総　　説

画像診断の新たな展開：MRIによる治療効果や予後の予測

九州大学大学院医学研究院 臨床放射線科学分野

畠 中 正 光，吉 浦　　敬，塩 山 善 之，本 田　　浩

はじめに

大まかに言って，画像診断はできるだけ被験者に負担をかけることなく，1）病変の有無を診断する，2）病変の良悪性を鑑別する，3）病変の進行度を診断する，という3つの大きな役割を期待されてきた．しかし，最近の画像診断技術の進歩には目を見張るものがあり，その役割は，「現状の正確な評価（従来の形態診断）」から「将来の予測（治療効果や予後の予測）」にまで及びつつある．治療効果や予後の予測に関しては，FDG-PET等をはじめとする核医学分野の研究が以前から盛んであるが，今回は磁気共鳴医学分野（MRI）の研究について，比較的最近のMRI技術である拡散強調画像（Diffusion-Weighted Imaging，DWI）およびDWIから計算される見かけの拡散係数（Apparent Diffusion Coefficient，ADC）を用いた腫瘍性病変の治療効果や予後の予測に関する研究成果を紹介する．

1．DWIとその臨床応用

拡散とは，エネルギーや粒子が濃度の不均一な状態から均一な状態に変化していくことを指す．MRIを用いて，プロトンのランダムな動きの程度を信号強度（コントラスト）として表現した画像がDWIであり，そこから計算されるプロトンの動きやすさの指標がADCである．乱暴な定義ではあるが，一般の臨床家にとっては正確な定義はかえってわかりにくい[1)2)]．

現在のMRI装置の技術的制約から大まかに計算すると，DWIの信号強度コントラストは直径数μm程度の三次元空間内でのプロトンのランダムな動きを表現していることになる．この文言には違和感を持たれる方が多いかもしれない．理論的には，拡散は時間の関数ではない．温度・拡散の対象となる粒子の大きさ・周りにある物質の粘性の関数（Stokes-Einsteinの式）である．しかし，現実世界では技術的制約のためにある程度の計測時間が必要となり，現在の臨床用MRI装置ではこの計測時間が数十msとなるために，上記のような範囲の三次元空間となる．現在のMRI装置のDWI条件下で計測可能なプロトンのランダムな動きの範囲は丁度細胞の大きさに近いため，DWIの信号強度は細胞レベルの組織構造（プロトンのランダムな運動を妨げる膜構造等の存在の多寡）を反映していることになり，脳梗塞の早期診断[3)]（図1，2）・病変の良悪性鑑別[4)〜7)]（図3）・再発病変の早期同定[8)]などに応用されてきた．最近では，DWIに方向性・定量性を加味したDiffusion Tensor Imaging（DTI）を用いて，伸縮に伴う骨格筋の微細構造変化とDTIのパラメータとの関連に関するin vivo研究も進んでおり，DWIが細胞レベルの微細構を直接反映していることが臨床用MRI装置でも確認されている[9)10)]．プロトンの拡散範囲が丁度細胞の大きさに近くなるように予めDWIのパラメータを設定していたように思われるが，筆者の個人的解釈では機械的制約で偶々こうなったのであり，その後臨床データが蓄積されて，後からそれらしく解釈が進んだように思う．筆者の経験では，MRIの技術者は生物学の知識はほとんど持っていないし，技術者はいつの時代でも最高のパフォーマンスに価値を置くものであって，あえてそれ以下に抑えておくようなことはしない．この辺りにいろいろな分野の専門家が集まって，侃侃諤諤，意見をぶつけ合ってこそ新たな価値ある研究が生まれる所以がある

Masamitsu Hatakenaka, Takashi Yoshiura, Yoshiyuki Shioyama and Hiroshi Honda
Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University
Future of Diagnostic Radiology: Prediction of Treatment Outcome using MRI

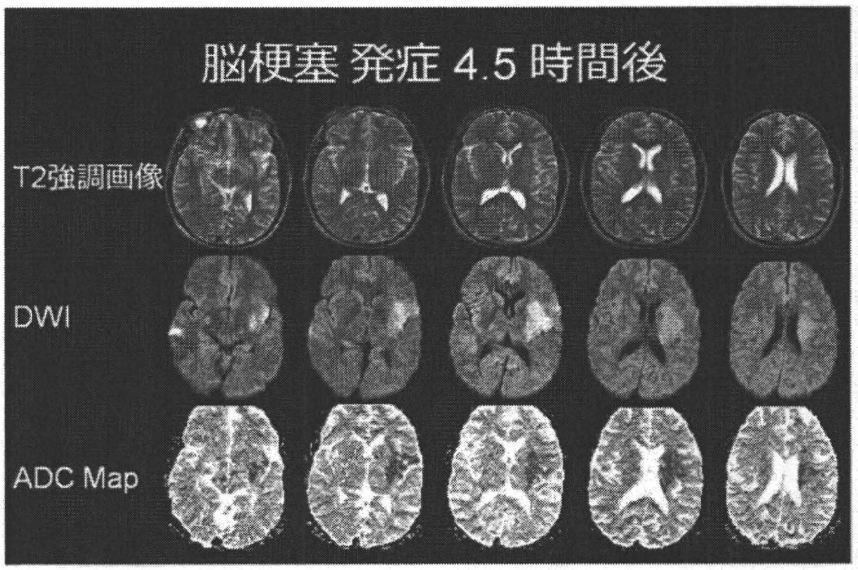


図1 DWIによる急性期脳梗塞の診断
T2強調画像では病変の同定は困難だが，DWIやADC mapでは容易である．

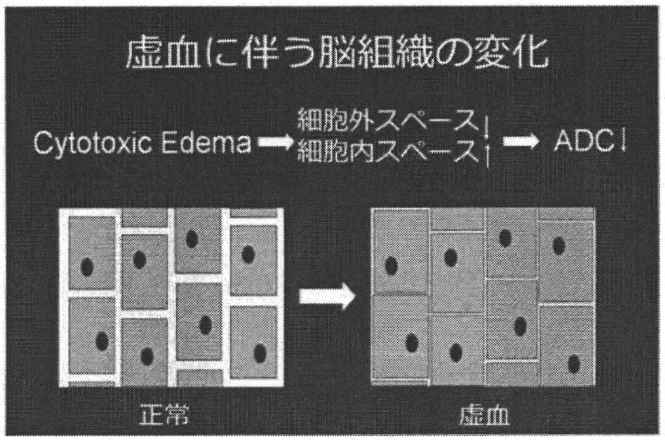


図2 急性期脳梗塞病巣の拡散に変化が生じるメカニズム
虚血に陥った細胞は膨張し，その結果細胞外腔のプロトンが自由に動ける空間が狭くなりADCが低下する（DWIでは高信号になる）のではないかと考えられている．

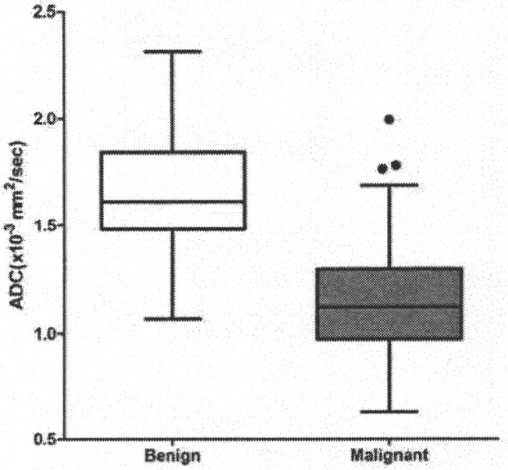


図3 乳腺腫瘍のADC比較
粘液癌などを除いて，一般に悪性腫瘍の方がADCは低い．

と思う．勿論，技術が進めばもっと短時間でDWI計測可能となる訳で，そうなるともっと小さな範囲内でのプロトンの動き易さ（たとえば細胞内の構造）を反映させることも可能となり，新たな展開が期待される．

2．治療前ADCによる腫瘍性病変の治療効果予測

脳腫瘍

Oh J等は，手術と術後の化学放射線治療が行われた28例のglioblastoma multiformeについて，治療前のADCが低い患者の生存期間は短かったと報告している[11]．Higano S等は，手術と術後の放射線治療が行われた37例のmalignant astrocytic tumorについてretrospectiveに調べた結果，治療前のminimum ADCが低いグループの方が予後不良であったと報告している[12]．Murakami R等も同様に手術と術後の化学放射線治療が行われた79例のmalignant supratentorial astrocytomaについて，治療前のminimum ADCが低いと予後が悪かったと結論している[13]．これに対し，Mardor Y等は，12例の脳腫瘍20病変（grade III-IVのglioma 3例，転移性脳腫瘍9例）に関して研究した結果，治療前のADCが低い方が放射線治療後の縮小率は大きかったと報告しており[14]，脳腫瘍に関する結果は必ずしも一致していない．

頭頸部癌

機能温存や社会的理由から化学放射線治療が選択されることが多い頭頸部癌に関しては，以下の報告がなされている．Kato H 等は，28 例の頭頸部扁平上皮癌について，（化学）放射線治療後の原発巣の縮小率と ADC には逆相関があった，つまり，治療前の原発巣の ADC が低い症例では縮小率が高かったと報告している[15]．Kim S らも同様に，33 例の頭頸部扁平上皮癌について，治療前 ADC が低い症例では縮小率が高かったと報告している[16]．ただし彼らは，原発巣ではなく転移リンパ節の ADC およびその縮小率を用いている．頭頸部は，空気と組織が隣接しており，アーチファクトが生じやすく原発巣をうまく描出するにはそれなりの工夫を要する．我々が頭頸部原発扁平上皮癌 40 例の局所制御（化学放射線治療効果は治療終了後数ヶ月間持続すると考えられるので，臨床的には治療終了直後の原発巣の縮小率よりもその後の再発の有無の方が重要になってくる）について解析した結果でも，治療前の原発巣 ADC が低い方が局所制御率は高かった．単変量解析では，T 因子・治療方法（化学放射線治療 vs. 放射線治療単独）と並んで治療前の原発巣 ADC は局所制御と関連していることが示され，多変量解析でも T 因子・治療前の原発巣 ADC と局所制御との関連が確認された（2010 European Congress of Radiology, No.1592, 図 4 ～ 7）．

メカニズム

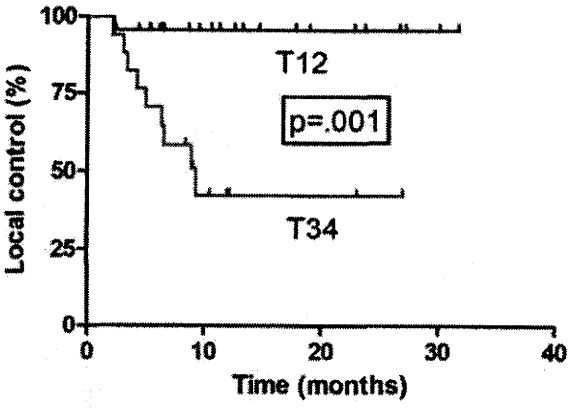


図 4　T 因子による頭頸部扁平上皮癌局所制御率の比較
T3, T4 群に比して，T1, T2 群の局所制御率が高い．結果は当然であるが，データの取得方法や解析方法の信頼性を示すものである．

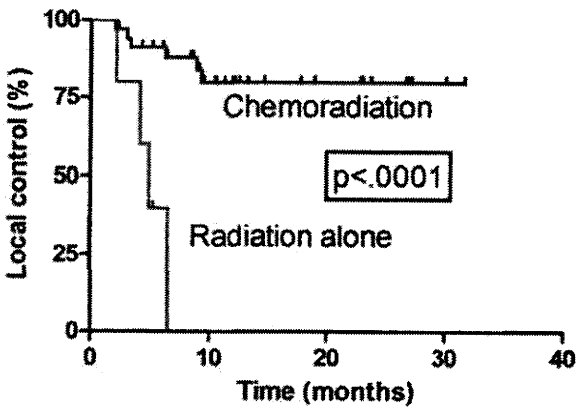


図 5　治療方法による頭頸部扁平上皮癌局所制御率の比較
放射線治療単独群に比して，化学放射線治療群の局所制御率が高い．図 4 同様，結果は当然であるが，データの取得方法や解析方法の信頼性を示すものである．

