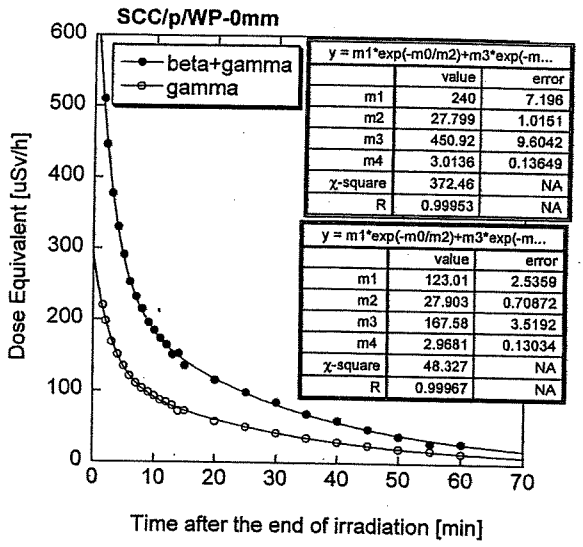
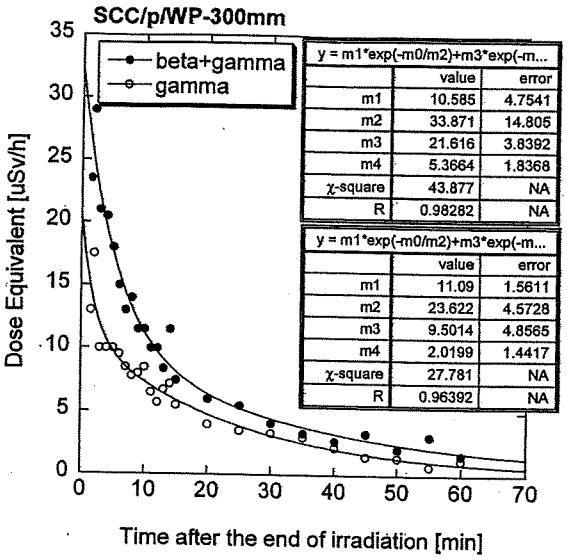
2.4 Measurement 4: Radioactivity in the patient (TWP)

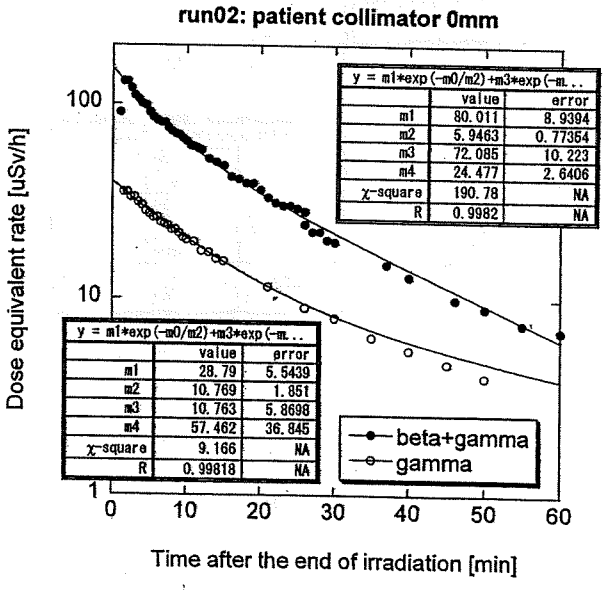


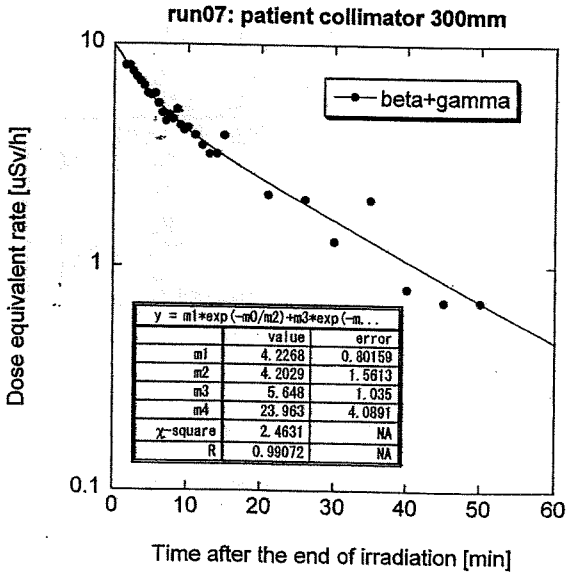


3. NIRS (Carbon ion beam of 290 MeV/n)

3.1 Measurement 1: Radioactivity in the patient collimator (PTC)

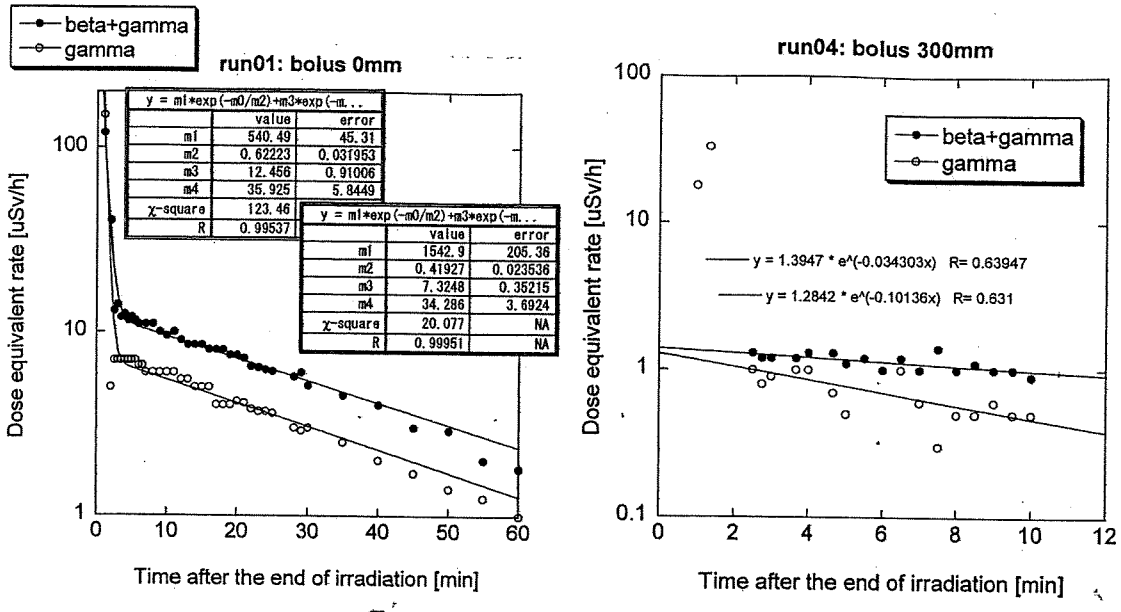
- The dose rate 300 mm downstream from the collimator was not measured for gamma-rays alone.



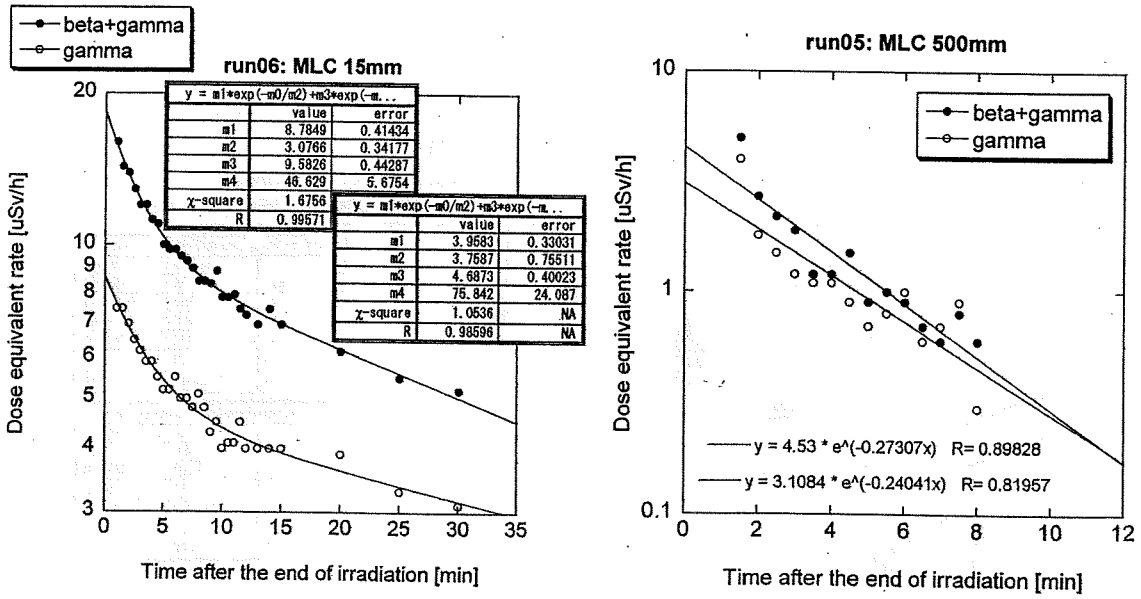


3.2 Measurement 2: Radioactivity in the bolus

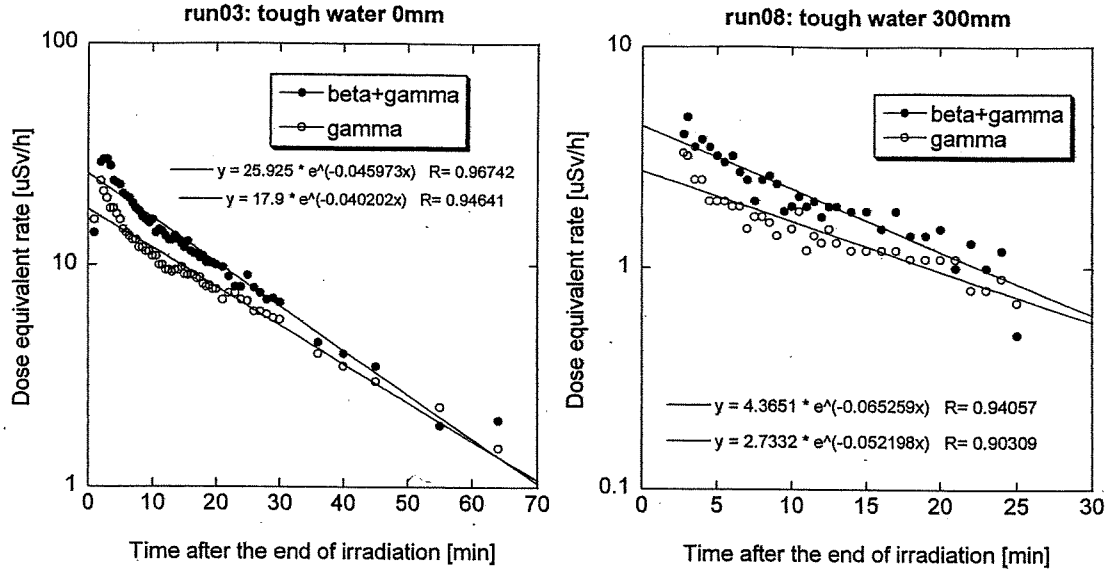
- The first measured values 300 mm downstream from the bolus were not included in the fitting because the measurement not succeeded.



