表2 調査用紙1頁

脳腫瘍調査用紙A（個人識別）

施設患者番号（カルテ番号）

地域コード A | 施設名 | 施設コード | 登録番号コード | 登録年月日 年 月 日

個人識別

患者氏名：ふりがな コード | 氏名 | 性別・1男 2女 | 1 2 3 4 明 大 昭 平 治 正 和 成 年号 年 月 日

現住所：郵便番号 | 99不明 | コード

本籍：郵便番号 | 99不明 | コード

出生地：都・道・府・県 99不明 コード | 職業 00なし あり( ) 99不明 コード | 人種：1日本人 2その他のアジア人 3白人 4黒人 5その他 9不明 コード

調査用紙B（治療）

治療開始年月日 年 月 日

手術：0なし 1減圧のみ 2試験切除又は部分切除 3 50%切除 4 75%切除 5 95%以上切除 6全摘出 9不明 第一回手術 コード 第二回手術 コード

放射線治療

時期：0照射なし（以下の項目を記入せず化学療法に移る） 照射あり 1術前 2術(中)後 3術前＋術(中)後 4その他 9不明 コード

照射法：1外照射 2内照射(組織内照射) 3radiosurgery 4その他 9不明 コード

1 Co^{60} 2Linac 3 β-tron 4重粒子 5Isotope 6その他 9不明 コード

放射線増感剤：0なし 1ニトロソウレア(ACNUなど) 2白金製剤(CDDPなど) 3代謝拮抗剤(5FUなど) 4その他の抗癌剤 5その他（ ） 9不明 コード

脊髄への照射：00なし あり（量 ） Gy 99不明 コード

主病巣に対する線量：（ ） Gy 99不明 コード

化学療法

導入療法：0化療なし（以下の項目を記入せず維持に進む） 化療あり 1術前 2術(中)後 3術前＋術(中)後 4その他 9不明 コード

投与法：1単剤投与 2多剤 (concomitant) 3多剤 (sequential) 9不明 コード

薬剤名(表1) A コード | B コード | C コード | D コード

維持：0なし 1単剤 2多剤 9不明 コード | 薬剤名 (a, b, c, d 表1) 99不明 | a | b | c | d

免疫療法：0なし 1腫瘍抗体 2ペプチド抗体 3非特異的免疫賦活剤 (PSK, OK432, BCG等) 4サイトカイン 5免疫担当細胞の応用 6その他 9不明 コード

遺伝子療法：0なし 1遺伝子導入による直接治療 (HSV-TKなど) 2免疫遺伝子的治療 3遺伝子導入による脱癌化 4造血細胞への抗癌剤耐性導入 5その他（ ） 9不明 コード

初期治療前後のPSの変化 (Karnofsky PS)：1社会生活可能(KPS90%) 2多少障害あるが一応社会生活可能(80%) 3家庭生活がとどこおりなく行える(70%) 4家庭生活介助にて可(60%) 5ほとんど臥床状態(50%～40%) 6入院が必要な臥床状態(30%) 7死期が近い状態(20%～10%) 9不明 治療前 コード | 治療後 コード

表3 調査用紙2頁

調査用紙C（原発性脳腫瘍）

診断	手術または診断確定日	年 月 日	発症から手術（または診断確定日）までの期間（月） 999不明 コード
	診断根拠	01手術材料 02髄液細胞診・培養 03X-ray, Isotope 04症状 05剖検 06CT 07MRI 08PET 09その他 99不明	コード
	既往歴	1primary 2recurrent 9不明 コード	他の腫瘍との合併 0なし 1他臓器がん 3中枢神経系 9不明 コード
	臨床悪性度	1無症状 2自覚症状のみ 3巣症状 4頭蓋内圧亢進 5意識障害 6昏睡またはそれに近い高度の意識障害 7呼吸中枢障害 9不明	コード
局在	腫瘍の数	1単発 2多発 3その他 9不明 コード	場所①：1テント上 2テント下 3テント上下 4その他 9不明 コード
	場所②：	1右 2左 3両側にまたがる 3中央（central neuroaxisに発生したもの） 5その他 9不明	コード
	発育部位	髄膜腫以外（表2-A） 髄膜腫（表2-B） 99不明 コード	大脳半球腫瘍の場合 1frontal 2temporal 3parietal 4occipital 5bifrontal 6その他のmultilobar 髄膜腫の場合 表2-B 細分類を記入 9不明 コード
	進展度	01該当せず 02大脳皮質回（functional）に限局 03大脳皮質回（nonfunctional）に限局 04脳葉内（functional）に限局 05脳葉内（nonfunctional）に限局 06脳葉に進展 07基底核部・視床下部に発生または進展 08正中に達する 09対側半球に及ぶ 10テント上下に及ぶ 11その他 99不明	コード
肉眼所見	性状	1diffuse 2circumscribed 9不明 コード	形状 1solid 2cystic 3both 9不明 コード
	浸潤	0なし 1くも膜 2硬膜 3頭蓋骨 4頭皮 5該当せず 9不明	コード
	頭蓋外転移（播種）	0なし 1脊髄 2その他の部位 9不明 コード	腫瘍の直径 縦（ ）cm, 横（ ）cm 8cm以上 9不明 コード
病理または臨床診断（表3）	診断名（ ） 9901不明		コード

調査用紙D（転移性脳腫瘍）（連続性浸潤を含む）

診断	手術または診断確定日	年 月 日	脳症状発症から手術（または診断確定日）までの期間（月） 99不明 コード
	診断根拠	01手術材料 02髄液細胞診・培養 03X-ray, Isotope 04症状 05剖検 06CT 07MRI 08PET 09その他 99不明	コード
	原発巣診断確定日から脳移転診断確定まで（ ヶ月） 999不明 コード		1初回治療 2再発治療 9不明 コード
	臨床悪性度	1無症状 2自覚症状のみ 3巣症状 4頭蓋内圧亢進 5意識障害 6昏睡またはそれに近い高度の意識障害 7呼吸中枢障害 9不明	コード
	脳移転診断確定時	原発巣再発 0なし 1あり 9不明 コード	他臓器移転 0なし 1あり 9不明 コード
局在	腫瘍の発育	1単発 2多発 3髄膜炎型 9不明	コード
	場所	1右 2左 3両側にまたがる 3中央 4該当せず 5不明 コード	1テント上 2テント下 3テント上下 4その他 9不明 コード
	部位（表2-A）	98多発のため該当項目なし 99不明	コード
原発巣	局在	01肺 02乳 03血液 04骨 05軟部組織 06皮膚 07骨 08腸 09直腸 10肝 11脾 12頭頸部 13甲状腺 14精巣 15膀胱 16子宮 17卵巣 18腎 19眼 20リンパ腺 21神経組織 22その他 99不明	コード
	治療	0なし 1手術・放治・化療 2手・放 3手・化 4放・化 5手術 6放治 7化療 8その他 9不明	コード
	ホルモン療法	0なし 1Oophorectomy 2Adrenalectomy 3Hypophysectomy 4Steroid 5その他 9不明	コード
	手術術式	0なし 1radical 2non-radical 9不明	コード
組織診断		01adeno 02squamous 03anaplastic 04oat cell (small cell) 05transitional 06AML 07ALL 08CML 09CLL 10other L 11sarcoma 12retinobl. 13neurobl. 14melanoma 15lymphoma 16clear cell 17large cell 18その他 診断名（ ） 99不明	コード

調査用紙E（転帰）

転帰	調査時の状況：1死亡 2生存 9不明（生存または不明の場合、最終生存確認年月日に移る） コード	剖検 0なし 1あり（死亡の場合のみ記入） 9不明 コード
	死亡年月日 99 99 99不明	年 月 日
	死因 1脳腫瘍による死（含転移性脳腫瘍） 2治療に起因する死 3事故あるいは他病死 4がんの原発部または他の臓器転移による死 9不明	コード
	他病死の場合、脳腫瘍（含転移性脳腫瘍）の再発 1あり 2なし 9不明	コード
	最終生存確認年月日（生存及び不明の場合のみ記入） 99 99 99 99不明	年 月 日
	調査年月日 年 月 日	記載者名

表4 原発性脳腫瘍組織分類

表3 原発性脳腫瘍組織分類

01 Gangliocytic, neuronal tumors
- 0101 Ganglioglioma
- 0102 Anaplastic (malignant) ganglioglioma
- 0103 Paraganglioma
- 0104 Gangliocytoma
- 0105 Dysplastic gangliocytoma of cerebellum
- 0106 Desmoplastic infantile ganglioglioma
- 0107 Dysembryoplastic neuroepithelial tumor
- 0108 Central neurocytoma
- 0109 Hypothalamic neuronal hamartoma

