

# Preauricular Infratemporal Fossa Surgical Approach: Modifications of the Technique and Surgical Indications

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## ABSTRACT

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A retrospective clinical analysis was performed to evaluate the effectiveness of the preauricular infratemporal fossa (ITF) surgical approach using modifications based on tumor pathology and extension, without compromising outcomes. Patients were surgically treated for tumors involving the ITF via a preauricular surgical approach during 1990 to 2000. Their clinical charts were reviewed to determine the association among pathological variables, details of the surgical procedure, and outcomes. Tumors in 65 patients were categorized as “malignant” and “benign.” The malignant group included 44 patients (mean age, 49.5 years). Squamous cell carcinoma was the most common pathology followed by sarcomas. To achieve complete tumor resection, the ITF approach and dissection were combined with other procedures in 74% of these patients. No surgical complications were encountered in 74.4%, and a clinical cure was obtained in 55% of patients (follow-up, 2 years). The benign group included 21 patients (mean age, 36.7 years). Juvenile angiofibromas and meningiomas constituted most of the tumors in this group. An ITF approach alone was sufficient to achieve complete tumor excision in 66.7% of these patients. A clinical cure was achieved in 85% of patients (follow-up, 2 years), and 76.2% had no surgical complications. Chi-square tests revealed significant correlations between tumor extensions and surgical treatment variables. These were more evident in the malignant group, indicating the use of wider surgical exposures and more aggressive, extirpative surgery. The preauricular surgical approach to the ITF can be used to achieve a complete resection of a variety of tumors arising from or extending into the ITF. This approach can be tailored to the nature of the tumor and its extensions.

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The earliest publications addressing surgical approaches to the infratemporal fossa (ITF) appeared in the 19th century and focused on the treatment of sphenopalatine neuralgia. These techniques were associated with high morbidity rates and failed to gain popularity.<sup>1</sup> Until the 1960s the ITF was considered surgically inaccessible, and tumors that extended into the ITF were considered inoperable. Innovative surgical approaches were introduced by pioneers such as Conley<sup>2</sup> and Barbosa.<sup>3</sup>

As part of skull base surgery, surgical approaches to the ITF have undergone significant changes. Perhaps the most important development is the formation of multidisciplinary teams involving otolaryngologists/head and neck surgeons, neurosurgeons, plastic surgeons, ophthalmologists, radiologists, and medical and radiation oncologists. A multispecialty team facilitates diagnosis, staging, and extirpation of the tumor, thereby improving outcomes and providing acceptable cosmesis and functional reconstruction. Approaches and modifications of existing techniques have evolved to minimize injury of important neurovascular structures within and adjacent to the ITF.

When selecting the surgical approach, a variety of factors, including the histology and biological behavior of the tumor, the patient's characteristics, and the surgeon's experience, should be considered.<sup>4</sup> The preauricular (subtemporal) ITF surgical approach was developed based on these concepts. Intuitively, this approach can be modified according to the nature and extensions of a tumor. However, the literature does not address this feasibility in an adequate manner, and some surgeons advocate the use of extensive approaches regardless of the nature and extensions of the tumor. Therefore, we studied the association among the characteristics of ITF tumors and the variables pertaining to their surgical treatment to demonstrate the effectiveness of the ITF preauricular approach modified according to the characteristics of individual tumors. Oncological outcome was considered to

ascertain if modifying the approach resulted in less favorable outcomes.

## PATIENTS AND METHODS

Patients with tumors involving the ITF who underwent surgical treatment via a preauricular ITF approach, at the University of Pittsburgh Medical Center (UPMC) during the period between 1990–2000, were included in the study. Their clinical charts were retrospectively reviewed and data were collected regarding patient demographics, tumor characteristics, treatment details and outcome.

Clinical and radiological reports were analyzed to establish the origin and extensions of the tumors. Based on Conley's classification,<sup>5</sup> tumors were classified as *primary* tumors, originating primarily from one of the ITF structures, or as *contiguous* tumors, originating from adjacent areas and locally extending into the ITF. Tumoral extensions were grouped according to anatomic sites (Table 1). They were then graded, depending on the number of structures that the tumor involved in each direction, as *minor degree* (single structure involved) and *major degree* (multiple structures involved). Pathological data were reviewed to determine the type and nature of the tumor, adequacy of the resection margin, and presence of perivascular and perineural invasion.

