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臨床放射線

中 咽 頭

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【放射線治療】2. 各　論

中咽頭

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はじめに

頭頸部癌は，機能温存，形態温存という放射線治療の特徴を最大限に生かせる部位である。特に中咽頭は摂食，構音，嚥下などの重要な機能をもち，大部分の腫瘍が，放射線感受性の高い扁平上皮癌である。以上の点より，中咽頭癌においては，放射線治療が予後改善とQOLの改善に重要な役割を持つ。中咽頭癌に対しては，CDDPを用いた化学放射線療法が一般的であるが，最新のトピックスとしては，1) IMRT（強度変調放射線治療），2) HPV（パピローマウイルス），3) 分子標的治療，などが挙げられよう。

1 中咽頭癌について

中咽頭癌のTNM分類は口腔領域癌と同じである（表1）。腫瘍サイズが2cm以内か4cm以内かでT1, T2, T3が分類される。リンパNステージに関しては，他の頭頸部癌と共通である。

表1　中咽頭癌に対するTNM

T1：	<= 2cm
T2：	> 2 to 4cm
T3：	> 4cm
T4：	Adjacent structures
N1：	Ipsilateral single <= 3cm
N2：	Ipsilateral single > 3 to 6cm
	Ipsilateral multiple <= 6cm
	Bilateral, contralateral <= 6cm
N3：	> 6cm

喫煙や飲酒との関連性については従来より指摘されていたが，近年 Human papilloma virus（HPV）ウイルスとの関連性が注目されている。

発症年齢的には60～70歳代で最多であり，95%が扁平上皮癌である。

初期症状は局所の疼痛ないしは，頸部リンパ節腫脹である。特に舌根由来では，局所症状が出現しにくいために進行して発見されることや，原発不明頸部リンパ節転移で見つかることが多い。

一般的に予後は，側壁（扁桃）や上壁（口蓋垂，軟口蓋下面）由来が前壁（舌根），後壁由来より良好とされるが，上壁原発の中には66～70Gyの外照射単独で制御困難な症例もある。

頸部リンパ節転移の頻度は，側壁（扁桃）が60～70%で反対側への転移頻度は10～15%である。扁桃由来以外は両側性リンパ節転移が多く，舌根：7～80%，上壁：40～50%，後壁：50～70%である。

放射線治療中の喫煙の悪影響については，Browmanらの報告[1]があり，低酸素による局所制御率の低下はもとより，粘膜炎等の有害事象の悪化は明らかであり，照射期間および前後の禁煙は不可欠である。

2 中咽頭癌に対する放射線治療

1）照射法

中咽頭癌における患者固定の基本はシェル固定である。原則的に下顎を進展させた状態で，口腔内は義歯を外し，可能な限り上顎口腔粘膜を照射範囲よ

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〔索引用語：中咽頭癌〕

表2　全頸部照射領域のCTV

上縁：下顎骨上縁（下顎頭）つまりZygomatic arch 上縁（Rouvierを含む）
前上縁ブロック：上顎洞の後部3分の1，口腔の後部3分の1（舌根は十分含む）
下縁：顎下部のできるだけ高位で接合面を作成する。
後縁：副神経節を含む（棘突起後方1～2cm）
前縁：顎下リンパ節を含むが，頤下リンパは顎下リンパ腫大時以外には含まず，口角も外す。
鎖骨上窩については，前後対向2門（前方1門でも可）で照射する。
外側縁：第二肋骨内側縁（肩甲舌骨筋中間腱鎖骨付着部）
下縁：鎖骨下縁（肺ブロックを使用）

り外すためにマウスピースを用いて軽度開口させておく。全頸部照射は，原則として4MVないし6MVのX線を用いた照射法で，half-field照射法を用いる。

線量評価は，原則的には照射野中心で行うが，厚みの異なる広範囲を照射する場合は，2カ所に評価点を分けて，照射することもある。

2）照射野

外照射野の設定の基本原則は，局所病変＋領域リンパ節照射である。片側扁桃原発でN0症例以外は，全頸部リンパ領域に予防照射が必要とされる。そのために，一般的には全頸部領域のCTVを40～50Gy照射する。表2に全頸部照射のCTVを，図1と図2に全頸部照射のX線写真での照射範囲を示す。

一般的には全頸部照射の後に，局所病変（照射前のGTV＋1cm）に追加照射するshrinking method法が一般的である。しかし，この局所病変への照射を最初から全頸部照射と同時に行うfield in filed法や，simultaneous integral boost（SIB）技術を用いたIMRT照射法も行われる（図3）。

3）照射線量

中咽頭癌に対する照射線量は，原則的に外照射単独の場合，GTV(primary)に対しては66～70Gy以上の照射線量が必要である。また，GTV（node）（腫大したリンパ節）にも60Gy以上の照射が必要である。そして，CTV領域に対する予防照射線量は，40～50Gy必要である。もし小線源療法が可能な領域は，小線源療法の併用を検討する。GTV（node）には電子線の使用も検討する。もし照射後に明らかに残存した頸部リンパ節には，照射後の手術的廓清も検討が必要である。

3　化学療法との併用

頭頸部癌において放射線治療単独と化学放射線療法とを比較した臨床試験では，おおむね後者の化学放射線療法併用群が局所制御率や生存率で上回ってきた。

Pignonらのmetaanalysisによっても同時化学放射線療法では放射線治療単独と比較して生存延長効果を認めている[2]。

Calaisらは，III～IV期の中咽頭癌を対象とした無作為比較試験においてCBDCA 70mg/m^2＋5FU 600mgの抗癌剤併用により，3年生存が31%より51%，3年局所制御率が42%より66%に向上したとしている[3]。

Denisらも上記臨床試験の最終報告を行い，5年生存が16%より22%に，5年局所制御率が25%より48%に向上したとしている[4]。

以上のように標準的な5年生存率は30～49%で局所制御率は54～85%であるが，国内データとしては日本放射線腫瘍学会（JASTRO）1998年集計結果では，5年原病生存率がI：II：III：IV＝67：63：50：37であり，側壁：上壁：前壁＝57%：62%：35%であった。本年2008年に10年ぶりの最新結果が札幌にて集計される予定である。

4　有害事象

照射中ー照射後56日以内の急性期有害事象には，以下のものがある。

易疲労感，皮膚の発赤・過敏，粘膜炎，嚥下困難・嚥下痛，嗄声，照射野内の一時的な脱毛，味覚・嗅覚の変化，口内乾燥感，体重減少，白血球減少

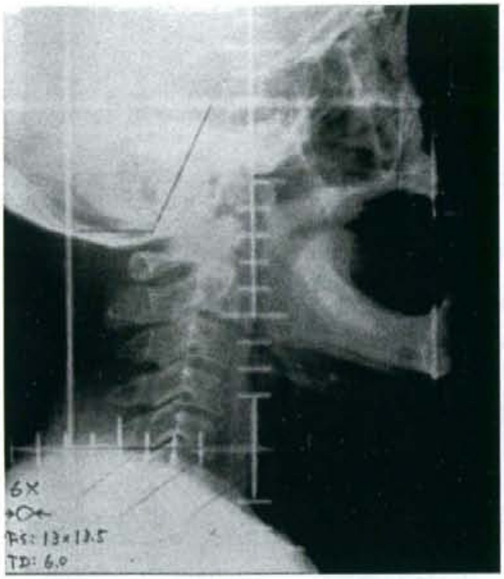

図 1　中咽頭癌における X 線シミュレータでの照射野（左右方向）

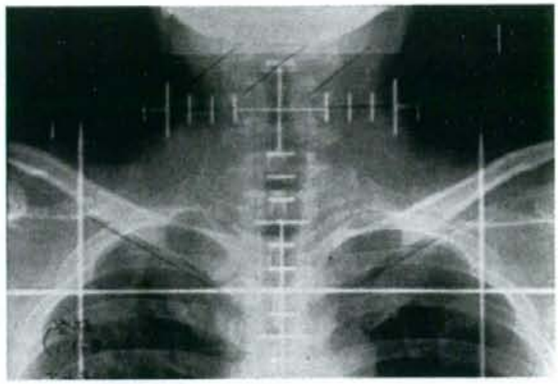

図 2　中咽頭癌における X 線シミュレータでの照射野（前後方向）

照射後 57 日以後に出現する晩期有害事象として頻度高くみられるものは，以下のものである。

一過性の頸部腫脹（リンパ浮腫），口内乾燥，う歯・歯牙脱落

頻度の少ない晩期有害事象として，照射野内の皮膚の肥厚，永続的な皮膚の色素沈着，頸の筋肉の炎症，永続性の頸部腫脹，聴覚障害，眼障害による失明，鼻腔からの排液・出血，味覚・嗅覚の変化，甲状腺機能低下（特に全頸部照射症例），脊髄障害（軽度の Lhermitte 徴候），骨・軟骨壊死，筋肉障害による咀嚼，発語，嚥下困難，放射線誘発癌，脊髄麻痺，脳壊死，がある。

