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두개 기저부 척삭종의 세포유전학 및 분자생물학의 최신 지견

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Update on the Cytogenetics and Molecular Genetics of Skull Base Chordoma

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Chordomas are rare, low-to-intermediate grade malignant tumors arising from notochordal remnants in the midline skeletal axis. They account for <1% of central nervous system tumors and <5% of all primary malignant bone tumors. It is characterized by slow growth, local recurrence, and low metastasis rates. An increasing variety of techniques is now available to detect genetic alterations in chordomas, herein, we review the current knowledge of the genetic alterations in the skull base chordomas. The distribution of copy number changes is composed by two approaches; the low-resolution banding karyotyping and high-resolution whole genome CGH approach. The mapping of candidate genes in chordoma genesis awaits the application of high resolution targeted approaches. Chromosome 1p36.13 and 7q33 represent a candidate region for a chordoma gene. In gene expression study, many genes, such as HER2/neu, epidermal growth factor receptor, c-Met, platelet-derived growth factor receptor A and B, KIT receptors, E-cadherin, neural cell adhesion molecule, progesterone receptor B, estrogen receptor alpha, transforming growth factor alpha and basic fibroblast growth factor, fibronectin, and Cathepsin K, are differentially expressed and act a potential therapeutic target.

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Introduction

Chordomas are rare, low-to-intermediate grade malignant tumors arising from notochordal remnants in the midline skeletal axis. They account for <1% of central nervous system tumors [1] and <5% of all primary malignant bone tumors. [2] Clinically they are slow-growing tumor characterized by local spread. Symptoms manifest late, even after years, and therefore the local extent of disease is often huge at diagnosis. The natural course of chordoma is quite grim; most patients do not survive 10 years because of high recurrence rates. [3, 4] Given the natural history and high local recurrence rates, treatment is based on local modalities. The current treatment of choice is aggressive surgical excision followed by local irradiation, but even with the best treatments available, overall survival time remains roughly 5 years. [5]

Given the rare nature of these tumors, relatively little is known about the molecular biology. With the recent introduction of targeted molecular therapeutics into clinical practice, an enhanced understanding of the molecular biology of chordomas is needed. An increasing variety of techniques is now available to detect genetic alterations in chordomas, including immunohistochemistry for the detection of products of altered gene expression, karyotype analysis, fluorescence in situ hybridization (FISH) of chromosome spreads to assess ploidy status and identify certain genetic rearrangements, Southern blotting and the polymerase chain reaction (PCR) for genomic DNA analysis, reverse transcriptase polymerase chain mRNA products, and DNA sequencing.

Herein, we review the current knowledge of the genetic alterations in the skull base chordomas.

Histopathology and Immunohistochemistry

Grossly, chordomas are multilobulated, gray, partially translucent, glistening, cystic or solid masses that resemble cartilage tumors or occasionally a mucin producing carcinoma. Microscopically, the tumor is characterized by a distinct, lobular architecture that is formed by the physaliphorous ('soap bubble') cells with ample vacuolated cytoplasm as well as by the 'signet ring' type; in between the cells, there are fibrous septae which are incomplete and densely infiltrated by lymphocytes. Chordomas are of three overlapping, chondroid and dedifferentiated. To the areas showing physaliphorous cells, an occasional tumor may show a typical spindle cell sarcoma arrangement or a round ell pattern, while others may show an epithelial arrangement. Following treatment with radiation therapy, areas of spindle cell sarcoma formation may be seen.

Differential diagnosis of chordomas includes primary bone tumors, cartilagineous neoplasms such as chondromas or chondrosarcomas, epithelial neoplasms such as mucinous-forming adenocarcinoma or salivary neoplasms, metstases, neurinoma, neurofibroma, meningioma, neuroblastoma, hemangioma and lymphoma. Chordomas are usually positive for keratin and S-100 protein and can be differentiated from epithelial neoplasms. [6, 7] Cartilage tumors and keratin negative and adenocarcinomas are S-100 negative. Cytokeratin antibodies and EMA (epithelial membrane antigen) positivity of chordoma is used to distinguish it from cartilaginous neoplasms, where the absence of these epithelial markers should be the rule. [8] Immunoperixidase staining is useful in distinguishing chordoma from adenocarcinoma and cartilage tumors. Some chordomas stain positive with vimentin antisera, which reflects mesenchymal differentiation. [9]

Cytogenetics, FISH and CGH

The cytogenetic description by conventional banding and FISH-based techniques is restricted to less than 100 cases of chordoma worldwide. Persons et al. [10] recorded twenty-nine cases of conventional chordoma with aberrant karyotype in the Mitelman Catalog of Chromosome Aberrations in Cancer (CGAP). Six additional tumors, recently published, can be added to this list. [11, 12] Out of 35 chordomas with aberrant karyotype, 18 are annotated as recurrences: two as

metastases, four as primary tumors, while no information is available for the remaining 11 tumors. The high rate of recurrent tumors among chordomas with aberrant karyotype is in keeping with the suggestion that in chordomas chromosome aberrations appear as late events in tumor progression.[13] The great majority are either hypo or quasi-diploid and only two are hyperdiploid.[13, 14] Only a few cases have simple karyotypes with one or more aberrations, but no underlying breakpoint was shared among chordomas characterized by a sole balanced translocation or rearrangement.[13, 15-18] So far there are no clues that specific translocations, resulting in chimeric genes, play a pathogenetic role in chordomas. As to numerical chromosome abnormalities, losses involve in the order chromosomes 3, 13, 10, 22, 4, 18, 14, 9 and Y, while gains affect preferentially chromosomes 7, 2 and 21 [CGAP]. Imbalances of chromosome arms or subchromosomal regions were also identified, most commonly loss of 3p, 3q or both segments, loss of 1p and 9q, but in most cases these were gross alterations, and their pattern appears to be not specific [CGAP]. A large variety of rearrangements, among which isochromosome 1q and loss of part or all of 1p were identified as equivalent recurrent changes associated with chordoma progression.[13, 19] Loss of 1pter-p34 has been detected in 14 cases,[11] suggesting that a tumor suppressor locus might map in 1p36.[20] CGH analysis evidenced copy number changes restricted to chromosome arms or smaller genomic regions, but due to the limited number of tumor samples, only a few generalities can be drawn. One, at apparent discordance with karyotype data, is that gains were more common than losses. One third of the tumors analyzed by CGH combined to FISH were hyperdiploid: a finding making the authors suggest that hypo or near diploid cell populations have a growth advantage in vitro.[21] Hypodiploidy is not a feature of human solid tumors. More precisely, the investigation of 16 chordomas showed that there was a median of six chromosomal imbalances per tumor, on average, 3.2 losses and 4.2 gains. Most common losses mapped on chromosomal arms 3p (50%) and 1p (44%) and most common gains involved 7q (69%), 20 (50%), 5q (38%) and 12q (38%).[21] Another study disclosed that the most frequently observed chromosomal imbalances were gains in chromosomes 1q, 7p, 7q, and 19q and loss in chromosome 9p.[24] The consensus region for gains on chromosome 7q was 7q36, where the homeobax gene HLXB9 and sonic hedgehog gene SHH reside: interestingly both genes are a plausible candidate as they are expressed throughout the notochord during embryogenesis.[22] Use of high resolution FISH techniques, such as COBRA did not pinpoint any clustering of breakpoints, but confirmed loss of chromosome arms 1p, 3p, 3q, 9p and chromosome 10.[11] Gains and losses are indicated by lines to the right and to the left of each chromosome ideogram. The distribution of copy number changes is composed by two approaches; the low-resolution banding karyotyping and high-resolution whole genome CGH approach. The mapping of candidate genes in chordoma genesis awaits the application of high resolution targeted approaches.

LOH and Microsatellite studies

The first LOH study on chordomas concerned the Rb locus (13q14) at which LOH was detected in two of 7 sphenooccpital/clivus tumors, and proposed by correlation with the clinical behavior as a marker of aggressive tumors.[23] Further LOH studies evidenced the loss of 17p, 9p and 18q, where known tumor suppressor genes are mapped.[25] It has been reported that the combined loss of p53 function and RB1 protein leads to genomic instability, a finding consistent with the model of progressive accumulation of genetic changes with increasing malignancy.[26]

Riva and colleagues' research with 28 chordoma specimens suggests that the possible importance of the short arm of chromosome 1.[27] The 1p36.13 band had been pinpointed by the recurrent breakpoints identified in two tumor recurrences of the founder of an Italian chordoma family and the haplotype and LOH information retrieved on this family.[19, 20] Typing of 31 region-specific microsatellites evidenced LOH across 1p36.13 in 25 out of 27 sporadic chordomas.[27, 34] The

first selection of region-specific genes was based on genes with functions-related to development or regression of the notochord such as Caspase 9 (CASP9) and Ephrin 2A (EPH2A). CASP9 is a ubiquitously expressed protease which triggers the apoptotic pathway by releasing cytochrome c from mitochondria and the cytosol.[28] EPH2A is a tyrosine kinase receptor involved in tail notochord formation during mouse embryo development.[29] Additional candidate genes come to the attention when a wider LOH region, which is shared by a lower percentage (40%) of chordomas is considered. They include the paired box 7 (PAX7) gene encoding a transcriptional factor expressed in the neural tube which is regulated by notochord specific signals,[30] the differentially screening-selected gene aberrant in neuroblastoma (DAN), involved in the negative regulation of cell proliferatin,[31] the Dishevelled 1 gene (DVL1), a key factor in Wnt signaling expressed in the neural tube[29] and a few genes belonging to the tumor necrosis factor receptor superfamily (TNFRSF-1B, -8, -9, -14), the DNA fragmentation factor (DFF-A and -B). Priliminary RT-PCR expression analysis of eight chordomas evidenced the lack of CASP9, EPHA2 and DVL1 transcripts in 5, 1, and 4 tumors, respectively. In recent study, tumor necrosis factor receptor superfamily genes were differently expressed compared with control in a higher percentage of tumors (40-53%), suggesting that the deregulation of these three genes might have a role in chordoma tumorigenesis.[34] Kelly and colleagues performed a genomic linkage analysis on families with multiple members who had chordomas and were able to isolate a locus on chromosome 7q33.[32] The absence of LOH may indicate that the disease gene exerts its oncogenic effect in a dominant way.

Gene expression study

Weinberger et al.[33] evaluated the specimens from ten patients for HER2/neu, epidermal growth receptor (EGFR) and c-Met expression. They found that HER2/neu expression was seen in 70% of cases, EGFR in 100% and c-Met in 100%; expression of c-Met and EGFR were correlated. Tamborini et al.[35] studied 31 cases of sacral, spinal or clival chordomas for expression of platelet-derived growth factor receptor (PDGF receptor) A and B and KIT receptors. PDGFB receptor expression and phosphorylation and the presence of PDGFB were seen in the samples analyzed, suggesting an autocrine/paracrine loop as a possible mechanism contributing to the pathogenesis of chordomas; similar findings were observed for PDGFA and KIT receptors but at lower expression levels. Mori et al.[36] reviewed seven cases of chordoma for the expression of E-cadherin, which was expressed in all chordomas cells, especially at intracellular adhesion sites, but epithelial cell adhesion molecule was not consistently expressed.

The expression of cell adhesion molecules (CAMs) including E-cadherin, alpha-catenin, beta-catenin, gamma-catenin and neural cell adhesion molecule (NCAM) has been associated with formation and maintenance of chordoma tissue architecture and found a diagnostic value for discriminating chordoma from chondrosarcoma.[39] Saad et al.[37] reviewed eight cases of pediatric chordomas and found a negative correlation between the percentage of cells expressing E-cadherin and tumor recurrence and survival; a similar finding was seen for the MIB-1 labeling index but they note that this observation differs from adult patients where the MIB-1 labeling index is much lower. Palini et al.[38] found that there was an association with p53 mutations and expression of human telomerase reverse transcriptase mRNA and the combination was predictive of aggressive tumor behavior.

Investigations on steroid hormone receptors, which are involved in tumor growth, evidenced that progesterone receptor B and estrogen receptor alpha were expressed in chordoma and hence associated with tumor progression.[40] High levels of transforming growth factor alpha and basic fibroblast growth factor expression were linked to higher rates of recurrence and strong fibronectin expression was also associated with poor prognosis, being thus considered an additional marker of aggressiveness.[41] Cathepsin K is a member of the papain family of cystine protease and is

considered to play an important role in osteoclast resorption. This protein was localized to the advancing tumor front in 44 specimens of chordoma using immunohistochemistry and RT-PCR.[42] This data indicates Cathepsin K as an important mediator of proteolytic degradation in chordoma spread, and a potential therapeutic target to reduce tumor spread and recurrence.

Conclusions

Chordomas is a peculiar tumor and is characterized by slow growth, local recurrence, and low metastasis rates. Given the rare nature of these tumors, relatively little is known about the molecular biology. An increasing variety of techniques is now available to detect genetic alterations in chordomas, including immunohistochemistry for the detection of products of altered gene expression, karyotype analysis, fluorescence in situ hybridization (FISH) of chromosome spreads to assess ploidy status and identify certain genetic rearrangements, Southern blotting and the polymerase chain reaction (PCR) for genomic DNA analysis, reverse transcriptase polymerase chain mRNA products, and DNA sequencing. Potential candidate genes should thus emerge, besides residing in genomic intervals, such as 1p36 and 7q33, which are though to be relevant for chordoma tumorigenesis and/or progression. In addition, microsatellite instability and LOH of the candidate genes is strongly involved in chordoma tumorigenesis and/or progression. In gene expression study, many genes, such as HER2/neu, EGFR, c-Met, PDGF receptor A and B, KIT receptors, E-cadherin, NCAM, progesterone receptor B, estrogen receptor alpha, transforming growth factor alpha and basic fibroblast growth factor, fibronectin, and Cathepsin K, are differentially expressed and act a potential therapeutic target. Further studies are warranted for understanding of molecular biology and targeted molecular therapeutics of skull base chordoma.

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크기가 큰 청신경 초종 치료의 최신 경향

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Recent Trends in Management of Large Vestibular Schwannomas

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Management strategy of large vestibular schwannomas (VS) is still on debate regarding complete removal for tumor control versus incomplete removal for cranial nerve preservation. Still surgery for VS is difficult task for most neurosurgeons to achieve good tumor control rate without neurological sequela. Introduction of radiosurgery has greatly changed therapeutic strategies for large VS, but it has limitations due to large tumor mass. Admist the on-going controversy over optimal therapeutic strategy for large VS, we reviewed literatures for recent trends of therapeutic strategy for large VS.

Near-total removal (NTR) and radical sub-total removal (R-STR) followed by radiosurgery showed comparable tumor control rate and favorable facial nerve preservation rate. If preservation of facial nerve is guaranteed, NTR alone is recommended. In case of incomplete surgical resection to save facial nerve integrity, adjuvant radiosurgery is beneficial for tumor control.

Key Words *Large vestibular schwannomas, Microsurgery, Radiosurgery, Multimodal treatment*

■ 크기가 큰 청신경 초종 치료의 역사적 고찰

청신경 초종의 첫 성공적인 수술은 1894년 Balance에 의해 이루어졌다.[2] 우측 소뇌다리뇌각(cerebellopontine angle)에 있는, 경계가 좋은 종양을 제거하였으며, 수술 시행 12년 후 환자가 생존해 있음을 보고하였다. 1917년 Cushing은 청신경 초종의 종양의 피막 내 부분 절제의 성공적 시행을 보고하였으며,[5] 1925년 Dandy에 이르러 종양의 완전 제거를 통한 수술적 완치를 보고하였다.[6] 1949년 Olivecrona가 안면신경을 보존하면서 청신경 초종 수술에 성공하였으며,[17] 1968년 House는 미로경유접근법(translabyrinthine approach)를 청신경 초종 수술에 성공적으로 재적용하였다.[9] 처음 Leksell이 1969년에 청신경 초종에 대한 방사선 치료를 시도하였으며,[16] 1974년 Yasargil에 의해 현미경을 이용한 수술법이 소개되었다.[29] 신경외과 수술의 마취에 대한 이해 향상 및 유발 전위를 이용한 안면신경에 대한 수술 중 감시 방법이 소개되면서, 1995년 Jannetta는 큰 청신경 초종의 치료에서의 단계적 수술법 (staged operation)의 개념을 제시하였다.[4]

Table 1. Classification of vestibular schwannomas according to its size and symptoms Size and symptoms

Size	Grade (Koos, 1985)	Stage (CPA syndrome)	Symptom
Small 〈 1.5 cm	I	〈 1 cm I	CN VIII only †
Medium 1.5–3 cm	II	1–2 cm II	+ CN V or VII ‡
	III	2–3 cm III	+ BS, Low CN, CbII §
Large* 〉 3 cm	IV	〉 3 cm IV	+ IICP ¶

* Giant: 〉 4cm, Huge: 〉 5cm
† Auditory & vestibular dysfunction
‡ Stage I + facial motor or sensory dysfunction
§ Stage II + low cranial nerve or cerebellar dysfunction or brainstem compression signs
¶ Stage III + symptoms of hydrocephalus

Abbreviation: CPA, cerebellopontine angle; CN, cranial nerve; BS, brain stem; CbII, cerebellum; IICP, increased intracranial pressure

Table 2. Reported recurrence rate after gross-total resection of vestibular schwannoma

	N	Recurrence
Acoustic Neuroma Registry[26]	1579	8%
Samii et al[22]	1000	0.7%
Cerullo et al[3]	55	9%
Mazzoni et al	104	8%
Gormley et al[8]	178	〈 1%

■ 크기에 따른 청신경 초종의 분류와 증상의 변화

일반적으로 직경 1.5cm 미만의 경우 "small size", 1.5에서 3cm 사이를 "medium size", 3cm 이상을 "large size"로 분류하며, "large size"로 분류된 종양 중 4cm 이상의 경우 "giant", 5cm 이상의 경우에는 "huge"로 분류한다.

증상의 정도에 따라 병기 (stage)를 나누고 있으며, 청력의 변화, 전정신경 장애에 의한 증상이 나타나는 경우를 병기 I, 여기에 삼차신경 장애 및 매우 드물지만 안면신경 장애 의한 증상이 동반되는 경우 병기 II, 하부뇌신경 장애 및 뇌간, 소뇌 장애에 의한 증상이 추가로 동반되는 경우를 병기 III, 상기 증상에 수두증에 의한 증상이 추가로 동반되는 경우 병기 IV로 분류하고 있다 (Table 1).

