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# 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２３年度　総括研究報告書

研究代表者　嘉山　孝正

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# Ⅰ．総括研究報告

厚生労働科学研究費補助金（医療機器開発推進研究事業）
総括研究報告書

# 高度医療技術の効率化及び標準化の開発に関する研究

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**研究要旨**
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について、「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」の両面から研究を進めた。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」についての研究を進め、後者については「経皮的凍結療法」、「Irreversible Electroporation (IRE)」、「収束超音波」、「ホウ素中性子捕捉療法(BNCT)」を採り上げ、本年度は、アーチファクトのない MRI 用穿刺針の開発、MRI 下での穿刺誘導に用いる光学式ナビゲーションシステムの開発、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−電子密度変換テーブルを作成するとともに、新しい局所治療法である経皮的凍結療法、収束超音波治療、Irreversible Electroporation (IRE)に関する臨床試験の研究計画書を作成し、試験開始手続きを進めた。

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## A. 研究目的

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。しかし、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のが現状である。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、その非的中針自体が、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、本年度中には、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進めた。

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を行い、プロトタイプを完成し、実用上の問題点につき検討した。

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、昨年度の研究に続き、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に関する基礎的検討を行った。

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。

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。
③有痛性後腹膜・骨盤内腫瘍に対する収束超音波治療の第 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収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。
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。
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。

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、治療の非侵襲性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、標的部位の動きの有無により、より臨床に即した技術への展開を図り、本年度の研究により明確なゴールが提示された。特に、穿刺された非的中針を新たなガイドとする考え方は、従来の工学的側面のみに依存した考え方に臨床的側面からの発想を導入した斬新なものである。ただし、MRI 上でアーチファクトの少ない細径穿刺針の開発は容易でなく、年度中に結果を出すに至らなかった。動きのない部位に用いる小型穿刺用プローブの開発は比較的容易であったため、実用装置への改良の道が示された。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、ビームを遮断しない穿刺手技の改良を要すものの、プロトタイプで実用化可能と判断された。極めて誤差の少ない穿刺誘導用画像として比較的早期での実用化が見込まれるが、装置の小型化が今後の課題と考えられる。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るが、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は、極めて大きな前進と言える。実臨床での使用における細かな修正が今後の課題である。
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、これを高度医療評価制度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、将来の本邦への導入において大きな意味をもつと考えられる。くわえて、これらの治療法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。また、BMCT における適応の判断に不可欠な 18F-FBPA PET 検査に用いる FBPA 製剤の合成系を完成したことは、病院設置型での導入が世界初となる BMCT を進める上で、極めて重要な初期段階をクリアしたものと思われる。

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については、未だ満足できる結果に至っていないが、その他の画像技術については、問題が明確化され、その一部で実用化に繋がる可能性の高い結果を得るに至った。また、BMCT に使用する FBPA 製剤の合成系を完成した。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、臨床試験開始のための手続きを行なった。

F. 健康危険情報

なし。

G. 研究発表

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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

別紙４

研究成果の刊行に関する一覧表

雑誌

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# Ⅲ. 研究成果の刊行物・別刷

# V. ASYMPTOMATIC CEREBROVASCULAR DISEASES

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## OVERVIEW

With the nationwide spread of MRI coupled with the regular brain checkup system in Japan, clinicians often incidentally come across the asymptomatic cerebrovascular diseases during routine medical examinations, and the importance of these disorders has been gradually recognized. For example, asymptomatic cerebral infarctions, also known as "silent brain infarctions," have recently been identified as an independent risk factor for stroke.[1] To reduce the number of the stroke patients and the patients requiring long-term care, asymptomatic cerebral infarction has become one of the diseases to which we should pay more attention, and assessing the appropriate clinical response to it is important. In addition, considering the mortality rate and morbidity are high once such a cerebral aneurysm ruptures, and that clinicians come across asymptomatic cerebrovascular diseases surprisingly frequently,[2-5] a set of guidelines presenting the appropriate clinical response and the steps we should take is eagerly awaited.

