的に有意に予後不良であった（$p=0.03$）。

b）10年無再発生存率：男性乳癌と女性乳癌では有意差は認めなかった。

助療法ができなかった可能性が考えられる。さらに，重複癌が多いことも生存率が低くなった一因になっているかもしれない。

また，無再発生存率は統計学的な有意差は認めなかったが，5年以降より男性で低くなる傾向があり（図4b），晩期に再発する可能性があることが予測される。本症例は若年であることから，長期の経過観察が必要になると考えられる。

まとめ

1）男性乳癌の年齢の中央値は64歳であり，女性乳癌の55歳と比べて10歳高かった。

2）ER陽性率は82.4%で女性乳癌より有意に高く，PgR陽性率も64.7%と高い傾向にあった。

3）10年生存率は女性乳癌と比べて有意に不良であった。10年無再発生存率では有意差はみられなかった。

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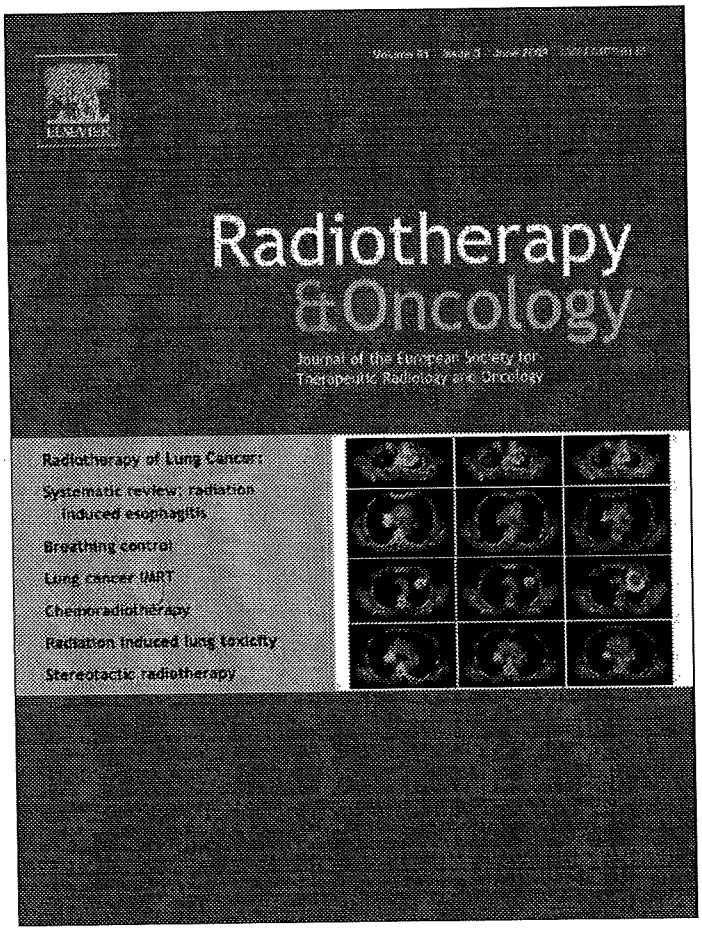

Radiotherapy and Oncology 91 (2009) 433–437

Contents lists available at ScienceDirect

Radiotherapy and Oncology

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Lung cancer RT

Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses

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ARTICLE INFO

Article history:
Received 3 October 2008
Received in revised form 29 December 2008
Accepted 30 December 2008
Available online 21 January 2009

Keywords:
Chemoradiotherapy
Elective nodal failure
Elective nodal irradiation
Non-small-cell lung carcinoma
Radiotherapy

ABSTRACT

Introduction: The role of elective nodal irradiation of non-small-cell lung cancer (NSCLC) patients treated with radiotherapy remains unclear. We investigated the significance of treating clinically uninvolved lymph nodes by retrospectively analyzing the relationship between loco-regional failure and the irradiated volume.

Methods: Between 1998 and 2003, patients with IA–IIIB NSCLC were treated with radiotherapy. The eligibility criteria for this study were an irradiation dose of 60 Gy or more and a clinical response better than stable disease. Typical radiotherapy consisted of 40 Gy/20 fr to the tumor volumes (clinical target volume of the primary tumor [CTVp], of the metastatic lymph nodes [CTVn], and of the subclinical nodal region [CTVs]), followed by off-cord boost to CTVp+n to a total dose 60–68 Gy/30–34 fr. The relationship between the sites of recurrence and irradiated volumes was analyzed.