종양의 크기는 병기와 직접적인 연관성이 있다. 일반적으로 청신경 초종은 크기가 클수록 그 증상의 정도가 심해지며, 큰 청신경 초종의 경우, 소뇌와 뇌간을 압박하여 증상을 유발하며, 안과적 장애를 포함하는 수두증에 의한 증상들이 발현할 가능성이 있다. 수술 중에 주변 중요 조직들과 심하게 유착이 되어 있는 경우가 많아 수술이 어렵고, 수술 후 발생하는 청력 소실은 대부분 호전되기 어려우며, 안면신경 및 하부뇌신경 장애를 포함한 주요 합병증이 발생할 가능성이 높다.[20]

따라서, 큰 크기의 청신경 초종을 치료함에 있어 종양 억제 (tumor control)와 더불어 안면 신경 및 하부 뇌신경의 기능 보존에 상당한 주의가 필요하다.

■ 과거의 치료 성적 및 최근 치료 경향

청신경 초종의 수술 후 재발률은 완전절제 (gross total resection, GTR)를 시행하였을 경우 대략 10% 내외로 보고되고 있으며 (Table 2),[3, 8, 22, 26] 아전절제 (subtotal resection, STR)을 시행하였을 경우 25~32%의 재발률이 보고되고 있다 (Table 3).[1, 12, 24]

큰 크기의 청신경 초종 (large size 이상)의 수술 후 안면신경마비

Table 3. Reported recurrence rate after incomplete resection of vestibular schwannoma

	N	F/U(years)	Extent of removal	Recurrence
Bloch et al[1]	52	5	NTR	3%
			R-STR	32%
Sakaki et al[24]	29	10	R-STR	25%
Kameyama[12]	19	10	R-STR	26%

Abbreviation: F/U, follow up; NTR, near-total resection; R-STR, radical sub-total resection

정도는 Yasargil 등이 37%, King & Morrison 등이 80%, House & Hitselberger 등이 40%, Ebersold 등이 24%로 보고하고 있어 술자에 따라 그 정도가 매우 다양하다 (Table 4). [7, 10, 13, 15, 23, 30]

Table 4. Functional preservation after surgery of large vestibular schwannoma

	Tumor size (cm)	Facial nerve palsy
Yasargil (1977)[30]	〉 3.0	37%
King & Morrison (1980)[13]	〉 2.5	80%
House & Hitselberger (1985)[10]	〉 4.0	40%
Samii (1985)[23]	〉 3.0	46%
Ebersold (1992)[7]	〉 4.0	24%
Lanman (1999)[15]	〉 3.0	47.4%

최근 들어 수술 기법의 발전과 수술 중 감시 기법의 발전, 그리고 방사선 수술의 발전으로 큰 크기의 청신경 초종을 치료하는데 있어 수술을 통한 부분적 절제 후 남은 종양에 대한 방사선 수술을 시행하는 단계적 치료 전략이 제시되었다. 크기가 큰 청신경 초종을 안면신경의 손상 없이 완전히 제거하는 것은 외과의의 상당한 경험이 요구되며, 그 정도의 숙련도를 가진 신경외과의는 소수라는 점, 최근 방사선 수술의 대중화로 청신경 초종 수술 건수가 감소 추세에 있어, 수술을 경험하기가 예전보다 더 어려워졌다는 현실이 이 전략의 타당성을 뒷받침한다. 또한, Iwai 등과 Prasad 등은 크기가 큰 청신경 초종을 아전절제 후 방사선 수술을 시행하였을 때, 완전절제를 시행하였을 때의 종양 억제 정도와 비슷한 90% 이상의 성적을 보여 주고 있으며, 안면신경마비의 빈도도 15% 이하로 현저히 낮음을 보고한 바 있어 (표 5), [11, 19] 최근에는 크기가 큰 청신경 초종의 치료에 있어 수술적 제거 후 방사선 수술을 시행하는 단계적 치료 전략이 많이 채택되고 있다. [25]

그러나, 아직 방사선 수술 합병증의 생물학적 발생 기전에 대한 이해가 불확실하고, 치료 효과에 대한 큰 규모의 연구도 없는데다, 8년 이상의 장기간 추적 관찰한 연구 자료는 거의 없는 실정이어서, 아직 수술적으로 완전 제거하는 치료 전략과의 우위를 비교하기는 이르다. 종양을 아전절제 해야 하는 상황 및 정도에 대한 기준이 모호하며, 수술을 진행함에 있어 수술 중 전기생리학적인 감시장치만으로도 안면신경기능을 충분히 보존할 수 있다는 주장도 있어, 아직 크기가 큰 청신경 초종의 치료 전략에 대한 논의는 아직 진행 중이다. [25, 27, 28]

Table 5. Reported outcomes after incomplete resection followed by radiosurgery for vestibular schwannoma

	N	Size	F/U(years)	Tumor control rate	FNP
Iwai et al[11]	14	42mm	3	93%	14.3%
Prasad et al[19]	57	UM	10	90%	11%

Abbreviation: F/U, follow up; FNP, facial nerve palsy; UM, unmeasured

환자의 나이, 기대 수명, 종양의 크기와 주변 조직과의 유착 정도, 환자의 전신 상태, 수술 후 합병증 이환률, 그리고 환자 본인의 선호도 등의 다양한 변수가 치료 전략에 영향을 미친다. 이 글에서는 서울대병원에서 치료한 크기가 큰 청신경 초종의 최근 치료 경험을 분석한 연구 결과의 고찰을 통해, 치료 전략에 대한 최근의 경향을 소개하고자 한다.

서울대병원에서의 크기가 큰 청신경 초종 치료 결과 분석 및 고찰[18]

연구 대상 및 방법

1990년부터 1999년까지 10년 동안 3cm 이상의 청신경 초종으로 수술 받은 환자를 대상으로 후향적 분석 (retrospective analysis)을 시행하였다. 모두 한 명의 신경외과의(HWJ)에게 수술 받은 환자들로, 신경섬유종증 2형 (neurofibromatosis type II)과 단계적 수술 (staged surgical operation)을 계획, 시행하였던 환자는 제외하였다. 총 50명의 환자가 연구에 포함되었으며, 평균 경과 관찰 기간은 113 개월 (58-167 개월)이었다.

종양의 성상

종양의 평균 지름은 36.4mm (30.0-47.2 mm)이었고, 평균 부피는 26.8cc (13.5-55.1 cc)였다. 환자의 40%가 고형 종양 (solid tumor)였으며, 고형성 병변에 낭성 병변이 섞여 있는 종양 (solid and cystic tumor) 이 52%, 그리고 낭성 병변만 있는 종양을 가지고 있는 환자가 8%였다.

Table 6. Recurrence rate, result of SNUH (N=50)

	GTR	NTR	R-STR/STR	R-STR+GKS
N	9	8	25	8
Recurrence	1	0	8	0
Recurrence rate	11%	0%	32%	0%

Abbreviation: SNUH, Seoul National University Hospital; GTR, gross-total resection; NTR, near-total resection; R-STR, radical subtotal resection; GKS gamma-knife surgery

Table 7. Facial nerve function preservation rate*, result of SNUH (N=50)

	GTR	NTR	R-STR	STR
N	9	8	31	2
FNP	4	3	4	0
Preservation rate	56%	62.5%	87%	100%

* Percentage of House-Brackmann grade 1 or 2 after surgery

Abbreviation: SNUH, Seoul National University Hospital; GTR, gross-total resection; NTR, near-total resection; R-STR, radical subtotal resection; STR, subtotal resection; FNP, facial nerve palsy

치 료

수술은 구불정맥굴뒤접근법 (retrosigmoid approach)를 통해 수술한 환자가 86%, 미로경유접근법 (translabyrinthine approach)를 통해 수술한 환자가 12%였으며, 구불정맥굴앞 및 뒤 접근법을 함께 사용 (combined pre- and retro-sigmoid approach) 하여 수술한 환자가 2%였다. 종양의 제거 정도는 완전절제(GTR)한 환자가 18%, 근전절제 (near-total resection, NTR)한 환자가 16%, 근치적 아전절제(radical sub-total resection, R-STR)한 환자가 62%, 그리고 아전절제(STR)한 환자가 4%였다 (Figure 1). 수술 후 추가적인 방사선 수술을 시행했던 환자는 근치적 아전절제를 시행하였던 환자 중 8명에서 감마나이프 수술 (gamma-knife surgery)을 시행하였다.

결 과

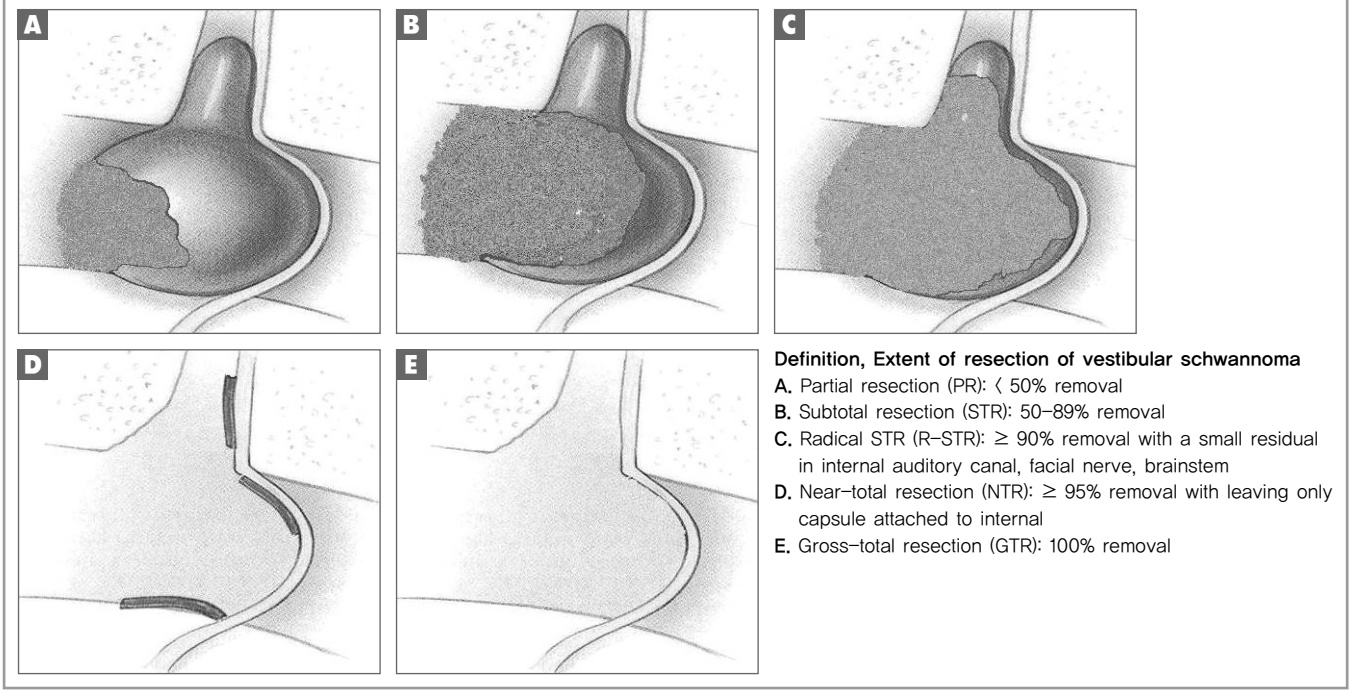
전체 재발률은 50명 중에 9명으로 18%였으며, 완전절제된 환자 중 1명이 재발되었고, 근전절제된 환자군과 근치적 아전절제 후 감마나이프를 추가로 치료했던 환자군에서는 재발이 없었으나, 수술 후 추가적인 방사선 수술을 받지 않은 근치적 아전절제와 아전절제 환자군에서는 32%에서 재발하였다 (표 6).

수술 후 안면신경 보존된 환자 (House-Brackmann grade 1 또는 2를 보인 환자)의 수는 50명 중 39명으로 보존률 78%을 보였다. 종양의 제거 정도에 비례하여 안면신경 보존률은 감소하였는데, 완전절제된 환자군의 경우 56%, 근전절제된 환자군의 경우 62.5%, 근치적 아전절제된 환자군은 87%, 그리고 아전절제된 환자군의 경우, 수는 적지만 100%의 안면신경 보존률을 나타내었다 (Table 7).

결 론

크기가 큰 청신경 초종을 수술함에 있어 안면신경을 확실하게 보존할 수 있는 상황에서라면, 가능한 근전절제를 시행하는 것이 바람

Fig. 1



직하며, 안면신경 보존을 위해 일부 종양을 남겨 근치적 아전절제가 된 경우에 있어서는 수술 후 남은 종양에 대한 추가적인 방사선 수술을 시행하는 것이 종양 재발을 억제하는데 큰 도움이 될 것으로 보인다.

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신경항법장치를 이용한 두개저외과수술의 장점

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Benefits of skull base surgery using neuronavigation system

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Objective : Skull base tumors frequently encase or extend into vital neurovascular structures. Preoperative planning and intraoperative identification of anatomic landmarks is important in complex tumors since it helps avoid or minimize surgical morbidity. The purpose of this study was to describe the usefulness of recent advances of neuronavigation technology in the management of skull base tumors.

Patients and Methods : From March 2006 to May 2008, 32 patients underwent neuronavigation-assisted surgery for skull base tumors. A Stryker Leibinger system was used for neuronavigation.

Results : The use of neuronavigation was beneficial both pre-and intraoperatively. Gross total removal of the skull base tumors was accomplished in 29 out of 32 patients who were confirmed with postoperative CT and MRI scans. All tumors were removed completely as judged by intraoperative inspection in all patients except for three. The morbidity rates (18.8%) were different depending on the performed surgical approaches.

Conclusions : Image guidance facilitates complex approaches to various pathologies and enables mapping of skull base anatomy, especially during translesional dissection of complex tumors distorting and invading the neurovascular and osseous structures. Neuronavigation will enhance the efficacy and safety of skull base surgery. Skull base surgery is the best target for it because of the minimum possible brain shift.

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Key Words *Neuronavigation, Skull base surgery, Image guidance.*

Introduction

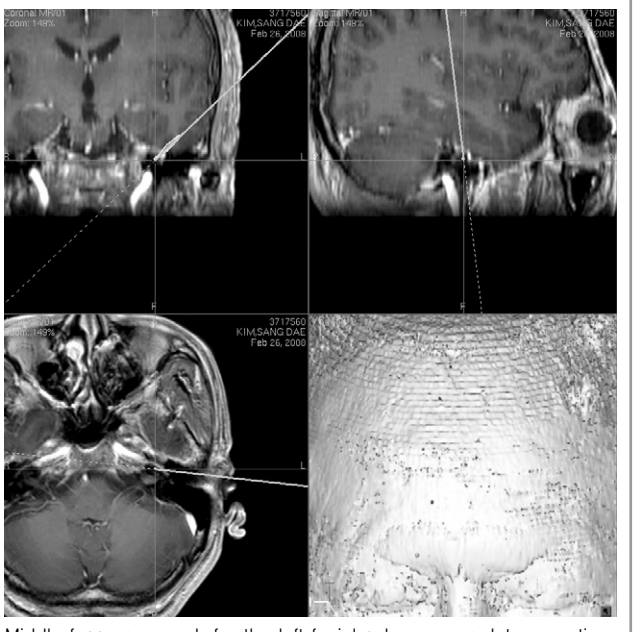
Tumors of the skull base frequently encase or extend into normal neural and vascular structures. Safe resection of the skull base lesions ultimately depends on the skill and experience of the surgeon, but evolving experience with image guidance over the past few years indicates the potential value of neuronavigation in skull base lesions. [4, 5, 12] Reported benefits include optimized positioning of the craniotomy site and the ability to define ideal vectors for approaching deep seated intrinsic lesions with minimal cortical trauma. The greatest value and versatility of surgical navigation in the skull base surgery is the fact that it provides guidance in planning the incision, determining the size of the craniotomy flap, and assessing the extent of bone resection at the skull base. Preoperative planning and intraoperative localization of anatomic landmarks are particularly important in complex skull base tumors and help avoid or minimize the surgical morbidity.

In this study, our preliminary experience with 35 consecutive patients operated on skull base lesions using an advanced image guidance system is reported.

Patients and Methods

From March 2006 to May 2008, 32 patients underwent neuronavigation-assisted surgery for skull base tumors (petroclival meningioma n=3, medial sphenoid wing meningioma n=3, olfactory groove meningioma n=2, tentorial meningioma n=3, foramen magnum menignioma n=1, acoustic schwannoma n=7, trigeminal schwannoma n=4, facial nerve schwannoma n=2, clival chordoma n=3, suprasellar gangioglioma n=1, pituitary stalk lymphoma n=1, brainstem hemangioblastoma n=1, and epidermoid cyst on the cerebellopontine angle n=1). A Stryker Leibinger system was used for neuronavigation. The decision as to which imaging modalities and which new tools of neuronavigation were to be applied, was guided by the approach considered, the nature of the lesion, and the structures at risk. For navigational planning, either computed tomography scans or T1-weighted magnetic resonance images with 2-mm thick axial slices with contrast injection were chosen. Preoperatively, CT or MR scans were performed after 5-6 adhesive fiducial markers were placed in a non-colinear fashion on the patient's head according to the surgical position. The CT or MR imaging data sets were transferred to the computer workstation at the planning room via a network. The computer reformatted the axial images into coronal and sagittal views and three-dimensional images. Intraoperative data for localization are acquired as one infrared camera activate and receive the signal emitted from reflective markers placed on a reference star array attached to a Mayfield clamp fixed to the patient's head. After patient positioning and application of the Mayfield head clamp, patient to image registration was performed using a non-sterile handheld pointer. Various reflective marker arrays were applied to surgical instruments so that they could be used as active pointers during the operation.

Fig. 1



Middle fossa approach for the left facial schwannoma. Intraoperative neuronavigation showing the precise localization of the tumor in the internal acoustic meatus.