02 Atrocytic tumors, glioma (詳細不明)
- 0201 Astrocytoma
- 0202 Pilocytic astrocytoma
- 0203 Pleomorphic xanthoastrocytoma
- 0204 Subependymal giant cell astroctyoma
- 0205 Astroblastoma
- 0206 Gliomatosis cerebri
- 0207 Anaplastic (malignant) astrocytoma
- 0208 Glioblastoma
- 0209 Glioma (詳細不明)

03 Oligodendroglial tumors
- 0301 Oligodendroglioma
- 0302 Anaplastic (malignant) oligodendroglioma
- 0303 Oligo-astrocytoma
- 0304 Anaplastic (malignant) oligo-astrocytoma
- 0305 Other mixed glioma

04 Ependymal, choroid plexus tumors
- 0401 Ependymoma
- 0402 Anaplastic (malignant) ependymoma
- 0403 Ependymoblastoma
- 0404 Myxopapillary ependymoma
- 0405 Subependymoma
- 0406 Choroid plexus papilloma
- 0407 Choroid plexus carcinoma

05 Medullo- and neuroblastomas
- 0501 Neuroblastoma
- 0502 Medulloepithelioma
- 0503 Medulloblastoma
- 0504 Primitive neuroectodermal tumor (PNET)
- 0505 Olfactory neuroblastoma
- 0506 Neuroepithelioma (retinoblastoma)

06 Pineal tumors
- 0601 Pineocytoma
- 0602 Pineoblastoma
- 0603 Pineal tumors of intermediate differentiation

07 Nerve and meningeal tumors
- 0701 Schwannoma (Neurilemmoma, Neurinoma)
- 0702 Neurofibroma (von Recklinghausen's disease)
- 0703 Malignant peripheral nerve sheath tumor (MPNST)
- 0704 Meningioma
- 0705 Atypical meningioma
- 0706 Papillary meningioma
- 0707 Anaplastic (malignant) meningioma

08 Vascular tumors
- 0801 Hemangioblastoma
- 0802 Hemangiopericytoma

09 Pituitary tumors
- 0901 Pituitary adenoma
- 0902 Non-functioning pituitary adenoma
- 0903 HGH producing pituitary adenoma
- 0904 PRL producing pituitary adenoma
- 0905 ACTH producing pituitary adenoma
- 0906 Other functioning (mixed) pituitary adenoma
- 0907 Pituitary carcinoma
- 0908 Granular cell tumor (Choristoma)
- 0909 Pituicytoma

10 Cystic lesions
- 1001 Craniopharyngioma
- 1002 Rathke cleft cyst
- 1003 Dermoid cyst
- 1004 Epidermoid cyst
- 1005 Colloid cyst of the third ventricle
- 1006 Other cystic lesion

11 Germ cell tumors
- 1101 Mature teratoma
- 1102 Immature (malignant) teratoma
- 1103 Germinoma
- 1104 Embryonal carcinoma
- 1105 Yolk sac tumor (Endodermal sinus tumor)
- 1106 Choriocarcinoma
- 1107 Mixed germ cell tumor

12 Chordoma and bone tumors
- 1201 Chordoma
- 1202 Malignant chordoma
- 1203 Chondroma
- 1204 Chondrosarcoma
- 1205 Plasmacytoma
- 1206 Tumor of skull and cartrilage (Osteomaなど)

13 Malignant lymphoma, sarcoma, melanoma, lipoma
- 1301 Malignant lymphoma
- 1302 Fibrous histiocytoma
- 1303 Malignant fibrous histiocytoma
- 1304 Other sarcoma (Sarcoma of soft tissue, fibrosarcoma, giant cell sarcoma, osteogenic sarcoma, liposarcomaなど)
- 1305 Malignant melanoma
- 1306 Lipoma

96 Multiple
- 9601 Multiple

97 その他
- 9701 その他

98 Unclassified tumors
- 9801 Unclassified tumors

99 不明
- 9901 不明

1) 1982年3月（1979-83年度分） code変更
2) 1989年1月（1984-99年度分） code変更
3) 2002年1月（2001年度分以降） code変更

記入時の注意

① 施設コード、登録番号コード、ふりがなコード、現住所コード、本籍地コード、出生地コード、職業コードは記入しないで下さい。施設名、氏名、住所などはそのまま文字で記入して下さい。

② 腫瘍局在、組織診断、化学療法剤の項は表1～3の中より該当する項目を選び番号を各コード欄に記入して下さい。

③ 組織診断名は、所定の欄に具体的に記入して下さい。（念のため）

④ 原発性脳腫瘍の場合は、調査用紙 A B C E
転移性脳腫瘍の場合は、調査用紙 A B D E
を完全に記入して下さい。

⑤ 各項目につき、不明の場合はコード欄に数字9を記入して下さい。

表5 調査資料利用依頼のための手続

脳腫瘍全国統計委員会では集積された資料を有意義に利用するために別に統計資料利用審査委員会を設置して，希望者の要請に応じている．この委員会の目的と手続は以下の通りである．

＜統計利用審査委員会規約＞

第1項 目的および対象

本委員会は協力施設に所属する者等が脳腫瘍全国統計の資料を利用して研究ならびに発表を行おうとする場合，その妥当性および学術的貢献度などを考慮して申請者に助言ないしは許可を与えることを目的とする．したがって，統計調査報告書を引用文献として利用する場合にはこの限りではない．

第2項 組 織

(1) 本委員会の委員は暫定的に地区代表委員会の委員によって構成され，委員長は脳腫瘍全国統計委員会の委員長が兼任する．
(2) 委員の任期は2年とする．
(3) 研究利用の承認は審査委員会の過半数の賛成によって行われる．
(4) 委員会の事務局は統計委員会により指定された集計施設内に置くこととする．

第3項 運 営

(1) 統計利用希望者はその目的および調査の方法を書面で事務局を通じ委員会に提出する．委員会は申請に対し，統計利用の適否，学問的価値および利用者の妥当性など総合的に判断し許可ないしは助言を行う．
(2) この研究によって作製された学術論文は投稿前に委員会の承認ないしは助言を受けるものとする．
(4) 必要に応じ経費を調達する．

付則1 論文の発表に際し，著者は脳腫瘍統計委員会の資料に依ったことを明記する．
付則2 本規則は昭和62年10月14日より発効する．

現在この審査を要求する場合の手続用紙**表1-29**は次のような項目が含まれている．この用紙は事務局(国立がんセンター中央病院 脳神経外科内)に申し込むことで郵送される．

り頭蓋内へ浸潤する腫瘍，血管奇形と籠腫的病変などを加えて，頭蓋内腫瘍および腫瘍様病変すべてを網羅している．

第3部 診断と治療

a. 診 断

画像診断では，神経上皮性腫瘍，神経細胞系および混合神経細胞・膠細胞腫瘍，松果体実質腫瘍，胎児性腫瘍，脳神経および脊椎神経腫瘍，髄膜の腫瘍，血管系腫瘍，嚢原発悪性リンパ腫，胚細胞腫瘍，頭蓋骨腫瘍，下垂体腫瘍，家族性腫瘍症候群それぞれについて，典型的な画像を提示して特徴を説明している．画像による腫瘍の種類の推定，他腫瘍との診断上の違いなどが記されていて，標準的診断法として臨床に役立つように工夫されている特集である．

b. 治 療

規約では当時，臨床研究の成果として報告された結果を，そのまま引用しているのみで，報告された研究が，どのくらいの信憑性をもっているかは記されていない．したがって，この後の改訂版においては，EBM(evidence based medicine)の観点から信頼レベルに分けて記載して，指針とする必要がある．

コメントを加えれば，現時点で，化学療法単独での維持療法の有用性を立証する報告はない．放射線治療併用でのニトロソウレア剤による治療では，無作為的多施設臨床試験の結果，有用とされた[2,3]．

1) 悪性神経膠腫に対する治療

既述したごとく，治療の第一は手術である．手術には組織診断を得ることも重要な目的であるが，腫瘍容積を可能なかぎり減量することが

あげられる．このことによって生存期間の延長を期待できる．取扱い規約では，機能障害を来すことなく可及的な摘出を期待している．そのほかに，手術の目的には頭蓋内圧亢進状況，巣症状の軽減があげられる．手術の適応，術前，術後管理，手術法についても取扱い規約の中で一般的な注意点を記している．

［化学療法］

脳腫瘍に対する化学療法を行う場合，他の臓器と違った特性の理解が必須である．血液脳関門の存在，脳における薬剤の到達性，投与経路，腫瘍の血流などの要素がその効果には大きく影響する．

従来，使用された抗がん剤の種類は限られたものであり，アルキル化剤，代謝拮抗薬，植物アルカロイド，白金製剤，procarbazineなどに限られている．これらの通常の使用量を掲載しているが，使用には経験と十分な知識を必要とする．規約には化学療法における実際が綴られているが，リスクを最小にして，しかも効果ある化学療法を実施するための要件などの記述が欠落している．早急に改訂する必要がある．