Results: A total of 127 patients fulfilled the eligibility criteria. Their median overall and progression-free survival times were 23.5 (range, 4.2–109.7) and 9.0 months (2.2–109.7), respectively. At a median follow-up time of 50.5 months (range, 14.2–83.0) for the surviving patients, the first treatment failure was observed in 95 patients (loco-regional; 41, distant; 42, both; 12). Among the patients with loco-regional failure, in-field recurrence occurred in 38 patients, and four CTVs recurrences associated with CTVp+n failure were observed. No isolated recurrence in CTVs was observed.

Conclusions: In-field loco-regional failure, as well as distant metastasis, was a major type of failure, and there was no isolated elective nodal failure. Radiation volume adequacy did not seem to affect elective nodal failure.

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Radiation therapy is an integral component of the multi-modal treatment of non-small-cell lung cancer (NSCLC). Recent phase III studies have demonstrated that concomitant chemoradiotherapy improves survival, and this has resulted in the general acceptance of concurrent chemoradiotherapy as one of the standard treatments for locally advanced NSCLC [1]. Despite the improved survival, however, most patients die from their disease as a result of local or distant failure.

Local failure remains a major challenge when treating NSCLC with radiotherapy. A number of studies of dose escalation to the gross tumor volume (GTV) have been conducted as a means of improving local control [2–5]. The conventional radiation fields for NSCLC typically encompass the entire mediastinum and ipsilateral hilum (elective nodal region) to deliver a dose of 40 Gy, even without evidence of disease in these areas, followed by a 20 Gy boost to the GTV. However, the conventional treatment has added considerable morbidity and can limit the dose escalation. In phase I–II dose escalation studies, there is a trend toward omitting the practice of elective nodal irradiation (ENI) after their experiences with toxicity, which is not based on direct evidence [2–5]. According to those studies, omitting ENI has not sacrificed treatment outcomes so far. They also analyzed patterns of recurrence in relation to irradiated volume in a dose escalation setting [6].

By contrast, the current literature provides limited information regarding patterns of failure when conventional fields and doses are used [7,8]. Since it is important to know whether loco-regional failure is within or outside the irradiation field, we retrospectively analyzed patterns of failure after radiation therapy for NSCLC, especially in regard to the relationship between local failure and irradiated volume.

Methods and materials

Patients

Between January 1998 and March 2003, 263 patients with newly diagnosed NSCLC were treated with thoracic radiation therapy,

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doi:10.1016/j.radonc.2008.12.013

with or without chemotherapy, at the National Cancer Center Hospital. All tumors were cytologically or histologically confirmed NSCLC. Patients' disease was staged by the tumor-node-metastasis (TNM) staging system (UICC, version 6, 2002). The diagnostic workup included a bone scan, brain scan by computed tomography (CT) or magnetic resonance imaging, CT scan of the chest, and CT or ultrasound imaging of the abdomen. The criteria for inclusion in this study were irradiation with a dose of 60 Gy or more as a part of the initial treatment and a clinical response better than stable disease. After excluding patients with metastatic disease, whose primary tumor was located in the apex of the lung (superior sulcus), and whose post-treatment evaluation was inadequate, the remaining 127 patients served as the subjects of the analysis.

Details of treatment

Radiotherapy

Gross tumor volume (GTV) was defined as the demonstrable extent of the primary tumor and the metastatic lymph nodes, GTVp and GTVn, respectively. GTVn was defined as abnormally enlarged regional lymph nodes measuring over 1.0 cm along their short axis. Clinical target volume (CTV) consisted of the adjacent mediastinum and ipsilateral hilum (CTV of the subclinical nodal region, CTVs) as well as CTVp and CTVn which were assumed to be equal to GTVp and GTVn, respectively. A planning target volume (PTV) margin of 1–1.5 cm was drawn around each CTV.