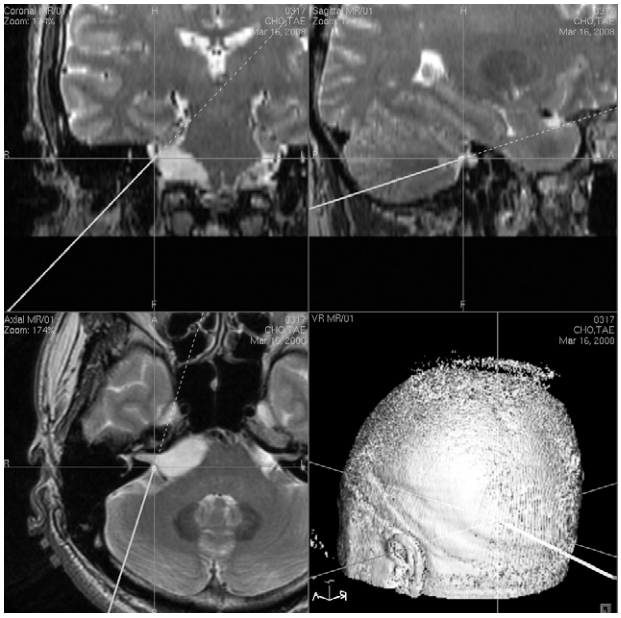
Results

The use of neuronavigation was beneficial both pre-and intraoperatively. The preoperative image preparation procedure and surgical planning were performed by a navigation-experienced neurosurgeon and took 10-15 minutes for data transfer and highlighting of tumors and anatomic landmarks. The intraoperative patient-to-image registration procedures were also performed by a navigation-experienced neurosurgeon and required 2 to 5 minutes with 5 to 6 skin fiducial markers. No pitfalls or technical difficulties were noted. Because of the relative immobility of the bone structures and/or the tumor, no significant deviation from the preoperative registration accuracy was noted at the end of the procedures. When compared to the intraoperative bony landmarks (for example, the clinoid processes) that were exposed during the surgical procedures it was estimated at <2mm in all our cases. As skull base tumors and basally located anatomic structures do not move due to CSF loss during dissection, a high localization accuracy of image guidance in skull base surgery can be assumed also for distorted vessels and neural structures. In the present study, gross total removal of the skull base tumors was accomplished in 29 out of 32 patients who were confirmed with postoperative CT and MRI scans. All tumors were removed completely as judged by intraoperative inspection in all patients except for three; in the first two patients with petroclival and medical sphenoid wing meningiomas, a piece of tumor that had infiltrated the cavernous sinus was left at the medical surface of the cavernous sinus. A third patient had a suprasellar ganglioglioma adherent to the hypothalamus. The morbidity rates (18.8%) were different depending on the performed surgical approaches.

Discussion

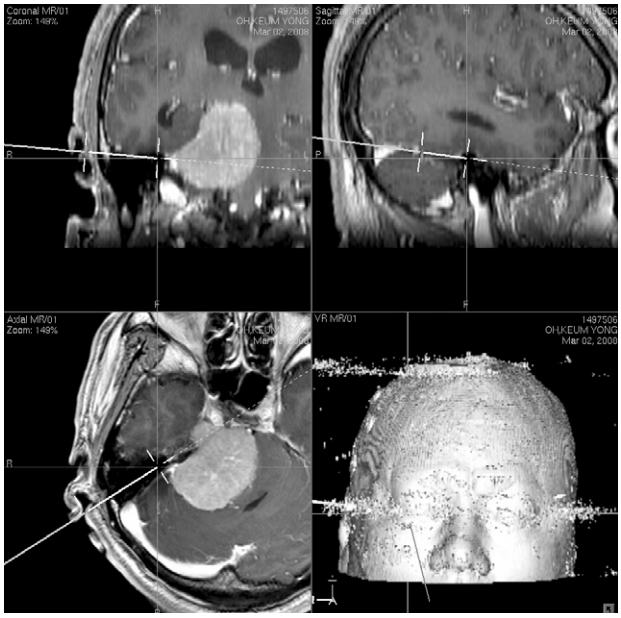
Operative neurosurgery has recently entered an exciting area of image-guided surgery or neuronavigation and application of this novel technology is beginning to have a significant impact in many ways on a variety of intracranial procedures. Neuronavigation was the most helpful for operations on deeply seated lesions, skull base tumors and

Fig. 2



Retrosigmoid approach for the right epidermoid cyst. Intraoperative neuronavigation demonstrating porus of the right internal acoustic meatus.

Fig. 3



Petrosal approach for the right petroclival meningioma. Neuronavigation enables precise preoperative planning for the tumor.

lesions in brain areas with high functionality.[2, 3, 11] With its high application accuracy, the system presented in this study provides useful feedback to the surgeon for preoperative anatomic orientation, precise planning and stimulation of the surgical approach, intraoperative navigation, avoidance of vital neurovascular structures, and assessment of the extent of possible resection. It provided anatomic structures and identifies the possible location of residual tumor. Skull base tumors benefit from computer-assisted neuronavigation, particularly while planning a critical approach.[6, 8-10] This technology can also help to identify prominent vascular and neural structures associated with skull base, in an effect to providing a visual warning that these structures are in the vicinity during an aggressive tumor resection.

The aim of this study was to evaluate the clinical accuracy, practicality, and impact of this navigation system on skull base procedures. Accuracy was always sufficient for image-guided surgery of any region of the skull base, with an average target registration error of below 1.2 mm. Although the impact of brain shift on image guidance and the need for intraoperative image updating is a controversial and unresolved issue, it is well known that skull base lesions are remarkable for the small extent of intraoperative brain shift. This factor predicts a high degree of reliability for neuronavigation in the treatment of skull base pathologies.[1] Preoperative changes with tumor resection, loss of CSF and patient position can limit the surgeon's access to the operative field. However, brain shift is not important in skull base tumor. Skull base surgery seems to be the ideal subspeciality for image-guidance technology. The tremendous advantage of neuronavigation becomes obvious during the treatment of skull base lesions more than in any other type of neurosurgery, because the osseous and neurovascular structures do not move during the surgical manipulation.

The latest generation of neuronavigation systems has come up with software improvements and new tools. Today, manual segmentation processes allow us to display vessels, nerves and tumor 2- or -dimensionally during surgery. In general, the tumor and the nervous tissue are more precisely visualized by MRI, whereas the bony structures (e.g, the temporal bone, including the middle ear, cochlea and internal auditory meatus) are better visualized by CT. Vascular structures are also better visualized by CT angiography or MR angiography. With appropriate preoperative image acquisition, image preparation, registration, and segmentation, CT and MR image fusion can be performed, leading to enhanced visualization and augmented reality.[7] For skull base surgery a fused image display can provide the surgeon with more precise information on the exact geometric relationship between the soft tissue stuctures seen on MRI, the bony structures observed on CT, and the vascular structures seen on CT or MR angiography.

The early identification of distorted and/or eroded vital neurovascular structures during the transtumoral dissection without anatomic landmarks is the most important benefit that is offered by neuronavigation. Therefore, we believe that the use of neuronavigation as presented in our series might additionally help to keep the complication rate low in patients suffering from extensive skull base lesions. The authors believe that careful selection of the most suitable, not standardized, but individually tailored approach, and knowledge about neurovascular structures will contribute to better outcomes in skull base surgery with lower morbidity and mortality.

In conclusion, although brain shift occurred following craniotomy and with brain retraction, the relative immobility of these lesions at the skull base permitted an accurate targeting of all lesions with an error range of 1.0-2.5 mm throughout the entire procedure. This relatively precise intraoperative feedback led to more accurate recognition of tumor landmarks. It is the authors' impression that a more aggressive resection of these lesions was achieved than could be without the device. The application of the neuronavigation system not only revealed benefits for operative planning, appreciation of anatomy, lesion location and the safety of surgery, but also greatly enhanced surgical confidence.

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임상적 비기능성 뇌하수체 종양의 미세현미경적 가성피막의 제거

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Microsurgical Pseudocapsule Resection of Clinically Non-functioning Pituitary Tumors

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Objective : The aim of this study was to investigate the precise histological characteristics of the boundary, using surgical specimens from patients who underwent intensive resection of "microsurgical pseudocapsule" of clinically non-functioning pituitary tumors (CNPTs). Furthermore, we compared the remission rate of CNPTs between subjects with (Group 1) and without (Group 2) intensive resection of microsurgical pseudocapsule in order to correlate the histological complete resection and endocrinological remission.

Patients and Methods : Between January 2000 and December 2007, 113 patients underwent intensive microsurgical dissection during the transsphenoidal surgery in one hospital (Group 1). In the other hand, 24 patients underwent conventional subcapsular resection without intentionally removing the microsurgical pseudocapsule in another hospital (Group 2).

Results : The overall surgical remission rate in Group 1 with intensive resection of microsurgical pseudocapsule were statistically higher than the rates in Group 2 (without intensive resection of microsurgical pseudocapsule) (p=0.032). However, there were no statistical differences in postoperative hormonal function change between Group 1 and 2.

Conclusions : Our results indicate that aggressive resection of psuedocapsules increases the cure rate without aggravating pituitary function.

Key Words *Pituitary tumors, Pseudocapsule, Transsphenoidal surgery, Remission.*

Introduction

Although the presence of a histological pseudocapsule around pituitary tumors was noted in the early 1900s,[2] how the pseudocapusle is formed and the histological characteristics of the pseudocapsule have not been clarified until now. In addition, terminology expressing the boundary of pituitary adenomas is unclear. Some researchers reported that pseudocapusle is originated from the condensation of the basement membranes of compressed peritumoral cell cord.[3] On the other hand, some investigator reported that the boundary between the adenoma and the pituitary gland consisted of fibrous tissue originated from the normal pituitary gland, and regarded the boundary as a pseudocapsule.

To describe clearly the boundary zone, we define a "true pseudocapsule" as a definitive capsule-like structure identifiable histologically, and a "microsurgical pseudocapsule" as a peritumoral structure distinguishable intraoperatively under an operating microscope. In this study, we studied the precise histological characteristics of the boundary, using surgical specimens from patients who underwent intensive resection of "microsurgical pseudocapsule" of clinically non-functioning pituitary tumors (CNPTs). Furthermore, we compared the remission rate of CNPTs between subjects with (Group 1) and without (Group 2) intensive resection of microsurgical pseudocapsule in order to correlate the histological complete resection and endocrinological remission.

Patients and Methods

Between January 2000 and December 2007, 137 patients with CNPTs underwent transsphenoidal surgery at two different hospitals. In one hospital, 113 patients underwent intensive microsurgical dissection during the transsphenoidal surgery by one neurosurgeon. In the other hospital, 24 patients underwent conventional subcapsular resection without intentionally removing the microsurgical pseudocapsule by another one neurosurgeon. The demographic data of the patient population was listed in Table 1.

The evaluation involved a complete history, physical and neurological examination, and radiological assessment. Neuroradiological studies included plain X-rays and magnetic resonance imaging (MRI). The adenomas were classified according to the Hardy radiological classification scheme.[7]

Techniques in pituitary surgeries have advanced strikingly with development of surgical techniques, instruments, endoscopes, and intraoperative MRI. Total resection of pituitary tumors of Hardy grades 1 to 3 has been intended. However, it was impossible to evaluate the significance of intensive resection of microsurgical pseudocapsule in some cases, including those with extreme lateral extension into the cavernous sinus, due to difficulties in achieving complete resection. According to these criteria, 97 patients who had prominent cavernous sinus invasion (Hardy grade IV) were excluded from this study.

In all cases, MRI examination was performed annually to evaluate whether the tumor was removed completely or had

Table 1. Baseline characteristics of the patients and the tumors with and without intensive resection of microsurgical pseudocapsule in clinically non-functioning pituitary tumors.

	Intensive resection of microsurgical pseudocapsule	
	With (group 1; n=113)	Without (group 2; n=24)
Age (year)	45.7 (range, 23-74)	48.5 (range, 36-70)
Male/female	52/61	15/9
Hardy classification		
II	13	5
III	100	19

recurred. Remission for a CNPT was defined as a lack of evidence of tumor remnant or re-growth, as determined by MRI examination. A combined pituitary function test was carried out to evaluate pituitary function before surgery, one year after surgery, and at subsequent 1.5 year intervals from 2 to 13 years postoperatively.

Chi-square test for independence was used to determine the statistical significance of differences in tumor sizes, postoperative remission rate, and postoperative pituitary function between Group 1 and Group 2. A p value <0.05 was considered statistically significant.

Results

During the surgery, microsurgical pseudocapsules were found in 57 (50.4%) of 113 patients in Group 1. The pseudocapsule was visualized as a well-developed capsule entirely covering the tumor mass; a thin fibrous envelop; a yellowish, discolored, normal gland-like thin membrane; or thick fibrous tissue after removal of the main tumor mass. Some pseudocapsules exhibited dense fibrosis or calcifications. In smaller tumors, the microsurgical pseudocapsule tended to exist more prominently in and cover the entire mass of the tumor, and was more easily removed. On the other hand, in larger tumors, the microsurgical pseudocapsule tended to be discontinuous or disrupted, not cover the entire tumor, and was more difficult to manipulate surgically. In these situations, intraoperative frozen histological examination was necessary to achieve complete tumor resection.

The pseudocapsule was removed readily along with the main tumor mass in 31 (54.4%) patients. The remaining 26 (45.6%) patients underwent aggressive resection of the remnant pseudocapsule, including multiple intraoperative biopsies. Aggressive resection of the microsurgical pseudocapsule was more often required in larger tumor than in smaller ones. Among these 26 patients, tumor cells infiltration was identified in the microsurgical pseudocapsule of 12 (46.2%) patients.

The overall surgical remission rate in Group 1 with intensive resection of microsurgical pseudocapsule were statistically higher than the rates in Group 2 (without intensive resection of microsurgical pseudocapsule) (p=0.032) (Table 2). However, there were no statistical differences in postoperative hormonal function change between Group 1 and 2 (Table 2).

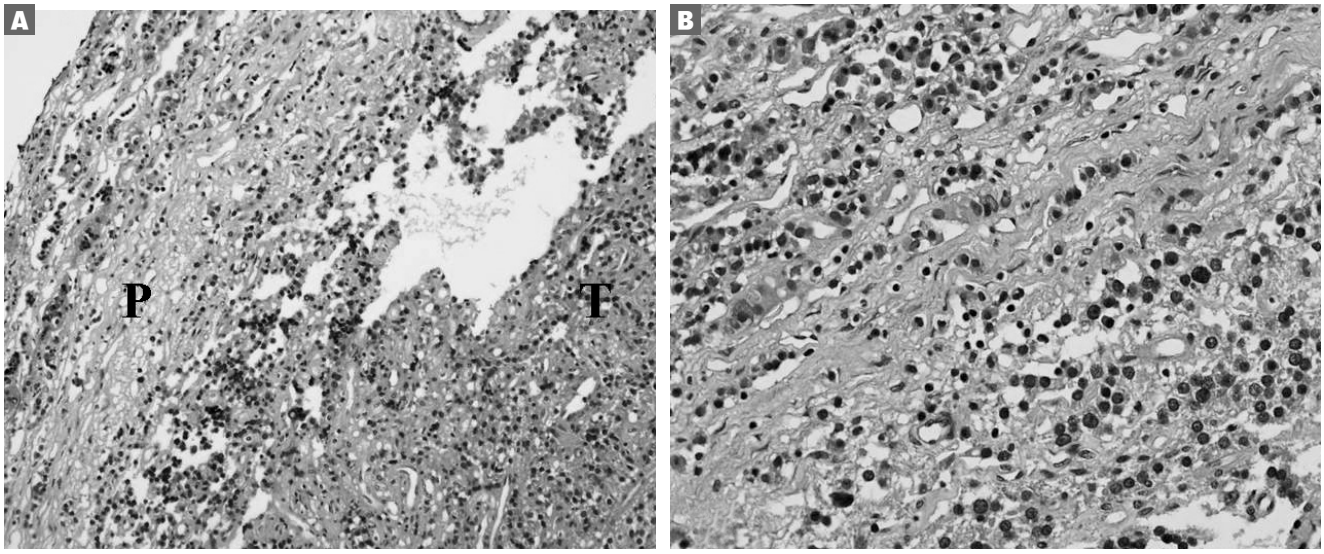
Discussion

Some investigators advocated that surgical plane for pituitary adenomas should be included the pseudocapsule which is an accumulation of basement membrane, collagen, fibroblasts, pericytes, and compressed capillaries.[1] On the other hand, other investigators reported that conventional conservative surgical methods are likely to leave tumor cells in the pituitary gland.[8] In our prospective study, we demonstrated the frequent infiltration of tumor cells within the microsurgical pseudocapsule, suggesting that tumor remnants in the microsurgical pseudocapsule could be a source of recurrence and an obstacle to achieving complete

Table 2. Postoperative remission rates and pituitary functions with and without intensive resection of mcrosurgical pseudocapsule in clinically non-functioning pituitary tumors.

	Intensive resection of microsurgical pseudocapsule	
	With (group 1; n=113)	Without (group 2; n=24)
Overall surgical remission rate	99.1%	83.3%
Postoperative pituitary function	52/61	15/9
Normal to normal	5 (4.4%)	0
Improved hypopituitarism	60 (53.1%)	12 (50.0%)
Persisted hypopituitarism	39 (34.5%)	9 (37.5%)
Aggravated hypopituitarism	9 (8.0%)	3 (12.5%)

Fig. 1



A. Photomicrographs of the tumor specimen obtained in en bloc with distinct pseudocapsule during surgery, showing a relatively thick layer of connective tissue as a pseudocapsule (P) at the interface between the pituitary adenoma (T) (Hematoxlyin & eosin stain, original magnification × 100).

B. With higher magnification, clusters of tumor cells are identified in the pseudocapsule (Hematoxylin & eosin stain, original magnification ×200).

remission. These results indicate that intensive removal of the pseudocapsule could provide a higher remission rate without deteriorating pituitary function. The results of the present study correspond with the results of earlier studies, which have reported that intensive resection of the microsurgical pseudocapsule is essential to achieving histologically and surgically total resection of the pituitary adenoma.[6]

From the surgical technical standpoint, identification of a microsurgical pseudocapsule is very important to achieve complete tumor removal. We also found frequent infiltration of tumor cells inside the microsurgical pseudocapsule. These infiltrates were difficult to remove from the normal gland surface with conventional tumor resection methods using curettage and were instead removed with fine instruments in a piece-by-piece fashion. From the author's experience, the microsurgical pseudocapsule was visualized in a variable fashion, such as a well-developed capsule entirely covering the entire tumor mass; a thin fibrous envelop; a yellowish, discolored, normal gland-like thin membrane; thick fibrous tissue; or a calcification. Careful inspection and intraoperative tissue biopsy at the boundary of pituitary tumors was useful for complete resection of tumors.