3.3 Measurement 3: Radioactivity in the irradiation devices (MLC)



3.4 Measurement 4: Radioactivity in the patient (TWP)

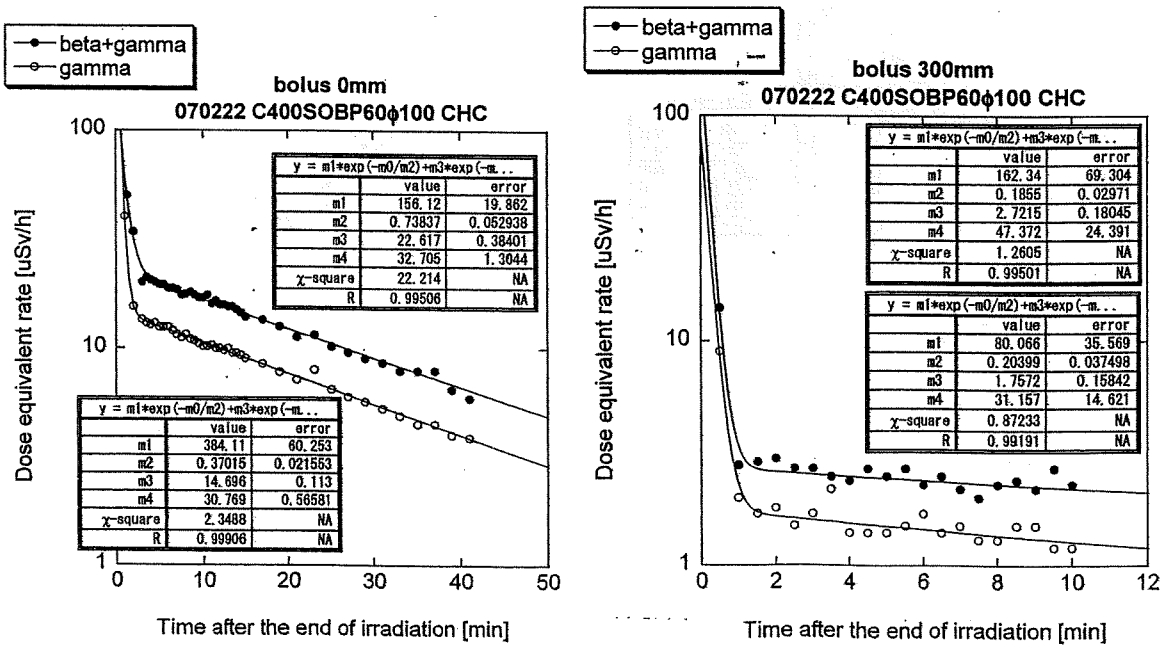


4. NIRS (Carbon ion beam of 400 MeV/n)

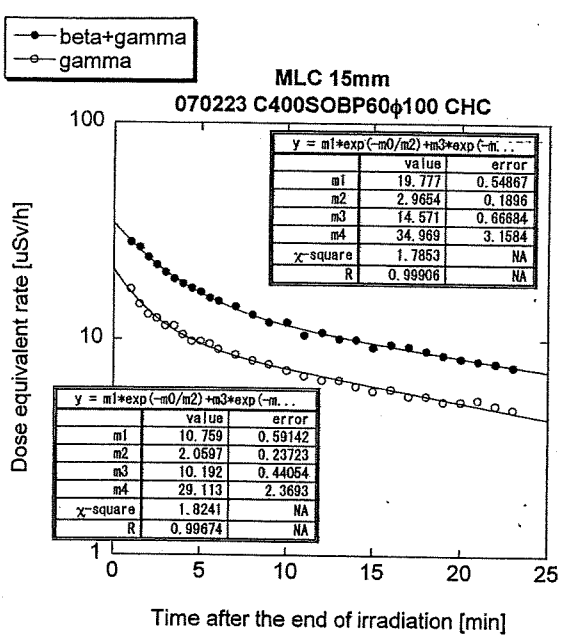
4.1 Measurement 1: Radioactivity in the patient collimator

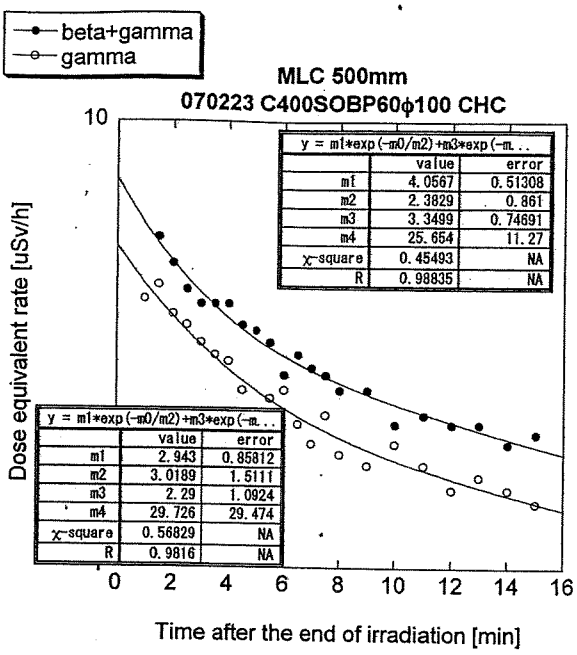
- This measurement was not performed because the patient collimator is not used in treatments with the 400 MeV/n beam.

4.2 Measurement 2: Radioactivity in the bolus

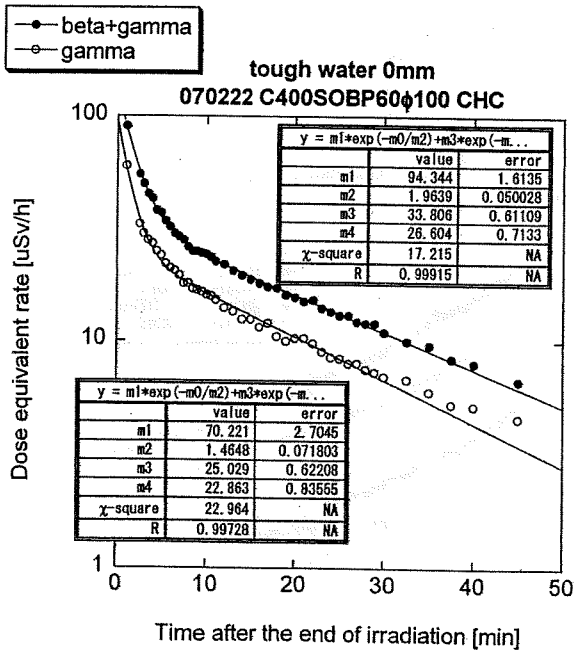


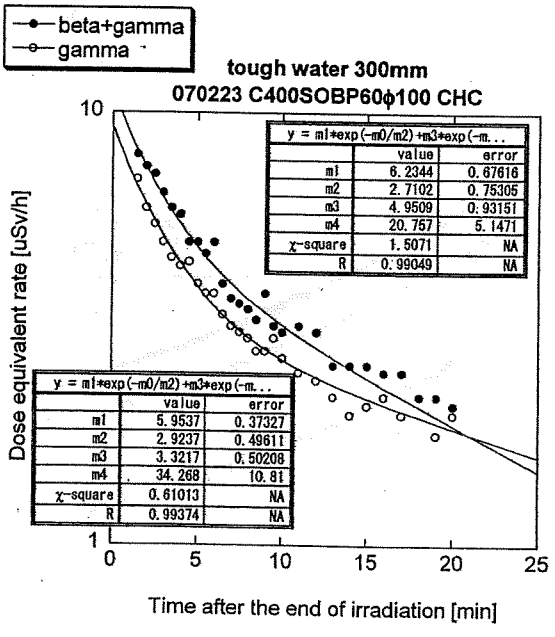
4.3 Measurement 3: Radioactivity in the irradiation device (MLC)