Treatment data included previous treatment modalities, plan of treatment, and the adjunctive use of postoperative radiotherapy and/or chemotherapy. Descriptions of the surgical techniques used at our institution have been previously reported<sup>6,7</sup> and are beyond the scope of the present study. The surgical variables recorded included incision design, osteotomies, subtemporal craniectomy, craniotomies, required orbital surgery, and procedures other than the preauricular approach necessary to complete excision of the tumor. Variables of

**Table 1** Anatomic Sites of Tumoral Extensions

Extensions	Sites
<i>Medial</i>	Pterygoid plates, pterygopalatine fossa, orbit, sinonasal tract, nasopharynx, and clivus
<i>Lateral</i>	Zygoma, mandible, parotid, and masseter
<i>Superior</i>	Greater wing of sphenoid, temporal bone, carotid canal, foramen jugulare, foramen ovale, maxillary nerve, and mandibular nerve
<i>Intracranial</i>	Gasserian ganglion, cavernous sinus, dura, and brain
<i>Posterior</i>	Vertebrae, internal carotid artery, internal jugular vein, and lower cranial nerves

reconstructive surgery included the need to use tissue flaps, type of flap, and the use of biocompatible alloplastic materials.

Complications of treatment, recurrence of tumors, the need for revision surgery, and patients' current oncological status were also noted. In the malignant group, final outcome was defined as patients who completed at least 24 months of follow-up or who died of their disease before this period elapsed.

Chi-square tests were performed to analyze the relationships between categorical variables of pathology and surgical treatment. Fisher's exact test was used when cell frequencies of the  $2 \times 2$  tables were small. Statistical significance was defined as  $p \leq 0.05$ . The statistical analysis of data was performed with Statistix<sup>®</sup> software (Analytical Software, Tallahassee, FL).

## RESULTS

Overall, the study included 65 patients, who were divided into a "malignant" or "benign" group based on the nature of their tumor. Because many were

referred from outside the United States, data were incomplete for some patients. However, they were included in the study, and all observations were based on the total available data.

### Malignant Group

Forty-four patients, including 26 males (59.1%) and 18 females (40.9%), had malignant tumors. Their ages ranged from 2 to 76 years with a mean  $\pm$  standard deviation (SD) of  $49.4 \pm 20.3$  years (median = 53 years). Nineteen patients (43.2%) were younger than and 25 patients (56.8%) were older than 60 years.

### PATHOLOGICAL DATA

Tumors originated at the ITF in 15 patients (34.1%), and 29 patients (65.9%) had tumors that originated at adjacent areas and then extended into the ITF (Table 2).

Squamous cell carcinomas were the most common pathology followed by sarcomas (Table 3). Metastatic neck nodes were found in six patients (30% of the squamous cell carcinomas). Of the 23 cases with available follow-up, perineural spread

**Table 2** Distribution of Extensions of 44 Malignant and 21 Benign Tumors

Extension	Malignant			Benign		
	None no. (%)	Minor no. (%)	Major no. (%)	None no. (%)	Minor no. (%)	Major no. (%)
<i>Medial</i>	4 (9.3)	4 (9.3)	35 (81.4)	2 (10)	1 (5)	17 (85)
<i>Lateral</i>	18 (41.9)	7 (16.2)	18 (41.9)	14 (70)	6 (30)	0 (0)
<i>Superior</i>	15 (34.9)	7 (16.3)	21 (48.8)	6 (30)	3 (15)	11 (55)
<i>Intracranial</i>	29 (67.4)	8 (18.6)	6 (14)	9 (45)	4 (20)	7 (35)
<i>Posterior</i>	41 (95.4)	1 (2.3)	1 (2.3)	19 (95)	0 (0)	1 (5)

**Table 3 Pathology of 44 Malignant and 21 Benign Tumors**

Type of Tumor	Primary	Contiguous	Total no. (%)
<i>Malignant</i>			
Squamous cell carcinoma	3	17	20 (45.4)
Sarcomas*	9	3	12 (27.3)
Adenoid cystic carcinoma	1	5	6 (13.6)
Adenocarcinoma	2	1	3 (6.8)
Basal cell carcinoma	0	1	1 (2.3)
Chordoma	0	1	1 (2.3)
Melanoma	0	1	1 (2.3)
<i>Benign</i>			
Nasopharyngeal angiofibroma	0	7	4 (19)
Meningioma	1	3	3 (14.3)
Schwannoma	3	0	3 (14.3)
Fibrous dysplasia	0	3	1 (4.8)
Encephalocele	1	0	1 (4.8)
Mucocele	1	0	1 (4.8)
Pigmented villonodular synovitis	0	1	1 (4.8)
Inflammatory pseudotumor	1	0	