The intensive resection of pituitary adenomas could be attributed to postoperative deterioration of pituitary function. However, Kawamata et al.[5] reported that intensive resection of pseudocapsules was advantageous in the treatment of GH-secreting pituitary adenomas and that it did not cause additional deterioration to pituitary function. Our results are consistent with the reported data, suggesting that aggressive resection of pseudocapsule does not affect pituitary function.

In conclusion, our results indicate that aggressive resection of psuedocapsules increases the cure rate without aggravating pituitary function.

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The Combined Transmastoid Transjugular Transtubercular High Cervical Approach for Resection of Jugular Foramen Tumors

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The Combined Transmastoid Transjugular Transtubercular High Cervical Approach for Resection of Jugular Foramen Tumors

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Objective : Deep location, hypervascularization, involvement of cranial nerves and vessels, and large extension within the posterior fossa are the main difficulties for surgical resection of the jugular foramen tumors. We describe a combined transmastoid transjugular transtubercular high cervical approach for radical resection of these tumors.

Methods : Six patients with jugular foramen tumors were surgically treated using combined transmastoid transjugular transtubercular high cervical approach between January 2000 and June 2008. The complex approach for total jugular foramen exposure can be simplified in a stepwise fashion: 1) postauricular infratemporal incision; 2) retrolabyrinthine mastoidectomy; 3) high cervical exposure; 4) Lateral suboccipital craniotomy and transtubercular exposure; 5) removal of the internal jugular vein (IJV), jugular bulb, and sigmoid sinus; and 6) intradural exposure.

Results : Gross total resection was achieved in 5 patients and subtotal resection in one patient. The histologic examination of the tumors revealed as follows: schwannoma (3 cases), meningioma (1 case), paraganglioma (1 case), and chondrosarcoma (1 case). The most frequent complication was a new deficit of lower cranial nerves. There were no facial nerve injury or cerebrospinal fluid leakage.

Conclusions : The combined transmastoid transjugular transtubercular high cervical approach described above allows for single-staged radical resection of large complex jugular foramen tumors. This approach has the advantage of providing total exposure of the jugular foramen with multidirectional angles of attack without facial nerve transposition.

Key Words *Jugular foramen, Skull base, Surgical approach, Paraganglioma, schwannoma, meningioma.*

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Introduction

Jugular foramen tumors are deeply located, may be highly vascularized, and involve important neurovascular structures and bone at the cranial base. They are rare and most commonly include paraganglioma, schwannomas, and meningiomas.[5] Surgical removal of these lesions remains a challenge, in spite of new developments of cranial base surgical techniques. Several surgical approaches have been developed to overcome these difficulties. According to Rhoton,[7] jugular foramen approaches can be subdivided into three main groups: a lateral group (the postauricular transtemporal approach subdivided in infralabyrinthine, translabyrinthine, and transcochlear approaches); a posterior group (retrosigmoid approach and its more extensive far-lateral and transcondylar variants); and an anterior group (preauricular subtemporal-infratemporal approach). Two other groups also exist but are not suitable alone for lesion resection: the superior group (middle fossa approach); and the inferior group (cervical approach upward to the jugular foramen).

The standard surgical approach is lateral, the infratemporal transpetrosal approach.[3] It permits one to gain superior and lateral access to the jugular foramen by drilling of the petrous bone. During this procedure, the facial nerve is frequently transposed anteriorly for allowing the drilling of the bone inferior to the labyrinth.[2] Manipulation of the facial nerve exposes the patient to a non-negligible risk of facial nerve palsy.[6] To limit the risk of facial nerve palsy, some surgeons advocate keeping the facial nerve in its bony canal if the nerve is not infiltrate by the tumor.[1]

Total exposure of the jugular foramen can be achieved, and multidirectional approaches can be performed, including suprajugular (infralabyrinthine), transjugular, infrajugular (retrosigmoid/trranscondylar) exposures.[4] Both intracranial and extracranial tumor can be removed in one-stage procedure. Paragangliomas, schwannomas of the lower cranial nerves, meningiomas, and chondrosarcomas at the jugular foramen and high cervical region are accessible through this approach. Transection of the external ear canal and permanent rerouting of the facial nerve is not necessary.

The complex approach for total jugular foramen exposure can be simplified in a stepwise fashion: 1) postauricular infratemporal incision; 2) retrolabyrinthine mastoidectomy; 3) high cervical exposure; 4) Lateral suboccipital craniotomy and transtubercular exposure; 5) removal of the internal jugular vein (IJV), jugular bulb, and sigmoid sinus; and 6) intradural exposure.

Methods

Patient population

Six patients with jugular foramen tumors were surgically treated using combined transmastoid transjugular transtubercular high cervical approach between January 2000 and June 2008. The relevant patient demographic characteristics, location of tumor, and surgical outcomes for the 6 patients underwent surgery via a juxtacondylar approach are listed in Table 1. There were 4 men and 2 women whose mean age was 42.7 years (range 27-55 years).

Table 1. Patient demographics, location of tumor, and surgical outcomes in 6 patients with jugular foramen tumor underwent surgery via a combined transmastoid transjugular transtubercular high cervical approach.

Patient	Age(yr)/Sex	Preoperative CN deficits	Site of tumor	New CN deficits	Extent of resection	Pathology
1	42/M	IX, X, XII	JF, CPA	-	Total	Schwannoma
2	42/F	X, XII	JF, CPA	IX	Total	Schwannoma
3	44/M	X	JF, CPA	-	Total	Schwannoma
4	46/F	IX, X, XII	JF, CPA, ME	-	Subtotal	Meningioma
5	27/M	-	JF, ME		Total	Paraganglioma
6	55/M	X, XII	JF, CC	X	Total	Condrosarcoma

CN=cranial nerve; JF=jugular foramen; CPA=cerebellopontine angle; ME=middle ear; CC=carotid canal.

The most common symptoms at the time of presentation included dysphonia, unsteadiness, and dysphagia. One patient with paraganglioma was presented with pulsatile tinnitus and hearing loss. Four patients were found to be suffering from at least one cranial nerve deficit in the preoperative evaluation.

Surgical Procedure

Position of Patient and Skin Incision

After induction of general anesthesia, the patient is placed in supine position with the head held in a Mayfield clamp and turned 45 degree to the opposite side. The opposite jugular vein must be free from compression. A nasogastric tube is inserted and intraoperative monitoring of facial and lower cranial nerves is performed. All contact areas are protected with foam pads or water bags. The skin incision had a question mark-shape, starting in the temporal region and circumscribing the ear as far as the anterior border of the sternomastoid muscle. The skin flap is elevated in two layers. The galeal layer is undermined from the skin flap and subsequently elevated with periosteum. The scalp is reflected anteriorly, and the posterior auricular muscle is seen behind the external ear canal. The posteolateral neck muscles are reflected posteiorly to expose the body of the mastoid.

Retrolabyrinthine Mastoidectomy

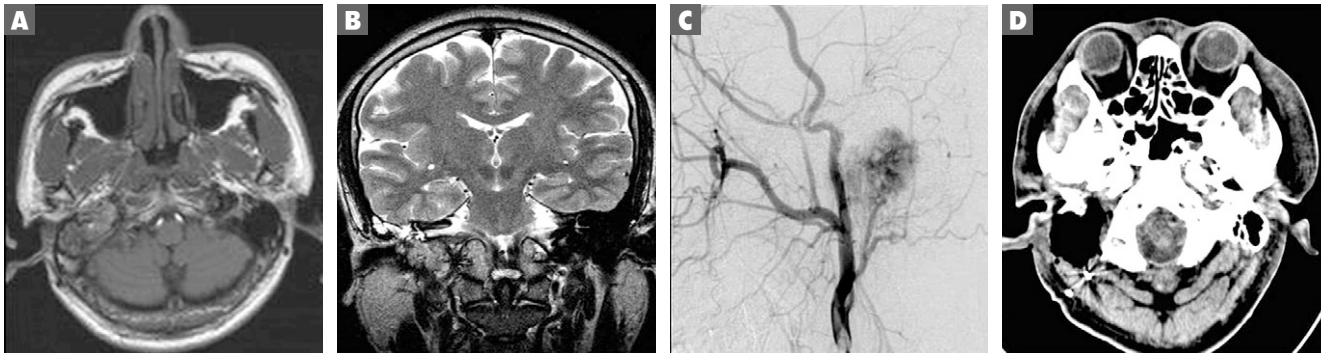
The entire body and tip of the mastoid, the spine of Henle, the posterior point of the root of the zygoma, the supramastoid crest, and the asterion must be exposed before the mastoidectomy performed. The outer mastoid triangle, which is formed by the posterior point of the root of the zygoma, the mastoid tip, and the asterion, marks the area of initial drilling for the mastoidectomy. The mastoid air cells are then systematically removed by saucerization. The sigmoid sinus and jugular bulb are completely skeletonized, and the mastoid air cells totally removed to expose the presigmoid dura, the superior petrosal sinus, sinodural angle, the middle fossa dura, and the retrosigmoid dura.

As air cells are removed from the mastoid tip region, the digastric ridge is encountered. For a retrolabyrinthine exposure, the bony labyrinthine must be clearly defined with diamond burr. The facial nerve is carefully skeletonized by using a diamond burr under contrast, copious irrigation to prevent thermal injury. The retrofacial air cells are removed to skeletonize the jugular bulb further.

High Cervical Exposure

To identify the extracranial portions of the lower cranial nerves, the internal carotid artery, and IJV, high cervical exposure should be performed. The digastric muscle is used as a guide for dissection of the XII and VII cranial nerves. The

Fig. 1



T1-weighted axial
A. and T2-weighted coronal
B. MR images showing a jugular foramen mass extending to middle ear cavity. Preoperative DSA image
C. revealing a hypervascular tumor supplied by ascending pharyngeal artery and occipital artery. Postoperative CT scan
D. demonstrating complete removal of paraganglioma.

XII cranial nerve crosses the external carotid artery inferior to the digastric muscle. The accessory nerve runs laterally to the IJV in the majority of cases. The vagus nerve run latero-inferior to the common carotid artery. Posterior retraction of the IJV helps expose the carotid branch of the glossopharyngeal nerve.

Suboccipital and Transtubercular Exposure

A lateral suboccipital craniotomy is then performed. The sigmoid sinus and jugular bulb must be totally exposed with rongeurs and a high-speed drill. Bone removal is next directed superiorly toward the jugular tubercle, a rounded prominence found at the junction of the basilar and condylar parts of the occipital bone. The jugular tubercle should be drilled away as much as possible. To minimize the heat injury to lower cranial nerves, the center of the tubercle is cored out with a high-speed diamond drill and copious irrigation, leaving an eggshell-thin layer of bone covering the dura that can be elevated with microdissector. The lower cranial nerves take a hairpin bend and exit under the jugular vein and bulb. The inferior petrosal sinus enters the anterior medial aspect of the jugular bulb by multiple channels coursing between the glossopharyngeal and the vagus nerve.

Removal of Internal Jugular Vein, Jugular Bulb, and Sigmoid Sinus

After complete exposure of the sigmoid sinus, jugular bulb, and IJV, the internal jugular vein is ligated just inferior to the tumor mass. The sigmoid sinus is occluded just above the tumor mass with a suture ligature. The lateral wall of the IJV is incised and removed with the tumor up to the jugular bulb and sigmoid sinus. The plane of dissection between the tumor and the medial wall of the jugular bulb is preserved.

Retrosigmoid Intradural Exposure

The dura mater is incised in the medial wall of sigmoid sinus. Minimal cerebellar retraction is needed to open the cerebellopontine cistern, exposing the intradural jugular foramen region. Sharp arachnoid dissection is performed, and the following structures can be visualized: Vth through XIIth cranial nerves, basilar artery, vertebral artery, posterior inferior cerebellar artery, and anterior inferior cerebellar artery.

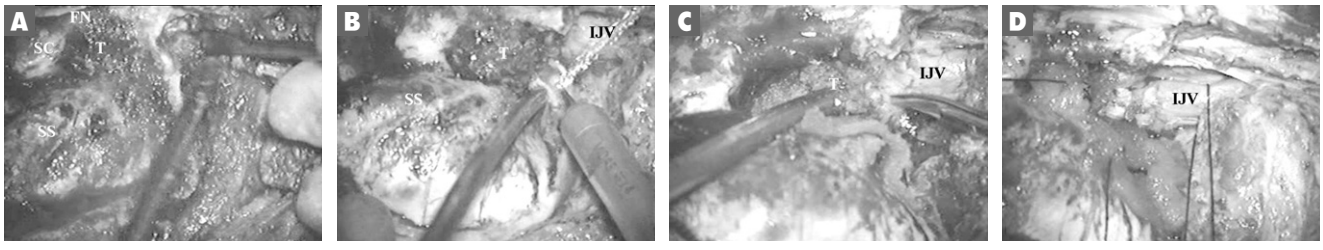
Closure

After adequate hemostasis, the wound is irrigated with antibiotic saline solution. Cranial base reconstruction and prevention of a cerebrospinal fluid leak is paramount to the success of surgery. A watertight dural closure should be the goal. If there is a large defect, an autologous fascial graft or pericranial flap followed by fibrin glue may be used. Autologous fat is used to pack the mastoid defect and remaining anatomic dead space. Temporary lumbar drainage can be used to facilitate healing of the dural closure.

Results

The location and the extent of the lesions were determined

Fig. 2



A. Intraoperative photograph (right-sided approach) demonstrating a glomus jugular tumor after retrolabyrinthine mastoidectomy and skeletonization of sigmoid sinus.
B. Extradural reduction of jugular tubercle is the key maneuver in this approach. The jugular tubercle should be drilled away as much as possible.
C. The tumor is carefully removed from the pars nervosa with care taken not to damage the lower cranial nerves.
D. After complete exposure of the sigmoid sinus, jugular bulb, and internal jugular vein, the internal jugular vein and sigmoid sinus were ligated.

FN=facial nerve; IJV=internal jugular vein; SC=semicircular canal; SS=sigmoid sinus; T=tumor.

preoperatively using the radiology reports (high resolution computed tomography with bone windows and magnetic resonance imaging), which was subsequently confirmed intraoperatively. The frequency of involvement of the various structures was as follows: jugular foramen, cerebellopontine angle, middle ear, carotid canal. The jugular bulb was already closed by the tumor in 3 cases. One patient underwent preoperative embolization.

Gross total resection was achieved in 5 patients and subtotal resection in one patient. The histologic examination of the tumors revealed as follows: schwannoma (3 cases), meningioma (1 case), paraganglioma (1 case), and chondrosarcoma (1 case). Meningioma showed no clear cleavage plans and total removal is not possible.

The most frequent complication was a new deficit of lower cranial nerves. Two patients developed lower cranial nerve palsy temporarily. There were no facial nerve injury or cerebrospinal fluid leakage. Postoperative radiosurgery was performed in one patient with meningioma.

Discussion

The combined transmastoid transjugular transtubercular high cervical approach described above allows for single-staged radical resection of large complex jugular foramen tumors. This approach has the advantage of providing total exposure of the jugular foramen with multidirectional angles of attack without facial nerve transposition.

In our experiences, the expanding tumors, such as schwannomas or chondrosarcomas, are fairly easy to remove and can be done without facial nerve transposition. However, facial nerve transposition may be needed in surgery for infiltrative tumors such as meningiomas or malignant tumors.

In anatomic study of the jugular foramen, cranial nerve, jugular bulb, and IJV are surrounded by a single connective tissue sheath.8) Therefore, jugular bulb and internal jugular vein can be separated from internal carotid artery and cranial nerves by microsurgical techniques. Dissection of dense connective tissue around the IJV is important for wide exposure of jugular foramen with gentle retraction of IJV instead of facial nerve transposition.

The multidisciplinary approach gives the best chance of radical removal with preservation of cranial nerves and vessels. To avoid postoperative complications, an adequate surgical exposure and reconstruction of the cranial base are required. Surgical morbidity and mortality are usually associated with damage to the lower cranial nerves. Identification and dissection in the neck and at the foramen magnum is helpful in the preservation of these nerves. When they are infiltrated yet still functioning, our strategy is to leave a small piece of tumor around them and if necessary (if there is proven postoperative residual tumor growth) administer radiotherapy.[5)]

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해면정맥동을 침범하는 뇌수막종의 치료

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Treatment of cavernous sinus meningioma: long-term outcome and lessons learned

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OBJECTIVE : We retrospectively analyzed the long-term outcomes in patients with cavernous sinus meningiomas (CSMNGs) treated with the various treatment modalities including surgical resection, radiotherapy, radiosurgery, and clinical observation to find out an optimal strategy in selecting a treatment option.

PATIENTS AND METHOD : Of the 77 consecutive patients with CSMNGs treated between 1986 and 2004, 60 were followed up for more than 36 months. Thirty-six (60.0%) patients were female. The mean age of the patients was 52±12 years, and the mean follow-up duration was 83±46 months. The population was divided into four groups including the microsurgery group (n=26, 43.3%), the observation group (n=11, 18.3%), the conventional radiotherapy (CRT) group (n=10, 16.7%), and the radiosurgery group (n=13, 21.7%) according to the initial treatment modality.

RESULTS : The actuarial tumor control rates were 84.9%, 78.3%, and 41.8% at 5, 10, and 15 years, respectively. Adjuvant radiation therapy using (CRT) after surgery seemed to be positively associated with tumor control, however it did not reach the statistical significance (p=0.277). The patients treated with CRT or radiosurgery as an initial management also showed better outcome in terms of tumor control, however which was not statistically significant (p=0.138). Tumor progression was observed in 12 patients; 7 (26.9%) of the surgery group, 3 (27.3%) of the observation group, 1 (11.1%) of the CRT group, and 1 (7.7%) of the radiosurgery group. Unfavorable KPS was identified in a total of 13 patients; 7 (26.9%) of the surgery group, 1 (9.1%) of the observation group, 4 (44.4%) of the CRT group, and 1 (7.7%) of the radiosurgery group. Finally, aggravation of the cranial neuropathy mostly developed in 8

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(30.8%) patients of the surgery group. Failure of tumor control was negatively related with the outcome of the functional status and the cranial neuropathy after long-term follow-up period. **Conclusion** : Considering a high rate of tumor progression after long-term follow-up period, CRT and radiosurgery seem to be optimal. However, in terms of the functional status and cranial neuropathy, observation also seems to be an effective modality. Based on our experience, selection of a treatment among various modalities for patients with CSMNGs should be done considering the age of patient, the presence of cranial neuropathy, and the tumor size.

