解析においても結果が異なることもあり，またメタ解析に対する批判的見解もある[8]。単純に論文として公表されたデータをメタ解析として再解析した場合と，データの更新，除外症例の再検討を行った場合のメタ解析の結果が異なることが示されており，メタ解析であるからといって盲目的に真実として受け止めてしまうのは危険である。

C　後ろ向き研究

一般的には前向き試験ではないという理由から信頼性の低いデータと扱われる。しかし，「ランダム化しないとわからない」，「後ろ向き試験の結果だから信頼できない」と単純に軽視してはならない。自らが行ってきた臨床経験をデータとして診療録の中から収集し緻密に検討し，その中に内在する真実（または仮説）を見つけ出す作業は大変な労力ではあるが，それを見出した時の感動は経験した者にしかわからない。もちろん，後ろ向き研究には限界はある。しかし，倫理性や実現可能性の問題から臨床試験が組めない疾患も多く，後ろ向き研究の重要性は揺るがない。また，後ろ向き研究の中から生じてきた仮説を証明するために前向き試験がある。

D　医の倫理

ヘルシンキ宣言は医の倫理に関する貴重な提言をしている。ヘルシンキ宣言は時に単なるお題目のように考えられがちであるが，臨床試験を行うすべての参加者が精読すべきものである。診療の現場で患者の権利を無視した医療行為やプロトコール治療を時に目にすることがある。患者に悪いことをしようとして医療行為を行っている医療従事者はいないと思われる。しかし，新たな治療法を開発する際には，必要最低限の診療レベルと患者が望む医療を受ける権利とを確保しなくてはならないはずであるが，時にこの当たり前のことがなおざりにされる。患者には自分自身が治る権利があり，また自分自身が望む医療を受ける権利がある。新薬の開発に際しても，現時点では標準治療がなく，他に手だてがない患者においてまず行われるべきであり，臨床試験の第Ⅰ相試験で安全性と毒性の評価を，第Ⅱ相試験では有効性の初期評価（奏功率など）を，そして第Ⅲ相試験では標準治療との比較を行い，標準治療を決定していくこととなる。このようなステップを省略することや，標準治療が確立している疾患に対し新規治療を同意なしに試すようなことがあってはならない。このような行為は犯罪であることを認識すべきである。近年学会レベルでも第Ⅰ相試験，または第Ⅱ相試験と銘打った発表を目にすることがあるが，臨床試験を立案するに当たっては十分な勉強・研修が必須である[9]。臨床試験を実行するに当たっては参加施設全体のコンセンサスを得るために議論を繰り返し，評価・運営に当たっては安全性評価や質の管理を行う別組織による監視機構も重要となる。

E　エビデンスの臨床応用

症例報告より多数の症例数を集めた報告が，後ろ向き試験より前向き試験が，またシングルアームの臨床試験よりランダム化比較試験が信頼性が高いエビデンスとされる。多くの臨床試験は年齢や全身状態など試験参加に際しての患者の状態や疾患に関する適格条件を設けており，試験を確実に成功させるための仕組みがあり，また試験の倫理性を保つことにも役立っている。しかし，目の前の患者に臨床試験の結果から得られた知見を当てはめる際に，間違いが生じやすい。つまり，20歳から65歳までで全身状態良好な症例を対象とした臨床試験の結果を，自分自身が担当しなければならない全身状態不良の80歳の患者に適応できるのであろうか？また，欧米のシステムが整った中で作られた診療結果と，自分自身の環境と医療技術において実行可能な診療との相違点を是非吟味しておきたい。無謀に邁進した診療は慎むべきであることは当然であるが，自身の環境と実力を悲観するあまりに腰の引けた診療になることもあり，がん診療を行う以上，前にも後ろにも引けない状態にあることは明言しておきたい。

また，薬剤を用いた臨床試験では，わずか1～2％の成績の差を数千人規模の大きなランダム化比較試験を組むことで証明するということが行われるが，製薬会社の資財にものをいわせた戦略と思いたくなるものもある。ホルモン受容体を有する中～高リスクの乳がん患者における補助療法としてのタモキシフェンの有用性は世界的コンセンサスが得られているが，5年間の内服治療であるため患者の負担も無視できない。5,187例という膨大な症例を対象にランダム化比較試験を行い，タモキシフェンの5年間の内服後にさらに女性ホルモンの生成を阻害するアロマターゼ阻害剤（レトロゾール）の長期内服により，再発率が6％低下することが証明された（しかし，生存率の改善はない）[10]。もちろん患者にとっての福音となる可能性もあるが，この治療を患者の意向と関係なくさらに5年間もレトロゾールを内服させた場合には，やっとの思いでタモキシフェンを5年間内服した患者にとって精神的および経済的負担は無視できない。時に統計学や

経済力により，患者の意向とは別の次元でエビデンスが作られていると思えてしまうことがある。エビデンスレベルの高い知見を患者に強制することなく，患者の意向をも十分聞き入れ，患者に語らせる医療（NMB）を実践していきたいものである。

Ⅳ 診療ガイドライン

欧米には膨大な診療ガイドラインが存在するが，一定の診療レベルを確保するための道具であるとともに，診療報酬を確保するための道具として整備された診療ガイドラインもある（http://www.nccn.org/physician_gls/index.html）。1,000とも2,000とも言われているガイドラインのうち，利用したい診療ガイドラインをいかに見つけ出すかも重要となる。診療ガイドラインを検索するインターネット上のホームページもあるので是非覗いて頂きたい（http://www.guideline.gov/）。本邦でも数年前より始まった厚生労働省指導の診療ガイドライン作りで20疾患が対象となった。がん関連では，乳がんを始め4疾患に対して診療ガイドラインが作成された。膨大な論文を系統的にレビューし，一定のフォームに従った抄録（構造化抄録）を作成し，推奨すべき（または推奨できない）診療内容と推奨レベルとを決定していく作業は大変な労力である。引用した論文は欧米中心のものが多く，本邦から発信された論文はわずかであり，日本の現状に合わないなどの批判もあろう。診療ガイドラインは法律でも規則でもなく，実臨床の現場で個々の患者や診療の環境に合わせて判断する際の一助として利用するものであり，診療の50～80％の症例に適用されることが望ましいとされる。今回出された診療ガイドラインが今後の臨床にどれだけ反映されていくかを調べる方法として，診療実態調査を行う方法がある。単に不出来なガイドラインと批判したり，「おれ流」に合わないと批判したりするのではなく，実臨床の内容を診療ガイドラインが推奨する形に修正し，また逆に実臨床からかけ離れた診療ガイドラインの内容も修正しながら，診療ガイドラインと実臨床の双方のレベルを上げていかなければならない。

Ⅴ 標準治療とは

誰がどのように「標準治療」を決定していくのか？多くの臨床試験でその有用性が確認され，一般診療の中に広く普及しているものであれば疑問の余地は少ない。しかし，エビデンスレベルは高いものの臨床の現場ではあまり行われていない治療法や，逆に臨床試験の形をとって積み上げられてきた知見ではないがすでに一般臨床で広く行われているものなども存在し，どこまでを標準治療とするのかは難しい。多くの臨床試験で安全性と有効性が確認され広く一般臨床で行われている診療としては，早期乳がんにおける乳房温存療法や，びまん性大細胞型Ｂ細胞リンパ腫におけるCHOP療法（またはCHOP療法＋リツキシマブ）などがある[6][7][11]。また，臨床試験による安全性や有効性の確認はなされていないが一般臨床で広く用いられている治療としては，早期胃がんや食道がんに対する内視鏡を用いた粘膜切除術，早期喉頭がんに対する根治的放射線治療などがあげられる。臨床試験による安全性や有効性の確認がなされていないからといって，これらの治療法と他の治療法との比較試験を今更行うということはないであろうし，そのような確認がなされたからといって日常臨床になんら恩恵をもたらすことはない。また逆に，広く一般臨床で行われているからといって，その治療法がすべて標準治療であるとは限らない。進行期食道がんや頭頸部腫瘍における化学療法同時併用放射線治療は近年非常に注目されている治療法ではあるが，用いる化学療法の種類，量，投与方法，また放射線治療の範囲や量に関してはまだ十分なコンセンサスが得られていない[12][13]。確かに，いくつかの臨床試験によりすばらしい治療法が開発されてはいるが，薬剤の種類や投与量・間隔，放射線治療に関しても照射線量や照射範囲など一定の見解はまだない。また，表面的には標準的治療のように見えても，治療法の内容を詳細に見ると薬剤投与量や照射線量・範囲などに個々の医師による独自の変更が加えられていることがある。高いエビデンスを一般臨床に適用する際に，「日本人には多すぎる」，「これまで自分が使い慣れている方法で」などの理由でオリジナルのスケジュールを歪曲させてしまうことがある。このような行為を是正しようとしても，必ず返ってくる反論は「これで困ったことがないからかまわない」である。臨床の現場で，臨床試験などで10～20％の治療成績が落ちることが示されている治療法を行ったとしても，その主治医は成績が悪いことを現場で実感することはないとされており，約50％の成績の低下がある場合において初めて主治医はその治療の「悪い」を実感するとされている。主治医には一見標準的治療のように見えているのかもしれない歪曲した治療法が，世の中に蔓延していることは喚起しておきたい。

