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SPECIAL CONTRIBUTION

Progress of Management and Outcome of Limited Stage Small Cell Lung Cancer in the Past Decade

Ritsuko U. Komaki[1]

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In the USA, an estimated 219,440 patients will be diagnosed with lung cancer in 2009. Small cell lung cancer comprises approximately 16-20% of all lung cancer. One fifth of them will have limited stage small cell lung cancer. The integration of thoracic radiotherapy (TRT) with systemic chemotherapy for the treatment of limited-stage small cell lung cancer (LSCLC) has been widely studied. Two meta-analyses, published in the early 1990s, confirmed that adding TRT to chemotherapy significantly improved long-term survival for patients with LSCLC. A recent overview of prospective research in LSCLC, included 26 randomized clinical trials initiated by cooperative groups in North America between 1972 and 1992, and only 5 studies showed statistically significant survival prolongation in the experimental arm compared with the control arm. *All five positive trials studied some aspect of TRT*. Traditionally, modest total doses of radiation, ranging from 45-50 Gy, were employed because of the observed responsiveness of small-cell lung cancer to radiotherapy. Although high clinical response rates are expected with combined modality therapy, durable local tumor control is poor when modest-dose, conventionally fractionated TRT is employed. Intensifying the radiotherapy course by accelerating the time to complete treatment (while maintaining the same nominal total radiation dose) appears to be an effective strategy in LSCLC. Intergroup trial 0096 (INT 0096) randomized patients to either conventional (180 cagy QD × 25 fractions [45 Gy in 5 weeks]) or hyperfractionated, accelerated (150 cagy BID × 30 fractions [45 Gy in 3 weeks]) TRT. TRT was initiated with the first cycle of etoposide/cisplatin (PE) chemotherapy. Mature results of this trial demonstrate statistically significant improvement in overall survival for the accelerated TRT. Five-year survival was 26% with accelerated RT compared with 16% for patients receiving conventional TRT. Patterns of recurrence reflected improved local and local plus distant recurrence rates with accelerated TRT, suggesting that local treatment has a significant impact on ultimate outcome in LSCLC. The cumulative rate of local tumor relapse was 75% with once-daily TRT compared with 42% with twice-daily TRT. The major increased toxicity of the accelerated regimen was a doubling of the severe (e.g. grade 3 + 4) acute esophagitis rate from 11% by daily RT to 27%, although TRT was not done by conformal radiotherapy. To improve local control better than 42% without increasing rate of esophagitis, Radiation Therapy Oncology Group (RTOG) has studied a concomitant boost (CB) strategy in LSCLC. This approach allows acceleration of TRT but only requires hyperfractionated TRT during part of the treatment course. Moreover, BID large field TRT can be avoided. A phase I trial has been completed assessing the MTD for concomitant boost TRT in LSCLC (R 9712). TRT was initiated with the first of 4 cycles of PE chemotherapy. Accelerated TRT, 61.2 Gy in 34 fractions of 1.8 Gy/Fx in 5 weeks, with BID TRT during the final 9 treatment days, was determined to be the maximum tolerated dose (MTD). A subsequent phase II study, RTOG 0239, employed the 61.2 Gy concomitant boost regimen with concurrent chemotherapy for LSCLC resulted in 17% acute Gr.3 + esophagitis compared to 27% with

[1]Department of Radiation Oncology, University of Texas, M.D. Anderson Cancer Center, Houston.

Reprints: Ritsuko U. Komaki, Department of Radiation Oncology, University of Texas, M.D. Anderson Cancer Center, Unit 97, 1515 Holcombe Blvd.-Unit 097, Houston, TX 77030, USA.

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BID TRT with 45 Gy in 3 weeks by INT 0096. The Patterns of Care Study published in 2003 noted that fewer than 10% of patients with LSCLC received this regimen hyperfractionated, accelerated (150 cagy BID × 30 fractions [45 Gy in 3 weeks]) TRT, while more than 80% were treated with QD TRT. The Cancer and Leukemia Group B (CALGB) have studied high-dose QD TRT. CALGB 8837, a phase I study, was designed to determine the maximum-tolerated dose (MTD) of TRT in both standard QD and accelerated BID schedules. The efficacy of radiotherapy can be predicted by calculating the biologic effective dose (BED). The BED reflects the tumor type (doubling time), dose per fraction, nominal total dose and may also take into account the time to complete therapy. In comparison to the accelerated 45 Gy BID regimen studied in INT 0096, both the CALGB TRT regimen of 70 Gy QD and the RTOG concomitant boost approach yield substantially higher Beds. For example, assuming a potential tumor doubling time of 5 days, the predicted increase in BED would range from 1.3 to 1.6 (e.g. 30% to 60% increase in efficacy) for the CALGB and RTOG experimental regimens compared with 45 Gy BID.

