Maxillomandibular Advancement Surgery: A Classic Procedure Refined

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The Center for Sleep Medicine Offers More Options for Patients With Obstructive Sleep Apnea Looking for Something Other Than CPAP

With the increasing prevalence and recognition of obstructive sleep apnea, there continues to be a strong and steady interest among providers and patients in treatments besides continuous positive airway pressure (CPAP).

The Mayo Clinic Center for Sleep Medicine, part of Pulmonary and Critical Care Medicine at Mayo Clinic’s campus in Rochester, Minnesota, is the front line of a multidisciplinary team of medical, surgical and dental experts who specialize in the care of patients with sleep-related breathing disorders.

The Emerging Option of Upper Airway Stimulation Therapy

A major determining factor of upper airway patency during sleep is the activity of the genioglossus muscle. Activation of this muscle via stimulation of the hypoglossal nerve is a creative new approach for treatment of obstructive sleep apnea (OSA). Hypoglossal nerve stimulation therapy is commonly referred to as Inspire, a reference to the name of the company — Inspire Medical Systems — that developed the treatment, which was approved by the Food and Drug Administration in 2014.

The Inspire upper airway stimulation system consists of a small impulse generator implanted beneath the clavicle, a tunneled breathing sensing lead placed between the external and intercostal muscles, and a tunneled stimulation lead. Figure 1
lead attached to the branch of the hypoglossal nerve that produces tongue protrusion (Figure 1, see page 1). When the sensing lead detects inspiration is occurring, the impulse generator sends a signal via the stimulation lead to the hypoglossal nerve, which results in slight forward displacement of the stiffened tongue. The impulse generator is similar in size and appearance to a cardiac pacemaker, and the latest version is magnetic resonance imaging compatible.

The pivotal study of hypoglossal nerve stimulation was the Stimulation Therapy for Apnea Reduction (STAR) trial, which was published by Patrick J. Strollo Jr., M.D., and others in The New England Journal of Medicine in 2014. The trial included 126 patients with OSA who had difficulty initiating or maintaining continuous positive airway pressure (CPAP) therapy. The stimulator was associated with a 68 percent reduction in the apnea-hypopnea index (AHI), from 29.3 events an hour to 9.0 events an hour at 12 months. Sixty-six percent of subjects achieved a reduction of at least 50 percent and an AHI of less than 20 events an hour. The AHI reduction was accompanied by improvements in daytime sleepiness and functional outcomes of sleep. The rate of serious adverse events was less than 2 percent.

Nonserious side effects included temporary pain at incision sites, transient tongue weakness and tongue soreness. Tongue soreness improved over time with acclimatization, device reprogramming or both. Maintenance of upper airway stimulation therapy efficacy at three and five years in the STAR cohort has subsequently been reported.

Treatment at Mayo Clinic
The hypoglossal nerve stimulation therapy program at Mayo Clinic’s campus in Minnesota is a joint effort of the Center for Sleep Medicine and Otorhinolaryngology — Head and Neck Surgery. The evaluation of potential candidates begins in the Center for Sleep Medicine. The eligibility requirements for Inspire stimulation therapy match those of the STAR trial:

- Age 22 years or older
- Moderate to severe OSA (AHI 15 to 65 events/hour)
- Body mass index (BMI) below 33 kg/m²
- Difficulty accepting or adhering to CPAP
- No significant comorbidities (neuromuscular disease, hypoglossal nerve palsy, severe cardiopulmonary disease, active psychiatric disease)
- No pronounced upper airway anatomic abnormalities (for example, grade 3 to 4 tonsils)
- Anterior-posterior predominant retropalatal collapse on drug-induced sleep endoscopy

This therapy is currently not considered appropriate for patients with mild OSA, children, patients with a body mass index of 33 kg/m² or more, or patients who are successfully using CPAP but may be curious about an alternative approach.

Screening requires drug-induced sleep endoscopy (DISE) performed by specialists on staff. Patients are excluded if DISE reveals complete concentric collapse at the retropalatal airway, as protrusion of the tongue will not resolve this pattern of airway obstruction.