［放射線治療］

放射線治療基準については，日本放射線腫瘍学会に準拠して記載されているが，照射方法に関しては早急に改訂が必要である．

そのほか，免疫賦活を目的とした，生体応答修飾物質(BMR)による治療については，まだ確実な効果を確認していない．

当時導入された新しい治療については，ガンマナイフ，リニアックナイフの放射線治療について概略を知ることができる．radiosurgeryの原理から，治療の基礎を理解し実際の治療を患者に受けさせようとするときに，医療者として最低限，理解しておくべき知識を説明している．

radiosurgeryは，小さな病巣に対して高線量を1回照射にて治療を完結する方法であるが，^{60}Coの小線源201個を同心円上に並べ，それから放射されるγ線が中心に収束するように設計された精密なコリメータを用いた治療装置である．一方，X線利用のliniac radiosurgeryは頭部を中心に治療台を回転させ，更にライナック治療放射線治療装置の線源を回転することによって立体的に病巣に集中して照射する方法である．更にサイバーナイフの原理の説明も加えてある．radiosurgeryの脳腫瘍の適応については，現在なお，臨床研究の域を出ていないが，数個，大きさ3cm以下の転移性脳腫瘍は適応の確認された腫瘍である．良性腫瘍では，聴神経腫瘍，髄膜腫，下垂体腺腫，頭蓋咽頭腫，血管芽腫，脊索腫，過誤腫などが，手術で摘出困難な場合に治療選択の一つとされる．悪性脳腫瘍については，転移性脳腫瘍については既述したとおりであるが，悪性星細胞腫，膠芽腫などの治療に術後分割外照射後のradiosurgeryを用いて好成績を収めたという報告がある．また，その後のケースコントロール研究で併用群に生存率の延長が得られたとの報告もあるが，文献的レベルは高くない[4,5]．

radiosurgeryによる放射線障害について，急性期障害として嘔気，ふらつき，けいれんなどが経験される．亜急性期障害としては一過性の腫瘍の増大が認められることがあることや，晩期障害の放射線感受性の比較的高い視神経や聴神経障害，あるいは放射線壊死が出現する可能性などがあるため注意が必要である．

おわりに

脳腫瘍取扱い規約は第2版が発刊されて，既に3年経過した．この数年の画像診断の進歩は著しく，正に隔世の感がある．その成果を利用して，手術における機能分野の確認と全摘出率の向上，放射線治療の強度変調放射線治療法(IMRT)など新たな治療手段が実施されている．最近の分子生物学的手法の発展進歩，これらを取り入れた病理診断の必要性などを考えると，2002年版の脳腫瘍取扱い規約も早急に改訂が必要である．特に，治療に関する章では，最近，特段と重要視されているEBMに基づいた記載が必要である．それは，脳腫瘍取扱い規約として世に出す以上，早急に果たさねばならない責務でもある．

文　献

1) 脳腫瘍全国統計委員会，日本病理学会(編)：臨床・病理　脳腫瘍取扱い規約，第1版，1995年，第2版，2002年，金原出版.
2) Green SB, et al: Comparisons of carmustine, procarbazine, and high-dose methylprednisolone as addition to surgery and radiotherapy for the treatment of malignant glioma. Cancer Treat Rep **67**: 121-132, 1983.
3) Fine HA, et al: Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. Cancer **71**: 2585-2597, 1993.
4) Nwokedi EC, et al: Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme. Neurosurgery **50**: 41-47, 2002.
5) Prisco FE, et al: Radiosurgical boost for primary high-grade gliomas. J Neurooncol **57**: 151-160, 2002.

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身体機能解析・補助・代替機器開発研究事業

新たな手術用ロボット装置の開発に関する研究

平成１７年度　総括・分担研究報告書

主任研究者　垣添　忠生

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A Flexible Endoscopic Surgical System: First Report on a Conceptual Design of the System Validated by Experiments

Toshiaki Kobayashi[1], Sean Lemoine[1,2], Akihiko Sugawara[1,2], Takaaki Tsuchida[1], Takuji Gotoda[1], Ichiro Oda[1], Hirohisa Ueda[3] and Tadao Kakizoe[1]

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A Flexible Endoscopic Surgical System: First Report on a Conceptual Design of the System Validated by Experiments

Toshiaki Kobayashi[1], Sean Lemoine[1,2], Akihiko Sugawara[1,2], Takaaki Tsuchida[1], Takuji Gotoda[1], Ichiro Oda[1], Hirohisa Ueda[3] and Tadao Kakizoe[1]

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Background: Surgery is a standard diagnostic and therapeutic procedure. However, its technical difficulty and invasiveness pose problems that are yet to be solved even by current surgical robots. Flexible endoscopes can access regions deep inside the body with less invasiveness than surgical approaches. Conceptually, this ability can be a solution to some of the surgical problems.
Methods: A flexible (surgical) endoscopic surgical system was developed consisting of an outer and two inner endoscopes introduced through two larger working channels of the outer endoscope. The concept of the system as a surgical instrument was assessed by animal experiments.
Results: Gastric mucosa of the swine could be successfully resected using the flexible endoscopic surgical system, thereby showing us the prospect and directions for further development of the system.
Conclusion: The concept of a flexible endoscopic surgical system is considered to offer some solutions for problems in surgery.

Key words: surgical robot – endoscopic surgery – surgery – robotics – endoscope

INTRODUCTION

We recently reported a new concept for endoscopic mucosal resection of gastric cancer with the use of a magnetic anchor. The anchor consisted of microforceps and a magnetic weight in order to grasp, stabilize and pull up the gastric mucosa (1). During the experiments, we thought that the procedure would be easier if one more endoscope was present to hold and stabilize the mucosa instead of the magnetic anchor.

Concerning flexible endoscopes, there are some ultrathin endoscopes that can be inserted into the working channels of standard endoscopes, such as gastrointestinal endoscopes. If the outer endoscope is able to contain larger and multiple working channels, several thin endoscopes could be inserted through the outer endoscope. This would allow for the resecting procedures. Such a system could also be applied to the fields where current surgical robots are targeting.

One of the problems with current surgical robots is inaccessibility to regions located deep inside the body, particularly regions reached through narrow and winding routes, such as the digestive tracts and blood vessels. However, some early gastric cancers can be resected endoscopically with much less invasiveness than surgery. These surgeries cannot be performed by current surgical robot systems because those regions were not originally considered places for the systems to operate.

An experimental flexible endoscopic surgical system was developed to cope with these problems of accessibility, consisting of a flexible outer endoscope with two working channels through which two inner flexible endoscopes could be inserted. These inner endoscopes were designed to have similar functions as flexible gastrointestinal endoscopes allowing for performance of standard endoscopic procedures even when introduced through the outer endoscope.

The uses of the flexible endoscopic system as a surgical instrument, as well as its functionality, were confirmed during gastric mucosal resection of the swine. This is in contrast to the current limitations for surgical robotics in terms of lesion access.

MATERIALS AND METHODS

FLEXIBLE SURGICAL ENDOSCOPE

As shown in Fig. 1, the flexible surgical endoscope consists of an outer flexible endoscope and two inner flexible endoscopes inserted into the working channel of the outer endoscope. The specifications of these endoscopes are listed in Table 1.

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The outer endoscope also has a 2.8 mm working channel and a charge coupled device (CCD) enabling the endoscope to operate in a similar fashion as standard gastrointestinal endoscopes. The endoscopic images are observed on cathode ray tube (CRT) monitors in the same manner as video-endoscopes.

Each of the inner endoscopes has a 2.0 mm working channel allowing accessories such as forceps and an electrocautery tip to be introduced and used. Unlike the outer endoscope, the inner endoscopes have optic fiber bundles for image visualization, instead of a CCD. These endoscopic images are also observed on CRT monitors. However, a video-adaptor, i.e. a small CCD video camera, must be connected onto each eye piece of the inner endoscopes in order to view the image on the monitors.

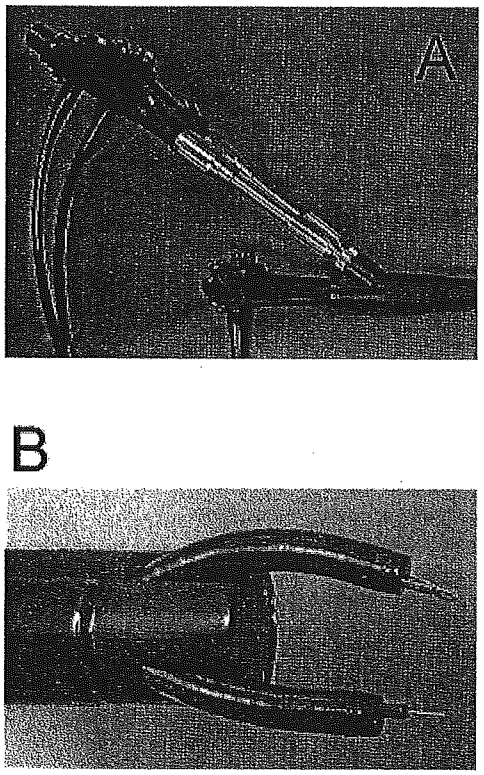

Figure 1. The flexible endoscopic surgical system. (A) The inner endoscope is inserted through a telescopic connecting device, which connects to the opening for the working channel of the outer endoscope near its control section. (B) At the tip of the outer endoscope two inner endoscopes protrude laterally, obtaining a certain distance between the two endoscopes.