PREDICTED BIOLOGIC EFFECTIVE DOSE (BED) OF THORACIC RADIOTHERAPY REGIMENS

In summary, defining an optimal TRT regimen in LSCLC remains critical and will have a major impact on clinical practice. Intergroup study 0096 clearly established that improving the efficacy of thoracic radiotherapy could significantly impact survival in patients with LSCLC, although local control and toxicity will need improvement. Superior outcomes on an experimental arm would lead to establishing a change in the standard of care for patients with LSCLC. Conversely, if the best outcomes were observed with accelerated 45 Gy BID TRT, then the results of this study would provide convincing and definitive evidence for practitioners to adopt this regimen. RTOG 0239 was a phase II study based on the arm 4 of RTOG 97-12 showed excellent local control and lower rates of severe acute esophagitis (ASCO 2009).

Brain metastases are an exceedingly common cause of morbidity and mortality in cancer patients. Without intervention up to 50% of patients with small cell carcinoma of the lung will fail in the CNS. Prophylactic cranial irradiation has been shown to decrease the incidence of brain metastasis and provide an overall survival benefit to patients with limited stage SCLC in complete remission. Despite a survival benefit, some practitioners have hesitated to utilize PCI citing fears of CNS dysfunction secondary to radiation effects.

Previous trials addressing neurocognitive function in patients with SCLC treated with PCI have largely been retrospective and failed to include baseline measures of cognitive function. Large prospective trials have addressed cognitive changes but have been criticized for their testing methods. Traditional indices such as the Karnofsky performance status (KPS) are measures of physical ability and do not address brain function. The mini-mental status examination (MMSE), employed in previous trials, is not a sensitive measure of cognition. MMSE detects only profound dysfunction and fails to measure subtle alterations in learning and memory, executive functioning etc. In contrast, standardized measures of brain function which are easily performed are both specific and sensitive. These measures of NCFT now being used both to stratify patients enrolled in randomized trials and as primary endpoints.

We have studied prospectively for limited small cell lung cancer patients who have been assessed by adequate neurocognitive function before PCI. Amazingly our study has shown 83% of them had already neurocognitive dysfunction before treatment without obvious brain metastasis which was most likely related with paraneoplastic syndrome or micro metastasis in the brain.

We have updated the results of a prospective study formally assessing neuropsychological function in patients with small cell carcinoma of the lung treated with prophylactic cranial irradiation. All patients enrolled were tested prior to cranial irradiation. When possible, patients underwent repeat testing following PCI at early and late intervals.

In 2008, the PCI99 Inter group presented results of a randomized phase III study 720 LS SCLC patients with a complete response to first-line therapy, randomized to receive 25 or 36 Gy PCI. Toxicities and treatment delivery were not different between two arms Patients who received 36 Gy had a nonsignificant decrease in brain metastases and, for unclear reasons, a worse overall survival (P = .03). Thus, PCI at 25 Gy is recommended for LS and ES SCLC patients who respond to first-line therapy.

In summary, we have made progress of the manage-

ment and outcome for limited stage small cell lung cancer by concurrent cisplatin based chemotherapy and TRT followed by PCI for CR patients. Now we need to improve better local control with higher dose of TRT and more effective systemic agents without increasing normal tissue toxicity.

和訳：

野中哲生[1]・中山優子[1]・早川和重[2,3]

索引用語 —— 小細胞肺癌，放射線治療，予防的全脳照射

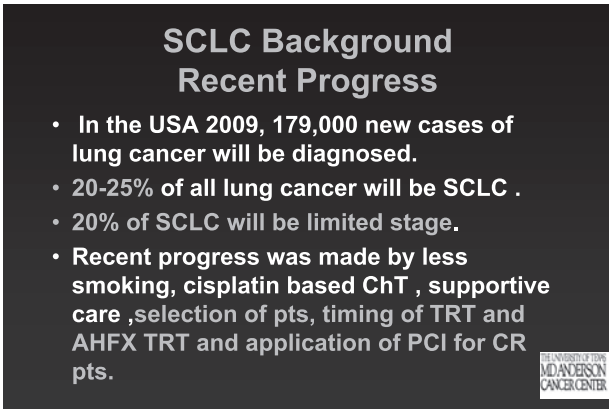
はじめに

米国の 2009 年肺がん新患数は推定 179,000 人である．小細胞肺癌は全肺癌の 20～25% を占め，そのうち約 20% が限局型小細胞肺癌（LSCLC：Limited-stage small cell lung cancer）といわれている（図 1）．