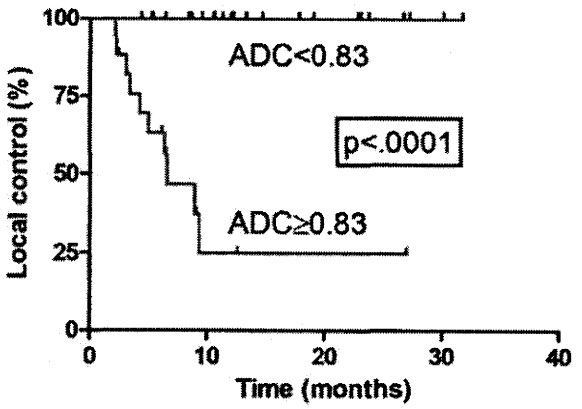


図 6　原発巣 ADC による頭頸部扁平上皮癌局所制御率の比較（T1～T4 症例）
原発巣 ADC が $0.83x10^{-3}mm^2/sec$ 未満の群では，全例局所制御されている．

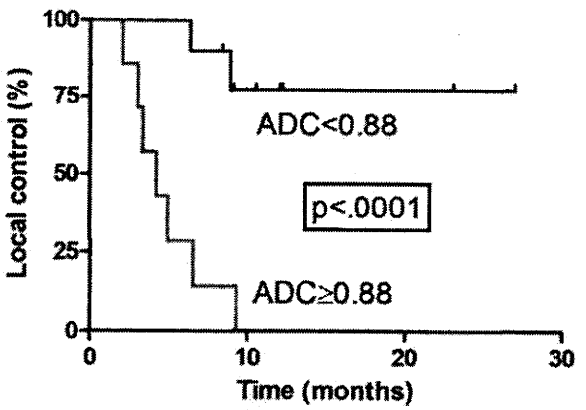


図 7　原発巣 ADC による頭頸部扁平上皮癌局所制御率の比較（T3～T4 症例）
図 4，6 を見比べると，T1, T2 症例は ADC が低く病変も小さいので局所制御されたとの解釈も成り立つが，T3, T4 症例に限って ADC の違いと局所制御率との関連を解析しても，原発巣 ADC が低い群の局所制御率が高い．

頭頸部癌に限らず体部の悪性腫瘍では，一般に治療前のADCが低い方が化学放射線治療効果が高いとする報告が多い．従来から，リンパ腫のように小さな細胞がコンパクトに配列されて細胞密度が高い腫瘍は放射線感受性が高いことが知られている．細胞密度が高い腫瘍は，プロトンが自由に動ける細胞外腔の割合が小さくADCも低値になると考えられており，ADCと治療効果との関連に関する研究結果は従来からの知見と一致している．Malignant astrocytic tumorなどの脳腫瘍の場合は，腫瘍内の悪性度の高い部分が予後に大きく影響すると考えられるので，腫瘍内にいくつかの計測部位を設けそのうち最低値を示すADCを腫瘍のADCと定義して研究することが多い．体部の腫瘍の場合は，同一臓器内の比較的組織形の似た悪性腫瘍内（扁平上皮癌内や腺癌内）でADCの比較を行うので，腫瘍全体の平均ADCを腫瘍のADCと定義することが多い．この辺りの計測方法の差が脳腫瘍とそれ以外の腫瘍との結果の違いに影響していると推定される．

3．治療開始後比較的早い段階でのADC変化率による腫瘍性病変の治療効果予測

治療効果の予測はできるだけ早い段階でなされた方がメリットは大きいので，治療開始前に予測できるに越したことはないが，治療開始後比較的早い段階でのADC変化の程度と治療効果との関連に関しても幾つかの報告がなされている．勿論，外科的治療の場合はこの予測方法は使用できないので，化学療法や放射線治療の場合が対象となる．結果を概略すると，治療開始後早期からADCの増加率が高い場合は治療効果も高く，ADCが変化しない場合や減少する場合は治療効果が低いとする報告が多い[17)～22)]．メカニズムとしては，治療効果の高い腫瘍では早期の段階からapoptosisや微小なnecrosisが生じやすいために，プロトンの拡散制限が取れやすいので，ADCが上昇するとの解釈が多い．

まとめ

MRIの特殊な撮像方法の一つであるDWIおよびそこから計算されるADCについて，最近の臨床応用である治療効果や予後の予測に関して最近の研究結果を概説した．勿論，病変の進行度（TNMやstaging）も治療効果と関連しているので予測因子の一つであるが，ADCと言う比較的新しいパラメータは脳梗塞の早期診断や腫瘍の良悪性鑑別だけでなく，画像による治療効果予測の新たな切り口として有望視されている．今回の概説をきっかけとして読者の画像診断に対する興味が少しでも増す事があれば望外の幸せである．

参 考 文 献

1] 青木茂樹 阿部修 編著 これでわかる拡散MRI 第1版 秀潤社 東京 2002.
2] 荒木勉 著 拡散MRIブラウン運動，拡散テンソルからq空間へ 第1版 秀潤社 東京 2006.
3) Burdette JH, Ricci PE, Petitti N and Elster AD : Cerebral infarction : time course of signal intensity changes on diffusion-weighted MR images. AJR Am J Roentgenol 171 : 791-795, 1998.
4) Wang J, Takashima S, Takayama F, Kawakami S, Saito A, Matsushita T, Momose M and Ishiyama T : Head and neck lesions : characterization with diffusion-weighted echo-planar MR imaging. Radiology 220 : 621-630, 2001.
5) Guo Y, Cai YQ, Cai ZL, Gao YG, An NY, Ma L, Mahankali S and Gao JH : Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. J Magn Reson Imaging 16 : 172-178, 2002.
6) Eida S, Sumi M, Sakihama N, Takahashi H and Nakamura T : Apparent diffusion coefficient mapping of salivary gland tumors : prediction of the benignancy and malignancy. AJNR Am J Neuroradiol 28 : 116-121, 2007.
7) Hatakenaka M, Soeda H, Yabuuchi H Matsuo Y, Kamitani T, Oda Y, Tsuneyoshi M and Honda H : Apparent diffusion coefficients of breast tumors : clinical application. Magn Reson Med Sci 7 : 23-29, 2008.
8) Vandecaveye V, De Keyzer F, Nuyts S, Deraedt K, Dirix P, Hamaekers P, Vander Poorten V, Delaere P and Hermans R : Detection of head and neck squamous cell carcinoma with diffusion weighted MRI after (chemo) radiotherapy : correlation between radiologic and histopathologic findings. Int J Radiat Oncol Biol Phys. 67 : 960-971, 2007.
9] Hatakenaka M, Matsuo Y, Setoguchi T, Yabuuchi H, Okafuji T, Kamitani T, Nishikawa K and Honda H : Alteration of proton diffusivity associated with passive muscle extension and contraction. J Magn Reson

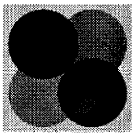
Imaging. 27 : 932-937, 2008.
10] Hatakenaka M, Yabuuchi H, Sunami S, Kamitani T, Takayama Y, Nishikawa K and Honda H : Joint position affects muscle proton diffusion : Evaluation with a 3-T MR system. AJR Am J Roentgenol. 194 : W208-211, 2010.
11) Oh J, Henry RG, Pirzkall A, Lu Y, Li X, Catalaa I, Chang S, Dillon WP and Nelson SJ : Survival analysis in patients with glioblastoma multiforme : predictive value of choline-to-N-acetylaspartate index, apparent diffusion coefficient, and relative cerebral blood volume. J Magn Reson Imaging. 19 : 546-554, 2004.
12) Higano S, Yun X, Kumabe T, Watanabe M, Mugikura S, Umetsu A, Sato A, Yamada T and Takahashi S : Malignant astrocytic tumors : clinical importance of apparent diffusion coefficient in prediction of grade and prognosis. Radiology. 241 : 839-846, 2006. Epub Oct 10, 2006.
13) Murakami R, Sugahara T, Nakamura H, Hirai T, Kitajima M, Hayashida Y, Baba Y, Oya N, Kuratsu J and Yamashita Y : Malignant supratentorial astrocytoma treated with postoperative radiation therapy : prognostic value of pretreatment quantitative diffusion-weighted MR imaging. Radiology. 243 : 493-499, 2007.
14) Mardor Y, Roth Y, Ochershvilli A, Spiegelmann R, Tichler T, Daniels D, Maier SE, Nissim O, Ram Z, Baram J, Orenstein A and Pfeffer R : Pretreatment prediction of brain tumors' response to radiation therapy using high b-value diffusion-weighted MRI. Neoplasia. 6 : 136-142, 2004.
15] Kato H, Kanematsu M, Tanaka O, Mizuta K, Aoki M, Shibata T, Yamashita T, Hirose Y, Hoshi H. Head and neck squamous cell carcinoma : usefulness of diffusion-weighted MR imaging in the prediction of a neoadjuvant therapeutic effect. Eur Radiol. 19 : 103-109, 2009. Epub Jul 19, 2008.
16] Kim S, Loevner L, Quon H, Sherman E, Weinstein G, Kilger A and Poptani H : Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinomas of the head and neck. Clin Cancer Res. 15 : 986-994, 2009.
17) Chenevert TL, Stegman LD, Taylor JM, Robertson PL, Greenberg HS, Rehemtulla A and Ross BD : Diffusion magnetic resonance imaging : an early surrogate marker of therapeutic efficacy in brain tumors. J Natl Cancer Inst. 92 : 2029-2036, 2000.
18) Mardor Y, Pfeffer R, Spiegelmann R, Roth Y, Maier SE, Nissim O, Berger R, Glicksman A, Baram J, Orenstein A, Cohen JS and Tichler T : Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. J Clin Oncol. 21 : 1094-1100, 2003.
19) Theilmann RJ, Borders R, Trouard TP, Xia G, Outwater E, Ranger-Moore J, Gillies RJ and Stopeck A : Changes in water mobility measured by diffusion MRI predict response of metastatic breast cancer to chemotherapy. Neoplasia. 6 : 831-837, 2004.
20) Hamstra DA, Chenevert TL, Moffat BA, Johnson TD, Meyer CR, Mukherji SK, Quint DJ, Gebarski SS, Fan X, Tsien CI, Lawrence TS, Junck L, Rehemtulla A and Ross BD : Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma. Proc Natl Acad Sci U S A. 102 : 16759-16764, 2005. Epub Nov 2, 2005.
21) Moffat BA, Chenevert TL, Lawrence TS, Meyer CR, Johnson TD, Dong Q, Tsien C, Mukherji S, Quint DJ, Gebarski SS, Robertson PL, Junck LR, Rehemtulla A and Ross BD : Functional diffusion map : a noninvasive MRI biomarker for early stratification of clinical brain tumor response. Proc Natl Acad Sci U S A. 102 : 5524-5529, 2005.
22) Koh DM, Scurr E, Collins D, Kanber B, Norman A, Leach MO and Husband JE : Predicting response of colorectal hepatic metastasis : value of pretreatment apparent diffusion coefficients. AJR Am J Roentgenol. 188 : 1001-1008, 2007.