External-beam radiotherapy with a 6, 10, or 15 MV photon beam was delivered using a linear accelerator. A majority of the patients were treated with anteroposterior opposing fields encompassing CTV to a dose of 40 Gy/20 fractions (2 Gy per fraction, 5 days per week), followed by an off-cord boost to the GTV by oblique opposing fields, to a total dose of 60–68 Gy/30–34 fractions. No attempt was made to encompass the supraclavicular areas in most patients; the supraclavicular areas were treated only electively. Initially, treatment planning was performed by using an X-ray simulator for the anteroposterior fields and a CT-port for the oblique opposing fields, but after the end of 1999, most treatment planning, especially to define the off-cord boost, was performed using a CT-based planning system (FOCUS, Computed Medical Systems).

The dose to the spinal cord was limited to 45–50 Gy. The size of the treatment fields was adjusted so that it did not exceed half of the hemithorax before introducing CT-based planning system, or so that the volume of normal lung tissue receiving a dose over 20 Gy would be less than 40%.

Chemotherapy

Systemic chemotherapy was used in 87 patients (68.5%), and the majority of the patients received platinum-based chemotherapy sequentially or concurrently with the radiation therapy. One of the representative regimens was 2–3 cycles of cisplatin 80 mg/sqm on day 1 and vinorelbine 25 mg/sqm on days 1 and 8 (or vindesine 3 mg/sqm on days 1, 8, and 15) in 21–28 days. The second most common regimen was cisplatin 80 mg/sqm on day 1, vindesine 3 mg/sqm on days 1 and 8, and mitomycin C 8 mg/sqm on day 1, in 21–28 days. The other regimens are summarized in Table 1.

Evaluation

Patients were followed at 4- to 6-week intervals for 6 months after treatment and at 3- to 6-month intervals thereafter. Chest X-ray and laboratory workups were performed at each post-treatment visit. Unless there were changes in the chest X-ray or in symptoms, a CT scan was performed about 2–3 months after the treatment for the assessment of the treatment response, and every 6–12 months thereafter. Follow-up information was obtained from the medical charts and death certificates.

Table 1
Baseline patient characteristics.

Characteristics	Patients	(%)
Median age (yr)	65 (36–83)	
Gender		
Male	106	83
Female	21	17
Performance status (WHO)		
0	12	9
1	109	86
2	6	5
Stage		
I (A/B)	5(1/4)	4
II (A/B)	12(3/9)	9
III (A/B)	110(59/51)	87
Histology		
Adenocarcinoma	64	50
Squamous cell carcinoma	39	31
Large cell carcinoma	4	3
NSCLC (not otherwise specified)	20	16
Chemotherapy (concurrent/sequential)	87(63/24)	69
Chemotherapy regimens		
Cisplatin + vindesine or vinorelbine	48	55
Carboplatin + paclitaxel	12	14
MVP (cisplatin + vindesine + mitomycin)	12	14
Nedaplatin or nedaplatin + paclitaxel	11	13
Others	4	5

When evaluating overall survival, an event was defined as death from any cause. When evaluating progression-free survival, an event was defined as documented tumor progression (loco-regional or distant) or death from any cause. Local or loco-regional failure was judged to have occurred if there was radiographic evidence of progressive disease. Absence of progression of residual disease for more than 6 months following treatment was considered evidence of loco-regional control. A recurrence in supraclavicular nodes was considered regional failure, not an elective nodal failure, because the supraclavicular regions are not routinely included within the radiation fields in our practice. Treatment failure was not always confirmed histologically. Elective nodal failure (ENF) was defined as recurrence in CTVs without evidence of local failure, as the first event or even after distant metastasis.

The adequacy of field borders was assessed in terms of CTVs coverage and PTV margin in patients with loco-regional failure. The failure patterns were analyzed to distinguish in-field recurrence from out-of-field recurrence; "in-field" included CTVs as well as CTVp and CTVn.

The Kaplan–Meier method was used from the start of the treatment to calculate the overall survival and progression-free survival of all the 127 patients.

Results

A total of 127 patients, median age 65 years (range, 36–83), met the criteria for evaluation in this study. The majority of patients had stage IIIA ($n = 59$) or IIIB ($n = 51$) disease. Other baseline characteristics of the patients and details of their treatment are summarized in Table 1.