Key Words *cavernous sinus, meningioma, multimodal treatment, long-term outcome*

서 론

두개내 뇌수막종은 일차성 뇌종양의 약 30% 정도를 차지하는 흔한 종양이다.[2] 이들의 치료 목표는 종양의 기원이 되는 경막을 포함한 종양의 완전 절제이나 위치에 따라서 완전절제가 어려워 수술만으로 완치되기 어려운 경우가 많다. 해면정맥동에 기원하는 수막종의 경우, 수술 중 내경동맥의 손상 내지는 폐색의 위험과 근처 뇌신경들의 손상에 의한 수술 후 신경학적 증상 악화의 가능성이 매우 높아 근치적 수술이 어렵다. 방사선 치료의 경우에도 충분한 방사선량이 조사되지 못했을 경우 종양의 성장을 막지 못하는 경우가 보고되고 있으며, 방사선에 의한 주변 신경 및 혈관의 손상 가능성도 있어 난점이 있다. 해면정맥동에서 기원하는 수막종의 적합한 치료에 대해 아직 뚜렷한 결론은 없는 상태이며, 큰 규모의 연구들에서도 논란이 많다. 일부에서는 적극적인 수술적 제거를 주장하고 있으며,[1, 3-5] 정위적 방사선치료를 지지하는 그룹도 있고,[7-9, 15] 적절한 수준의 수술적 제거 후 추가적인 정위적 방사선 치료를 선호하는 그룹도 있다.[10-14]

본 연구에서는 해면정맥동을 침범하는 뇌수막종 환자의 다양한 치료 경험을 후향적으로 분석하여 각 치료 방법에 따른 장기간 추적 관찰 결과를 평가하고, 가장 적절한 치료 방법을 모색해보고자 한다.

대상 및 방법

1986년부터 2004년까지 서울대병원에서 치료받은 해면정맥동을 침범하는 뇌수막종 환자 77명중 36개월 이상 추적관찰이 가능하였던 환자를 대상으로 하였다. 총 60명의 환자가 이 연구에 포함되었으며, 환자를 치료 방법에 의거하여 총 4개의 군 (수술을 시행한 군, 방사선치료를 시행받은 군, 정위적 방사선 수술을 시행받은 군, 경과 관찰 군)으로 구분하였다. 정위적 방사선 수술에는 감마나이프 수술이 이용되었다. 각 군의 무진행 생존기간 (progression free survival), 재발률 (recurrence rate), 치료 전 후의 뇌신경 장애 정도 및 Karnofsky Performance Score (KPS) 전 후 비교를 통해 치료 성적을 비교하였다. 무진행 생존기간은 Kaplan-Meier 방법을 통해 산출하였고, 재발률과 KPS, 뇌신경 증상 변화에 영향을 주는 요인들을 콕스 비례위험모형 (Cox proportional hazards model) 및 이분형 로지스틱 회귀분석법 (Binary logistic regression analysis)을 이용하여 비교 분석하였다.

환자의 분포 및 특성

환자들의 성별은 남자가 24명, 여자가 36명이었고, 평균 연령은 52세(15-73세)이었으며, 평균 추적관찰 기간은 83개월(36-269)이었다. 이 환자들의 주증상으로는 시력, 시야 장애가 17명(28.3%)로

가장 많았으며, 안면부위 감각이상이 6명(10%), 안검하수가 6명(10%), 반마비 및 보행실조가 5명(8.3%), 발작(seizure)을 보인 환자가 5명(8.3%), 복시를 보인 환자가 4명(6.7%), 두통, 어지러움증을 보인 환자가 8명(13.3%), 기타 다른 원인으로 발견된 환자가 9명(15%)였다 (Table 1).

총 26명(43.3%)의 환자가 수술적 치료를 시행 받았으며, 이 중 수술적 치료만 받은 환자는 14명(23.3%), 수술 후 방사선 치료를 받은 환자가 7명(11.7%), 수술 후 감마나이프 수술을 시행받은 환자가 5명(8.3%)이었고, 방사선 치료만 시행받은 환자가 10명(16.7%), 감마나이프 수술만 시행받은 환자가 13명(21.7%), 경과 관찰만 시행한 환자가 11명(18.3%)였다 (Table 2). 경과 관찰한 그룹의 평균연령이 62세로 가장 많았으며, 종양의 평균 크기는 감마나이프 수술을 시행받은 그룹에서 28mm로 가장 작았다 (Table 3). 종양의 인근 구조물로의 침습정도를 평가하기 위해 Sekhar가 제시한 분류를 이용하였으며, 1단계 (grade I)은 해면정맥동의 일부만 침습한 경우, 2단계 (grade II)는 해면정맥동의 여러 부분을 침습하면서 내경동맥을 한쪽으로 밀거나 일부 감싸는 경우, 3단계 (grade III)는 내경동맥을 완전히 감싸는 경우, 4단계 (grade IV)는 내경동맥을 감싸면서 동맥의 협착 소견까지 보이는 경우, 5단계 (grade V)는 양측 해면정맥동을 침습하는 경우로 분류하였다. 비교적 수술적 치료를 받았던 환자군에 낮은 Sekhar 단계의 환자 비율이 비교적 높았고, 방사선 치료만을 시행받은 그룹과 경과 관찰을 하였던 그룹에 높은 Sekhar 단계의 환자들이 속하였다. 경과 관찰군에서 뇌신경 장애 증상의 빈도가 낮았다.

결 과

전체 해면정맥동을 침습하는 수막종의 무진행 생존기간은 중앙값이 168개월 (95% 신뢰구간 134.6-202.4개월), 평균이 169.6개월 (95% 신뢰구간 134.1-205.1개월) 이었다 (Fig. 1). 5년 무진행 생존

Table 1. Presenting symptoms at the time of diagnosis of cavernous sinus meningioma

Symptoms	No. Cases
Visual disturbance	17 (28.3%)
Trigeminal symptoms	6 (10.0%)
Ptosis	6 (10.0%)
Hemiparesis or Ataxia	5 (8.3%)
Seizure	5 (8.3%)
Diplopia	4 (6.7%)
Dizziness or Headache	8 (13.3%)
Others*	9 (15.0%)

* 6 incidentally found + 2 exophthalmos + 1 hearing difficulty

Table 2. Initial management of patients

Management	No. cases
Surgery only*	14 (23.3%)
Surgery + radiotherapy	7 (11.7%)
Surgery + GKRS	5 (8.3%)
Radiotherapy only	10 (16.7%)
GKRS only	13 (21.7%)
Observation	11 (18.3%)

* Gross-total resection in 4 cases
Abbreviation: GKRS, gamma-knife radiosurgery

Table 3. Characteristics of the groups divided according to the initial management

		Surgery	Observation	Radiotherapy	GKRS
Mean age (yr)		47±13	62±8	50±6	50±11
Mean size (mm)		41±13	37±9	44±10	28±6
Mean F/U (mo)		97±48	80±71	63±25	74±14
Preop CN deficit		16 (61.5%)	3 (27.3%)	9 (90.0%)	9 (69.2%)
Sekhar (1996)	Grade I	5	1	0	4
	Grade II	8	1	0	3
	Grade III	9	4	3	3
	Grade IV	4	4	3	2
	Grade V	0	1	4	1
WHO grade	Grade I	23	3*		
	Grade II	2			
	Grade III	1			

* Surgery was carried out due to tumor progression afterwards.

Abbreviation: yr, years; mo, months; F/U, follow-up; GKRS gamma-knife radiosurgery; Preop CN, preoperative cranial nerve

률은 84.9%, 10년 무진행 생존률은 78.3% 그리고 15년 무진행 생존률은 41.8%였다.

수술을 시행하였던 그룹 중 수술 후 방사선치료를 추가로 시행하였던 군과 그렇지 않은 군을 비교하였을 때, 통계적으로 유의하지는 않으나 (p=0.277) 수술 후 방사선 치료를 추가로 시행하였던 그룹에서 더 나은 종양 억제율을 보였다 (Fig. 2A). 방사선 치료를 시행한

Table 4. Clinical outcomes according to the initial management

		Surgery(N=26) No of pt (%)	Observation (N=11) No of pt (%)	RTx(N=10) No of pt (%)	GKRS(N=13) No of pt (%)
Recurrence		7 (26.9)	3 (27.3)	1 (11.1)	1 (7.7)
Unfavorable KPS*		7 (26.9)	1 (9.1)	4 (44.4)	1 (7.7)
CN function	Aggravation	8 (30.8)	1 (9.1)	1 (11.1)	1 (7.7)
	Improvement	8 (30.8)	2 (18.2)	4 (44.4)	6 (46.2)
	Stationary	10 (38.5)	8 (72.7)	4 (44.4)	6 (46.2)
Other Cx		4†	1‡	3§	1‖

* In case of the KPS assessment worsened
† Two cases with cognitive dysfunction after RTx; one case of panhypopituitarism after RTx; one case with 2nd radiation-induced tumor (olfactory neuroblastoma)
‡ One hydrocephalus treated with ventriculoperitoneal shunt
§ Two cognitive dysfunction; one panhypopituitarism
‖ One radiation-induced peritumoral edema treated with steroid

Table 5. The results of the statisticalanalysis regarding tumor progression

	Univariate		Multivariate		
	HR	P-value	HR	P-value	95% CI
Gender	0.857	0.794			
Age (〉50 years)	1.070	0.908			
F/U duration	0.976	0.054	0.975	0.031	0.952-0.998
Preoperative CN dysfunction	1.572	0.500			
Sx duration (〉12 months)	0.761	0.678			
Size (〉30mm)	1.996	0.374			
Size (〉40mm)	1.862	0.304			
Sekhar grade 4/5	1.334	0.749			
Initial radiation treatment	0.399	0.151	0.280	0.050	0.078-1.000

Abbreviation: HR, hazard ratio; CI, confidence interval; F/U, follow-up; CN, cranial nerve; Sx, symptom

Table 6. The results of the statistical analysis regarding the functional status using KPS

		Univariate		Multivariate		
		OR	P-value	OR	P-value	95% CI
Gender		2.059	0.255			
Age (〉50 years)		0.550	0.372			
F/U duration		0.998	0.803			
Preoperative CN dysfunction		1.007	0.991			
Sx duration (〉12 months)		1.304	0.734			
Size (〉30mm)		0.147	0.077	0.159	0.140	0.014-1.827
Recurrence		0.171	0.012	0.137	0.025	0.024-0.778
Sekhar grade 4/5		1.471	0.749			
Initial treatment modality	Observation	3.684	0.252			
	Radiotherapy	0.553	0.448			
	GKRS	4.421	0.189	1.070	0.960	0.077-14.88
Usage of radiotherapy		0.214	0.020	0.506	0.486	0.075-3.437

Abbreviation: OR, odd ratio; CI, confidence interval; F/U, follow-up; CN, cranial nerve; Sx, symptom; GKRS, gamma-knife radiosurgery

그룹과 그렇지 않은 그룹을 비교하였을 때, 역시 통계적으로 유의하지는 않으나 (p=0.138) 방사선 치료를 시행한 그룹이 더 나은 종양 억제율을 보였다 (Fig. 2B).

각 치료 그룹간의 재발률(recurrence rate), KPS 변화, 뇌신경 장애 악화 정도는 표 4에 정리하였다. 특이할 사항은 위에서 언급한 대로 수술적 치료군과 경과 관찰군의 경우 재발률이 높았으며, 수술적 치료군에서 뇌신경 장애 정도가 악화되는 비율이 높았고, 방사선 치료군의 경우 인지기능장애를 포함한 전반적인 삶의 질 저하가 다른 군에 비해 두드러졌다.

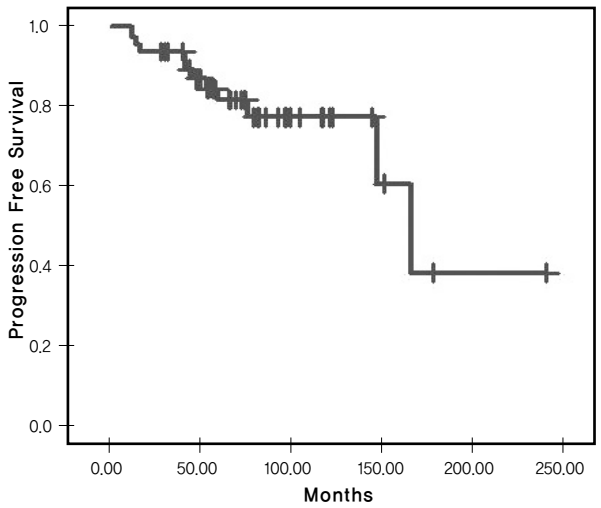
재발률의 다변량 콕스 비례위험모형을 이용한 분석을 시행하였을 때, 초기 방사선 치료가 재발억제와 연관이 있으며, 추적 관찰 기간과 재발률이 긍정의 상관관계를 갖는다 (Table 5). 종양의 크기와 재발유무가 삶의 질 감소(KPS의 감소)에 영향을 주는 것을 나타났으며 (Table 6), 뇌신경 장애 증상의 악화에 재발유무만이 통계적으로 유의한 영향을 주는 것으로 나타났다 (Table 7).

고 찰

해면정맥동을 침범한 수막종의 치료 성적을 후향적으로 분석한 이 연구를 통해 몇 가지 사실을 정리해 볼 수 있다. 해면정맥동을 침범하는 뇌수막종의 경우, 상당한 치료 기술 및 방법의 발전에도 불구하고, 장기간 추적 관찰 시, 재발하는 경우가 많다. 이는 종양의 위치가 해부학적으로 복잡하고, 시신경, 경동맥을 포함하는 중요 구조물들과 닿아있어 수술 및 방사선 치료에 제약이 있어 완전히 종양을 근절하지 못하기 때문으로 생각된다. 유의한 종양 성장 억제 효과는 방사선 치료에서만 보였다는 점도 주목할 부분이다. 방사선 치료가 어떤 방식으로든 치료 계획에 포함되어야 함을 의미한다.

뇌신경 장애를 포함, 별다른 증상이 없는 고령의 환자들을 경과 관찰하였을 때, 증상의 진행이 없고 KPS 악화 비율이 수술을 포함한 다각적 치료를 시도하였던 군들에 비해 낮은 사실 역시 주목할 만 하다. 이러한 사실을 근거로 노인 환자에서 뇌신경 장애 증상이

Fig. 1



The median overall progression-free survival of meningioma involving cavernous sinus was 168 months (95% CI, 134.6-201.4). The actuarial progression-free survival rates were 84.9%, 78.3%, and 41.85 at 5, 10, and 15 years, respectively.

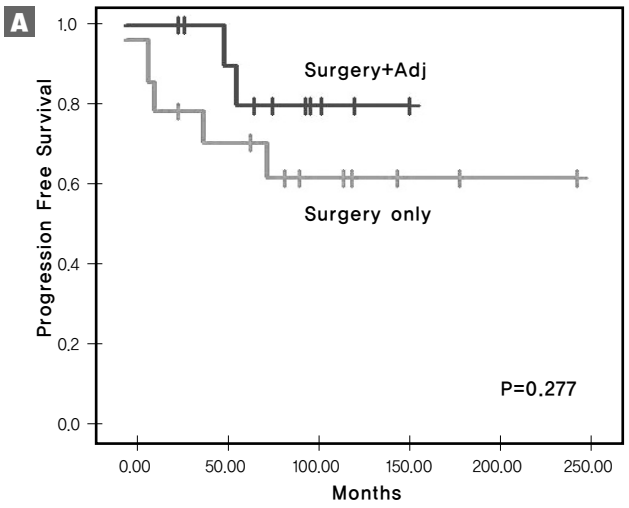
Table 7. The results of the statistical analysis regarding the favorable outcome of cranial neuropathy

		Univariate		Multivariate		
		OR	P-value	OR	P-value	95% CI
Gender		1.316	0.683			
Age (>50 years)		1.895	0.342			
F/U duration		0.997	0.635			
Preoperative CN dysfunction		0.296	0.144	0.274	0.221	0.034-2.178
Sx duration (>12 months)		0.913	0.901			
Size (>30 mm)		0.458	0.352			
Size (>40 mm)		0.368	0.141	0.573	0.562	0.087-3.769
Recurrence		0.065	p<0.001	0.071	0.003	0.012-0.419
Sekhar grade 4/5		1.471	0.749			
Initial treatment modality	Observation	4.444	0.187	7.579	0.157	0.459-125.1
	Radiotherapy	4.000	0.223			
	GKRS	5.333	0.136	3.425	0.365	0.239-49.10
Initial radiation treatment		1.208	0.778			

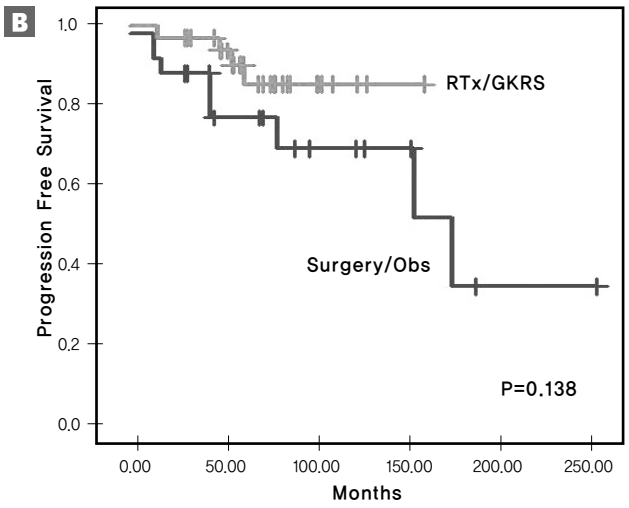
Abbreviation: OR, odd ratio; CI, confidence interval; F/U, follow-up; CN, cranial nerve; Sx, symptom; GKRS, gamma-knife radiosurgery

Fig. 2

Comparison of tumor control between the groups using the log rank test

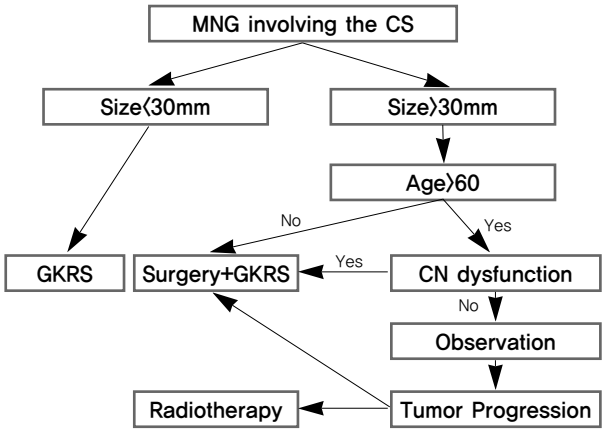


The surgery only group versus the surgery plus adjuvant treatment group. The actuarial progression-free survival rates were 70.7% and 61.9% at 5, and 10 years respectively in the surgery only group. And the actuarial progression-free survival rates were 90.0% and 80.0% at 5, and 10 years respectively in the patients treated with surgery plus adjuvant therapy using conventional radiotherapy or radiosurgery. However, difference in tumor control between two groups did not reach the statistical significance (p=0.277).