Establishing coverage for the procedure from insurers may result in a delay between the initial determination of eligibility and surgery. Currently, commercial insurers typically deny initial requests for Inspire coverage, but the appeal process is generally successful. For government insurance, coverage decisions have been mixed.

Follow-up care
Approximately one month after device implantation, patients return for device education and activation. The impulse generator is controlled via a hand-held remote (Figure 2). Patients are advised to use the device nightly and slowly self-titrate the stimulation level over a limited range for one month. Polysomnography to formally titrate stimulation parameters occurs approximately two months after implantation. Hours-of-use information can be collected during device interrogation at follow-up visits.

For more information
Maxillomandibular advancement surgery (MMA) can be an effective treatment for obstructive sleep apnea (OSA). In MMA, the bones of the upper and lower jaw are repositioned to relieve airway obstruction. The procedure also suspends the attached pharyngeal airway muscles in an anterior position and simultaneously increases pharyngeal soft tissue tension. In contrast to all other surgical procedures for OSA, there are effects at all airway levels, from the nasal cavity to the hypopharynx. At Mayo Clinic, the vast majority of patients, even those with severe OSA, have a successful outcome. In fact, more than half of patients achieve elimination of obstructive sleep apnea (apnea-hypopnea index less than 5).

Common sentiment has been that MMA is reserved for patients with craniofacial dysmorphia (mandibular retrognathia). But, in fact, patients with normal osseous structures (that is, OSA in the context of excess soft tissue, including obesity) are often surgical candidates and have similarly good outcomes. Another view is that MMA is a “salvage” surgical option after other soft tissue procedures, such as uvulopalatopharyngoplasty (UPPP), have been tried and failed. MMA should be considered for any patient with moderate to severe OSA if surgical management is desired.

In this craniofacial operation, pre-surgical virtual scanning with 3-D imaging is utilized to maximize accuracy and efficiency in the operating room (Figure 1). After the operation, patients are typically monitored overnight in an ICU setting, with an overall two- to three-night inpatient hospital stay. Pain is typically less than that encountered with soft palatal procedures, such as UPPP, and at discharge, most patients’ pain can be managed with nonopioid analgesics. Manipulation of facial sensory nerves during surgery results in paresthesia that actually blunts the pain response in the short term. Importantly, since current internal bone fixation devices utilized with MMA don’t require jaw wiring, patients can begin eating a soft mechanical diet immediately.

Changes in facial appearance are variable depending mostly on the preoperative anatomy (dysmorphic versus nondysmorphic) and the degree of obesity. Studies show that 70 percent of patients judge that their facial appearance is improved after MMA (Figures 2 and 3); 20 to 25 percent report essentially no change in appearance. Long-term negative sequelae are rare, but this operation must be viewed like other orthopedic surgeries — the final result and condition will occur in nine to 12 months.

Recovery proceeds over approximately six weeks, with a gradual return to normal work or school activities commencing in most patients by three weeks. Postoperative polysomnography is usually performed sometime after three months, when soft tissue edema has resolved.

Figure 1. Pre-surgical virtual scanning with 3-D imaging maximizes accuracy and efficiency in the operating room.

Figure 2. Patient’s facial appearance before maxillomandibular advancement surgery.

Figure 3. Patient’s facial appearance after maxillomandibular advancement surgery.
The Gaining Popularity of Oral Appliances

Since their first use in the early 1980s, oral appliances have become an increasingly popular treatment for obstructive sleep apnea (OSA). Sought after because of their relative ease of use and portability, oral appliances have proved efficacious in cases of mild to moderate OSA.

More recent research suggests that oral appliances can also improve important outcomes in selected patients with more severe disease. Newer innovations in oral appliance therapy include compliance recorders to help in long-term follow-up and emerging technologies to remotely adjust the appliance to optimize upper airway patency.

Dentists in Mayo Clinic Dental Specialties work closely with specialists in the Center for Sleep Medicine to provide an array of oral appliance options as part of a comprehensive treatment plan for patients with OSA. This past year, more than 240 oral appliances were custom-designed and dispensed.