(参考文献のうち，数字がゴシック体で表示されているものについては，著者により重要なものと指定された分です．)

プロフィール

畠中　正光（はたけなか　まさみつ）
九州大学准教授（九州大学病院・放射線部・副部長）医博
◆**略歴**：1960年高知県に生まれる．1985年九州大学医学部卒業．1993年九州大学大学院医学系研究科博士課程卒業．2006年より現職．
◆**研究テーマと抱負**：MRIやCTを使って，画像診断の新たな展開を模索しています．
◆**趣味**：濫読

Yamashita *et al. Radiation Oncology* 2010, **5**:32
http://www.ro-journal.com/content/5/1/32



RADIATION ONCOLOGY

RESEARCH Open Access

Prescreening based on the presence of CT-scan abnormalities and biomarkers (KL-6 and SP-D) may reduce severe radiation pneumonitis after stereotactic radiotherapy

Hideomi Yamashita*, Shino Kobayashi-Shibata, Atsuro Terahara, Kae Okuma, Akihiro Haga, Reiko Wakui, Kuni Ohtomo and Keiichi Nakagawa

Abstract

Purpose: To determine the risk factors of severe radiation pneumonitis (RP) after stereotactic body radiation therapy (SBRT) for primary or secondary lung tumors.

Materials and methods: From January 2003 to March 2009, SBRT was performed on 117 patients (32 patients before 2005 and 85 patients after 2006) with lung tumors (primary = 74 patients and metastatic/recurrent = 43 patients) in our institution. In the current study, the results on cases with severe RP (grades 4-5) were evaluated. Serum Krebs von den Lungen-6 (KL-6) and serum Surfactant protein-D (SP-D) were used to predict the incidence of RP. A shadow of interstitial pneumonitis (IP) on the CT image before performing SBRT was also used as an indicator for RP. Since 2006, patients have been prescreened for biological markers (KL-6 & SP-D) as well as checking for an IP-shadow in CT.

Results: Grades 4-5 RP was observed in nine patients (7.7%) after SBRT and seven of these cases (6.0%) were grade 5 in our institution. A correlation was found between the incidence of RP and higher serum KL-6 & SP-D levels. IP-shadow in patient's CT was also found to correlate well with the severe RP. Severe RP was reduced from 18.8% before 2005 to 3.5% after 2006 ($p = 0.042$). There was no correlation between the dose volume histogram parameters and these severe RP patients.

Conclusion: Patients presenting with an IP shadow in the CT and a high value of the serum KL-6 & SP-D before SBRT treatment developed severe radiation pneumonitis at a high rate. The reduction of RP incidence in patients treated after 2006 may have been attributed to prescreening of the patients. Therefore, pre-screening before SBRT for an IP shadow in CT and serum KL-6 & SP-D is recommended in the management and treatment of patients with primary or secondary lung tumors.

Introduction

Stereotactic body radiation therapy (SBRT) has been widely used as a safe and effective treatment method for primary or metastatic lung tumors [1]. According to the protocol of Japan Clinical Oncology Group (JCOG) 0403 study [2,3], the absolute contraindication to SBRT was pregnancy. Relative contraindications consisted of (a) a history of irradiation to the concerned site, (b) severe interstitial pneumonitis or pulmonary fibrosis, (c) severe diabetes or connective tissue disease, and (d) common use of steroids. However, these complications preclude other treatment methods in some cases and radiation therapy becomes the only available treatment. Favorable initial clinical results, and local control rates around 90% have been reported [4-10].

Although the mechanisms are not completely understood, it is critical to review the biologic factors involved in radiation lung damage. Current evidence suggests that many factors and various lung parenchymal cells contribute to the pathogenesis of radiation lung damage [11].

* Correspondence: yamashitah-rad@h.u-tokyo.ac.jp
[1] Department of Radiology, University of Tokyo Hospital, Hongo, Bunkyo-ku, Tokyo, Japan
Full list of author information is available at the end of the article

The progression of radiation-induced damage is the result of an early activation of an inflammatory reaction leading to the expression and maintenance of an elevated cytokine cascade [12]. Kong *et al.* [13] concluded that blood biomarkers such as transforming growth factor (TGF)-beta1, interleukin (IL)-6, krebs von den Lungen-6 (KL-6), surfactant proteins (SP), and IL-1ra could accurately predict radiation-induced lung damage. Serum KL-6 and SP-D were also evaluated as predictive biomarlers for radiation pneumonitis (RP) in this study.

For normal tissues, the use of a single dose rather than a conventional fractionated dose can increase the risk of complications. However, few cases with severe toxicity have been reported [14-16]. In the current study, cases of severe RP (grades 4-5) that received SBRT for lung tumors in our institution were evaluated. In our previous report [17], the overall incidence rate of grades 2-5 RP was 29% (7/25 cases) and three patients (12%) died from RP from May 2004 to April 2006 at the median follow-up time of 18 months after completing SBRT. A significant decrease of the incidence rate of severe RP was observed for the period entering into 2006. The purpose of this study was to determine the risk factors of severe RP after SBRT for primary or secondary lung tumors.

Methods and materials

Subjects

From January 2003 to March 2009, SBRT was performed on 117 patients with lung tumors in our institution. SBRT was performed for primary lung cancers in 74 cases (63%) and for metastatic or recurrent lung tumors in 43 cases (37%) (Table 1). These consecutive 117 patients were evaluated retrospectively. There were 98 males and 19 females, and the median age was 72 years (range; 28-84 years). Thirteen patients (11%) had a shadow of interstitial pneumonitis (IP) in the CT before SBRT, 23 patients (20%) had high serum KL-6 value, and 19 patients (16%) had high SP-D value. The upper limit of serum KL-6 and SP-D was defined as 500.0 U/mL and 110.0 ng/mL, respectively.

Table 1: Characteristics of the tumor

Subject	N	(%)
Biopsy proved primary lung cancer	60	51
cT1N0M0	39	33
cT2N0M0	19	16
the others	2	2
Unconfirmed histology (suspected of primary lung cancer)	14	12
Metastatic or recurrent lung cancer	43	37
Total	117	100

All patients enrolled in this study satisfied the following eligibility criteria: a) solitary or double lung tumors; b) tumor diameter < 40 mm; c) no evidence of regional lymph node metastasis; d) Karnofsky performance status scale > or = 80%; and e) tumor not located adjacent to major bronchus, esophagus, spinal cord, or great vessels. Patients with an active malignant lesion other than lung were excluded. Therefore, no chemotherapy was combined with SBRT. There were 32 patients (27%) who were treated before 2005. After 2006, patients with a high risk for RP who had an obvious IP shadow on CT with a 3-mm slice before SBRT together with a high value of serum KL-6 & SP-D were excluded from receiving SBRT.

In the high resolution chest CT, IP shadow was defined as a mandatory observation beneath the pleura and a honeycomb lung. IP shadows were graded by their radiographically estimated total lung volume as follows: slight, less than 10%; moderate, 10-50%; and severe, >50%.

Planning procedure and treatment

The treatment methods which included the definition of the internal target volume (ITV) were performed according to JCOG 0403 phase II protocol [2,3]. The following gives a brief description of the treatment methods, which were described in detail in our previous report [17]. SBRT was performed daily with a central dose of 48 Gy in four fractions over 4-8 days. Each CT slice was scanned with an acquisition time of four seconds to include the whole phase of one respiratory cycle. The axial CT images were transferred to a 3-dimension RT treatment-planning machine (Pinnacle3, New Version 7.4i, Philips). Spicula formation and pleural indentation were included within the ITV. The mediastinal lymph nodes were not included from the irradiation field. The setup margin (SM) between ITV and the planning target volume (PTV) was 5 mm in all directions. There was an additional 5 mm leaf margin to PTV, according to JCOG0403 protocol, in order to make the dose distribution within the PTV more homogeneous. No pairs of parallel opposing fields were used. The target reference point dose was defined at the isocenter of the beam. The iso-dose distribution of an SBRT treatment was shown in Figures 123.

The dose limitation for pulmonary parenchyma was mean lung dose (MLD) < 18.0 Gy, percentage of total lung volume receiving greater than or equal to 20 Gy (V20) < 20%, and V15 < 25% according to JCOG0403 protocol.

Radiation method

SBRT was given in at least 8 ports by linear accelerator (Elekta Synergy System, Elekta Ltd, Crawley, UK) after the Synergy system was available in our institution from February 2007. At least eight beams (I-rotation angle was 0 degree only in two beams) were used. CT verification of

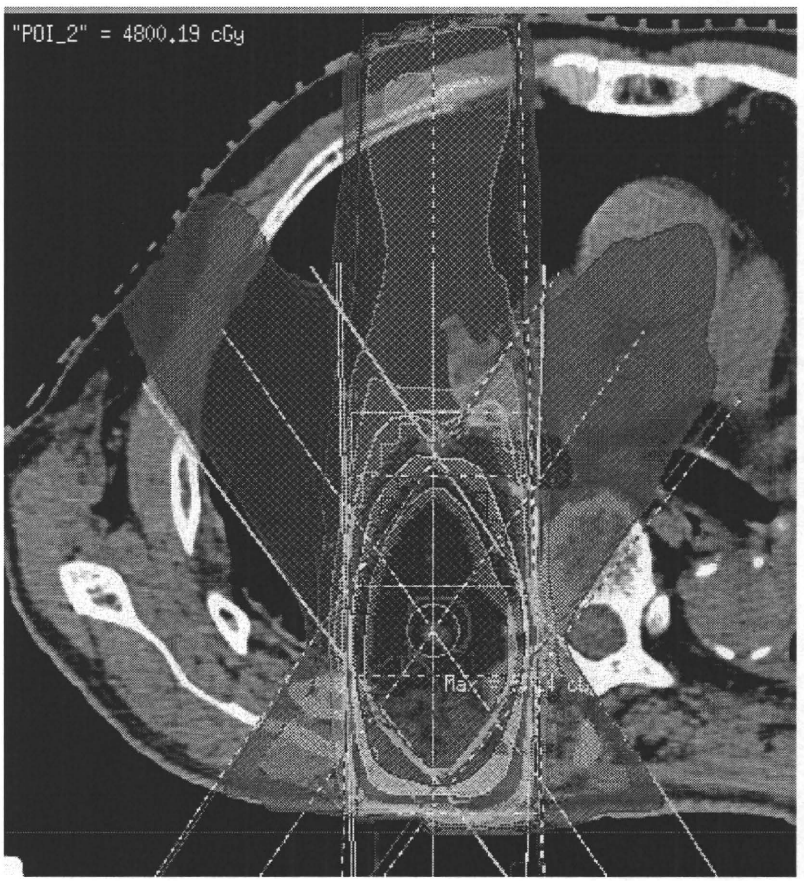


Figure 1 An example of dose distribution of SBRT (Pt. No. 5).

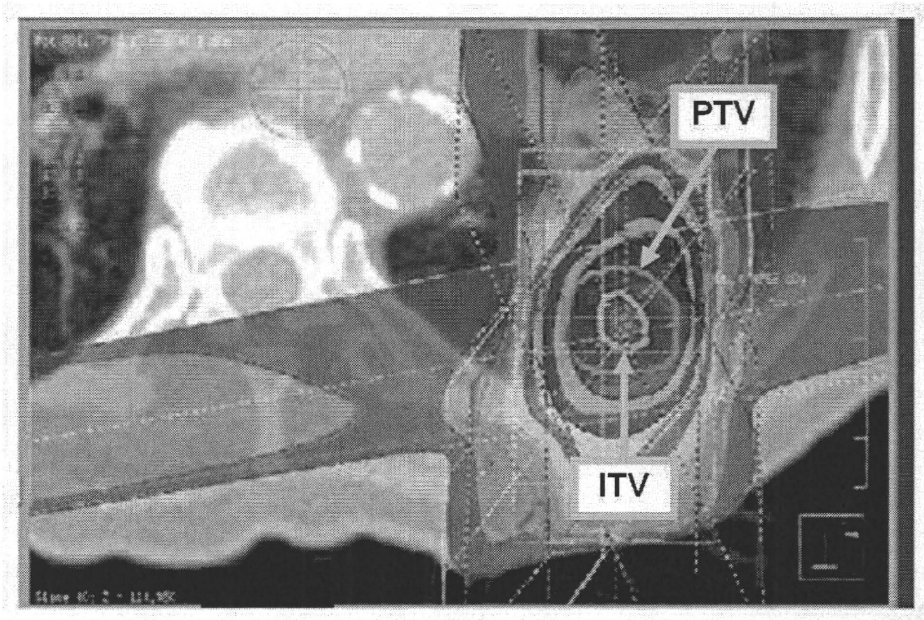


Figure 2 An example of dose distribution of SBRT (Pt. No. 7).

