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General Summary

We have 5 research areas, which are otology, rhinology, laryngology, head and neck surgery, and sleep science. The researchers in these areas worked on developing safe and effective surgical techniques. They also do basic research in their specialized fields and have achieved excellent results.

Research Activities

Research issues in otology

Our research projects span experiments on the fundamental aspects of middle ear mucosa regeneration and its clinical application, research on gene therapy targeting epithelium with residual cholesteatoma, and the development of a navigation system utilizing virtual-reality technology to increase the safety of surgery. In addition, cases of cholesteatoma surgery performed at our hospital are recorded in our database, which is used to analyze the condition of patients, to select operative methods, and to review postoperative outcomes. We perform approximately 300 middle ear surgeries annually at our hospital. Cochlear implantations performed every year have also yielded favorable results. We perform skull-base surgery, including that for cholesteatoma in the petrous part of the temporal bone, in conjunction with the Department of Neurosurgery, and have found that hearing and facial nerve function can be preserved in many cases. We also perform acoustic tumor surgery. For secretory otitis media we select the treatment method in individual patients depending on the degree of development of the mastoid air cells. In the field of neuro-otology, we have introduced vestibular evoked myogenic potential (VEMP) testing to evaluate saccular function in patients with such conditions as vestibular neuritis, Meniere's disease, and dizziness of unknown cause to facilitate diagnosis and treatment. Moreover, we are examining the prevalence of abnormal saccules in various disorders as measured with VEMP testing, the ictal and nonictal phases of Meniere's disease, and the incidence of VEMP abnormalities according to disease stage. We also adopted the video head impulse test (vHIT) for examining the function of the semicircular canal.

Research in rhinology

We are analyzing data on factors related to the intractability of rhinosinusitis obtained from patients undergoing endoscopic sinus surgery (ESS) and from prospective studies of

the postoperative course. We perform special care for skull-base diseases, such as pituitary tumors and cerebrospinal fluid leak, with a good relationship with the Department of Neurosurgery. In an attempt to expand the indications for ESS from paranasal sinus tumors to skull-base surgery, including that for spinal fluid leakage, skull-base tumors, and pituitary gland tumors, and to improve the safety of ESS, we have performed high-technology navigation surgery in which 3-dimensional endoscopic images and stereonavigation images are superimposed. We have planned clinical studies and developed treatment methods for patients with a variety of olfactory disorders. To clarify the pathogeneses of eosinophilic chronic rhinosinusitis and allergic fungal rhinosinusitis, we investigate how environment fungi and bacteria induce activation and degranulation of human eosinophils and the airway epithelium.

Research on head and neck tumors

For common advanced cancers we perform radical surgery (e.g., total pharyngolaryngectomy combined with reconstruction by means of free intestinal flap transfer for hypopharyngeal cancer and total laryngectomy for laryngeal cancer); however, we perform larynx-preserving surgery (partial hypopharyngectomy combined with reconstruction by means of free-flap transfer and partial laryngectomy) to preserve function, especially vocal function, to the greatest extent possible. We have obtained favorable outcomes in terms of both laryngeal preservation and survival. For conservative therapy and postoperative treatment for advanced cancer, we perform radiotherapy, alone or with concurrent chemotherapy with cisplatin and fluorouracil, and have obtained favorable results. In regard to research on cancer, we are performing basic studies and applying their findings to future studies and to clinical practice. Such fundamental studies include extraction of DNA from specimens obtained during surgery, the evaluation of epidermal growth factor receptor expression, and targets for molecularly targeted agents, such as the expression of human papilloma virus, which has been implicated in the development of mesopharyngeal cancer and oral cancer.

Research on vocal and swallowing functions

Phonosurgery: We are performing outpatient day surgery using a flexible fiberoptic laryngoscope and performing laryngomicrosurgery using the microflap method under general anesthesia for vocal fold polyps, vocal cord nodules, and vocal cord cysts. For many years we have performed injections of atelocollagen into the vocal folds as outpatient day surgery for unilateral recurrent nerve paralysis; however, we are also performing laryngeal framework surgery for patients who are considered poor candidates for atelocollagen injection.

Diagnosis and treatment of spasmodic dysphonia: Since December 2004 we have performed botulinum toxin treatment as a first-line therapy for spasmodic dysphonia with the approval of the ethics committee of the university. The prevalence of this disorder has been increasing; therefore, evaluating methods for diagnosis and treatment is of clinical importance.

Research on sleep apnea syndrome

To verify whether allergic rhinitis is involved in sleep disorders, research for patients with pollinosis has been performed. Continuous positive airway pressure treatment will be the first choice for patients with obstructive sleep apnea syndrome of greater than moderate severity. On the other hand, the effectiveness and safety of surgical treatment are still unknown. We will be able to present the adaptation of surgical treatment for sleep disorders. Long-distance sleep examinations have been performed since 2009. These research studies are joint projects with the Ota Sleep Science Center.

