厚生労働科学研究費補助金
医療機器開発推進研究事業
高度医療技術の効率化及び標準化の開発に関する研究

平成２０年度から平成２４年度

総合研究報告書

研究代表者　堀田　知光

平成２５（２０１３）年５月

目　　次

Ⅰ．総合研究報告

厚生労働科学研究費補助金（医療機器開発推進研究事業）
総合研究報告書

高度医療技術の効率化及び標準化の開発に関する研究

研究代表者　堀田知光　国立がん研究センター中央病院　理事長

研究要旨

本研究は、当初放射線治療におけるMRI像の「座標ずれ」を補正するとともに、従来のMRI画像とCT画像のFusion像に基づく計画策定から、MRI画像におけるプロトン密度を電子密度に変換して直接計画を策定する技術の開発を目的に開始されたが、研究3年目の段階で、同様の発想による放射線治療計画用 MRI シミュレイターが企業により開発されたことから、研究目的を「外科的治療に匹敵する非侵襲的局所治療を行うための高度医療技術の開発」に大きく変更し、「局所療法を正確に誘導する高度画像技術」と「確実な治療効果を挙げ得る高度局所療法」の両面から研究を行なった。前者については、「CT、MRI の volume data と患者の体表位置情報から任意穿刺方向の画像を表示する技術」、「磁性体不可のMRI下で穿刺を誘導する画像技術」、「Adaptive Radiation Therapy のために種々の画像情報を統合する技術」、「ホウ素中性子捕捉療法(BNCT)のための PET-CT 画像による画像支援技術」についての研究を行い、後者については「経皮的凍結療法」、「Irreversible Electroporation (IRE)」、「集束超音波」、「ホウ素中性子捕捉療法(BNCT)」を採り上げた。この結果、アーチファクトのない MRI 用穿刺針の開発は完遂できなかったが、穿刺誘導に用いる光学式ナビゲーションシステムのプロトタイプを完成、放射線治療装置付属のコーンビームCT装置で線量分布を表示可能とするCT値ー電子密度変換テーブルを完成、世界初の病院設置型BNCTを開始するための基礎的研究を完了するとともに、局所治療法である経皮的凍結療法、集束超音波治療、Irreversible Electroporation (IRE)の先進医療Bによる臨床試験を開始する体制を固めた。

研究分担者

荒井保明	国立がん研究センター中央病院 放射線診断科科長
伊丹　純	国立がん研究センター中央病院 放射線治療科科長
金澤　右	岡山大学医歯薬学総合研究科 放射線医学教授
寺内隆司	国立がん研究センターがん予防・検診研究センター検診開発研究部室長
佐久間一郎	東京大学大学院工学系研究科 医用工学教授
竹内義人	国立がん研究センター中央病院 放射線診断科医長
稲葉吉隆	愛知がんセンター中央病院 放射線診断・IVR部部長
曽根美雪	国立がん研究センター中央病院 放射線診断科医長
成田善孝	国立がん研究センター中央病院 脳脊髄腫瘍科副科長
栗原宏明	国立がん研究センター中央病院 放射線診断科医員
吉村亮一	東京医科歯科大学大学院 医歯学総合研究科、放射線腫瘍学助教
馬屋原博	国立がん研究センター中央病院 放射線治療科医員

A. 研究目的

当初放射線治療におけるMRI像の「座標ずれ」を補正するとともに、従来のMRI画像とCT画像のFusion像に基づく計画策定から、MRI 画像におけるプロトン密度を電子密度に変換して直接計画を策定する技術の開発を目的に開始されたが、研究3年目の段階で、同様の発想による放射線治療計画用 MRI シミュレイターが企業により開発されたことから、研究目的を「外科的治療に匹敵する非侵襲的局所治療を行うための高度医療技術の開発」に変更した。ゲノム解明や分子レベルからの創薬によりがんに対する薬物療法は飛躍的に進歩したが、未だ大部分の癌腫において治癒を齎すレベルには達しておらず、治癒を齎す治療法の主軸は依然として侵襲的な外科治療に委ねられている。よって、外科治療に匹敵あるいは凌駕する非侵襲的治療法の開発は、がん患者の QOL 向上のみならず、合併症低減や治療期間短縮等に伴う医療費抑制など、超高齢化社会となりつつある本邦のがん医療全般に好ましい影響を与える点で、極めて重要な課題である。このような非侵襲的治療を可能とするためには、１）局所治療法を正確に病巣に誘導する高度画像誘導技術、２）病巣において確実な治療効果をあげうる高度局所治療法、の開発が必須であり、本研究はこれらのための高度医療技術を開発するとともに、臨床試験により評価し、標準化することを目的に行なわれた。

B. 研究方法

高度画像誘導技術については、経皮的穿刺治療

における誘導技術として、１）CT や MRI で得た volume データと患者体表の位置情報より体表面からの任意方向の画像を表示する技術、２）磁性体を持ち込むことのできない MRI 装置内での穿刺を誘導する技術を、放射線治療における誘導技術として、３）種々治療画像の統合による Adaptive Radiation Therapy の技術、４）ホウ素中性子捕捉療法(BNCT)のための PET-CT 画像による画像支援技術を採り上げ、その開発を行った。また、新しい局所治療技術については、１）経皮的凍結療法、２）集束超音波療法、３）Irriversible Electroporation (IRE)、４）BNCT を採り上げ、機器導入等の環境が整った経皮的凍結療法、集束超音波療法、electric poration について、その安全性と有効性を評価するための第 I/II 相臨床試験計画を立案した。

(倫理面への配慮)

臨床研究計画書作成にあたっては、ヘルシンキ宣言、臨床試験倫理指針を遵守し、被験者本人に対する文書を用いた説明と文書による同意の取得を必須とするとともに、参加施設の施設倫理審査委員会の承認を受けて試験を行うこととした。試験中に発生した有害事象については、速やかに研究代表者に報告されるとともに、効果安全性評価委員会の評価を受けることとしている。また、被験者の個人情報については、試験の信頼性を担保するため登録時にはこれを要求するが、登録後は与えられた症例登録番号のみで運用し、さらに登録時に用いられた個人情報は、不正なアクセスに対し厳重に保護され、かつ、すべての閲覧が記録されるシステムとされているコンピュータ内に保管することにより、個人情報保護対策を万全とした。

C.　研究結果

I. 画像誘導技術

１）CT や MRI で得た volume データと患者体表の位置情報より体表面からの任意方向の画像を表示する技術

磁気誘導を用いた同様の技術は、すでに穿刺用超音波誘導画像の補助的手段としての機器が臨床応用されているが、その利点を最大限に生かすためには、「標的部位の動きの有無」（呼吸などにより移動する部位か、あるいは、頭蓋内、後腹膜、骨盤腔のように移動の限られた部位か）、ならびに、仮想穿刺ラインを確認するための「確認画像」の２つの点からこの技術応用を再検討した。動きのない部位における従来の磁気誘導の誤差は臨床的に許容可能な範囲であり、この場合には従来の超音波装置との連動がかえって装置の大型化を招く原因となっていたため、磁気誘導単独による装置の小型化、特に穿刺用プローブの小型化を行い、プロトタイプのプローブを完成した。一方、胸部や腹部など動きある部位の穿刺では、例え呼吸同期を行った場合にも必ず一定の誤差が生じる。しかし、21G 程度の細い穿刺針が標的をそれたとしても臨床的には問題とはならず、その先行穿刺針自体が、座標軸のない体内において次の穿刺を行なう上での座標軸となるため、穿刺は遥かに容易となる。このような初めに穿刺した針をガイドに次の針を穿刺する技術はタンデム法として確立している。よって、21G 程度の細径針で、MRI 下でアーチファクトが少なく、ガイドとなり得る穿刺針の開発を行なった。しかしながら、各種の素材について検討を行なったが、十分な性能を有す針の開発には至らなかった。