What might a typical patient expect with this process?
The patient undergoes an initial consultation to determine candidacy. Dental impressions are obtained and devices are ordered and manufactured at U.S.-based laboratories SomnoMed (Figures 1 and 2) and Great Lakes Orthodontics. The finished product is typically delivered within four weeks, at which point fitting occurs and patients are educated on usage.

Most oral appliances are designed as mandibular advancers and are adjusted using a specialized tool. Gradual advancement over time reduces the potential for side effects such as discomfort of the jaw, muscles and teeth. Occlusal changes can gradually develop; most patients adapt to them over time. In general, at least eight teeth are needed on each arch to allow anchoring of the device. Temporomandibular joint dysfunction may not always be a contraindication to use of an oral appliance.

For those who don’t have the minimum amount of teeth or cannot use a mandibular advancement device, a tongue stabilizing device is available. The device acts by tongue advancement by suction, thereby increasing the luminal diameter of the upper airway. Calibration and efficacy of oral appliances are determined through a combination of symptom relief, clinical follow-up with both the dental and sleep medicine specialists, and objective sleep testing at the Center for Sleep Medicine, which may be as simple as overnight oximetry.

Care of the Patient With Lung Cancer at Mayo Clinic: Mayo Clinic Tumor Board Provides Multidisciplinary Expertise

Multidisciplinary management for patients with complex lung cancer can be operationalized through multidisciplinary clinics where various specialists interview and examine patients, order and perform diagnostic procedures in an expedited manner, and consider treatment options. To coordinate these consultations and large amounts of clinical data, multidisciplinary management is practiced through team meetings known as tumor boards.

The Mayo Clinic multidisciplinary lung cancer tumor board consists of medical oncologists, radiation oncologists, pulmonologists, thoracic surgeons, radiologists, pathologists and palliative care physicians.

Imaging studies and pathology specimens are reviewed by expert radiologists and pathologists prior to the meeting. The case is presented by the coordinating provider and all diagnostic information is presented by the expert radiologist and pathologist (Figure 1). The presentation is followed by a multidisciplinary discussion of the best management and treatment strategies for these patients. The conclusions and recommendations are subsequently communicated back to the patient and referring
The lung cancer tumor board meeting occurs weekly and is broadcast in real time to Mayo Clinic Care Network members (Figure 2). Colleagues from Mayo Clinic Care Network are able to participate in the discussions of the patients reviewed and also have an opportunity to present their own cases of complex patients for discussion.

This multidisciplinary team assembly provides the most up-to-date treatment options for patients with lung cancer, explores enrollment in clinical trials, and enhances cross-discipline education from the exchange of information and expert opinion.

**Figure 1.** The case is presented to the lung cancer tumor board by the coordinating provider; a multidisciplinary discussion ensues.

**Figure 2.** The lung cancer tumor board meeting occurs weekly. All diagnostic information is presented by the expert radiologist and pathologist and the meeting is broadcast in real time to Mayo Clinic Care Network members.

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**Noninvasive Radiologic Biomarkers to Individualize Lung Cancer Therapy**

Computer-Aided Nodule Assessment and Risk Yield (CANARY) is a novel image analysis software application. It was developed to noninvasively predict the histology and risk stratify pulmonary nodules of the lung adenocarcinoma spectrum, which comprises almost all indolent lung cancers.

CANARY analysis is based on the radiological density and texture of the analyzed nodule. CANARY detects and quantifies the presence of nine different recurring adenocarcinoma tissue types (exemplars) and displays a glyph portraying the proportion of nodule volume occupied by each exemplar (Figure). Based on the proportional distribution of these exemplars, CANARY allows the classification of indeterminate and screen-detected nodules into histopathologic categories:

- Adenocarcinoma in situ
- Minimally invasive adenocarcinoma
- Invasive adenocarcinoma

Independent clustering of the CANARY glyphs stratifies these lesions into three distinct prognostic categories: good, intermediate and poor. Good nodules demonstrate an essentially 100 percent post-resection disease-free survival in early-stage disease. CANARY-based risk stratification has been externally validated in multiple data sets, including the National Lung Screening Trial.
Clinical application of CANARY

At Mayo Clinic, CANARY is routinely used in Pulmonary and Critical Care Medicine’s Lung Nodule, Mass and Adenopathy Clinic and during multidisciplinary lung cancer tumor board conferences.