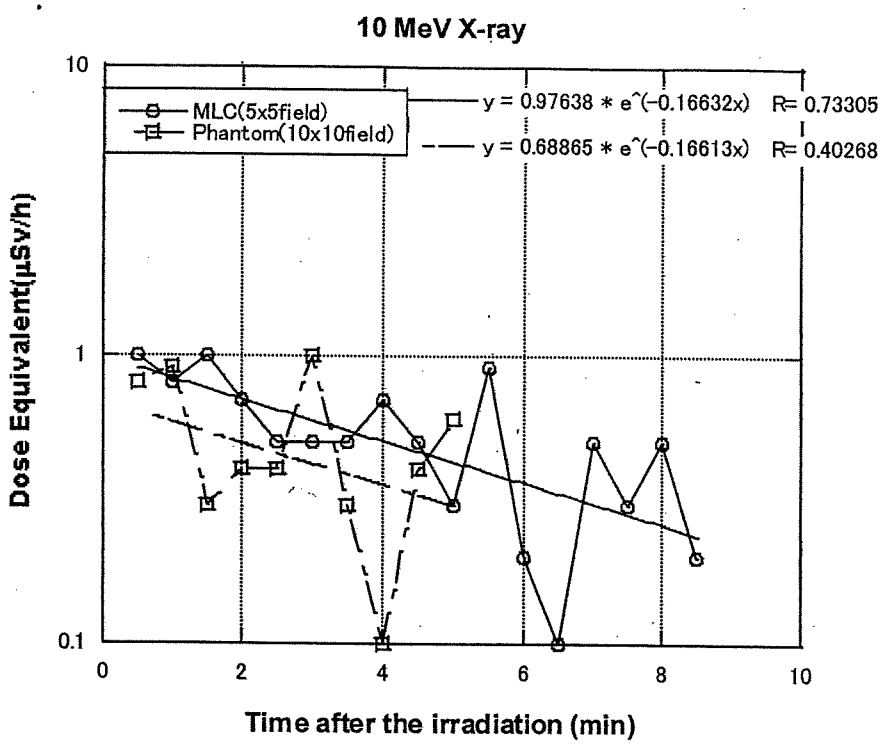


4.4 Measurement 4: Radioactivity in the patient (TWP)



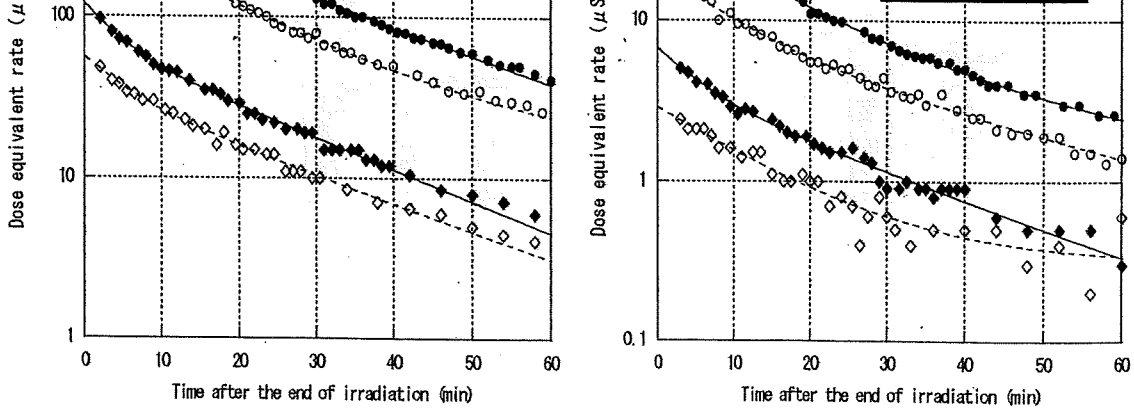


5. NIRS (Medical Linear Accelerator)

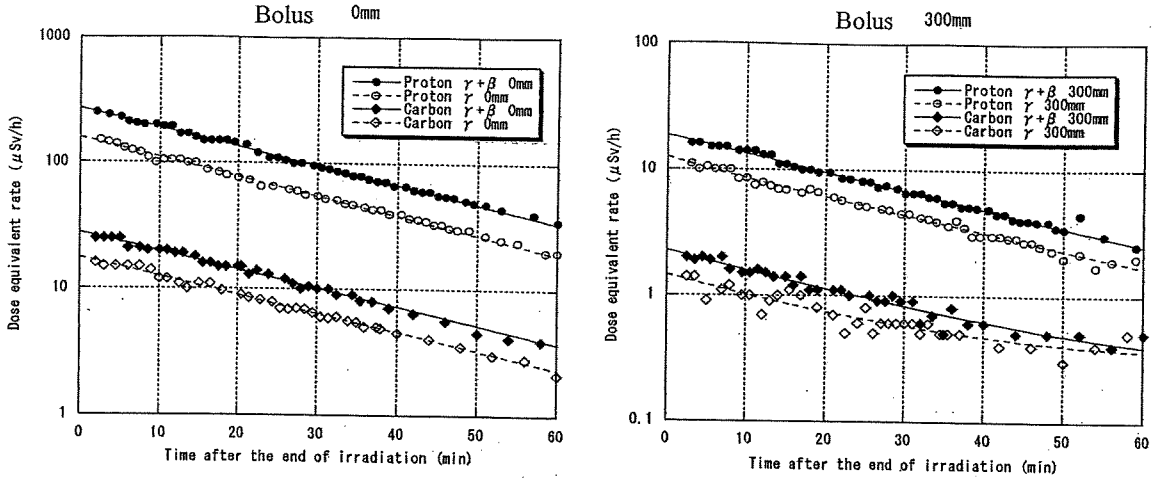


6. HIBMC (Proton beam of 210 MeV; carbon ion beam of 320 MeV/n)

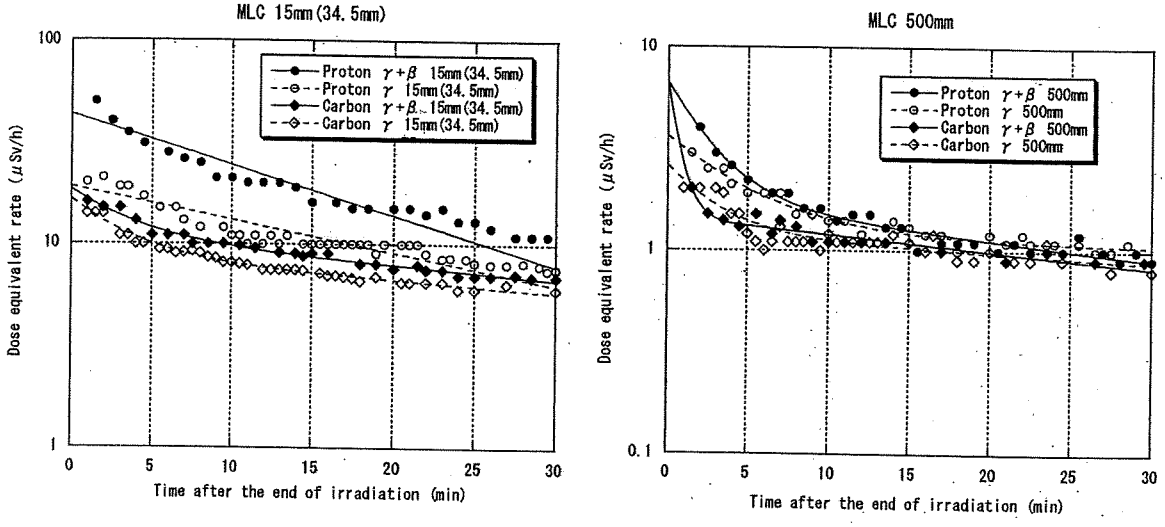
6.1 Measurement 1: Radioactivity in the patient collimator (PTC)



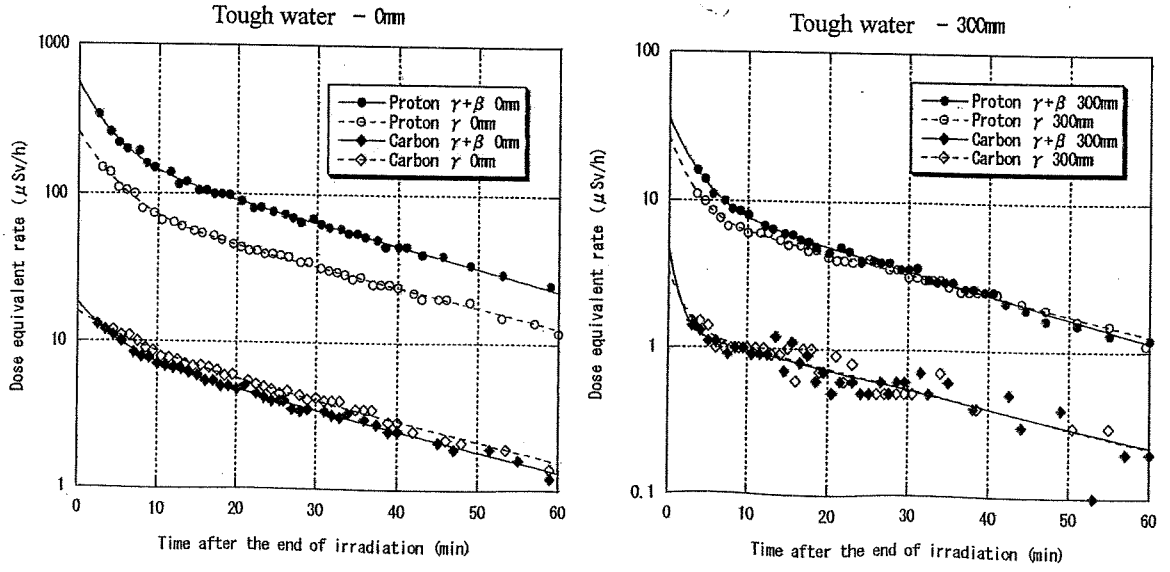
6.2 Measurement 2: Radioactivity in the bolus



6.3 Measurement 3: Radioactivity in the irradiation device (MLC)



6.4 Measurement 4: Radioactivity in the patient (TWP)



Appendix II. Study organization

Chief Researcher

Tujii, H.	National Institute of Radiological Sciences (NIRS)

Assigned Researchers

Akahane, K.	Research Center for Charged Particle Therapy, NIRS
Endo, M.	Research Center for Charged Particle Therapy, NIRS (2005)
Kanai, T.	Research Center for Charged Particle Therapy, NIRS
Matsufuji, N.	Research Center for Charged Particle Therapy, NIRS
Nishizawa, K.	Research Center for Charged Particle Therapy, NIRS
Sato, Y.	NIRS / Gunma University (2005, 2006)
Uwamino, Y.	Nishina Center for Accelerator-Based Science, RIKEN

Cooperating Researchers

Akagi, T.	Device management department, Hyogo Ion Beam Medical Center
Fukuda, S.	Research and Development Section , WERC
Nakamura, T.	Professor emeritus of Tohoku University
Nakayama, T.	Radiation Safety Technology Center (NUSTEC)
Nishio, T.	Clinical Analysis Center, National Cancer Center Hospital East
Nishizawa, K.	Professor emeritus of Nagoya University
Ono, T.	Gunma University
Sakae, T.	Proton Medical Research Center, University of Tsukuba
Yamashita, H.	Shizuoka Cancer Center
Yonai, S.	Research Center for Charged Particle Therapy, NIRS

Working Group Members

Akagi, T.	Device Management Department, Hyogo Ion Beam Medical Center
Kanai, T.	Research Center for Charged Particle Therapy, NIRS
Kono, R.	Clinical Analysis Center, National Cancer Center Hospital East
Matsufuji, N.	Research Center for Charged Particle Therapy, NIRS
Nakamura, T.	Professor emeritus of Tohoku University
Nishio, T.	Clinical Analysis Center, National Cancer Center Hospital East
Sakae, T.	Proton Medical Research Center, University of Tsukuba
Shimizu, M.	Hyogo Ion Beam Medical Center
Urakabe, E.	Shizuoka Cancer Center
Uwamino, Y.	Nishina Center for Accelerator-Based Science, RIKEN
Yonai, S.	Research Center for Charged Particle Therapy, NIRS

陽子線がん治療におけるGEANT4の活用

西尾 禎治*・亀岡 覚*

Utilization of Monte Carlo Simulation Toolkit GEANT4 for Proton Therapy

Teiji Nishio* and Satoru Kameoka*

Key words: Monte Carlo simulation toolkit GEANT4, Proton therapy, Treatment planning, Dose calculation, Verification tool

1. はじめに

現在，国民病の一つにもなっている“がん”の国内での患者数は300万人といわれ，国民の3人に1人ががんで亡くなる時代になっている[1]．また，がん患者数は，2015年には約540万人になると予想され，国民の3人に2人が生涯の内に一度はがんに罹り，2人に1人ががんで亡くなる時代が近づいている[2]．がんの3大治療法の一つに放射線治療がある．放射線を腫瘍に照射することでがんを治療する方法である．国内では，全患者数の内の25%に何らかの形で放射線治療が実施されている[3]．尚，欧米においては，その数値は60%である[4]．がんの放射線治療は，人体が持つ機能の温存率が高いこと，治療によって患者が受ける身体的な負担が少ないなどの利点がある．

近年の半導体，機械，コンピュータ，ソフトウエアといった技術は急速な進歩を遂げ，それらの進歩に伴い放射線を腫瘍に集中させる照射が可能となり，放射線がん治療(放射線治療)も高精度化の時代に突入している．その腫瘍に放射線を集中させることが出来る治療法の一つに陽子線がん治療(陽子線治療)がある．陽子線治療は腫瘍に対する高い線量集中性を持つため，腫瘍へ的確に照射するための線量計算，また，患者体内を模擬した物質中での線量検証といった作業が非常に大切である．陽子線治療では，実際の患者の体内でどのような線量分布になっているかを正確に把握したいのであるが，その際，患者体内での線量分布を直接的に測定することは，現時点では不可能であるため，計算精度の高いシミュレーションシステムが必要不可欠となる．陽子線治療において，モンテカルロ計算ツールキットGEANT4(GEometry ANd Tracking 4)[5]は，高い計算精度と豊富な機能の環境が用意されており，非常に有用性の高いシミュレーションツールであると思われる．

本論文では，陽子線治療におけるGEANT4の多岐に渡る有用性を紹介する．

2. 陽子線治療

陽子線治療は数ある放射線治療のひとつである．陽子線は陽子核をビームとしており，エネルギー阻止能の関係でビームが停止する寸前の場所で大きなエネルギーを損失する特性を持っている．その結果，その部分にブラッグピークと呼ばれる高い線量領域が形成される．腫瘍部分にそのピーク位置が集中するようにビーム照射位置及び入射エネルギーを調整することで，陽子線治療を実現させている．**図1**は陽子線治療と一般的な放射線治療(X線利用)における深部方向の線量分布特性である．陽子線治療は腫瘍に線量を集中させ，腫瘍部以外の線量投与を極力抑えることが可能な治療法である．

国立がんセンター東病院の陽子線治療施設では，235MeVまで陽子核を加速できる常伝導のサイクロトロンと3つの陽子線治療室がある(**図2**参照)[6,7]．その内，2つの治療室は235MeVの陽子線を，患者に対して

* 国立がんセンター東病院臨床開発センター粒子線医学開発部
Particle Therapy Division, Research for Innovative Oncology, National Cancer Center, Kashiwa

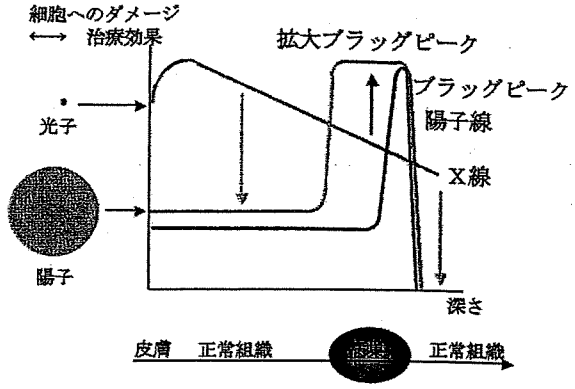


図1　陽子線及びX線がん治療での線量分布特性の概念図.