科学的に証明された信頼性の高い優れた治療法の確立はもちろん重要ではあるが，その治療法が広く臨床の現場で用いられていることもまた重要である。どの程度臨床の現場に普及しているか，臨床の現場でどのような形で行われているかを知るには，その実態を調査するしかない。さまざまな調査方法があり，アンケート調査は簡便な方法ではあるが，回収率の問題や，一つ一つのデータの信憑性には問題がある。また，直接施設を訪問し，診療録を一つ一つ見ながら検討項目を抽出する方法もある。施設と症例のサンプリングを行い診療の実態調査を行う研究（Patterns of Care Study）が進められており，この方法は時間と手間が非常にかかる手法ではあるが，本邦でも厚生労働省より研究助成を受け研究班が結成された[14]。現在，乳がん，食道がん，肺がん，子宮がん，前立腺がんの5疾患について調査・研究が進められており，米国の研究班との共同研究も開始された。診療実態を調査しそこに内在する問題点を抽出し，施設への直接のフィードバックや，論文としての公表，医療者向けの教育訓練などを行い，診療レベルの向上を図る必要がある。

Ⅵ 最後に

がん診療におけるEBMのあり方，エビデンスや診療ガイドラインの利用法について概説した。がん診療に関わるすべての医療者が，より良い医学判断を行い，良いがん診療の向上に努めて頂くことを願ってやまない。

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上咽頭癌に対するCDDP/5FUと放射線治療の交替療法

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論文要旨

上咽頭癌（Ⅱ～Ⅳ期）に対し多施設共同でCDDP（50mg/m²/日×2日間）と5FU（800mg/m²/日，5日間）を用いた化学療法と放射線療法を組み合わせた交替療法を行った。67例（Ⅱ～Ⅲ期：41例，Ⅳ期：26例）に対し化学療法と放射線療法を交互に行い，三回の化学療法が予定通り施行できた症例は57例（85%）であった。全症例の3年全生存率は90.5%であり，3年無病生存率は78.3%であった。初回再発部位は，原発巣が4例，頸部リンパ節が2例，遠隔転移が8例であった。約半数にGrade 3～4の骨髄抑制が，また約30%の症例にGrade 3～4の重篤な粘膜炎を認めた。治療関連死は見られなかったが，3例でGrade 3～4の肝臓または腎臓の有害事象を認めた。本療法は治療完遂率も高く成績も良好であったが，重篤な粘膜炎および肝臓・腎臓の有害事象を認めることがあり慎重な全身管理が求められる。

Key words：上咽頭癌（nasopharyngeal cancer），化学放射線療法（chemoradiation），放射線治療（radiotherapy）

はじめに

上咽頭癌は解剖学的特性と，化学療法および放射線治療に対する感受性が高いことから，早期例では放射線単独治療が，また進行期においては化学療法と放射線治療を組み合わせた治療法が行われる[1,2]。近年，化学療法と放射線治療を組み合わせた治療法により良好な成績が報告されているが，最適な組み合わせに関してはいまだ統一した見解はなく，化学療法後に放射線治療を行う方法や，二者の同時併用，また放射線治療後に化学療法を行う方法など様々な組み合わせが試みられている[3-10]。しかし，これまでの臨床試験の結果からは化学療法の有用性は放射線治療との同時併用においてのみ示されているだけである[3,6]。Intergroup（INT）0099では放射線単独治療と化学放射線治療を比較するランダム化比較試験を行い，後者において著明な予後の改善が得られたことを報告している[3]。多くの研究者が注目した研究結果ではあるが，放射線単独治療群の成績が悪すぎることや，化学療法の完遂率が不良である点などの指摘もあり，これを以て直ちに標準治療とするのは時期尚早と言える[3,11]。また，化学療法と放射線療法の同時併用が治療成績の向上に繋がるとしても，至適薬剤の組み合わせや容量に関しては統一した見解は得られていない[3,6]。

今回我々は，白金製剤であるcis-platinum-diamminedichloride（CDDP）と代謝拮抗剤5-fluorouracil（5FU）の二剤を用いた化学療法と放射線治療を組み合わせた交替療法の有用性と安全性を評価するため，統一した治療スケジュールを用いて多施設共同で前向きに症例を蓄積してきた[12]。その短期経過観察の結果を報告する。

対象および方法

愛知県がんセンター，福島医科大学，琉球大学，三重大学，長崎大学および信州大学の6施設で以下の条件を満たす症例を対象に治療を行った。適格規準は，上咽頭原発であること，年齢70歳以下であること，全身状態良好（ECOGのperformance statusが0～2）であること，扁平上皮癌（WHO分類のType Ⅰ～Ⅲ）であること，UICC分類第5版にて病期Ⅱ～Ⅳ期（ただし，遠隔転移例は除く）であること，良好な骨髄機能（白血球数3,500mm³以上，血小板100,000mm³以上，Hb 10.0g/dL以上）を有すること，良好な肝機能を有すること，良好な腎機能を有すること（24時間クレアチニン・クリアランス60ml/min以上）および文書による

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表 1　症例内訳

年令	15～70	(中央値：49)
性別	男	51
	女	16
全身状態	0	37
	1	24
	2	6
組織型	I	12
(WHO分類)	II	26
	III	29
病期	II	16
	III	25
	IV	26
T病期	1	20
	2	25
	3	7
	4	15
N病期	0	5
	1	24
	2	25
	3	13

同意が本人から得られることである[12]。

治療スケジュールの詳細はすでに報告済みであるためその概略のみを記す[12]。まず化学療法を先行させ，続いて予防領域を含めた広い照射野で 30.6～36 Gy までを照射する。次に二回目の化学療法を施行し，引き続き放射線治療を予定総線量である 66 Gy まで投与し，照射終了後より三回目の化学療法を行う。投与線量に関しては，腫瘍の縮小率などを考慮し主治医の判断により追加照射を行い，最大許容総線量は 80 Gy とした。放射線治療には 4～10MV-X 線を用いて，一回線量 1.8 Gy で週 5 回法にて照射した。化学療法は 5FU (800mg/m²/日)を 5 日間連続で持続点滴静注した後，CDDP (50 mg/m²/日) を二日間連続で持続点滴静注した。CDDP 投与時には腎障害を予防するため一日尿量 3,500～4,000cc が確保されるよう水分負荷をかけた。二および三回目の化学療法を開始するに当たっては，白血球数 3,000mm³ 以上，血小板数 100,000mm³ 以上，また十分な肝・腎機能が確保されていることを確認した後に行うこととした。また，白血球数 1,000mm³ 以下，血小板数 25,000mm³ 以下になった場合には次回化学療法を 25%減量し，血清クレアチニン値が 1.5mg/dL 以上の場合には CDDP のみを 25%減量した。

治療を開始した日を観察開始日とし，イベントが発生するまでの期間を算出した。無病生存の算出では腫瘍の再発またはあらゆる原因による死亡をイベントとし，全生存の算出ではあらゆる原因による死亡をイベントとした。生存率の算出には Kaplan-Meier 法を[13]，二群間の有意差検定には一般化 Wilcoson 検定を用い p 値

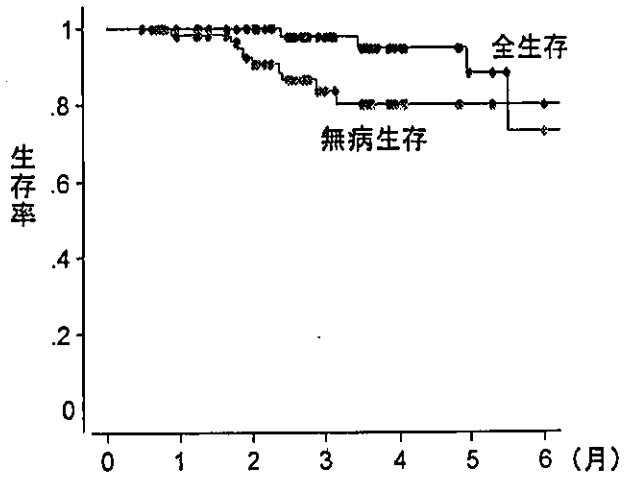

図 1　全症例の全生存および無病生存

0.05 以下をもって有意差ありと判定した。また，総治療期間は観察開始日から最終化学療法が施行された日または最終の放射線治療が行われた日のうち遅い方の日までとし，総照射期間は放射線治療開始日から放射線治療終了日までとした。有害事象の評価には，National Cancer Institution Common Toxicity Criteria (NCI-CTC) version 2.0 を用いて評価した[14]。

