Prevention of Frey syndrome during parotidectomy

DULGUEROV, Pavel, et al.

Abstract
To evaluate the incidence of Frey syndrome (auriculotemporal nerve syndrome) after parotidectomy with and without placement of a subcutaneous implant and to examine the relationship between different implants and postoperative wound complications (hematoma, seroma, salivary fistula).

Reference

DOI: 10.1001/archotol.125.8.833
PMID: 10448728
Prevention of Frey Syndrome During Parotidectomy

Pavel Dulguerov, MD; Didier Quinodoz, MD; Grégoire Cosendai; Pierre Piletta, MD; Francis Marchal, MD; Willy Lehmann, MD

Objective: To evaluate the incidence of Frey syndrome (auriculotemporal nerve syndrome) after parotidectomy with and without placement of a subcutaneous implant and to examine the relationship between different implants and postoperative wound complications (hematoma, seroma, salivary fistula).

Design: A prospective nonrandomized controlled trial.

Setting: A primary care and referral university hospital center.

Patients: All patients scheduled for parotidectomy from April 1994 through August 1998 were eligible. Seventy patients were enrolled (2 refused). All 70 patients were evaluated for wound complications. Sixty patients with a follow-up of more than 1 year were evaluated for Frey syndrome.

Intervention: The choice of implant was left to the individual surgeon: 24 patients had no implant; 7, lyophilized dura implant; 7, polygactin 910–polydioxanone (Ethisorb) implant; and 32, expanded polytetrafluoroethylene (e-PTFE) implant.

Outcome Measures: The incidence of Frey syndrome was evaluated (1) subjectively by history (clinical Frey syndrome) and (2) objectively by using 2 newly developed tests. Both hemifaces were tested, with the normal side being used as a control.

Results: Clinical Frey syndrome was present in 12 patients: 11 without implants (11/24 [53%]) and 1 with an implant (1/46 [2%]) \( (P < .001) \). Objective tests were positive in 24 patients: 16 (76%) of 21 without implants and 8 (20%) of 39 with implants \( (P < .001) \). In the implanted patients, the objective tests were positive in 71% (5/7) of those with lyophilized dura, 14% (1/7) of those with Ethisorb, and 8% (2/29) of those with e-PTFE implants \( (P < .001) \). Wound complications included hematoma in 5 patients (7%), seroma in 4 patients (6%), and salivary fistula in 15 (21%). Salivary fistula occurred more frequently with Ethisorb (57%) and e-PTFE (25%) implants \( (P = .04) \).

Conclusions: In patients without an implant, the incidence of Frey syndrome is 50% for subjective and 80% for objective evaluation. In patients with an implant, these incidences are 3% and 10%, respectively. Some implants are associated with a higher incidence of salivary fistula.


From the Division of Head and Neck Surgery (Drs Dulguerov, Quinodoz, Marchal, and Lehmann), Cochlear Implants Center (Mr Cosendai), and Clinic of Dermatology and Venereology (Dr Piletta), Geneva University Hospital, Geneva, Switzerland.

The syndrome of facial gustatory sweating and flushing, described by Lucie Frey in 1923, has come to bear her name because Frey not only correctly described the symptoms, but also put them in context of the autonomic innervation of the parotid gland and facial skin. Since symptoms occur during meals, she postulated that parasympathetic fibers that normally stimulate the parotid gland to produce saliva somehow influence the skin sweat glands, resulting in sweat secretion. A few years after Frey’s publication, André Thomas, a French neurologist, proposed the aberrant regeneration theory as a physiopathological explanation of the syndrome. The postulated etiology is an aberrant regeneration of the sectioned parasympathetic fibers, which, after losing their parotid targets, regenerate to innervate the vessels and sweat glands of the overlying skin. Their activation, following aberrant regeneration, produces an activation of the new targets during eating, resulting in a local vasodilatation (“gustatory flushing”) and localized sweating (“gustatory sweating”). Although Ford and Woodhall supported this explanation in the English-language literature, the aberrant regeneration theory did not gain support until the experimental work of Glaister et al, and the clinical work of Laage-Hellman.
**PATIENTS AND METHODS**

From April 1994 to August 1998, all patients undergoing parotid surgery at the Clinic of Otolaryngology–Head and Neck Surgery of the University of Geneva, Geneva, Switzerland, were offered to participate in this prospective non-randomized trial aimed at diminishing parotidectomy complications. Details on facial nerve data have been published previously.