２）磁性体を持ち込むことのできない MRI 装置内での穿刺を誘導する技術

非磁性体のみが許容される MRI 下の誘導画像技術について検討し、MRI 画像が影響を受けない距離からのレーザービームの照射により穿刺ラインを示す技術を開発し、これを行なうプロトタイプの装置を完成した。磁気誘導に比べ誤差が数 mm 以下と少ない点、穿刺部周囲に器具がないため穿刺手技の障害とならないことが確認されたが、術者の手や穿刺針自体もビームを遮断する原因となるため、穿刺手技の工夫、実用可能な装置とするための改良を行い、実用可能な段階に到達した。

３）種々治療画像の統合による Adaptive Radiation Therapy の技術

Coned Beam CT、2 方向透視、体表レーザースキャンデータの統合により、CT 撮影なしに Adaptive Radiation Therapy を可能とする技術として、放射線治療装置に付属のコーンビーム CT 装置(CBCT)を用いて線量分布まで表示可能とする、CT 値−電子密度変換テーブルを完成した（従来は、CBCT から CT 値を求めること不可能であったため、別途、治療計画用 CT 撮影を行わなければ線量分布を算出、表示することができなかった）。この過程で、呼吸が CBCT からの電子密度情報に大きく影響することが判明したため、あわせて、治療計画用 CT 時と治療時の患者の体形変化を検知可能にするための、レーザービームを用いた体表面位置決め支援システムの開発した。今年度は、プロトタイプを用いて実用上の問題点につき検討し、今後改良すべき点を明らかにした。

４）ホウ素中性子捕捉療法(BNCT)のための PET-CT 画像による画像支援技術

18F-FBPA PET 検査に用いる FBPA 製剤の合成について、収量 500MB q 以上（２回検査分）、放射化学純度 99%以上、比放射能 25MB q / μ mol の合成系を完成した。また、ターゲットのリチウムの放射化によって発生する大量の放射性ベリリウムの廃棄貯蔵をはじめ、世界初の病院設置型 BNCT 開始に必要な基礎的検討を完了した。

Ⅱ.局所治療技術

以下に概要を示す各局所治療技術についての臨床

試験計画書を作成し、試験を行なう体制を整備し、また、試験開始のための手続きを行なった。
①腹部・骨盤内実質臓器に対する経皮的凍結治療の第 I/II 相試験（JIVROSG-1101）
目的：切除適応のない腹部・骨盤内実質臓器の悪性腫瘍（すでに保険収載されている小径腎がんを除く）に対する経皮的凍結治療の安全性、有効性の評価。
試験方法：日本腫瘍 IVR 研究グループ(JIVROSG)による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法（Ann Oncol. 20:1943-7, 2009）を使用。主要評価項目を安全性の評価、副次的評価項目を臨床的有効性の評価（局所治癒割合、1 年後局所無再発割合）、有害事象の発現頻度と程度の評価として、目標症例数 22 例、症例登録期間 2 年、全試験期間 3 年を予定。
研究代表施設の施設倫理委員会の承認を得たが、先進医療 B として行なうにあたっての種々の変更が必要となり、これらに対する整備を行なった。
②有痛性骨軟部・骨盤内腫瘍に対する経皮的凍結治療の第 I/II 相試験（JIVROSG-1102）
目的：既存の治療が不適あるいは不応で、薬物の増量以外に疼痛を軽減する手段のない骨軟部・骨盤内腫瘍に対する経皮的凍結治療の安全性、有効性の評価。
試験方法：JIVROSG による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法を使用。主要評価項目を安全性の評価、副次的評価項目を疼痛改善の程度と期間、有害事象の内容と頻度として、目標症例数 22 例、症例登録期間 3 年、全試験期間 3 年 6 ヶ月を予定。
上記①と同様に、先進医療 B として試験を行なうための準備を進めた。
③有痛性後腹膜・骨盤内腫瘍に対する集束超音波治療の第 I/II 相試験（JIVROSG-1103）
目的：既存の治療が不適あるいは不応で、薬物の増量以外に疼痛を軽減する手段のない有痛性後腹膜腫瘍に対する集束超音波治療の安全性、有効性の評価。
試験方法：JIVROSG による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法を使用。主要評価項目を安全性の評価、副次的評価項目を疼痛改善の程度と期間、有害事象の内容と頻度として、目標症例数 22 例、症例登録期間 3 年、全試験期間 3 年 6 ヶ月を予定。
なお、集束超音波療法の機器についての基礎的検討が不十分であったため、機器の基本性能に関する検証を行なった。この結果、十分な基本性能を確認するとともに、特性を確認した。
④腹部実質臓器に対する Irreversible Electroporation (IRE)治療の第 I/II 相試験（JIVROSG-1104）
目的：切除適応のない腹部実質臓器の悪性腫瘍に対する IRE 治療の安全性、有効性の評価。
試験方法：JIVROSG による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法を使用。主要評価項目を安全性の評価、副次的評価項目を腫瘍壊死効果、腫瘍縮小効果、有害事象の内容と頻度として、目標症例数 22 例、症例登録期間 3 年、全試験期間 5 年を予定。
当初、本年度中に試験を開始する予定であったが、先進医療 B として行なうにあたっての変更が必要となったため、上述の経皮的凍結療法と合わせて、試験計画の整備、変更を行なった。
⑤骨軟部腫瘍に対する Irreversible Electroporation (IRE)治療の第 I/II 相試験（JIVROSG-1105）
目的：切除適応のない骨軟部腫瘍に対する IRE 治療の安全性、有効性の評価。
試験方法：JIVROSG による多施設共同研究として施行。高度医療評価制度での施行を予定。第 I 相試験部分には JIVROSG 3x3 法を使用。主要評価項目を安全性の評価、副次的評価項目を腫瘍壊死効果、腫瘍縮小効果、有害事象の内容と頻度として、目標症例数 22 例、症例登録期間 3 年、全試験期間 5 年を予定。
当初、本年度中に試験を開始する予定であったが、先進医療 B として行なうにあたっての変更が必要となったため、上述の経皮的凍結療法と合わせて、試験計画の整備、変更を行なった。

D. 考察
超高齢化社会となりつつある本邦のがん医療においては、治療の非侵襲化が重要な課題であり、薬物療法に大きな期待がもたれている。しかし、ゲノム解明や分子レベルからの創薬により薬物療法は飛躍的に進歩しているものの、未だ大部分の癌腫において治癒を齎すレベルには達していない。また、薬物療法に要する費用が医療全般を圧迫する大きな要因ともなっている。よって、外科治療に匹敵、あるいはこれを凌駕する非侵襲的治療法の開発は、本邦のがん医療における愁眉の課題と言える。本研究は、これを可能とするための高度医療技術を開発するとともに、臨床試験により評価し、標準化することを目的に行われた。
画像誘導技術では、1）CT や MRI で得た volume データと患者体表の位置情報からの任意方向の画像を表示する技術については、既存の技術を生かしながらも従来の超音波装置の補助的手段としての発想から脱却し、先行穿刺針を新たなガイド用座標として使用する考え方を追加することで、従来の工学的正確さのみを重視した考え方から脱皮した新たな技術を開発する道筋をつけることに成功した。この発想の転換は、本研究の大きな成果

であったと考えられる。一方、MRI 上でアーチファクトの少ない細径穿刺針の開発は、上述の先行穿刺針に使用可能な針も視野に置き検討したが、満足できる性能を有す針を開発するには至らず、今後の研究に課題を残した。２）MRI 装置内での穿刺を誘導する技術としてのレーザービームを用いた装置については、極めて誤差の少ない穿刺誘導用画像装置のプロトタイプが完成し、臨床評価が行なわれ、この中で、ビームを遮断しない穿刺手技の改良についても併行して検討された。最終的な今後の臨床評価に待たねばならないが、本研究の成果は今後の MRI ガイド下 IVR の発展に寄与することが期待される。３）Adaptive Radiation Therapy のための画像技術の統合は、それぞれの技術が一定度の完成域に到達しなければ実現困難なものであり、これまでの研究による放射線治療装置付属の CBCT を用いて線量分布表示可能とする CT 値−電子密度変換テーブルの完成を受けて、実臨床状況下での検証と修正を行なった。画像から直接的に放射線照射野を決定できる技術は Adaptive Radiation Therapy を行なうにあたり最も重要な用件であり、本研究成果は今後の Adaptive Radiation Therapy の発展に大きく寄与するものと思われる。