結　果

症　例

1997 年 7 月から 2002 年 12 月までに本スケジュールで治療された症例は 67 例であった（表 1)。男性 51 例，女性 16 例であり，全症例の年齢の中央値は 49 歳 (15～70) であった。全症例の 76%の症例が臨床病期 III～IV 期であった。観察期間の中央値は 43 ヶ月 (15～81) であった。

治療完遂率および治療期間

三回の化学療法が予定通り施行された症例は 57 例 (85%) であり，化学療法の施行回数が二回であったものが 8 例，一回のみが 1 例であった。また 1 例では心不全の発症のため一度も投与されることなく放射線治療のみが施行された。

原発巣に投与された線量の中央値は 66.5 Gy (54～80) であり，60 Gy 未満の症例は 4 例 (5 %) であった。頸部リンパ節転移巣への総線量の中央値は 63.9 Gy (32.4～80) であった。頸部リンパ節予防領域への総線量の中央値は 37.2 Gy (27～52.2) であった。

総治療期間の中央値は 89 日間 (62～141) であり，総照射期間の中央値は 71 日間 (48～105) であった。

全生存率および無病生存率

全症例の 3 年全生存率は 90.5%であり，3 年無病生存率は 78.3%であった（図 1)。臨床病期 II～III 期 (41 例) の 3 年無病生存率は 90.1%であったのに対し，IV

表 2　有害事象

有害事象	Grade 0-1	2	3	4	Grade 3-4の頻度(%)
白血球	5	31	30	1	46
好中球	18	30	16	3	28
血小板	57	4	4	2	8
ヘモグロビン	27	27	11	2	19
肝臓	62	3	1	1	2
腎臓	63	3	1	0	1
嘔吐	25	31	11	0	16
口内炎	16	31	16	4	29

期（26例）のそれは60.2%であった（p=0.035）。また，WHO分類Type Ⅱ～Ⅲ（中～低分化：55例）の3年無病生存率は83.5%であったのに対し，Type Ⅰ（高分化：12例）のそれは54.0%であり，後者は有意に不良であった（p=0.012）。総治療期間が12週未満であった24例の3年無病生存率は70.7%，また12週以上であった43例のそれは82.0%であり両者に有意差は見られなかった（p=0.260）。また，総照射期間が10週未満であった37例の3年無再発生存率は78.6%であり，また10週以上であった30症例のそれは77.2%であり両者に有意差はなかった（p=0.952）。

再発した14例の初回再発部位は，原発巣が4例，頸部リンパ節が2例，遠隔転移が8例（肺および骨が各3例，皮膚および肝臓が各1例）であった。

有害事象

観察された有害反応の一覧を表2に示す。白血球減少を中心としたGrade 3～4の骨髄抑制が約半数に観察され，また約30%の症例にGrade 3～4の重篤な粘膜炎を認めた。治療関連死は見られなかったものの，3例でGrade 3～4の肝臓または腎臓の有害事象を認めた。腎障害を来した症例には一時的な人工透析が導入され，重篤な障害を残すことなく腎機能は改善した。

考　察

Pignonは口腔および咽喉頭癌を対象とした70のランダム化比較試験をメタ解析し，化学療法を放射線治療と同時期に行う場合においてのみ化学療法の有用性が示され，放射線治療前後に行う補助化学療法の有用性は示されなかったことを報告している[15]。上咽頭癌において放射線治療前に化学療法を施行した場合の奏功率はおよそ80%と良好であるものの[10,16]，補助療法としての照射前・後に行う化学療法の有用性を検討したランダム化比較試験ではその有用性は示されなかった[4,5,9,10]。これに対し，INT0099を始めとするいくつかのランダム化比較試験において放射線単独治療に比べ化学療法同時併用放射線治療が優れていることが示された[3,6]。

至適化学療法の組み合わせは確立していないものの，CDDPを放射線療法と同時期に用いることに対する異論は少ない[1,3,12,17,48]。現時点では，頭頸部腫瘍における化学療法同時併用放射線治療を行う際のCDDP単剤の場合の標準的投与法は，100mg/m²を3週サイクルに3回行うというものである[19]。INT 0099では照射と同時期にCDDP（100mg/m²）を3サイクル投与した後，維持療法としてCDDP（80mg/m²）と5FU（1 g/m²，4日間）を4週間隔で3回行う方法を用いている[3]。しかし，化学療法の完遂率は照射と同時期の化学療法では62%，また維持療法では56%と低率であった[3]。一方，Chengらが行った方法はINT 0099に比べ低容量であり，照射と同時期にCDDP（60mg/m²）と5FU（1 g/m²，5日間）を6週間あけて2サイクル行い，維持療法としてはCDDP（100mg/m²）と5FU（1 g/m²，5日間）を2サイクル行うというものであり，化学療法の完遂率は91%と良好であった[20]。Linらは CDDP（20mg/m²）と5FU（400mg/m²）を4日間持続点滴投与する少量分割による投与法を用い高い完遂率を報告しているが[6]，Tanらが行った少量分割法（CDDP 25 mg/m²，4日間連続投与，3サイクル）では化学療法の完遂率は75%にとどまり[18]，必ずしも少量分割法が治療完遂率を高める良い方法とは言えない。我々の方法は照射と同時期にCDDPと5FUを投与しているが，同日の施行を避け化学療法を連日7日間で終了させた後に照射を行う交替療法を採用しているためか完遂率は比較的良好であった。今後も化学療法の至適組み合わせと容量についての研究が必要である。

化学放射線療法の適応となる対象に関しても見解は分かれる。病期Ⅱの治療成績は良好で化学療法の同時併用による上乗せ効果は少なく，特にN0症例においては化学療法の併用は不要とする見解もある[11,20]。一方，一部の試験では病期Ⅰ～Ⅳ期までを含めたものも存在し，いまだ統一した見解は得られていない[4]。しかし，全般にリンパ節転移を認めない病期ⅡA期の成績は良好であり，化学療法併用による上乗せ効果はあるとしてもわずかであり，相当数の症例を用いた試験でなければその有用性を検出することは難しい[17]。放射線単独治療では制御困難な症例を対象に化学療法を併用していくことが，その有用性を明らかにする上で重要である。Erkalは447例を用いた全生存率に関する予後因子解析を行い，T3～4はT1に比べ相対危険度が2.50～5.22，N2～3はN0に比べ1.86～2.72と高いことを報告している[17]。現時点での化学放射線療法の適応は遠隔転移を認めない病期ⅡB～ⅣB期を中心とした進行期例を対象と考えるのが妥当であろう。

今回の研究では，有害事象として骨髄抑制の他，粘膜炎や消化器症状が多く認められ，また一部の症例では重

篤な肝・腎障害が認められた。欧米と異なり本邦では腫瘍内科医の数は極めて少なく，頭頸部外科医または放射線腫瘍医によって化学療法が行われる。慎重な全身管理と有害事象に対する適切な対応が要求される本療法を施行するにあたっては，本邦においても腫瘍内科医，頭頸部外科医および放射線腫瘍医を含めたより良いチーム医療の構築が必須である。

結　論

CDDP/5FUを用いた化学療法と放射線治療の交替療法の治療完遂率は良好であり，短期治療成績も良好であった。しかし，約30%の症例で重篤な粘膜炎が認められ，また一部の症例では重篤な肝臓および腎臓の有害事象などが認められることがあるため慎重な全身管理が必要である。

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ALTERNATIVE THERAPY USING CDDP/5FU AND RADIOTHERAPY FOR NASOPHARYNGEAL CANCER

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We conducted a prospective study of an alternative chemoradiation protocol comprising CDDP (50mg/m²/day, 2 days), 5FU (800mg/m²/day, 5days) and radiotherapy (66Gy in 36 fractions) for locally advanced nasopharyngeal cancer (stage II-IV). We treated 67 patients (stage II-III: 41 patients, IV : 26) using this protocol. Fifty-seven patients (85%) received the full-course, three-cycle chemotherapy. Three-year overall survival rate of all patients was 90.5%, and 3-year disease-free survival rate was 78.3%. The recurrent sites were the primary site in four patients, neck lymph node in two and distant metastasis in eight. Severe myelosuppression (grade 3-4) was observed in half of the patients, and severe mucositis (grade 3-4) in about 30%. Chemotherapy induced severe dysfunction of liver or kidney (grade 3-4) was seen in three patients. This treatment strategy may be very useful, but careful medical management is essential.