360度，どの方向からも照射可能なシステムになっており，その回転駆動装置は直径10メートル，重さ150トンほどもある．陽子線治療装置では，駆動部分を有した非常に大きな装置を利用しているが，腫瘍に対する治療においては数mm精度での照射が要求される．尚，235MeVの陽子線は患者体内で30cm程の深さまで到達し，深部にあるがんも治療可能である．がんの形状・大きさ・その位置，そしてがんへの処方線量は患者ごとに異なる．そのため，陽子線をがんへ的確に，決まった線量で照射するためのシステムが必要となる．その内訳は，照射領域形成システム（図3及び図4参照），線量管理システム，照射ガントリーシステム，患者位置

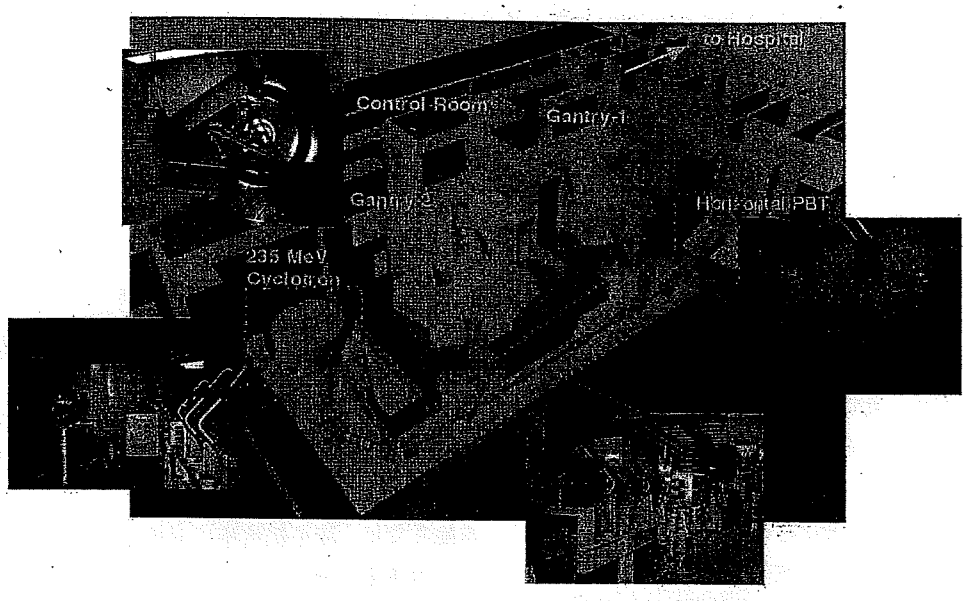


図2　国立がんセンター東病院における陽子線治療施設の鳥瞰図.

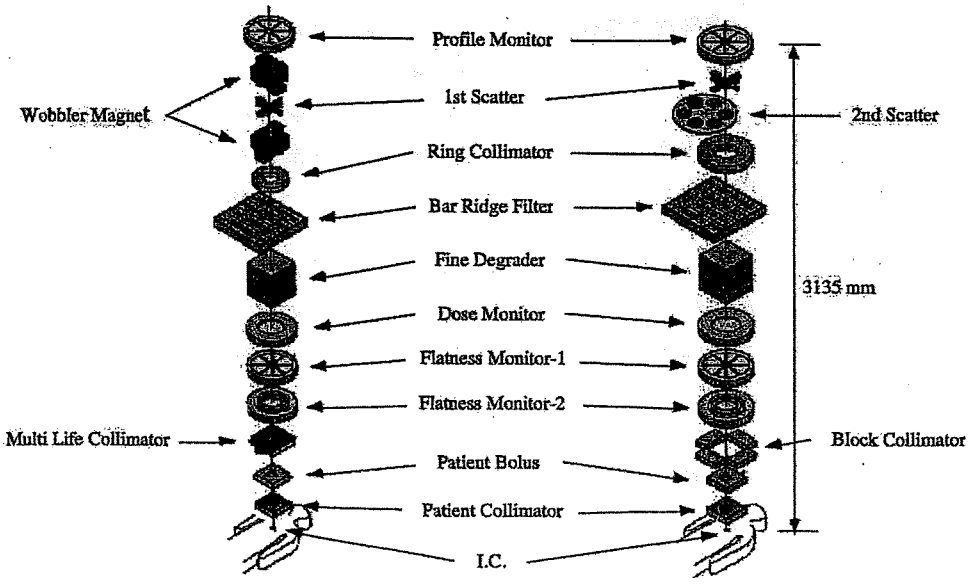


図3　ワブラー法用（左）及び2重散乱体法（右）のための陽子線照射野形成機器.

決めシステム，呼吸同期照射システム，治療計画システム，患者ボーラス・コリメータ加工システム及び線量校正・検証システムとなる．GEANT4によるシミュレーションを実施するには，計算の必要性に応じて，これらのシステムの幾何学的及び物質的な情報を正確に入力して扱わなければならない．

3. 陽子線線量分布の検証

GEANT4による陽子線の線量分布シミュレーションを実施するには，照射領域形成システムの装置条件に対応した計算結果を算出するかを検証する必要がある．図5は，当センターの2重散乱体法の照射領域形成システムをGEANT4で計算出来るように設定した際の配置

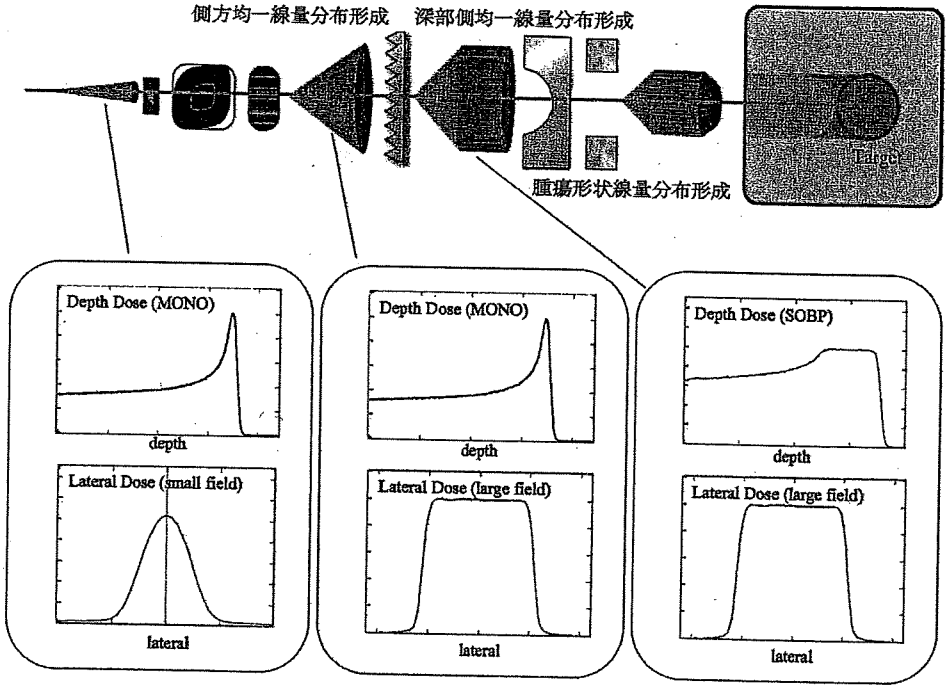


図4 照射野形成法の概念図．

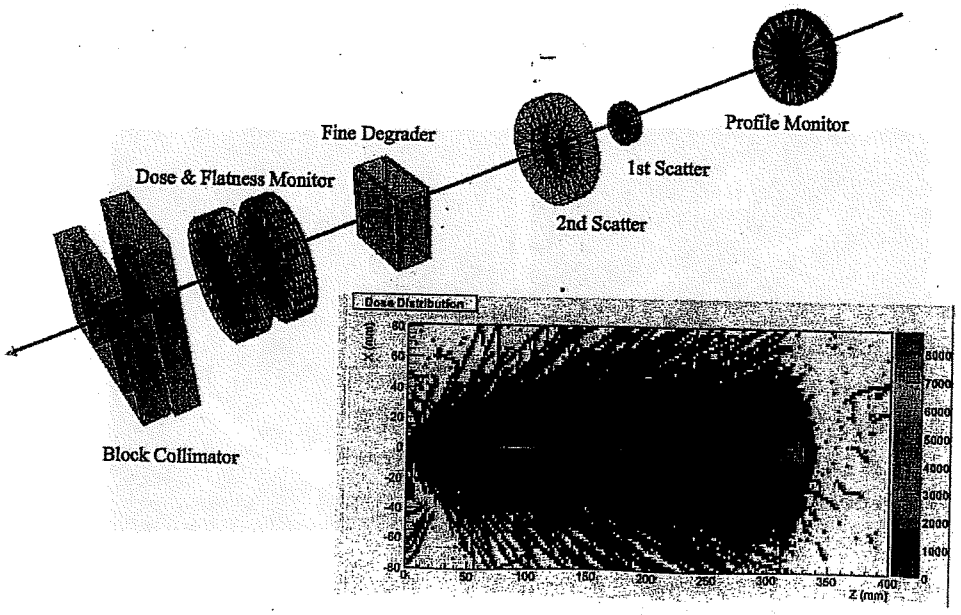


図5 GEANT4における2重散乱体法での照射領域形成システムの装置配置図と水中における235MeVの陽子線の線量分布プロファイルの計算結果．

図である．陽子線を治療に利用する際は，単一エネルギー(MONO energy)の陽子線が作る鋭いブラッグピークを，腫瘍の厚さに応じて均一な線量分布となるように重ね合わせることで形成される拡大ブラッグピーク(Spread Out Bragg Peak: SOBP)を利用する．照射領域形成システムに設置されたアルミ製の楔状フィルターを利用し，ビームエネルギーの吸収とそのビーム量の比率を制御することでSOBPを形成する．ビーム軸に垂直な面内での均一な線量分布は，ワブラー法及び2重散乱体法によって形成される．ワブラー法は，1対の垂直方向及び水平方向への偏向電磁石によってビームを円形に走査し形成したドーナッツ形状のビームを散乱体で大きく散乱させ，均一な線量の照射野を形成する方法である．2重散乱体法は，第1散乱体でビームを広いガウス分布に拡大させ，その下流に設置された第2散乱体により，更にビーム中心部分を大きく散乱させて均一な線量分布を持つ照射野を形成する方法である[8]．

