Background: Xerostomia is a permanent and devastating sequela of head and neck irradiation, and its numerous consequences affect most aspects of the patient’s life. A new method of preserving and protecting a single submandibular gland from radiation damage through the Seikaly-Jha procedure (SJP) has recently been described.

Objective: To report the long-term outcomes of the SJP.

Design: Inception cohort.

Patients: The trial was conducted between February 1, 1999, and February 1, 2002. All patients were followed up through the head and neck cancer clinic at the Cross Cancer Institute. All data were collected by a dedicated research nurse. Salivary function was evaluated at regular intervals with salivary flow studies and questionnaires.

Results: Ninety-six patients were enrolled in the study, and 38 had a minimum of 2 years’ follow-up. The cohort of 38 patients was composed of 2 groups: 26 patients had preservation of one submandibular gland through the SJP, while the remaining 12 did not. Salivary flow was preserved in the SJP group, in which 83% of patients reported normal amounts of saliva 2 years after radiotherapy, compared with none in the SJP group. There were no disease recurrences on the side of the transferred gland or in the submental space. There were no surgical complications attributed to the transfer procedure.

Conclusions: The SJP prevented xerostomia in 83% of the study patients. The approach appears to be oncologically sound and safe.

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encouraging and resulted in the prevention of xerostomia in 81% of the patients. The objective of this study was to report the long-term outcomes of the Seikaly-Jha procedure (SJP) of submandibular gland transfer.

### METHODS

#### PATIENTS

A phase 2 clinical trial was conducted between February 1, 1999, and February 1, 2002, to evaluate the SJP in patients with head and neck cancer. The trial was approved by the internal review board and the human ethics committee. All patients were enrolled in the study and followed up through the multidisciplinary head and neck cancer clinic at the Cross Cancer Institute. The inclusion criteria for patients in the trial were the following: (1) previously untreated and biopsy-confirmed diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx and patients with unknown head and neck primary tumor with unilateral metastases to the neck nodes; (2) must be undergoing primary surgery as part of their treatment plan; (3) Karnofsky score of 70 or higher; (4) expected survival greater than 1 year; and (5) signed informed consent.

Patients were deemed ineligible if they had the following: (1) carcinomas of the oral cavity or nasopharynx, N3 neck disease, bilateral neck node involvement, preepiglottic space involvement, involvement of level I nodes on either side of the neck, recurrent disease, or any prior head and neck malignancy other than basal and squamous cell carcinoma; (2) prior malignancies unless disease-free for 3 years or longer; (3) prior chemotherapy; (4) salivary gland malignancy; (5) salivary gland disease, for example, Sjogren syndrome; (6) prior head and neck irradiation; or (7) prior neck surgery for any reason.

#### SUBMANDIBULAR GLAND TRANSFER SURGERY

The method of submandibular salivary gland transfer used was the SJP. The gland transfer was always performed on the uninvolved neck on the side contralateral to the primary tumor.

A neck incision was performed from the mastoid tip to the mentum approximately 4 cm below the body of the mandible. The neck flaps were elevated in the subplatysmal plane, preserving the greater auricular nerve. The marginal mandibular nerve and distal facial vessels were identified superiorly, dissected free from the surrounding structures, and preserved. The fascia over the sternocleidomastoid muscle was incised, and the muscle was lifted off the underlying structures. The spinal accessory nerve was identified and dissected free up to the posterior belly of the digastric muscle. A level II and III neck dissection was then performed, preserving the jugular vein, spinal accessory nerve, hypoglossal nerve, sensory rootlets of the neck, and proximal facial vessels. Level I was then dissected separately, and all facial and preglandular nodes were removed piecemeal. The submental space was cleared from the contralateral belly of the digastric to the ipsilateral mylohyoid muscle, and the submandibular gland was left in place.