Publications

Kurihara S, Fujioka M, Hata J, Yoshida T, Hirabayashi M, Yamamoto Y, Ogawa K, Kojima H, Okano HJ. Anatomical and Surgical Evaluation of the Common Marmoset as an Animal Model in Hearing Research. *Front Neuroanat.* 2019 Jun 6; **13**: 60. doi: 10.3389/fnana.2019.00060. eCollection 2019. PubMed PMID: 31244619; PubMed Central PMCID: PMC6563828.

James AL, Tono T, Cohen MS, Iyer A, Cooke L, Morita Y, Matsuda K, Yamamoto Y, Sakagami M, Yung M. International Collaborative Assessment of the Validity of the EAONO-JOS Cholesteatoma Staging System. *Otol Neurotol.* 2019 Jun; **40**(5): 630-637. doi: 10.1097/MAO.0000000000002168. PubMed PMID: 31083088.

Takahashi M, Yamamoto-Fukuda T, Akiyama N, Motegi M, Yamamoto K, Tanaka Y, Yamamoto Y, Kojima H. Partial Epithelial-Mesenchymal Transition Was Observed Under p63 Expression in Acquired Middle Ear Cholesteatoma and Congenital Cholesteatoma. *Otol Neurotol.* 2019 Sep; **40**(8): e803-e811. doi: 10.1097/MAO.0000000000002328. PubMed PMID: 31348131.

Motegi M, Yamamoto Y, Tada T, Takahashi M, Sampei S, Sano H, Morino T, Komori M, Miura M, Yamamoto K, Yaguchi Y, Sakurai Y, Kojima H. Clinical Characteristics of Pars Tensa Cholesteatoma: A Comparative Study of Area-Based Classification Systems Proposed by the Japanese Otological Society and the European Academy of Otolaryngology - Neuro-Otology. *J Int Adv Otol.* 2019 Aug; **15**(2): 184-188. doi: 10.5152/iao.2019.6349. PubMed PMID: 31287432; PubMed Central PMCID: PMC6750777.

Takahashi M, Yamamoto Y, Koizumi H, Motegi M, Komori M, Yamamoto K, Yaguchi Y, Kojima H. A quantitative study of the suppression of the development of the mastoid air cells by the presence of congenital cholesteatoma. *Acta Otolaryngol.* 2019 Jul; **139**(7): 557-560. doi: 10.1080/00016489.2019.1606439. Epub 2019 May 3. PubMed PMID: 31050578.

limura J, Miyawaki T, Kikuchi S, Tsumiyama S, Mori E, Nakajima T, Kojima H, Otori N. A new "J septoplasty" technique for correction of mild caudal septal deviation. *Auris Nasus Larynx.* 2020 Feb; **47**(1): 79-83. doi: 10.1016/j.anel.2019.04.009. Epub 2019 May 9. PubMed PMID: 31078357.

Yamamoto-Fukuda T, Akiyama N, Kojima H. Keratinocyte growth factor (KGF) induces stem/progenitor cell growth in middle ear mucosa. *Int J Pediatr Otorhinolaryngol.* 2020 Jan; **128**: 109699. doi: 10.1016/j.ijporl.2019.109699. Epub 2019 Oct 4. PubMed PMID: 31614241.

Akiyama N, Yamamoto-Fukuda T, Yoshikawa M, Kojima H. Regulation of DNA methylation levels in the process of oral mucosal regeneration in a rat oral ulcer model. *Histol Histopathol.* 2020 Mar; **35**(3): 247-256. doi: 10.14670/HH-18-147. Epub 2019 Jul 9. PubMed PMID: 31286466.

Tsuyumu M, Tsurumoto T, limura J, Nakajima T, Kojima H. Ten-year adherence to continuous positive airway pressure treatment in patients with moderate-to-severe obstructive sleep apnea. *Sleep Breath.* 2020 Feb 19. doi: 10.1007/s11325-020-02033-0. [Epub ahead of print] PubMed PMID: 32076950.

Nakayama T, Sugimoto N, Okada N, Tsurumoto T, Mitsuyoshi R, Takaishi S, Asaka D, Kojima H, Yoshikawa M, Tanaka Y, Haruna SI. JESREC score and mucosal eosinophilia can predict endotypes of chronic rhinosinusitis with nasal polyps. *Auris Nasus Larynx.* 2019 Jun; **46**(3): 374-383. doi: 10.1016/j.anel.2018.09.004. Epub 2018 Sep 19. PubMed PMID: 30243753.

Nakayama T, Hirota T, Asaka D, Sakashita M, Ninomiya T, Morikawa T, Okano Nakayama T, Hirota T, Asaka D, Sakashita M, Ninomiya T, Morikawa T, Okano M, Haruna S, Yoshida N, Takeno S, Tanaka Y, Yoshikawa M, Ishitoya J, Hizawa N, Isogai S, Mitsui C, Taniguchi M, Kojima H, Fujieda S, Tamari M. A genetic variant near TSLP is associated with chronic rhinosinusitis with nasal polyps and aspirin-exacerbated respiratory disease in Japanese populations. *Allergol Int.* 2020 Jan; **69**(1): 138-140. doi: 10.1016/j.allit.2019.06.007. Epub 2019 Jul 17. PubMed PMID: 31326260.