Stereotactic Hypofractionated High-Dose Irradiation for Stage I Nonsmall Cell Lung Carcinoma

Clinical Outcomes in 245 Subjects in a Japanese Multiinstitutional Study

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BACKGROUND. Stereotactic irradiation (STI) has been actively performed using various methods to achieve better local control of Stage I nonsmall cell lung carcinoma (NSCLC) in Japan. The authors retrospectively evaluated results from a Japanese multiinstitutional study.

METHODS. Patients with Stage I NSCLC (n = 245; median age, 76 years; T1N0M0, n=155; T2N0M0, n=90) were treated with hypofractionated high-dose STI in 13 institutions. Stereotactic three-dimensional treatment was performed using noncoplanar dynamic arcs or multiple static ports. A total dose of 18–75 gray (Gy) at the isocenter was administered in 1–22 fractions. The median calculated biologic effective dose (BED) was 108 Gy (range, 57–180 Gy).

RESULTS. During follow-up (median, 24 months; range, 7–78 months), pulmonary complications of National Cancer Institute-Common Toxicity Criteria Grade > 2 were observed in only 6 patients (2.4%). Local progression occurred in 33 patients (14.5%), and the local recurrence rate was 8.1% for BED ≥ 100 Gy compared with 26.4% for < 100 Gy ($P < 0.05$). The 3-year overall survival rate of medically operable patients was 88.4% for BED ≥ 100 Gy compared with 69.4% for < 100 Gy ($P < 0.05$).

CONCLUSIONS. Hypofractionated high-dose STI with BED < 150 Gy was feasible and beneficial for curative treatment of patients with Stage I NSCLC. For all treatment methods and schedules, local control and survival rates were better with BED ≥ 100 Gy compared with < 100 Gy. Survival rates in selected patients (medically operable, BED ≥ 100 Gy) were excellent, and were potentially comparable to those of surgery. *Cancer* **2004;101:1623–31.**

KEYWORDS: stereotactic, radiotherapy, altered fractionation, nonsmall cell lung carcinoma, Stage I, dose escalation, multicenter study, local control, survival rate.

Nonsmall cell lung carcinoma (NSCLC) represents a leading cause of mortality worldwide. Lung carcinomas are being detected increasingly early, thanks to routine use of computed tomography (CT)

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scans. For patients with Stage I (T1N0M0 or T2N0M0) NSCLC, full lobar or greater surgical resection represents a treatment choice that promises local control rates ≥ 80% and overall survival rates > 50% after 5 years.[1] However, surgical resection is often not feasible or involves excessive risk for some patients with lung carcinoma with tobacco-related illness, severe cardiovascular disease, or other medical conditions. A small proportion of patients who are eligible for surgery may refuse procedures for personal reasons. Radiotherapy can offer a therapeutic alternative for these patients, but outcomes for conventional radiotherapy are unsatisfactory, and are potentially amplified by selection bias, with local control rates of 40–70% and 5-year survival rates of only 5–30%.[2–4] Doses of conventional radiotherapy to treat NSCLC have been suggested to be too low to achieve tumor control. However, providing a higher dose to the tumor without increasing adverse effect was previously impossible, due to technical uncertainties over focusing irradiation only on the tumor-bearing area of the lung.

With the increasing accuracy of localization for tumor-bearing areas using various imaging techniques, hypofractionated or single high-dose stereotactic irradiation (STI) has been actively investigated for Stage I NSCLC in Japan.[5–8] STI can also substantially reduce overall treatment time from several weeks for a conventional radiotherapy schedule to a few days, offering important advantages to the patient. A landmark study by Uematsu et al.,[5] one of the pioneers of STI for extracranial lesions, revealed excellent survival rates for medically operable patients, approximating those for full lobar surgical resection. Under the guidelines of the Japanese Society of Radiation Oncology study group,[9] Stage I NSCLC has been treated using small-volume STI in numerous Japanese institutions since the late 1990s, with far fewer symptomatic adverse effects than conventional radiotherapy. Although optimal STI techniques and schedules for Stage I NSCLC remain unclear, the number of patients with Stage I NSCLC treated nationwide using small-volume, high-dose STI has accumulated rapidly. Although differences in techniques and schedules may vary widely, retrospective investigation of the results of STI for Stage I NSCLC from the many institutions that have used small-volume, high-dose irradiation in this short period should yield some meaningful data. The current study retrospectively evaluated Japanese multiinstitutional results for high-dose STI for Stage I NSCLC, and sought to answer the following questions: 1) What is the optimal dose to limit toxicity and still obtain local control? 2) Are the results from single-institution studies reproducible? 3) Are STI results comparable to those of surgery?

TABLE 1
Patient Characteristics

Total no. of patients	245
Age	35–92 yrs (median, 76 yrs)
PS	PS 0, 94; PS 1, 104; PS 2, 47
Pulmonary chronic disease	Positive, 196; negative, 96
Histology	Squamous cell carcinoma, 110; adeno carcinoma, 109; others, 26
Stage	Stage IA, 155; Stage IB, 90
Tumor diameter	7–58 mm (median, 28 mm)
Medical operability	Inoperable, 158; operable, 87

PS: performance status.

MATERIALS AND METHODS

Eligibility Criteria

All patients enrolled in the current study satisfied the following eligibility criteria: 1) identification of T1N0M0 or T2N0M0 primary lung carcinoma on chest and abdominal CT scans, bronchoscopy, bone scintigraphy, or brain magnetic resonance imaging scans; 2) histologic confirmation of NSCLC; 3) tumor diameter < 60 mm; 4) performance status ≤ 2 according to World Health Organization guidelines; and 5) inoperable tumor due to poor medical condition or refusal to undergo surgery.

No restrictions were utilized concerning the location of eligible tumors, irrespective of whether they were located adjacent to a major bronchus, blood vessel, chest wall, or the esophagus or spinal cord. However, the spinal cord was kept out of the high-dose area.

Patients were informed as to the concept, methodology, and rationale of this treatment. Written informed consent was obtained from all patients. The study was approved by the ethics committee of each institution and was performed in accordance with the 1983 revision of the Helsinki Declaration.

Patient Characteristics

A summary of patient characteristics is provided in Table 1. From April 1995 to February 2003, 245 patients with primary NSCLC were treated with hypofractionated high-dose STI in 13 institutions. Of the 245 patients, 158 (65%) were considered to be medically inoperable, due predominantly to chronic pulmonary disease, advanced age, or other chronic illness. The remaining 87 patients (35%) were considered to be medically operable, but had refused surgery or had been advised to select STI by medical oncologists.

Treatment Methods

All patients were irradiated using stereotactic techniques. For the purposes of the current study, all ste-

TABLE 2
Treatment Schemes

Beam energy	6-MV X-ray, 12; 4-MV X-ray, 1
Measures for respiratory motion	Respiratory gating, 5; breath hold, 2; non, 6
Fixation of patients	Vacuum pillow, 5; body frame, 4; non, 4
Irradiation port shape	Regular, 4; conformal, 9
Fraction numbers	1–25 (multiple, 11; single, 2)
Irradiation mode	Multiple (6–20) static ports, 7; dynamic arc, 6
Single dose (at the isocenter)	3–35 Gy
Total dose (isocenter) of stereotactic irradiation	20–69 Gy
Conventional radiotherapy	30–44 Gy/15–20 fractions in 27 patients; non, 218 patients
BED = nd(1+d/a/b) at the isocenter	57–180 Gy (median, 108 Gy)

BED: biologic effective dose; Gy: gray.

reotactic techniques fulfilled three requirements: 1) reproducibility of the isocenter ≤ 5 mm, as confirmed in every fraction; 2) slice thickness on CT scan ≤ 3 mm for three-dimensional (3D) treatment planning; and 3) irradiation with multiple noncoplanar static ports or dynamic arcs. Table 2 summarized various techniques and instruments introduced to achieve STI in 13 institutions. To fulfill the first requirement, a CT scan or two-directional portal graph was undertaken before every treatment regimen in 12 institutions, whereas real-time tumor tracking using a gold marker inserted around the tumor[10] was performed in 1 institution. A CT scanner sharing a common couch with the linear accelerator was placed in an irradiation room in two institutions.[11,12]

Treatment planning with irregularly shaped beams using noncoplanar multiple (3–10) dynamic arcs or multiple static ports (6–20 ports) was established with the help of a 3D treatment-planning computer. Beam shaping was performed in some institutions using an integrated motorized multileaf collimator with 0.5–1-cm leaf width at the isocenter. Furthermore, various techniques using breathing control or gating methods and immobilization devices such as a vacuum cushion with or without a stereotactic body frame were utilized to reduce respiratory internal margins. Respiratory gating or breath-hold methods were used in seven institutions.