From this perspective, a new section has been established for asymptomatic cerebrovascular diseases in the Japanese Guidelines for the Management of Stroke 2009 at the time of revising the 2004 guidelines. Nonetheless, although data on both of the ischemic and the hemorrhagic lesions have gradually accumulated, the quantity of data with high evidence levels (eg, epidemiology, natural course, and the outcomes of therapeutic intervention for asymptomatic cerebrovascular disease) is relatively small, because these conditions are by their very nature asymptomatic. Therefore, when a patient with an asymptomatic cerebrovascular disease is currently encountered in a routine medical examination, it is very difficult to state with conviction that the clinician will have adequate knowledge as to the correct clinical course.

To develop a set of guidelines on asymptomatic cerebrovascular diseases, we have focused on the information on which specialists and general physicians can base appropriate treatment of those disease entities frequently encountered in actual medical examinations.

In this chapter, asymptomatic cerebrovascular diseases are classified into the following 4 sections: (1) asymptomatic cerebral infarction (including white matter lesions); (2) asymptomatic intracerebral hemorrhage (ICH); (3) asymptomatic cervical/intracerebral vascular stenosis/occlusion; and (4) unruptured cerebral aneurysm/unruptured cerebral arteriovenous malformation (AVM). The chapter attempts to describe the current knowledge and set out the methods that specialists and general physicians treating asymptomatic cerebrovascular diseases should acquire. There are some areas for which the amount of evidence that has been accumulated as mentioned previously is insufficient depending on the section; however, we believe the guidelines set out hereafter have been reached with consensus.

In the future, it will be necessary to accumulate larger and more comprehensive bodies of data in this field with a high evidentiary level.

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[1] For the Joint Committee on Japanese Guidelines for the Management of Stroke 2009, English version.

[2] For the Joint Committee on Japanese Guidelines for the Management of Stroke 2009.

1052-3057/$ - see front matter



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## 1. Asymptomatic (Silent) Cerebral Infarction (Including Cerebral White Matter Lesions)

*1-1. Asymptomatic cerebral infarction*

### Recommendations

1. Patients with asymptomatic cerebral infarction are at high risk for developing symptomatic cerebral infarction and cognitive impairment, thus, follow-up including MRI and cervical Doppler echography is necessary (Grade B).
2. Nonetheless, antiplatelet therapy for asymptomatic lacunar infarction should be performed carefully (Grade C1). Hypertension is the most significant risk factor for asymptomatic cerebral infarction so that appropriate and sufficient antihypertensive therapy is needed for hypertensive patients (Grade B). Antihypertensive therapy with Ca antagonist inhibits increases in the number of asymptomatic cerebral infarctions (Grade B).
3. It is extremely important to inform patients with asymptomatic lacunar infarction that they should avoid needlessly increasing their stress levels (Grade C1).
4. In asymptomatic patients with border-zone (watershed) cerebral infarctions, major stenosis/occlusion of the truncal cerebral artery or of the proximal portion of the cerebral arteries or arteries of the neck needs to be fully investigated (Grade C1).

**Note**

The Japanese general population is encouraged to present for regular screening examinations. Those for the brain are called Brain Check-Up, or the popular term, 'Brain Dock' in Japan, and it is during these routine examinations that asymptomatic brain diseases can be discovered. The Japanese Society for Detection of Asymptomatic Brain Diseases which overseas these check-ups has defined the lacunar imaging appearance of stroke, dilated perivascular spaces (known as état criblé) and asymptomatic cerebral infarction as follows.[6]

Lacunar infarction: MRI T2-weighted image or proton density weighted images (PDWI) show a clear high intensity area with ill-defined margins and an irregular shape with a maximum diameter ≥3 mm. The lesion is displayed as a low intensity area on MRI T1-weighted images and an iso-intensity to high-intensity area on fluid attenuation inversion recovery (FLAIR) images. On PDWI and FLAIR images, a low-intensity area in the center can be often shown.