局所治療技術では、新たな局所治療技術である経皮的凍結治療、収束超音波治療、IRE 治療に関する 5 本の臨床試験計画書が作成され、試験開始のための手続きが進められたが、これらの治療法は欧米では一部で行われているものの、本邦では小腎がんに対する経皮的凍結治療を除き、いずれも薬事法未承認の治療であり、これを先進医療 B による多施設共同研究として行うことの意義は、治療法としての評価のみならず、将来の本邦への新規機器や技術の導入において大きな意味をもつと考えられる。一方、これらの治療技術についての前向き臨床試験による評価は世界的に見てもほとんどなく、科学的意義も極めて大きいと考えられる。高度医療評価制度から先進医療医療 B への制度変更に伴う諸手続きのため、試験の開始は遅れたが、今後も継続して進めて行く予定である。また、BNCT の稼働は本研究終了となるが、適応の判断に不可欠な 18F-FBPA PET 検査に用いる FBPA 製剤の合成系の完成を初め、病院設置型での導入が世界初となる BNCT を開始するための重要な初期段階を完了することができた点は本研究の大きな成果と判断される。

E. 結論

外科的治療に匹敵する非侵襲的局所治療を行うための高度医療技術の開発、評価を目的に、「局所療法を正確に誘導する高度画像技術」と「確実な治療効果を挙げ得る高度局所療法」のふたつの大きなテーマとして研究を行った。MRI 対応試験穿刺針の開発は不発に終わったが、その他の画像技術については、明確な進歩と実用化への道筋を示すことができたとともに、一部は臨床的評価を開始するに至った。また、世界初の病院設置型 BMCT を開始するための初期段階の研究を完了した。新しい３つの局所治療技術については、５つの臨床試験計画書を完成し、先進医療 B として行なう臨床試験の手続きを進めた。

F. 健康危険情報

なし。

G. 研究発表

（研究代表者）堀田知光

1. Ogura M, Itoh K, Ishizawa K, Hotta T, et al: Phase II study of ABV (doxorubicin with increased dose, bleomycin and vinblastine) therapy in newly diagnosed advanced-stage Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG9705). Leuk Lymphoma 54:46-52, 2013
2. Yamaguchi M, Tobinai K, Oguchi M, Hotta T, et al: Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211. J Clin Oncol 30:4044-6, 2012
3. Kagami Y, Itoh K, Tobinai K, Hotta T, et al: Phase II study of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) therapy for newly diagnosed patients with low- and low-intermediate risk, aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG9508. Int J Hematol 96:74-83, 2012
4. Watanabe T, Tobinai K, Shibata T, Hotta T, et al: Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial. J Clin Oncol 29:3990-8, 2011
5. Chou T, Tobinai K, Uike N, Hotta T, et al: Melphalan-prednisolone and vincristine-doxorubicin-dexamethasone chemotherapy followed by prednisolone/interferon maintenance therapy for multiple myeloma: Japan Clinical Oncology Group Study, JCOG0112. Jpn J Clin Oncol 41:586-9, 2011

（研究分担者）荒井保明

1. Sato Y, Watanabe H, Sone M, Arai Y, et al: Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602. Ups J Med Sci 118:16-22, 2013
2. Ikeda M, Arai Y, Park SJ, et al: Prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: an Asian

cooperative study between Japan and Korea. J Vasc Interv Radiol 24:490-500, 2013
3. Sone M, Arai Y, Kiuchi T, et al: [Shared web-based data center for multi-institutional clinical trials: evaluation of UMIN-INDICE (university hospital medical information network-internet data and information center for medical research)in clinical trials of JIVROSG (Japan interventional radiology in oncology study group)]. Gan To Kagaku Ryoho 39:619-23, 2012
4. Sofue K, Arai Y, Takeuchi Y, et al: Safety and efficacy of primary metallic biliary stent placement with tract embolization in patients with massive ascites: a retrospective analysis of 16 patients. J Vasc Interv Radiol 23:521-7, 2012
5. Osuga K, Arai Y, Anai H, et al: Phase I/II multicenter study of transarterial chemoembolization with a cisplatin fine powder and porous gelatin particles for unresectable hepatocellular carcinoma: Japan Interventional Radiology in Oncology Study Group Study 0401. J Vasc Interv Radiol 23:1278-85, 2012
6. Inaba Y, Arai Y, Yamaura H, et al: Phase II clinical study on stent therapy for unresectable malignant colorectal obstruction (JIVROSG-0206). Am J Clin Oncol 35:73-6, 2012
7. Arai Y, Ohtsu A, Sato Y, et al: Phase I/II study of radiologic hepatic arterial infusion of fluorouracil plus systemic irinotecan for unresectable hepatic metastases from colorectal cancer: Japan Clinical Oncology Group Trial 0208-DI. J Vasc Interv Radiol 23:1261-7, 2012
8. Arai Y: Clinical trials of interventional oncology. Int J Clin Oncol 17:301-5, 2012
9. Sugawara S, Sone M, Arai Y, et al: Radiological insertion of Denver peritoneovenous shunts for malignant refractory ascites: a retrospective multicenter study (JIVROSG-0809). Cardiovasc Intervent Radiol 34:980-8, 2011
10. Iwasa S, Ikeda M, Okusaka T, Arai Y, et al: Transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. Jpn J Clin Oncol 41:770-5, 2011
11. Inaba Y, Arai Y, Yamaura H, et al: Phase I/II study of hepatic arterial infusion chemotherapy with gemcitabine in patients with unresectable intrahepatic cholangiocarcinoma (JIVROSG-0301). Am J Clin Oncol 34:58-62, 2011
12. Iguchi T, Idani H, Asami S, Arai Y, et al: Hepatic arterial infusion chemotherapy prior to standard systemic chemotherapy in patients with highly advanced unresectable liver metastases from colorectal cancer: a report of three patients. Acta Med Okayama 65:49-53, 2011
13. Hamaguchi T, Shirao K, Ohtsu A, Arai Y, et al: A phase II study of biweekly mitomycin C and irinotecan combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: a report from the Gastrointestinal Oncology Group of the Japan Clinical Oncology Group (JCOG0109-DI Trial). Gastric Cancer 14:226-33, 2011
14. Arai Y, Inaba Y, Sone M, et al: Phase I/II study of transjugular transhepatic peritoneovenous venous shunt, a new procedure to manage refractory ascites in cancer patients: Japan Interventional Radiology in Oncology Study Group 0201. AJR Am J Roentgenol 196:W621-6, 2011
15. Sone M, Arai Y, Shimizu T, et al: Phase I/II multiinstitutional study of uterine artery embolization with gelatin sponge for symptomatic uterine leiomyomata: Japan Interventional Radiology in Oncology Study Group study. J Vasc Interv Radiol 21:1665-71, 2010

（研究分担者）伊丹　純

1. Murakami N, Suzuki S, Ito Y, Itami J, et al: ^{106}Ruthenium plaque therapy (RPT) for retinoblastoma. Int J Radiat Oncol Biol Phys 84:59-65, 2012
2. Mayahara H, Sumi M, Ito Y, Itami J, et al: Effect of chemotherapy on survival after whole brain radiation therapy for brain metastases: a single-center retrospective analysis. J Cancer Res Clin Oncol 138:1239-47, 2012
3. Mayahara H, Ito Y, Morizane C, Itami J, et al: Salvage chemoradiotherapy after primary chemotherapy for locally advanced pancreatic cancer: a single-institution retrospective analysis. BMC Cancer 12:609, 2012
4. Kuroda Y, Murakami N, Morota M, Itami J, et al: Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer. J Radiat Res 53:588-93, 2012
5. Itami J, Sumi M, Beppu Y, et al: High-dose rate brachytherapy alone in postoperative soft tissue sarcomas with close or positive margins. Brachytherapy 9:349-53, 2010