Planning CT scans were performed with 2 or 3-mm slice thickness and displayed using a window level of −700 Hounsfield units (HU) and a window width of 2000 HU. In some institutions, irradiation and planning CT scans were performed under breath-hold conditions. In other institutions, irradiation and planning CT scans were performed under free shallow breathing, with images taken using slow scanning (4 seconds per slice).

The clinical target volume (CTV) marginally exceeded the macroscopic target volume by 0–5 mm. The planning target volume (PTV) comprised the CTV, a 2–5-mm internal margin, and a 0–5-mm safety margin. An example of an STI dose distribution for Stage I lung tumors is shown in Figure 1. A high dose was concentrated on the tumor-bearing area while sparing surrounding normal lung tissues using STI.

Irradiation schedules also differed among institutions. The number of fractions ranged between 1 and 25, with single doses of 3–12 Gy. A total dose of 18–75 Gy at the isocenter in 1–25 fractions was administered with 6-MV X-rays within 20% heterogeneity in the PTV dose. Twenty-seven patients had received conventional irradiation doses of 30–44 Gy in 15–20 fractions before STI due to physician preferences. No chemotherapy regimens were administered before or during radiotherapy.

To compare the effects of various treatment protocols with different fraction sizes and total doses, a biologic effective dose (BED) was utilized in a linear-quadratic model.[13] BED was defined as $nd(1+d/\alpha/\beta)$, with units of grays, where n is the fractionation number, d is the daily dose, and α/β is assumed to be 10 for tumors. BED was not corrected with values for tumor-doubling time or treatment term.

The median BED at the isocenter was 108 Gy (range, 57–180 Gy). BED was ≥ 100 Gy in 173 patients and < 100 Gy in 72 patients.

Dose constraints were set for the spinal cord only. The BED limitation for the spinal cord was 80 Gy (α/β was assumed to be 2 Gy for chronic spinal cord toxicity). This dose constraint for the spinal cord was achieved in all patients who satisfied all eligibility criteria.

Evaluation

The objectives of the current study were to retrospectively evaluate toxicity and the local control and survival rates according to BED. Follow-up examinations were performed by radiation oncologists for all patients. The first examination took place 4 weeks after treatment, and patients were subsequently seen every 1–3 months. Tumor response was evaluated using previously published National Cancer Institute (NCI) criteria.[14] Chest CT scans (slice thickness, 2–5 mm) were usually obtained every 3 months for the first year, and repeated every 4-6 months thereafter. A complete response (CR) indicated that the tumor had completely disappeared or was replaced by fibrotic tissue. A partial response (PR) was defined as a ≥ 30% reduction in the maximum cross-sectional diameter. Distinguish-

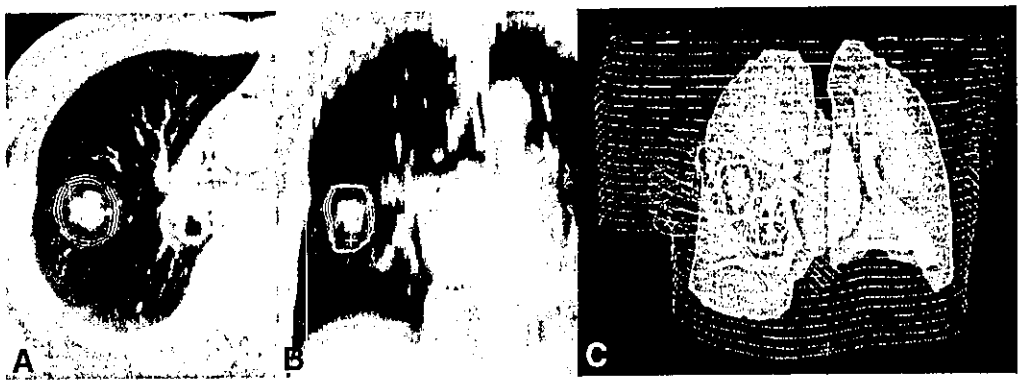

FIGURE 1. An example of three-dimensional treatment planning. (A) Isodose curves on axial CT through the center of the PTV. (B) Isodose curves on a coronal reconstructed image through the center of the PTV. (C) Three-dimensional Image showing all radiotherapy arcs and isodose curves.

ing between residual tumor tissue and radiation fibrosis was difficult. Any suspicious residual confusing density after radiotherapy was considered to be evidence of PR, so the actual CR rate may be higher than presented in the current study. Local disease recurrence was considered to have occurred only when enlargement of the local tumor continued for > 6 months on follow-up CT scans. Findings on CT scans were interpreted by two radiation oncologists. Absence of local disease recurrence was defined as locally controlled disease.

Lung, esophagus, bone marrow, and skin were evaluated using Version 2 of the National Cancer Institute-Common Toxicity Criteria (NCI-CTC).

Statistical Analysis

Local disease recurrence rates in the two groups were compared using the chi-square test. BED among patient groups at each pulmonary toxicity grade was compared using Kruskal–Wallis tests. Cumulative survival curves were calculated and drawn using Kaplan–Meier algorithms with the day of treatment as the starting point. Subgroups were compared using log-rank statistics. Values of $P < 0.05$ were considered to be statistically significant. Statistical calculations were conducted using Version 5.0 StatView software (SAS Institute Inc., Cary, NC).

RESULTS

All patients completed treatment with no particular complaints. The median period of follow-up was 24 months (range, 10–78 months). BED (α/β is assumed to be 2 Gy for chronic toxicity of the spinal cord) did not exceed 80 Gy in any of the patients.

Local Tumor Response

Of the 245 patients evaluated using CT scans, CR and PR were achieved in 57 (23.3%) and 151 (61.6%) patients, respectively. The overall response rate (CR+PR) was 84.8%. Overall response rates for tumors with BED ≥ 100 Gy ($n = 173$) and < 100 Gy ($n = 72$) were 84.5% and 83.3%, respectively. An example of a CR is shown in Figure 2.

Toxicity

Treatment toxicities are summarized in Table 3. Symptomatic radiation-induced pulmonary complications (NCI-CTC criteria Grade > 1) were observed in 17 patients (6.9%). No significant differences in BED were identified among patient groups at each pulmonary toxicity grade. Pulmonary fibrosis or emphysema before treatment was observed in 15 (88%) of the 17 patients with pulmonary complications > Grade 1. Pulmonary symptoms resolved in most patients with or without steroid therapy, but continuous oxygen supply was required in three patients who displayed poor respiratory function before irradiation. Chronic segmental bronchitis and wall thickening causing atelectasis on the peripheral lung was observed in one patient. Grade 3 esophagitis was temporarily observed in two patients with tumors adjacent to the esophagus. Grade 3 or 4 dermatitis was observed in two patients with tumors adjacent to the chest wall. No vascular, cardiac, or bone marrow complications had been encountered as of the last follow-up.

Disease Recurrence

Local disease recurrence occurred in 13.5% of all patients, with rates being significantly lower for BED ≥ 100 Gy (8.1%) compared with < 100 Gy (8.1% vs. 26.4%, $P < 0.01$). Patients with Stage IB disease displayed significantly higher rates of local disease recurrence compared with patients with Stage IA disease. However, no differences in the local disease recurrence rate were observed between patients with Stage IA disease and patients with Stage IB disease for BED

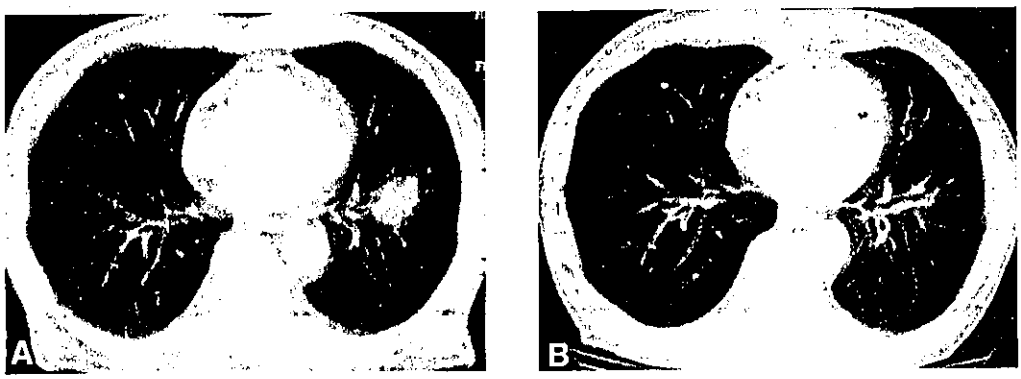

FIGURE 2. An example of a patient with a complete response (CR). The patient was an 80-year-old male with T2N0 adenocarcinoma. (A) Computed tomography scan (CT) before stereotactic irradiation (STI) of 70 gray/10 fractions/5 days. (B) CT scan 6 months after STI. CR was acquired and no radiation-induced pneumonia was apparent.