Thamboo A, Dholakia SS, Borchard NA, Patel VS, Tangbumrungtham N, Velasquez N, Huang Z, Zarabanda D, Nakayama T, Nayak JV. Inferior Meatus Augmentation Procedure (IMAP) to Treat Empty Nose Syndrome: A Pilot Study. *Otolaryngol Head Neck Surg.* 2020 Mar; **162**(3): 382-385. doi: 10.1177/0194599819900263. Epub 2020 Jan 14. PubMed PMID: 31935161.

- Ideura M, Nishio SY, Moteki H, Takumi Y, Miyagawa M, Sato T, Kobayashi Y, Ohyama K, Oda K, Matsui T, Ito T, Suzumura H, Nagai K, Izumi S, Nishiyama N, Komori M, Kumakawa K, Takeda H, Kishimoto Y, Iwasaki S, Furutate S, Ishikawa K, Fujioka M, Nakanishi H, Nakayama J, Horie R, Ohta Y, Naito Y, Kakudo M, Sakaguchi H, Kataoka Y, Sugahara K, Hato N, Nakagawa T, Tsuchihashi N, Kanda Y, Kihara C, Tono T, Miyanojara I, Ganaha A, Usami SI.** Comprehensive analysis of syndromic hearing loss patients in Japan. *Sci Rep.* 2019 Aug 19; **9**(1): 11976. doi: 10.1038/s41598-019-47141-4. PubMed PMID: 31427586; PubMed Central PMCID: PMC6700179.
- Morita Y, Tono T, Sakagami M, Yamamoto Y, Matsuda K, Komori M, Hato N, Hashimoto S, Takahashi H, Kojima H.** Nationwide survey of congenital cholesteatoma using staging and classification criteria for middle ear cholesteatoma proposed by the Japan Otological Society. *Auris Nasus Larynx.* 2019 Jun; **46**(3): 346-352. doi: 10.1016/j.anl.2018.10.015. Epub 2018 Nov 8. PubMed PMID: 30416024.
- Motegi M, Inagaki A, Minakata T, Sekiya S, Takahashi M, Sekiya Y, Murakami S.** Developmental delays assessed using the Enjoji Scale in children with cochlear implants who have intellectual disability with or without autism spectrum disorder. *Auris Nasus Larynx.* 2019 Aug; **46**(4): 498-506. doi: 10.1016/j.anl.2018.12.003. Epub 2018 Dec 19. PubMed PMID: 30579692.
- Inagaki A, Motegi M, Sato Y, Hattori H, Murakami S.** The inflammatory pseudotumor presenting periodic acid-Schiff-positive inclusions with acute unilateral facial nerve palsy. *Auris Nasus Larynx.* 2019 Jun; **46**(3): 465-468. doi: 10.1016/j.anl.2018.06.009. Epub 2018 Jul 2. PubMed PMID: 30042020.
- Morino T, Takagi R, Yamamoto K, Kojima H, Yamato M.** Explant culture of oral mucosal epithelial cells for fabricating transplantable epithelial cell sheet. *Regen Ther.* 2018 Dec 17; **10**: 36-45. doi: 10.1016/j.reth.2018.10.006. eCollection 2019 Jun. PubMed PMID: 30581895; PubMed Central PMCID: PMC6298907.
- Hosokawa Y, Omura K, Aoki S, Miyashita K, Akutsu M, Tsunemi Y, Kashiwagi T, Haruna S, Otori N, Tanaka Y.** Predictors of Visual Acuity and Usefulness of a Treatment Algorithm in Rhinogenous Optic Neuritis. *Ear Nose Throat J.* 2019 Sep 24: 145561319865490. doi: 10.1177/0145561319865490. [Epub ahead of print] PubMed PMID: 31550936.
- Omura K, Nomura K, Aoki S, Hosokawa Y, Tanaka Y, Otori N, Kojima H.** Resection of inverted papilloma in nasal cavity with transseptal access and crossing multiple incisions minimizes bleeding and reveals the tumor pedicle. *Auris Nasus Larynx.* 2020 Jun; **47**(3): 410-414. doi: 10.1016/j.anl.2019.10.006. Epub 2019 Nov 12. PubMed PMID: 31732283.
- Takaishi S, Saito S, Endo T, Asaka D, Wakasa Y, Takagi H, Ozawa K, Takaiwa F, Otori N, Kojima H.** T-cell activation by transgenic rice seeds expressing the genetically modified Japanese cedar pollen allergens. *Immunology.* 2019 Oct; **158**(2): 94-103. doi: 10.1111/imm.13097. Epub 2019 Aug 23. PubMed PMID: 31323138; PubMed Central PMCID: PMC6742765.
- Kasai Y, Morino T, Kikuchi S, Mitsuyoshi R, Takahashi M, Yamamoto K, Yaguchi Y, Yamato M, Kojima H.** Analysis of human nasal mucosal cell sheets fabricated using transported tissue and blood specimens. *Regen Ther.* 2019 Jun 27; **11**: 88-94. doi: 10.1016/j.reth.2019.05.001. eCollection 2019 Dec. PubMed PMID: 31304201; PubMed Central PMCID: PMC6603308.