5 術後照射

術後照射の適応は，一般的に以下の条件を一つでも満たした症例に対して行われる。

複数リンパ節転移陽性例，リンパ節節外浸潤陽性例，断端陽性例，悪性組織例（undifferentiated cell など）

術後照射の照射野は，疾患と症例に応じて，また手術時所見によって設定されることが多いが，全頸部照射野か部分頸部照射野が設定される。

現在の術後照射線量は 50Gy/2Gy が原則であるが，手術時所見に応じて 60Gy まで照射することがある。脊髄線量は 40 ～ 46Gy 以内に制限する。なお術後照射は手術手技による影響が多大であるために，照射野決定前に必ず耳鼻科・放射線治療科カンファレンスで，術者の意向を聴取しておくことが望ましい。また，術後照射も可能な限り，抗癌剤併用が望ましい。

6 HPV ウイルスとの関連

最近の研究[5) 6)]によると頭頸部癌における HPV ウイルスの感染頻度は有意に高く，特に中咽頭が 35.6%，口腔癌が 23.5%，喉頭癌が 24%とされる。この中で特に HPV16 のサブタイプが最も高頻度であり，各々 86.7%，68.2%，68.2%であった。中咽頭癌の中では扁桃原発が特に HPV との関連性が高いとされる。またオラルセックスとの関連性も指摘されている。将来的に HPV ワクチンがこれらの癌予防に役立つ可能性がある。

7 IMRT（強度変調放射線治療）

原則的にはターゲットとして GTV-primary（MRI

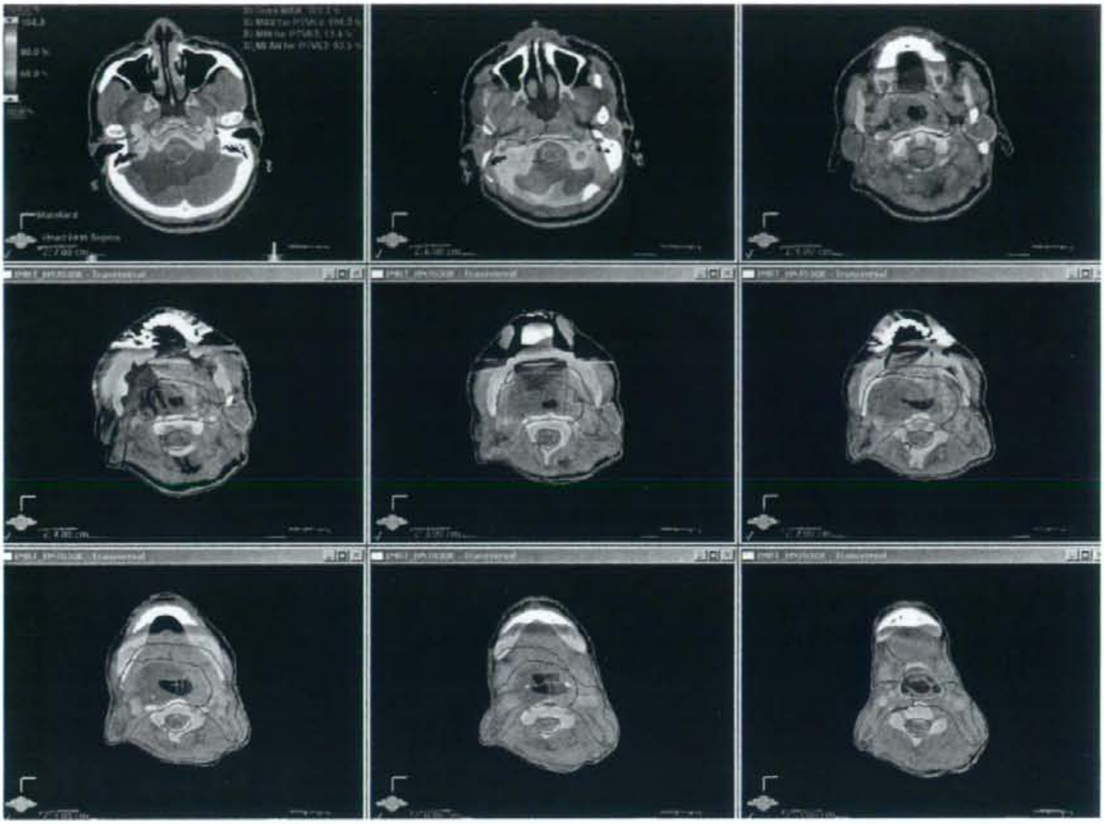

図３　中咽頭癌に対するIMRT（IMRTによる線量分布）

で確認できる肉眼的原発巣）とGTV-node（MRIやPETで確認できる転移腫大リンパ節）とCTV（ルビエールからII-VIの領域リンパ節）を入力するとともに，脊髄，脳幹，唾液腺，喉頭等のリスク臓器との相関で最適線量を決定する。近年はHigh risk PTV，Intermediate risk PTV，Standard risk PTVを決める方法もある。IMRTに関しては腫瘍のGTVと共に特にCTVリンパ領域の輪郭入力[7]が不可欠である。これらのリンパ領域については，RTOG（http://www.rtog.org/hnatlas/main.html）やEORTCのホームページで公開されているために，これらを利用したい。

中咽頭癌に対するIMRTはRTOG：H00-22が既に登録終了し，解析された。このH00-22プロトコールではT1-2 N0-1の中咽頭癌が対象となっている。放射線治療単独であるが，GTVには66Gy/30fx，CTVには54～60Gy/30fxを照射している。参考にRTOG02-25の上咽頭プロトコールではGTV 70Gy/33fx，CTV 59.4Gy/33fxとなっている。また正常組織に関する線量制約においても，PTV 66 95%，PTV 50 95%の他に，耳下腺は30Gyが50%以下または平均線量が26Gy以下，脊髄は最大線量45Gy以下，脳幹では54Gy以下，その他の領域では72.6Gy以下としている。

H00-22のASTRO 2006における中間解析[8]では線量制約において完全にプロトコールを遵守できた患者はいなかったという（89%がminor deviation，11%がmajor variation）。急性期有害事象としては口内乾燥感（Xerostomia）：grade 2 49.3%，grade 3 1.5%（conventional RTではgrade 2～3 84%），口内粘膜炎（Mucositis）：grade 2 29.9%，grade 3 25.4%，grade 4 1.5%，頸部皮膚炎（Skin）：grade 2 19.4%，grade 3 10.4%，顎骨壊死（Osteoradionecrosis）：grade 2～4 6.2%で

あった。平均観察期間1.6年の時点で67人照射中3人の局所再発がみられている。2008年ASTRO（#219）の最終報告でも，唾液腺機能温存が証明された。

Chaoらは，文献9で74人の初期経験を報告し，4年局所制御率が87%でありまた4年全生存率も87%としている。この中でGTV特にGTV-LNの設定が重要としている。

De Arrudaらも，文献10で50人の治療経験で2年局所無再発率が98%，2年無遠隔転移率が84%としている。

Leeらも文献11において20カ月以上観察された症例において，grade 2以上の口内乾燥症状が67%より12%に有意に低下したとしている。

上記いずれのIMRT報告においても，有害事象の発生率は従来法より明らかに低い。ただ，IMRTが生存率改善に直結しているかについてはHodgeらはIMRT以外の要素の影響があり結論できないとしている[12]。

8 分子標的治療

頭頸部癌においても，分子標的治療の有用性が報告されるようになってきた。最近の臨床試験においては，Bonnerらが文献13またPfisterらが文献14において，Cetuximab：C225が放射線治療と併用することによって，有意に局所無再発生存期間，無増悪期間，全生存期間が改善するとされた。わが国においても大腸癌に引き続くErbituxの臨床適応拡大が期待される。

おわりに

IMRTの導入により従来より明らかに有害事象の軽減した根治照射が可能となってきた。また化学療法の併用で治療成績が向上し，新たな分子標的治療の併用も期待される。現在にわが国において中咽頭癌は手術と放射線治療との境界領域であるが，今後は患者への負担の少ない放射線治療の意義が改めて見直されるべき時であろう。