Table 1. Specifications of the flexible endoscopic surgical system

	Outer endoscope	Inner endoscope
Total length (mm)	975	1395
Working length (mm)	665	1050
Insertion portion diameter (mm)	20	4.9
Tip bending (degree) (up/down, right/left)	210/120, 120/120	210/120, 120/120
Field of view (degree)	140	120
Depth of field (mm)	4–100	3–50
Channel diameter (mm)	7, 7, 2.8	2

These combined endoscopes are manipulated manually by three physicians together with the help of several assistants. The system, as a whole, operates similar to surgical robotic systems.

PHYSICIANS

Two series of experiments were conducted. The first series was performed by a senior endoscopist and three resident physicians in order to assess the system with consideration to its endoscopic nature. The senior endoscopist was trained within the specialty of internal medicine, whereas one of the resident physicians was in training for internal medicine and the other two were for surgery.

The purpose of the subsequent series was to assess the concept of the flexible surgical endoscope from the viewpoint of surgeons. Consequently, the procedure was performed by two senior endoscopists, one having more than 15 year experience as a surgeon and the other having some surgical training, in addition to two residents who were in training for surgery.

These two series were performed on separate occasions, with none of the physicians performing in both series.

TEST SUBJECT

Three female swine, under intravenous anesthesia, were laid on an examination table in the left lateral position. Within the first experiment, a 35.6 kg and a 34.1 kg swine were used. In the following experiment, a 41.8 kg swine was used. During these experiments, the law for the humane treatment and management of animals was observed.

PROCEDURE

The procedure was similar to standard endoscopic mucosal resection with the exception of one more endoscope for stabilization of the gastric mucosa.

First, an incision was made in the mucosa surrounding the region of stomach intended for resection (2,3). The outer endoscope was inserted through the esophagus into the gastric cavity. Subsequently, using the telescopic connecting devices (Fig. 1), the inner endoscopes were inserted into the working channels of the outer endoscope and introduced into the gastric cavity.

The outer endoscope was placed near the region in which the first incision was made. Thereafter, the resecting procedure was performed using an electrosurgical knife through one of the working channels of the inner endoscopes, whereas the other contained forceps. Within the procedure, the operator decided which side of the working channels would use the electrosurgical knife.

These procedures were observed on three CRT monitors, each of which was connected to its endoscopic counter part.

The resecting procedures were performed on the anterior wall of the gastric angle, the anterior wall of the middle gastric body and the greater curvature of the middle gastric body in the

first series for the assessment of endoscopic features. Within the following series, the resecting procedures were performed on two regions adjacent to the greater curvature of the lower gastric body.

RESULTS

Concerning insertion of the outer endoscope through the esophagus into the gastric cavity, some difficulties were encountered owing to the large diameter of the outer endoscope and the relatively small size of the swine in both experimental series. However, the outer endoscope was introduced into the gastric cavity.

As for insertion of the inner endoscopes through the working channels of the outer endoscope, there were no difficulties experienced, even when the outer endoscope was bent due to insertion through the esophagus. Access to regions of the gastric wall was limited to the greater curvature due to the rigidity of the outer endoscope.

Maneuverability of the flexible endoscopic surgery system was satisfactory regarding the experiments were the first experiences for the physicians involved, despite some problems to solve.

The images from the outer endoscope were similar to those of standard gastrointestinal video-endoscopes due to the CCD system used in the outer endoscope. However, the images from the inner endoscopes were inferior to those of the outer endoscope. This inferiority was attributed to the limited number of optical fibers within the inner endoscope and deterioration of the image caused by conversion from optical images to electrical images through the use of a video-adapter. Consequently, during most of the procedure, endoscopic images were mainly observed using the monitor for the outer endoscope.

Some differences in use of the inner endoscopes for the resecting procedures between the first series and the second series were noticed. In the first series, the physicians appeared to have difficulties in some of the procedures such as accessing the mucosa, stabilization of the mucosal flap and resection procedures. These procedures were considered standard techniques for actual surgery, which means surgical experiences are required even to maneuver the flexible endoscopic surgical system.

Within the second series conducted by endoscopists with surgical experience, the resecting procedures were satisfactory, despite the fact this was their first experience using the system (Fig. 2). Through cooperation between the operator and assistants using verbal commands, manipulation of the inner endoscopes and the outer endoscope could be achieved. The functions of the inner endoscopes could be modified by changing the instruments inserted into the working channels. The flexible nature of the inner endoscopes allowed additional functions such as stabilization of the gastric wall by the longitudinal flank of the endoscope, as shown in Fig. 2C.

Within all the experiments, resecting procedures were completed without any complications such as perforation of the gastric wall. Consequently, five mucosal pieces, with sizes of

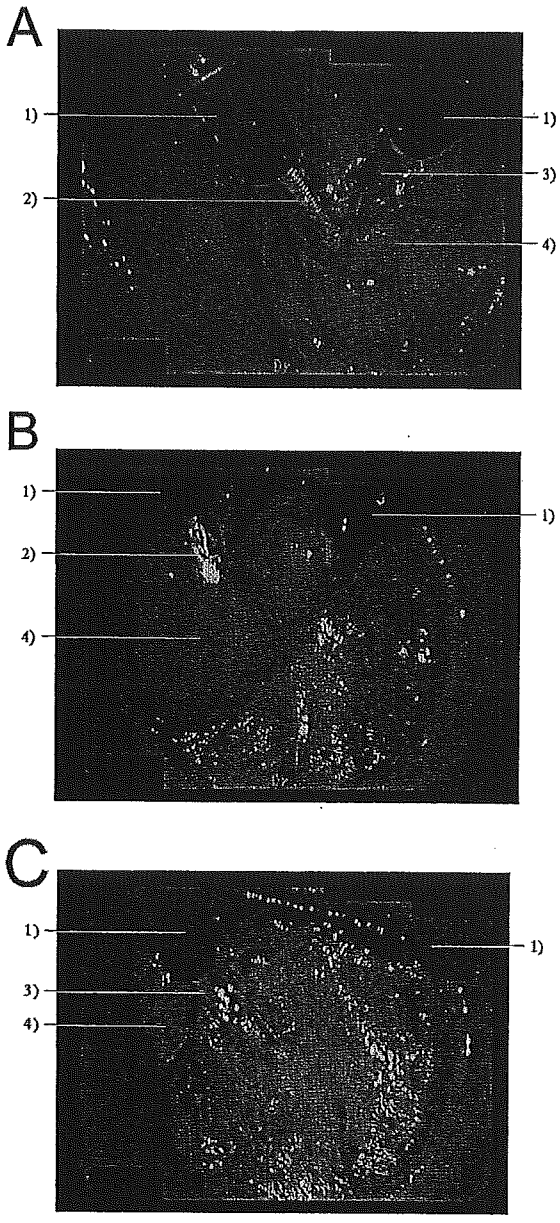

Figure 2. Images of the resecting procedures. (1) Inner endoscope, (2) forceps, (3) electrosurgical knife and (4) mucosal flap. (A) The right inner endoscope, with an electrosurgical knife introduced through its working channel, was maneuvered by the operator. The left inner endoscope, with forceps, was maneuvered by an assistant. (B) The tip of the right inner endoscope is holding up the mucosal flap in order to assist the forceps of the left inner endoscope to grasp the mucosal flap. (C) The right inner endoscope is pulling up the mucosal flap using forceps concealed in this image. In addition, using the flexibility of the endoscope, the gastric wall is stabilized by the longitudinal flank of the inner endoscope.

2.8×1.6 cm^2, 2.8×2.7 cm^2 and 2.6×2.0 cm^2 in the first series, and 3.2×2.7 cm^2 and 4.0×3.4 cm^2 in the second series were each resected in a single piece.

DISCUSSION

Surgical procedures are good options for diagnosis and treatment providing several advantages over non-surgical

approaches, especially in cases of malignant diseases. Although surgery is well accepted as a standard procedure in medicine there are still some problems left unsettled.

The technical difficulty of surgery is a common problem particularly for trainees, but even for experienced surgeons who have some technical limitations. Surgical procedures are difficult for regions deep in the body because the visual field for surgeons is limited, the number of surgical instruments which can be introduced is limited and the movements of these instruments are limited. One of the exemplary regions of this problem is the pelvic cavity, which includes surgery of rectal and prostate cancers.

Invasiveness is an inherent drawback to surgery, discouraging patients to undergo surgical treatment even when it is appropriate. It is true that surgery should be avoided when there are other less invasive alternatives.