図6は190MeVのMONOの陽子線を水に照射した場合で，線量モニターを通過した後で実測された線量分布結果及びGEANT4による線量計算結果である．その比較検証より，実測結果に対してGEANT4の計算結果はおおよそ一致している．深部線量分布形状で，ブラッグピーク形状の線量が立ち上がる部分で多少の相違が観測された．**図7**は水中における190MeVのSOBP(60mm)の陽子線の線量分布の実測及び計算結果である．レンジの線量の落ち際で多少の相違が観測された．それらの相違は，実測値に対する計算パラメータの更なる検証を実施することで改善していくものと思われる．

図8は頭頸部の陽子線治療において，現在，臨床で利用している治療計画装置に搭載された，当センターで開発したペンシルビーム法線量計算アルゴリズム

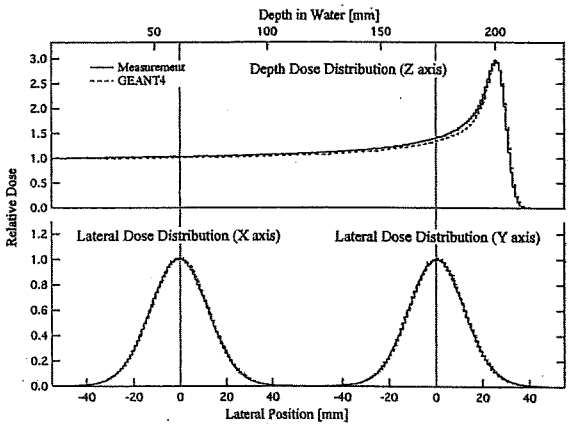


図6　190MeV陽子線のMONOの深部及びビーム入り口における側方の線量分布の実測及びGEANT4による計算結果．実線が実測，破線がGEANT4での計算結果である．

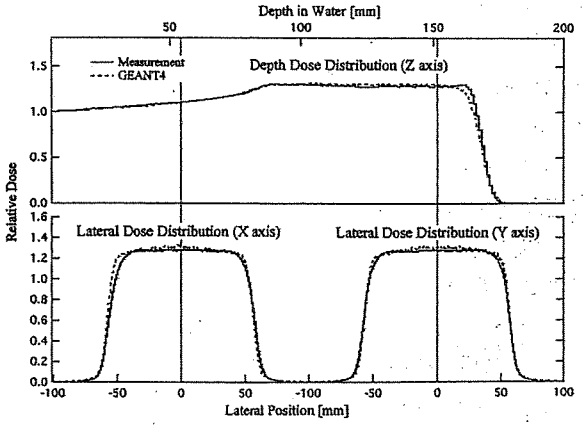


図7　190MeV陽子線のSOBP(60mm)の深部及びSOBP中心における側方の線量分布の実測及びGEANT4による計算結果．実線が実測，破線がGEANT4での計算結果である．

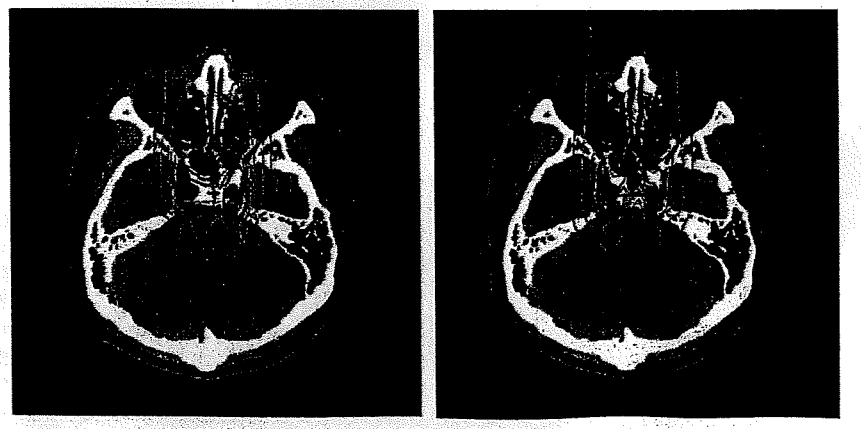


図8　頭頸部の陽子線治療におけるペンシルビーム法(左)及びGEANT4(右)による線量分布計算結果．
線量分布は処方線量点で規格化された等高線表示となっている．

(NCC-PBA)[9]及びGEANT4による線量分布計算結果である．NCC-PBAは陽子線の線量計算精度において重要となる，水中での陽子線の多重クーロン散乱をガウス形状として数式計算することで側方に広がりを持った細いペンシルビーム形状の陽子線線量分布を基本単位として線量分布計算に利用する．多重クーロン散乱の効果を数式処理するので計算時間が短くて済むが，その一方で不均一物質が複雑に入り組んだ領域における計算精度は高くないといった問題点を含んでいる．GEANT4はNCC-PBAで計算精度が弱いとされる領域における計算精度は高いが，計算時間が数時間と非常に長くなってしまう問題点がある．GEANT4の計算は，DICOM形式の患者のCT画像を利用し，治療計画装置上で計算結果を表示出来るように構築されている．現時点では，実際の患者の治療計画の中でGEANT4を簡易的に扱えるまでには至っていないが，近い内に実現する見込みである．尚，治療計画装置が持つ線量計算機システムは48CPUのIBM/BladeCenterで構築されている．図8の結果をGEANT4で算出するのに約2時間の計算時間を要している．また，NCC-PBAの計算精度が弱いとされる不均一物質が複雑に入り組んだ小領域のみにGEANT4の計算を適応させ，線量計算時間の高速化と高精度化の実現を目的とする，双方の計算アルゴリズムを組み合わせたHybrid(PBA-GEANT4)アルゴリズムの研究も実施している．

4. 陽子線投与線量校正値の補正係数計算

陽子線治療のための線量計算を実施する上で，線量分布と同様またはそれ以上に重要なのは患者毎の処方線量を正確に投与することである．患者毎の投与線量は，陽子線を治療と同条件にて，均一な物質(当センターではポリエチレンブロックを利用)に照射した場合において，基準点での電離箱線量計による線量計測値をそのまま利用する．例えば2Gyの線量を腫瘍へ処方したい場合は，電離箱線量計の出力値が2Gyになるように線量モニターの値を患者毎に校正する(**図9**参照)．但し，実際には患者体内で決まった処方線量を投与したいのだが，線量モニター値の線量実測による校正は均一な物質で実施されるため，患者体内のある基準点で2Gyの投与線量が均一物質に移した基準点で同じ投与線量になる保証はない．これは患者体内と均一物質中での陽子線の散乱効果の相違が主原因で起こるので，その相違を精度良く計算出来る必要がある．このように，患者毎の陽子線投与線量の精度を向上させるためには，患者体から均一物質への置き換えに伴う線量分布形状の変化を補正する係数を算出する必要があり，高い線量計算精度が要求される．この線量分布の変化量をGEANT4で計算し，患者毎の陽子線投与線量の精度向上のための補正係数を高精度で算出するシステムの構築を実施しているところである．

5. 陽子線の生物学的効果比の検証

放射線の線量に対する生物への影響は，放射線がどんな種類であるかに依存する線エネルギー付与(linear energy transfer: LET [keV/μm])と相関があることが裏付けられている．マイクロオーダーの大きさを持つ細胞に対するエネルギー付与量を表している．その影響の度合いは，放射線生物学的効果比(relative biological

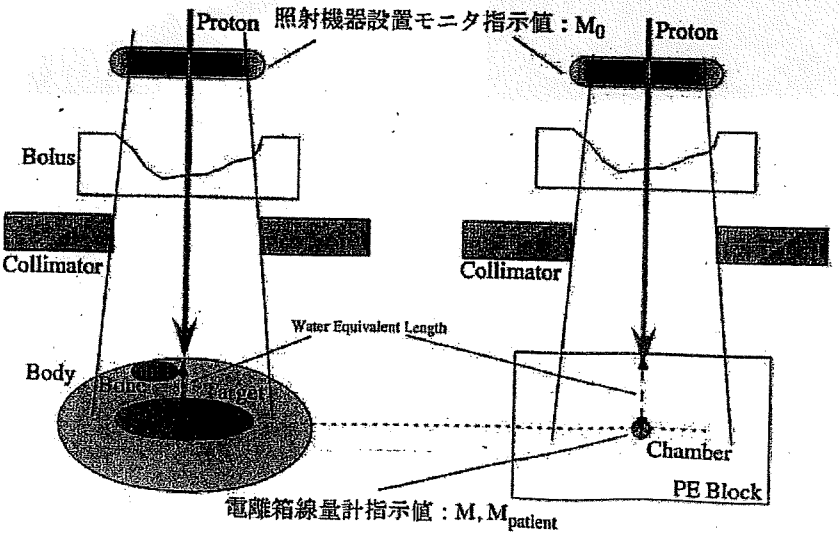


図9 患者毎の投与線量校正値の決定法の概念図．

effectiveness: RBE)で表される．放射線照射によるある生物反応を基準にしたとき，光子線で必要となる線量と別の放射線で必要となる線量の比で定義される値である．陽子線のLETは持っている運動エネルギーの値に応じて変化するため，患者体内でどのようなLETを持った陽子線がどのような形で分布しているかを知る必要がある．そのため，GEANT4を用いることで，様々な物質内，最終的には患者体内でのLET分布計算が可能となる．また，GEANT4の特長として，LET計算精度として重要な反跳電子のトラッキングまで計算で追従することが可能であり，そのLET計算精度は高いとされている．**図10**は染色された細胞写真，GEANT4による陽子線のレンジ近傍におけるLET分布計算結果及びLETによるRBEの相関グラフである．尚，細胞サイズレベルの組織等価線量測定技術(micro dosimetry)の開発も進んでおり，その実験値の検証にもGEANT4を十分利用することが出来る．

6. 陽子線線量検証ツールの検証

陽子線治療を精度良く実施するには，数多くの線量検証の実施が必要となる．それらを円滑に，且つ観測したい現象を精度良く観るために様々な検証ツールが開発されている．例えば，**図11**に示すようなプラスチックシンチレータ検出器を利用して，陽子線の線量分布を3次元で測定し，更に時間による陽子線の線量分布の変化を測定することで，4次元の陽子線線量分布検証ツールを構築することが可能である[10]．プラスチックシンチレータ検出器の場合は，陽子線のエネルギーに応じて線量と発光量との関係をGEANT4で精度良く計算すれば，そのツールの仕様を検証することが可能である．このように，放射線測定に関連した様々な検証ツールの仕様を，GEANT4を利用することで算出することが出来る．

7. まとめ

陽子線治療において，GEANT4は実際の患者体内での線量分布計算を主軸として，測定器の特性検証から生物学的な現象のシミュレーションまで，様々な場面で活用することが出来るツールである．また，陽子線治療に限定せず，放射線治療，更には核医学や放射線診断を含む放射線医療分野全域に渡り，GEANT4の有用性は非常に高いだろう．今後，放射線医療分野において，GEANT4の活用範囲は益々拡大していくと期待できる．