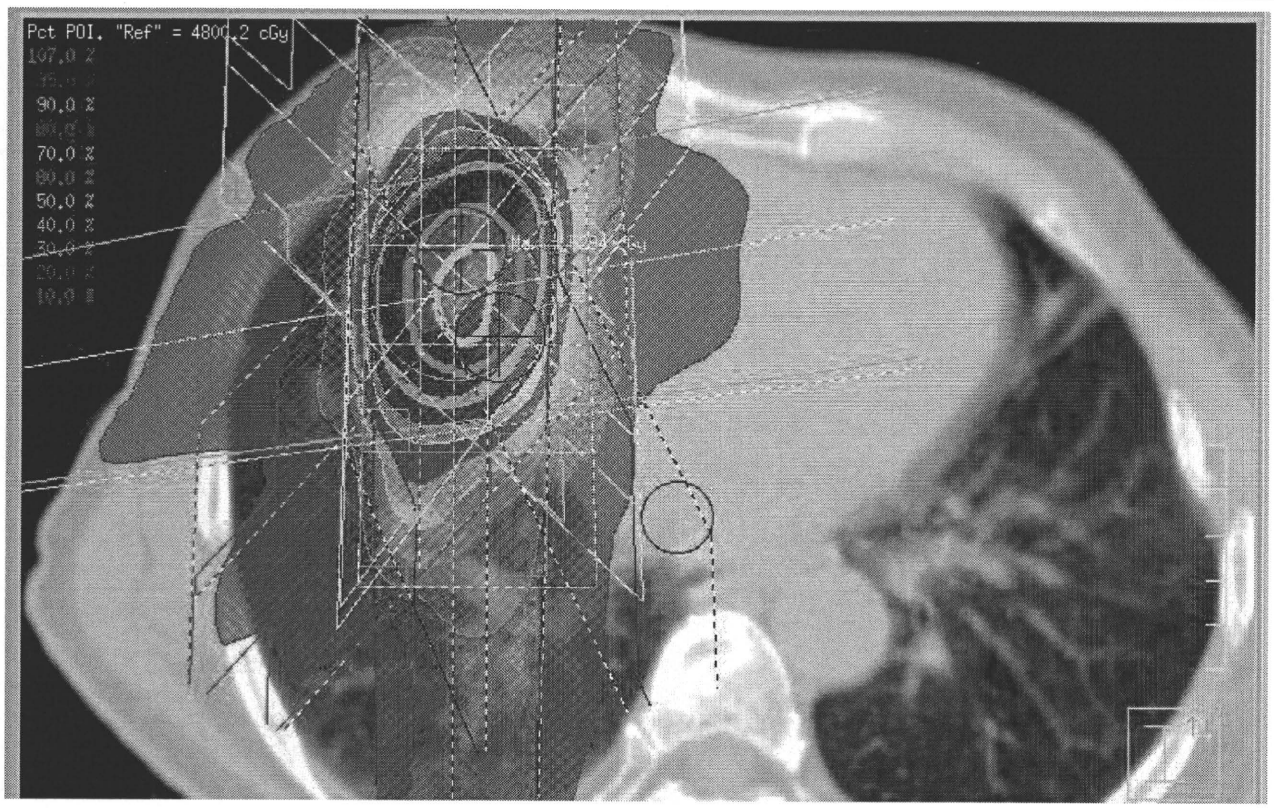


Figure 3 An example of dose distribution of SBRT (Pt. No. 8).

the target isocenter was performed before each treatment session using a kilovoltage-based cone-beam CT (CBCT) unit in the same room and in a treatment position. The Linac machine was Elekta Synergy with the cone-beam CT. The details of the radiation method before 2007 were described in our previous report [17]. The collapsed cone (CC) convolution method in Pinnacle^3 was used as the heterogeneous correction method for lung. The breathing suppression was done with a body frame and an abdominal pressure board (Figure 4).

Definition of RP grading

The toxicity data were collected retrospectively from the patient files. Basically, the RP grading system used followed the Common Terminology Criteria for Adverse Events (CTCAE) v3.0, and the grades were as follows: Grade 1, asymptomatic (radiographic findings only); Grade 2, radiographic findings plus symptomatic and not interfering with activities of daily living (ADL); Grade 3, radiographic findings plus symptomatic and interfering with ADL or O2 indicated; Grade 4, radiographic findings plus life-threatening (ventilatory support indicated), and Grade 5, radiographic findings plus death. Patients with mild pulmonary CT changes after SBRT were categorized as Grade 1. The radiographic findings common to the 5 grades were (a) shadow distribution just beneath pleura, (b) honeycomb lung, (c) traction bronchitis/dilation of small bronchus, (d) ground-glass opacity (GGO), or (e) infiltrative shadow (consolidation), which was not recognized in the CT before SBRT.

Follow-up

CT exams with 3-mm slices were performed at 2, 4, 6, 9, 12, 15, 18, and 24 months after SBRT for asymptomatic

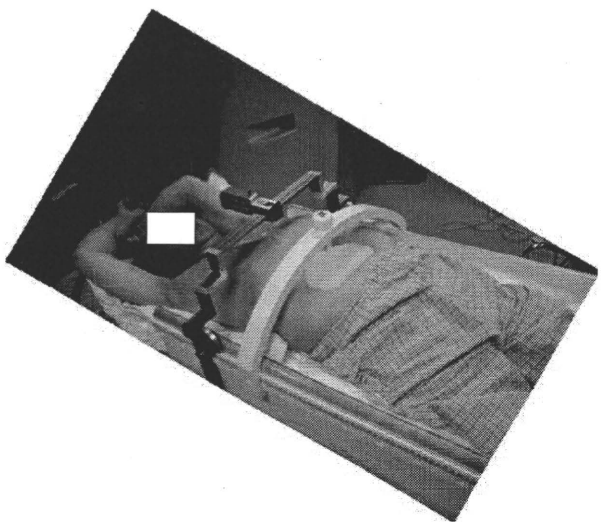


Figure 4 Body frame and abdominal pressure board.

Table 2: Characteristics of nine patients with G4-5 of RP

Case No.	s KL-6	S SP-D	IP shadow	RP grading	Onset time	State	V20 (%)	V40 (%)	MLD (cGy)	Stage	PTV (cc)	D95 (Gy)	Location	
1	950	286	moderate	5	3.0 Mo	Postoperative	6.7	2.7	938	IV	26.4	46.29	Lt	hilum
2	582	95	slight	5	2.0 Mo	Fresh	7.6	1.9	568	IA	47.5	45.57	Lt	hilum
3	852	136	severe	5	6.0 Mo	Postoperative	11.2	4.6	791	IV	120.9	45.00	Rt	S6
4	1590	NA	slight	5	6.0 Mo	Fresh	5.6	1.9	426	IA	29.4	44.05	Rt	S10
5	NA	NA	(-)	4	0.4 Mo	Fresh	5.0	1.5	291	IA	42.5	47.80	Lt	S8
6	289	101	slight	5	5.9 Mo	Fresh	7.0	2.0	440	IA	56.5	48.90	Rt	S10
7	497	321	(-)	4	4.0 Mo	Postoperative	2.6	0.9	269	IV	7.7	45.48	Lt	S10
8	833	135	slight	5	2.1 Mo	Fresh	6.3	2.3	492	IA	20.9	47.62	Rt	S5
9	883	235	slight	5	1.0 Mo	Fresh	3.7	0.7	288	IB	23.9	44.80	Rt	S2
	(0-500)	(0-110)												

Abbreviation; NA = not available

patients. Additionally, on the same day as CT, serum KL-6, SP-D, white blood cell (WBC), lactate dehydrogenase (LDH), C-reactive protein (CRP), and tumor markers were measured in the blood plus an oxygen saturation was measured from a fingertip.

Statistical Analysis

The relationship between G4-5 RP and pre-SBRT factors was compared with the X^2 test. The cumulative probability of RP was calculated and drawn applying the Kaplan-Meier algorithms with day of treatment as the starting point. Subgroups were compared using log-rank statistics. Values of $p < 0.05$ were considered statistically significant. Statistical calculations were conducted using version 5.0 StatView software (SAS Institute, Cary, NC).

Results

The median follow up time for all 117 patients was 14.7 months (range; 0.3-76.2 months). The control rate within the radiation field was 86.3% (101/117 cases).

RP of grade 4 or higher was observed in nine patients (7.7%) and the median time of showing symptoms was 4.0 months (range; 0.4-6.0 months) (Table 2). All of these nine RPs were due to acute exacerbation of IP (Figures 5678910) and steroid pulse therapy combined with an oral anti-pneumocystis carinii drug was administered to these patients. Grade 4 RP with intubation was seen in two cases and the other seven cases were grade 5. Grade 3 RP was seen in two patients during this time period. Grade 4 or higher RP was noted in six out of 32 patients (18.8%) before 2005 and in only three out of 85 patients (3.5%) after 2006 (Figure 11). This difference had a statistical significance (log-rank $p = 0.042$ and $X^2 p = 0.018$).

Serum KL-6 was determined in 8 of the 9 patients with grades 4-5 RP and in 95 of the 108 patients with grades 0-3 RP. Of the 8 patients with grades 4-5 RP, serum KL-6 (U/mL) was elevated in 6 patients (75%) (Table 2). Serum SP-D was determined in 7 patients with grades 4-5 RP and in 93 patients with grades 0-3 RP. Of the 7 patients with grades 4-5 RP, serum SP-D (ng/mL) was evaluated in 5 patients (71%) (Table 2). Additionally, the IP shadow was seen in seven cases (78%) in the CT before SBRT within or outside of radiation field. The radiation dose prescribed was within the protocol in all 117 patients. The appearance of grades 4-5 RP and serum KL-6 value (1-year cumulative incidence; 32% vs. 3% and log-rank $p < 0.0001$ & X2 $p = 0.0002$), SP-D value (1-year; 29% vs. 3% and log-rank $p = 0.0001$ & X2 $p = 0.0002$), or IP shadow in CT before SBRT (1-year; 57% vs. 2% and log-rank p <

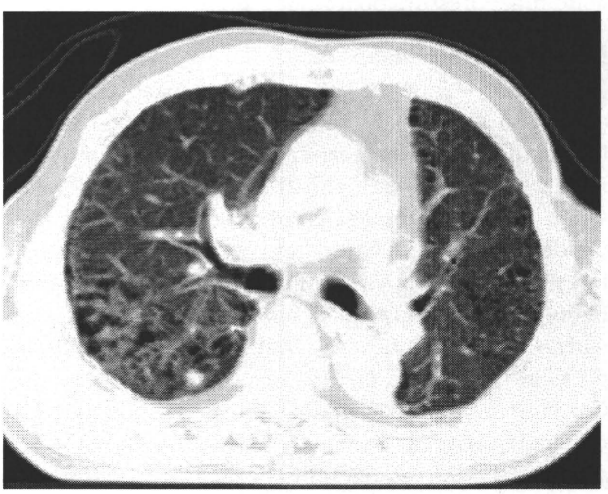


Figure 5 CT images before SBRT (Pt. No. 5).