The beginning of this study antedates the creation of an ethics committee in our department.

In all patients, parotidectomy was performed using standard surgical techniques with intraoperative facial nerve monitoring.

The parotidectomy operation was classified in superficial, total, and radical parotidectomy. While enucleation was never performed, some procedures classified as superficial parotidectomy could have been better named lateral superficial parotidectomy and, similarly, some procedures classified as total parotidectomy should be named near-total parotidectomy.

Laage-Hellman’s landmark studies represent the first serious attempt to analyze the incidence of Frey syndrome (auriculotemporal nerve syndrome). In a retrospective evaluation of 123 parotidectomies, 46% of patients complained of gustatory sweating and 98% tested positive on the Minor test. Laage-Hellman also investigated the delay in appearance of Frey syndrome symptoms after parotidectomy: the minimal delay was 5 weeks, the median delay was 8 weeks, and in only 1 patient did the Minor test become positive after 1 year. Laage-Hellman concluded that Frey syndrome was an unavoidable sequela of parotidectomy that is not overtly symptomatic in all patients. Comparable results were obtained by several other investigators.

Laage-Hellman’s studies represent the first serious attempt to analyze the incidence of Frey syndrome. The choice of the individual implant was left to the individual surgeon; nevertheless, in general, the use of different materials was chronological: (1) a mesh made of polyglactin 910 (Vicryl) and polydioxanone (Ethisorb; Ethicon, Spreitenbach, Switzerland), (2) lyophilized dura (Lyodura, B. Braun Melsungen AG, Melsungen, Germany), (3) expanded polytetrafluoroethylene (e-PTFE) (Gore-Tex; SAM Facial Implant, W. L. Gore & Associates Inc, Flagstaff, Ariz). Some patients did not have any implant placed.

The occurrence of postoperative wound complications was noticed daily during the hospital stay and patients were asked about and examined for any complications at each postoperative visit. Postoperative hematoma was considered to be present when the wound was open and bright red fluid or material was expressed. Postoperative fistula was considered to be present when clear fluid was expressed from the wound. The duration of wound care by dressing changes or rinsing was noted. If a collection of fluid was present under a closed wound and no drainage was required, this complication was called a seroma.

The patients were seen at least 1 year after parotidectomy to assess the presence of Frey syndrome. The mean ± SD follow-up was 24 ± 10 months. The presence of Frey syndrome was assessed by subjective and objective techniques.

Subjective evaluation or “clinical Frey syndrome” was classified in 3 groups: (1) yes-consultation corresponds to patients who either consulted for or complained spontaneously of gustatory sweating; (2) yes-questions corresponds to patients who, when questioned about sweating during eating, responded by the affirmative; and (3) non corresponds to patients who denied gustatory sweating on questioning.

Objective Frey syndrome evaluation was performed with 2 new methods: the iodine-sublimated paper histogram (ISPH) method and the blotting paper technique. Technical details have been previously reported, as well as a calibration with known quantities of sodium chloride. Briefly, the blotting paper technique is a quantitative measure of the amount of sweat generated, by measuring the weight change in a blotting paper before and after the absorption of the sweat. The ISPH method is a modification of the classic Minor test. Regular office paper sheets, which naturally contain various amounts of starch, have been sublimated with iodine, taking an amber color. Wetting this paper results in a localized color change from amber to blue, corresponding to the reduction of starch by water, similarly to color changes of the Minor iodine-starch mixture. The colored paper sheet was scanned in a 8-bit gray-scale mode, and the digital image was subjected to a histogram algorithm. Since the stencils were scanned in a 8-bit mode, the available range of darkness is from 256 (white) to 0 (black). The amber color of the stencil background was used as a threshold value (142 in this case; Figure 1, center). The data with values darker than the threshold are divided in 3 histogram bins of equal width. The darkest bin corresponds to the rather complicated topology of the lateral facial area. In both methods, the stencil was applied on both sides of the face during a gustatory stimulation for 1 minute. The contralateral side was used as a control. Gustatory stimulation was evoked by the suction of slice of lemon. The lemon slice was placed in the mouth and the patient was asked to gently suck on the slice, without undue chewing.