TABLE 3
Toxicity

Pneumonitis[a]
Grade 0, 32.8%
Grade 1, 59.6%
Grade 2, 4.1%
Grade 3, 1.2%
Grage 4, 1.2%
Esophagitis[a]
Grade 0, 95.6%
Grade 1, 2.4%
Grade 2, 1.2%
Grade 3, 0.8%
Dermatitis[a]
Grade 0, 98.0%
Grade 1, 0.8%
Grade 2, 0.4%
Grade 3, 0.4%
Grade 4, 0.4%
Pleural effusion (1.6%)
Rib fracture (0.8%)
Bone marrow suppression (0.0%)

[a] Graded according to National Cancer Institute-Common Toxicity Criteria (Version.2.0).

≥ 100 Gy. Rates of local disease recurrence were also significantly lower in the total group and Stage IA and Stage IB subgroups for BED ≥ 100 Gy compared with < 100 Gy. In particular, when BED was < 100 Gy, the local disease recurrence rate in patients with stage IB disease was 41.4% (12 of 29) compared with 16.3% (7 of 43) for patients with Stage IA disease. For BED ≥ 100 Gy, the local disease recurrence rate was 7.5% for BED ≥ 120 Gy (n = 80) and 9.8% for BED ≥ 140 Gy (n = 40). The local disease recurrence rates for adenocarcinoma and squamous cell carcinoma were 13.6% (15 of 110) and 13.8% (15 of 109), respectively.

The patterns of first disease recurrence are listed in Table 4. Some sites of disease recurrence overlapped, and isolated local, lymph node, and distant disease recurrences were observed in 8.6%, 3.3%, and 9.8% of patients, respectively. The local disease recurrence rate of patients with Stage IB was twice that of patients with Stage IA disease, whereas lymph node and distant disease recurrence rates were basically identical in the two subgroups.

Survival

The overall 3 and 5-year survival rates were 56% and 47%, respectively. The cause-specific 3 and 5-year survival rates were both 78%. Overall survival rates differed significantly according to medical operability. For example, intercurrent deaths occurred in 19.1% of inoperable patients and in 3.4% of operable patients (Fig. 3). Overall survival rates according to BED in all patients revealed significant differences between the subgroups for BED < 100 Gy and ≥ 100 Gy (Fig. 4). Overall survival rates according to BED in operable patients revealed identical 3 and 5-year survival rates of 88% for BED ≥ 100 Gy (Fig. 5). Overall 5-year survival rates according to stage in operable patients irradiated with BED ≥ 100 Gy were 90% for patients with Stage IA disease and 84% for patients with Stage IB disease (Fig. 6).

DISCUSSION

Surgical resection remains the standard management for patients with Stage I NSCLC. The 5-year overall survival rates for patients undergoing resection range from 55% to 72% for Stage I NSCLC.[15–17] Results for treating early-stage NSCLC using conventional radiotherapy are disappointing. Qiao et al.[18] reviewed 18 studies on Stage I NSCLC treated using conventional radiotherapy alone, and reported that the 3-year overall and cause-specific survival rates were 34 ± 9% (mean ± standard error of the mean) and 39±10%, respectively. Although CR represents an important

TABLE 4
Patterns of First Disease Recurrences According to Stage and BED

Site of disease recurrence[a]	Total no. of patients (%)	Stage IA (%)	Stage IB (%)	BED < 100 Gy (%)	BED ≥ 100 Gy (%)
Local disease recurrence	33/245 (13.5)	15/155 (9.7)	18/90 (20.0)	19/72 (26.4)	14/173 (8.1)
Regional lymph node recurrence	20/245 (8.2)	12/155 (7.7)	8/90 (8.9)	8/72 (11.1)	12/173 (6.9)
Distant metastasis	36/245 (14.7)	23/155 (14.8)	13/90 (14.4)	14/72 (19.4)	22/173 (12.7)

BED: biologic effective dose; Gy: gray.
[a] Some of the disease recurrences overlapped each other.

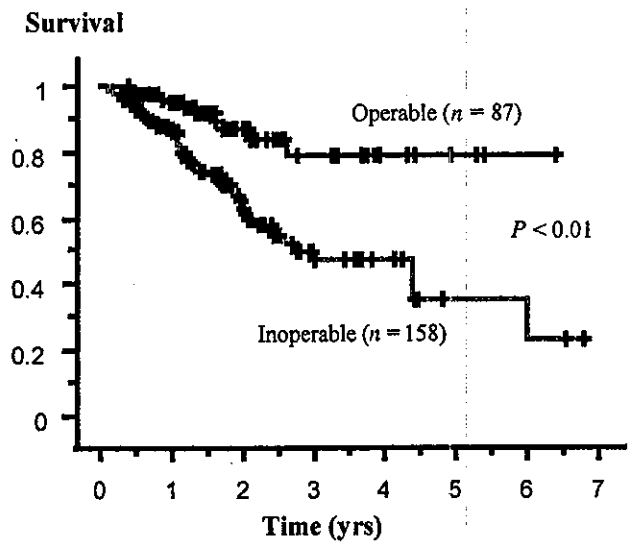

FIGURE 3. Overall survival rate according to medical operability.

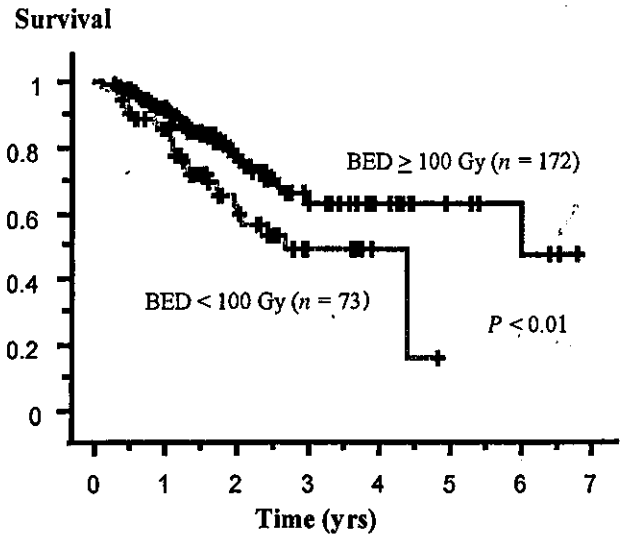

FIGURE 4. Overall survival rate according to the biologic effective dose in all patients.

prognostic factor, particularly for tumors < 5 cm in diameter,[19,20] local disease recurrence is common after conventional radiotherapy for early-stage NSCLC.[18,21,22] Several studies have shown the value of dose escalation in Stage I NSCLC.[18–20] Although increased radiation dose to the tumor is essential, escalating the dose is difficult under conventional radiotherapy techniques, given the relatively large amount of normal lung tissue enclosed in the high-dose region, including internal and safety margins to accommodate respiratory movements and daily setup errors. The most common reactions caused by radiation dose escalation are pneumonitic changes, which can induce acute symptoms of fever and cough, leading to interstitial fibrosis and subsequent reduction in lung capacity. In patients with already compromised respiratory function, such reductions can prove fatal.

Because excessive dose escalation, which improves local control in patients with NSCLC,[18,23,24] is so hard to obtain using conventional techniques, new approaches must be taken to improve outcomes. In 1995, Blomgren et al.[25] introduced a new STI technique for extracranial radiotherapy that was analogous to cranial radiosurgery. The advantages of this radiotherapeutic technique include narrow X-ray beams, concentrated in such a manner as to provide intense irradiation to small lesions at high doses, and a small number of treatment fractions. The ability to concentrate radiotherapy on a small tumor while sparing surrounding tissues had already been made possible using STI. Results from treating small brain metastases are excellent, with local control rates of approximately 90%. Application of STI techniques to the treatment of small lung tumors is reasonable, as the ratio of high-dose radiation volume to normal tissue volume should be smaller than that for the brain. Moreover, the limited volume of radiation damage on the lung or adjacent structures is unlikely to result in the severity of symptoms possible with damage to cerebral tissues. The current data reveal that Grade 3 or 4 radiation pneumonitis was observed in few patients (4%). Acute esophagitis, dermatitis, and chronic bronchitis were also observed in relatively few patients for whom tumors bordered on these organs. No other life-threatening toxicities were encountered.