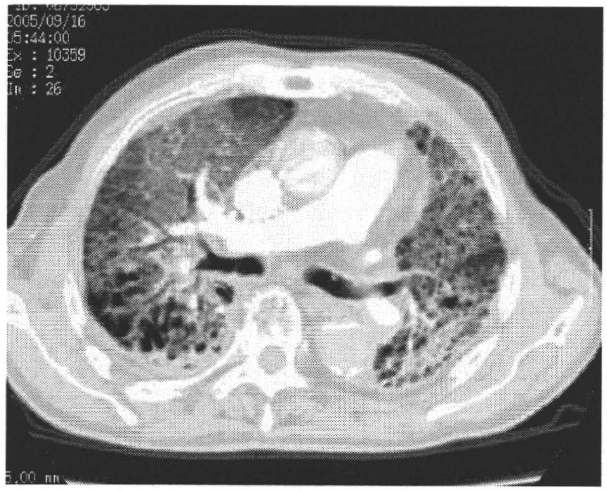


Figure 6 CT images of radiation pneumonitis after SBRT (Pt. No. 5). The finding was acute exacerbation of IP.

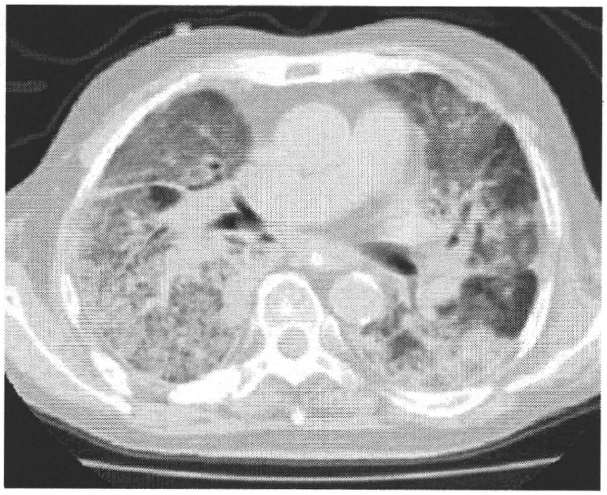


Figure 8 CT images of radiation pneumonitis (acute exacerbation of IP) after SBRT (Pt. No. 7).

0.0001 & X2 p < 0.0001) showed positive correlations (Table 3).

The risk factors of RP other than serum KL-6, SP-D, and IP shadow in CT are shown in Table 4. The mean PTV for nine patients with severe RP was 29.4 cc (range: 7.7-120.9 cc) and was 42.5 cc (range: 7.5-239.4 cc) of for the other low-grade RP patients. None of these risk factors were different for those patients with and without grades 4-5 RP.

Discussion

This was a retrospective study to evaluate the incidence rate and risk factors of severe RP after SBRT for primary (74 patients), metastatic and recurrent (43 patients) lung tumors. Grades 4-5 RP were noted in 9 patients (7.7%); IP shadow in the CT, and high serum KL-6 & SP-D values before SBRT showed positive correlations with grades 4-5 RP. Seven of the 117cases (6.0%) were of grade 5 in our institution. After 2006, severe grades 4-5 RP were significantly reduced.

According to Borst *et al.* [15], the crude incidence rate of grade 2 RP was 10.9% for the SBRT on 128 patients with malignant pulmonary lesions who were treated with 6-12 Gy per fraction with a median MLD of 6.4 Gy (range: 1.5-26.5 Gy). According to Rusthoven *et al.* [16], grades 2-3 RP was rare, occurring in only one out of 38 patients (2.6%) with one to three lung metastases after SBRT of 48-60 Gy in 3 fractions. They used the dose con-

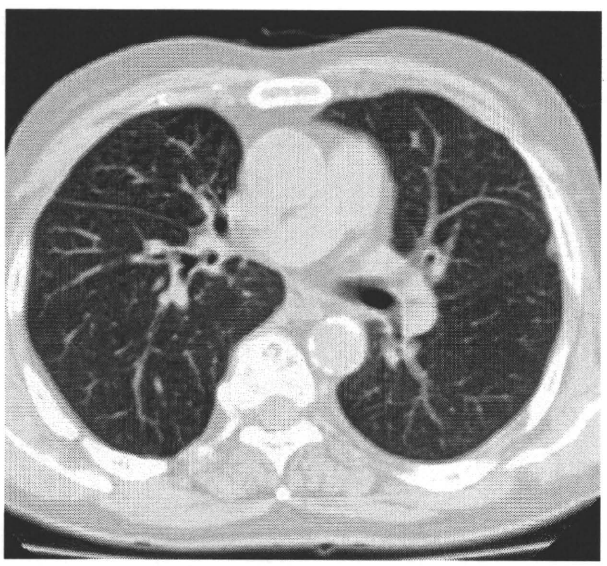


Figure 7 CT images before SBRT (Pt. No. 7).

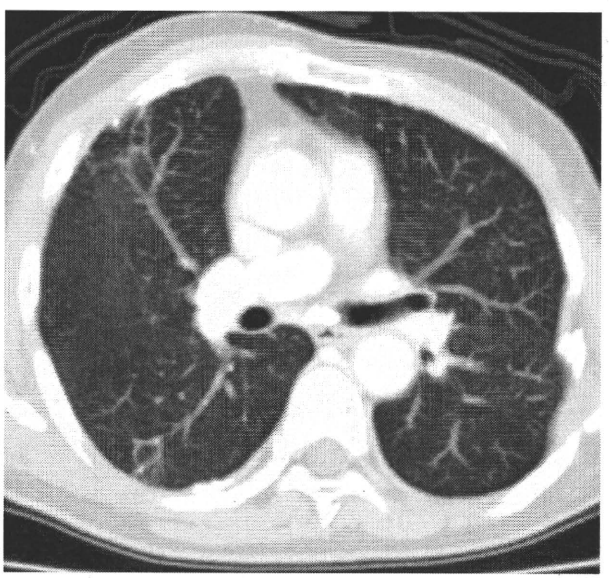


Figure 9 CT images before SBRT (Pt. No. 8).

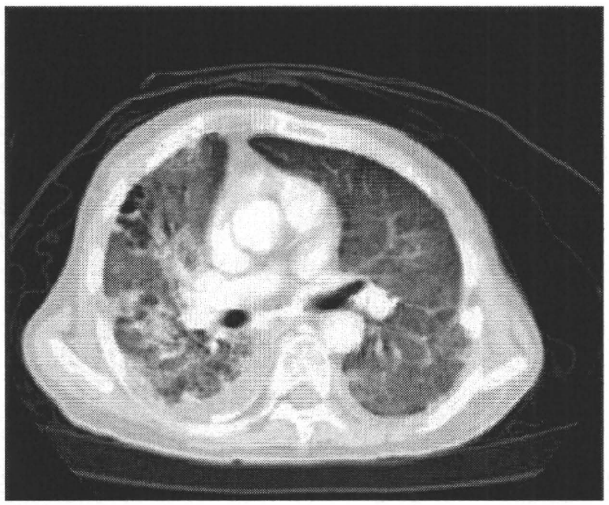


Figure 10 CT images of radiation pneumonitis (acute exacerbation of IP) after SBRT (Pt. No. 8).

straint of V15 < 35%. According to Nagata *et al.* [1], no severe symptomatic pulmonary complications (NCICTC Grade 3 or larger) were encountered. Timmerman *et al.* [14] reported in 2006 that a SBRT treatment dose of 60-66 Gy total in three fractions was administered during 1 to 2 weeks for 70 patients with clinically staged T1-2N0M0 (tumor size < or = 7 cm) biopsy-confirmed non-small cell lung cancer (NSCLC). This resulted in toxicity of grades 3 to 5 in a total of 14 patients (20%) and grade 5 was seen in four patients (5.7%). Le QT *et al.* [18] reported in 2006 that after single-fraction SBRT (15-30 Gy) was performed for 32 patients (21 NSCLC and 11 metastatic tumors), two patients (6%) suffered from RP of grade 5.

Moreover, according to Rusthoven *et al.* [16], patients were required to have adequate lung function, which was defined as stable arterial hemoglobin saturation above 90% with minimal exertion, forced expiratory volume (FEV) of 1.0% higher than the predicted value of 40% or more than 1 L and carbon monoxide diffusing capacity (DLCO) higher than the predicted 40% value. In our institution, the exclusion criteria of SBRT consisted of an FEV of 1.0% at less than 750 mL, and an obvious IP shadow on the roentgen examination according to JCOG 0403 protocol.

RP of grades 4-5 occurred in six out of 32 patients (18.8%) before 2005 and in only three out of 85 patients (3.5%) after 2006 (Figure 11). The significant reduction of severe grades 4-5 RP after 2006 in our institution is believed to be due to the selection of appropriate patients. After 2006, patients were excluded from SBRT if they had an obvious IP shadow on the CT-scan (slice thickness 3.0 mm), and if serum KL-6 and SP-D levels were high. All of the severe RP cases in our institution consisted of acute exacerbation of IP outspreading over the radiation field. Admittedly, these nine patients with severe RP represent a small sample. Whether our results are a coincidence that biomarkers and CT shadows are indeed significantly different in patients with grades 4-5 toxicity compared to patients without RP awaits confirmation in further studies.

KL-6 is the indicator that specificity is high for IP and is clinically evaluated for the purpose of diagnosing IP. In addition, KL-6 is important as an index of the activity of IP because it becomes significantly high for IP with activ-

Table 3: Relationship between G4-5 RP and pre-SBRT factors

Pre-SBRT factors	G4-5 RP	G0-3 RP	Total	X2 test	1-year cumulative incidence of G4-5 RP	log-rank
Serum KL-6						
high value	6	17	23	$p = 0.0002$	32%	$p < 0.0001$
within normal level	2	78	80		3%	
not available	1	13	14			
Serum SP-D						
high value	5	14	19	$p = 0.0002$	29%	$p = 0.0001$
within normal level	2	79	81		3%	
not available	2	15	17			
IP shadow in CT						
(+)	7	6	13	$p < 0.0001$	57%	$p < 0.0001$
(-)	2	102	104		2%	

Table 4: Risk factors of severe RP

	Patients with G4-5 RP	Patients without G4-5 RP	*p* value
Total	9 (8%)	108 (92%)	
Patient specific factors			
Pulmonary function			
VC (L)			
mean +/- SD	3.27 +/- 0.65	2.75 +/- 0.85	*N.S.*
range	2.76-4.01	1.54-4.07	
FEV 1.0 (L)			
mean +/- SD	2.11 +/- 0.68	1.87 +/- 0.82	*N.S.*
range	1.59-3.24	0.59-3.24	
K-PS (%)			
90	5 (56%)	52 (48%)	*N.S.*
80	4 (44%)	56 (52%)	
Age (y)			
mean +/- SD	73.3 +/- 6.8	70.1 +/- 14.1	*N.S.*
range	68-80	24-93	
COPD			
With	2 (22%)	22 (20%)	*N.S.*
Without	8 (78%)	86 (80%)	
Treatment specific factors			
Size of the PTV (cc)			
mean +/- SD	29.4 +/- 33.2	42.5 +/- 13.7	*N.S.*
range	7.7-120.9	7.5-239.4	
Mean lung dose (Gy)			
mean +/- SD	5.0 +/- 2.3	4.2 +/- 1.4	*N.S.*
range	2.7-9.4	1.7-7.9	
Lung V20 (%)			
mean +/- SD	5.9 +/- 2.7	5.8 +/- 2.6	*N.S.*
range	2.6-11.2	1.0-11.0	
Target location			
Central	2 (22%)	17 (16%)	*N.S.*
Peripheral	7 (78%)	91 (84%)	

Abbreviation:
COPD = chronic obstructive pulmonary diseases
RP = radiation pneumonitis
G4-5 = grades 4-5
PTV = planning target vlume
FEV = Forced expiratory volume
K-PS = Karnofsky Performance status
N.S. = not significant

ity. In the human body, KL-6 does not develop in a type I alveolus epithelial cell. However, KL-6 develops in a type II alveolus epithelial cell, in a bronchial epithelial cell, and in a bronchus gland cell. The expression of KL-6 increases in the hyperplasia of the type II of alveolus epithelial cell in IP. A small quantity of KL-6 is present in the liquid coating the alveolus in normal lungs, and its density increases during hyperplasia of the type II alveolus epithelial cell for IP. In addition, because inflammation occurs, blood vessel permeability rises, and KL-6 in the

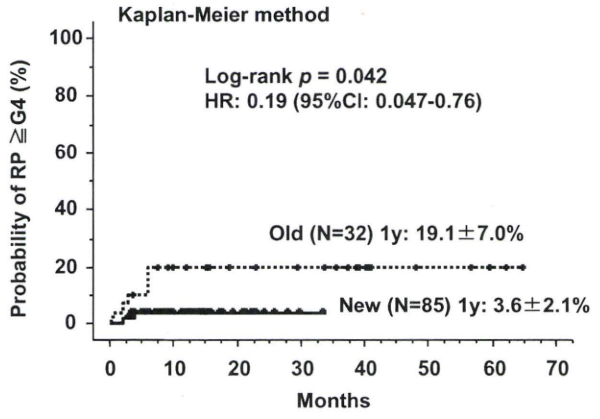


Figure 11 Cumulative probability curves of severe radiation pneumonitis of grades 4-5 divided by pre-2005 (old group) and post-2006 (new group).

alveolus coating liquid shifts easily into the blood. As a result, KL-6 in the blood rises in the IP. When an injury to the lung stroma is evaluated, KL-6, SP-A, SP-D, and MCP-1 are examined. Of these, there is a report that KL-6 was highest in both sensitivity (93.9%) and specificity (96.3%) [19]. Furthermore, SP-D levels at 50 to 60 Gy (midway during radiation therapy) showed greater sensitivity and positive predictive values for RP detection (74% and 68%, respectively) than SP-A (26% and 21%, respectively) [20].