\*Chondro-, fibro-, lipo-, osteo-, etc.

was evident in 15 (65.2%) and perivascular spread was found in 8 (34.8%). Despite attempts to obtain a wide margin of resection, the margins were microscopically "positive" in 19 of 44 patients (43%).

#### TREATMENT

Of the 44 patients, 33 (75%) had previously been treated elsewhere, with either single modality (13 patients, 29.5%) or multimodality treatments (20 patients, 45.5%). Only 11 patients (25%) had received no previous treatment.

Surgical extirpation involved ITF dissection with no other procedures in 11 patients (25%). Resection was combined with other procedures in 33 patients (75%). Additional postoperative radiotherapy was given to 28 patients and chemotherapy was given to 12 patients. Ultimately, all patients received multimodality treatment, either during their initial treatment or as adjunctive treatment after the ITF dissection.

#### SURGICAL APPROACH

Various incisions were used (Table 4), but a coronal incision with a preauricular extension was the most

common (31 patients, 70.5%; bicoronal, 47.7%; and hemicoronal, 22.8%). However, an additional incision was required in 15 of these 31 patients (48.4%). A combined pre- and postauricular

**Table 4 Distribution of Bony Cuts in 44 Patients with Malignant Tumors and 21 Patients with Benign Tumors**

Type	Malignant no. (%)	Benign no. (%)
<i>Standard Orbitozygomatic Osteotomies</i>		
None	9 (20)	2 (10)
Zygomatic osteotomies	4 (9.3)	16 (80)
Orbitozygomatic osteotomies	30 (69.8)	1 (5)
Zygomaticomaxillary	0 (0)	1 (5)
<i>Additional Osteotomies</i>		
None	38 (88.4)	18 (90)
Supraorbital	3 (7)	1 (5)
Le Fort I	2 (4.6)	1 (5)
<i>Subtemporal Craniectomy Craniotomy</i>		
None	14 (32.6)	8 (40)
Temporal	18 (41.8)	4 (20)
Frontotemporal	5 (11.6)	7 (35)
Bifrontal	4 (9.4)	0 (0)
Orbitocranial	1 (2.3)	0 (0)
Temporoparietoccipital	1 (2.3)	0 (0)
Pterional	0 (0)	1 (5)

approach was used in four patients (9.1%) because their lesions necessitated temporal bone resection. A frontotemporal incision was used in three cases (6.8%). A modified Weber-Fergusson incision for a facial translocation incision was used in three patients (6.8%) who underwent surgery early in the series. A cervical incision that extended into a preauricular incision was sufficient in three cases (6.8%). Only 6 of the 44 patients (14%) required no osteotomy or osteotomy.

Surgical procedures, other than an ITF dissection, were often needed to complete resection of the tumors. Surgical control of the internal carotid artery (ITA) circulation (transcervical or transtemporal) was required in 7 of the 44 patients (16.3%), but no carotid artery was sacrificed. One ICA required primary repair after injury during a transtemporal dissection. A partial maxillectomy was required in 3 of 43 patients (7.0%). A complete maxillectomy was needed in 14 patients (32.6%), and an orbital exenteration (i.e., radical maxillectomy) was necessary in 9 of the 43 patients (20.9%). A radical parotidectomy was performed in 10 of the 43 cases (23.3%) and a superficial parotidectomy in 2 of the 43 cases (4.7%). A partial mandibulectomy was needed in 12 of the 39 cases (30.8%) and a hemimandibulectomy in 2 of the 39 cases (5.1%).

Chi-square tests revealed many significant correlations between tumor extensions and surgical approach variables and surgical procedures (Table 5).