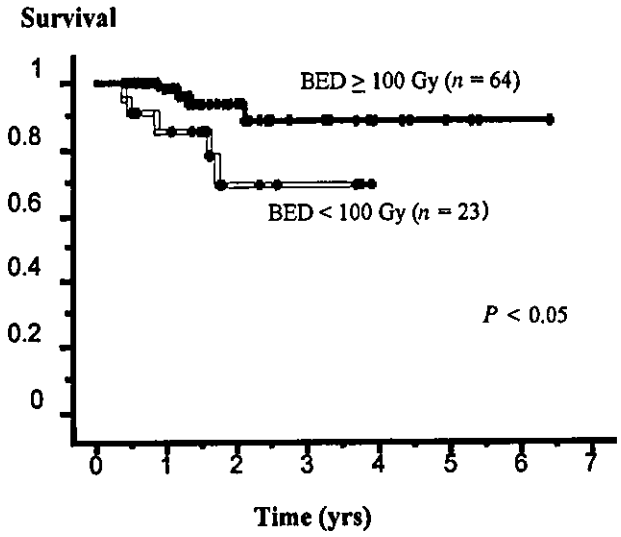

FIGURE 5. Overall survival rate according to the biologic effective dose in medically operable patients.

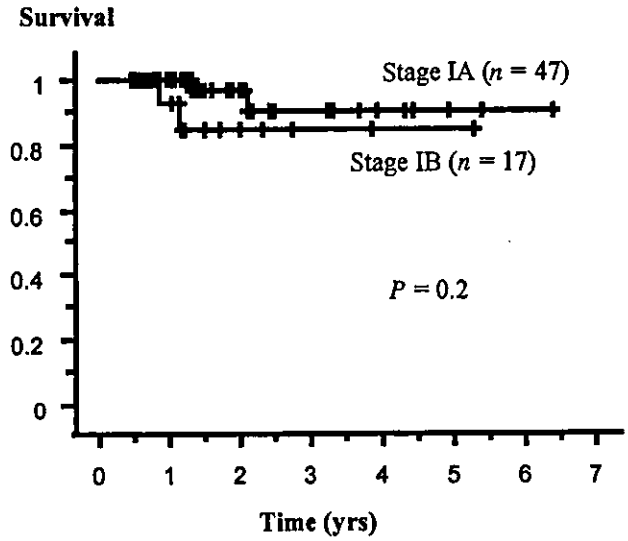

FIGURE 6. Overall survival rate according to stage in medically operable patients irradiated with biologic effective dose ≥ 100 gray.

However, the chronic effects of hypofractionated irradiation on major vessels, bronchus, esophagus, heart, and spinal cord remain unknown. Lethal pulmonary bleeding has been reported after a schedule of 24-Gy single-dose irradiation (BED = 81.6 Gy).[26] Long and careful follow-up is therefore warranted.

Recently, STI for small lung tumors using a linear accelerator has gained acceptance as an effective treatment modality. Irradiation methods and local disease recurrence rates from several institutions in which STI has been performed for primary Stage I NSCLC are listed in Table 5.[5-7,27-29] Although BED analysis using the linear-quadratic model is not quite appropriate for radiotherapy with a large single dose or short treatment period,[30] the model is useful to compare outcomes from a variety of treatment schedules using different single doses and number of fractions. Cheung et al.[31] summarized several clinical studies. In their study, crude local recurrence rates with conventional radiotherapy were 36–70%, with BED of 59.6–76.4 Gy at an α/β ratio of 10. They recommended dose escalation to increase the local control rate. STI appears to represent an ideal modality for dose escalation. Local tumor recurrence rates of Stage I NSCLC after STI with a BED of 99–137 Gy were 0–6% for a median follow-up period of 19–60 months.[5-7,27,28] The comparatively high local disease recurrence rate reported by Hof et al.[29] may be attributable to lower BED. In the current study, the local control rate was 91.9% for BED ≥ 100 Gy. For BED < 100 Gy, the local control rate was poor, particularly in patients with Stage IB disease. Given our clinical results, additional dose escalation studies may be possible. However, patients receiving BED ≥ 120 Gy or ≥ 140 Gy did not display significantly better local control rates than patients receiving lower BED, even for patients with Stage IB disease. Satisfactory BED to achieve local control for Stage I NSCLC is approximately 100 Gy. Representative examples of dose regimens performed in the current study that provided approximate BEDs > 100 Gy were 48 Gy/4 fractions or 50 Gy/5 fractions. However, treatment outcomes for patients who received conventional irradiation before STI in our study were not significantly different from those of other patients. Although a longer follow-up is necessary to determine final control rates of tumors in our study, local control rates for STI may be equivalent to surgical results, as most local disease recurrences generally occur within 3 years after treatment.[18]

In our study, the overall survival rates were excellent for limited patients considered operable before treatment and with BED ≥ 100 Gy. The 88% three-year overall survival rate in operable patients treated with BED ≥ 100 Gy was consistent with single institutional results (a 3-year overall survival rate of 88% in 29 medically operable patients) reported by Uematsu et al.[5] The patients in that study (from the Medical Defense College, Saitama, Japan) were not included in the current multiinstitutional study. Survival rates after STI for BED ≥ 100 Gy may well match those after lobectomy for Stage I NSCLC. We believe that good treatment outcomes from STI depend on a high BED, a large single dose, a short treatment period, and delivery of a modest dose to a large lung volume. STI can reduce substantially overall treatment time from

TABLE 5
Comparison of STI Methods and Local Control Rates for Stage I Nonsmall Cell Lung Carcinoma

Author	No. of patients	Total tumor dose (Gy)	Single dose (Gy)	Treatment time (days)	BED (Gy)[a]	Safety Margin (mm)[b]	Breath-hold or respiratory gating	Image-guided repositioning	Median follow-up (mos)	Local disease recurrence (%)
Uematsu et al.[5,27]	50	50–60	5–6	5–12	100–120	0	No	Yes	60	6
Nagata et al.[6,28]	27	48	12	12–13	106	0	No	Yes	19	0
Fukumoto et al.[7]	17	48–60	6–7.5	14	99–137	0	Yes	Yes	24	6
Hof et al.[29]	10	19–26	19–26	1	55–94	5	Yes	No	15	20

Gy: gray; STI: stereotactic irradiation; BED: biological effective dose (α/β = 10).

[a] BED was recalculated at the isocenter.

[b] Safety margin: subtract the clinical target volume and maximum respiratory motion from the planning target volume.

several weeks of conventional radiotherapy to a few days, offering important advantages to the patient.

In conclusion, hypofractionated high-dose STI with BED < 150 Gy represents a feasible and beneficial method for obtaining curative treatment of patients with Stage I NSCLC. Local control and survival rates were better for BED ≥ 100 Gy than for BED < 100 Gy for all treatment methods and schedules. Survival rates for STI in selected patients (medically operable and BED ≥ 100 Gy) were excellent and reproducible among institutions, irrespective of specific treatment methods, and were potentially equivalent to those of surgery. The current study was a retrospective review, and unknown selection biases for treated and analyzed patients may have been present. Moreover, treatment parameters were very heterogeneous. However, STI may become a standard radical treatment strategy for Stage I NSCLC, at least for compromised patients. More patients and longer follow-up, or a prospective Phase II study based on a single treatment schedule followed by a Phase III trial comparing surgical outcomes with those of STI, are necessary to determine standard treatments for Stage I NSCLC.