Conclusion

The frequency of severe RP in our institution has recently shown a decrease, by prescreening patients for serum KL-6 and SP-D as biomarkers of severe RP. When SBRT was performed on patients presenting with an IP shadow in CT and a high value of serum KL-6 before treatment, severe radiation pneumonitis occurred at a high rate. Therefore, pre-screening of patients before SBRT appears to be a useful strategy in treating lung tumors.

Authors' contributions

HY collected and analyzed data and performed statistical analysis. HY and SK-S drafted the manuscript. AT, KO, AH, and RW reviewed the data and revised the manuscript. KO and KN designed the study and revised the final version. All authors have read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

None.

Author Details

Department of Radiology, University of Tokyo Hospital, Hongo, Bunkyo-ku, Tokyo, Japan

Received: 11 February 2010 Accepted: 9 May 2010
Published: 9 May 2010

References

1. Nagata Y, Negoro Y, Aoki T, *et al.*: **Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame.** *Int J Radiat Oncol Biol Phys* 2002, **52**:1041-1046.
2. Matsuo Y, Takayama K, Nagata Y, *et al.*: **Interinstitutional variations in planning for stereotactic body radiation therapy for lung cancer.** *Int J Radiat Oncol Biol Phys* 2007, **68**:416-425.
3. Nishio T, Kunieda E, Shirato H, *et al.*: **Dosimetric verification in participating institutions in a stereotactic body radiotherapy trial for stage I non-small cell lung cancer: Japan clinical oncology group trial (JCOG0403).** *Phys Med Biol* 2006, **51**:5409-5417.
4. Uematsu M, Shioda A, Suda A, *et al.*: **Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience.** *Int J Radiat Oncol Biol Phys* 2001, **51**:666-670.
5. Nakagawa K, Aoki Y, Tago M, *et al.*: **Megavoltage CT-assisted stereotactic radiosurgery for thoracic tumors original research in the treatment of thoracic neoplasms.** *Int J Radiat Oncol Biol Phys* 2000, **48**:449-457.
6. Wulf J, Hädinger U, Oppitz U, *et al.*: **Impact of target reproducibility on tumor dose in stereotactic radiotherapy of targets in the lung and liver.** *Radiother Oncol* 2003, **66**:141-150.
7. Hara R, Itami J, Kondo T, *et al.*: **Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors.** *Cancer* 2006, **106**:1347-1352.
8. Onimaru R, Fujino M, Yamazaki K, *et al.*: **Steep dose-response relationship for stage I non-small-cell lung cancer using hypofractionated high-dose irradiation by real-time tumor-tracking radiotherapy.** *Int J Radiat Oncol Biol Phys* 2008, **70**:374-381.
9. Hof H, Muenter M, Oetzel D, *et al.*: **Stereotactic single-dose radiotherapy (radiosurgery) of early stage non small-cell lung cancer (NSCLC).** *Cancer* 2007, **110**:148-155.
10. Le QT, Loo BW, Ho A, *et al.*: **Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors.** *J Thorac Oncol* 2006, **1**:802-809.
11. Kong FM, Ten Haken R, Eisbruch A, *et al.*: **Non-small cell lung cancer therapy-related pulmonary toxicity: an update on radiation pneumonitis and fibrosis.** *Semin Oncol* 2005, **32**:S42-54.
12. Rubin P, Johnston CJ, Williams JP, *et al.*: **A perpetual cascade of cytokines postirradiation leads to pulmonary fibrosis.** *Int J Radiat Oncol Biol Phys* 1995, **33**:99-109.
13. Kong FM, Ao X, Wang L, Lawrence TS: **The use of blood biomarkers to predict radiation lung toxicity: a potential strategy to individualize thoracic radiation therapy.** *Cancer Control* 2008, **15**:140-150.
14. Timmerman R, McGarry R, Yiannoutsos C, *et al.*: **Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer.** *J Clin Oncol* 2006, **24**:4833-4839.
15. Borst GR, Ishikawa M, Nijkamp J, *et al.*: **Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy.** *Radiother Oncol* 2009, **91**:307-313.
16. Rusthoven KE, Kavanagh BD, Burri SH, *et al.*: **Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases.** *J Clin Oncol* 2009, **27**:1579-1584.
17. Yamashita H, Nakagawa K, Nakamura N, *et al.*: **Exceptionally high incidence of symptomatic grade 2-5 radiation pneumonitis after stereotactic radiation therapy for lung tumors.** *Radiat Oncol* 2007, **2**:21.
18. Le QT, Loo BW, Ho A, *et al.*: **Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors.** *J Thorac Oncol* 2006, **1**:802-809.
19. Ohnishi H, Yokoyama A, Kondo K, *et al.*: **Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases.** *Am J Respir Crit Care Med* 2002, **165**:378-381.
20. Kong FM, Ao X, Wang L, Lawrence TS: **The use of blood biomarkers to predict radiation lung toxicity: a potential strategy to individualize thoracic radiation therapy.** *Cancer Control* 2008, **15**:140-150.

doi: 10.1186/1748-717X-5-32
Cite this article as: Yamashita *et al.*, Prescreening based on the presence of CT-scan abnormalities and biomarkers (KL-6 and SP-D) may reduce severe radiation pneumonitis after stereotactic radiotherapy *Radiation Oncology* 2010, **5**:32

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 3, pp. 660–669, 2011

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.10.004

CRITICAL REVIEW

STEREOTACTIC RADIOTHERAPY OF PRIMARY LUNG CANCER AND OTHER TARGETS: RESULTS OF CONSULTANT MEETING OF THE INTERNATIONAL ATOMIC ENERGY AGENCY

YASUSHI NAGATA, M.D.,* JOERN WULF, M.D.,† INGMAR LAX, PH.D.,‡ ROBERT TIMMERMAN, M.D.,§ FRANK ZIMMERMANN, M.D.,¶ IGOR STOJKOVSKI, M.D.,‖ AND BRANISLAV JEREMIC, M.D.‖

*Hiroshima University Hospital, Department of Radiation Oncology, Hiroshima, Japan; †Institut of Radiation Oncology, Lindenhospital, Bern, Switzerland; ‡Division of Oncology and Hospital Physics, Radiumhemmet, Karolinska University Hospital, Sweden; §Department of Radiation Oncology, The University of Texas Southwestern Medical Center, Dallas, USA; ¶Department of Radiation Oncology, University Hospital, University Basel, Basel, Switzerland; and ‖International Atomic Energy Agency, Vienna, Austria

To evaluate the current status of stereotactic body radiotherapy (SBRT) and identify both advantages and disadvantages of its use in developing countries, a meeting composed of consultants of the International Atomic Energy Agency was held in Vienna in November 2006. Owing to continuous developments in the field, the meeting was extended by subsequent discussions and correspondence (2007–2010), which led to the summary presented here. The advantages and disadvantages of SBRT expected to be encountered in developing countries were identified. The definitions, typical treatment courses, and clinical results were presented. Thereafter, minimal methodology/technology requirements for SBRT were evaluated. Finally, characteristics of SBRT for developing countries were recommended. Patients for SBRT should be carefully selected, because single high-dose radiotherapy may cause serious complications in some serial organs at risk. Clinical experiences have been reported in some populations of lung cancer, lung oligometastases, liver cancer, pancreas cancer, and kidney cancer. Despite the disadvantages expected to be experienced in developing countries, SBRT using fewer fractions may be useful in selected patients with various extracranial cancers with favorable outcome and low toxicity. © 2011 Elsevier Inc.

Stereotactic body radiation therapy, Non–small-cell lung cancer, Lung metastases, Liver cancer, Pancreatic cancer, Kidney cancer.

INTRODUCTION

Cancer is one of the major health concerns worldwide. The burden of cancer is increasing globally, with 20 million new cases expected per year in 2020, half of which will be in developing countries (1). The inability to cope with the growing economic and societal burden of cancer is emblematic of the tremendous health disparities reflected in developing countries, which have only 5% of the global resources spent on cancer (2–3).

The proportion of cancer patients in developing countries requesting radiotherapy (RT) is likely higher than in regions of high income because of the types of cancers and the stages at which these tumors are diagnosed (4). Moreover, patients in developing countries are dealing with some issues that are not common in the developed world. They include patient transportation to the facility (5), social support, accessible local housing, and noncompliance with treatment. It was shown (6) that the use of short courses in selected patients could be cost effective and convenient, especially for patients coming from remote areas.

Although many countries have not yet established RT service, others have aging RT services, which are usually restricted to a few centers, mainly concentrated in large urban areas. RT is affordable for developing countries with large populations, but some regions with small populations have not invested in RT (7–10). Emerging new technologies for cancer treatment, however, are spreading widely, in both developed and developing countries. One of these, stereotactic body radiotherapy (SBRT), has been increasingly used in recent decades.

Reprint requests to: Yasushi Nagata, M.D., Hiroshima University Hospital, Department of Radiation Oncology, Kasumi 1-2-3 Hiroshima, Japan. Tel: (+81) 82-257-1545; Fax: (+81) 82-257-1546; E-mail: nagat@hiroshima-u.ac.jp

Conflict of interest: none.

Received April 30, 2010, and in revised form Sept 30, 2010. Accepted for publication Oct 2, 2010.

The International Atomic Energy Agency (IAEA) has a crucial role in both developing new RT facilities and upgrading existing facilities, including equipment and human resources in developing countries. By organizing meetings of experts, the IAEA gathers advice in RT to establish RT facilities in member states. With such an aim, a meeting of consultants was held in Vienna in November 2006 to advise the IAEA on the state of the art of the use of SBRT in primary lung tumors and other body tumors. This article represents a summary of that meeting and subsequent (2007–2010) communication between experts on the recent developments in SBRT deemed necessary because of the fast developments in the field.

Stereotactic radiation characteristics

Characteristics attractive to developing nations. Several characteristics would make SBRT attractive to developing nations. Shortened treatment time with fewer fractions than usually used in developing countries would be a major consideration. This in turn would generally enable improved access to RT treatments in departments worldwide. In addition, shorter treatment (outpatient or inpatient) would also be more cost effective for both patients and hospitals. This would be realized by lessening travel from prolonged distances to and from hospitals, and secondly for hospitals having limited inpatient capabilities. Other attractive characteristics would include improved overall results such as local control, overall survival, and disease-specific survival. Lower toxicity, in addition, would also be an important issue from the standpoint of both better quality of life and less costly symptomatic care (including frequent hospitalization in a patient population having a notorious record of having excessive comorbidities) needed in such cases.