謝 辞

本研究は高エネルギー加速器研究機構の佐々木節氏を代表とする，平成15年度採択JST/CRESTの「高度放

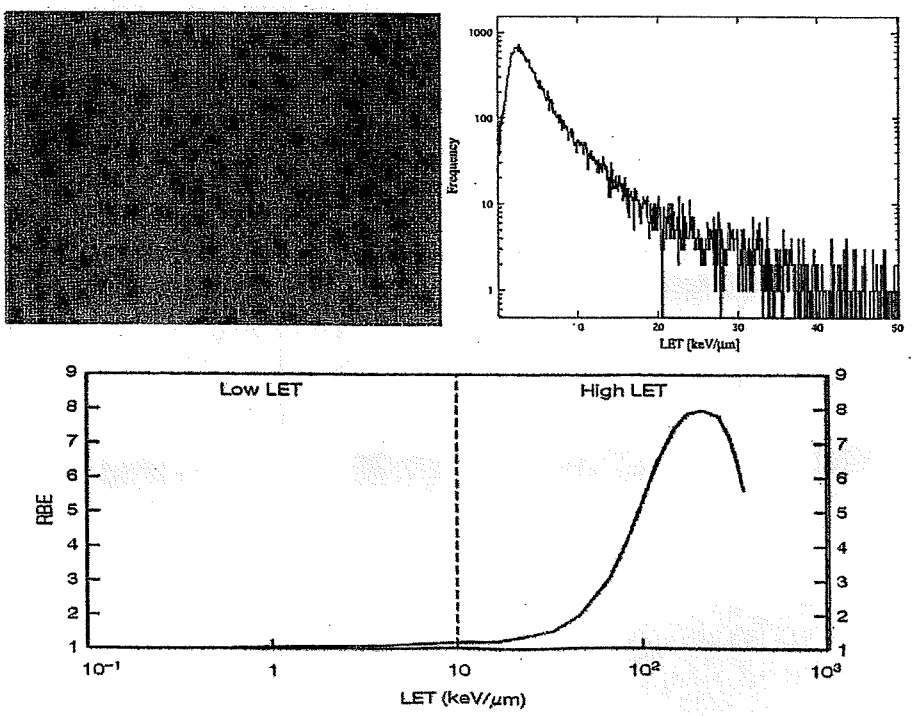


図10 染色された細胞写真(左上)，GEANT4による陽子線のレンジ近傍におけるLET分布計算結果(右上)及びLETによるRBEの相関グラフ(下)．

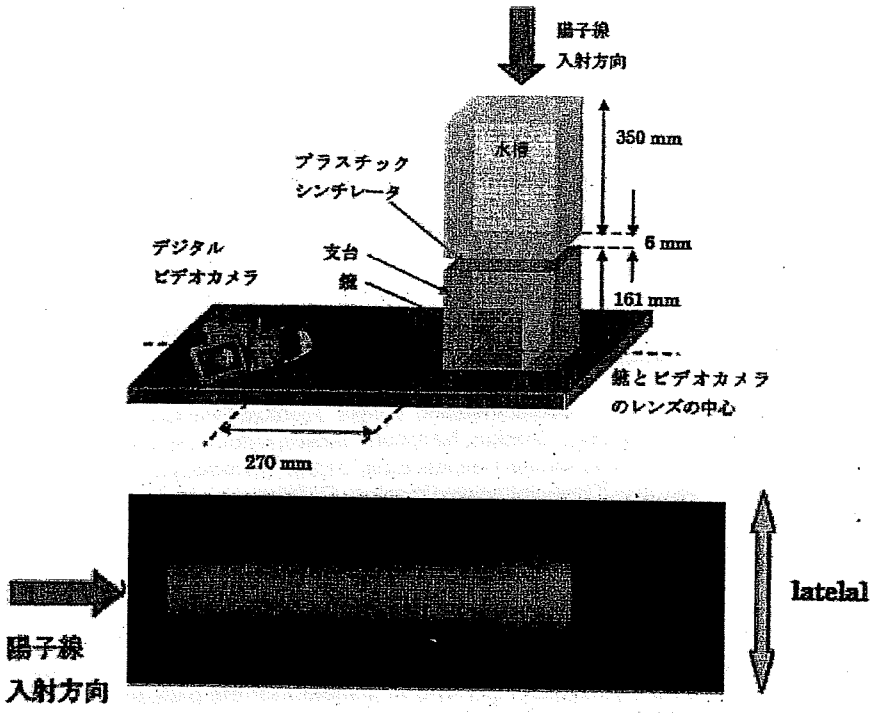


図11 プラスチックシンチレータ検出器を用いた4次元陽子線線量分布検証ツールの概念図及び実測された陽子線の発光分布.

射線医療のためのシミュレーション基盤の開発」により行われた．佐々木節氏をはじめとする研究メンバーならびに関連事務局の皆さまに深く感謝いたします．特に陽子線治療計画装置へのGEANT4の実装に関しては富山商船高専の阿蘇司氏の御協力に感謝いたします．また，図の一部は当センターの松浦妙子氏，放射線医学総合研究所の松藤成弘氏及び北里大学の丸山研究室の大学院生より頂きました．有り難うございます．

参 考 文 献

1) 厚生労働省：人口動態統計，(2005)
2) 厚生労働省：「がん生存者の社会的適応に関する研究」報告書，(2002)
3) JASTRO構造調査：日本放射線腫瘍学会誌，**15**，115/121 (2005)
4) Fast facts about radiation therapy, Fact Sheet, ASTRO (2004)
5) S. Agostinelli, J. Allison, K. Amako, et al.: GEANT4: a simulation toolkit, Nucl. Instrum. Meth., **A502**, 250/303 (2003)
6) T. Nishio: Present status and planning of facilities for proton and heavy ion cancer treatment in Japan – National Cancer Center, J. At. Energy Soc., **41**-11, 1134/1138 (1999)
7) T. Tachikawa, T. Sato, T. Ogino, T. Nishio: Proton Treatment devices at National Cancer Center (Kashiwa, Japan), Radiation and Inductries, **84**, 48/53 (1999)
8) W. Chu, B. A. Ludewigt, T. R. Renner: Instrumentation for treatment of cancer using proton and light-ion beams, Rev. Sci. Instrum., **64**-8, 2055/2122 (1993)
9) T. Nishio, K. Suegara, M. Yamada, T. Ogino: Construction of the proton treatment planning system possessing high versatility and development environment, pn. J. Med. Phys. Proc. JSMP2003, **23**-3, 67/68 (2003)
10) Y. Fukushima, M. Hamada, T. Nishio, K. Maruyama: Development of an easy-to-handle range measurement tool using a plastic scintillator for proton beam therapy, Phys. Med. Biol., **51**, 5927/5936 (2006)

Jpn J Clin Oncol 2009;39(1)37–42
doi:10.1093/jjco/hyn125

A Phase I Trial of 5-Fluorouracil with Cisplatin and Concurrent Standard-dose Radiotherapy in Japanese Patients with Stage II/III Esophageal Cancer

Takako Eguchi Nakajima[1], Takashi Ura[2], Yoshinori Ito[3], Ken Kato[1], Keiko Minashi[4], Keiji Nihei[5], Shuichi Hironaka[6], Narikazu Boku[6], Yoshikazu Kagami[3] and Kei Muro[2]

[1]Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo, [2]Medical Oncology Division, Aichi Cancer Center Hospital, Nagoya, [3]Radiology Oncology Division, National Cancer Center Hospital, Tokyo, [4]Gastrointestinal Oncology Division, National Cancer Center Hospital East, Chiba, [5]Radiology Division, National Cancer Center Hospital East, Chiba and [6]Gastrointestinal Oncology Division, Shizuoka Cancer Center, Shizuoka, Japan

Received September 8, 2008; accepted October 6, 2008

Objective: In Japan, 5-fluorouracil (5-FU) 400 mg/m^2 on Days 1–5, 8–12, 36–40 and 43–46 with cisplatin (CDDP) 40 mg/m^2 on Days 1, 8, 36 and 43 plus concurrent radiotherapy with 2 weeks planned interruption (60 Gy) was standard for the patients with esophageal cancer. This Phase I trial was designed to determine the maximal tolerated dose (MTD) and dose-limiting toxicity (DLT) of 5-FU on Days 1–4 and 29–32 with CDDP on Days 1 and 29 plus concurrent radiotherapy (50.4 Gy) among the Japanese.
Methods: Escalating doses of 5-FU and CDDP were administered with concurrent radiotherapy (50.4 Gy). Treatment was continued until DLT appeared.
Results: Twelve patients with previously untreated clinical Stage II/III squamous cell esophageal carcinoma were studied. One of six patients given Level 1 (5-FU 800 mg/m^2 on Days 1–4 and 29–32 with CDDP 75 mg/m^2 on Days 1 and 29) developed a DLT of incomplete protocol treatment due to Grade 3 esophagitis. The MTD was not reached at Level 2 (5-FU 1000 mg/m^2 with CDDP 75 mg/m^2). The complete response rate was 67% at Level 1 and 100% at Level 2.
Conclusions: Dose Level 2 with 50.4 Gy radiotherapy was recommended for Japanese patients.

Key words: esophageal cancer – chemoradiotherapy – 5-fluorouracil – cisplatin – Japanese

INTRODUCTION

Chemotherapy with concurrent radiation therapy is one of the treatment options for patients with localized esophageal carcinoma [International Union Against Cancer (UICC) classification clinical stage I/II/III] selected for nonsurgical treatment. On the basis of the results of the Radiation Therapy Oncology Group (RTOG) Phase III intergroup trial (INT 0123, RTOG 94-05), the standard regimen for such patients is 5-fluorouracil (5-FU) 1000 mg/m^2 on Days 1–4 and 29–32 with cisplatin (CDDP) 75 mg/m^2 on Days 1 and 29 plus concurrent radiotherapy (50.4 Gy) (1). In that trial, patients were randomly assigned to receive combined treatment with 5-FU and CDDP plus a higher dose (64.8 Gy) of radiation therapy or the same chemotherapy regimen plus a standard dose (50.4 Gy) of radiation therapy. There was no significant difference in 2-year survival (31 versus 40%) or in local/regional failure or persistence of disease (56 versus 52%) between the high- and standard-dose arms. As for toxicity, the rate of treatment-related mortality was higher in the high-dose arm, but was apparently unrelated to the higher dose of radiation.

In Japan, different chemoradiotherapy regimens have been used to treat localized esophageal carcinoma. In the Japan Clinical Oncology Group Phase II trial (JCOG9516), patients with advanced esophageal carcinoma, who had either T4 tumors or distant lymph node metastasis (M1 Lym), received

For reprints and all correspondence: Takako Eguchi Nakajima, Gastrointestinal Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: taeguchi@ncc.go.jp

5-FU 700 mg/m^2 on Days 1–4 and 29–32 with CDDP 70 mg/m^2 on Days 1 and 29 plus concurrent radiotherapy (60 Gy) (2). This regimen was well tolerated and considered a treatment option for unresectable esophageal cancer. In the JCOG9906 Phase II trial, patients with UICC clinical stage II/III esophageal carcinoma (excluding those with T4 tumors) received 5-FU 400 mg/m^2 on Days 1–5, 8–12, 36–40 and 43–46 with CDDP 40 mg/m^2 on Days 1, 8, 36 and 43 plus concurrent radiotherapy with 2 weeks planned interruption (60 Gy) (3). The 3-year survival rate was 47.1% (90% CI, 37.5–56.7), and the complete response (CR) rate was 62.2%. Acute toxic effects were manageable. Late toxicity, however, was considerable and needed to be reduced (i.e. ≥Grade 3 pericardial effusion, 16%; ≥Grade 3 dysphagea/stenosis or fistula of the esophagus, 13%; ≥Grade 3 pleural effusion, 9%).