état criblé: T2-weighted images show a high-intensity area with a clear margin and regular and uniform shape measuring <3 mm. The lesion is isointense to low-intensity on T1-weighted images, and isointense to low-intensity without a high-intense margin, running along the perforating arteries or medullary vessels on PDWI and FLAIR images. However, état criblé located one-third below the basal ganglia are often over 3 mm in diameter.

Asymptomatic cerebral infarction: imaging shows a change with an infarction-like appearance, which meets the following condition:[7] (1) absence of neurologic deficits (including a right-left differences in deep tendon reflexes, and dementia considered to be of a vascular nature) corresponding to the lesion; and (2) no recognition of symptoms (including transient ischemic attack) corresponding to the lesion by the patient or his or her family either in the past or present. Most cases of asymptomatic cerebral infarction are deep brain lacunar strokes,[8] but may rarely be watershed cerebral infarctions.

**Evidence**

In the Cardiovascular Health Study, a large-scale cohort study pursuing the MRI findings in elderly patients (aged ≥65 years) without previous symptomatic stroke, the risk of developing stroke was investigated during a mean follow-up period of 4 years. It revealed that the incidence of stroke was 1.87%/year in those with asymptomatic cerebral infarctions and significantly higher than that those without asymptomatic cerebral infarctions (0.95%/year)[9] (IIb). Therefore, asymptomatic cerebral infarctions were concluded to be an independent predictor for stroke in the elderly. In the Rotterdam Scan Study which pursued the MRI findings of elderly patients without previous symptomatic stroke, the incidence of new cerebral infarctions (asymptomatic: n = 81, symptomatic: n = 12) identified in the second MRI in patients with asymptomatic cerebral infarctions was significantly higher (odds ratio, 2.9) than that in patients without asymptomatic cerebral infarctions[10] (IIb). This study also investigated the relationship with the development of symptomatic stroke during a mean follow-up period of 4.2 years. The results revealed that the proportional hazard ratio (after adjusted for other factors) for stroke was as high as 3.9 (95% confidence interval [CI], 2.3-6.8) in the asymptomatic cerebral infarction group; thus, it was concluded that patients with asymptomatic cerebral infarctions are in the high risk group for developing stroke. The Rotterdam Scan Study also evaluated the relationship with the development of cognitive impairment during a mean follow-up period of 3.6 years. The hazard ratio for the development of dementia was as high as 2.26 (95% CI, 1.09-4.70) in the asymptomatic cerebral infarction group, demonstrating that patients with asymptomatic cerebral infarctions are also in the high risk group for cognitive impairment[11,12] (IIb).

To date, however, there is no high level evidence regarding the effect of antiplatelet therapy for the prevention of cerebral infarction in patients with asymptomatic cerebral infarctions. Platelet function in such patients was however

reported to be accentuated compared with the control group and platelet activation was observed.[13,14] Administration of antiplatelet agents, however, should be considered only after full investigation of the individual patients at present. This is because, particularly in Japan, hypertensive intracerebral hemorrhage (ICH) was reported to occur in 21% of patients in whom a stroke developed from asymptomatic cerebral infarctions in a follow-up investigation after a medical checkup of the brain;[15] therefore, adequate blood pressure control is a prerequisite when antiplatelet agents are administered, because hypertension is the most significant risk factor for asymptomatic cerebral infarction[15,16] (IIb). In the PICA study, a recent multicenter trial in Japan, antihypertensive therapy with nilvadipine, a Ca antagonist, 4-8 mg/day was demonstrated to inhibit an increase in the number of asymptomatic cerebral infarctions[16] (IIb).