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上 咽 頭

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はじめに

上咽頭癌は，原発巣が頭蓋底に近接しており外科的切除が困難であること，および放射線感受性が比較的高いことから，病期にかかわらず高エネルギーX線による放射線治療が治療の主体となる。上咽頭は多数のリスク臓器に周囲を囲まれているため，上咽頭癌は強度変調放射線治療（intensity-modulated radiation therapy：IMRT）の良い適応で，局所制御の向上と有害事象の低減が期待されている。さらに近年，進行期症例においては，化学療法の併用が標準となりつつある。この稿では，上咽頭癌の特徴および治療法の最近の動向と，自施設での治療成績について述べる。

1 解　剖

上咽頭は軟口蓋より上方の咽頭腔であり，前方は後鼻孔を通じて鼻腔と連続し，下方は中咽頭に連続する。上方は蝶形骨体部や斜台，後方は頸椎によって区分され，下壁は軟口蓋となる。上咽頭癌の発生部位は，後上壁，側壁，下壁の3亜部位に細分され，後上壁，側壁に好発する。上咽頭の粘膜は多列線毛上皮と扁平上皮からなり，加齢とともに扁平上皮の割合が増える。間質はリンパ組織に富み，上皮にも小リンパ球の浸潤がみられる。

2 疫　学

上咽頭癌の発生には人種や地理上の分布に明らかな特徴があり，欧米の白色人種での発症頻度は年間10万人あたり1人以下なのに対し，中国や東南アジアでの発症頻度は20人以上である。性別では男性の方が2～3倍，女性より罹患率が高いとされている。発癌にはEpstein-Barr virus（EBV）の関与があることが知られている。日本での発症頻度は比較的まれであり，日本頭頸部癌学会による2003年の頭頸部癌の初診登録例3,219例の報告のうち，上咽頭癌は71症例（2.2%）で，男性58例，女性13例であった[1]。

3 臨床症状と進展様式

初発症状としては頸部リンパ節の無痛性の腫脹や，鼻症状，聴覚症状があらわれる。腫瘍による耳管開口部の閉塞や口蓋帆挙筋への浸潤により，耳閉感や中耳炎が生じる。上咽頭局所の病変の進展により，前方は鼻腔，後外側は咽頭頭底筋膜をこえて傍咽頭間隙や頸動脈間隙へ，側方は翼突筋，後方は椎前筋，上方は蝶形骨洞や斜台へ，下方は中咽頭へと浸潤が拡大する。さらに進展が増悪すると，翼状突起や篩骨洞，上顎洞，眼窩尖部，側頭下窩，椎体や下咽頭に浸潤が及ぶ。比較的病変が大きくならないと症状があらわれないため，初発時に脳神経症状を認めることもまれではなく，破裂孔や正円孔，卵円孔を経由した頭蓋内浸潤が起こり，海綿静脈洞周

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〔索引用語：上咽頭癌，放射線治療，化学放射線療法〕

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Original Article

Long-term Prognostic Assessment of 185 Newly Diagnosed Gliomas—Grade III Glioma Showed Prognosis Comparable to That of Grade II Glioma

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Objective: We evaluated the prognoses of newly diagnosed gliomas through WHO Grades II, III and IV to assess the overall tendency of treatment results for glioma in our institute. Furthermore, statistical analysis was performed to determine factors influencing the prognosis.
Methods: A total of 185 newly diagnosed glioma patients were operated on from 2000 to 2006. The primary endpoint was the overall survival from the date of surgery. The factors assessed as to whether they influenced the prognosis were the WHO grades of sex, age, location of the lesion, pre-operative Karnofsky Performance Status (KPS), extent of resection and whether or not radiation therapy was performed.
Results: The WHO grades influenced the survival significantly ($P < 0.0001$). The Grades II and III showed no statistically significant difference in survival ($P = 0.174$), whereas Grades III and IV showed a significant difference ($P < 0.0001$). The factor influencing survival as well as the grades was the KPS ($P < 0.0001$). The comparison of survival over WHO grades in the same KPS group was performed for 2 KPS groups (KPS = 100, KPS 80–90), and these also showed significant differences ($P = 0.0009$ and 0.0143, respectively).
Conclusions: Despite the different distributions of the KPS, the Grade III glioma patients showed survival comparable to that of the Grade II. On the other hand, the Grade IV glioma patients showed significantly poorer survival compared with Grade II or III.

Key words: glioma – long-term prognosis – WHO grade

INTRODUCTION

Traditionally, researchers have categorized gliomas into two groups, the 'malignant' or 'high-grade' group and the 'low-grade' group, especially when discussing their prognoses. WHO Grade II gliomas, sometimes combined with Grade I gliomas, are considered to be 'low-grade', and WHO Grades III and IV combined are considered to be 'high-grade' or 'malignant'. This categorization is fairly convenient when determining adjuvant therapeutic modalities because the 'malignant' group is almost always treated by concomitant radiation therapy (RT) and chemotherapy.

Though the prognosis of gliomas in general had been considered to be poor, recent developments in diagnostic technologies and treatment modalities seem to have contributed to its improvement. This has resulted in the fact that some 'malignant' glioma patients may be able to expect

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long-term survival under certain conditions. However, there has been little discussion as to whether the old 'low-grade and malignant' categorization is appropriate when evaluating prognostic tendencies of gliomas at present.

In our institute, in striving to achieve extensive but safe resection of tumors, a number of new technological methods have been introduced in recent years, one of which is the intra-operative magnetic resonance imaging (iMRI) (1), which was introduced in 2000. After 6 years of surgical operations using iMRI and the accompanying treatment experiences, we felt the urge to evaluate the prognoses of the glioma patients whom we treated. In addition, we thought that it would be very informative to compare the overall survival of each WHO grade group. We evaluated the prognoses of newly diagnosed glioma through Grades II, III and IV to assess the overall tendency of treatment results for glioma in our institute.

PATIENTS AND METHODS

A total of 304 glioma patients operated on at our hospital from 1 January 2000 to 30 June 2006 were reviewed. The histological diagnoses were available for all cases and were classified according to the grading system defined by the 2000 WHO classification for tumors (2) of the central nervous system. We excluded WHO Grade I cases (11 patients) as they have extremely good prognoses. In order to assess the significance of the first surgery, we also excluded the patients who had undergone initial treatment at other institutes and were referred to our institute for the treatment of recurrent lesions. As a result, the prerequisite for inclusion in this analysis was to be newly diagnosed WHO Grades II, III and IV glioma patients who underwent operations in our institute from 1 January 2000 to 30 June 2006. A total of 185 patients were included in this analysis.

The detailed description of the patients is shown in Table 1, and the histological variation of each WHO grade group is shown in Table 2. Among these patients, 153 (82.7%) were operated on by using iMRI-guided navigation. The extent of resection was assessed by comparing pre- and post-operative iMRI (3). The pre-operative tumor volume was defined as an area of contrast-enhanced T1-weighted images (4), or, if the tumor does not show contrast enhancement, as an area of increased signal intensity on T2-weighted images corresponding to the mass lesion. An area of abnormal signal intensity was computed for each slice and multiplied by the slice width (1.5 mm), and a cumulative value was obtained by adding the values for the individual slices (5).

All surgical specimens were collected, processed and prepared for histological diagnosis in our neuropathologic laboratory. The specimens were thoroughly prepared with regular hematoxylin–eosin staining and necessary immunohistochemical antibodies were applied including MIB-1 antibody. For the entire study period, every diagnosis was conducted by one sole neuropathologist, Prof. Osami Kubo, who is one of the councillors of the Japanese Society of Neuropathology.

Table 1. Characteristics of the patients in each WHO grade group

	Total	Grade II	Grade III	Grade IV
Number of cases	185	66	57	62
Sex				
Men	106	34	34	38
Women	79	32	23	24
Age (years old)				
Median	44.0	35.0	39.0	54.5
Range	8–78	11–70	22–78	8–78
Location				
U	168	61	51	56
B	7	1	4	2
I	10	4	2	4
KPS				
Median	100.0	100.0	100.0	80.0
Range	10–100	70–100	50–100	10–100
Extent of resection (%)				
Median	95.0	95.0	95.0	95.0
Range	biopsy–100	biopsy–100	biopsy–100	biopsy–100
RT	131	26	51	54

U, unilateral supra-tentorial lesion; B, bilateral supra-tentorial lesions; I, infra-tentorial lesion; KPS, Karnofsky performance status; RT, Number of patients who received radiation therapy; WHO, World Health Organization.