Surgical robots such as the da Vinci system and the Zeus system are highly advanced medical instruments allowing for fine movements when appropriately manipulated by surgical experts. These systems are expected to solve some surgical problems such as invasiveness and the difficulty (4–8). Thus far, the systems have been able to solve some of the problems associated with surgery.

As for the invasiveness of surgery, endoscopic surgeries such as laparoscopy can be performed with robotic systems, utilizing smaller incisions than those of other standard open surgical approaches. The precise movements of surgeons are facilitated by robotic systems. However, laparoscopic procedures can be performed even without the robotic systems with the same amount of invasiveness.

Current robotic systems may also pose problems (4–8), such as the limited number of surgeons who can manipulate the system, which is usually one. Additional training for the specific manipulating methods of the systems is another problem, as well as introduction costs. Consequently, it is currently not clear what the benefits of these robotic systems are, especially when assessed from the patient side. Moreover, problems which even surgical experts suffer from have not been solved.

Flexible endoscopes have been developed to cope with the problems of accessing regions through narrow tracts such as the esophagus and the tracheobronchial tree. Even in these regions flexible endoscopes can perform surgical procedures similar to standard surgery. Therefore, endoscopes are naturally considered functional even in other cavities such as the abdomen and pelvic cavities.

It would be easier and more functional to perform an operation using several endoscopic instruments introduced through the end of one endoscope, rather than conducting resection using only one endoscopic instrument introduced into one endoscope, as done in standard endoscopic procedures. The simplest model for this concept is the flexible endoscopic surgical system we developed and examined within these trials.

We assumed that there would be several problems with the flexible endoscopic surgical system when used clinically as it is merely a conceptual model to confirm its feasibility of use. However, despite those problems, the system was able to perform surgical resection. In addition, the problems encountered within the first experiment were inherent in all technical procedures.

Of interest, these problems showed us that, when indicated for resecting procedures, the flexible endoscopic surgical system is easier to manipulate by surgeons and not by endoscopists despite its endoscopic appearances.

The images of the inner endoscopes were not satisfactory because a CCD was not used in these endoscopes. Consequently, resecting procedures were monitored by images from the outer endoscope which contained the CCD. In this situation, the operator had to control the inner endoscope via observations on the monitor of the outer endoscope. This is different from standard endoscopic procedures in which images are observed on the monitor of the endoscope which the operator is controlling.

In general, it is not easy for trainees to understand appropriate surgical procedures, i.e. where to cut and where to stabilize. Verbal communication during operation is important to facilitate appropriate assistance, which was not adequately utilized in the first series. These issues are to be learned through years of experience and cannot be achieved instantly.

As mentioned above, the difference between the two experiments may reveal that for these flexible endoscopes, surgical experience is an important factor, when the system is indicated for surgical procedures. The limitation of the inner endoscopes, not having CCD may have emphasized this issue. Consequently, the next system is to consist of two inner endoscopes with a CCD for each. This would allow the operators to control the inner endoscopes in such a manner as used for standard gastrointestinal endoscopic procedures.

Furthermore, we think that there should be two styles of design for future flexible endoscopic surgical systems; one with increased surgical maneuverability designed particularly for the techniques of surgeons, the other preserving flexible endoscopic maneuverability for endoscopists. Although it has not been decided yet which design is more appropriate for a future surgical system, endoscopists may be able to become accustomed to the flexible endoscopic surgical system with surgical maneuverability when the system is popularized.

In addition to the merits mentioned above, flexible endoscopic materials can theoretically be made compatible with X-ray systems such as fluoroscopes and computed tomography (CT) systems, exemplified by such procedures as X-ray guided bronchoscopy. In the future, the materials used for flexible endoscopic constructions are expected to acquire compatibility with the magnetic fields of magnetic resonance imaging (MRI) systems.

As mentioned before, limitations in visualization pose surgical problems even for experienced surgeons. This may only partially be solved by the subjective ability of surgeons to presume the identity of invisible objects using their tactile sense and their intuition. Actually, the compatibility with imaging systems was one of the important requirements for the design of the flexible endoscopic surgical system,

allowing visibility of anatomical information invisible to the surgeon's eyes.

In order to make one more step towards the future for less invasive and more effective medical treatments, we believe that future surgical systems should acquire the accessibility to narrow regions located deep inside the body together with the compatibility of imaging systems such as CT and MRI. Thus, from the flexible nature and structural characteristics of a non-jointed, smooth outer sheath, we selected the flexible endoscope as the conceptual basis of development for our system. It is the combination of these and the aforementioned aspects that allows for minimization in invasiveness, through the use of pre-existing natural structures and tracts for lesion access to deep regions, and with the presence of multiple interchangeable inner-scopes, an increase in distal tip functionality at the surgical site. Although there are several factors still to discuss and develop, the concept of the flexible endoscopic surgical system is considered an appropriate development for a future surgical robotic system with this current system being a successful step towards that furture.

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References

1. Kobayashi T, Gotohda T, Tamakawa K, Ueda H, Kakizoe T. Magnetic anchor for more effective endoscopic mucosal resection. *Jpn J clin Oncol* 2004;34:118–23.
2. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;3:219–25.
3. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D, et al. A new endoscopic mucosal resection procedure using an insulation-tipped electrosurgical knife for rectal flat lesions: report of two cases. *Gastrointest Endosc* 1999;50:560–3.
4. D'Anniballe A, Fiscon V, Trevisan P, Pozzobon M, Gianfreda V, Sovernigo G, et al. The da Vinci robot in right adrenalectomy: considerations on technique. *Surg Laparosc Endosc Percutan Tech* 2004;14:38–41.
5. Schiff J, Li PS, Goldstein M. Robotic microsurgical vasovasostomy and vasoepididymostomy: a prospective randomized study in a rat model. *J Urol* 2004;171:1720–5.
6. Ruurda JP, Broeders IA, Simmermacher RP, Borel Rinkes IH, Van Vroonhoven TJ, Theo JM. Feasibility of robot-assisted laparoscopic surgery: an evaluation of 35 robot-assisted laparoscopic cholesystectomies. *Surg Laparosc Endosc Percutan Tech* 2002;12:41–5.
7. Falk V, Diegler A, Walther T, Autschbach R, Mohr FW. Developments in robotic cardiac surgery. *Curr Opin Cardiol* 2000;15:378–87.
8. Hollands CM, Dixey LN. Applications of robotic surgery in pediatric patients. *Surg Laparosc Endosc Percutan Tech* 2002;12:71–6.

^{11}C-Acetate Positron Emission Tomography Imaging for Lung Adenocarcinoma 1 to 3 cm in Size With Ground-Glass Opacity Images on Computed Tomography

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Background. Positron-emission tomography (PET) with ^{18}F-fluorodeoxy-glucose (FDG) frequently gives false-negative results for well-differentiated adenocarcinomas of the lung, especially, those with ground-glass opacity images. Recently, PET with ^{11}C-acetate (AC) has been reported to detect slow-growing tumors that have failed to be identified by FDG-PET, such as well-differentiated hepatocellular carcinomas and prostate cancers. To determine the usefulness of AC-PET in detecting well-differentiated adenocarcinomas of the lung, we performed both AC-PET and FDG-PET on pulmonary nodules with ground-glass opacity images on computed tomography (CT).

Methods. Fifty-four pulmonary nodules 1 to 3 cm in size, which showed ground-glass opacity images over their whole or peripheral area on CT, were examined by both AC-PET and FDG-PET.

Results. Thirty-seven nodules were adenocarcinoma of the lung, while 17 were inflammatory. Of the 37 adenocarcinomas, 19 (51%) were positively identified by AC-PET and 14 (38%) by FDG-PET. Of the 23 adenocarcinomas which were not identified by FDG-PET, 8 (35%) were positively identified by AC-PET; all were well-differentiated adenocarcinomas. Of the 17 inflammatory nodules, 8 were chronic and 9 were acute ones. While none of the 8 chronic inflammatory nodules were identified by either technique, 9 acute ones showed a variety of the results with AC- and FDG-PET.

Conclusions. AC-PET detected approximately one third of well-differentiated adenocarcinomas of the lung which were not identified by FDG-PET. AC-PET could be useful to diagnose pulmonary nodules with ground-glass opacity images which were not identified by FDG-PET.

(Ann Thorac Surg 2005;80:2020–5)

Recent advances in positron emission tomography (PET) with ^{18}F-fluorodeoxy-glucose (FDG) have contributed significantly to the ability to differentiate between benign and malignant pulmonary nodules. However, FDG-PET sometimes gives false-negative results, particularly for low-grade malignant tumors, such as bronchioloalveolar carcinoma and carcinoid, owing to their low glucose metabolism [1–4]. We previously reported that while FDG-PET did not produce false-negative results for squamous cell, large cell, or small cell carcinomas, 60% of well-differentiated adenocarcinomas 1 to 3 cm in size failed to be identified by FDG-PET [2]. Therefore, other PET tracers should be used for imaging suspected well-differentiated adenocarcinoma of the lung.