限局型小細胞肺癌における胸部への放射線治療

LSCLC に対する治療では 1990 年代に報告された Meta-analysis の結果から，化学療法単独だけではなく胸部への放射線治療（TRT：Thoracic radiotherapy）の併用が標準的な治療として位置付けられ，その併用時期については可能な限り早期に併用することが重要であるとされた．[1,2] TRT の線量は通常分割で 45～50 Gy とすることが一般的であり，一次効果は良好であったが，十分な局所制御期間は得られなかった．Turrisi らは LSCLC 症例に対し化学療法はシスプラチン（CDDP）＋エトポシド（VP-16）を用い，照射方法別に通常分割群（QD 群：1 回 1.8 Gy，1 日 1 回，総線量 45 Gy/5 週間），加速多分割群（BID 群：1 回 1.5 Gy，1 日 2 回，総線量 45 Gy/3 週間）に症例を割り付ける無作為比較試験を行った（INT 0096，図 2）．[3] 治療成績は QD 群の 5 年生存率が 16%，局所再発率が 75% であったのに対し，BID 群では 5 年生存率 26%，局所再発率 42% と有意に良好な結果が得られた．また，BID 群で局所再発だけではなく遠隔転移の発生が有意に低率であったため，LSCLC の治療では局所に強力な治療を施行することによって良好な局所制御率を導くことが可能となり，さらに生存率の向上が期待できることが示唆された（図 3）．この研究では 3 次元的な放射線治療が施行されていなかったこともあり，BID 群で重篤な食道炎が 27% と，QD 群の 11% に比較して有意に高率で認められたことが問題となった．

RTOG（Radiation Therapy Oncology Group）は INT 0096 における BID 群の治療効果を担保し，さらに急性期に認められた有害事象を抑えることに注目し，TRT の至適線量・照射方法を検討するための第 I 相試験（RTOG 9712）を行った．[4] このトライアルでは化学療法は CDDP＋VP-16 を 4 コース，照射法には Concomitant boost（CB）法を用いた．TRT の Maximum tolerated dose（MTD）は 61.2 Gy（1 コース目の化学療法に同時併用，1 回 1.8 Gy，34 分割/5 週間，最後の 9 回のみ 1 日 2 回（CB））であった．この結果が引き続き行われた第 II 相試験（RTOG 0239）で用いられた（図 4，5）．[5] RTOG 0239 では重篤な食道炎の発生は 18% であり INT 0096



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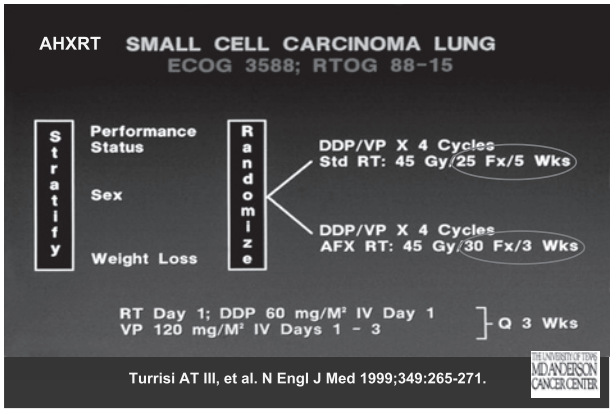
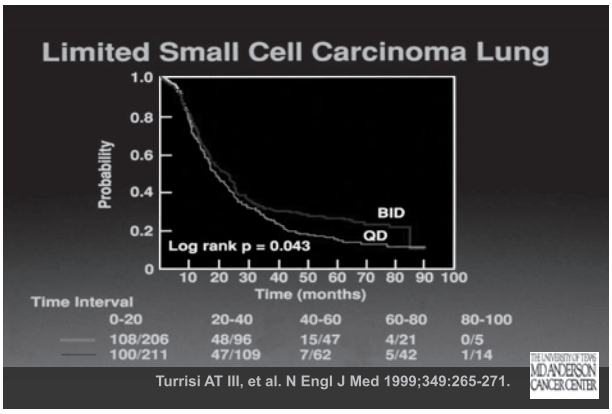


図 2.