（研究分担者）金澤　右

1. Sone M, Arai Y, Kiuchi T, Kanazazwa S, et al: [Shared web-based data center for multi-institutional clinical trials: evaluation of UMIN-INDICE (university hospital medical information network-internet data and information center for medical research)in clinical trials of JIVROSG (Japan interventional radiology in oncology study group)]. Gan To Kagaku Ryoho 39:619-23, 2012
2. Matsui Y, Hiraki T, Gobara H, Kanazazwa S, et al: Phrenic nerve injury after radiofrequency ablation of lung tumors: retrospective evaluation of the incidence and risk factors. J Vasc Interv Radiol 23:780-5, 2012
3. Kanazawa S: Current status of interventional oncology. Int J Clin Oncol 17:299-300, 2012
4. Hiraki T, Kanazawa S: Lung radiofrequency ablation: potential as a therapy to oligometastasis

and oligorecurrence. Pulm Med 2012:196173, 2012
5. Iguchi T, Idani H, Asami S, Kanazawa S, et al: Hepatic arterial infusion chemotherapy prior to standard systemic chemotherapy in patients with highly advanced unresectable liver metastases from colorectal cancer: a report of three patients. Acta Med Okayama 65:49-53, 2011

（研究分担者）寺内隆司

1. Minamimoto R, Terauchi T, Jinnouchi S, et al: Observer variation study of the assessment and diagnosis of incidental colonic FDG uptake. Ann Nucl Med, 2013
2. Daisaki H, Tateishi U, Terauchi T, et al: Standardization of image quality across multiple centers by optimization of acquisition and reconstruction parameters with interim FDG-PET/CT for evaluating diffuse large B cell lymphoma. Ann Nucl Med 27:225-32, 2013
3. Tateishi U, Terauchi T, Akashi-Tanaka S, et al: Comparative study of the value of dual tracer PET/CT in evaluating breast cancer. Cancer Sci 103:1701-7, 2012
4. Terauchi T, Terashima H, Kojima S, et al: A conserved residue, PomB-F22, in the transmembrane segment of the flagellar stator complex, has a critical role in conducting ions and generating torque. Microbiology 157:2422-32, 2011
5. Terauchi T, Kojima S, Homma M: [Structure and function of energy transduction protein complex of bacterial flagellar motor]. Seikagaku 83:822-33, 2011

（研究分担者）佐久間一郎

1. Liao H, Fujiwara K, Ando T, Sakuma I, et al: Automatic laser scanning ablation system for high-precision treatment of brain tumors. Lasers Med Sci 28:891-900, 2013
2. Abolmaesumi P, Fichtinger G, Peters TM, Sakuma I, et al: Introduction to special section on surgical robotics. IEEE Trans Biomed Eng 60:887-91, 2013
3. Liao H, Noguchi M, Maruyama T, Sakuma I, et al: An integrated diagnosis and therapeutic system using intra-operative 5-aminolevulinic-acid-induced fluorescence guided robotic laser ablation for precision neurosurgery. Med Image Anal 16:754-66, 2012
4. Liang JT, Doke T, Onogi S, Sakuma I, et al: A fluorolaser navigation system to guide linear surgical tool insertion. Int J Comput Assist Radiol Surg 7:931-9, 2012
5. Ando T, Kobayashi E, Liao H, Sakuma I, et al: Precise comparison of protoporphyrin IX fluorescence spectra with pathological results for brain tumor tissue identification. Brain Tumor Pathol 28:43-51, 2011

（研究分担者）竹内義人

1. Ikeda M, Arai Y, Park SJ, Takeuchi Y, et al: Prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: an Asian cooperative study between Japan and Korea. J Vasc Interv Radiol 24:490-500, 2013
2. Sone M, Arai Y, Kiuchi T, Takeuchi Y, et al: [Shared web-based data center for multi-institutional clinical trials: evaluation of UMIN-INDICE (university hospital medical information network-internet data and information center for medical research)in clinical trials of JIVROSG (Japan interventional radiology in oncology study group)]. Gan To Kagaku Ryoho 39:619-23, 2012
3. Osuga K, Arai Y, Anai H, Takeuchi Y, et al: Phase I/II multicenter study of transarterial chemoembolization with a cisplatin fine powder and porous gelatin particles for unresectable hepatocellular carcinoma: Japan Interventional Radiology in Oncology Study Group Study 0401. J Vasc Interv Radiol 23:1278-85, 2012
4. Inaba Y, Arai Y, Yamaura H, Takeuchi Y, et al: Phase II clinical study on stent therapy for unresectable malignant colorectal obstruction (JIVROSG-0206). Am J Clin Oncol 35:73-6, 2012
5. Arai Y, Ohtsu A, Sato Y, Takeuchi Y, et al: Phase I/II study of radiologic hepatic arterial infusion of fluorouracil plus systemic irinotecan for unresectable hepatic metastases from colorectal cancer: Japan Clinical Oncology Group Trial 0208-DI. J Vasc Interv Radiol 23:1261-7, 2012

（研究分担者）稲葉吉隆

1. Ikeda M, Arai Y, Park SJ, Inaba Y, et al: Prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: an Asian cooperative study between Japan and Korea. J Vasc Interv Radiol 24:490-500, 2013
2. Osuga K, Arai Y, Anai H, Inaba Y, et al: Phase I/II multicenter study of transarterial chemoembolization with a cisplatin fine powder and porous gelatin particles for unresectable hepatocellular carcinoma: Japan Interventional Radiology in Oncology Study Group Study 0401. J Vasc Interv Radiol 23:1278-85, 2012
3. Inaba Y, Arai Y, Yamaura H, et al: Phase II clinical study on stent therapy for unresectable malignant colorectal obstruction (JIVROSG-0206). Am J Clin Oncol 35:73-6, 2012
4. Arai Y, Ohtsu A, Sato Y, Inaba Y, et al: Phase I/II study of radiologic hepatic arterial infusion of fluorouracil plus systemic irinotecan for unresectable hepatic metastases from colorectal cancer: Japan Clinical Oncology Group Trial 0208-DI. J Vasc Interv Radiol 23:1261-7, 2012
5. Inaba Y, Arai Y, Yamaura H, et al: Phase I/II study of hepatic arterial infusion chemotherapy with gemcitabine in patients with unresectable

intrahepatic cholangiocarcinoma (JIVROSG-0301). Am J Clin Oncol 34:58-62, 2011

（研究分担者）曽根美雪

1. Sato Y, Watanabe H, Sone M, et al: Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602. Ups J Med Sci 118:16-22, 2013
2. Sone M, Arai Y, Kiuchi T, et al: [Shared web-based data center for multi-institutional clinical trials: evaluation of UMIN-INDICE (university hospital medical information network-internet data and information center for medical research)in clinical trials of JIVROSG (Japan interventional radiology in oncology study group)]. Gan To Kagaku Ryoho 39:619-23, 2012
3. Sugawara S, Sone M, Arai Y, et al: Radiological insertion of Denver peritoneovenous shunts for malignant refractory ascites: a retrospective multicenter study (JIVROSG-0809). Cardiovasc Intervent Radiol 34:980-8, 2011
4. Arai Y, Inaba Y, Sone M, et al: Phase I/II study of transjugular transhepatic peritoneovenous venous shunt, a new procedure to manage refractory ascites in cancer patients: Japan Interventional Radiology in Oncology Study Group 0201. AJR Am J Roentgenol 196:W621-6, 2011
5. Sone M, Arai Y, Shimizu T, et al: Phase I/II multiinstitutional study of uterine artery embolization with gelatin sponge for symptomatic uterine leiomyomata: Japan Interventional Radiology in Oncology Study Group study. J Vasc Interv Radiol 21:1665-71, 2010