## RECONSTRUCTION

Reconstruction was necessary in 41 patients. It was achieved with vascularized flaps in 31 patients (75.6%) and with bio-implants (hydroxyapatite, titanium) in 5 cases (12.2%). Bio-implants were used alone in two cases (4.9%). Primary reconstruction with titanium plates, mesh, or both was possible in three cases (7.3%). The flaps used for reconstruction were as follows: 17 temporalis muscle transposition flaps, 11 rectus abdominis microvascular free flaps, and 3 latissimus dorsi microvascular free flaps. Two cases had an additional pericranial flap.

## OUTCOMES

No surgical complications were encountered in 32 of the 43 patients (74.4%). Minor cosmetic disfigurement, hematoma, infection, or breakdown occurred in 10 of the 43 patients (23.3%). Major complications occurred in two patients (5%): an intracranial mucocele that required another surgery and a postoperative transient ischemic attack. The development of complications was associated with the extent of surgery, such as the need for craniotomy ( $p = 0.043$ ) or orbital exenteration ( $p = 0.036$ ).

Follow-up data were complete for 40 patients (mean  $\pm$  SD, 22.5  $\pm$  24.2 months; range 1 to 118 months; median, 15 months). Outcomes are based on these 40 patients.

Distant metastases developed in nine patients (20.5%). Recurrence or persistence of tumor at

**Table 5** Probability Values of Associations between Malignant Tumoral Extensions and Surgical Treatment

	Medial	Lateral	Superior	Intracranial	Posterior
<i>Incision</i>	0.032*	0.001*	0.011*	0.626	0.023*
<i>Standard osteotomies</i>	0.007*	0.426	0.055*	0.007*	0.908
<i>Additional osteotomies</i>	0.039*	0.109	0.438	0.006*	0.991
<i>Subtemporal craniectomy</i>	0.282	0.074	0.007*	0.534	0.282
<i>Craniotomy</i>	0.001*	0.309	0.013*	0.022*	0.841
<i>Parotidectomy</i>	0.091	0.005*	0.848	0.367	0.946
<i>Mandibulectomy</i>	0.913	0.031*	0.544	0.222	0.521
<i>Maxillectomy</i>	0.029*	0.327	0.055*	0.801	0.839
<i>Orbital exenteration</i>	0.406	0.091	0.240	0.108	0.902

\*Statistically significant, chi-square tests.

the local area occurred in 14 cases (35%) after a mean of 19 months (range, 1 to 78 months). These cases were managed with surgery in six cases (42.9%), radiotherapy in five cases (35.6%), and chemotherapy in three cases (21.5%). A clinical cure was obtained in 22 patients (55%). Ten patients (25%) were alive with disease, and seven patients (17.5%) died from their disease. Only one patient (2.5%) died from other causes. Fourteen patients were followed for more than 24 months. Of these 14 patients, 7 patients (50%) had no evidence of disease, 4 patients (28.6%) were still suffering from their disease, and 3 patients (21.4%) died because of their disease.

Outcome (death) and local recurrence ( $p < 0.0001$ ) as well as final outcome and use of postoperative radiotherapy ( $p = 0.011$ ) were significantly related.

### Benign Group

Twenty-one patients (12 males, 57.1%; 9 females, 42.9%) had benign tumors. Their ages ranged from 10 to 69 years (mean  $\pm$  SD,  $36.7 \pm 19$  years; median, 36 years).

### PATHOLOGICAL DATA

Tumors originated in the ITF in seven patients (33.3%). In 14 patients (66.7%), tumors had local extensions from an adjacent area (Table 2).

Juvenile angiofibromas were the most common pathology followed by meningiomas (Table 3). Margins of resection were microscopically positive for tumor in 6 of 15 patients (40%).

### TREATMENT

Surgery was the primary treatment for 11 of 19 patients (57.9%). Seven patients (36.8%) were treated for recurrences that developed after a previous surgery. One patient (5.3%) was treated for a recurrence after undergoing a previous surgery and radiotherapy.

Fourteen patients (66.7%) underwent ITF dissection alone. ITF was combined with other

procedures in seven patients (33.3%). Three patients (15%) received radiotherapy.

### SURGICAL APPROACH

A coronal incision was used in 16 patients (76.2%; bicoronal, 57.1%; hemicoronal, 19.1%; Table 4). However, an additional incision was required in 3 of these 16 patients (18.8%). Facial translocation incisions were used in four patients (19.1%). A cervical incision was extended preauricularly in one case (4.8%). Two patients (10%) required no bony manipulation.