[1]神奈川県立がんセンター放射線腫瘍科；[2]第 50 回肺癌学会総会会長；[3]北里大学医学部放射線科学．

責任著者：野中哲生，神奈川県立がんセンター放射線腫瘍科，〒241-0815　神奈川県横浜市旭区中尾 1-1-2（e-mail: tnonaka@kcch.jp）．



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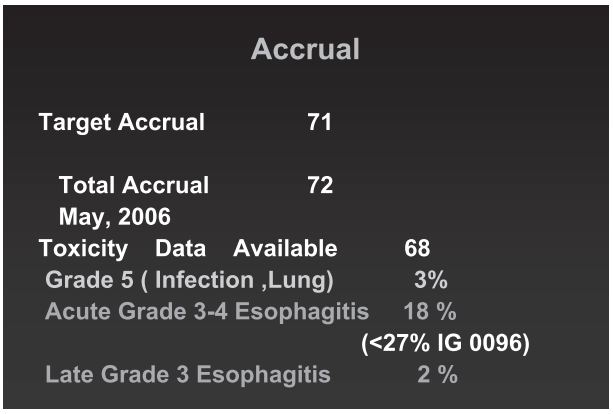

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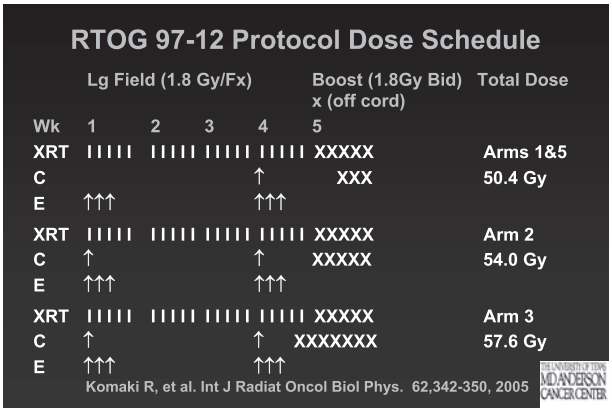

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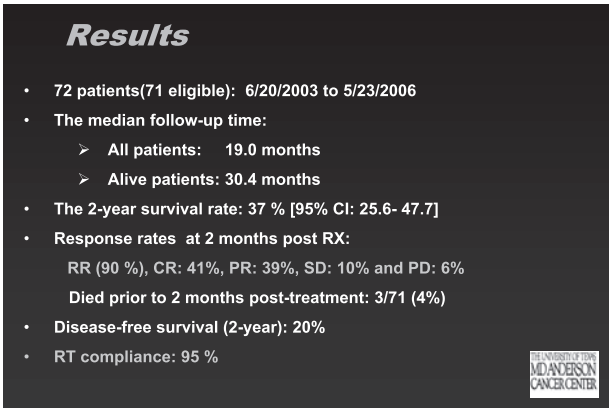

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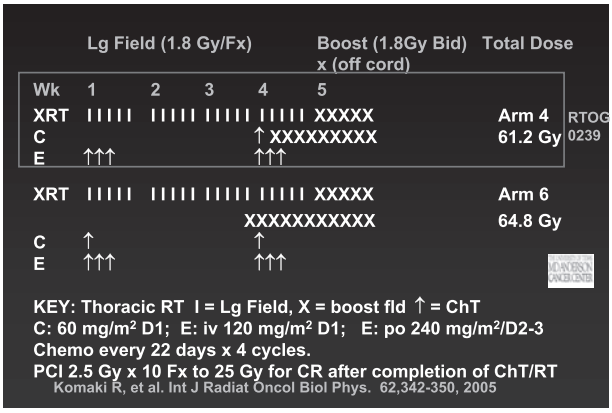

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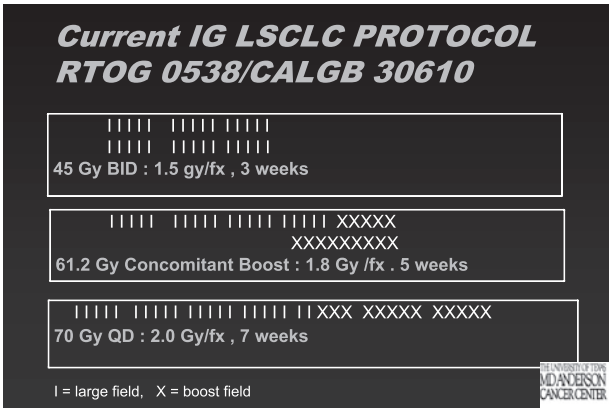

図 8.