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Clinical outcomes of stereotactic radiotherapy for stage I non-small cell lung cancer using a novel irradiation technique: patient self-controlled breath-hold and beam switching using a combination of linear accelerator and CT scanner☆

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Breath-hold;
CT-guided

Summary We have developed a novel irradiation technique for lung cancer that combines a linear accelerator and CT scanner with patient-controlled breath-hold and radiation beam switching. We applied this technique to stereotactic three-dimensional (3D) conformal radiotherapy for stage I non-small cell lung cancer (NSCLC) and evaluated the primary therapeutic outcomes. A total of 35 patients with stage I (15 IA, 20 IB) primary NSCLC (20 adeno, 13 squamous cell, and 2 others) were treated with this technique. Patients ranged from 65 to 92 years old (median, 78 years). Twenty-three (66%) patients were medically inoperable due to mainly chronic pulmonary disease or high age. Three-dimensional treatment plans were made using 10 different non-coplanar dynamic arcs. The total dose of 60 Gy was delivered in 10 fractions (over 5–8 days) at the minimum dose point in the planning target volume (PTV) using a 6 MV X-ray. After adjusting the isocenter of the PTV to the planned position by a unit comprising CT and linear accelerator, irradiation was performed under patient-controlled breath-hold and radiation beam switching. All patients completed the treatment course without complaint. Complete response (CR) and partial response (PR) rates were 8/35

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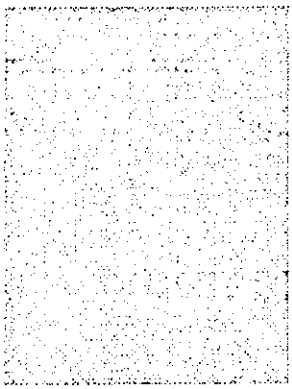

(23%) and 25/35 (71%), respectively. Pulmonary complications of National Cancer Institute-Common Toxicity Criteria grade >2 were noted in three (9%) patients. During follow-up (range, 6—30 months; median, 13 months), two (6%) patients developed local progression and five (14%) developed distant or regional lymph node metastases. Two-year overall survival rates for total patients and medically operable patients were 58 and 83%, respectively. In conclusion, this new irradiation technique, utilizing patient-controlled radiation beam switching under self-breath-hold after precise alignment of the isocenter, allows safe high-dose stereotactic radiotherapy with sufficient margins around the CTV and reduced treatment times. Based on the initial results, excellent local control with minimal complications is expected for stage I NSCLC.

1. Introduction

Lung cancer is the leading cause of mortality among males in Japan. Despite continued research into novel therapeutic strategies, 5-year survival rates for lung cancer remain at approximately 15% [1]. One of the main reasons for this disappointing survival rate is the relatively late diagnosis of lung cancer. However, lung cancers are increasingly being detected in the earlier stages, thanks to the routine use of computed tomography (CT). For early stage lung cancers, the cure rate is 29—72% if surgical resection of the tumor can be achieved [2]. Surgical resection may not be an option for lung cancer patients with tobacco-related illnesses, severe cardiovascular disease, or other medical conditions. Other patients refuse surgery for personal reasons. Historical 5-year survival rates for early stage lung cancer patients treated using conventional radiotherapy are 0—42% [3]. Recently, fractionated high-dose stereotactic radiotherapy (SRT) has been actively performed for early stage lung cancer [4—6]. In a landmark study by Uematsu, SRT was performed using a novel combination of CT scanner and linear accelerator (linac) [4,7]. This combined unit allowed visualization of the tumor at the time of radiotherapy, directing multiple non-coplanar beams of radiation to converge on the tumor with great accuracy. Such real-time CT-guided treatment provides precise targeting of the tumor and maximal sparing of normal lung tissues.

SRT has focused attention on the need to control tumor motion due to respiration using methods that prevent enlargement of the irradiated lung volume, such as respiratory gating, active breath control, or breath-holding. We developed a new irradiation technique comprising breath-hold and patient-controlled radiation beam switching with a moving CT scanner and linac unit (linac-CT) [8]. The current study aimed to apply this technique to SRT for stage I non-small cell lung cancer (NSCLC) and to evaluate the resultant primary clinical outcomes.

2. Material and methods

2.1. Eligibility criteria

All patients enrolled in this study satisfied the following eligibility criteria: (1) identification of T1N0M0 or T2N0M0 primary lung cancer on chest and abdomen CT, bronchoscopy, bone scintigram, and brain magnetic resonance imaging; (2) histologically confirmed NSCLC; (3) tumor diameter <60 mm; (4) performance status according to World Health Organization guidelines ≤2; (5) demonstrated ability to maintain breath-hold for more than 10 s; (6) demonstrated ability to understand and perform self-breath-hold and radiation beam control. Patients were informed as to the concept, methodology, and rationale of this treatment. Written informed consent was obtained from all patients. This study was approved by the ethics committee of our institution.

2.2. Patient characteristics

Between July 2000 and October 2002, a total of 38 patients were identified as candidates for the irradiation procedure. However, three patients (8%) were excluded, as they could not suitably perform self-breath-holding and beam switching techniques. A summary of patient characteristics is provided in Table 1. A total of 35 patients were treated using this irradiation procedure. Fourteen patients displayed pulmonary emphysema or fibrosis before treatment. Twelve patients were considered medically operable, but had refused surgery or were advised to select SRT by medical oncologists. The remaining 23 patients were judged medically inoperable due to poor respiratory function, advanced age, or other chronic illness.

2.3. Treatment methods

Treatments were delivered using our newly developed unit, comprising a linear accelerator (linac)

Table 1 Patient characteristics

Total number of cases	35
Age (years)	
Median	78.0
Range	65–92
Gender	
Male	27
Female	8
Histology	
Adenocarcinoma	20
Squamous cell carcinoma	13
Unclassified non-small cell lung cancer	2
Stage	
IA (T1N0)	15
IB (T2N0)	20
Tumor diameter (mm)	
Median	33
Range	10–48
Performance status	
WHO-0	15
WHO-1	17
WHO-2	3
Reason for non-surgical treatment	
Poor respiratory function	12
Other disease	5
Old age	6
Patient refusal	4
Physician recommendation	8

(EXL-15DP, Mitsubishi Electric, Tokyo, Japan) coupled to a CT scanner (Hi-Speed DX/I, GE Yokogawa Medical Systems, Tokyo, Japan) and sharing a common couch (Fig. 1A). The center of the CT image was aligned with the isocenter of the linac accelerator when the couch was rotated 180°. During scanning, the CT-gantry moved along rails on the floor while the table remained stationary [8]. Accuracy of matching between linac isocenter and CT image center was $\leq$0.5 mm.

In order to reproduce and maintain tumor position during irradiation, patients were trained in procedures for self-breath-holding at inspiration. Reproducibility of tumor position under self-breath-hold was measured by three repeated CT scans that were performed to obtain randomly timed images of 2 mm thickness in the vicinity of the tumor during self-breath-hold. Maximum difference in the center of tumor position for the three CT scans was then calculated. The uncertainty concerning the reproducibility of patient-controlled breath-hold has previously been presented [9]. Chest CT under self-breath-hold was performed for each patient and a plan was established with the help of a three-dimensional (3D) treatment-planning computer (FOCUS, version 3.2.1, CMS, St. Louis, MO). Patients were positioned on the CT table and a skin marker for the temporary isocenter was placed using the cross-hair laser system. An example of the 3D treatment plan is showed in Fig. 2. Clinical target volume (CTV) was equal to the gross tumor volume (GTV) delineated on CT images displayed with a window level of −300 Hounsfield units (HU) and a window width of 1700 HU. Planning target volume (PTV) was determined on CT images as the CTV plus the maximum difference of the tumor position measured on the aforementioned three repeated CT scans performed during self-breath-holding with an additional margin of 5 mm to compensate full internal margin including intra-session reproducibility. Since the tumor position was adjusted to the planned position before every session using CT images, set-up error was neglected [8]. Elective nodal irradiation to the hilar and mediastinal regions was not delivered.

A flowchart of the irradiation process is shown in Fig. 3. The isocenter of the PTV was visually adjusted with CT images of 2 mm thickness taken before every radiotherapy fraction to correspond to the planned isocenter under patient self-breath-hold using the CT scanner unified with the linac (Fig. 1B). The couch was rotated 180° so that the rotational center of the CT-gantry corresponded to the isocenter of the linac. A signal indicating readiness to start irradiation was given by a radiation technologist when alignment was obtained (Fig. 1C). Irradiation was started only when both switches for the patient and the console of the linac were turned on. The actual switching of the radiation beam was delayed <0.1 s behind the patient's switching. The linac delivered a maximum of 400 monitor units/min. Patients determined their breath-holding time and controlled radiation beam as often as needed until the prescribed monitor units were completed. Radiation technologists were able to stop irradiation whenever necessary.

Tumor position during each radiotherapy session was complementarily verified using an electronic portal-imaging device. Electronic portal images (EPIs) were real-time and taken every 2 s during irradiation. Whenever the tumor was visually determined to move beyond the PTV on EPI, the radiation technologist turned off the radiation beam and irradiation was restarted after realigning the tumor under patient self-breath-hold. Mean time for one radiotherapy session, including patient set-up, adjustment of the isocenter, and irradiation, was approximately 30 min.