Obvious barriers to implementation in developing nations. There may be several barriers for successful implementation of SBRT of lung cancer in developing countries. They can be broadly separated into pretreatment and treatment issues, including low incidence in certain regions such as sub-Saharan Africa. The lack of modern and comprehensive diagnostic tools, such as computed tomography (CT) and positron emission tomography, would largely jeopardize appropriate diagnosis and staging of potential candidates. In addition, the vast majority of patients would fall into a locally advanced or metastatic category because of a lack of screening and early detection programs that may result in identification of suitable cases, *i.e.,* those having Stage I non–small-cell lung cancer. Of treatment-dependent obstacles, capital costs for obtaining an immobilization system would be the major issue, assuming that existing external-beam RT machines (primarily linear accelerators) have been properly maintained. Lack of previous exposure and experience with three-dimensional RT, seen as the logical parent of SBRT, may be an important obstacle. Barriers to successful implementation of SBRT also include insufficient staffing, inadequate training of personnel, and lack of a dedicated team for introducing and implementing this technique.

CURRENT STATUS OF SBRT DELIVERY IN THE DEVELOPED WORLD

Historical aspects and early experience

Intracranial stereotactic radiosurgery (SRS) was a novel treatment method when introduced in the middle of the 20th century, with conceptual parallels to brachytherapy in regard to the tight spatiotemporal distribution in dose delivery. The clinical experience with intracranial SRS, together with the technical developments in conventional RT, initiated the development of SBRT characterized by a very high dose per fraction, delivered in a short time. This was started at the Swedish Karolinska University hospital in 1991 with tumors in the liver and lungs (11, 12). In parallel the method was developed in Japan and clinically introduced in 1994 for lung tumors. During the last 5 years of the 1990s, SBRT was introduced in several centers in Europe, Japan, and the United States (13–19). The early reports had already shown very promising results with regard to local control and toxicity for the hypofractionation schedules that were adopted, with 10 to 15 Gy per fraction given in a few fractions during a short time (15, 20). However, owing to the new aspects introduced in SBRT, clinical experience was initially gathered at a very slow rate, and it was only during the past decade that outcome data from several centers were available to confirm the initial promising results.

Experience in primary lung tumors

Many studies with SBRT were conducted around the world in treating both primary and metastatic cancers within the lungs because of their high prevalence, the high rates of cancer-associated deaths, and the desire for more effective treatments. The experience in treating primary lung cancer using SBRT has been obtained mainly in patients unfit for surgical resection (*i.e.,* medically inoperable patients). Furthermore, nearly all reports described outcomes in patients with Stage I disease, particularly for peripheral tumor locations. Inasmuch as medically inoperable lung cancer patients are at risk for death of other causes, survival in these patients is ultimately compromised. Still, the benefits of SBRT were demonstrated by dramatically improved rates of local control.

Local tumor response. The local control rates of primary lung cancer with SBRT have been previously reported by several authors (Table 1): 94 % (47/50) for 50 to 60 Gy in five fractions with a median follow-up time of 36 months (21, 23); 92 % (22/24) for 60 Gy in eight fractions with a median follow-up time of 24 months (22, 24) 87 % (30/37) for 60 Gy in three fractions with a median follow-up time of 15 months (19); 85% for 48 to 60 Gy in eight fractions with a median follow-up time of 17 months (25); 95% for 45 to 56.2 Gy in three fractions with a median follow-up time of 10 months (26); 90% for 30 to 40 Gy in

Table 1. Local control rates of stereotactic radiotherapy for primary lung cancer

Study	Total dose (Gy)	Daily dose (Gy)	Reference point	Local control	Median follow-up time
Uematsu *et al.*, 2001 (21, 23)	50–60	10	80% margin	94%(47/50)	36 months
Arimoto *et al.*, 1998 (24)	60	7.5	Isocenter	92%(22/24)	24 months
Timmerman *et al.*, 2003 (19)	60	20	80% margin	87%(30/37)	15 months
Onimaru *et al.*, 2003 (25)	48–60	6–7.5	Isocenter	80%(20/25)	17 months
Wulf *et al.*, 2004 (26)	45–56.2	15–15.4	80% margin	95%(19/20)	10 months
Nagata *et al.*, 2005 (28)	48	12	Isocenter	97%(44/45)	30 months
Lee *et al.*, 2003 (27)	30–40	10	90% margin	90%(8/9)	21 months
Fakiris *et al.*, 2009 (29)	60–66	20–23	80% margin	88%(70)	50 months
Baumann *et al.*, 2009 (30)	45	15	67% margin	92%(57)	35 months
Timmerman *et al.*, 2010 (31)	60	20	80% margin	98%(54/55)	36 months

four fractions with a median follow-up time of 21 months (27); 97% (44/45) for 48 Gy in four fractions with a median follow-up time of 22-30 months (28); 88% for 60 to 66 Gy in three fractions with a median follow-up time of 50 months (29); and 92% for 45 Gy in three fractions with a median follow-up time of 35 months (30). The Radiation Therapy Oncology Group (RTOG) 0236 demonstrated a very good 3-year local control rate that was as high as 98% (31). Even though the definition of local control is different between each trial, a biologic effective dose (BED) larger than 100 Gy may be effective for SBRT of solitary lung cancers with a local control rate above 85%.

Survival. In a series of Stage IA disease (T1N0M0), the 1-year and 5-year local relapse-free survival rates were 100% and 95%. The disease-free survival rates after 1, 3, and 5 years were 80%, 72%, and 72%, respectively, and the overall survival rates were 93%, 83%, and 83%, respectively. In the Stage IB (T2N0M0) series of Nagata *et al.* (28), local relapse-free survival rates were 100%. The disease-free survival after 1, 3, and 5 years were 92%, 71%, and 71%, respectively, and the overall survival rates were 82%, 72$, and 72%, respectively. Onishi *et al.* (32) reported the results for 13 institutions in Japan, which summarized 245 patients: 155 with Stage IA lung cancer and 90 with Stage IB lung cancer. There were 87 operable and 158 inoperable patients, and their results showed that the intercurrent death rate was especially high in the inoperable patient group. Moreover, the 5-year survival rates of operable patients irradiated with more than BED = 100 Gy were 90% for Stage IA and 84% for Stage IB disease, and their clinical results were as good as those obtained by surgery.

Toxicities. The great concern of pulmonary toxicity with SBRT treatment was moderated by the very low rates of complications in early studies. Most pulmonary complications are less than Grade 2 according to the National Cancer Institute Common Terminology Criteria version 2.0. It is not uncommon for patients to experience rib fracture or chest wall pain months after SBRT, especially if tumors adjacent to the chest wall have been treated. Some of these patients, but not all, will have pleural effusions associated with the chest wall pain. The problem seems mostly to be self limited, and conservative management with over-the-counter analgesics or anti-inflammatory medicines is typically effective.

However, a few serious complications have recently been reported by several institutions in Japan (33). These include Grade 5 pulmonary complications, radiation pneumonitis, hemoptysis, and radiation esophagitis. Most cases of Grade 5 radiation pneumonitis were accompanied with interstitial pneumonitis.

Another concern of toxicity was the effects on the central bronchus, pulmonary artery, esophagus, heart, and spinal cord, for which a hypofractionated dose had not been followed up for a sufficiently long time. Lethal pulmonary bleeding and esophageal ulcer have been previously reported (33). Timmerman *et al.* also reported a series of complications with SBRT (34). Chang *et al.* reported on safely treating central tumors considering dose constraints with the SBRT technique (35). Nonetheless, central tumors adjacent to mediastinal organs should be carefully considered (36). Toxicities as reported in several articles are shown in Table 2.

The most important issue is to maintain the dose constraints of organs at risk (OAR) to avoid serious complications. The dose constraints of the OAR, including the spinal cord, pulmonary artery, bronchus, and heart under the Japan Clinical Oncology Group (JCOG) 0403 protocol, are shown in Table 3. The RTOG has enacted normal tissue

Table 2. Clinical toxicities after stereotactic radiotherapy for primary lung cancer

Study	Number of cases	Lung ≥Grade 3	Lung Grade 5	Other Grade 5
Uematsu *et al.*, 2001 (23)	50	0%	0%	
Arimoto *et al.*, 1998 (24)	24	NA	0%	
Lee *et al.*, 2003 (27)	28	0	0%	
Onimaru *et al.*, 2003 (25)	45	2%	0%	Esophagus
Wulf *et al.*, 2004 (26)	61	0	0%	
Nagata *et al.*, 2005 (28)	45	0	0	
Timmerman *et al.*, 2006 (34)	70	20%	9%	Hemoptysis, pericarditis
J-CERG, 2009 (33)	2,106	NA	0.6%	Esophagus, hemoptysis

Table 3. Dose and volume constraints for organs at risk in stereotactic body radiotherapy of lung tumors according to Japan Clinical Oncology Group 0403

Organ	Dose	Volume	Dose	Volume
Lung	40 Gy	≤100 cc	MLD	≤18 cc
	V_{15}	≤25%	V_{20}	≤20%
Spinal cord	25 Gy	Maximum		
Esophagus	40 Gy	≤1 cc	35 Gy	≤10 cc
Pulmonary artery	40 Gy	≤1 cc	35 Gy	≤10 cc
Stomach	36 Gy	≤10 cc	30 Gy	≤100 cc
Intestine	36 Gy	≤10 cc	30 Gy	≤100 cc
Trachea, main bronchus	40 Gy	≤10 cc		
Other organs	48 Gy	≤1 cc	40 Gy	≤10 cc

Abbreviation: MLD = Mean Lung Dose, Other organs do not include chest wall & liver.

constraints for RTOG 0618 treating operable patients with early-stage primary lung cancer (Table 4).

Clinical trials. Prospective Phase II testing of SBRT in operable patients is currently ongoing in Japan (JCOG 0403) and the United States (RTOG protocol 0618). In medically inoperable patient groups, a Nordic multi-institutional consortium is comparing three-fraction SBRT to conventional RT in an ongoing randomized Phase II study. The RTOG has finished a Phase II study of three-fraction SBRT for peripheral tumors and is planning a Phase I study with five fractions in patients with central tumors. Finally, the JCOG is finishing a Phase II study using a four-fraction treatment for peripheral tumors and is starting a Phase II study using a higher dose specifically for T2 tumors as JCOG 0701.

Experience in metastatic lung tumors

The experience in treating lung metastasis has been mostly with oligometastases. In contrast to patients with primary lung cancer, patients with metastases do not inherently have poor pulmonary function secondary to tobacco abuse. As such, the toxic effects of treatment would not be expected to be identical between these differing populations. In addition, there is increasing evidence that it may be more difficult to attain local control in metastatic tumors than in primary lung cancer. This would argue for a higher treatment dose (controlled for tumor volume) for metastatic tumors than for primary presentations. Unfortunately, the results of treating lung metastases were frequently included in the reports of patients treated with primary lung cancers, making interpretations of the results more difficult (20, 37–39). Recently a few articles were published that focused on lung metastases (40, 41). Still, SBRT has a relatively high rate of local control per lesion, making it an effective treatment for selected patients with oligometastases.