（研究分担者）成田善孝

1. Shibui S, Narita Y, Mizusawa J, et al: Randomized trial of chemoradiotherapy and adjuvant chemotherapy with nimustine (ACNU) versus nimustine plus procarbazine for newly diagnosed anaplastic astrocytoma and glioblastoma (JCOG0305). Cancer Chemother Pharmacol 71:511-21, 2013
2. Narita Y: Drug Review: Safety and Efficacy of Bevacizumab for Glioblastoma and Other Brain Tumors. Jpn J Clin Oncol, 2013
3. Hashimoto K, Narita Y, Miyakita Y, et al: Comparison of clinical outcomes of surgery followed by local brain radiotherapy and surgery followed by whole brain radiotherapy in patients with single brain metastasis: single-center retrospective analysis. Int J Radiat Oncol Biol Phys 81:e475-80, 2011

（研究分担者）栗原宏明

1. Yoshimoto M, Kurihara H, Honda N, et al: Predominant contribution of L-type amino acid transporter to 4-borono-2-F-fluoro-phenylalanine uptake in human glioblastoma cells. Nucl Med Biol, 2013
2. Nagao T, Kinoshita T, Hojo T, Kurihara H, et al: Sentinel lymph node biopsy using indigo carmine blue dye and the validity of '10% rule' and '4 nodes rule'. Breast 21:455-8, 2012
3. Nagao T, Hojo T, Kurihara H, et al: Sentinel lymph node biopsy in breast cancer patients with previous breast augmentation surgery. Breast Cancer, 2011

（研究分担者）吉村亮一

1. Murakami N, Suzuki S, Ito Y, Yoshimura R, et al: ^{106}Ruthenium plaque therapy (RPT) for retinoblastoma. Int J Radiat Oncol Biol Phys 84:59-65, 2012
2. Kuroda Y, Murakami N, Morota M, Yoshimura R, et al: Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer. J Radiat Res 53:588-93, 2012
3. Toita T, Ohno T, Kaneyasu Y, Yoshimura R, et al: A consensus-based guideline defining clinical target volume for primary disease in external beam radiotherapy for intact uterine cervical cancer. Jpn J Clin Oncol 41:1119-26, 2011
4. Tayier A, Hayashi K, Yoshimura R: Low-dose-rate interstitial brachytherapy preserves good quality of life in buccal mucosa cancer patients. J Radiat Res 52:655-9, 2011

（研究分担者）馬屋原博

1. Mayahara H, Sumi M, Ito Y, et al: Effect of chemotherapy on survival after whole brain radiation therapy for brain metastases: a single-center retrospective analysis. J Cancer Res Clin Oncol 138:1239-47, 2012
2. Mayahara H, Ito Y, Morizane C, et al: Salvage chemoradiotherapy after primary chemotherapy for locally advanced pancreatic cancer: a single-institution retrospective analysis. BMC Cancer 12:609, 2012
3. Hashimoto K, Narita Y, Miyakita Y, Mayahara H, et al: Comparison of clinical outcomes of surgery followed by local brain radiotherapy and surgery followed by whole brain radiotherapy in patients with single brain metastasis: single-center retrospective analysis. Int J Radiat Oncol Biol Phys 81:e475-80, 2011

H. 知的財産権の出願・登録状況

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

II. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ogura M, Itoh K, Ishizawa K, Hotta T, et al	Phase II study of ABV (doxorubicin with increased dose, bleomycin and vinblastine) therapy in newly diagnosed advanced-stage Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG9705)	Leuk Lymphoma	54	46-52	2013
Yamaguchi M, Tobinai K, Oguchi M, Hotta T, et al	Concurrent chemoradiotherapy for localized nasal natural killer/T-cell lymphoma: an updated analysis of the Japan clinical oncology group study JCOG0211	J Clin Oncol	30	4044-6	2012
Kagami Y, Itoh K, Tobinai K, Hotta T, et al	Phase II study of cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) therapy for newly diagnosed patients with low- and low-intermediate risk, aggressive non-Hodgkin's lymphoma: final results of the Japan Clinical Oncology Group Study, JCOG9508	Int J Hematol	96	74-83	2012
Watanabe T, Tobinai K, Shibata T, Hotta T, et al	Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial	J Clin Oncol	29	3990-8	2011
Chou T, Tobinai K, Uike N, Hotta T, et al	Melphalan-prednisolone and vincristine-doxorubicin-dexamethasone chemotherapy followed by prednisolone/interferon maintenance therapy for multiple myeloma: Japan Clinical Oncology Group Study, JCOG0112	Jpn J Clin Oncol	41	586-9	2011
Sato Y, Watanabe H, Sone M, Arai Y, et al	Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602.	Ups J Med Sci	118	16-22	2013
Ikeda M, Arai Y, Park SJ, Inaba Y, et al	Prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: an Asian cooperative study between Japan and Korea	J Vasc Interv Radiol	24	490-500	2013

Sone M, Arai Y, Kiuchi T, Kanazawa S, Takeuchi Y, et al	[Shared web-based data center for multi-institutional clinical trials: evaluation of UMIN-INDICE (university hospital medical information network-internet data and information center for medical research)in clinical trials of JIVROSG (Japan interventional radiology in oncology study group)]	Gan To Kagaku Ryoho	39	619-23	2012
Sofue K, Arai Y, Takeuchi Y, et al	Safety and efficacy of primary metallic biliary stent placement with tract embolization in patients with massive ascites	J Vasc Interv Radiol	23	521-7	2012
Osuga K, Arai Y, Anai H, Takeuchi Y, Inaba Y, et al	Phase I/II multicenter study of transarterial chemoembolization with a cisplatin fine powder and porous gelatin particles for unresectable hepatocellular carcinoma	J Vasc Interv Radiol	23	1278-85	2012
Inaba Y, Arai Y, Yamaura H, Takeuchi Y, et al	Phase II clinical study on stent therapy for unresectable malignant colorectal obstruction (JIVROSG-0206)	Am J Clin Oncol	35	73-6	2012
Arai Y, Ohtsu A, Sato Y, Takeuchi Y, Inaba Y, et al	Phase I/II study of radiologic hepatic arterial infusion of fluorouracil plus systemic irinotecan for unresectable hepatic metastases from colorectal cancer	J Vasc Interv Radiol	23	1261-7	2012
Arai Y	Clinical trials of interventional oncology	Int J Clin Oncol	17	301-5	2012
Sugawara S, Sone M, Arai Y, et al	Radiological insertion of Denver peritoneovenous shunts for malignant refractory ascites: a retrospective multicenter study (JIVROSG-0809)	Cardiovasc Interv Radiol	34	980-8	2011
Iwasa S, Ikeda M, Okusaka T, Arai Y, et al	Transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization	Jpn J Clin Oncol	41	770-5	2011
Inaba Y, Arai Y, Yamaura H, et al	Phase I/II study of hepatic arterial infusion chemotherapy with gemcitabine in patients with unresectable intrahepatic cholangiocarcinoma (JIVROSG-0301)	Am J Clin Oncol	34	58-62	2011
Iguchi T, Idani H, Asami S, Arai Y, Kanazawa S, et al	Hepatic arterial infusion chemotherapy prior to standard systemic chemotherapy in patients with highly advanced unresectable liver metastases from colorectal cancer: a report of three patients	Acta Med Okayama	65	49-53	2011
Hamaguchi T, Shirao K, Ohtsu A, Arai Y, et al	A phase II study of biweekly mitomycin C and irinotecan combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: a report from the Gastrointesti	Gastric Cancer	14	226-33	2011