Table 2. Histological variation in each WHO grade group

WHO grade	Histological diagnosis	Cases
Grade II	Astrocytoma	30
	Oligoastrocytoma	27
	Oligodendroglioma	5
	Ependymoma	3
	Pleomorphic xanthoastrocytoma	1
Grade III	Anaplastic astrocytoma	30
	Anaplastic oligoastrocytoma	21
	Anaplastic oligodendroglioma	3
	Anaplastic ependymoma	3
Grade IV	Glioblastoma	62

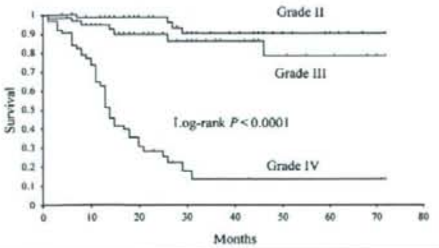
Adjuvant therapy included fractionated external-beam RT (50–60 Gy total, 2 Gy fraction for 5 days per week, unless modulated); and concomitant chemotherapy based on nimustine hydrochloride (ACNU) (6) with or without vincristine and/or procarbazine, temozolomide or autologous vaccine therapy. The clinical administration of temozolomide had not been approved during the study period (except the last few months); thus, it was not used as the first-line chemotherapy for primary glioma patients in this study. Patients to be treated with RT were selected by the following criteria. If the diagnosis was Grade III or IV, radiation was primarily recommended. If the diagnosis was Grade II, radiation was recommended if the patient's post-operative MRI showed any residual tumor and/or the MIB-1 index was 5% or higher. Maintenance therapy followed the initial therapy. In case of recurrence, the salvage therapy included re-operation using other chemotherapeutic agents or RT if the initial therapy did not include it.

The primary endpoint was the overall survival from date of surgery. Comparison of survival among WHO grades was performed using Cox's proportional hazard models.

Next, the patient's background was assessed to investigate whether there was any other factor that influenced the survival more than the WHO grades. The factors assessed were the WHO grades of sex, age, location of the lesion (U, supra-tentorial unilateral lesion; B, supra-tentorial bilateral lesions; I, infra-tentorial lesion), pre-operative Karnofsky Performance Status (KPS), extent of resection and whether or not RT was performed. These seven background factors were used as variables to apply Cox's proportional hazard models.

RESULTS

The median observation time was 13.0 months. Kaplan–Meier survival curves were drawn for WHO Grades II, III and IV (Fig. 1). There was a significant difference in survival among grades ($P < 0.0001$). The number of the patients at risk at 0, 12, 24, 36, 48, 60 and 72 months is also indicated in Fig. 1.



Months	0	12	24	36	48	60	72
Number of patients at risk							
Grade II	66	58	38	20	14	7	3
Grade III	57	40	27	15	9	7	4
Grade IV	62	34	10	3	2	2	1

Figure 1. Overall survival for each grade group. Kaplan–Meier survival curves for Grade II, III and IV are shown. Cox proportional hazard models showed significant difference among grades ($P < 0.0001$). The number of patients at risk at major time points (0, 12, 24, 36, 48, 60 and 72 months) is described at the bottom. The survival of each grade was compared and statistically analyzed by using Cox proportional hazard models. Grades II and III showed no statistically significant difference ($P = 0.1742$), whereas Grades III and IV showed a significant difference ($P < 0.0001$).

Subsequently, the survival of each WHO grade was compared and statistically analyzed by using Cox's proportional hazard models. Grades II and III showed no statistically significant difference ($P = 0.174$), whereas Grades III and IV showed a significant difference ($P < 0.0001$).

As for the influence of background factors on survival, the P values were $P < 0.0001$ for WHO grades, $P = 0.525$ for sex, $P = 0.997$ for age, $P = 0.727$ for location, $P < 0.0001$ for KPS, $P = 0.374$ for the extent of resection and $P = 0.804$ for RT. Only the KPS showed as much influence on survival as the WHO grades.

DISCUSSION

At the outset, it should be clarified that the data presented here were genuinely from a single institute. It may be apparent that the fraction of Grade III was much greater than that of other institutes or other studies, and the Grade III/IV patients were much younger than generally expected. One of the features of our institute is that most of the operative patients were referred from other hospitals or institutes. As is well known, the Grade IV gliomas develop symptoms much more rapidly than Grade II or III, and often need immediate treatment as soon as they are found. Furthermore, there is a tendency for Grade IV gliomas to be found in older age groups when compared with Grade II or III. Sometimes, those patients are not considered for operative therapy because of their age. Thus, those who were referred to our hospital tended to be younger and to contain a smaller fraction of Grade IV. As a result, we had a greater fraction of Grade III patients than Grade IV.

Our data clearly showed that the Grade III group, normally categorized in the malignant glioma entity, showed survival comparable to that of Grade II glioma, which is in the low-grade glioma entity. On the contrary, Grade III and IV glioma, usually combined as malignant glioma, showed significantly different survival.

We have used the same (or at least very similar) treatment strategy for the Grades III and IV gliomas. Once histologically diagnosed as Grade III or IV, the patients were always given RT and concomitant chemotherapy. On the contrary, Grade II glioma patients were not always treated by RT or chemotherapy as is explained in the Patients and Methods section. We have come to an interesting fact: though treated similarly, Grades III and IV showed significantly different prognoses; on the contrary, Grades II and III gliomas were treated based on different therapeutic strategies, and showed comparable prognoses in terms of survival.

As for background factors, the KPS influenced the survival as much as the grades. We examined the distribution of the patients for grades and KPS, shown in Table 3. It indicates that there are a certain number of patients in each WHO grade for the KPS = 100 and the KPS 80–90. Then, comparison of survival over grades was performed for the two KPS groups with KPS = 100 and KPS 80–90; this

Table 3. Distributions of number of patients for KPS and WHO grades

KPS	Grade II	Grade III	Grade IV
100	55	34	12
80–90	9	15	22
60–70	2	7	16
40–50	0	1	8
<30	0	0	4

comparison also showed significant differences ($P = 0.0009$ and 0.0143, respectively). This supported the conclusion that the difference of survival among grades was independent of the deviations among patients' backgrounds.

Subsequently, the survival of each WHO grade in the KPS = 100 group was compared and statistically analyzed using Cox's proportional hazard models. The P values for grade II versus III and Grade III versus IV were 0.532 and 0.0294, respectively. Despite the fact that the patients' backgrounds have some biases throughout the grades, Grade III achieves survival comparable to Grade II, if diagnosed, treated and observed properly. On the contrary, Grade IV still remains in the uncontrollable disease category.

CONCLUSIONS

The results indicated that the Grade III glioma patients have prognoses comparable to that of the Grade II patients and the Grade IV glioma patients showed significantly poorer prognoses compared with Grade II or III. Among the patients' background factors, the KPS influenced the survival of gliomas as much as the WHO grades. However, the comparison of survival among the same KPS groups also showed significant differences over grades, indicating that the differences of survival over grades are independent of patients' background factors.

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Conflict of interest statement

None declared.

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Advanced Computer-aided Intraoperative Technologies for Information-guided Surgical Management of Gliomas: Tokyo Women's Medical University Experience

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Key words
- intraoperative MRI
- intraoperative neuronavigation
- medical information technology
- information-guided management
- robotic neurosurgery

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Abstract

The availability of the intraoperative MRI and real-time neuronavigation has dramatically changed the principles of surgery for gliomas. Current intraoperative computer-aided technologies permit perfect localization of the neoplasm, precise estimation of its volume, and clear definition of its interrelationships with the eloquent brain structures. This allows maximal tumor resection with minimal risk of postoperative disabilities. Under such conditions the medical treatment has become significantly dependent on the quality of the provided information and can be designated as information-guided management. Therefore, appropriate management of the wide spectrum of the intraoperative medical data and its adequate distribution between members of the surgical team for facilitation of the clinical decision-making is very important for attainment of the best possible outcome. Further progress in advanced neurovisualization, robotics, and comprehensive medical information technology has a great potential to increase the safety of the neurosurgical procedures for parenchymal brain tumors in the eloquent brain areas.