Radio-labeled acetate has long been used for the measuring lipid and cholesterol synthesis in biochemistry [5, 6]. Clinically, ^{11}C-acetate (AC) has been widely used as a PET tracer for evaluating myocardial oxidative metabolism [7, 8]. Recently, AC has also been reported to be a useful PET tracer in detecting slow-growing tumors which have failed to be identified by FDG-PET, such as well-differentiated hepatocellular carcinomas and prostate cancers [9, 10]. Higashi and colleagues [11] have also reported a patient with bronchioloalveolar carcinoma that was positively identified by AC-PET but not by FDG-PET. In the present study, to evaluate the effectiveness of AC-PET in detecting well-differentiated adenocarcinomas of the lung, we performed both AC-PET and FDG-PET on 54 small pulmonary nodules suspected of being adenocarcinomas based on computed tomography (CT) findings.

Material and Methods

Patients and Tumor Tissues

The pulmonary nodules of 1 to 3 cm in size, which were suspected of being well-differentiated adenocarcinoma of

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Table 1. FDG-PET and Acetate-PET Findings in Adenocarcinomas and Inflammatory Nodules

Procedures	Adenocarcinoma	Inflammation	Total
FDG-PET			
Positive	14	5	19
Negative	23	12	35
Acetate-PET			
Positive	19	5	24
Negative	18	12	30
Total	37	17	54

FDG = fluorodeoxyglucose; PET = positron emission tomography.

the lung owing to the presence of ground-glass opacity images over their whole or peripheral area on CT [12–15], were performed of both FDG-PET and AC-PET to evaluate the usefulness of AC-PET. The study was approved by the Ethical Committee of Saiseikai Central Hospital in December 2003. The reason why we excluded the nodules less than 1 cm was that the spatial resolution of the current generation of PET scanners is 0.7 to 0.8 cm, making it difficult to image pulmonary nodules of less than 1 cm [2]. Between January 2004 and April 2005, 54 pulmonary nodules with ground-glass opacity images in 50 patients were enrolled. Three patients have a few nodules, which were located in the different lobes of each other in each patient. During the same period, 85 pulmonary nodules up to 3 cm with solid images in 82 patients were examined only by FDG-PET. Of the 54 nodules, 37 were adenocarcinoma of the lung and 17 were inflammatory. The diagnosis was confirmed histologically after surgical resection in all 37 of the adenocarcinomas, 8 of the nodules with chronic inflammation, 2 with active tuberculosis, and 1 with active nonspecific inflammation. The remaining 6 nodules were clinically diagnosed as acute inflammatory nodules because of natural reduction on follow-up CT. The lung adenocarcinomas were classified as well-, moderately, and poorly differentiated. The percentage area showing ground-glass opacity on CT was graded as more than 90%, 30% to 90%, or less than 30%.

Positron Emission Tomography Scanning

Positron emission tomography scanning was performed at Nishidai Clinic, Tokyo, Japan. Patients were instructed to fast for at least 4 hours before PET scanning. After a written informed consent had been obtained, AC- and FDG-PET were performed on the same day within 2 weeks of CT scanning. The AC-PET was performed before FDG-PET. The dose of ^{11}C-AC administered was 125 μCi/kg (4.6 MBq/kg). The PET imaging was performed approximately 10 minutes after the administration of ^{11}C-AC using a PosiCam.HZL mPower scanner (Positron, Houston, Texas).

The ^{18}F-FDG was administered approximately 30 minutes after AC-PET imaging was completed, ensuring that a gap of at least 120 minutes was left between the administration of ^{11}C-AC and that of ^{18}F-FDG, namely, more than 6 decay half-lives of ^{11}C (20 minutes). The dose of ^{18}F-FDG was 125 μCi/kg (4.6 MBq/kg) for nondiabetic patients and 150 μCi/kg (5.6 MBq/kg) for diabetic patients, as reported previously [2–4]. The FDG-PET imaging was performed approximately 45 minutes after the administration of FDG.

No attenuation-corrected emission scans were initially obtained in two-dimensional, high-sensitivity mode for 4 minutes per bed position, and taken from the vertical skull through to the mid thighs. Immediately thereafter, a two-bed–position, attenuation-corrected examination was performed, with 6 minutes for the emission sequence and 6 minutes for the transmission sequence at each bed position. The images were reconstructed by the emission scans and the preinjection transmission scans in a 128 × 128 matrix by using ordered subset expectation maximization corresponding to a pixel size of 4 × 4 mm, with section spacing of 2.56 mm.

Positron Emission Tomography Data Analysis

Images were reviewed by two observers (N.K. and K.U.) who were unaware of the patients' clinical details. A consensus was reached if there was any difference of opinion. PET images were evaluated by visual assessment, namely, lesions showing similar or greater AC or FDG uptake than the mediastinal blood pool were diagnosed as positive for tumor. The AC and FDG uptakes of the positive nodules were measured on the basis of the contrast ratio, as reported previously [2–4]. Briefly, regions of interest were chosen in the nodules and contralateral lung. The highest standard uptake value in the tumor regions of interest (T) and the contralateral normal lung regions of interest (N) were then measured and the contrast ratio was calculated as $(T - N)/(T + N)$ in each nodule as an index of AC and FDG uptake.

Evaluation by Receiver Operating Characteristics Curve

Usefulness of detecting well-differentiated adenocarcinoma by FDG- and AC-PET was evaluated by receiver operating characteristics (ROC) curves. The contrast ratio values of 27 well-differentiated adenocarcinomas and 27 other lesions (10 moderately or poorly differentiated adenocarcinomas and 17 inflammatory nodules) of FDG-PET and AC-PET were compared on ROC curve by using SPSS software (SPSS, Chicago, Illinois).

Statistical Analysis

Positive PET findings with malignancy and benign nodules were defined as true positive (TP) and false positive

Table 2. Summary of Results of FDG-PET and Acetate-PET

Variables	FDG-PET	Acetate-PET
Sensitivity	0.38	0.51
Specificity	0.71	0.71
Positive predictive value	0.74	0.79
Negative predictive value	0.34	0.40
Accuracy	0.48	0.57

FDG = fluorodeoxyglucose; PET = positron emission tomography.

Table 3. Correlation Between Histologic Grade of Differentiation of Adenocarcinomas and PET Findings

PET Imaging Findings	Histologic Differentiation WD	MD	PD	Total
Acetate positive, FDG positive	5	5	1	11
Acetate positive, FDG negative	8	0	0	8
Acetate negative, FDG positive	0	3	0	3
Acetate negative, FDG negative	14	1	0	15
Total	27	9	1	37

FDG = fluorodeoxyglucose; MD = moderately differentiated; PD = poorly differentiated; PET = positron emission tomography; WD = well differentiated.

(FP), respectively. Negative PET findings with malignancy and benign nodules defined as false negative (FN) and true negative (TN), respectively. The diagnostic values of PET scanning were assessed by calculating sensitivity and specificity. Sensitivity was calculated as TP/TP + FN, specificity as TN/TN + FP, positive predictive value as TP/TP + FP, negative predictive value as TN/FN + TN, and accuracy as TP + TN/total. All data were analyzed for significance by using the two-tailed Student *t* test. Values of *p* less than 0.05 were accepted as significance. All values in the text and tables are given as mean ± SD.

Results

Table 1 shows the PET findings of adenocarcinomas and inflammatory nodules. Mean sizes were 2.1 ± 0.7 cm for the 37 adenocarcinomas and 1.7 ± 0.8 cm for the 17 inflammatory nodules; this difference was not significant. Of the 37 adenocarcinomas, 19 were positively identified by AC-PET and 14 by FDG-PET. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were not significant different between the FDG-PET and AC-PET (Table 2). Eleven adenocarcinomas were positively identified by both AC- and FDG-PET, 8 were positively identified by AC-PET but not by FDG-PET, 3 were positively identified by FDG-PET but not by AC-PET, and the remaining 15 failed to be identified by either technique (Table 3). Of the 17 inflammatory nodules, 3 were positively identified by both AC-PET and FDG-PET, 2 were positively identified by AC-PET but not by FDG-PET, 2 were positively identified by FDG-PET but not by AC-PET, and the remaining 10 were negative by either technique (Table 4).

Table 4. FDG-PET and Acetate-PET Findings in Inflammatory Nodules

PET Imaging Findings	Chronic Inflammation	Acute Inflammation	Total
Acetate positive, FDG positive	0	3	3
Acetate positive, FDG negative	0	2	2
Acetate negative, FDG positive	0	2	2
Acetate negative, FDG negative	8	2	10
Total	8	9	17

FDG = fluorodeoxyglucose; PET = positron emission tomography.