As compared with the JCOG9906 regimen, the RTOG regimen was characterized by: (i) a strong recommendation for base treatment planning on computed tomographic (CT) findings, (ii) ≥2 radiation fields, (iii) no planned interruption of radiotherapy, (iv) a lower radiation dose, (v) smaller radiation fields and (vi) higher doses of 5-FU and CDDP. We speculate that the RTOG regimen will overcome the weak points of the JCOG9906 regimen, such as a high incidence of late toxicity (especially pericardial effusion), without compromising efficacy. We therefore conducted a Phase I trial to determine whether the dose of the RTOG chemotherapy regimen could be the recommended dose (RD) for Japanese patients with UICC clinical stage II/III squamous cell esophageal carcinoma (excluding those with T4 tumors).

PATIENTS AND METHODS

Subjects and Eligibility

National Cancer Center Hospital (Tokyo and East), Aichi Cancer Center Hospital and Shizuoka Cancer Center Hospital participated in this trial. The National Cancer Center Hospital, Tokyo coordinated the study and was responsible for data collection and analysis. Patient enrollment was started in April 2004 and completed in January 2005.

Eligibility criteria included the following: histologically proved squamous cell, adenosquamous cell or adenocarcinoma of the thoracic esophagus, excluding the esophagogastric junction; UICC clinical stage II/III disease, excluding T4 tumors; no prior treatment for esophageal cancer; an age of 20–70 years; an Eastern Cooperative Group performance status (PS) of 0 or 1 and written informed consent. Eligible patients also had to have a white blood cell count of ≥4000/mm^3, a platelet count of ≥100 000/mm^3, a hemoglobin concentration of ≥10 g/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤2.5 times the upper limit of normal; a total serum bilirubin concentration of ≤1.5 mg/dl; a serum creatinine concentration of ≤1.2 mg/dl, a 24-h creatinine clearance of ≥50 ml/min, a PaO_2 of ≥70 torr while breathing room air and no electocardiographic abnormalities.

Patients were excluded if they had any of the following: esophageal fistula; massive pleural effusion, pericardial effusion or ascites; evidence of interstitial pneumonia or pulmonary fibrosis on chest X-ray film; active gastrointestinal bleeding; a history of other malignancies, except for mucosal carcinoma or a cancer from which the patient had not remained disease free for 5 years; prior thoracic radiation; a history of severe cardiovascular disease or severe diabetic mellitus; active infection; pregnancy; nursing infants or psychiatric illness. All patients provided written informed consent. The institutional review boards of the National Cancer Center Hospital, Tokyo, the National Cancer Center Hospital, East and Shizuoka Cancer Center Hospital reviewed and approved the protocol.

Pretreatment Evaluation

The pretreatment evaluation included a complete history, physical examination, assessment of PS, serum chemistry profile, complete blood cell count, arterial blood gas analysis, chest radiography, electrocardiography, endoscopy with biopsy and CT scans of the neck, chest and abdomen. The clinical TNM system stage was defined according to the 2002 (version 6.0) UICC Classification of Malignant Tumors (4).

Treatment Details

This Phase I trial was an open-label, nonrandomized and dose-escalation study. Groups of 6–12 patients received sequentially increasing doses of 5-FU and CDDP (Table 1), concurrently with a fixed dose of 50.4 Gy radiotherapy.

Chemotherapy

Two cycles of chemotherapy were given at an interval of 28 days. CDDP was given over the course of 2 h with ≥3000 ml/day hydration on Day 1 and ≥2000 ml/day hydration on Days 2–4. Diuretics were given to produce a urine volume of ≥2000 ml/day on Day 1 and ≥1500 ml/day on Days 2–4. In addition, antiemetics were given before administration of CDDP. 5-FU was given as a 24-h continuous infusion on Days 1–4. After treatment according to the protocol, follow-up treatment with 5-FU and CDDP was strongly recommended.

Table 1. Dose escalation schema

Dose level	5-Fluorouracil (mg/m^2/day)	Cisplatin (mg/m^2)	Radiotherapy (Gy)
−1	700	70	50.4
1	800	75	50.4
2	1000	75	50.4

Radiotherapy

Radiotherapy was delivered with megavoltage equipment (≥6 MV) using a multiple-field technique. Three-dimensional treatment planning was required. Patients received 1.8 Gy/day of radiation for 5 days per week, and the total radiation dose was 50.4 Gy. For carcinoma of the middle or lower thoracic esophagus, the use of three or four fields was strongly recommended. The clinical target volume (CTV) included the primary tumor with a 2-cm margin craniocaudally, metastatic lymph nodes and regional lymph nodes. The regional lymph nodes bilaterally included the supraclavicular fossa and superior mediastinal lymph nodes for carcinoma of the upper thoracic esophagus, and the mediastinal and perigastric lymph nodes for carcinoma of the middle or lower thoracic esophagus. In addition, the celiac axis lymph nodes were included for carcinoma of the lower thoracic esophagus. Planning target volume (PTV) was defined as the CTV plus a 1- to 2-cm margin in the cranio-caudal direction and a 0.5- to 1-cm margin in the lateral direction in consideration of respiratory organ motion and daily set-up error. After the PTV had been treated up to a dose of 41.4 Gy, an additional dose of 9.0 Gy was given to a reduced irradiated volume, including only the primary tumor and metastatic lymph nodes with margins, for a total dose of 50.4 Gy. The dose was prescribed to the center of the PTV. Lung inhomogeneity corrections were not used. Spinal-cord exposure was maintained <44 Gy. The percentage of pulmonary volume receiving (20?Gy was limited to (25%, and the mean heart dose was limited to (40?Gy.

Dose Escalation

The trial design was based on a conventional dose-escalation schema, with the primary objective of defining the maximal tolerated doses (MTDs) of 5-FU and CDDP in combination with a fixed dose of radiotherapy. The doses of 5-FU and CDDP were escalated in a stepwise fashion and given to the cohorts of 6–12 patients. Initially, six patients received each dose level. If dose-limiting toxicity (DLT) occurred in ≤2 of the six patients, the next dose level was administered. If ≥3 of the six patients in the cohort had DLT, the MTD was defined as one level below the dose causing such DLT. Six additional patients then received the MTD level; if toxicity was tolerable, the MTD was defined as the RD. If no DLT occurred at Level 2, this dose level was defined as the RD.

DLT was defined as any of the following: Grade 3/4 nonhematologic toxicity, except for the common toxicity of chemoradiotherapy for esophageal cancer such as anorexia, nausea, vomiting, temporary electrolyte abnormalities, oral mucositis, pharyngitis and esophagitis; Grade 4 thrombocytopenia or febrile neutropenia persisting for ≥4 days; inability to complete the protocol treatment within 60 days from the start of chemoradiotherapy because of toxicity; radiation pneumonitis requiring steroid treatment. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Late radiation toxicity, occurring ≥90 days from the start of radiotherapy, was scored according to the RTOG/EORTC late radiation morbidity scoring scheme.

Dose Modification

If WBC < 2500/mm^3, platelets < 75 000/mm^3, creatinine > 1.5 mg/dl, total bilirubin > 1.5 mg/dl, AST/ALT > 2.5 times the upper limit of normal, body temperature ≥ 38.0°C due to infection or Grade 3/4 esophagitis or dysphagia occurred, both chemotherapy and radiotherapy were withheld until such toxicity resolved. If WBC < 1000/mm^3, neutrophils < 500/mm^3, platelets < 25 000/mm^3, body temperature ≥ 38.0°C due to infection, Grade 3/4 esophagitis or dysphagia, or radiation pneumonitis requiring steroid treatment occurred during radiotherapy alone, radiotherapy was withheld until such toxicity resolved.

Efficacy Assessment and Definitions

Patients were scheduled to undergo endoscopy with biopsy and CT scanning 3–4 weeks after the completion of radiotherapy. For the primary esophageal tumor, a CR was defined as no evidence of residual or recurrent tumor on endoscopy, as verified histologically; all other responses were defined as non-CR. For lymph nodes, CR was defined as a reduction in lymph-node size from ≥1 to <1 cm; all other responses were defined as non-CR.

Follow-up Evaluation

A history and physical examination, toxicity assessment, serum chemistry profile, complete blood cell count, gastrointestinal endoscopy, chest X-ray and CT scanning of the neck, chest and abdomen were performed every 3 months during the first year after the start of chemoradiotherapy.

RESULTS

Patient Characteristics

Twelve patients were enrolled between April 2004 and January 2005. Toxicity and response were assessable, and complete follow-up data were available for all patients. Median follow-up time was 26 months (range, 21–28 months). The patients' characteristics are listed in Table 2. Median age was 59.5 years (range, 47–68 years). Median PS was 1, and 11 patients were men. All patients had squamous cell carcinoma. The clinical disease stage was IIA in four patients, IIB in one and III in seven.

Treatment Status

All but one patient who received Level 1 completed the protocol treatment within 60 days from the start of chemoradiotherapy. The median treatment period was 44 days (range,

Table 2. Patient characteristics

Characteristic	No.	%
No. of patients	12	
Level 1	6	
Level 2	6	
Histology		
Squamous cell	12	100
Sex		
Male	11	92
Female	1	8
Age, years		
Median	59.5	
Range	47–68	
Performance status (ECOG)		
0	5	42
1	7	58
Location of primary tumor		
Upper	1	8
Middle	7	58
Lower	4	34
UICC clinical stage		
IIA	4	34
IIB	1	8
III	7	58
T1	0	0
T2	2	17
T3	10	83

ECOG, Eastern Cooperative Oncology Group; UICC, International Union Against Cancer.

40–67 days). Radiotherapy was transiently withheld because of toxicity in five patients given Level 1, but could be resumed after recovery in all of these patients. The second course of chemotherapy was withheld because of Grade 2 leukopenia in two patients given Level 1.

Toxicity

Table 3 describes the hematologic toxicities according to the dose level. At Level 1, two of six patients (33%) had Grade 3 hematologic toxicity. At Level 2, three of six patients (50%) had Grade 3 hematologic toxicity. No patient had Grade 4 hematologic toxicity, and no patient received granulocyte colony stimulating factor or blood transfusion.

Nonhematologic toxicities are listed in Table 4. Grade 3 esophagitis occurred in three patients at Level 1 and one patient at Level 2. One of the patients given Level 1 could not complete the planned treatment within 60 days because of Grade 3 esophagitis, defined as DLT.

Table 3. Hematologic toxicity

	Level 1				Level 2			
No. of cases	6				6			
Toxicity grade	1	2	3	4	1	2	3	4
Leukocytes	1	3	2	0	0	3	3	0
Neutrophils	2	3	1	0	1	3	2	0
Hemoglobin	1	4	0	0	4	1	1	0
Platelets	3	1	0	0	1	1	1	0

All toxicities including esophagitis were manageable, and the MTD was not reached, even at Level 2. We considered 5-FU 1000 mg/m^2 with CDDP 75 mg/m^2 plus 50.4 Gy radiotherapy to be the RD.

Late toxicity due to radiotherapy was evaluated 90 days after the start of radiotherapy (Table 5). Only one patient had Grade 2 toxicity (pleural effusion). All other toxicities were mild and manageable (median follow-up period, 26 months; range 21–28 months).