The radiation treatment group versus the group without radiation treatment. The actuarial progression-free survival rates were 77.0% and 69.3% at 5, and 10 years respectively in the group without radiation treatment. And the actuarial progression-free survival rates were 90.0% and 85.3% at 5, and 10 years respectively in the patients treated with radiation treatment using conventional radiotherapy or radiosurgery. However, difference in tumor control between two groups did not reach the statistical significance (p=0.138).

Fig. 3



Our suggestion for management of patients with cavernous sinus meningiomas.

없는 경우, 경과 관찰하는 것도 하나의 치료 전략이 될 수 있으리라 생각된다.

종양의 성공적인 성장 억제를 위해서는 감마나이프를 포함하는 방사선 수술 또는 방사선 치료를 통한 적극적인 치료계획이 필요할 것으로 보인다. 다만, 뇌의 상당한 영역에 방사선을 조사하는 치료는 장기간 경과 관찰을 하였을 때, 인지 기능 장애, 호르몬 장애, 방사선에 의한 종양 발현 등의 합병증 발생 가능성이 비교적 높으므로, 해면정맥동을 침범하는 작은 크기의 수막종의 치료는 감마나이프와 같은 방사선 수술이 적합할 것으로 생각된다. 감마나이프 등 방사선 수술의 경우 효과적으로 치료 가능한 종양 크기 정도에 제한이 있고, 주변에 시신경 등 방사선에 취약한 중요 구조물들이 있는 것을 감안하면, 크기가 큰 종양을 치료함에 있어서는, 수술을 통한 종양 크기를 줄이고, 남은 종양에 대해서 감마나이프를 시행하는 것이 보다 효과적인 치료라 생각된다.

그림 3에 해면정맥동을 침범하는 수막종의 저자들이 제안하는 효과적인 치료 알고리즘을 도시하였다. 진단 당시 종양의 크기가 3㎝ 이하일 경우 바로 감마나이프 수술을 고려하고, 만약 3㎝ 이상일 경우 환자의 나이를 고려하여, 60세 이하의 젊은 나이의 경우에는 수술을 통해 제거할 수 있는 종양을 최대한 제거하여 크기를 줄인 다음, 남은 종양에 대한 감마나이프 수술을 시행하는 방법을 택한다. 만약 60세 이상의 고령이고 뇌신경 장애의 증상이 없는 경우에는 그냥 경과 관찰해 볼 수 있으나, 뇌신경 장애가 있거나 종양이 진행하여 증상이 악화되는 경우에는 수술 후 감마나이프 또는 내과적

문제 등으로 전신마취를 통한 수술이 어려울 경우, 방사선 치료를 고려한다.

결 론

해면정맥동을 침범하는 뇌수막종은 해부학적 위치, 주변 뇌신경 및 혈관들 간의 관계로 수술을 통한 완전 제거가 어려우며, 이를 시도하였을 때, 상당한 합병증 및 위험이 뒤따른다. 낮은 합병증 이환률, 장기간의 종양 억제를 위해서는 감마나이프 등의 방사선 치료가 효과적이며, 종양의 크기가 큰 경우 수술을 통해 크기를 줄인 이후에 감마나이프를 시행하는 것이 좋다. 고령이고 뇌신경 장애 증상이 없는 큰 종양의 경우, 악화 없이 안정적인 경우가 많으므로, 경과 관찰이 추천된다.

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두개저 외과수술에서 뇌척수액 비루의 치료

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Treatment of Cerebrospinal Fluid leakage in Skull Base Surgery

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Objective : In various skull base approaches, the risk of cerebrospinal fluid (CSF) leakage exists and the leakage may lead to a life-threatening condition such as meningoencephalitis. The incidence of its occurrence varies in previous literatures and the management dealing the leakage was not established. In this study, we reviewed our experiences dealing CSF leakage after a skull base surgery and suggest a guideline of managing CSF leakage.

Patients and Methods : From 2001 to 2007, 273 patients who underwent skull base surgery for managing tumor were reviewed retrospectively. The charts were analyzed for the date of surgery, age and sex of the patient, the presence or absence of CSF leak, and when present, its managements.

Results : Among the 273 patients, six patients had CSF leakage after surgery. The incidence of CSF leakage in this series was 2.19%. The risk of CSF leakage was highest in the retrosigmoid and combined approaches (3.03%). Two of these patients with CSF leakage developed bacterial meningitis, and these two patients with meningitis were treated with intravenous antibiotics. Among the six patients, the CSF leakage had improved without a direct surgical repair of dural defect in four patients; the others underwent a surgical repair.

Conclusions : Our results indicate that postoperative CSF leakage can be managed activity restriction, and lumbar-subarachnoid drainage, but in case of refractory leakage, wound revision and surgical dural defect repair enables the patients to reduce hospital days and further complications.

교신저자 안 정 용

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Key Words *Cerebrospinal fluid leakage, Surgical approach, Skull base surgery, Treatments.*

Introduction

In surgeries approaching to the skull base including the transoral, subfrontal, pterional transsylvian, subtemporal, petrosal, transtentorial occipital, retrosigmoid and midline suboccipital approach, the risk of cerebrospinal fluid (CSF) leakage exists and the leakage may lead to a life-threatening condition such as meningoencephalitis. The incidence of its occurrence varies in previous literatures and the management dealing the leakage was not established. In this study, we reviewed our experiences dealing CSF leakage after a skull base surgery and suggest a guideline of managing CSF leakage.

Patients and Methods

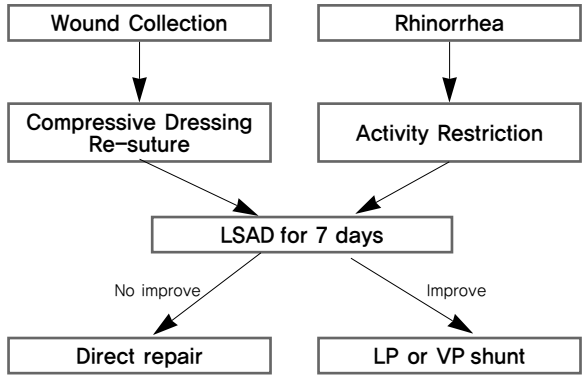
From 2001 to 2007, 273 patients who underwent skull base surgery for managing tumor were reviewed retrospectively. The charts were analyzed for the date of surgery, age and sex of the patient, the presence or absence of CSF leak, and when present, its managements.

We diagnosed CSF leakage clinically. A CSF rhinorrhea was diagnosed when an intermittent, clear nasal discharge occurred on straining, leaning forward, or lowering of head. A wound CSF collection was diagnosed when fluid with a similar character was seen exuding through the wound of the operation or palpable fluid collection beneath the wound. All patients with CSF leakage had lumbar-subarachnoid drainage and activity restriction initially. If the CSF leakage stopped after lumbar-subarachnoid drainage, lumboperitoneal shunt or ventriculoperitoneal shunt was performed. And if CSF leakage continued, direct surgical repair for dural defect was performed (Fig. 1).

Results

From January 2001 to December 2007, 273 patients underwent skull base surgeries at department of neurosurgery in out institution. There were 116 male and 157 female patients. The mean age was 45 years (range 2-78). The surgical approach included the subfrontal, pterional transsylvian, transpetrosal, transcondylar, transtentorial occipital, retrosigmoid and midline suboccipital approach (Table 1). Among the 273 patients, six patients had CSF leakage after surgery. The clinical characteristics of these patients were listed at Table 2. The incidence of CSF leakage in this series was 2.19%. The risk of CSF leakage was highest in the retrosigmoid and combined approaches (3.03%). Two of these patients with CSF leakage developed bacterial meningitis, and these two patients with meningitis were treated with intravenous antibiotics. Among the six patients, the CSF leakage had improved without a direct surgical repair of dural defect in four patients; the others underwent a surgical repair.

Fig. 1

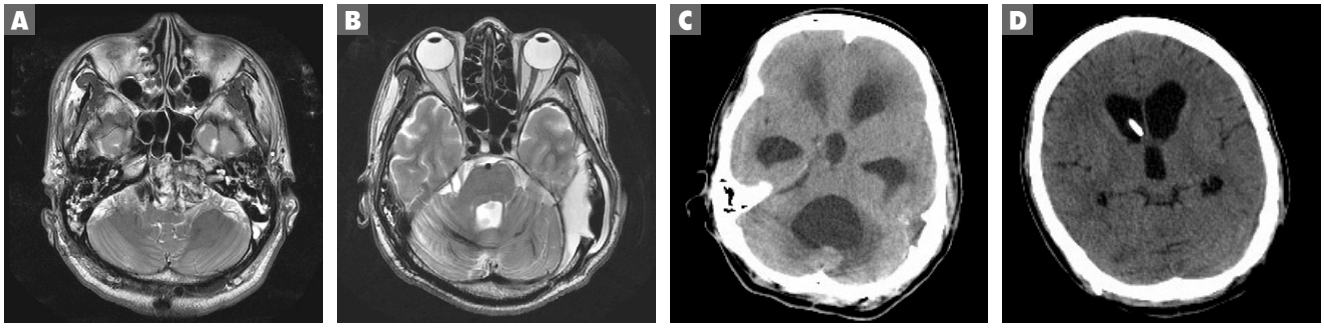


The management flow chart of cerebrospinal fluid leakage after skull base surgery. LSAD: Lumbar-subarachnoid drainage, LP: Lumboperitoneal, VP: Ventriculoperitoneal.

Table 1. Surgical approaches to skull base and cerebrospinal fluid leakage (n=273)

Approach	n	CSF leakage
Pterional	71	2
Retrosigmoid	66	2
Subfrontal	46	1
Transpetrosal	28	1
Transcondylar	23	0
Midline suboccipital	19	0
Occipital transtentorial	7	0
Other	13	0

Fig. 2



Patient 1. Preoperative MRI
A. demonstrates a clival tumor. Postoperative MRI
B. and CT scan
C. show wound CSF collection and hydrocephalus. Final CT scan
D. after venticulo-peritoneal shunt reveals improved hydrocephalus and no wound collection.

Illustrative cases

Patient 1

(Fig.2. A-D) A 32-year-old male patient admitted to our hospital suffered from dizziness and diplopia. He had diagnosis of chordoma of clivus 5 years ago and took a tumor removal with transoral approach. The MRI scan demonstrated recurrence of tumor, and he underwent surgical removal of tumor with combined far lateral and posterior petrosal approach. The pathology was chordoma. After the operation, the wound was swollen and he had headache. Postoperative MRI scan and CT scan revealed mild CSF collection and hydrocephalus. After repeated lumbar-subarachnoid drainage, the CSF collection was improved but hydrocephalus was still last. So, he underwent ventriculo-peritoneal shunt and no more hydrocephalus and CSF leakage happened.

Patient 2

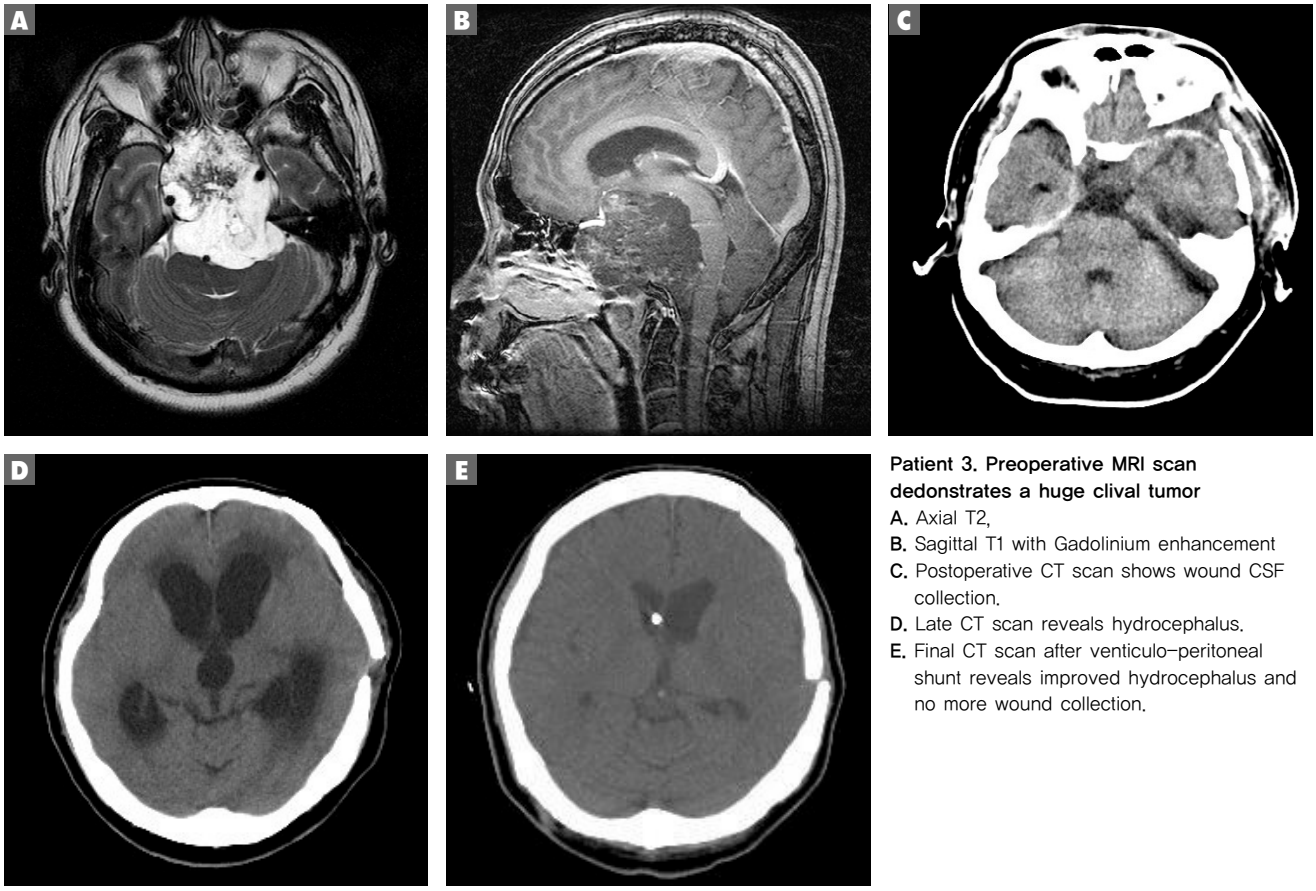
A 34-year-old male patient admitted to our hospital for headache. The MRI scan revealed a huge tumor around the clivus and cavernous sinus, and he underwent surgical removal of tumor with pterional intradural and extradural approach. The pathology was chordoma. Three days after

Table 2. Clinical Chracteristics of six patients with postoperative cerebrospinal fluid leakage and their management

	Sex/ Age	Pathology	Location	Surgical approach	Postoperative presentation	Initial management of cerebrospinal fluid leak	Results and additional treatments
1	M/32	Chordoma	Clivus	Combined far lateral and posterior petrosal	Wound collection	VP shunt after LSAD	No further leakage
2	M/48	Meningioma	Sphenoid wing	Pterional transsylvian	Rhinorrhea	LP shunt after LSAD	No further leakage
3	M/34	Chordoma	Clivus	pterional intradural and extradural	Rhinorrhea	VP shunt after LSAD	No further leakage
4	M/39	Meningioma	Olfactory groove	Subfrontal	Rhinorrhea Meningitis	LSAD	Need direct repair
5	F/54	Schwannoma	Cerebellopontine angle	Retrosigmoid suboccipital	Wound collection	Aspiration VP shunt after LSAD	No further leakage
6	F/54	Schwannoma	Cerebellopontine angle	Retrosigmoid suboccipital	Wound collection Meningitis	Aspiration LSAD	Need direct repair

LSAD : Lumbar-subarachnoid drainage ; VP shunt : ventriculoperitoneal shunt ; LP shunt : Lumboperitoneal shunt

Fig. 3



Patient 3. Preoperative MRI scan dedonstrates a huge clival tumor
A. Axial T2,
B. Sagittal T1 with Gadolinium enhancement
C. Postoperative CT scan shows wound CSF collection.
D. Late CT scan reveals hydrocephalus.
E. Final CT scan after venticulo-peritoneal shunt reveals improved hydrocephalus and no more wound collection.

operation, clear CSF rhinorrhea developed and the CT scan revealed hydrocephalus. He underwent ventriculo-peritoneal shunt surgery after repeated lumbar-subarachnoid drainage. After shunt surgery, the CSF rhinorrhea did not happened any more.

Discussion

There are variable approaches that enable to reach skull base and to extirpate skull base tumors safely.[7] Despite the improvement of these approach, the risk of CSF leakage after surgery is still as high as 20%.[10] The CSF leakage can be life-threatening, because it can bring about meningitis and encephalitis.

In this series of 273 patients, the incidence of CSF leakage was 2.19% and it is highest in the retrosigmoid approach. This result was not quite defferent from previous reports.[1-6, 9, 11, 12, 13]

We prefer to manage wound CSF collection initiaaly with aspiration, re-suture of skin, replacement of a compressive dressing, activiry restriction and lumbar-subarachnoid drainage. Leonetti et al. reported 15 patients of wound collection and after these initial management, only two patients underwent additional wound revision surgery.[8] We had 3 patients with wound collection, and after these initial management, only one patient needed additional wound revision. In three patients with CSF rhinorrhea, two patients showed improvement of leakage after lumbar-subarachnoid drainage, and one needed wound revision surgery. After initial management and direct surgical repair, all patients recovered from CSF leakage. But eventually all of these six patients underwent CSF shunting surgery a few months or

years later due to hydrocephalus. We suggested that the cause of delayed development of hydrocephalus was the violations of arachnoid granulation.