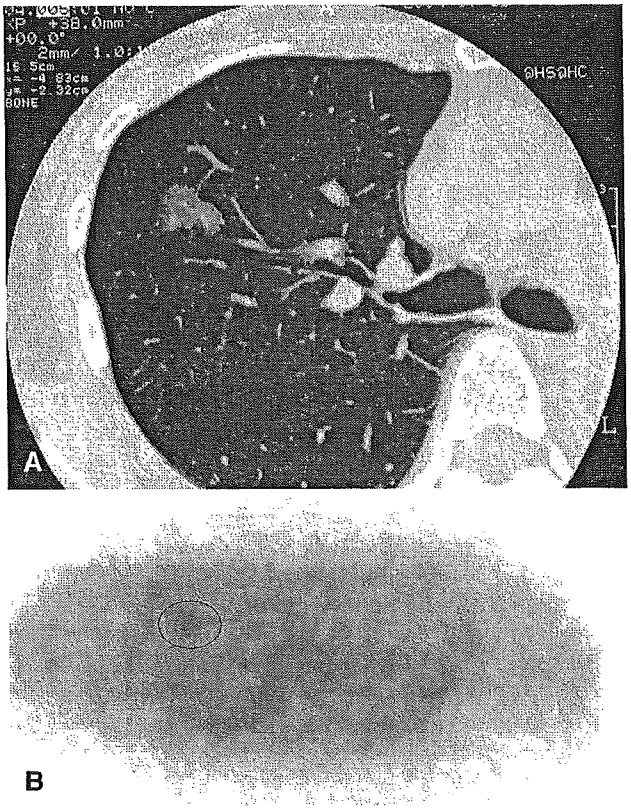

Fig 1. (A) Computed tomography findings of well-differentiated adenocarcinoma with ground-glass opacity findings. (B) Acetate-positron emission tomography showed positive at the tumor (encircled).

Table 3 also shows the correlation between the histologic grade of differentiation and the PET findings in the 37 adenocarcinomas. The histologic grades were well differentiated in 27 adenocarcinomas, moderately differentiated in 9, and poorly differentiated in 1. Of the 23 adenocarcinomas which failed to be identified by FDG-PET, 8 (36%) were positively identified by AC-PET, all of which were well-differentiated ones (Fig 1), whereas none of moderately or poorly differentiated adenocarcinomas were positive with AC-PET and negative with FDG-PET. Well-differentiated adenocarcinomas were more frequently positive with AC-PET and negative with FDG-PET than moderately or poorly differentiated adenocarcinomas ($p = 0.051$). Of the 15 adenocarcinomas which failed to be identified by either technique, 14 (93%) were well-differentiated ones and the remaining 1 (7%) was moderately differentiated. Well-differentiated ade-

Table 5. Correlation Between Percent of GGO Area and Histologic Grade of Differentiation of Adenocarcinomas

	Histologic Differentiation			
Percent of GGO Area	WD	MD	PD	Total
≥90%	19[a]	1	0	20
30%–90%	5	0	0	5
<30%	3	8	1	12
Total	27	9	1	37

[a] Well-differentiated adenocarcinoma showed more than 90% of GGO area more frequently than moderately or poorly differentiated ($p < 0.01$).

GGO = ground-glass opacity; MD = moderately differentiated; PD = poorly differentiated; WD = well-differentiated.

nocarcinomas were more frequently negative with both AC-PET and FDG-PET than moderately or poorly differentiated adenocarcinomas ($p = 0.03$).

Both AC and FDG uptake of these adenocarcinomas were usually weak by visual assessment. In the 19 adenocarcinomas detected by AC-PET, the mean values of contrast ratio and standard uptake value were 0.3 ± 0.1 (range, 0.25 to 0.42) and 2.3 ± 0.7 (range, 1.1 to 3.4), respectively. In the 13 adenocarcinomas detected by FDG-PET, the mean values of contrast ratio and standard uptake value was 0.4 ± 0.2 (range, 0.25 to 0.8) and 3.2 ± 1.8 (range, 1.0 to 7.4), respectively.

Table 4 shows the FDG- and AC-PET findings in the 17 inflammatory nodules. While none of the 8 nodules with chronic inflammation were detected by either AC- or FDG-PET, 9 nodules with acute inflammation showed a variety of the results.

Table 5 shows the correlation between the percentage area of ground-glass opacity and the histologic grade of differentiation in the 37 adenocarcinomas. Ground-glass opacity was apparent over more than 90% of the tumor area in 20 adenocarcinomas, 30% to 90% in 5, and less than 30% in the remaining 12. Well-differentiated adenocarcinomas showed more than 90% of ground-glass opacity area more frequently than moderately or poorly differentiated ones ($p < 0.01$).

Figure 2 shows the ROC curves of FDG- and AC-PET for detecting 27 well-differentiated adenocarcinoma in the 54 nodules with ground-glass opacity images. The ROC curve of AC-PET was superior to that of FDG-PET. The areas under the curve were 0.573 in AC-PET and 0.318 in FDG-PET. The 95% confidential limits showed little overlap between the AC-PET (range, 0.414 to 0.733) and FDG-PET (range, 0.174 to 0.461).

The tumor size did not show any correlation not only with contrast ratio values and standard uptake value of FDG-PET ($r = 0.31$ and $r = 0.38$, respectively) but also with contrast ratio values and standard uptake value of AC-PET ($r = 0.1$ and $r = 0.08$, respectively).

Comment

While a criterion for diagnosing pulmonary malignancy with FDG-PET has frequently used the standard uptake value with a cut-off value of 2.5 [16], it has been reported that several factors can affect the standard uptake value, such as the body size [17], blood glucose concentration [18], time after injection [19], and lesion size [20]. Actually, the mean standard uptake value of malignant pulmonary nodules has been reported to be various, ranging from 5.5 to 10.1 [21–24]. We previously compared the results of standard uptake value, contrast ratio with contralateral lung, and contrast ratio with cerebellum for diagnosing pulmonary nodules with faintly positive FDG uptake by visual estimation, and reported the cut-off value of 0.4 by the contrast ratio with contralateral lung to show the highest sensitivity, while the standard uptake value of 2.5 showing the sensitivity of 0 [25]. We therefore used the contrast ratio with contralateral lung in the present study. Both AC and FDG uptake in the present adenocarcinomas were usually weak. The mean contrast ratio values of AC and FDG uptake of the positive adenocarcinomas in the present study were 0.3 ± 0.1 and 0.4 ± 0.2, respectively, both of which were near the cut-off value for diagnosing lung cancers. It could be due to that most of adenocarcinomas in the present study were well-differentiated ones, which were known to show weak or negative PET imaging frequently [1–4].

Well-differentiated adenocarcinomas of the lung have been reported to show a high false-negative identification rate on FDG-PET because of their low glucose metabolism and low tumor cell density [1–4]. These observations were confirmed by the present study in which 22 of the 27 well-differentiated adenocarcinomas (81%) failed to be detected by FDG-PET (as shown in Table 3). While ^{11}C-AC has been reported to be a useful PET tracer for slow-growing tumors, such as well-

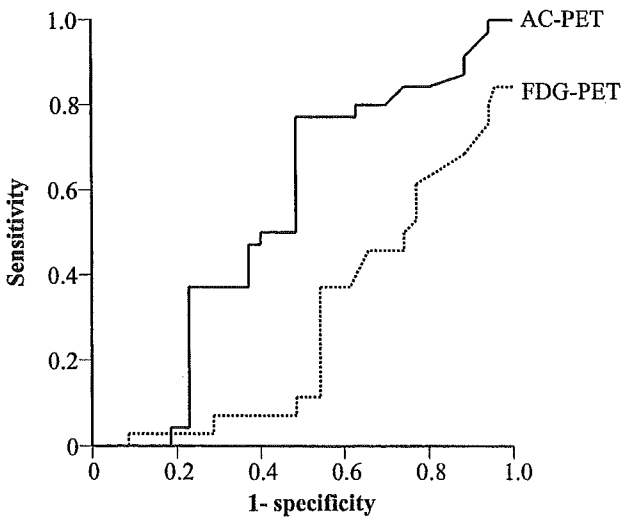

Fig 2. The receiver operating characteristic curve of ^{11}C-acetate positron emission tomography (AC-PET; solid line) *and ^{18}F-fluorodeoxy-glucose PET* (FDG-PET; dotted line) *for detecting 27 well-differentiated adenocarcinoma in the 54 nodules with ground-glass opacity images. The areas under the curve were 0.573 in AC-PET and 0.318 in FDG-PET. The 95% confidence limits were from 0.414 to 0.733 in AC-PET and from 0.174 to 0.461 in FDG-PET.*

differentiated hepatocellular carcinomas and prostate cancers [9, 10], the present study showed that there was no significant difference in sensitivity between AC-PET and FDG-PET with respect to adenocarcinomas of the lung. However, of the 23 adenocarcinomas not identified by FDG-PET, 8 (35%) were positively identified by AC-PET; all of these were well-differentiated adenocarcinomas. Therefore, AC-PET was able to detect approximately one third of well-differentiated adenocarcinomas that were not detected by FDG-PET.