At a median follow-up time of 50.5 months (range, 14.2–83.0) of the surviving patients, 95 had experienced treatment failure. Median survival time was 23.5 months (range, 4.2–109.7), and median time to progression was 9.0 months (range, 2.2–109.7). The 2-year cumulative survival rate and 2-year progression-free survival rate were 51.4% and 27.6%, respectively. The survival

curves are shown in Fig. 1. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Eighty-seven (69%) patients received chemotherapy concomitantly or sequentially with the radiotherapy. The overall survival time of the patients who received chemotherapy was 21.7 months (range, 7.6–33.9), as opposed to 19.1 months (range, 6.8–32.7) among those who did not receive chemotherapy, and the difference was not statistically significant ($p = 0.10$). There were no statistically significant differences in disease-free survival nor loco-regional control according to whether the patients had received chemotherapy. Concurrent use of chemoradiotherapy did not affect survival among the 87 patients who received chemotherapy (data not shown).

There were 53 patients with a first loco-regional failure, alone ($n = 41$) or with distant metastasis ($n = 12$), and the majority of the failures were in-field ($n = 38$, 72%). Nine (21%) patients had out-of-field recurrences in the form of supraclavicular node metastasis ($n = 5$) or pleural metastasis ($n = 4$), with or without local recurrence. There were no isolated ENFs (Table 2).

Four patients (7%) experienced nodal failure in CTVs simultaneously with local or distant failure. Three of them had received a prophylactic dose of 40 Gy to the CTVs, and the other had inadequate margin of the CTVs field. Other characteristics of these patients are shown in Table 3. There were no "marginal only" failures among in-field failures; all the failures at the field borders were associated with out-of-field failures.

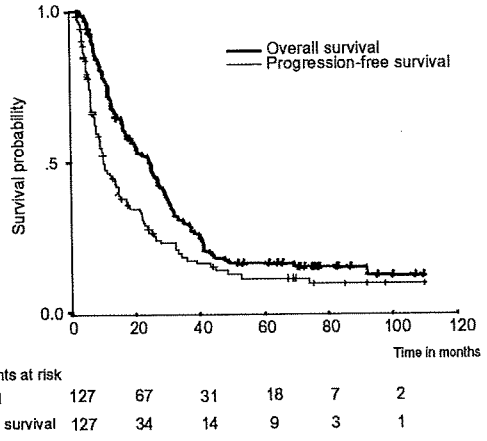

Fig. 1. Overall and progression-free survival curves of all the 127 patients. Patients with early progressions were excluded because of the criteria for inclusion in this study: a clinical response better than stable disease.

Table 2
Details of all the first failures.

Types of event	Patients	%
Loco-regional alone	41	43%
In-field		
CTVpn	30	
CTVpn + CTVs[a]	2	
In-field + out-of-field		
CTVpn + pleural effusion	2	
CTVpn + supraclavicular nodes	2	
Out-of-field		
Supraclavicular nodes	3	
Pleural effusion[b]	2	
Loco-regional + distant	12	13%
In-field + out-of-field		
CTVpn + CTVs	2	
Distant alone	42	44%
All events	95	

[a] One also had concurrent failure in the contralateral hilum.
[b] One also had concurrent supraclavicular recurrence.

Conventional X-ray simulation was performed in 8 (6%) patients, while 70 (55%) had CT-based simulation and remaining 49 (39%) had both (initially with X-ray simulation, followed by CT-based simulation for off-cord boost). A majority ($n = 122$, 96%) of the patients were treated with anteroposterior opposing fields as elective nodal irradiation, followed by oblique opposing fields to the total dose.

ENI was incomplete ($n = 12$) or not performed ($n = 6$) in 18 of the 53 patients with loco-regional failure because of diminished pulmonary function or deteriorated performance status. All the incomplete ENIs were due to insufficient CTVs coverage. In 12 of the 18 patients, the failure was in the tumor volume, in 3 patients it was in the pleura, and in 2 patients it was in the supraclavicular nodes. Only 1 patient had recurrence in both the tumor volume and the uninvolved nodal area.

Discussion

In this series of NSCLC cases treated with conventional fields and doses, the loco-regional failures after radiotherapy mainly occurred in the tumor volumes, and there were no isolated ENFs.