Conclusions

In the surgeries approaching skull base, there is a CSF leakage which can develop life-threatening meningitis. It can be managed activity restriction, and lumbar-subarachnoid drainage, but in case of refractory leakage, wound revision and surgical dural defect repair enables the patients to reduce hospital days and further complications.

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전두동골절 수술 후에 발생한 점액낭종에 의한 안구돌출증

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Exophthalmos caused by mucocele developed after surgery for frontal sinus fracture

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Hyeon-Seon Park, M.D., Hyung-Chun Park, M.D., Chong-Oon Park, M.D., Eunyoung Kim, M.D.

Mucoceles arise from the gradual accumulation of mucus material caused by obstruction of the sinus ostium. They may enlarge sufficiently to compress orbital or intracranial structures.
We present a case of severe exophthalmos caused by frontal sinus mucocele developed after operation for frontal sinus fracture. At initial operation for depressed fracture of the anterior wall of left frontal sinus, all frontal sinus mucosa was extirpated and the space was obliterated with bovine artificial bone. The fractured pieces of the bone were replaced and fixed with titanium mesh and screws. The reason for the delayed development of mucocele in this patient was the unintentionally remained sinus mucosa and blockage of the natural drainage pathway by bone graft. Exophthalmos was relieved after surgical drainage of mucocele, resection of mucosa as much as possible and recreation of drainage pathway by the removal of grafted bovine bone.
This case reminds surgeons that natural drainage pathway of sinus should be kept intact whenever possible, otherwise a mucocele may develop even many years after operation.

교신저자 김 은 영

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Key Words *Exophthalmos, frontal sinus, frontal sinus fracture, mucocele*

Introduction

Mucoceles are the result of accumulation and retention of mucoid material within the sinus, which follows obstruction of the sinus ostium.[1] Accidental or iatrogenic traumatic causes account for the majority of these cases.[9] The frontal sinus fracture is one of the most common causes of frontal sinus mucocele. The damage of the nasofrontal duct and drainage system can induce the mucocele. Unintentionally remained mucosa after stripping of mucosa and obliteration for frontal sinus fracture can cause mucocele.[5]

We present a case of severe exophthalmos caused by frontal sinus mucocele developed after operation for frontal sinus fracture and discuss the management of frontal sinus fracture and mucocele.

Case

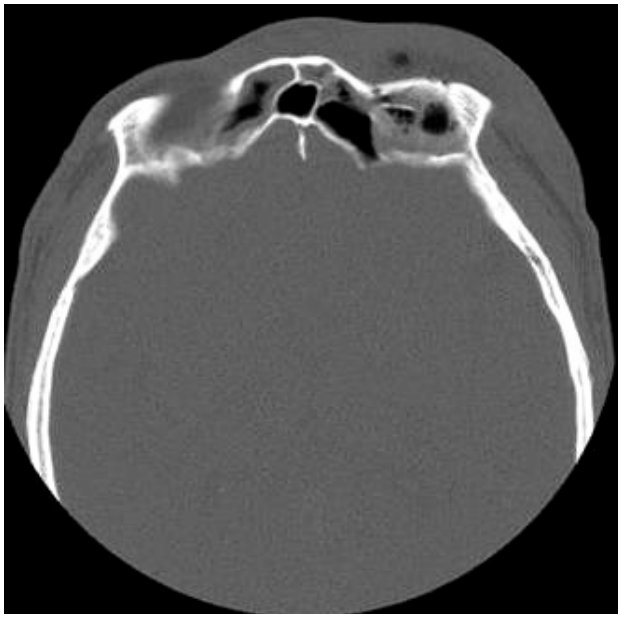
A 51-year-old man visited the hospital with a complaint of progressive protrusion of his left eye for 3 years (Fig. 1).

Eight years ago he fell down stairs and suffered from a depressed fracture of anterior wall of left frontal sinus. Computed tomographic (CT) scan at that time disclosed multiple comminuted depressed fracture of the anterior wall of frontal sinus (Fig. 2). Through a coronal incision all frontal sinus mucosa was extirpated and the space was obliterated with bovine artificial bone (Lubbock Co). The fractured pieces of the bone were replaced and fixed with titanium mesh and screws.

His left eye started protruding progressively 6 years after the operation. He did not complain diplopia though the proptosis of left eye was severe and vertical dystopia was noted on examination.

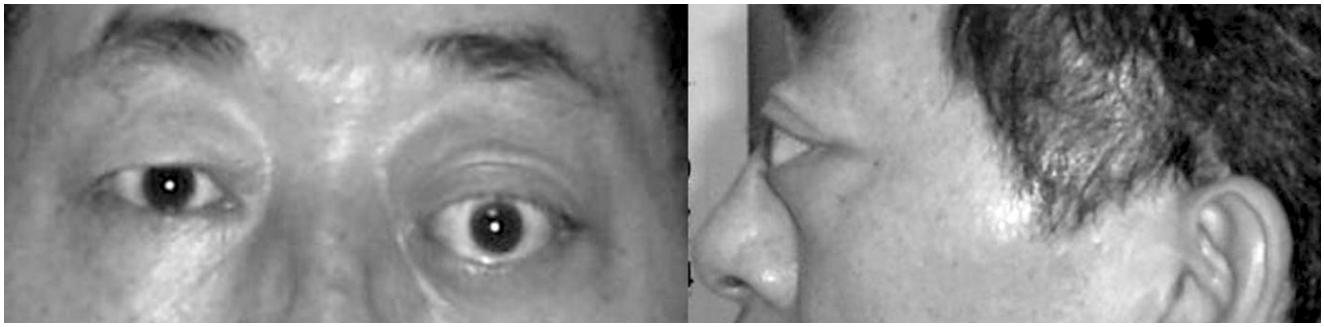
Magnetic resonance imaging (MRI) demonstrated a round cystic mass occupying the left frontal sinus and left orbit causing proptosis, measuring 3.7 cm x 2.4 cm x 3.6 cm, with high signal intensity on T1WI and iso signal on T2WI (Fig. 3). Facial CT displayed cystic mass in the left frontal sinus and

Fig. 2



The axial view of the CT taken 8 years before showing multiple comminuted depressed fracture of the anterior wall of frontal sinus on the left side.

Fig. 1



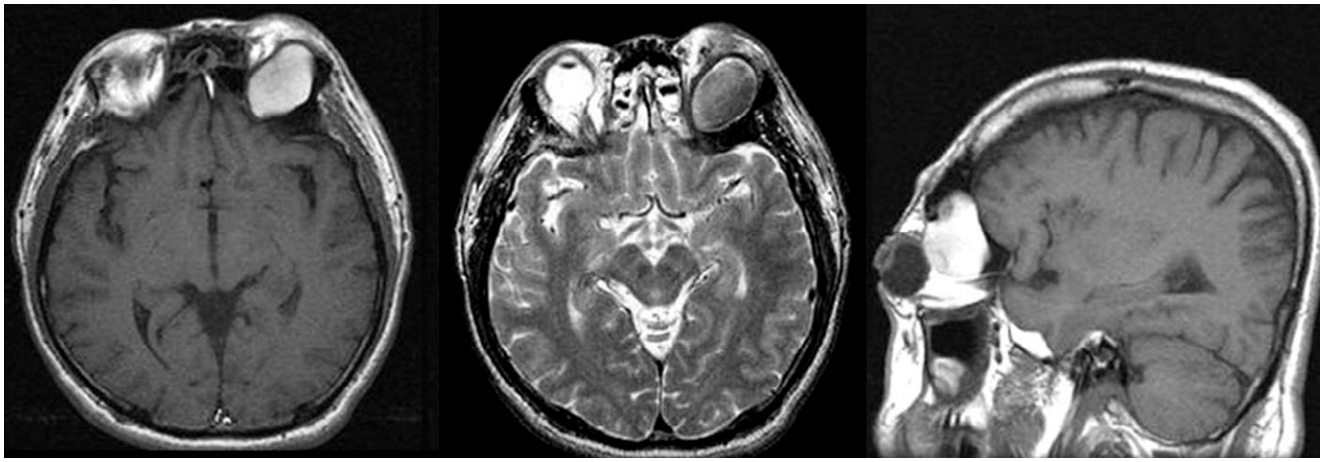
Preoperative face photograph showing proptosis and inferior displacement of the globe on the left side.

orbit and grafted bone packed in the left frontal sinus.

Through a bicoronal approach a rectangular window, 2 × 3 cm, was made on the anterior wall of frontal sinus using a combination of oscillating saw and osteotome. A lateral three quarters of the left sinus was found to be completely packed by the bovine bone grafted in the previous operation and the medial quarter was open and covered with normal mucosa. The grafted bovine bone was removed to reach the mucocele which distended down to the orbit. The mucocele was opened, and yellowish thick content was drained out with suction (Fig. 4). Mucosa of the mucocele was removed as much as possible. The posterior wall of frontal sinus was found to be intact. The periorbita was intact despite absence of most part of the orbital roof. The bone flap was fixed with plates and screws after a free communication between mucocele and nasal cavity.

The proptosis improved remarkably after operation. Postoperative MRI and CT showed that the mucocele disappeared (Fig. 5).

Fig. 3

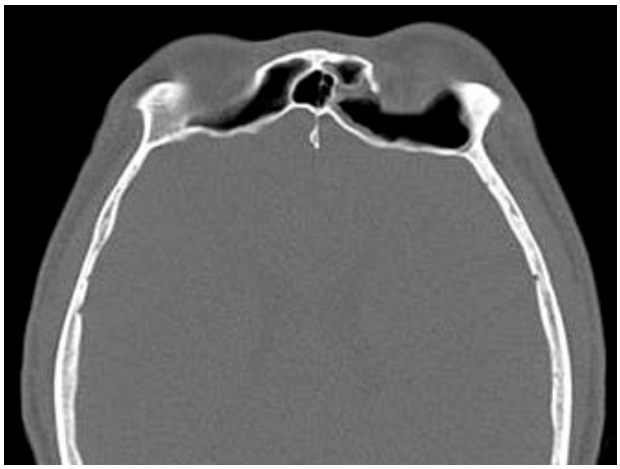


Preoperative T1- and T2-weighted MR images showing a round cystic mass occupying the left frontal sinus and left orbit causing proptosis with high signal intensity on T1WI and iso signal on T2WI.

Fig. 4

Intraoperative photograph revealing the yellowish mucocele after removal of the grafted bone.

Fig. 5



Postoperative axial CT scans demonstrating normal frontal sinus and complete resolution of mucocele.

Discussion

Mucoceles are the dilated mucus-filled sinus that is lined by mucous membrane. They are most commonly found in the frontal and ethmoidal sinuses, are infrequent in the sphenoid sinus and occur rarely in the maxillary sinuses.[6] They result from obstruction of a sinus ostium and frequently are related to a previous condition as chronic sinusitis, trauma, surgery or expansible lesion.[6] With continued secretion and accumulation of mucus, the increasing pressure causes erosion of the bone of the sinus, and release of natural osteolytic factors lead to the destruction of surrounding bony structures. These allow the mucocele to expand slowly in the path of less resistance.[6,8] This may be into the orbit, adjacent sinuses, nasal cavity, intracranial or through the skin. Because of this, the most common initial symptoms are those of visual changes and headaches, while the most common abnormal finding is proptosis.[3]

The frontal sinus fracture is one of the most common causes of mucocele. The frontal sinus fracture can be classified or organized in a number of ways. The fracture can involve the anterior table, the posterior table, or both. The nasofrontal aperture (ostium) may or may not be involved. The fractures may be displaced or nondisplaced, and may be simple or comminuted.[7]

If the fracture causes only the severe depression of anterior table and does not involve the nasofrontal aperture, the common treatment is adequate exposure, anatomic reduction, and plating. In heavily comminuted fractures, care must be taken to be certain that no mucosa is trapped within the fracture lines. For severe nasofrontal aperture fracture, the sinus should almost always be obliterated with bone or fat graft after complete removal of mucosa. If the nasofrontal aperture fracture is relatively minor in a patient who otherwise would not need operative intervention, it might be safe to reimage the patient in 1 to 3 months to be certain that the nasofrontal aperture has remained opened and the sinus is aerated. If this was found not to be the case, then obliteration should be performed. Some, however, advocate reestablishing drainage into the nose, such as with the endoscopic Lothrup procedure with stenting of the nasofrontal aperture.[2] Management of posterior table fractures is considerably more controversial. Some authors recommend open exploration of essentially all posterior table fractures. Others advocate a treatment algorithm based on the amount of displacement coupled with knowledge about the presence or absence of a cerebrospinal fluid leak.[4] If the posterior table is severely comminuted it is probably prudent to "cranialize" the sinus. This involves removing the posterior table, sealing the nasofrontal aperture, drilling out all mucosa, placing a pericranial flap between the bone and the brain, and allowing the brain to expand anteriorly.[7]

The cause of a mucocele in this case is obliteration of sinus which was assumed to have unintentionally remained small piece of mucosa. Complete removal of sinus mucosa can not guaranteed even though thorough removal of mucosa is done because the mucosa can be left in the holes through which vessels pass and crevices in the bone.

The definitive treatment of mucoceles is primarily surgical. Though traditionally mucoceles were treated with open obliterative procedure, functional endoscopic drainage and marsupialization has become the standard and generally uncontested treatment.2,3 Open surgery was required in this case as the frontal sinus had been obliterated with grafted bone.

Conclusion

The operative management of frontal sinus fractures is somewhat variable depending on the type and extent of the fracture and possible associated injuries. This case reminds surgeons that the extirpation of all sinus mucosa is not always possible and natural drainage pathway of sinus should be kept intact unless all sinus mucosa could be removed, otherwise a mucocele may develop even many years after operation.

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반복된 뇌실질 출혈로 진단이 늦어진 시상부 신경교모세포종

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Delayed Diagnosis of Thalamic Glioblastoma Presenting as Repeated Intracerebral Hemorrhages

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Although rare, neoplasms can be obstructed by intracerebral hemorrhage, delaying histological diagnosis and proper treatment. We report the case of a 30-year-old male presenting with serial intracerebral hemorrhages in the left thalamus. Stereotactic biopsy failed to make histologic diagnosis; open biopsy, two months after the initial hemorrhage, diagnosed glioblastoma. The characteristics of hemorrhage from glioblastoma drawn from our experience and a comprehensive review of the literature include the following: (1) under 14 years of age or old age (2) deep seated supratentorial or posterior fossa location (3) disproportionately diffuse brain edema (4) suspiciously enhancing mass lesion (5) irregular shape and heterogeneous appearance with solid areas of blood, multiple hemorrhage, and a ring-shaped hemorrhage. Direct proof of hemorrhagic origin is necessary for diagnosis and treatment of intracerebral hemorrhage with atypical location, imaging findings, or clinical course.

Key Words *Glioblastoma, Intracerebral hemorrhage, Thalamus, Diagnosis.*

Introduction

Spontaneous intracerebral hemorrhage (ICH) in intracranial neoplasms accounts for 1.4 to 10% of ICH.[1, 5, 18, 19] Conversely, the frequency of intracranial neoplasms in spontaneous ICH ranges from 0.8 to 7.4%. Any type of intracranial neoplasm can cause ICH, however frequency varies widely among tumor type. In general, fast growing, highly vascularized neoplasms, with irregular and fragile vascular architecture are most frequently associated with ICH.[9] The great majority of underlying neoplasms is malignant, and may be primary or metastatic.[14, 16, 18] Glioblastoma predominates among primary brain tumors, whereas metastatic tumors are mostly melanoma, choriocarcinoma, bronchogenic, or renal cell carcinoma.

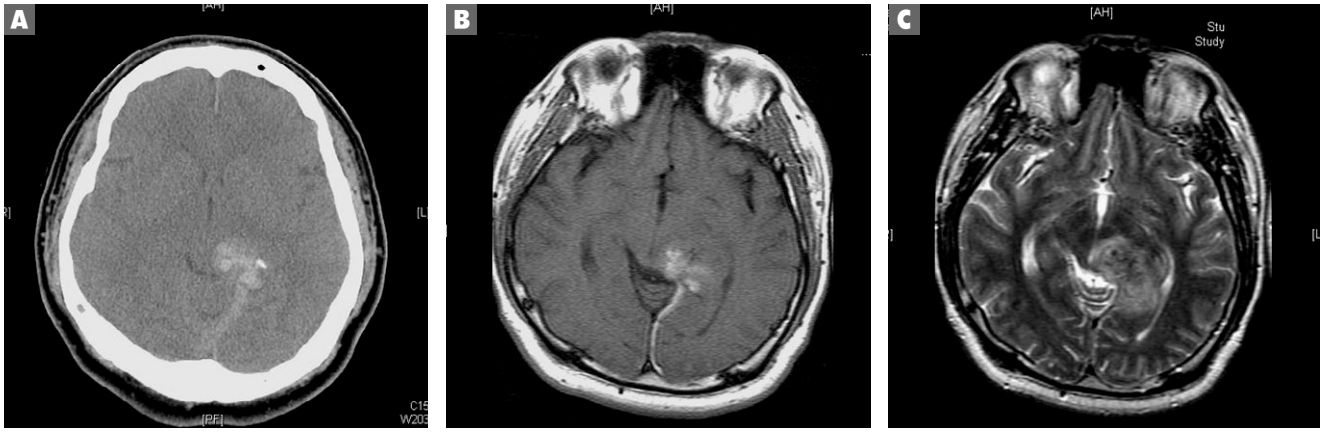
Although rare, neoplasms can be hidden behind an ICH and delay histological diagnosis and proper treatment. We report an unusual presentation of glioblastoma, with repeated intracerebral hemorrhage and discuss their peculiar clinical characteristics and treatments from the literature review.

Case Report

A 30-year-old hypertensive male presented with sudden onset of severe headache, vomiting, and decreased level of consciousness. The patient's medical and surgical history was unremarkable. A non-contrast CT scan showed hyperdense ICH in the left thalamus with subarachnoid extension (Fig. 1A). Magnetic resonance imaging (MRI) revealed subacute hemorrhage with profound perihematomal edema (Fig. 1B and C). There was no definite gadolinium enhancement. Cerebral angiography was negative for vascular abnormalities or tumor blush. The patient underwent conservative care for three weeks and was discharged. Three days later, the patient complained of recurrent symptoms and returned to the emergency room. Repeat CT showed newly-developed ICH at the same site with intraventricular extension (Fig. 2A). The patient became stuporous, underwent extraventricular drainage, and was transferred to our hospital for further evaluation and treatment.