	nal Oncology Group of the Japan Clinical Oncology Group (JCOG0109-DI Trial)				
Arai Y, Inaba Y, Sone M, et al	Phase I/II study of transjugular transhepatic peritoneovenous venous shunt, a new procedure to manage refractory ascites in cancer patients: Japan Interventional Radiology in Oncology Study Group 0201	AJR Am J Roentgenol	196	W621-6	2011
Sone M, Arai Y, Shimizu T, et al	Phase I/II multiinstitutional study of uterine artery embolization with gelatin sponge for symptomatic uterine leiomyomata: Japan Interventional Radiology in Oncology Study Group study	J Vasc Interv Radiol	21	1665-71	2010
Murakami N, Suzuki S, Ito Y, Itami J et al	^{106}Ruthenium plaque therapy (RPT) for retinoblastoma	Int J Radiat Oncol Biol Phys	84	59-65	2012
Mayahara H, Sumi M, Ito Y, Itami J, et al	Effect of chemotherapy on survival after whole brain radiation therapy for brain metastases: a single-center retrospective analysis	J Cancer Res Clin Oncol	138	1239-47	2012
Mayahara H, Ito Y, Morizane C, Itami J, et al	Salvage chemoradiotherapy after primary chemotherapy for locally advanced pancreatic cancer: a single-institution retrospective analysis	BMC Cancer	12	609	2012
Kuroda Y, Murakami N, Morota M, Itami J, et al	Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer	J Radiat Res	53	588-93	2012
Itami J, Sumi M, Beppu Y, et al	High-dose rate brachytherapy alone in postoperative soft tissue sarcomas with close or positive margins	Brachytherapy	9	349-53	2010
Matsui Y, Hiraki T, Gobara H, Kanazazwa S, et al	Phrenic nerve injury after radiofrequency ablation of lung tumors: retrospective evaluation of the incidence and risk factors	J Vasc Interv Radiol	23	780-5	2012
Kanazawa S	Current status of interventional oncology	Int J Clin Oncol	17	299-300	2012
Hiraki T, Kanazawa S	Lung radiofrequency ablation: potential as a therapy to oligometastasis and oligorecurrence	Pulm Med 2012	196173		2012
Minamimoto R, Terauchi T, Jinnouchi S, et al	Observer variation study of the assessment and diagnosis of incidental colonic FDG uptake	Ann Nucl Med			2013
Daisaki H, Tateishi U, Terauchi T, et al	Standardization of image quality across multiple centers by optimization of acquisition and reconstruction parameters with interim FDG-PET/CT for evaluating diffuse large B cell lymphoma	Ann Nucl Med	27	225-32	2013
Tateishi U, Terauchi T, Akashi-Tanaka S, et al	Comparative study of the value of dual tracer PET/CT in evaluating breast cancer	Cancer Sci	103	1701-7	2012

Terauchi T, Terashima H, Kojima S, et al	A conserved residue, PomB-F22, in the transmembrane segment of the flagellar stator complex, has a critical role in conducting ions and generating torque	Microbiology	157	2422-32	2011
Terauchi T, Kojima S, Homma M	[Structure and function of energy transduction protein complex of bacterial flagellar motor]	Seikagaku	83	822-33	2011
Liao H, Fujiwara K, Ando T, Sakuma I, et al	Automatic laser scanning ablation system for high-precision treatment of brain tumors	Lasers Med Sci	28	891-900	2013
Abolmaesumi P, Fichtinger G, Peters TM, Sakuma I, et al	Introduction to special section on surgical robotics	IEEE Trans Biomed Eng	60	887-91	2013
Liao H, Noguchi M, Maruyama T, Sakuma I, et al	An integrated diagnosis and therapeutic system using intra-operative 5-aminolevulinic-acid-induced fluorescence guided robotic laser ablation for precision neurosurgery	Med Image Anal	16	754-66	2012
Liang JT, Doke T, Onogi S, Sakuma I, et al	A fluorolaser navigation system to guide linear surgical tool insertion	Int J Comput Assist Radiol Surg	7	931-9	2012
Ando T, Kobayashi E, Liao H, Sakuma I, et al	Precise comparison of protoporphyrin IX fluorescence spectra with pathological results for brain tumor tissue identification	Brain Tumor Pathol	28	43-51	2011
Ikeda M, Arai Y, Park SJ, Takeuchi Y, Inaba Y, et al	Prospective study of transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: an Asian cooperative study between Japan and Korea	J Vasc Interv Radiol	24	490-500	2013
Sugawara S, Sone M, Arai Y, et al	Radiological insertion of Denver peritoneovenous shunts for malignant refractory ascites: a retrospective multicenter study (JIVROSG-0809)	Cardiovasc Interv Radiol	34	980-8	2011
Shibui S, Narita Y, Mizusawa J, et al	Randomized trial of chemoradiotherapy and adjuvant chemotherapy with nimustine (ACNU) versus nimustine plus procarbazine for newly diagnosed anaplastic astrocytoma and glioblastoma (JCOG0305)	Cancer Chemother Pharmacol	71	511-21	2013
Narita Y	Drug Review: Safety and Efficacy of Bevacizumab for Glioblastoma and Other Brain Tumors.	Jpn J Clin Oncol,			2013
Hashimoto K, Narita Y, Miyakita Y, et al	Comparison of clinical outcomes of surgery followed by local brain radiotherapy and surgery followed by whole brain radiotherapy in patients with single brain metastasis: single-center retrospective analysis	Int J Radiat Oncol Biol Phys	81	E475-80	2011

Yoshimoto M, Kurihara H, Hon da N, et al	Predominant contribution of L-type amino acid transporter to 4-borono-2-F-fluoro-phenylalanine uptake in h uman glioblastoma cells	Nucl Med Biol			2013
Nagao T, Hojo T, Kurihara H, et al	Sentinel lymph node biopsy in brea st cancer patients with previous bre ast augmentation surgery	Breast Cancer			2011
Nagao T, Kinos hita T, Hojo T, Kurihara H, et a l	Sentinel lymph node biopsy using i ndigo carmine blue dye and the val idity of '10% rule' and '4 nodes rul e'	Breast	21	455-8	2012
Kuroda Y, Mura kami N, Morota M, Yoshimura R, et al	Impact of concurrent chemotherapy on definitive radiotherapy for wome n with FIGO IIIb cervical cancer	J Radiat Res	53	588-93	2012
Toita T, Ohno T, Kaneyasu Y, Yoshimura R, et al	A consensus-based guideline definin g clinical target volume for primary disease in external beam radiothera py for intact uterine cervical cancer	Jpn J Clin Oncol	41	1119-26	2011
Tayier A, Hayas hi K, Yoshimura R	Low-dose-rate interstitial brachythera py preserves good quality of life in buccal mucosa cancer patients	J Radiat Res	52	655-9	2011
Hashimoto K, N arita Y, Miyakit a Y, Mayahara H, et al	Comparison of clinical outcomes of surgery followed by local brain ra diotherapy and surgery followed by whole brain radiotherapy in patient s with single brain metastasis: singl e-center retrospective analysis	Int J Radiat Onco l Biol Phys	81	E475-80	2011

Ⅲ. 研究成果の刊行物・別刷

Leukemia & Lymphoma, January 2013; 54(1): 46–52
© 2013 Informa UK, Ltd.
ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2012.705000

informa
healthcare

ORIGINAL ARTICLE: CLINICAL

Phase II study of ABV (doxorubicin with increased dose, bleomycin and vinblastine) therapy in newly diagnosed advanced-stage Hodgkin lymphoma: Japan Clinical Oncology Group study (JCOG9705)

Michinori Ogura[1], Kuniaki Itoh[2], Kenichi Ishizawa[3], Yukio Kobayashi[4], Kensei Tobinai[4], Tomohiro Kinoshita[5], Masami Hirano[6], Ryuzo Ueda[7], Taro Shibata[8], Shigeo Nakamura[1], Kunihiro Tsukasaki[9], Tomomitsu Hotta[10], Masanori Shimoyama[4] & Yasuo Morishima[1]; for the Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG)