Categorical data were compared with the Fisher exact test, and continuous data were analyzed with the bilateral Student t test using the statistical algorithms of the SPSS 7.5 software package (SPSS Inc, Chicago, Ill).

Laage-Hellman’s landmark studies represent the first serious attempt to analyze the incidence of Frey syndrome (auriculotemporal nerve syndrome). In a retrospective evaluation of 123 parotidectomies, 46% of patients complained of gustatory sweating and 98% tested positive on the Minor test. Laage-Hellman also investigated the delay in appearance of Frey syndrome symptoms after parotidectomy: the minimal delay was 5 weeks, the median delay was 8 weeks, and in only 1 patient did the Minor test become positive after 1 year. Laage-Hellman concluded that Frey syndrome was an unavoidable sequela of parotidectomy that is not overtly symptomatic in all patients. Comparable results were obtained by several other investigators. These studies represent the entire world literature on Frey syndrome in which objective testing was performed (Table 1).

The only method used for the evaluation of sweat secretion in Frey syndrome was originally described by Victor Minor, a Russian neurologist. In Minor’s test, a solution containing 1.5 g of iodine, 10 g of castor oil, and 88.5 g of absolute alcohol is painted on the skin. After drying, the areas are powdered with starch. The water in the sweat produces blue coloring of the iodine-starch mixture. One reason for the paucity of studies with an objective evaluation is that Minor’s test is rather cumbersome and, not infrequently, patients tend to refuse it. We recently described a modification of Minor’s test in which iodine is sublimated on office paper, which natu-
rally contains starch. This iodine-sublimated paper changes color when wet, because starch is reduced, similarly to the reaction of Minor test.16

Recently, several studies have reported the prevention of Frey syndrome during parotid surgery.11,12,15,17-21 All these studies follow the concept of a barrier placed between the parotid wound and the overlaying skin, an idea pioneered by Kornblut et al.8 We conducted a prospective study in which various barrier materials were used.

**RESULTS**

During the 4-year study period, 70 patients had a parotidectomy. The study group included 40 males and 30 females with a mean ± SD age of 50 ± 17 years (range, 12-83 years). The right side was involved in 37 patients and the left in 33. Superficial parotidectomy was performed in 43 (61%) patients, total parotidectomy in 26 (37%) patients, and radical parotidectomy in 1 (1%) patient. A neck dissection was performed in 6 patients—a supraomohyoid selective neck dissection in 5 and a radical neck dissection in 1. The mean ± SD duration of the procedures was 148 ± 57 minutes.

The mean ± SD size of the parotid lesions removed was 2.4 ± 1.2 cm. The pathological diagnosis was a benign process in 62 patients and a malignant process in 8. Benign processes included adenomas (48 patients), non-epithelial tumors (2 patients), tumoralike lesions (9 patients), and infections (3 patients). The adenoma group consisted of 37 pleomorphic adenomas, 9 adenolymphomas, and 2 other monomorphic adenomas. The tumoralike lesions group consisted of 6 cysts (3 lymphoepithelial cysts, 1 lymphoepithelial cyst associated with acquired immunodeficiency syndrome, and 2 salivary duct cysts), and 3 parotid adenopathies. The infection group consisted of 1 parotid abscess, 1 parotid tuberculosis, and 1 chronic sialadenitis. The malignant lesions were 6 carcinomas and 2 melanomas; postoperative irradiation was performed in 6 of these 8 patients.

Of the 70 patients, 46 had an implant and 24 had no implant placed. The 46 implants placed were 7 Ethisorb, 7 lyophilized dura, and 32 e-PTFE sheets (Table 2). Only 60 patients could be evaluated 1 year after surgery; 3 died (n = 2) or were lost to follow-up (n = 1) (all 3 in patients with no implant) and 7 had a follow-up shorter than 12 months (all with e-PTFE implants).

The clinical evaluation showed that 5 (8%) of 60 patients consulted with complaints of gustatory sweating. All of these patients had no implant placed (Figure 2). Therefore, the incidence of patients consulting with gustatory sweating symptoms is 24% in the nonimplant group and 0% in the other groups (P<.001).