Introduction

Medical treatment in the 20th century was mainly based on feedback-controlled principles. Correspondingly, up to date clinical decision-making is significantly influenced by personal intuition and previous experience of the doctor. Both of those issues are extremely important. The experienced neurosurgeon is able to simulate the whole upcoming surgery in his or her own mind and perform it thereafter precisely and efficiently. This is significantly facilitated with the advances of modern neuroimaging and intraoperative neuronavigation. At present, various diagnostic data obtained with CT, MRI, PET, SPECT, digital angiography etc. may not only be visually inspected and analyzed, but co-registered, fused, and incorporated into computer-based devices for guidance during the surgical procedure. Nevertheless, usually it is not the various images, but the long-life training of the surgeon, that provides perfect orientation in the surgical field, evaluation of the functional importance of the various anatomic structures, and estimation of the optimal resection of the lesion taking into account possible positive and negative consequences of the various intraoperative manipulations and actions. Therefore, up to date the complex neurosurgical procedure, for example removal of glioma in the eloquent brain area, in the best hands represents more an art than science or technique.

It can be expected, however, that in the third millenium the practical medicine will be transformed into a "feed-foward" process with scientifically based prediction of the various risks and their preemptive management. It will necessitate the development of special computer-aided systems for comprehensive analyses of the various diagnostic and management data and precise simulation of the treatment course of the particular patient. Under such conditions the treatment process, which can be designated as information-guided management [1], will become significantly dependent on the quality of the provided information.

Main Problems with the Surgical Management of Gliomas

Requirements of the constantly growing quality standards of medical care enforce neurosurgeons to provide safe and effective management of any intracranial pathology independent on its location. Meanwhile, the decades of clinical experience provide clear evidence that, in the majority of cases, routine surgical technique does not permit aggressive removal of parenchymal brain tumors located in the vicinity of eloquent brain structures without a significant risk of permanent postoperative neurological disability. From another side, incomplete resection of the neoplasm, which is still not uncommon practice, may have a significant negative impact on patient survival. While the effectiveness of aggressive removal of intracranial gliomas is not formally proved to date and the rate of their optimal resection is still questionable [2, 3], there is a general agreement that radical resection of the neoplasm is associated with a better prognosis even in cases of malignancies. Lacroix et al. [4] showed that 98% or more resection of glioblastoma multiforme is associated with a significant improvement of the long-term outcome, whereas according to the last edition of the Brain Tumor Registry of Japan [5], the five-year survival rate of patients with such neoplasm is increasing from 11% in cases of 95% resection to 18% in cases of 100% resection.

The main problems with the surgical management of gliomas are well known. First, these tumors arise from the cerebral tissue itself and due to their propensity for infiltrative growth frequently could not be clearly distinguished from the normal brain through the conventional operating microscope, which is especially evident at the periphery of the neoplasm. Second, an intraaxial location of the tumor results in frequent affection of the functionally important cerebral structures, which certainly should be clearly defined and preserved during removal of the neoplasm in order to avoid a postoperative neurological deterioration. Third, while recent progress in MRI technology and intraoperative neuronavigation has significantly facilitated surgery for malignant brain tumors, the effect of brain shift caused by evacuation of the cerebrospinal fluid or lesion removal can result in significant mislocalization errors if guidance is based on the preoperative images [6–8]. It might be expected, however, that introduction of more advanced computer-aided intraoperative devices into clinical practice can diminish or solve the abovementioned problems and facilitate maximal tumor resection with minimal risk of postoperative complications.

Advanced Computer-Aided Intraoperative Technologies for Management of Gliomas

The introduction of technologies for computer-aided diagnosis and treatment has dramatically changed the process of clinical decision-making. At present, preoperative integration of the various diagnostic data and their use for surgical planning and neuronavigation have become routine practice in the majority of neurosurgical centers. Further development of intraoperative imaging devices, such as ultrasonography, CT, and MRI, provided an opportunity to obtain real-time medical information at the time of surgery, and therefore profoundly increased its preciseness. Among the various tools designed for intraoperative imaging, intraoperative MRI (iMRI) seems to be the most promising, because of the absence of radioactivity, high resolution, possibilities to obtain images in different planes, and the opportunity to use various sequences and techniques depending on the goals of the investigation.

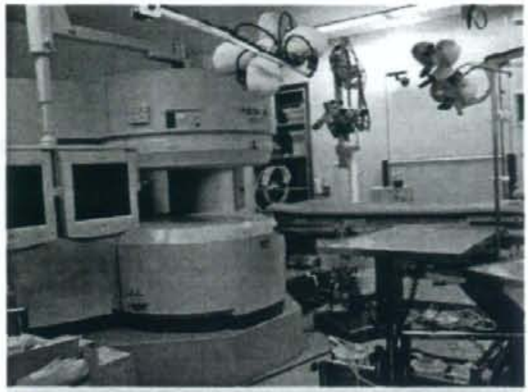

Fig. 1 General view of the intelligent operating theater in the Tokyo Women's Medical University with the hamburger-like open intraoperative MRI scanner (AIRIS II™, Hitachi Medical Co., Chiba, Japan).

Intraoperative MRI

The requirements for an optimal iMRI scanner are determined by the type and quality of images desirable during the neurosurgical procedure. It is clear that use of devices with higher magnetic field strength can provide better quality and resolution, but may be associated with a greater risk of distortion artifacts, which can result in significant mislocalization errors if used for neuronavigation [9]. While some techniques, such as diffusion tensor imaging or proton magnetic resonance spectroscopy [10, 11] definitely require an iMRI scanner with a magnetic field strength of, at least, 1.5 Tesla, it should be noted that the majority of neurosurgical procedures are guided by structural, but not by metabolic or functional neuroimaging. Furthemore, integration of the intraoperative neurophysiological and histopathological data with the anatomic information provided by iMRI with low magnetic field strength practically resolves the problem of the slightly lower image quality.

An open iMRI scanner (AIRIS II™, Hitachi Medical Co., Chiba, Japan) installed in Tokyo Women's Medical University (TWMU) has a magnetic field strength of 0.3 Tesla [12, 13]. It has a hamburger-like shape with a 43 cm gantry gap and a permanent magnet producing a vertical magnetic field with resonance frequency of 12.7 MHz (○ **Fig. 1**). The low magnetic field strength creates a narrow 5-Gauss line, which extends 2 m from both sides, 2.2 m in front, 1.8 m backwards, and 2.5 m upwards. It permits the surgeon to use some conventional surgical devices and instruments in the working space outside the 5-Gauss line (○ **Fig. 2**). It should be specially noted that this iMRI scanner does not require a cooling system, which significantly reduces its operating costs by approximately 10000 Japanese yen (around 100 US $) per month.

The originally developed radiofrequency receiver coil integrated with the Sugita head-holder (Head-holder coil; Mizuho Ltd., Tokyo, Japan) significantly improves the quality of intraoperative images. It provides an opportunity to perform MRI investigations with minimal distortion artifacts and maximum structure contrasting in any plane irrespectively to the orientation of the object, which allows fixation of the patient's head in the most desirable position for tumor removal. Integration of the head-holder coil with a modified Komai stereotactic frame [14] permits us to perform stereotactically guided surgical

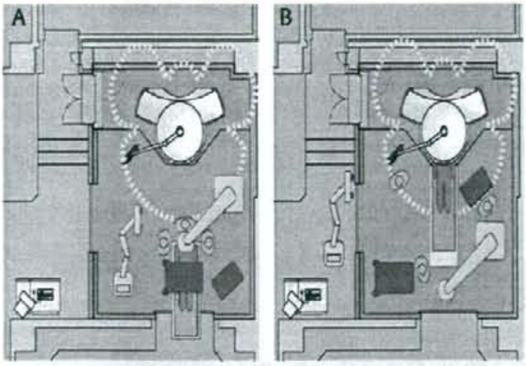

Fig. 2 Scheme of the internal organization of the intelligent operating theater in the Tokyo Women's Medical University during a surgical procedure (**A**) and MRI scanning (**B**). The low magnetic field strength of the device (0.3 Tesla) provides narrow distribution of the 5-Gauss line (*dotted line*), which permits the surgeon to use some conventional surgical devices and instruments.