[1]*Department of Hematology and Cell Therapy and Department of Pathology, Aichi Cancer Center Hospital, Nagoya, Japan,* [2]*Division of Hematology and Oncology, National Cancer Center Hospital East, Kashiwa, Japan,* [3]*Department of Hematology, Tohoku University, Graduate School of Medicine, Sendai, Japan,* [4]*Department of Hematology and Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan,* [5]*Department of Hematology and Oncology and Department of Pathology, Nagoya University Graduate School of Medicine, Nagoya, Japan,* [6]*Department of Medicine, Fujita Health University School of Medicine, Toyoake, Japan,* [7]*Department of Hematology, Graduate School of Medical Science and Medical School, Nagoya City University, Nagoya, Japan,* [8]*JCOG Data Center, Multi-institutional Clinical Trial Support Center, National Cancer Center, Tokyo, Japan,* [9]*Department of Hematology, Nagasaki University School of Medicine, Nagasaki, Japan, and* [10]*Department of Hematology and Oncology, Tokai University School of Medicine, Isehara, Japan*

Abstract

The role of dacarbazine in ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) therapy in Hodgkin lymphoma (HL) remains unclear. This phase II study assessed the efficacy and safety of ABV therapy with an increased doxorubicin dose (30 mg/m^2) in advanced-stage HL. The primary endpoint was complete response rate (%CR). Patients received six or eight cycles of ABV every 4 weeks followed by involved-field radiation therapy (IFRT) in residual disease and initial bulky mass. Seventy-two patients were enrolled. An interim analysis in 46 assessable patients showed that %CR had exceeded the stopping criteria. However, the 2-year progression-free survival (%PFS) rate of 49.4% (95% confidence interval [CI] 32.2–66.6) was markedly lower than the 79.2% PFS (95% CI 70.6–87.7) seen in our previously reported study (JCOG9305) of ABVd with two-thirds the dose of dacarbazine of the original ABVD. Therefore, the study was closed early. The %CR in the 70 eligible patients after ABV was 31.4% (95% CI 20.9–43.6) and was increased to 70.0% (95% CI 57.9–80.4) after the addition of IFRT. ABV was inferior to ABVd for PFS in patients with advanced HL, suggesting that dacarbazine is indispensable in ABVD/ABVd.

Keywords: ABV therapy followed by IFRT, first-line chemotherapy, Hodgkin lymphoma, phase II study

Introduction

Following the development of two representative curative combination chemotherapy regimens for advanced Hodgkin lymphoma (HL), the MOPP regimen (mechlorethamine, vincristine, procarbazine and prednisone) and the ABVD regimen (doxorubicin, bleomycin, vinblastine and dacarbazine) [1,2], several randomized trials were performed to establish the standard chemotherapy for patients with advanced HL. ABVD became the standard of treatment for patients with newly diagnosed advanced HL after a landmark phase III trial (the Cancer and Leukemia Group B [CALGB] 8251 study) showed that ABVD was as effective as alternating therapy of MOPP/ABVD, and more effective than MOPP, with fewer toxic events [3]. An American and Canadian intergroup phase III study also demonstrated that ABVD was as effective as the MOPP/ABV hybrid regimen, with fewer toxic effects [4].

The incidence of HL in Japan is approximately one-third that in Western countries [5,6]. Key drugs such as mechlorethamine in MOPP and dacarbazine in ABVD had not been approved by the Japanese government for clinical use in HL even as late as the 1990s. From October 1989 to February 1993, the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG) conducted a phase II study (JCOG8905)

Correspondence: Current address: Michinori Ogura, MD, PhD, Department of Hematology and Oncology, Nagoya Daini Red Cross Hospital, 2-9 Myoken-cho, Showa-ku, Nagoya, Aichi 466-8650, Japan. Tel: + 81-52-8321121. Fax: + 81-52-832-1130. E-mail: mi-ogura@naa.att.ne.jp. Current address of T. Kinoshita: Department of Hematology and Cell Therapy, Aichi Cancer Center, Nagoya, Japan. Current address of S. Nakamura: Department of Pathology, Nagoya University School of Medicine, Nagoya, Japan. Current address of T. Hotta: National Cancer Center, Tokyo, Japan.

Received 12 March 2012; revised 15 June 2012; accepted 17 June 2012

involving combination chemotherapy, alternating C-MOPP (cyclophosphamide, vincristine, procarbazine and prednisolone) and ABVd (with a lower dacarbazine dose than in ABVD) [7]. The dose of dacarbazine in ABVd was reduced to two-thirds (250 mg/m^2) that in the original ABVD (375 mg/m^2) regimen due to the side effect of intolerable severe emesis in a pilot study at that time. Subsequently, the emesis with dacarbazine has been greatly reduced with the development of promising anti-emetic regimens including 5-hydroxytryptamine 3 receptor and neurokinin 1 antagonists, which make standard ABVD more tolerable. The progression-free survival (PFS) rate at 4 years in patients with stage III/IV HL in the JCOG8905 study and that at 5 years in patients treated with MOPP/ABVD in the CALGB 8251 study were 65.7% and 65%, respectively [3,7]. Because the efficacy of C-MOPP/ABVd in the JCOG8905 study is considered almost equivalent to that of MOPP/ABVD in Western countries [4,8], the ABVd regimen is considered to be as effective as the original ABVD regimen.

After the results of CALGB 8251 were published [3], the JCOG-LSG conducted a multi-institutional phase II study (JCOG9305) to investigate the efficacy and safety of ABVd therapy for Japanese patients with newly diagnosed stage II–IV HL, although dacarbazine was administered off-label [9]. The complete response rate (CR) and 5-year PFS of all eligible patients were 81.4% and 78.4%, respectively. Thus, the JCOG9305 study showed sufficient efficacy and acceptable toxicity of ABVd therapy followed by post-chemotherapeutic involved-field radiation therapy (IFRT) for previously untreated patients with stage II–IV HL. The role of dacarbazine as a key drug in ABVd/ABVD therapy remains unclear, although dacarbazine was effective against HL as a single agent with an overall response rate of 56% in the Southwest Oncology Group study [10]. Phlebitis and emesis are serious side effects of this drug. Although the dacarbazine dose was reduced to two-thirds (250 mg/m^2) of that in the original ABVD regimen, grade 2 phlebitis and grade 2/3 nausea/vomiting were observed in 43% and 34%/11% of patients, respectively [9].

The JCOG-LSG conducted a phase II study (JCOG9705) to investigate the efficacy and safety of ABV therapy without dacarbazine and with the doxorubicin dose increased by 20%, in an effort to find a less toxic and equally effective treatment in patients with newly diagnosed advanced-stage HL. We report the results of JCOG9705 here.

Materials and methods

This trial was a prospective, multi-institutional phase II study conducted by the JCOG-LSG. The study protocol was approved by the Protocol Review Committee of the JCOG and by the institutional review board at each institution. Written informed consent was obtained from each patient before enrollment. This study was registered with UMIN-CTR (www.umin.ac.jp/ctr/), identification number C000000068.

Eligibility criteria

Eligible patients included: those who were newly diagnosed with HL according to the Rye classification [11]; those aged 15–69 years;those diagnosed at clinical stages IB, IIB, III, IV or any stage with bulky disease (>1/3 mediastinal widening by plain chest film or ≥ 10 cm maximum dimension of nodal mass on computed tomography [CT] scan) according to the Ann Arbor staging system [12] and the Cotswolds system [13]; those with evaluable lesions by CT scan; those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, 2 or 3 [14]; and those with no involvement to the central nervous system and no other active malignancies. Other eligibility criteria included leukocytes ≥ 3000/μL, neutrophils ≥ 1200/μL, platelets ≥ 10×10^4/μL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 times the upper limit of normal (ULN), total bilirubin ≤ 2.0 mg/dL, creatinine ≤ 1.5 mg/dL, PaO_2 ≥ 65 mmHg, ejection fraction (EF) ≥ 50%, and negative for hepatitis B surface antigen, anti-hepatitis C virus antibody, anti-human immunodeficiency virus antibody and anti-human T-lymphotropic virus type-I antibody. Exclusion criteria included women who were pregnant or nursing; patients with diabetes mellitus receiving insulin; those with severe infection or severe hepatic, pulmonary or psychiatric disease; or those with cardiac disease that could deteriorate due to administration of doxorubicin.