Table 4. Dose constraints for normal tissue related to steepness of dose gradients from target according to Radiation Therapy Oncology Group 0618 for stereotactic body radiotherapy in operable patients with lung cancer

Organ	Volume	Dose (cGy)
Spinal cord	Any point	18 Gy (6 Gy/fraction)
Esophagus	Any point	27 Gy (9 Gy/fraction)
Ipsilateral brachial plexus	Any point	24 Gy (8 Gy/fraction)
Heart/pericardium	Any point	30 Gy (10 Gy/fraction)
Trachea and ipsilateral bronchus	Any point	30 Gy (10 Gy/fraction)
Whole lung (right & left)	V_{20}	Less than 5–10% of total lung volume
Skin	Any point	24 Gy (8 Gy per fraction)

Experience in liver tumors

Treatment of liver tumors is the second highest indicator for SBRT. Surgical data have shown that local treatment of liver tumors—mostly hepatocellular carcinoma and metastases—can be curative in up to 25–30% of patients if patient selection is appropriate (42). Nevertheless a significant proportion of patients will not be suitable for surgery because of age, medical comorbidity, or intrahepatic localization of the tumor (bilobar, adjacent to large vessels/portal structures). For these cases, SBRT is completely noninvasive and compares favorably with actuarial local control rates of at least 80% after 2 years (16, 20, 43, 44). Acute toxicity is mild. Clinically relevant subacute or late toxicities are not reported, if OAR have been kept out of the high dose area. Nevertheless, local control is dependent on dose, with recurrences occurring even after years, (*e.g.,* with single doses below 26 Gy/isocenter or 3 × 10 Gy/planning target volume [PTV] enclosing 65% isodose) (45, 46). By contrast, some authors have shown that significantly higher doses can be applied safely, such as single doses above 30 Gy/isocenter or 3 × 20 Gy/PTV enclosing 80% isodose, if the normal tissue dose constraints are respected (46–49).

Experience in retroperitoneal (pancreas and kidney) tumors

Abdominal retroperitoneal tumors pose a difficult challenge in view of their proximity to the poorly tolerant bowel. In the case of pancreas tumors, trials have shown conflicting results about the benefit of therapy. Although Hoyer *et al.* indicated little benefit and increased toxicity in patients treated with 45 Gy in three fractions (50), Koong *et al.* used a single dose ranging from 15 to 25 Gy and were able to control tumors in most patients with acceptable toxicity (51, 52).

Although renal cancers are thought to be radioresistant when treated with conventional fractionation schedules, Wersaell *et al.* found extremely high rates of local control with a three- to four-fraction SBRT regimen (53). These results concurred with the high local control rates observed when SRS with a large dose per fraction was used to treat brain metastases of the same histology.

Biology of dose delivery to tumor and normal tissues

Unlike normofractionated RT, the biologic purpose of SRT is for lethal rather than sublethal cell damage in the

high-dose area without repair. Additionally, because of the short overall treatment time (single dose, hypofractionation within 1 to 3 weeks), avoiding the repopulation of tumor cells is another advantage. On the other hand, the presumption is that reoxygenation and redistribution of cells in the cell cycle will not occur with the prescribed dose. The OAR are prevented from serious damage by sparing these tissues from the high-dose area.

Besides dose escalation trials for lung and liver tumors (47, 49), prospective institutional-based reports on the clinical results of SBRT have been published. Unfortunately, comparison of these results is difficult because different dose fractionation schedules have been used, and there is lack of uniformity in normalization and prescribed doses. To overcome this problem, some authors used the BED based on the formula BED (Gy) = dose/fraction × fraction number (1 + fraction dose / α/β using an α/β of 10 Gy for tumor tissue (54, 55). They found a BED of about 100 Gy to be appropriate to achieve a tumor control probability of about 90% for lung tumors. Because it has not been proved that the LQ (linear quadratic) model will be reliable at such high fraction doses, other radiobiologic models might be better suited to predict the effect of SBRT, including modifications of the multitarget model (56).

MINIMUM METHODOLOGY/TECHNOLOGY REQUIREMENTS

Imaging for planning

Imaging for treatment planning is usually based on CT data, whereas magnetic resonance imaging or positron emission tomography can assist this purpose. Before definite scanning, potential breathing mobility has to be evaluated. Depending on the method used to decrease breathing mobility, the amount of motion should be analyzed (it has to be performed to determine the appropriate margins for PTV definition). This can be done by either four-dimensional CT, multislice CT, dynamic scans (repeated scans at the same couch position), or evaluation of the target position during maximum inspiration and expiration. Although this approach is based on slices, which show the scanned tumor position in a very short (<1 second) time, resulting in a sharp image, the target can also be scanned by slow CT. With this technique the tumor is scanned very slowly (*e.g.,* scan time for a slice of 3 seconds). The image shows a blurred shape of the target, including and depending on internal motion (57), which represents the orbit of the moving target. This technique might have advantages, especially when cone-beam CT is used for target verification before irradiation, because the slow scan time (about 1 minute) will cause the shape of the target to also seem blurred (58).

Planning processes

Clinical experience from SBRT has indicated that geometric errors (of a magnitude that is not too uncommon in RT) may lead to more severe consequences than errors in dose delivery. Thus, if priorities need to be determined, geometric aspects should be emphasized more than dose aspects in the planning and delivery processes of SBRT.

Treatment planning in SBRT is done on commercial treatment planning systems, which are also used for RT planning in general. The CT data must account for the different densities in the body for the dose calculation. For dose calculation of tumors in the lungs, pencil beam algorithms have a limited accuracy but are acceptable for use (59). Point kernel–based superposition/convolution algorithms give a more accurate estimate of the dose to the tumor and surrounding lung tissue (60). The error in the dose calculation for tumors in the lungs is reduced if the photon energy is restricted a maximum of 6 MV. Small field sizes are often used in SBRT because of the small size of the PTV. Thus, accurate beam modeling is important (both profiles and depth doses) for field sizes down to 3 cm × 3 cm, preferably down to 2 cm × 2 cm. Image registration tools for the geometric verification process, dose–volume histogram calculation tools, and tools (for example rulers) to calculate the position of the isocenter in the reference system defined by the fiducials must be included.

Radiation beam delivery equipment

Clinical experience with SBRT stems primarily from the use of conventional linear accelerators, and to a lesser extent from more specialized accelerators, but not from the use of conventional cobalt units. The latter is not recommended for SBRT because of the lack of clinical experience and the inferior physical characteristics of the beams.

The following recommendations are given for the linear accelerator for SBRT: Photon energies of 6 MV (or close to that) for tumors in the lungs. For tumors below the diaphragm (not passing through lung tissue), 6 to 20 MV. It is important to keep the treatment time reasonably short, preferably in the range of half an hour per target, as a maximum. The reason is mainly to avoid geometric errors from patient motion during a very long treatment time, but also to some extent to avoid a possible dose–rate effect. The following aspects are related to a short treatment time. A multileaf collimator (leaf width maximum 1 cm) should preferably be used to shape the beams, but customized blocks may be acceptable. The preferred dose rate should be at least 400 MU/min, but at least 250 MU/min can be acceptable Motorized wedges should preferably be used, but manual wedges may be acceptable. The size of the mechanical isocenter sphere should be within 1 mm in radius. Equipment (*e.g.,* lasers, video cameras, X-ray sources) in the treatment room used for setup should be accurately adjusted to the isocenter. The deviation of the actual isocenter point from the planned one should be aimed to be within 1 mm in the reference system defined by the fiducials (Figure). The mechanical sag on the treatment couch with the patient in treatment position and CT couch must be checked, and should be of the same order. This is of primary importance for targets extended in the cranial-caudal direction.

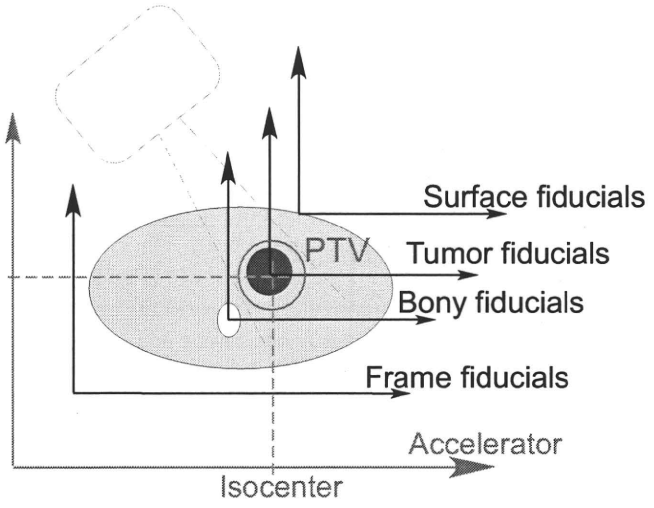


Fig. Patient treatment in the stereotactic body frame (ELEKTA Instr.). The correct isocenter position of the target and adequate suppression of breathing mobility by increased abdominal pressure is proved on the treatment couch by a mobile computed tomography device with gantry movements (Tomoscan M, Philips, Inc.).

Immobilization

Immobilization of the patient should be comfortable and also rigid to avoid intrafractional motions to ensure accurate repositioning of the patient between treatment planning and irradiation sessions. Both goals are usually achieved by tightly moulded vacuum pillows, which are attached to a stereotactic frame (e.g. SBF) or are used frameless (*e.g.*, Body-Fix). Specific attention should be directed to providing comfortable support for the arms and legs/knees, because they are most prone to become uncomfortable during a long treatment procedure (verification and irradiation might last up to 60 min).

Geometric verification

Geometric verification is a very important issue for SBRT because its single dose is usually more than 10 Gy and therefore constitutes 20–33% of the whole dose. A single misalignment will result in local failure or severe complication. The most simple verification method widely accepted is an anterior–posterior portal film taken before each session to compare with DRR (Digitally reconstructed radiographs) to check bony anatomy. EPID (Electronic portal imaging device) images can be used alternatively, but the sensitivity to detect setup error may be inferior to portal film. A more useful method is using the CT on rails. It is possible for CT images taken before and after SBRT to detect not only intertreatment setup error but intratreatment setup error. Recently, a couple of image-guided RT machines have been developed. With either the on-board or the in-room imaging apparatus, the position of a patient can be confirmed before every treatment day.

Target volumes and margins

Ideally, both gross tumor volume (GTV) and clinical target volume (CTV) should be geometrically defined in an unambiguous way in the reference system used. In clinical practice, however, there will always be some degree of breathing motion during imaging (even with gating there will be a residual motion) and differences in tumor position during imaging and treatment. ICRU 62 defines an internal margin (IM) and an internal target volume (ITV) for the physiologic movements and variations of the CTV during therapy. One way to get an estimate of the IM is to do the imaging during several breathing cycles (see Imaging for Planning, above). In the clinical practice of SBRT, ITV is not always defined explicitly, but PTV is usually drawn with standard margins to a CTV that has been defined by normal dose-planning imaging. The standard margins are determined from geometric verification imaging of patient cohorts and basically are valid only for the use of a particular set of conditions like patient fixation and breathing reduction, and also choice of reference system and method for setup and geometric verification. However, owing to similar geometric requirements using different methods for SBRT, a relatively narrow range of margins between CTV and PTV is currently used in clinical practice. With the immobilization equipment and methods for reduction of the target motion described in this report, the longitudinal margin is generally 10 mm. In the transverse plane, margins are usually 5 mm and up to 10 mm. Table 5 shows the margins used at different centers (16,18,19, 32,36,44,48–50,65,66).

Training requirements

The process of SBRT differs greatly from general RT in method and, more importantly, regarding patient selection, dose prescription/fractionation, target definition, and as a consequence toxicity patterns. Thus, training in SBRT is of major importance, and the following recommendations have been made: General methods for SBRT should be studied by RO (Radiation oncologist), medical physicist (MP), and radiation therapy technologist (RTT); patient selection criteria by RO; patient immobilization and accounting for internal organ motions by MP and RTT; imaging acquisition technique by MP and RTT; target definitions by RO; dose planning by MP; dose prescription by RO and MP; geometric verification by MP and RTT; treatment by RTT; toxicity patterns by RO; and follow-up by RO.

Personal experience is important not only in patient selection but also in proper use of the equipment, target definition, three-dimensional treatment planning, and follow-up of patients. Some vendors offer practical teaching courses with experienced faculty after the purchase of SBRT equipment.

QUALITY ASSURANCE REQUIREMENTS

General recommendations on quality assurance (QA) in RT also apply to SBRT. QA recommendations focused on SBRT have also been published (61), as have practice guidelines for the performance of SBRT (62). However, some aspects of QA that are of particular importance for SBRT are given below.