A meta-analysis on the effect of aspirin 75-650 mg/day in 52,251 subjects including healthy volunteers showed a significant preventive effect with a relative risk of 0.74 (95% CI, 0.68-0.82) only on myocardial infarction but no significant effect on stroke (during the mean follow-up period of 4.6 years, the incidence of all strokes was 0.3%/year.)[17] (Ia). A risk-stratified analysis revealed that aspirin significantly inhibited the development of stroke in the high-risk group with obvious cardiovascular disease, whereas it tended to increase the incidence of stroke in the low risk group. In contrast, aspirin significantly increased the frequency of ICH during both primary and secondary prevention, although it was mild (relative risk, 1.35). Consequently, it has been concluded that aspirin for the primary prevention of stroke should be administered upon full consideration of baseline risk factors for atherosclerosis and so on, and that preferable dose of aspirin was 75-81 mg/day, if used. Although antiplatelet therapy is indicated for patients with truncal cerebral artery stenosis or carotid stenosis, caution must be exercised when lowering blood pressure. In addition, anticoagulant therapy should be considered for patients with atrial fibrillation and probable cardioembolic stroke.

A case-control study of 1588 healthy subjects without neurological abnormality revealed that asymptomatic cerebral infarctions were observed significantly more in patients with metabolic syndrome (odds ratio, 2.18; 95% CI, 1.38-3.44)[18] (III).

Some reports have suggested that patients with asymptomatic cerebral infarctions are more likely to develop symptomatic cerebral infarctions[19,20] have a higher mortality rate,[20] and are more likely to be complicated by pneumonia.[21] Also, patients with major depression were likely to develop delirium or dementia if asymptomatic cerebral infarctions were present.[22] In addition, asymptomatic cerebral infarctions have been related to the severity of carotid atherosclerosis,[20] and coronary artery/carotid stenosis.[23]

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## 1. Asymptomatic (Silent) Cerebral Infarction (Including Cerebral White Matter Lesions)

*1-2. Cerebral white matter lesions*

### Recommendations

1. Cerebral white matter lesions are mainly ischemic changes. In particular, patients with severe

**Recommendations, *continued***

periventricular hyperintensity (PVH) are at high risk for developing stroke and cognitive impairment; thus, an aggressive approach for treatable risk factors, especially for hypertension, should be considered (Grade B).

2. Patients with metabolic syndrome (MetS) and high blood total homocysteine levels are in the high risk group for developing cerebral white matter lesions. The correction of these conditions is recommended to avoid worsening of the cerebral white matter lesions and the development of stroke (Grade C1).

**Note**

The Japanese Society for Detection of Asymptomatic Brain Diseases defines the imaging criteria for cerebral white matter lesions as follows:[24]

Cerebral white matter lesions: T2-weighted images or PDWIs show a faint high-intensity area in the periventricular or deep and subcortical white matter. The lesion is a clearly defined high intensity area on FLAIR images. It is isointense or mildly intense, equivalent to the cerebral gray matter on T2-weighted images. Cerebral white matter lesions can be classified into periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH).

**Evidence**

In many cases, cerebral white matter lesions progress over the time course and usually do not improve[25] (IIb).

In a report of a follow-up investigation after a routine brain check-up in Japan, the presence of severe white matter lesions and asymptomatic cerebral infarctions were the most significant risk factors for developing stroke. Particularly, the odds ratio for severe cerebral white matter lesions was 10.6, which was higher than that of 8.8 for asymptomatic cerebral infarctions[26] (IIb). According to the final report of the PICA study, a multicenter trial in Japan, the severity of PVH and DSWMH was particularly related to the subsequent development of symptomatic cerebral infarctions, and it was found to be one of their predictors. The Rotterdam Scan Study, which pursued MRI of elderly patients without obvious previous stroke, investigated the relationship with the development of symptomatic stroke during a mean follow-up period of 4.2 years. The proportional hazard ratio (after adjustment for other factors) for developing stroke was as high as 4.7 (2.0-11.2) in the severe PVH group and 3.6 (1.4-9.2) in the DSWMH group. It was concluded that patients with severe cerebral white matter lesions were in the high-risk group for developing stroke[27] (IIb). Many large-scale clinical studies other than this have demonstrated that cerebral white matter lesions have a high risk of stroke[28-30] (IIb).