Other surgical procedures were necessary to complete the excision of the tumors. Surgical control of the carotid circulation was required in 5 of 20 patients (25%). A partial maxillectomy was performed in 3 of 20 patients (15%), and total maxillectomy was performed in 1 of 20 patients (5%). Orbital exenteration (i.e., radical maxillectomy) was needed in 2 of 20 patients (10%). A partial mandibulectomy was needed in 3 of 19 cases (15.8%).

Chi-square tests revealed significant associations between tumor extensions and the variables of surgical treatment (Table 6).

### RECONSTRUCTION

Reconstruction was needed in 20 patients. It was achieved with vascularized flaps in 9 of 20 patients (45%) and combined with bio-implants in 3 cases (15%). Bio-implants were used alone in two cases (10%). Primary reconstruction was achieved with titanium plates, mesh, or both in six cases (30%). Two types of vascularized flaps were used for reconstruction: 10 temporalis muscle transposition flaps and 2 rectus abdominis microvascular free flaps.

### OUTCOMES

No surgical complications were encountered in 16 patients (76.2%). Minor complications occurred in four patients (19%). There was only one (4.8%) major complication. Postoperatively, one patient developed optic neuropathy and blindness but recovered completely after endoscopic decompression.

**Table 6** Probability Values of Associations between Benign Tumoral Extensions and Surgical Treatment

	Medial	Lateral	Superior	Intracranial	Posterior
<i>Incision</i>	0.018*	0.1511	0.482	0.679	0.001*
<i>Standard osteotomies</i>	0.677	0.739	0.692	0.226	0.029*
<i>Additional osteotomies</i>	0.163	0.378	0.472	0.602	0.000*
<i>Subtemporal craniectomy</i>	0.672	0.478	0.038*	0.425	0.381
<i>Craniotomy</i>	0.001*	0.478	0.319	0.216	0.664
<i>Parotidectomy</i>	N/A	N/A	N/A	N/A	N/A
<i>Mandibulectomy</i>	0.866	0.260	0.117	0.302	0.828
<i>Maxillectomy</i>	0.927	0.599	0.766	0.203	0.877
<i>Orbital exenteration</i>	0.927	0.535	0.655	0.161	0.877

\*Statistically significant, chi-square tests; N/A, not applicable.

Follow-up data were available for 20 patients (mean follow-up  $\pm$  SD,  $28.3 \pm 36.6$  months; median, 14.5 months; range, 1 to 154 months). Local recurrence occurred in four cases (20%) a mean of 58.3 months (range, 8 to 152 months) after treatment.

## DISCUSSION

The anatomy of the ITF can be a source of confusion for neurosurgeons and head and neck surgeons. Some refer to the ITF as the region below the greater wing of the sphenoid, lateral to the medial pterygoid muscle and lateral pterygoid plate. A more inclusive definition includes the anatomic area caudal to the base of the middle cranial fossa. This definition includes both the superior aspect of the parapharyngeal space and the masticator space; thus, most of the major cerebral vessels and cranial nerves pass through the ITF.<sup>8</sup>

The ITF is inaccessible to clinical examination. Therefore, tumors involving this region present unique diagnostic and therapeutic challenges. Such tumors often manifest with insidious and nonspecific signs and symptoms and are often diagnosed at advanced stages. A thorough history and physical examination, with a high degree of suspicion that prompts the use of radiological assessment, are essential to obtain an early diagnosis.<sup>1</sup>

Previously, ITF tumors were considered inoperable. Advances in microsurgery and skull base surgery encouraged the development of multiple surgical approaches to the ITF, aiming to facilitate oncologically sound resections while minimizing the morbidity. Lateral skull base approaches were largely designed to minimize brain retraction. Thus, they encompass bone removal, to gain adequate tumor exposure, and meticulous identification and preservation of vital neurovascular structures.<sup>9</sup>

The preauricular approach to the ITF was developed and modified with these concepts in mind.<sup>10,11</sup> This surgical approach is suitable for the resection of tumors arising in ITF and for intracranial tumors arising in the boundaries of the anterior temporal bone or greater wing of the sphenoid and extending into the ITF. It does not allow, however, the safe resection of any portion of the tympanic bone.<sup>6</sup>