To individualize patient management, CANARY data are specifically applied in challenging cases of multifocal adenocarcinoma of the lung, and in solitary nodules in high-risk surgical candidates. Glyph stability and change in composition is incorporated into joint decision-making with the patient. While further investigation regarding the longitudinal changes of these lesions is needed, researchers anticipate CANARY will become a very valuable tool in these complex cases.

Ongoing research

CANARY recently has shown promise in its ability to noninvasively predict epithelial growth factor receptor (EGFR) status of adenocarcinoma of the lung. This application could allow better selection of subjects for EGFR-targeted therapy without necessitating biopsy.

Differentiation of benign and malignant pulmonary nodules

Funded by the Department of Defense, a multidisciplinary team of researchers from Mayo Clinic and Vanderbilt University used the National Lung Screening Trial database to develop a radiomic model to differentiate benign from malignant screen-detected and incidentally detected pulmonary nodules ranging in size from 7 to 30 mm. Multivariate analysis identified several variables — including nodule location, size, shape, density, texture and surface characteristics — that differentiated benign from malignant pulmonary nodules, with an area under the curve of 0.94. This model has been internally validated and external validation is ongoing.

Advances in Lung Cancer Immunotherapy and Management of Immune-Mediated Adverse Events

Over the last few years, immunotherapy using immune checkpoint inhibitors targeting programmed cell death receptor 1 (PD-1) or programmed cell death receptor ligand 1 (PD-L1) has revolutionized the therapeutic approach to advanced-stage non-small cell lung cancer and numerous other malignancies (Figure 1).

Monotherapy, using the anti-PD-1 antibody pembrolizumab, is now Food and Drug Administration (FDA) approved for patients with stage IV non-small cell lung cancer without a driver mutation and 50 percent or greater tumor cell PD-L1 expression by immunohistochemistry staining. Moreover, the combination
of systemic platinum-based chemotherapy and pembrolizumab was also recently approved for first line therapy of metastatic nonsquamous non-small cell lung cancer independent of PD-L1 status.

Nivolumab (anti-PD-1) and atezolizumab (anti-PD-L1) also are FDA approved for second line therapy of stage IV lung cancer. For this indication, with the exception of pembrolizumab, which requires 1 percent or greater PD-L1 expression, no PD-L1 expression level is required to initiate therapy.

On average, objective response rates to immunotherapy range around 20 to 30 percent and sustained long-term responses have been observed. However, since the majority of patients do not benefit from second line immunotherapy, many efforts are being made to improve durable responses. The newest addition is a Mayo Clinic investigator-initiated study, the Trial of Measles Virotherapy in Combination With Atezolizumab in Patients With Metastatic Non-Small Cell Lung Cancer, which explores the combination of the intratumoral administration of the measles virus with systemic PD-L1 targeted immunotherapy using atezolizumab for second line therapy of non-small cell lung cancer.

Immune-mediated adverse events
PD-1/PD-L1 targeted immunotherapy is generally well-tolerated and has fewer acute side effects compared with standard cytotoxic chemotherapies. However, these new therapeutic agents have been linked to a growing number of immune-mediated adverse events (imAEs). ImAEs are observed in 70 percent of patients and include autoimmune colitis, thyroiditis, hypophysitis, dermatitis and pneumonitis (Figure 2). The severity of imAEs ranges from asymptomatic to life-threatening presentations, while the time course can be either transient or chronic and relapsing.

Mayo Clinic’s true multidisciplinary team approach includes experts in medical oncology, rheumatology, pulmonary medicine, gastroenterology, endocrinology and neurology to optimally manage patients with imAEs. Besides stopping immunotherapy, patients are most commonly treated with immunosuppression (most commonly corticosteroids).