Seven patients (10%) gave a positive history on questioning: 6 in the group without an implant and 1 patient with a lyophilized dura implant. Overall, 11 (53%) of 21 patients without implants had a positive clinical evaluation for Frey syndrome (Figure 2). The incidence in patients with an implant was 3% (1/39) (P<.001).

All patients with clinical Frey syndrome tested positive on the objective tests. Objective Frey evaluation tests...
were positive in 24 (40%) of 60 patients. Tests were positive in 16 (76%) of 21 patients without an implant and in 8 (20%) of 39 patients with an implant. This difference was highly significant (P < .001). In patients with an implant, objective Frey testing was positive in 5 (71%) of 7 patients with lyophilized dura, 1 (14%) of 7 patients with Ethisorb, and 2 (8%) of 25 patients with e-PTFE implants (Figure 3). A Fisher exact test on the whole group is highly significant (P < .001). Considering Ethisorb and e-PTFE data, 3 (9%) of 32 patients tested positive. The area of sweating was always limited and away from the parotid area, located anteriorly toward the oral commissure, superiorly in the temporal hairline, or posteriorly behind the ear.

Not only was gustatory sweating more frequent without a barrier or with lyophilized dura, but the quantity of the sweating (data not shown) and the sweating surface (Figure 4) were also significantly more important.

Postoperative hematoma occurred in 5 patients (7%) and seroma in 4 patients (6%). The incidence of hematoma and seroma were not statistically different among the different implants used (Table 3). Postoperative salivary fistula occurred in 15 patients (21%), 2 of whom also had a postoperative hematoma. Postoperative salivary fistula was most frequent after Ethisorb mesh implants (4 patients [57%]), followed by e-PTFE sheets (8 patients [25%]). The incidence of postoperative salivary fistula was statistically different between the implant groups (P = .04). Overall, 21 patients (30%) had a postoperative wound collection of some kind.

All parotid fistulas eventually closed with conservative treatment. In 2 patients, the e-PTFE was exposed at the wound edges and was pulled out easily, without any anesthesia, and without significant pain reported by the patients. In the remaining patients with fistula, the implant was not exposed and was left in place. The

**Table 2. Distribution of Patients According to Implant Type and Incidence of Frey Syndrome**

<table>
<thead>
<tr>
<th>Implant Type</th>
<th>Lyophilized Dura</th>
<th>Ethisorb</th>
<th>e-PTFE</th>
<th>No Implant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyophilized Dura</td>
<td>7/7</td>
<td>7/7</td>
<td>32/24</td>
<td>24/21</td>
<td>70/60</td>
</tr>
<tr>
<td>Consultation for Frey syndrome</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (24)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Frey syndrome history on questioning</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
<td>6 (29)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Clinical Frey syndrome (total)</td>
<td>1 (14)</td>
<td>0</td>
<td>0</td>
<td>11 (53)</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Objective Frey syndrome</td>
<td>5 (71)</td>
<td>1 (14)</td>
<td>2 (8)</td>
<td>16 (76)</td>
<td>24 (40)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients. Ethisorb indicates mesh made of polyglactin 910 and polydioxanone; e-PTFE, expanded polytetrafluoroethylene.*
mean ± SD duration of drainage of parotid fistula cases was 20 ± 11 days. The relationship between parotid collection and different implants used in the prevention of Frey syndrome is shown in Table 2. Once the initial period was over, no long-term complications were encountered, in particular there were no cases of delayed implant extrusion. The postoperative mean ± SD follow-up for patients receiving Ethisorb, lyophilized dura, and e-PTFE implants was 40 ± 8, 38 ± 7, and 18 ± 6 months, respectively.

There was no statistical relation between clinical Frey syndrome or the ISPH test results, patient’s age, type of parotidectomy, size of the lesion removed, or histopathological diagnosis.