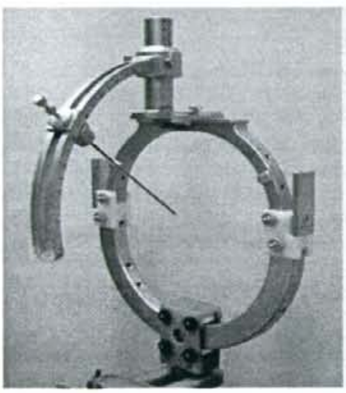

Fig. 3 Radiofrequency receiver coil integrated with a modified Komai stereotactic frame for stereotactically guided surgical procedures under the control of intraoperative MRI.

procedures under the control of iMRI (○ **Fig. 3**). Use of the device provides an opportunity to perform intraoperatively not only volumetric, but diffusion-weighted imaging (DWI) and functional investigations, with a sufficient quality of images comparable to those obtained on scanners with higher magnetic field strengths (○ **Fig. 4**). Intraoperative use of DWI seems to be especially promising, because it can permit us to identify motor nerve fibers, such as the pyramidal tract [15–17]. The technique is operator-independent and the images do not require any post-processing modifications, therefore it can be installed into the neuronavigation system without any delay in time.

Intraoperative MR images are usually taken for verification of the brain shift and deformation, for evaluation of the residual part of the lesion, and for diagnosis of complications. In our practice iMRI investigations are usually performed when approach to the tumor is attained and when the lesion is removed for evaluation of its possible remnants. Nevertheless, it can be done during the procedure as many times as necessary. When the image is obtained it is immediately converted into DICOM format and transferred into the intraoperative neuronavigation system through the local network.

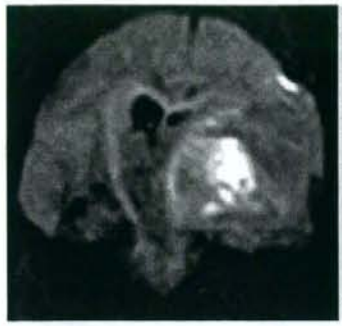

Fig. 4 Intraoperative DWI obtained on MRI scanner with a magnetic field strength of 0.3 Tesla: both pyramidal tracts are clearly seen and the shift on the affected side can be easily evaluated.

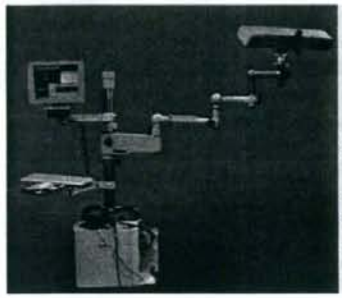

Fig. 5 Intraoperative neuronavigation system (PRS navigator, Toshiba Medical Co. Ltd., Tokyo, Japan).

Intraoperative real-time updated neuronavigation

The main advantage of the real-time updated neuronavigation based on the intraoperative neuroimaging is avoidance of the adverse effects caused by brain shift and deformation, which allows precise identification of the tumor position and its interrelationships with surrounding brain structures. In our practice we use a previously developed navigator for the photon radiosurgery system (○ **Fig. 5**). It allows fast and easy updating of the information obtained with iMRI. The mislocalization errors of the device constitute 0.8 mm in average, 1.5 mm at maximum, and 0.5 mm at minimum, and typically do not exceed 1 mm. The system permits co-registration, fusion and three-dimensional reconstruction of the various images, and provides easy-to-understand information. The different areas of the perilesional brain can be color-coded (○ **Fig. 6**) according to the safety of manipulations and probable risk of complications [18]. The device may be integrated with a special sound alarm that is automatically activated when surgical manipulations would come in close proximity to the high-risk area [19].

It should be noted that anatomic data alone are not sufficient for guidance of tumor resection, even if obtained with iMRI. The location of the eloquent brain strucutres has known individual variability and may be displaced during tumor growth. It necessitates the use of comprehensive neurophysiological monitoring and intraoperative cortical and subcortical brain mapping with or without awake craniotomy, with further integration of the neurophysiological and anatomical data.

Influence on clinical results

The first case with the use of iMRI was done in TWMU on March 13, 2000 and up to now more, than 600 neurosurgical procedures, mainly directed at the removal of parenchymal brain tumors, have been accomplished. The development of a system for advanced neurosurgical management significantly increased

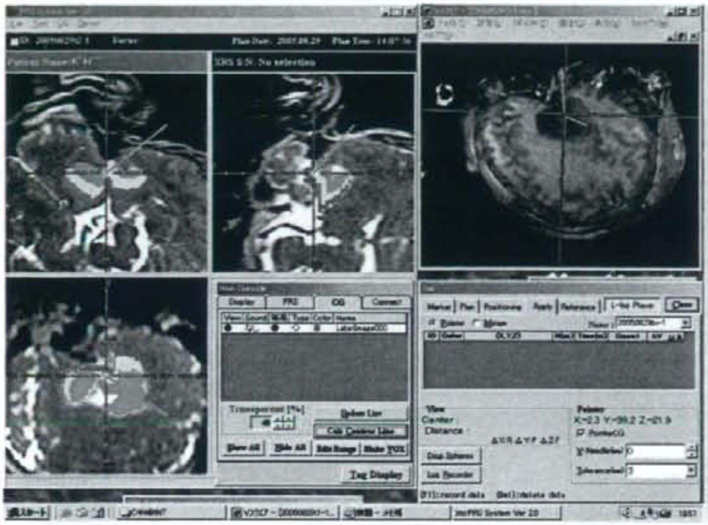
Fig. 6 Intraoperative neuronavigation with color-coded safety areas of tumor resection.

the resection rate of gliomas (up to 93% on average), and reduced residual tumor volume (median: 0.17 mL) [20]. In 46% of cases total tumor removal was attained, which is much greater compared to 12%, recorded in the last edition of the Brain Tumor Registry of Japan [5]. Moreover, a gradual improvement of our surgical results was noted in parallel with the growing experience and technological achievements: in the latest cases the median residual tumor volume was just 0.025 mL [20]. While the rate of temporary postoperative neurological complications was not low (34%), permanent neurological morbidity was noted just in 14% of cases, despite the fact that 83% of gliomas were located in or in the nearest vicinity to eloquent brain structures. Optimal surgical results were reflected in an improved 5-year survival rate of our patients, which constituted 90, 78, and 13% for grade II, III, and IV gliomas, respectively. For comparison, the corresponding rates recored by the Brain Tumor Registry of Japan, are 75%, 40%, and 7% [5].

Intraoperative Presentation and Distribution of the Medical Information

Appropriate management of the intraoperative medical information may have a significant impact on the clinical decision-making, and, therefore, may influence the outcome. During a neurosurgical procedure a wide spectrum of data, such as various pre- and intraoperative images, details of the intraoperative neuronavigation, parameters of the neurophysiological monitoring, nuances of the cortical mapping, and main characteristics of the current patient condition, should be provided. Moreover, these data have to be constantly updated, presented in a real-time regime, and widely distributed between members of the surgical team. As an optimum, the scientific information from evidence-based sources, integrated using probability assessment techniques, should be also available upon request. It is evident that, for the purpose of high quality surgery, all information should be not only precise and proved, but presented in a most compact, comfortable and friendly way for optimal visualization, easy understanding, and effective use. All data should be preferably co-registered and formatted for possible installation into constantly maintained databases, which is extremely important for precise risk evaluation, comprehensive outcome analysis, and effective planning and simulation of the further surgical procedures.

The main information-sharing device we use is the Intraoperative Examination Monitor for Awake Surgery (IEMAS). It provides for the surgeon, anesthesiologist, and other members of the surgical team the wide spectrum of data about the condition of the patient, nuances of the surgical procedure, and details of cortical mapping. The whole set of both anatomic and functional information, such as view of the patient's mimic and face movements during answering of the test questions, type of examination task, position of the surgical instruments on the navigation display, parameters of the bispectral index monitor, and general surgical field of view through the operating microscope and/or endoscope, is presented compactly in one screen with several displays, which allows fast integrated real-time analysis of the multiple data, nearly without interruption of the surgical manipulations (Fig. 7). All members of the surgical team can visualize these data on several in-room liquid crystal displays (LCD).