Ho and Yeung [9] reported that while well-differentiated hepatocellular carcinomas had a high AC uptake and a low FDG uptake, poorly differentiated ones had a low AC uptake and a high FDG uptake. Thus, hepatocellular carcinomas could be detected with 100% sensitivity by using both AC-PET and FDG-PET [9]. In contrast, Oyama and colleagues [10] reported that all 22 of their patients' prostate cancers were positively identified by AC-PET. However, the present study showed that 15 of the 37 lung adenocarcinomas (41%) could not be detected by either AC- or FDG-PET, and 14 of these 15 (93%) were well-differentiated adenocarcinomas. There are several reasons why well-differentiated adenocarcinomas of the lung may frequently go undetected by both AC-PET and FDG-PET. Firstly, well-differentiated lung adenocarcinomas may accumulate AC and FDG to only a limited extent due to lower metabolism of these substances compared with hepatocellular carcinomas and prostate cancers. Secondly, because well-differentiated adenocarcinomas frequently show ground-glass opacity images over a large area (as shown in Table 5), the density of the tumor cells is low compared with moderately or poorly differentiated ones, and that could be false-negative results of PET imaging, regardless of the degree of tracer uptake by the tumor cells. Thirdly, because all the adenocarcinomas in the present study were less than 3 cm in size, their AC or FDG uptake may have been below the limit of detection compared with larger ones.

The tracer ^{11}C-acetate has been widely used as a PET tracer for the evaluation of myocardial oxidative mechanism [7, 8]. The mechanism underlying AC uptake in tumor cells, although as yet unknown, is thought to be different from that involved in myocardial uptake. In an in vitro study using several cancer cell lines, Yoshimoto and colleagues [25] suggested that AC is preferentially metabolized to membrane lipids in tumor cells and that AC uptake by tumor cells reflects their growth activity as measured by enhanced membrane synthesis. On the other hand, Ho and Yeung [9] reported that the AC uptake of hepatocellular carcinomas showed negative correlation with their malignant potential. In the present study, while some of the well-differentiated adenocarcinomas were positively identified by AC-PET but not by FDG-PET, some of the well-, moderately, and poorly differentiated adenocarcinomas were positively identified by both technique. Based on our present data, we hypothesize the following: (1) Whereas FDG may be accumulated by aggressive lung cancer cells [26, 27], AC might be accumulated by slow-growing ones, as in the case with hepatocellular carcinomas and prostate cancers [9, 10]. (2) Whereas most lung cancers can accumulate both AC and FDG because of containing tumor cells having different growth activity, some well-differentiated adenocarcinomas, which only contain less aggressive tumor cells, may be able to accumulate only AC.

Both chronic and acute inflammatory pulmonary nodules are well known to show ground-glass opacity images on occasions. In the present study, while all of the chronic inflammatory nodules were negative by both AC-PET and FDG-PET, the acute ones showed a variety of the results. That could be because the acute inflammatory nodules have a variety of percentages of inflammatory cells having different grades of metabolic activity, such as leukocytes, lymphocytes, and macrophages, according to the phase of inflammation.

Positron emission tomography with AC could be useful for some of pulmonary nodules with ground-glass opacity images that could not be identified by FDG-PET. In the present study, most of the nodules studied were well-differentiated adenocarcinomas because the nodules were selected on the basis of the presence of ground-glass opacity images. Therefore, AC-PET needs to be studied in other histologic types of lung cancer to clarify its usefulness in detecting lung cancers in general.

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References

1. Higashi K, Ueda Y, Seki H, et al. Fluorine-18-FDG PET imaging is negative in bronchioloalveolar carcinoma. J Nucl Med 1998;39:1016–20.
2. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. Lung Cancer 2004;45:19–27.
3. Nomori H, Watanabe K, Ohtsuka T, et al. Fluorine 18-tagged fluorodeoxyglucose positron emission tomographic scanning to predict lymph node metastasis, invasiveness, or both, in clinical T1N0M0 lung adenocarcinoma. J Thorac Cardiovasc Surg 2004;128:396–401.
4. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K. Visual and semiquantitative analyses from F-18 fluorodeoxyglucose (FDG) PET scanning in pulmonary nodules 1 to 3 cm in size. Ann Thorac Surg 2005;79:984–8.
5. Howard BV. Acetate as a carbon source for lipid synthesis in cultured cells. Biochim Biophys Acta 1977;488:145–51.
6. Long VJW. Incorporation of 1-11C-acetate into the lipids of isolated epidermal cells. Br J Dermatol 1976;94:243–52.
7. Brown M, Marshall DR, Sobel BE, Bergmann SR. Delineation of myocardial oxygen utilization with carbon-11-labeled acetate. Circulation 1987;76:687–96.
8. Lear JL. Relationship between myocardial clearance rates of carbon-11-acetate-deribed radiolabel and oxidative metabolism: physiologic basis and clinical significance. J Nucl Med 1991;32:1957–60.
9. Ho C, Yeung DW. C-11 acetate PET imaging in hepatocellular carcinoma and other liver masses. J Nucl Med 2003;44:213–21.
10. Oyama N, Akino H, Kanamaru H, et al. 11C-acetate PET imaging of prostate cancer. J Nucl Med 2002;43:181–6.

11. Higashi K, Ueda Y, Matsunari I, et al. 11C-acetate PET imaging of lung cancer: comparison with 18F-FDG and 99mTc-MIBI SPET. Eur J Nucl Med Mol Imaging 2004; 31:13–21.
12. Aoki T, Nakata H, Watanabe H, et al. Evolution of peripheral lung adenocarcinomas: CT findings correlated with histology and tumor doubling time. Am J Roentgenol 2000;174: 763–8.
13. Nakata M, Saeki H, Takata I, et al. Focal ground-glass opacity detected by low-dose helical CT. Chest 2002;121: 1464–7.
14. Nomori H, Ohtsuka T, Naruke T, Suemasu K. Differentiating between atypical adenomatous hyperplasia and bronchioloalveolar carcinoma using the computed tomography number histogram. Ann Thorac Surg 2003;76:867–71.
15. Nomori H, Ohtsuka T, Naruke T, Suemasu K. Histogram analysis of computed tomography numbers of clinical T1N0M0 lung adenocarcinoma, with special reference to lymph node metastasis and tumor invasiveness. J Thorac Cardiovasc Surg 2003;126:1584–9.
16. Langen KJ, Braun U, Rota Kops E, et al. The influence of plasma glucose levels of fluorine-18-fluorodeoxyglucose uptake in bronchial carcinomas. J Nucl Med 1993;34:355–9.
17. Kim CK, Gupta NC, Chandramouli B, Alavi A. Standarized uptake values of FDG: body surface area correction is preferable to body weight correction. J Nucl Med 1994;35: 164–7.
18. Lindholm P, Minn H, Leskinen-Kallio S, Bergman J, Ruotsalainen U, Joensuu H. Influence of the blood glucose concentration on FDG uptake in cancer—a PET study. J Nucl Med 1993;34:1–6.
19. Hamberg LM, Hunter GI, Alpert NM, Choi NC, Babich JW, Fischman AJ. The dose uptake ratio as an index of glucose metabolixm: useful parameter or oversimplification? J Nucl Med 1994;35:1308–12.
20. Menda Y, Bushnell DL, Madsen MT, McLaughlin K, Kahn D, Kernstine KH. Evaluation of various corrections to the standardized uptake value for diagnosis of pulmonary malignancy. Nucl Med Commun 2001;22:1077–81.
21. Dewan NA, Gupta NC, Redepenning LS, et al. Diagnostic efficacy of PET-FDG imaging in solitary pulmonary nodules. Chest 1993;104:997–1002.
22. Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. J Nucl Med 1996;37:943–8.
23. Imdahl A, Jenkner S, Brink I, et al. Validation of FDG positron emission tomography for differentiation of unknown pulmonary lesions. Eur J Cardiothorac Surg 2001;20: 324–9.
24. Lowe VJ, Fletcher JW, Gobar L, et al. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol 1998;16:1075–84.
25. Yoshimoto M, Waki A, Yonekura Y, et al. Characterization of acetate metabolism in tumor cells in relation to cell proliferation: acetate metabolism in tumor cells. Nucl Med Biol 2001;28:117–22.
26. Higashi K, Ueda Y, Yagishita M, et al. FDG PET measurement of the proliferative potential on non-small cell lung cancer. J Nucl Med 2000;41:85–92.
27. Vesselle H, Schmidt RA, Pugsley JM, et al. Lung cancer proliferation correlates with [F-18] fluorodeoxyglucose uptake by positron emission tomography. Clin Cancer Res 2000;6:3837–44.

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