### Table 3. Frequency of the Wound Complications According to Type of Implant

<table>
<thead>
<tr>
<th>Wound Complication</th>
<th>Total (N = 70)</th>
<th>Lyophilized Dura (n = 7)</th>
<th>Ethisorb (n = 7)</th>
<th>e-PTFE (n = 32)</th>
<th>No Implant (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seroma</td>
<td>4 (6)</td>
<td>1 (14)</td>
<td>0.0</td>
<td>2 (6)</td>
<td>1 (4)</td>
<td>.70</td>
</tr>
<tr>
<td>Hematoma</td>
<td>5 (7)</td>
<td>0.0</td>
<td>1 (14)</td>
<td>3 (9)</td>
<td>1 (4)</td>
<td>.70</td>
</tr>
<tr>
<td>Salivary fistula</td>
<td>15 (21)</td>
<td>0.0</td>
<td>4 (57)</td>
<td>8 (25)</td>
<td>3 (13)</td>
<td>.04</td>
</tr>
<tr>
<td>Any fluid collection</td>
<td>24 (34)</td>
<td>1 (14)</td>
<td>5 (71)</td>
<td>13 (40)</td>
<td>5 (21)</td>
<td>.06</td>
</tr>
</tbody>
</table>

* Data are given as number (percentage) of patients. Ethisorb indicates mesh made of polyglactin 910 and polydioxanone; e-PTFE, expanded polytetrafluoroethylene.

This study confirms previous reports on the incidence of Frey syndrome without preventive measures. Our results in the group without a barrier implant showed a 53% incidence of clinical Frey syndrome and a 76% incidence of Frey syndrome by using an objective testing method. Our incidence of clinical Frey syndrome seems to be slightly higher than the average from the literature listed in Table 1. A possible reason for this is our aggressive questioning: for the “yes-questions” category, patients were directly and thoroughly asked about possible secretion, draining, and sweating during eating. Nevertheless, it is reasonable to conclude that the incidence of clinical Frey syndrome, ie, patients that are aware of a gustatory facial sweating, is about 40% to 50%.

Our objective test data in patients without a preventive barrier implant (76%) are somewhat lower than the average incidence from the literature (86%). One possible explanation is the different tests used. All previous investigators have used the Minor test. Although we have classified this test as objective, it is unclear (1) how technical variations (differences in the solutions concentrations, differences in the exposure time, etc) influence the results; and (2) what threshold is used for a positive test (few sweat gland drops, slight color changes, etc). Also, while it is possible to take pictures of Minor test hemifaces and perform image analysis on these pictures, none of the previous studies reported doing so. Finally, the Minor test is interpreted without any reference, since both patients’ hemifaces are usually not tested. The objective tests developed for this study have been calibrated with known quantities of sodium chloride and have several advantages over the Minor test. The ISPH method does not require painting of various solutions on the face, thus avoiding patient discomfort and potential allergies. Because the test is well tolerated, bilateral testing is used, which allows for a normal reference. While we have noticed clear differences in results when the same patients were tested on warm days and after an effort (data not shown), the differences are bilateral and therefore cancelled out in the calculation of results. Finally, contrary to the Minor test, of an objective analysis of data is performed by the computer image histogram analysis, allowing the setting an objective threshold for test positivity. This test is simple to perform and the technical details have been provided elsewhere.

Several authors have found a higher incidence of clinical Frey syndrome after more extensive surgery, although this difference disappears when objective tests are used. We were unable to find such a difference because objective tests were used and because of the confounding role of the prevention barriers implanted.

The comparison of the different Frey syndrome prevention barriers used shows that they were effective in preventing clinical Frey syndrome (only 1 in 39 patients with an implant had clinical Frey syndrome [3%]). This case occurred after placement of lyophilized dura, and was located very anteriorly, close to the corner of the mouth, and probably in front of the implant placed. When ISPH test data are examined, Ethisorb and e-PTFE were more efficacious than lyophilized dura. While it seems logical that nonresorbable material such as e-PTFE gives better and more permanent results, the difference between 2 resorbable materials such as lyophilized dura and Ethisorb is purely speculative. Probably some of the difference results from the resorption characteristics of the material, which are not known precisely, and might vary among patients. Also, the 2 patients with a positive ISPH test result in the e-PTFE group had a limited and peripheral Frey syndrome, probably because the implant was not big enough or was not sutured correctly to cover the entire exposed skin. Our final impression, partially supported by the data, is that the less resorbed an implant, the better the barrier it is.