There are several possible reasons for these results. First, micrometastasis in the CTVs may have been controlled by prophylactic delivery of 40 Gy to the region, and depending on the location of the primary tumor, the sites of occult metastasis may often have received additional unintentional radiation doses. Kepka et al. reported an isolated ENF rate of 9% in 185 patients treated with the ENI using 3-dimensional conformal radiotherapy (3D-CRT). Their analysis showed that the ENF occurred more frequently in the regions that received under 40 Gy than in the regions that received higher doses (69% vs. 31%, respectively, $p = 0.04$) [7]. However, despite the same ENF rate of 9% in 1705 patients in the four trials conducted by the Radiation Therapy Oncology Group (RTOG), a retrospective evaluation of in-field progression revealed that neither in-field progression nor survival was affected by the adequacy of ENI [8]. Field adequacy did not have any negative impact on regional control in our series either (Tables 3).

Second, the amount of micrometastasis in unenlarged mediastinal regional nodes may have been small enough to be controlled by chemotherapy, which has been shown to have activity that reduces the incidence of distant micrometastasis in advanced NSCLC. However, the degree of systemic and local efficacy of chemotherapy did not reach statistical significance in our series, probably because of the small number of patients and their heterogeneity (data not shown).

Third, since the failure sites in the majority of patients were distant, they would have died of their disease before the ENF became apparent. As a result, the loco-regional failure rates may have been lower than their true values because we did not investigate regional sites once a patient developed distant metastasis.

The therapeutic significance of treating subclinical nodal regions during and after surgery for NSCLC has been questioned. Some studies have established the presence of considerable microscopic nodal disease in clinically uninvolved lymph nodes [9,10], but the role of mediastinal lymphadenectomy remains controversial and has been limited to the precise staging of the disease [11–13]. A study by Izbicki et al. which compared systemic mediastinal lymphadenectomy with mediastinal lymph node sampling showed that radical systemic mediastinal lymphadenectomy had no effect on the disease-free or overall survival of patients with limited nodal involvement [13,14]. The role of adjuvant radiotherapy after complete resection also remains unclear [15–17]. A systemic

Table 3
Patients with CTVs failure.

	Patient #1	Patient #2	Patient #3	Patient #4
Age (yr)/Sex	45/Female	74/Female	61/Male	78/Male
Reason for inoperability	Unresectable	Unresectable	Decreased pulmonary function	Unresectable, age
Stage	IIIA	IIIA	IIB	IIIB
Primary location	Left lower lobe	Right upper lobe	Right lower lobe	Left upper lobe
Histology	Adenocarcinoma	Adenocarcinoma	Squamous cell carcinoma	Adenocarcinoma
Chemotherapy	Yes	Yes	No	No
Response	Partial response	Partial response	Partial response	Partial response
Site of first failure	Distant and loco-regional	Distant and loco-regional	Loco-regional	Loco-regional
Field border adequacy	Yes	Yes	No	Yes
Dose to CTVs failure	40	40	0	40
Death	No	No	Yes	No

review and meta-analysis [18] showed that postoperative radiotherapy was detrimental to patients with early NSCLC, although there may have been some efficacy in patients with N2 tumors. These arguments also raise questions about the clear benefit of ENI in regard to survival.

In-field loco-regional failure was a major site of failure in the current study: all the recurrences in the CTVs were associated with failure in the gross tumor volume. Thus, more intensive treatment strategies are needed to enhance loco-regional control without sacrificing safety. One possible strategy is to reduce the ENI field in regard to the patients' risk factors while escalating the total dose. Such an attempt has already been made in regard to surgery: Asamura et al. retrospectively reviewed the prevalence of lymph node metastasis with respect to the location of the primary tumor or other characteristics to decide on the optimal lobe-specific extent of systematic lymph node dissection for NSCLC [19,20]. By using such predictors, including the location of the primary tumor, histology, or nodal stage [21–24], it is possible to identify the nodal areas at risk and to optimize the extent of ENI in radiation therapy as well. On the other hand, more precise diagnosis by novel technology, such as positron emission tomography [25], may enable the omission of ENI and avoid unnecessary irradiation to areas at low risk for subclinical disease.

In terms of the technical feasibility of dose escalation, Grills et al. found that intensity-modulated radiation therapy without ENI for NSCLC increased the deliverable mean target dose in node-positive patients by 25–30% over 3D-CRT and by 130–140% over traditional ENI [26].