Additionally, a special surgical information strategy desk has been designed to facilitate the search of an optimal solution in a constantly changing surgical situation [21,22]. Seven LCDs of this system provide for the surgeon the whole spectrum of the integrated information about the situation in the surgical field, chemical neuronavigation, neurophysiological monitoring, intraoperative images, histopathological investigation, etc. All data are presented in a real-time regime and their visualization can be easily changed or combined in a different way just by a click of the network switch. The system makes possible the transfer of information into the distant areas (at present up to 200 m), therefore, an urgent consulting service with specialists located outside the operating theater, can be provided (Fig. 8). All surgical data are progressively incorporated and collected within the system, along with updated relevant technological and scientific information, for possible use during the planning of further surgical procedures. Analysis of this information permits preoperative simulation and significantly improves the

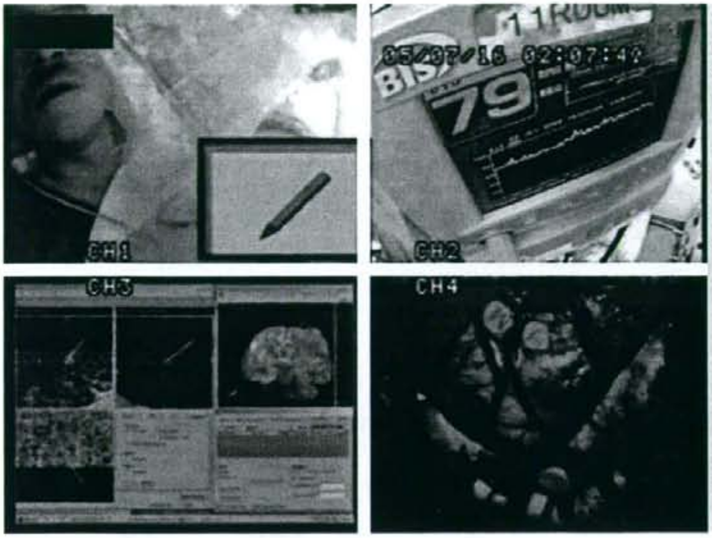

Fig. 7 Intraoperative examination monitor for awake surgery (IEMAS): view of the patient face and verb-generation task (*upper left*), parameters of the bispectral index monitor (*upper right*), position of the surgical instruments on the navigation display (*lower left*), and general surgical field of view with marks used for functional brain mapping (*lower right*) are presented simultaneously in one screen, which allows one fast integrated real-time analysis of the multiple data.

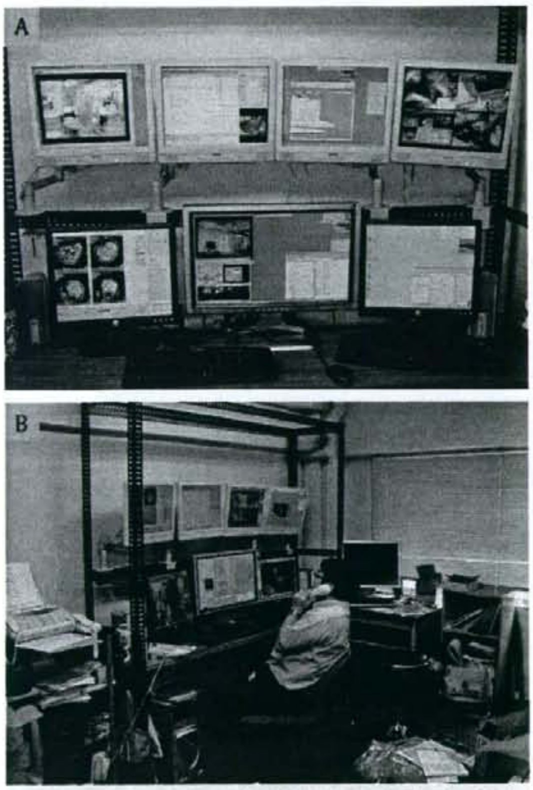

Fig. 8 Surgical information strategy desk: its overview (**A**) and use by the senior neurosurgeon supervising removal of a glioma from eloquent brain area from the neurosurgical office (**B**).

ability of a surgeon to define an optimal treatment strategy. At the time of surgery, the system permits one to get real-time information whether the actual surgical procedure corresponds well to the preliminary developed treatment plan or not.

Future Perspectives

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Use of iMRI and real-time updated neuronavigation have proved their great efficacy in the neurosurgical management of parenchymal brain tumors. Anyway, several problems still require solution, and the necessity of further technological improvements is evident.

Computer-based system for correction of distortion artifacts

Speaking precisely, our intraoperative neuronavigation system, is not "real-time", but nearly "real-time". Therefore, the risk of small mislocalization errors, particularly caused by brain deformation and its movements due to surgical manipulations, could not be excluded. Even if the gap between the estimated and real target positions is small, it may be of critical importance in cases of lesions located within or in the nearest vicinity to eloquent brain areas. Therefore, the development of the special computer-based system for "advanced vision neuronavigation", which would permit constant real-time estimation and correction of the mislocalization errors, will be of great importance for further increase of preciseness and safety of the neurosurgical procedures.

Robotic neurosurgery

The incorporation of robotic systems into neurosurgical practice can potentially increase the preciseness of surgical manipulations, and significantly reduce the risk of neurological deficits if surgery is performed in highly vulnerable brain areas. The robotic systems can perform automatic distinction between the tumor and surrounding tissue, and may provide an opportunity for highly selective management of the neoplasm with extremely

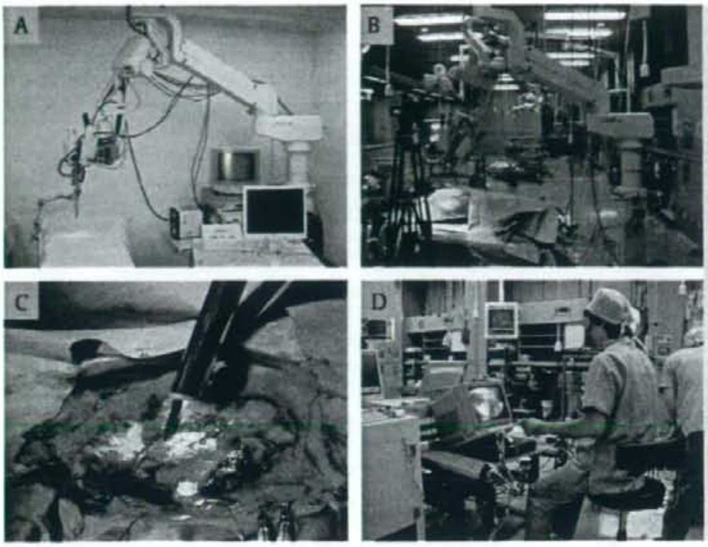

Fig. 9 iMRI-compatible neurosurgical robotic system (A) showed its preciseness in animal experiments (B and C) and allows distant control of all manipulations by the neurosurgeon (D).

high precision (up to 10 μm). Other potential advantages of robotics include the opportunity to perform manipulations in extremely limited space, and the possibility of initial computer-aided modelling and simulation of the planned surgical action.
The introduction of the robotic technologies into clinical medicine started in the 1990s with such systems as da Vinci™ and Zeus™ (Intuitive Surgical Inc., Sunnyvale, CA, U.S.A), and Robodoc™ (CUREXO Technology Co., Sacramento, CA, U.S.A). In the same time we had developed a special neurosurgical robotic system, designated as the Hyper Utility Mechatronic Assiastant for Neurosurgery (HUMAN) or NeuRobot (Hitachi Medical Co., Chiba, Japan). For the first time in the world it was clinically applied in Shinshu University (Matsumoto, Japan) in August 2002 and proved the possible practical utility, particularly for third vetnriculostomy [23]. Currently, an advanced iMRI-compatible model of this device is undergoing experimental testing (◦ **Fig. 9**).
The next generation of neurosurgical robots requires integration of the advanced intraoperative neurovisualization and computer technology for comprehensive data assessment. Currently we are developing a manipulator based on the integration of the chemical neuronavigation for identification of the neoplasm in the surgical field and micro-laser for its ablation [24–26]. The management area is determined automatically with a specially designed camera. A mid-infrared continuous wave micro-laser with a wave length of 2.8 μm provides optimal absorption parameters of the brain tissue and extremely limited thermal action. The system has less than 0.5 mm positioning accuracy. All surgical actions are planned and controlled by the neurosurgeon who is located in front of the distant desk, which allows precise planning and simulation of the procedure. It should be noted that this device has been developed not for removal of the whole bulk of the tumor, but for management of its residuals in the highly eloquent brain structures where high levels of preciseness and safety are needed. It is expected that such highly selective pin point neurosurgery will permit us to eliminate the neoplasm while keeping intact functionally important brain structures. The clinical testing of the device is expected in the nearest future.

Information-guided treatment simulation and pre-emptive risk management

In order to improve the safety and effectiveness of neurosurgical procedures their precise planning is absolutely necessary. Therefore, it is important to develop special computer-aided modalities and tools for neurosurgical simulation based both on the previous clinical experience and available scientific data. To attain such a purpose merely installation of the surgical records and video into databases is not sufficient, but rather a special system for their automatic analysis with possible immediate extraction of the very particular information important for intraoperative decision-making should be created. Such a system should permit prediction of the possible risks and inform the surgeon about their probability. The possible consequences of the various surgical manipulations have to be analyzed and the optimal solution "what to do" in constantly changing surgical situation should be offered. Moreover, as optimum such a system should simulate not only the surgical procedure, but the whole clinical course of the particular patient with comparison of the different treatment options, evaluating the various risks, and providing scientifically-based choice of the optimal treatment strategy for attainment of the best possible outcome. The development of such a complex computer-aided system based on the construction of the virtual neurosurgical reality is currently under way.