The resorption characteristics of the implant are to be put in perspective with the wound complications it produces. A seroma is the mildest form, since by our definition it resolves without any treatment. We had the impression that hematomas were not directly related to the implant, but might result more from perioperative events,
such as inadequate hemostasis under hypotensive anesthesia with rebound bleeding, and uncontrolled postoperative hypertensive episodes. Therefore, the most annoying wound complication is salivary fistula, which was clearly more frequent with Ethisorb mesh, but also with e-PTFE. Once the acute period (4–6 weeks) had passed, no specific problems with the implants were encountered.

The ideal Frey prevention barrier has to either remain in place permanently or be replaced by a body fibrosis, which is dense enough to prevent the growth of parasympathetic parotid fibers toward the facial skin eccrine glands. In many respects, e-PTFE implants represent the ideal solution since they are not resorbable, exhibit good biocompatibility, and low tissue reactivity.25,26 However, probably because of this low and slow biointegration, e-PTFE, like the Ethisorb, seems to act as a foreign body in the postparotidectomy wound and stimulates saliva secretion. If our initial enthusiasm with e-PTFE has been somewhat chilled by these wound side effects, it remains at the present time our implant of choice, until more suitable materials become available. The lack of long-term complications and in particular delayed extrusion, during an average follow-up of 2 years, is encouraging.

A review of the literature of other techniques used in preventing Frey syndrome is given in Table 4. Probable the only technique of potential interest is the so-called superficial musculoaponeurotic system (SMAS) flap technique. While evaluation in early studies using the SMAS technique was done mainly by history, recent data using the Minor test are less favorable. Only a randomized trial, using an evaluation with an objective test, comparing the SMAS flap technique and the barrier method advocated herein can demonstrate the best method of preventing Frey syndrome during parotidectomy.

We conclude with the following points:

1. The iodine-sublimated paper histogram (ISPH) test for facial gustatory sweating is an easy-to-perform, well-tolerated, objective test.

2. The incidence of clinical Frey syndrome after parotidectomy is 40% to 50%. When objective tests are used (ie, ISPH), the incidence is about 80%.

3. The use of an implant placed in the wound as a prevention barrier reduces the incidence of clinical Frey syndrome to 3%. When objective tests are used (ie, ISPH), the incidence with e-PTFE is reduced to 10%. Therefore, the best Frey syndrome prevention barrier appears to be a nonresorbable implant.

4. Some of the implants used (mainly Ethisorb, but also e-PTFE) result in a high incidence of parotid fistula; therefore, the search for the best implant should continue.

Accepted for publication March 11, 1999.


Reprints: Pavel Dulguerov, MD, Division of Head and Neck Surgery, Geneva University Hospital, 24 rue Micheli-du-Crest, 1211 Geneva 14, Switzerland (e-mail: pavel.dulguerov@hcuge.ch).

<table>
<thead>
<tr>
<th>Prevention Technique (Reference)</th>
<th>Evaluation</th>
<th>Follow-up</th>
<th>Incidence, %</th>
<th>With Prevention</th>
<th>Without Prevention</th>
<th>P (χ² Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auriculotemporal nerve avulsion27</td>
<td>History</td>
<td>?</td>
<td>20</td>
<td>24</td>
<td>.70</td>
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<tr>
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<td>43</td>
<td>23</td>
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<td>97</td>
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<td>12.5</td>
<td>47</td>
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<td>0</td>
<td>...</td>
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<td></td>
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<tr>
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<td>3</td>
<td>12.5</td>
<td>.02</td>
<td></td>
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<tr>
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<td>?</td>
<td>0</td>
<td>...</td>
<td>...</td>
<td></td>
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<td>0</td>
<td>...</td>
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<td>SMAS dissection13</td>
<td>History</td>
<td>1 y</td>
<td>1</td>
<td>83</td>
<td>&lt;.01</td>
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<td>1 y</td>
<td>3</td>
<td>87</td>
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<td></td>
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<tr>
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<td>1 y</td>
<td>70</td>
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</tbody>
</table>

*SMAS indicates superficial musculoaponeurotic system; ellipses, not reported.

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