Because omitting ENI is likely to leave microscopic disease untreated, there is concern that it may result in increased failure in these areas. However, the preliminary results of dose escalation trials have shown that isolated ENF outside the irradiated volume occurred in fewer than 6% of the cases and that omission of ENI did not seem to sacrifice outcome [2–5,27]. There is insufficient evidence to support the use of ENI for any patient with localized NSCLC (Stages I–III), irrespective of whether chemotherapy is administered [28]. There has been only one randomized trial that compared high-dose thoracic radiotherapy without ENI and standard dose radiotherapy with ENI, and it showed a survival benefit of high-dose thoracic radiotherapy without ENI [29]. One possible explanation for this finding is that incidental doses to elective nodal areas may contribute to the eradication of the subclinical disease. The pattern of ENF according to nodal regions was described by Rosenzweig et al., who implemented the use of involved-field radiation therapy with dose escalation in 524 patients [6]. Since the majority of the 42 ENFs that were observed occurred in the areas that received less than 45 Gy, the incidental doses to elective nodal areas may have been substantial despite the attempt not to treat these regions in their study. In addition, Zhao et al. reported that involved-field radiation therapy with a dose escalated to 70 Gy delivered a considerable dose to CTVs, and when the primary tumor was large or centrally located, the percentages of CTVs in the lower paratracheal region, subcarinal region and ipsilateral hilar region receiving over 40 Gy were 33%, 39%, and 98%, respectively [30].

Because of the retrospective nature of our study, no conclusions about the value of ENI for NSCLC can be drawn. However, the finding that in-field loco-regional failure, as well as distant metastasis, was a major type of failure with the standard field and dose of thoracic radiotherapy confirmed the need for more intensive treatment.

Further investigation to verify the true significance of ENI or to identify best candidates for ENI is necessary before it is abandoned in the context of dose escalation.

Conclusion

The loco-regional failures after radiotherapy in this series of NSCLC cases treated with conventional fields and doses mainly occurred in the tumor volumes, and there were no isolated ENFs. The results confirmed the need for more intense treatment to improve local control.

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Jpn J Clin Oncol 2009;39(11)707–712
doi:10.1093/jjco/hyp095

Gender Difference in Treatment Outcomes in Patients with Stage III Non-small Cell Lung Cancer Receiving Concurrent Chemoradiotherapy

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Received May 9, 2009; accepted July 8, 2009; published online August 19, 2009

Objective: To identify any gender differences in the outcomes of concurrent platinum-based chemotherapy and thoracic radiotherapy for unresectable stage III non-small cell lung cancer (NSCLC).
Methods: A comparative retrospective review of the clinical characteristics and treatment outcomes between female and male NSCLC patients receiving chemoradiotherapy.
Results: Of a total of 204 patients, 44 (22%) were females and 160 (78%) were males. There was no difference in age, body weight loss, performance status or disease stage between the sexes, whereas never-smokers and adenocarcinoma were more common in female patients (55% vs. 3%, $P < 0.001$, and 73% vs. 55%, $P = 0.034$, respectively). Full cycles of chemotherapy and radiotherapy at a total dose of 60 Gy were administered to ~70% and >80% of the patients, respectively, of both sexes. Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients. Severe esophagitis was encountered in <10% of the patients, irrespective of the sex. The response rate was higher in the female than in the male patients (93% vs. 79%, $P = 0.028$), but the median progression-free survival did not differ between the sexes. The median survival time in the female and male patients was 22.3 and 24.3 months, respectively ($P = 0.64$).
Conclusions: This study failed to show any gender differences in the survival or toxicity among patients treated by concurrent chemoradiotherapy. These results contrast with the better survival in female patients undergoing surgery for localized disease or chemotherapy for metastatic disease.

Key words: gender – female – non-small cell lung cancer – chemotherapy – radiotherapy

INTRODUCTION

Lung cancer in women differs from that in men with respect to its incidence, association with smoking, and histological distribution (1). Several epidemiological studies have shown that female smokers have a 1.5- to 3-fold higher risk of developing lung cancer than male smokers, suggesting that women may have an increased susceptibility to the carcinogens in tobacco. Never-smokers with lung cancer are more likely to be female than male, and in East Asian countries, as high as 70% of the women diagnosed with lung cancer have never smoked in their lives. Women are more likely to develop adenocarcinoma than squamous cell carcinoma, the latter being more common in men. This difference cannot be explained fully by differences in the smoking patterns, and potentially suggests basic differences in the etiology of lung cancer between the sexes (1).