The most significant risk factor for cerebral white matter lesions is hypertension.[26,31] Cerebral white matter lesions were reportedly significantly milder in a hypertension treatment group than in a nontreatment group. Consequently, the importance of aggressive blood pressure control from an early stage was pointed out[32,33] (III). No report has as yet confirmed that excessive blood pressure lowering aggravated cerebral white matter lesions.

A study involving 1030 healthy Japanese subjects (age range, 28-78 years; mean age, 52.7 years) who had undergone a medical checkup found a significant relationship between the MetS and cerebral white matter lesions. The results suggested that the MetS would be useful for identifying relatively young individuals at high risk of developing cerebral white matter lesions in the future[34] (III).

In studies including a cross-sectional analysis in the Northern Manhattan Study, when blood total homocysteine levels were higher, the severity of cerebral white matter lesions was also significantly higher[35,36] (III).

Relationships between the severity of cerebral white matter lesions and major depression,[37] cognitive impairment,[38-43] emotional disorder,[44] or mild cognitive impairment[45] have been reported. In patients with multiple lacunar strokes, a significant negative correlation was noted between the extent of PVH and cognitive function.[46] A study of healthy subjects revealed that the severity of cerebral white matter lesions was related to functions requiring speed such as verbal recall, that is, subcortical frontal lobe functions, and that the dilatation of the ventricles was related to cortical functions such as the verbal cognitive function.[47]

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## 2. Asymptomatic Intracerebral Hemorrhage

### Recommendations

1. Aggressive blood pressure control is required for the prevention of symptomatic intracerebral hemorrhage (ICH) in patients with asymptomatic ICH and microbleeds (Grade C1).

### Recommendations, *continued*

2. Antiplatelet therapy and anticoagulant therapy for asymptomatic ICH or microbleeds accompanying ischemic stroke should be performed only in the high risk cerebral infarction group in whom the prevention of ischemic stroke has a higher priority than hemorrhagic stroke, while exercising blood pressure control (Grade C1).

#### Evidence

#### 1. Asymptomatic ICH

In terms of the causes of asymptomatic ICH, hypertensive ICH is most frequent, the majority of which consists of lateral putaminal hemorrhages (external capsule)[48,49] (III). In addition, concurrent cerebral infarction is present in 50% of patients with asymptomatic ICH associated with hypertensive ICH[48,49] (III).

Symptomatic ICH has been noted in as many as 23%-33% of patients with symptomatic hypertensive ICH[50,51] (III).

No studies have as yet been published on the frequency or natural history of asymptomatic ICHs associated with secondary ICHs attributable to amyloid angiopathy, cerebral arteriovenous malformations (AVMs), or angiomas.

The administration of antiplatelet or anticoagulant therapy to patients with asymptomatic ICHs has not been shown to increase the risk of new bleeding.

#### 2. Microbleeds

The frequency of microbleeds increases when the following factors are present: elderly[52-54] (IIb), hypertension[53,54] (IIb), advanced severity of cerebral white matter lesions[55-57] (IIb) and previous stroke[57,58] (IIb-III).

The frequency of microbleeds in atherothrombotic cerebral infarctions does not differ compared with normal controls and is higher in patients with cardioembolic stroke, ICH, and lacunar infarctions. In particular, the frequency is high in patients with ICHs and lacunar infarctions[55-57] (IIb).

No consistent conclusion has been drawn for microbleeds; one report states that they are a risk of new ICHs or lacunar infarctions,[59] whereas another report documents that they do not present any such risk.[60]

Microbleeds are related to decreases in frontal cognitive functions[61] (IIb).

There is no evidence that the presence of microbleeds increases the risk of acute ICHs during thrombolytic therapy in patients with acute cerebral infarction[62-65] (IIb-III).

There is no report that the administration of antiplatelet or anticoagulant therapy to patients with microbleeds increases the risk of new bleeding.

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