Treatment

The ABV regimen consisted of 6–8 cycles of doxorubicin (30 mg/m^2), bleomycin (9 mg/m^2; upper limit, 15 mg total) and vinblastine (6 mg/m^2; upper limit, 10 mg total), administered simultaneously as intravenous injections on days 1 and 15 of each cycle. The duration of each cycle was 4 weeks. Treatment was adjusted to six cycles of ABV if CR was obtained after four cycles or to eight cycles of ABV if CR or a partial response (PR) was obtained after six cycles. Bleomycin was omitted in cycles 7 and 8. The maximum total dose of bleomycin was defined to be 180 mg except for those patients in whom mediastinal radiation therapy was planned after ABV therapy. For these patients, the maximum total dose of bleomycin was defined to be 120 mg. If the pretreatment leukocyte and/or platelet counts were < 2500/μL and 7.5×10^4/μL, respectively, or the serum AST/ALT was ≥ 5 times the ULN, and/or total bilirubin was ≥ 2.1 mg/dL, treatment was postponed until recovery, with a maximum delay of 4 weeks. Vinblastine was discontinued if signs of neurotoxicity ≥ grade 3 were observed. Doxorubicin was discontinued if any of the following occurred: cardiac hypofunction (ejection fraction ≤ 40%), ≥ grade 2 arrhythmia, ischemic cardiac disease or pericarditis, or heart failure ≥ grade 3. Bleomycin was suspended until recovery if the PaO_2 level decreased to < 65 mmHg or decreased by > 15 mmHg of the previous PaO_2 level.

IFRT was indicated for patients with an initial bulky mass who experienced CR after six or eight cycles of ABV or PR after eight cycles of ABV. The first half of a total planned radiation dose of IFRT was delivered to cover the maximum diameter of the initial bulky mass. The latter half of the total planned radiation dose of IFRT was delivered to the residual mass after chemotherapy. IRFT to the residual mass in patients with stage IB, IIB, III or IV who achieved PR after ABV therapy was defined as follows: (1) no IFRT to bone marrow involved by HL; (2) IFRT (30 Gy) every 4–5 weeks should be delivered to lymph nodal lesions followed by booster radiation of 4–10 Gy if necessary; (3) both paraaortic nodes and spleen should be irradiated simultaneously if the HL lesion is observed in either tissue or both; (4) solitary ipsilateral pulmonary lesions should be

irradiated with IFRT of 18 Gy, but bilateral pulmonary lesions or pulmonary lesions more than 50% of the lateral lung area should not be irradiated; (5) hepatic lesions should be irradiated with 20 Gy; (6) bone lesions should be irradiated with 24 Gy followed by an IFRT boost of 10 Gy if necessary.

Patients with no bulky disease who achieved PR after eight cycles of ABV therapy received radiation therapy; antiemetic drugs were recommended as appropriate.

Central pathology review

A central pathology review was performed according to the method reported previously [9]. Names of the participating reviewers are provided in the "Appendix." Antigens routinely examined by immunohistochemistry included CD3, CD20, CD15 and CD30. Antibodies against CD79a, CD5, cyclinD1, CD10, bcl-2 and CD56 were utilized as necessary. Six hematopathologists and two hematologists reviewed the pathology specimens and classified them according to the World Health Organization (WHO) classification system [15]. The diagnosis by the central pathology review committee was used in this study.

Response and toxicity criteria

CR was defined as the disappearance of all measurable lesions and symptoms of disease for at least 4 weeks. PR was defined as a reduction of at least 50% in the sum of the products of the perpendicular diameters of all measurable lesions and the lack of appearance of new lesions for at least 4 weeks. An unconfirmed CR (CRu) was defined as maintenance of PR without chemotherapy for ≥ 3 months after completion of the study. Progressive disease was defined as a 25% increase in the size of any existing lesion or the development of any new lesions. All other circumstances were considered to indicate stable disease. Response was evaluated by CT scan after cycles 2, 4, 6 and 8 of ABV therapy, and after IFRT.

Pulmonary toxicity was evaluated by monitoring the partial pressure of oxygen in arterial blood just before the administration of ABV therapy. Cardiac toxicity was evaluated by electrocardiogram and echocardiography just before the administration of ABV therapy. Toxicities were evaluated according to the toxicity grading criteria of the JCOG [16], which include the expanded and modified version of the National Cancer Institute (NCI) Common Toxicity Criteria version 1.0.

Statistical analysis and endpoints

The primary endpoint was the CR rate (CR + CRu) in all eligible patients. Secondary endpoints were toxicity, overall survival (OS) and CR duration. At the time of analysis, PFS was used instead of CR duration. OS was calculated from the date of registration until death due to any cause or censored at the last follow-up date. PFS was calculated from the date of registration to the date of relapse or progression, death due to any cause, or censored at the date of the last follow-up for patients with no reported adverse events. Analyses of the CR and overall response rate (ORR: CR + PR) were performed using point estimates and the 95% confidence interval (CI). OS and PFS were estimated according to the Kaplan–Meier method. Sample size was determined using Simon's two-stage minimax design ($P_0 = 0.7$, $P_1 = 0.8$, alpha = 0.1, beta = 0.2) [17]. At the first-stage decision, if the total number of responders (CR + PR) was 32 of the 46 eligible patients or fewer (i.e.ORR ≤ 69.6%), the study was to be discontinued. At the second (final) stage, if the total number of responders (CR + PR) was 65 of the 86 eligible patients or fewer (i.e.ORR ≤ 75.6%), the protocol treatment was deemed ineffective.Because up to 20% of patients were ineligible based on the central pathology review, the sample size was decided to be 108 patients who were enrolled for 3 years.The analyses were performed using SAS release 9.1 (SAS Institute, Cary, NC).

Role of the funding source

This work was supported by the National Cancer Center Research and Development Fund (23-A-16 and 23-A-17) and Grants-in-Aid for Cancer Research (8S-1, 11S-1, 11S-4, 14S-1, 14S-4, 17S-1, 17S-5, 20S-1 and 20S-6) from the Ministry of Health, Labor and Welfare of Japan. The funding source played no role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the paper for publication.

Results

Decision process using Simon's two-stage minimax design

Twenty-five hospitals participated in JCOG9705. The participating institutions and investigators are listed in the "Appendix." Between January 1998 and May 2000, 72 patients were enrolled in JCOG9705. In May 2000, according to the decision rule, the first-stage decision to stop enrollment and compare the PFS of this study to that of JCOG9305 was made for 36 patients, since the PFS of JCOG9705 was poor. In October 2000, an updated analysis was performed for 46 patients (as per the first-stage decision criteria) who were evaluable for response. The CR rate and 2-year PFS were 71.7% (95% CI 56.5–84.0) and 49.4% (95% CI 32.2–66.6), respectively.The PFS at 2 years (49.4%) in this study was markedly lower than that of JCOG9305 (79.2% [95% CI 70.6–87.7]), excluding those with non-bulky, stage IIA disease [9].The low PFS was considered to reflect too many early relapses after ABV–IFRT.Therefore, in accordance with the recommendations of the JCOG Data and Safety Monitoring Committee, the study was closed early in December 2000.

Patient characteristics

The final analysis of the results of JCOG9705 was conducted in December 2005. Seventy-two patients were enrolled in JCOG9705; two were deemed ineligible, one due to a change of pathological diagnosis after enrollment and the other due to a change in clinical stage from IIIA to non-bulky IIA. The clinical characteristics of the 70 eligible patients are shown in Table I. There were 36 men and 34 women, and the median age was 31.5 years. B symptoms at entry were observed in 39 patients (55.7%). PS was 0 or 1 for the majority (94.3%) of eligible patients. Bulky disease (maximum diameter ≥ 10 cm) was present in 34 patients (48.6%). Unfavorable localized disease (bulky stage IA, bulky IIA, IB and IIB) and advanced disease (stages III and IV) were present in 29 (41.4%) and 41 patients (58.6%), respectively. The numbers of patients with an International Prognostic Score (IPS) [18] of 0–2 and ≥ 3 were 33 (47.1%) and 37 (52.9%), respectively. Fourteen percent of patients had stage IV disease. In the JCOG8905 and