Prospective cohort studies and a large population-based study have consistently shown that female gender is a favorable prognostic factor in patients with non-small cell lung cancer (NSCLC). These studies, however, included patients

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with all stages of cancer, and the therapies administered are not specified (2–4). The existence of a gender difference in survival remains controversial among patients with locally advanced NSCLC receiving radiation-based treatment. Some studies have shown better survival in females than in males (5–7), whereas others have shown no difference in survival between the sexes (8,9). Many patients in these studies, however, received radiotherapy alone, which is no longer the standard treatment for locally advanced disease. Furthermore, all but one of these studies included patients with stage I–II disease who were considered unsuitable for surgical treatment because of poor general condition. One study that addressed gender differences in unresectable stage III NSCLC patients treated by chemoradiotherapy showed a median survival time in women of 19.7 months and in men of 21.7 months ($P = 0.26$) (10). The objectives of this study were to compare the outcomes of concurrent chemoradiotherapy between female and male patients with stage III NSCLC.

PATIENTS AND METHODS

Study Population

Patients with unresectable stage III NSCLC who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital between 1994 and 2005 were eligible for this study. A total of 204 patients were identified. Patients treated by sequential chemotherapy and thoracic radiotherapy were excluded from this study, because we consider that the standard of care for unresectable stage III NSCLC without effusion is concurrent chemoradiotherapy, and sequential treatment is only given to patients in poor general condition or those with tumors too large for radiotherapy initially, which are expected to shrink sufficiently for radiotherapy after chemotherapy. All patients underwent a systematic pre-treatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, computed tomographic (CT) scans of the chest and abdomen, CT or magnetic resonance imaging of the brain, and bone scintigraphy. Chemotherapy consisted of cisplatin combined with either vinorelbine ($n = 125$), vindesine with or without mitomycin ($n = 46$), or other drugs ($n = 6$) repeated every 4 weeks, carboplatin and docetaxel ($n = 10$) administered weekly, and nedaplatin and paclitaxel administered every 4 weeks ($n = 17$).

A retrospective review of the medical charts of the patients was conducted to determine the gender, age, smoking history, body weight loss, performance status, clinical stage, histology, success of treatment delivery, incidence/severity of hematological toxicity and esophagitis, tumor responses, and survival parameters. The histological classification of the tumor was based on the criteria of the World Health Organization (11). Toxicity was graded according to the Common Terminology Criteria for Adverse Events v3.0. Objective tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (12).

Statistical Methods

The demographic, clinical and histopathologic characteristics were compared between the genders. The χ^2 and Mann–Whitney tests were used to evaluate the differences in the categorical and continuous variables, respectively. Overall survival was measured from the start of chemotherapy to death from any cause. For progression-free survival (PFS), both the first evidence of disease progression and death from any cause were counted as an event. A patient who did not develop any event at the last follow-up was censored at that time. Survival curves were calculated according to the Kaplan–Meier method. Cox's proportional hazard models were used to adjust for potential confounding factors such as tumor stage and performance status (13). The significance of P value was set to be <0.05. All of the above-mentioned analyses were performed using the Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Demographics

Of the 204 patients, 44 (22%) were females and 160 (78%) were males (Table 1). There were no differences in age, body weight loss or performance status between the sexes, whereas never-smokers were more common among female patients (55% vs. 3%, $P < 0.001$). Adenocarcinoma accounted for the main histological type in both sexes, but was more common in female patients (73% vs. 55%, $P = 0.034$). No difference in the distribution of the clinical stage was noted between the sexes.

Treatment Delivery

The delivery of chemoradiotherapy was good in both sexes. Three to four cycles of chemotherapy were administered in 68% of the female patients and 69% of the male patients. A total radiation dose of 60 Gy was given to 89% of the female patients and 86% of the male patients.

Toxicities

Grade 3–4 neutropenia was observed in 64% of the female patients and 63% of the male patients (Table 2). The frequency of febrile neutropenia was also the same between the sexes. Severe esophagitis was encountered in $<10\%$ of the patients, irrespective of the sex.

Treatment after Recurrence

The use of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) was evaluated in