における BID 群の 27% を下回る結果が得られ（図 6），治療成績は奏功率 90%，2 年生存率 37% と良好であった（図 7，エンドポイントが INT 0096 と異なるためか単純な比較はされなかった）．TRT に CB 法を導入することによって，広い照射野での多分割照射が避けられるため重篤な有害事象の発症を低減し，かつ病変に対しては強度の高い治療を施行することが可能となった．一方，CALGB（The Cancer and Leukemia Group B）では BID および QD の至適線量を第 I 相試験で検討した結果，MTD がそれぞれ 45 Gy/30 分割/3 週間以上，70 Gy/35

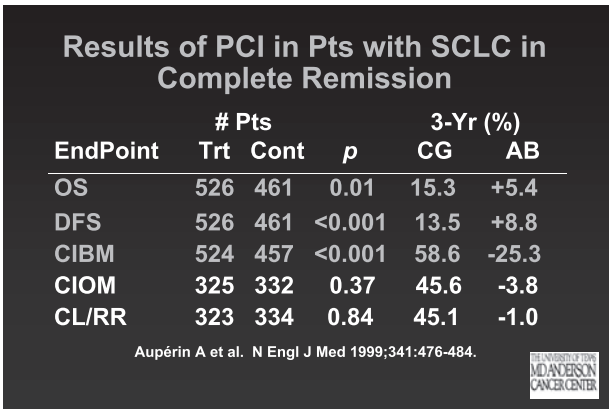

図 9.

図 10.

分割/7 週間以上であった.[6] 現在 RTOG と CALGB の共同で TRT を BID 群（45 Gy), CB（61.2 Gy), QD 群（70 Gy）とした無作為比較試験が進行中である（RTOG 0538/CALGB 30610，図 8）.

予防的全脳照射

LSCLC では中枢神経再発が約 50% に見られると報告されていることから,[7] 予防的全脳照射（PCI：Prophylactic cranial irradiation）による脳転移の制御も LSCLC の治療成績向上における命題の一つであった．Aupérin らは Meta-analysis の手法で局所の完全寛解（CR）が得られた 987 例の LSCLC 症例において PCI が予後に与える影響について解析した.[8] PCI が施行された 526 例の治療成績は 3 年全生存率 20.7% で，コントロール症例の 15.3% と比べ有意に良好であった．また PCI によって原病死のリスクおよび中枢神経再発のリスクが有意に低下したと報告した（図 9）.

PCI の有用性が報告された一方で，PCI による脳の高次機能障害についても検討された.[9-11] Komaki らが MD アンダーソンキャンサーセンターにおいて初回治療で CR となった LSCLC の 69 例を対象に PCI による中枢神経障害について前向きに検討を行ったところ,[10,11] PCI 施行前に思考や記憶など何らかの認識障害を有する症例が約 50% に認められた．対象となった 69 例のうち 67 例で 25 Gy/10 分割の PCI が施行されたが，PCI 終了後の認識障害は有意に増悪していた．しかしながら，その後の経過で認識障害は PCI 施行前と同レベルに改善し，その他の機能障害の出現も認められなかった（中枢神経に再発した症例は除く）. また, PCI の線量/分割については Le Péchoux らによる初回治療で CR が得られた 720 例を対象とした第 III 相試験で，25 Gy/10 分割（通常照射：SD）と 36 Gy/18 分割あるいは 1 日 2 回 24 分割（高線量照射：HD）の治療成績が検討された.[12] HD 群では SD 群と比較して有意な中枢神経再発の抑制効果は認められず，さらに生存期間は SD 群を下回る結果であった（図 10）．また，脳の高次機能障害は HD 群で SD 群よりも高い確率で出現した．したがって，現時点では標準的な PCI は 25 Gy/10 分割とされている.

まとめ・今後の展望

今後，分子標的薬剤を含めた新規薬剤の開発が期待され，さらにこれらと放射線治療を組み合わせることによって治療成績が向上する可能性があると思われる．また，胸部放射線治療については照射するタイミングや線量だけではなく，治療計画におけるターゲットの決定方法も重要であると考えられる.

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