Conclusion

The incorporation of computer-aided diagnostic and management technologies into everyday clinical practice can significantly improve the quality of the neurosurgical service. It can enable us to optimize the choice of the treatment strategy in each individual case, based not on the individual experience of the particular surgeon, but on the integration of the whole spectrum of the clinical and scientific data. Computer-aided simulation of the treatment course of the particular patient can permit a clear determination of the roadmap to the best possible outcome. Further progress in advanced neurovisualization, robotics, and comprehensive medical information management, has a great potential to increase the safety of the neurosurgical procedures, and hopefully will result in improvements of the long-term outcome of patients with gliomas.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Patterns of Local Recurrence in Rectal Cancer: A Single-Center Experience

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ABSTRACT A cohort of patients operated at the National Cancer Center Hospital in Tokyo for rectal carcinoma, at or below the peritoneal reflection, was reviewed retrospectively. The purpose was to study the risk factors for local relapse and the patterns of local recurrence. Three hundred fifty-one patients operated between 1993 and 2002 for rectal carcinoma, at or below the peritoneal reflection, were analyzed. One hundred forty-five patients, with preoperatively staged T1 or T2 tumors without suspected lymph nodes, underwent total mesorectal excision (TME). Lateral lymph node dissection (LLND) was performed in suspected T3 or T4 disease, or when positive lymph nodes were seen; 73 patients received unilateral LLND and 133 patients received bilateral LLND. Of the 351 patients 6.6% developed local recurrence after 5 years. TME only resulted in 0.8% 5-year local recurrence. In lymph-node-positive patients, 33% of the unilateral LLND group had local relapse, significantly more ($p = 0.04$) than in the bilateral LLND group with 14% local recurrence. Local recurrence in the lateral, presacral, perineal, and anastomotic subsites was lower in the bilateral LLND group as compared with in the unilateral LLND group. We conclude that, in selected patients, surgery without LLND has a very low local recurrence rate. Bilateral LLND is more effective in reducing the chance of local recurrence than unilateral LLND. Either surgical approach, with or without LLND, requires reliable imaging during work-up.

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For rectal cancer, surgery is the principal treatment in order to cure. Total mesorectal excision (TME) removes the primary tumor with its surrounding mesorectum as an intact package, preventing residual tumor cells in the mesorectum from developing into local recurrence.[1,2] In advanced lesions neoadjuvant (chemo)radiotherapy can downstage tumors, but good surgical quality is still essential in order to achieve total clearance of tumor cells.[3]

The Japanese concept of surgical treatment of rectal cancer has evolved from anatomical studies in which three lymphatic flow routes were identified.[4,5] The upper route is along the superior rectal artery to the inferior mesenteric artery; the lateral route reaches from the middle rectal artery to the internal iliac and obturator basins; and the downward route extends to the inguinal lymph nodes. The upper and lateral routes were shown to be the main two routes of rectal cancer spread, with the peritoneal reflection as the limitation between the two lymphatic areas.[6] Consequently, lateral lymph node dissection (LLND) was developed in Japan in order to resect the tumor with the primary locoregional lymph node basins beyond the mesorectal plane.[7] LLND has resulted in better survival and lower recurrence rates than conventional surgery.[8,9]

A problem is that the lateral lymph node routes are anatomically close to the pelvic autonomic nerve plexus, requiring challenging surgery to preserve these during LLND.[10] In order to prevent damage to autonomic nerves, nowadays case-oriented policy is practised in Japan, adopting LLND only in advanced disease at or below the peritoneal reflection.

The aim of this study is to evaluate the treatment of rectal cancer between 1993 and 2002 at the National Cancer Center Hospital (NCCH), looking at patterns of local recurrence and the risk factors for local recurrence.

PATIENTS AND METHODS

Patients

From 1993 to 2002, 923 patients were operated for confirmed primary adenocarcinoma of the rectum at the National Cancer Center Hospital (NCCH) in Tokyo. Surgery was performed according to the guidelines of the Japanese Research Society for Cancer of the Colon and Rectum.[11,12] The rectum was defined as located below the lower border of the second sacral vertebra. The peritoneal reflection is the most important landmark in defining the location of the tumor, and *low* rectal carcinoma is defined as a tumor of which the major part is located at or below the reflection.[13]

For this analysis the following patients were excluded: metastasis at the time of surgery ($n = 134$) and in situ carcinoma ($n = 22$). Of the remaining 767 patients, only patients with rectal carcinoma at or below the peritoneal refection were selected, resulting in 360 patients.

Neoadjuvant chemotherapy was given to some patients with suspicion of stage T4 disease ($n = 3$) in other hospitals, before referral to the NCCH. Neoadjuvant radiotherapy was not routinely given, so no patients received preoperative radiotherapy. Sometimes in the case of positive lymph nodes, adjuvant radiotherapy ($n = 5$) or chemoradiotherapy ($n = 1$) was given. The nine patients who received neoadjuvant chemotherapy and adjuvant (chemo)radiation were excluded, leaving 351 patients for analysis.

Methods

Until 2002 preoperative evaluation at the NCCH consisted of computed tomography (CT) imaging and endoscopic ultrasonography for all patients. Based on preoperative imaging and intraoperative findings, standard total mesorectal excision (TME) was performed in T1 or T2 stage disease without suspected lymph nodes. Lateral lymph node dissection (LLND) was added to TME in stage T3 or T4 rectal cancer at or below the peritoneal reflection, or when positive mesorectal lymph nodes were suspected. Unilateral LLND was performed when the tumor was located lateral in the low rectum, bilateral LLND when the tumor was located centrally. When the lateral lymph nodes were 1 cm or larger on preoperative imaging or intraoperative findings, bilateral extended lymph node dissection was performed, consisting of dissection of the complete internal iliac artery and the autonomic nerve system. When there was no suspicion on positive lateral lymph nodes, autonomic nerve preservation (ANP) was carried out.

Accurate documentation of lymph node status and localization is obtained because all lymph nodes are harvested and recorded from the fresh specimen. The definition of mesorectal lymph nodes is pararectal location or in the direction of the mesentery. Lateral lymph nodes are located along the iliac or obturator arteries.

Follow-up of all patients consisted of thorax, abdominal, and pelvic CT imaging every 6 months. Median follow-up of patients alive was 7.9 years.

All patients who developed local recurrence, defined as any recurrence of rectal cancer in the lesser pelvis, were identified. Local recurrence was diagnosed clinically, radiologically or histologically.

For all locally recurrent patients the available preoperative images and the images at the time of discovery of the local recurrence were retrieved. A specialized oncologic radiologist (R.G.H.B.-T.) reviewed the images. Examining the images, the site of the local recurrence was determined. The sites were classified into the following regions: lateral, presacral, perineal, anterior or anastomotic. The same borders for the respective sites were used as defined by Roels et al.[14] When no images were available, the location of recurrence was classified using the radiology reports and clinical data. In one patient insufficient information was provided to determine the location of recurrence with certainty.

Statistical Analysis

Statistical analysis was performed using the SPSS package (SPSS 12.0 for Windows; SPSS Inc., Chicago, IL) and R version 2.5.1. *T*-tests and chi-square tests were used to compare individual variables. Survival and cumulative recurrence incidences were estimated using the Kaplan–Meier method. Differences between the groups were assessed using the log-rank test. All p-values were two-sided and considered statistically significant at 0.05 or less. For local recurrence, cumulative incidences were calculated accounting for death as competing risk.[15] Similarly, cumulative incidences were calculated for subsite of local recurrence, with death and other types of local recurrence as competing risks, and for cancer-specific survival, with death due to other causes as competing risk. Multivariate analyses of local recurrence and overall survival were performed by first testing the effect of covariates in a univariate Cox regression. Covariates with trend-significant effects (p-value < 0.10) were then selected for multivariate Cox regression. The following variables were studied for local recurrence and overall survival: age, sex, operative procedure, degree of lateral lymphadenectomy, T-stage, mesorectal lymph node N-stage, lateral lymph node positivity, maximum tumor diameter, differentiation, and autonomic nerve preservation.