In our patients, the surgical approach often began with a coronal incision, which provides good exposure and is associated with a good cosmetic outcome. An additional incision was needed to complete surgery in 48.4% of the malignant cases and in 18.8% of the benign cases. A facial translocation approach was used in some of the earliest cases in both groups. Despite the superior exposure offered by the translocation approach, it was abandoned because its cosmetic results were inferior. The medial canthus and lacrimal apparatus are interrupted, and the frontal branches of the facial nerve must be transected.<sup>12</sup>

Craniofacial osteotomies or osteotomies were essential in ~90% of patients in both groups to obtain adequate exposure of the tumor and a safe and complete resection. Orbitozygomatic osteotomies were the standard in the malignant group, whereas zygomatic osteotomies were sufficient in most of the benign cases. Our results confirm the findings of cadaveric dissections that quantified the enhancement of the surgical exposure of the ITF when orbitozygomatic osteotomies are used.<sup>13</sup> Additional facial osteotomies (i.e., mandible, superior orbit, nasal) were seldom used in either group. A craniotomy was required in about two-thirds of the cases and a subtemporal craniectomy was needed in half of the cases. Vascularized flaps were the main method of reconstruction in both groups.

In the malignant group, significant correlations were found among variations, the preauricular surgical approach, and the extensions of the tumor (Table 5). The incision design was influenced by the extension of the tumor regardless of its direction. Orbitozygomatic osteotomies, standard or with extensions, were used in patients whose tumors had medial and intracranial extensions. Likewise, the need for a subtemporal craniectomy was used to control superior extensions, and the need and type of craniotomy were associated with superior and intracranial extensions. A parotidectomy and mandibulectomy were used for tumors with lateral extensions, whereas a maxillectomy was needed for tumors with a medial extension. These associations were expected and confirm that the surgery can be tailored to the nature and extensions of a tumor.

There were fewer significant correlations between the extent of the tumor and the different modifications of the surgical exposure in the benign group (Table 6). The differences between the two groups could be explained by the need for aggressive and wider extirpation of malignant tumors. In contrast, benign tumors often can be removed piecemeal without compromising outcomes.

Surgical treatment provided reasonable local control (malignant, 65%; benign, 80%) and disease-free survival (malignant, 55%; benign, 85%) in both groups. Moreover, in both groups, 75% of the cases

had no surgical complications. In the malignant group (i.e., intracranial extension, invasion of the soft tissues of the orbit), complications were significantly associated with the need for a craniotomy ( $p = 0.043$ ) or orbital exenteration ( $p = 0.036$ ); that is, the incidence of morbidity was higher with more advanced surgery. In the malignant group, disease-free survival may have been improved by the use of postoperative radiotherapy.

Our study supports the intuitive clinical assumption that the preauricular ITF surgical approach can be modified according to the nature and extent of a tumor. Incisions should be designed to provide adequate exposure of a tumor in all directions while facilitating cosmetic and functional reconstruction. Osteotomies are usually needed to enhance the surgical exposure in tumors with medial extensions. Likewise, the design of the craniotomy reflects the extent of superior or intracranial extensions. Other surgical procedures may be required to access medial or lateral extensions. Every attempt should be made to achieve complete tumor removal, but unnecessary procedures should be avoided to minimize morbidity rates. The use of adjunctive radiotherapy, chemotherapy, or both should be considered to improve the outcome of patients with malignant tumors.

## CONCLUSION

The preauricular surgical approach to the ITF is versatile and can be used to achieve complete resection of a variety of tumors whose primary treatment is surgery. This approach can be tailored according to the nature of disease and its extensions.

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## Commentary

This article analyzes a large series of cases involving surgical removal of both benign and malignant lesions via a preauricular infratemporal fossa approach. It is timely in that careful analysis of long-term outcomes is essential to validate extensive surgery, particularly for malignant lesions. A clinical cure was obtained in 55% of patients with malignant lesions at 2 years. In the benign group, a clinical cure was achieved in 85% of patients after the same period.

Longer follow-up, of course, is necessary to verify these outcomes. In the case of malignant lesions, recurrences often appear within 2 years, but re-review is necessary to validate disease-free survival of 5 years and longer. The same is true for the benign group.

Despite this shortcoming, this series demonstrates reasonable outcomes for an otherwise universally fatal disease with an acceptable morbidity rate and no mortality. I urge the authors to continue to follow these patients and to issue supplementary reports periodically.

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