The pathogenesis, risk factors, diagnostic criteria and individualized management of patients experiencing immunotherapy-related imAEs outside of controlled clinical trials, however, remains unclear. A diagnosis of an imAE, published in Melanoma Research in 2016, represents a diagnosis of exclusion and depends on the active elimination of alternative diagnosis.

For more information

Education Opportunities

For more information or to register for courses, visit https://ce.mayo.edu/pulmonary-medicine/node/1664, call 800-323-2688 (toll-free) or email cme@mayo.edu.

Multidisciplinary Update in Pulmonary & Critical Care Medicine 2018
This course offers lectures, case presentations, and pulmonary and critical care literature reviews. The education design, instructional method and learning format are chosen to best serve the educational needs and objectives specific for this activity. A multidisciplinary faculty provides state-of-the-art updates in pulmonary and critical care medicine. Presentations by leaders in pulmonary and critical care medicine, pulmonary pathology, and radiology provide a comprehensive approach to the current evaluation and management of various respiratory diseases.

20th WCBIP/WCBE World Congress Joint Meeting of the World Association for Bronchology and Interventional Pulmonology (WABIP) & The International Broncho-Esophagological Society (IBES) 2018
June 13-16, 2018, in Rochester, Minn.
The World Association for Bronchology and Interventional Pulmonology (WABIP) and the International Broncho-Esophagological Society (IBES) hold a biennial congress — the World Congress for Bronchology and Interventional Pulmonology and the World Congress for Bronchoesophagology — with host sites rotating among the Asia-Pacific region, the Americas and Europe. Attendees participate in high-caliber scientific programs, including discussions about disease states, new techniques and technologies, and hands-on procedure workshops.

Endobronchial Ultrasound Bronchoscopy (EBUS)
June 14, 2018, in Rochester, Minn.
Endobronchial ultrasound has revolutionized the assessment of mediastinal and hilar lymphadenopathy and lung cancer staging. This WCBIP/WCBE World Congress introductory four-hour, hands-on course lays the foundations for mediastinal lymph node assessment and sampling using low- and high-fidelity simulation, imaging matching, and slide preparation. This course is designed for physicians and health care providers who treat disorders of the larynx, pharynx, esophagus and lungs, including otolaryngologists, gastroenterologists, pulmonologists and thoracic surgeons.

Rigid Bronchoscopy
June 14, 2018, in Rochester, Minn.
Rigid bronchoscopy remains the cornerstone of airway therapeutic pulmonology. This WCBIP/WCBE World Congress hands-on, cadaver-based course offers the opportunity to realistically explore various rigid techniques to include utilizing various ablative and stenting methods. The course is designed for physicians and health care providers who treat disorders of the larynx, pharynx, esophagus and lungs, including otolaryngologists, gastroenterologists, pulmonologists and thoracic surgeons.

Percutaneous Tracheostomy 2018
June 15, 2018, in Rochester, Minn.
Percutaneous bedside tracheostomy placement offers certain advantages over surgical tracheostomy placement in selected patients. This WCBIP/WCBE World Congress four-hour, hands-on course familiarizes the learner with the basic technique of ultrasound and bronchoscope-directed percutaneous tracheostomy placement using a human cadaver model. The course is designed for physicians and health care providers who treat disorders of the larynx, pharynx, esophagus and lungs, including otolaryngologists, gastroenterologists, pulmonologists and thoracic surgeons.

Small and Large Bore Chest Tube Insertion and Introduction to Pleuroscopy
June 15, 2018, in Rochester, Minn.
Thoracostomy tube selection and placement remain critical interventional pulmonology skills. This WCBIP/WCBE World Congress four-hour, hands-on course familiarizes the learner with basic thoracic ultrasound techniques, large and small bore chest tube placement, and basic rigid and flex-rigid pleuroscopy using a human cadaver model. The course is designed for physicians and health care providers who treat disorders of the larynx, pharynx, esophagus and lungs, including otolaryngologists, gastroenterologists, pulmonologists and thoracic surgeons.