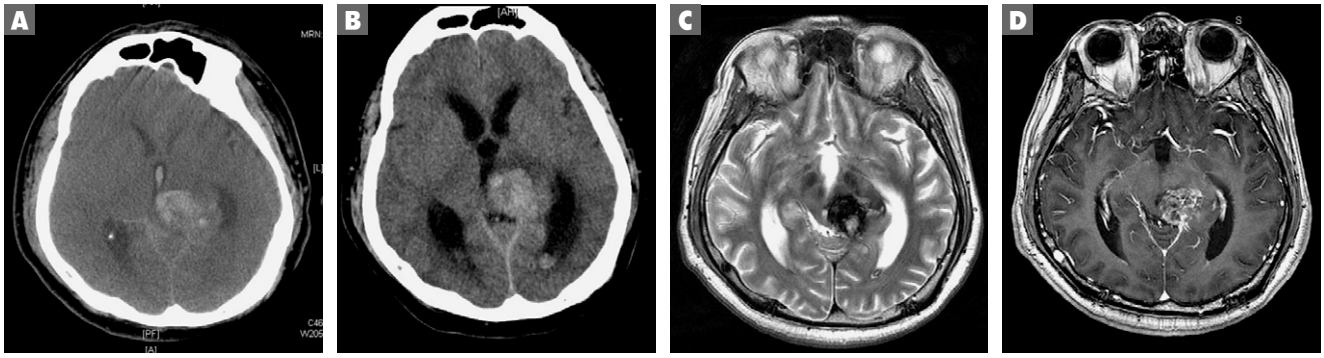
On arrival, the patient was lethargic but opened his eyes transiently to voice. There was right-sided weakness involving the face, arm and leg. Routine laboratory investigations, including coagulation parameters and platelet counts, were normal. He underwent conservative treatment,

Fig. 1



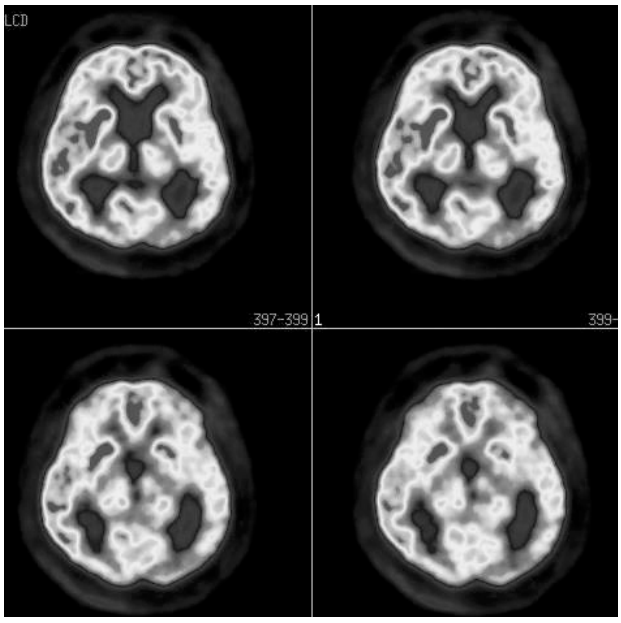
A. A non-contrast CT scan showed hyperdense ICH in the left thalamus with subarachnoid extension.
B. T1-weighted axial MR image revealed subacute hemorrhage with high-signal intensity.
C. T2-weighted axial MRI showed high-signal intensity mass with perihematomal edematous change.

Fig. 2



A. Second brain CT showed newly developed ICH at the same site with intraventricular extension.
B. Third brain CT scan revealed increased amount of hemorrhage with ventricular enlargement.
C. Preoperative T2-weighted axial image revealed heterogeneous signal mass.
D. Preoperative gadolinium-enhanced T1-weighted axial image showed a well-demarcated mass with strong enhancement.

Fig. 3



There was perihematomal depression of metabolism on 2-fluoro-2deoxy-D-glucose positron emission tomography.

including CSF drainage and anti-edema therapy with mannitol. Ten days after admission, the catheter was removed and there were no clinical symptoms of progressive hydrocephalus. One month later, the patient's mental status decreased and CT revealed increased hemorrhage with cerebellar extension (Fig. 2B). There was also mild enlargement of the ventricular size. Preoperative MRI revealed heterogeneous signal mass on T_2-weighted images, which was slightly enhanced on T_1-weighted images (Fig. 2C and D). There was perihematomal depression of metabolism on 2-fluoro-2deoxy-D-glucose positron emission tomography (Fig. 3). A stereotactic biopsy showed reactive gliosis and hematoma. Due to the negative result, open biopsy was planned through occipital craniotomy. After proper hematoma removal, a soft, reddish-gray, hypervascular tumor was found and removed with suction and bipolar forceps. Histopathological examination revealed glioblastoma, intermingled with hemorrhage (Fig. 4). Postoperative radiotherapy and concomitant temozolomide (75 mg/m^2) chemotherapy for six weeks, with a subsequent six courses of adjuvant temozolomide (150-200 mg/m^2) chemotherapy for six months were performed. Final MRI obtained at 6 months postoperation demonstrated decreased size. Ten months postoperatively there has been no recurrent bleeding.

Discussion

Our patient presented with an unusual stroke-like onset; the lesion should have been differentiated from vascular lesions, including vascular anomalies and aneurysm. Patients with brain tumor may initially present with an acute hemorrhage that mimics a pure hemorrhagic stroke. In the

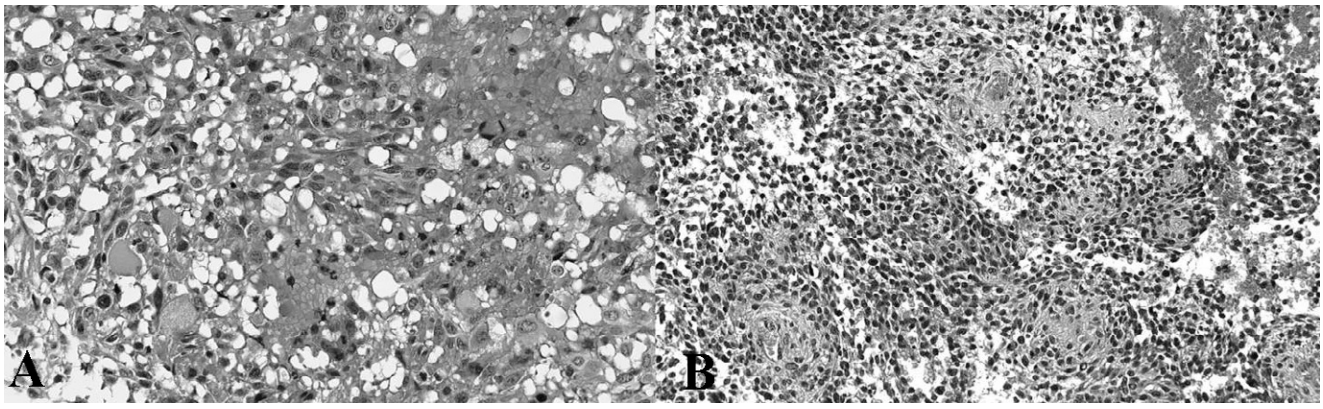
case of recurrent bleeding, physicians must be able to differentiate brain tumor and hemorrhagic stroke immediately. Furthermore, diagnosis delay may allow further neoplasm spread, and cause increased morbidity and mortality.

In addition, cerebral neoplasms with acute ICH as the initial presentation are usually incorrectly diagnosed and have inadequate treatment. In spontaneous intracranial hemorrhages caused by neoplasms, the reported incidence of ICH as the first clinical sign of neoplastic disease ranges from 9-58%.[14, 18] CT scan is not always able to clearly identify tumor-related ICH. If patients are treated conservatively, the correct diagnosis will be delayed or missed. In such situations, open or stereotactic biopsy will confirm suspicious findings, and provide information for treatment. Adjacent tissue should routinely be histologically evaluated because tumor tissue may be small. When only small fragments of specimen are obtained during stereotactic biopsy, as was in our case, it may be difficult to confirm true tumor pathology. In recurrent bleeding of unknown origin, open biopsy is a better choice for tissue confirmation and relief of the mass effect.

In the literature review, incidence of hemorrhage in glioblastoma is significantly higher in patients under 14 years of age or old age.[8, 18] Hemorrhage is more commonly intratumoral than intracerebral. Hemorrhages occurring in glioblastoma are frequently deep into the hemisphere, basal ganglia, or corpus callosum. In addition, although rarely occurs in posterior fossa, tumoral hemorrhage is common.[7] In 26-58% of cases, bleeding from a tumor usually is symptomatic and may be responsible for the first signs of a previously unsuspected neoplasm.[8, 14] Some of these patients were difficult to suspect of brain tumor initially.[3] Characteristic radiological findings included: a neoplastic core; small, multifocal clots usually at the margin of the tumor; and, surrounding, often extensive, edema.[8] The histological features of intratumoral hemorrhage include tumor necrosis as well as vascular changes such as vessel-wall hyalinization, degeneration or necrosis of vessel walls, thrombosis, and presence of many thin-walled vessels and ruptured vessels.[5]

It is important to know the best method to exclude the possibility of brain tumor in patients who present with acute hemorrhage. With CT, it has been reported that an irregular shape and atypical location can hint at tumor-related ICH. A heterogeneous appearance with solid areas of blood, multiple hemorrhages, and a ring-shaped hemorrhage could also be suspected.[6, 10] Enhanced peritumoral vascularization, particularly at the margins, may account for this feature, as well as the fact that the tumor can cause vascular erosions in non-neoplastic tissue.[14] Also, peritumoral edema is an important feature in the differential diagnosis, because it is rarely seen in the acute phase of spontaneous ICH while it is a very common feature in expanding, space-occupying

Fig. 4



Histopathological examination (A: periphery, B: center) diagnosed glioblastoma with high degree of anaplasia, intermingled with hemorrhage.

lesions.[2] The presence of a tumor should also be suspected if ICH are found in atypical locations e.g. subcortical, close to dural membranes, such as the falx or tentorium, close to major cerebral veins or sinuses, or if they are calcified.[4] Although access to MRI can be limited, it is clearly superior to CT for work-up of patients with acute ICH.[15] As in our case, tumor-related hemorrhage was retrospectively suspected from initial MRI study, which showed profound perihematomal edematous change on T_2-weighted images.

The mechanism of bleeding has not been defined, but several hypotheses have been presented. Speed of tumor growth, vascular invasion, infarction, and necrosis may all be the contributing factors.[13] The site of fastest growth of a neoplasm is often in the peripheral zone and brain tissue in this area undergoes necrosis or infarction; together with the blood supply, brain here is stretched, causing it to bleed.[11] Vascular invasion by tumor aggregates may cause luminal obstruction, infarction or necrosis of the tumor, and associated hemorrhage into the neoplasm.[12] In addition, factor associated with hemorrhage into neoplasm includes fibrinolysis resulting from thromboplastin activity of brain tissue.[13] Also, local suppression of the tissue factor-dependent coagulation cascade is a contributing factor that permits the occurrence of intratumoral hemorrhage.[17]

In conclusion, our case indicates that glioblastoma should be taken into account as a possible cause of the repeated ICH. The repeated intracranial hemorrhages in young patients are suspect for bleeding due to a brain tumor when there is no evidence of other common causes such as cerebral aneurysm, vascular malformation, or hypertensive cerebrovascular disease. Direct proof of hemorrhagic origin is essential for diagnosis and treatment of an ICH with atypical location, image findings, or clinical course.

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대한두개저외과학회지 투고 규정

논문의 성격 및 게재 자격

1. 논문 투고 자격은 대한두개저외과 학회 정회원, 준회원 및 간행위원회에서 인정하는 사람으로 한다.
2. 본지는 두개저외과와 관련되어 질병의 원인 규명, 진단 및 치료에 기여할 수 있는 과학적이고 독창적인 내용으로서 간행위원회에서 심의한 원저, 임상 및 증례 및 종설 등을 게재하며, 논문의 게재 여부와 순위는 간행위원회에서 결정한다. 내용이 부적합하거나 투고규정에 위배될 때 원고의 수정을 권유하거나 게재를 보류 또는 거절할 수 있다.
3. 타지에 이미 게재된 논문은 투고할 수 없으며, 본지에 게재된 논문은 임의로 타지에 게재할 수 없다.

원고작성 내용 및 형식

1. 문서작성 프로그램을 이용하여 A4 용지(21×29.7cm)의 한쪽 면을 이용하여 작성하되 글자는 명조체 계통의 12 point 크기로 좌측정렬을 하며, 줄간은 아래 한글의 경우 240%, 한글워드의 경우 2행 간격(double space)으로 사방으로 최소한 2.5cm의 여백을 두어 인쇄한다.
2. 원고는 국문으로 쓰는 것을 원칙으로 하되 필요하면 한자 혹은 원어로 표기할 수 있다. 한자나 원어는 한글 뒤 괄호 안에 표기할 수 있고, 외국어를 사용할 때는 대소문자의 구별을 정확히 하여야 한다. 영문약어는 최소화하며 최초 사용 시 원어를 풀어서 표기한 다음 괄호 안에 약어를 쓴다.
3. 학술용어는 '의학용어집'에 준하여 사용하고, 인명, 지명 그 밖의 고유명사는 그 원어를, 숫자는 아라비아 숫자를, 도량형은 미터법을 사용하여야 한다.
4. 논문 제출형식은 1) 제목(title), 2) 초록(abstract), 3) 서론(introduction), 4) 재료 및 방법(materials and methods), 5) 결과(result), 6) 고찰(discussion), 7) 요약(summary) 또는 결론(conclusion), 8) 참고문헌(references), 9) 그림에 대한 설명(legends for figures), 10) 도표 및 그림(tables and figures)의 순으로 하며 각각 새로운 쪽에서 시작한다.

5. 원고의 구성

1) 표지

논문의 한글제목, 한글소속, 한글저자명 및 영문제목, 영문저자명, 영문소속 순으로 표기한다. 교신저자 (corresponding author)의 성명과 연락처(주소, 전화번호, e-mail주소, 팩스번호)와 별책부수는 제목 쪽의 하단에 표시한다.

2) 초록

초록은 영문으로 작성하되 200단어 이내로 연구목적, 대상 및 방법, 결과 및 결론을 간략하게 요약한 내용이 포함되어야 한다. 초록의 말미에는 Index medicus에 등재된 용어로 영문색인단어(key words)를 5단어 이내로 삽입하여야 한다.

3) 서론

연구의 배경과 목적을 3-4문자 이내로 간결하게 기술하되 원고내용과 관련되지 않은 내용은 피하고, 본 논문의 결과나 결론을 포함하지 않는다.

4) 대상 및 방법

연구대상의 선택, 연구방법 및 통계적 검증의 순서로 기술한다.

5) 결과

표나 그림의 내용을 이용하여 구체적이고 논리적으로 기술하되 표나 그림의 모든 내용을 반복해서 기술하지 않는다.

6) 고찰

본 연구결과에 대한 고찰 및 직접 관련이 있는 다른 자료와의 연관점을 비교하여 결과의 의미와 향후 연구에 대한 영향을 간결하게 기술하며, 서론이나 결과의 내용과 중복되지 않도록 한다.

7) 참고문헌

참고문헌은 본문에 나타난 것만 인용하고, 원저는 20편 이내, 증례보고는 15편 이내로 한다(단 종설의 경우는 예외로 한다). 제1저자의 성의 알파벳 순서에 따라 배열하며 아라비아숫자로 어깨번호를 반괄호안에 표시한다. 동일 저자의 경우 연도순으로 나열하며, 국내문헌도 영문표기를 원칙으로 하나, 영어표기나 불가능한 경우에만 한글로 작성할 수 있다. 외국논문의 경우 참고문헌 저자는 6인까지 있는 경우에는 모두 기재하고 7인 이상은 6인까지 기재 후 et al을 붙인다. 저자표시는

성의 last name을 다 쓰고 first name과 second name은 첫 글자를 대문자로 붙여 쓰며, 이때 initial에는 마침표 (.)를 사용하지 않는다. 저자명 사이에는 쉼표 (,)로 구분하고 마지막 저자 또는 et al 뒤에는 마침표(.)를 찍어 제목과 구분한다. 국문논문의 경우도 동일하다. 인용논문의 제목은 첫 글자는 대문자로 하고, 부제목이 있는 경우 쌍점 (:)을 붙인 후 소문자로 기재하며 제목 뒤에는 마침표 (.)를 붙여준다. 잡지 명은"List of Journals Indexed in Index Medicus"에 의거하여 약어로 기재하며 이 때 잡지 명 뒤에는 마침표(.)를 붙이지 않는다. 이어서 권수(호수) : 시작쪽-끝쪽의 순으로 기재한 후 쉼표 (,)를 찍고 연도를 표시한다.

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6. 사진은 흑백 또는 컬러로 선명해야 하며, 컬러인쇄의 경우는 별도비용이 저자에게 청구된다. 크기는 3×5 인치의 크기로 광택인화지를 사용하며, 사진뒷면에 그림번호, 저자의 이름, 그림의 상하를 표시해 준다. 그림설명과 도표는 영문으로 작성함을 원칙으로 하고, 표의 제목과 그림설명은 논문을 읽지 않아도 이해할 수 있도록 상세히 기술하여야 한다.
7. 증례보고는 상기 원고 구성 규정에 준하지 않으며 간단히 기술하여 내용이 A4 용지 5매를 초과하지 않도록 한다. 영어 초록은 150 단어 이내로 하며 서론, 증례, 고찰의 순서로 기술한다. 결론 또는 요약은 필요한 경우에만 시술하고 저자는 4인 이내만 인정되며 인용하는 참고문헌은 15편 이내로 한다.

투고, 심사 및 게재

1. 원고는 원본과 복사본 2부(사진은 원본과 동일한 것)를 작성하여 발간 2개월 전까지 아래 주소의 간행위원회로 제출한다. 연 2회(6월, 12월) 발행하므로 연중 원고를 접수한다.

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2. 논문심사료, 게재료, 인쇄제본료, 기본 별책료 등은 학회에서 부담한다. 별책부수를 논문표지에 명기하며, 별책부수를 표기하지 않은 것은 본지 관례에 따른다(50부). 별책은 추후 저자에게 배부하며 추가 별책료는 저자가 출판사로 지불한다.
3. 원고의 교정은 저자가 책임지며 심사 후 게제가 결정된 원고는 수정 보완된 내용이 수록된 디스켓 또는 CD 1부와 수정된 원고 1부를 간행위원회 앞으로 제출한다.