Table 4. Non-hematologic toxicity

	Level 1				Level 2			
No. of cases	6				6			
Toxicity grade	1	2	3	4	1	2	3	4
Fatigue	4	1	0	0	4	0	0	0
Anorexia	0	3	3	0	4	2	0	0
Nausea	4	1	0	0	3	0	0	0
Vomiting	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	2	0	0	0
Stomatitis	2	1	0	0	3	1	0	0
Dysphagea-esophageal related radiation	2	1	3	0	3	1	1	0
Febrile neutropenia	0	0	0	0	0	0	1	0
Infection without neutropenia	0	1	0	0	0	0	0	0
Fever	3	0	0	0	1	0	0	0
Dyspnea	0	1	0	0	0	0	0	0
Pericarditis	0	1	0	0	0	0	0	0
Creatinine	1	2	0	0	1	1	0	0
Bilirubin	3	0	0	0	0	1	0	0
Aspartate aminotransferase	1	0	0	0	3	0	0	0
Alanine aminotransferase	3	0	0	0	1	0	0	0
Albumin	3	3	0	0	2	3	0	0
Sodium, serum-low	6	0	0	0	4	0	0	0
Potassium, serum-high	2	0	0	0	1	1	0	0

According to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Table 5. Late radiation toxicity

	Level 1				Level 2			
No. of cases	6				6			
Toxicity grade	1	2	3	4	1	2	3	4
Esophagitis	4	0	0	0	1	0	0	0
Pneumonitis	3	0	0	0	2	0	0	0
Pericardial effusion	3	0	0	0	1	0	0	0
Pleural effusion	1	1	0	0	1	0	0	0

According to the RTOG/EORTC late radiation morbidity scoring scheme.

Response

Four (67%) of six patients who received Level 1 had a CR. Three of them had recurrence in lymph nodes, and two patients died of disease progression. The two patients who had a non-CR at Level 1 had lung/bone and liver metastases, respectively, and died of disease progression. At Level 2, all patients had a CR (100%). Two of them had recurrence in lymph nodes and lung, respectively. At a median follow-up of 26 months (range, 21–28 months), two patients given Level 1 and six given Level 2 were still alive.

DISCUSSION

Our primary endpoint was to determine the RD of 5-FU and CDDP with concurrent radiotherapy of 50.4 Gy. The results of this Phase I trial indicated that 5-FU 1000 mg/m^2 on Days 1–4 and 29–32 with CDDP 75 mg/m^2 on Days 1 and 29 plus concurrent 50.4 Gy radiotherapy was well tolerated as the RD and may be clinically beneficial for Japanese patients with squamous cell esophageal cancer. Toxic effects were generally mild to moderate and could be managed by conventional strategies.

The standard non-surgical treatment for localized carcinoma of the esophagus is chemoradiation, based on the results of the RTOG 85-01 study (local/regional control rate, 54%; median survival, 14 months; and treatment-related mortality rate, 2%) (5). Subsequently, however, the INT 0122 (RTOG 90-12) Phase II trial did not demonstrate an improved local/regional control rate (61%) or a survival advantage (median survival, 20 months) of neoadjuvant 5-FU and CDDP followed by concurrent 5-FU, CDDP and high-dose radiotherapy (64.8 Gy), as compared with the results of RTOG 85-01 (6,7). Moreover, the treatment-related mortality rate was 9%. Another high-dose radiotherapy regimen showed no advantage of a brachytherapy boost after treatment with 5-FU, CDDP and 50.4 Gy external-beam radiation therapy in the RTOG 92-07 study. The local/regional control rate was 37%, and median survival was 11 months (8). The treatment-related mortality rate was 10%. Thereafter, the INT 0123 (RTOG 94-05) study, a randomized Phase III trial, confirmed the efficacy of 5-FU 1000 mg/m^2 on Days 1–4 and 29–32 with CDDP 75 mg/m^2 on Days 1 and 29 plus concurrent 50.4 Gy radiotherapy as compared with 64.8 Gy high-dose radiotherapy (local/regional control rate, 45%; median survival, 18 months; and treatment related mortality rate, 2%) (1).

In the JCOG 9906 Phase II trial, however, a different regimen of chemoradiotherapy (5-FU 400 mg/m^2 on Days 1–5, 8–12, 36–40 and 43–46 with CDDP 40 mg/m^2 on Days 1, 8, 36 and 43 plus concurrent 60 Gy radiotherapy with 2 weeks planned interruption) was used to study the role of chemotherapy as a radiosensitizer (3). The local/regional control rate and median survival were promising (62% and 29 months), but treatment-related mortality was 5.3% (pericarditis in one patient, pleural effusion in one and pneumonitis in two). Late toxicity, especially a 16% incidence of $\geq$Grade 3 pericardial effusion, needed to be reduced.

Studies assessing long-term survival and late toxicity in patients with esophageal cancer who received chemoradiotherapy are scant (9–11). In contrast, radiation-induced heart disease after thoracic radiotherapy has been studied extensively in patients with Hodgkin's lymphoma. A causal relationship between thoracic radiotherapy and coronary artery disease has been suggested (12–17). Pleural effusion after thoracic radiotherapy has also been reported, mainly in patients with Hodgkin's lymphoma (18,19). Ishikura studied late toxicity in 139 patients with esophageal cancer treated by the JCOG 9906 regimen. The median follow-up was 53 months (11). Eight patients had $\geq$Grade 3 pericarditis, two had Grade 4 heart failure, eight had Grade 3 pleural effusion, three had Grade 3 radiation pneumonitis and two died of acute myocardial infarction. With the JCOG 9906 regimen, 40 Gy delivered by anteroposterior–posteroanterior opposed portals was radiated to a wide nodal area, and $>$60% of the entire heart volume received at least 40 Gy in most patients. About 60% of patients with clinical stage II/III esophageal cancer have recurrence of residual disease (3). Salvage surgery improves the survival of such patients who have recurrence after chemoradiation, but is associated with high morbidity and mortality (20,21). A relation between thoracic radiotherapy and postoperative pulmonary complications is suspected (22).

The RTOG regimen of radiotherapy strongly recommends treatment planning by CT, $\geq$2 radiation fields, and smaller radiation fields, which we speculate reduces irradiation to 'high-risk' organs, with consequent late toxicity and the risk of salvage surgery. We think that higher doses of 5-FU/CDDP and radiotherapy without planned interruption may produce efficacy similar to that of the JCOG 9906 regimen, despite the smaller radiation dose and fields.

In conclusion, the RDs of 5-FU and CDDP with concurrent radiotherapy (50.4 Gy) in Japanese patients with UICC clinical stage II/III esophageal carcinoma (excluding T4 tumors) were 1000 mg/m^2 on Days 1–4 and 29–32, and 75 mg/m^2 on Days 1 and 29, respectively, which were the

doses used in the RTOG regimen. On the basis of the results of this Phase I trial, we have already started a Phase II trial of the RTOG regimen in patients meeting similar eligibility criteria.

Conflict of interest statement

None declared.

References

1. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. *J Clin Oncol* 2002;20:1167–74.
2. Ishida K, Ando N, Yamamoto S, Ide H, Shinoda M. Phase II study of cisplatin and 5-fluorouracil with concurrent radiotherapy in advanced squamous cell carcinoma of the esophagus: a Japan Esophageal Oncology Group (JEOG)/Japan Clinical Oncology Group trial (JCOG9516). *Jpn J Clin Oncol* 2004;34:615–9.
3. Minashi K, Muro K, Kato K, Ohtsu A, Ishkura S, Boku N, et al. A phase II study of chemoradiotherapy in patients (pts) with stage II-III esophageal squamous cell carcinoma (ESCC): Japan Clinical Oncology Group trial (JCOG 9906). In: Gastrointestinal Cancers Symposium. Orland: American Society of Clinical Oncology 2008.
4. Sobin L, Witteking C. Classification of malignant tumours. 6th edn. New Jersey: International Union Against Cancer (UICC) 2002.
5. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *J Am Med Assoc* 1999;281:1623–7.
6. Minsky BD, Neuberg D, Kelsen DP, Pisansky TM, Ginsberg RJ, Pajak T, et al. Final report of Intergroup Trial 0122 (ECOG PE-289, RTOG 90-12): Phase II trial of neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus. *Int J Radiat Oncol Biol Phys* 1999;43:517–23.
7. Minsky BD, Neuberg D, Kelsen DP, Pisansky TM, Ginsberg R, Benson A, 3rd. Neoadjuvant chemotherapy plus concurrent chemotherapy and high-dose radiation for squamous cell carcinoma of the esophagus: a preliminary analysis of the phase II intergroup trial 0122. *J Clin Oncol* 1996;14:149–55.
8. Gaspar LE, Winter K, Kocha WI, Coia LR, Herskovic A, Graham M. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report. *Cancer* 2000;88:988–95.
9. Cwikiel M, Albertsson M, Hambraeus G. Acute and delayed effects of radiotherapy in patients with oesophageal squamous cell carcinoma treated with chemotherapy, surgery and pre- and postoperative radiotherapy. *Acta Oncol* 1994;33:49–53.
10. Gergel T, Proulx G, Leichman L, Nava H, Kuettel M. Diagnostic dilemmas in oncology: case 3. Pericardial effusion after esophageal radiation. *J Clin Oncol* 2001;19:4344–5.
11. Ishikura S, Nihei K, Ohtsu A, Boku N, Hironaka S, Mera K, et al. Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. *J Clin Oncol* 2003;21:2697–702.
12. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. *Hum Pathol* 1996;27:766–73.
13. Byhardt R, Brace K, Ruckdeschel J, Chang P, Martin R, Wiernik P. Dose and treatment factors in radiation-related pericardial effusion associated with the mantle technique for Hodgkin's disease. *Cancer* 1975;35:795–802.
14. Totterman KJ, Pesonen E, Siltanen P. Radiation-related chronic heart disease. *Chest* 1983;83:875–8.
15. Boivin JF, Hutchison GB, Lubin JH, Mauch P. Coronary artery disease mortality in patients treated for Hodgkin's disease. *Cancer* 1992;69:1241–7.
16. Corn BW, Trock BJ, Goodman RL. Irradiation-related ischemic heart disease. *J Clin Oncol* 1990;8:741–50.
17. Joensuu H. Acute myocardial infarction after heart irradiation in young patients with Hodgkin's disease. *Chest* 1989;95:388–90.
18. Rodriguez-Garcia JL, Fraile G, Moreno MA, Sanchez-Corral JA, Penalver R. Recurrent massive pleural effusion as a late complication of radiotherapy in Hodgkin's disease. *Chest* 1991;100:1165–6.
19. Morrone N, Gama e Silva Volpe VL, Dourado AM, Mitre F, Coletta EN. Bilateral pleural effusion due to mediastinal fibrosis induced by radiotherapy. *Chest* 1993;104:1276–8.
20. Imdahl A, Schoffel U, Ruf G. Impact of neoadjuvant therapy of perioperative morbidity in patients with esophageal cancer. *Am J Surg* 2004;187:64–8.
21. Balart J, Balmana J, Rius X, Salazar R, Gallen M, Navarro S, et al. Treatment of oesophageal cancer with preoperative chemoradiotherapy may increase operative mortality. *Eur J Surg Oncol* 2003;29:884–9.
22. Lee H, Vaporciyan A, Cox J, Tucker SL, Putnam JB, Jr, Ajani JA. Postoperative pulmonary complications after preoperative chemoradiation for esophageal carcinoma: correlation with pulmonary dose-volume histogram parameters. *Int J Radiat Oncol Biol Phys* 2003;57:1317–22.