Any suspicious nodes (enlarged or hard) from level II and III neck dissection specimens and all level I lymph nodes (mean number, 3 [range, 2-5]) were sent for frozen section evaluation. While the lymph nodes were being cleared, the facial vessels were identified proximally at the posterior and lower aspect of the submandibular triangle and distally as they enter the face. The submandibular gland was released from the surrounding fascial structures and mylohyoid muscle, but remained pedicled on the facial vessels, submandibular ganglion, and duct.

Retrograde or reverse flow in the facial artery was assessed by ligating the proximal end just medial to the posterior belly of the digastric muscle and partially cutting the artery distal to the ligature. If there was no retrograde flow, the transfer was abandoned. If, however, flow was observed, the facial artery and vein were ligated and cut just proximal to their branches supplying and draining the gland. This left the gland pedicled on the distal facial vessels and thus supplied and drained via the retrograde flow through these vessels. The gland was then swung anteriorly, and the remainder of the fascial attachments were released.

The mylohyoid muscle was bisected. The gland was then repositioned in the submental space anterior and superficial to the anterior belly of the digastric muscle (Figure 1). The gland was positioned deep to the anterior belly of the digastric muscle in the first 10 patients. The bisected mylohyoid muscle allowed repositioning of the submandibular duct and submandibular ganglion. The gland was anchored between the anterior bellies of the digastric muscles to the periosteum of the mentum with absorbable sutures. The anterior, posterior, and inferior borders of the gland were marked with 25-gauge wire to help identify the position of the gland after surgery. The platysma muscle was approximated over a suction drain with absorbable suture, and the skin was closed.

The transfer was abandoned if any of the nodes on the side of the transfer were involved with metastatic cancer on frozen section or if there was no retrograde flow in the facial artery.

### PEARLS AND PITFALLS OF THE SJP

To date, we have performed the transfer on more than 150 patients and found its success and the adequacy of the gland mobilization dependent in part on the following maneuvers: (1) The facial artery must be ligated proximal to the first arterial branch to the submandibular gland. (2) The retromandibular vein at times joins the facial vein fairly distally, which does not allow adequate mobilization of the gland anteriorly. The retromandibular vein in these situations can be safely sacrificed. (3) We have identified veins that run with the submandibular duct and submandibular ganglion and within the fascia surrounding the facial artery. These veins do not hinder anterior mobilization and should be preserved. When the facial vein is missing, these veins are the only ones draining the submandibular gland. (4) A small cuff of fascia should be left on the gland, as it provides a place to anchor the suture and avoids the placement of sutures through the glandular tissue. (5) The deep dissection of the submandibular gland must be performed bluntly to avoid damaging the ganglion and duct. The ganglion usually lies more anteriorly than expected under the mylohyoid muscle. (6) When a mandibular split is used for the surgical approach, the surgeon must ensure that the closure sutures do not violate or encroach on the submandibular duct opening when closing the floor of mouth. (7) The lymph nodes should be sent for frozen section examination.
after the neck dissection while the gland transfer is being performed to eliminate undue delays.

RADIOTherapy

Radiotherapy was started within 4 to 6 weeks after surgery. Patients were treated in an immobilization device using linear accelerators with appropriate photon (6- and 18-MV photons) and electron (9- and 12-MeV energies) at a source-to-axis distance of 100 cm. Beam verification films were obtained for each field and repeated whenever any field adjustments were made. A combination of lateral opposing, anterior, or angled-down bilateral superior oblique fields was used for the primary tumor and positive nodes. The maximum spinal cord dose was restricted to 46 Gy. Tissue-equivalent compensators were used to ensure homogeneity of dose distribution so that variation within the target volume did not exceed 10% of the target dose. Boost doses were specified at the sites of gross disease areas and the potential site of spread were not shielded. This shield always remained in front of the hyoid bone. Disease areas and the potential site of spread were not shielded. The primary target volume included more than 80% of major salivary glands (parotid glands and the nontransferred submandibular salivary gland) and had greater than 50 Gy delivered to that volume via external beam. The dose prescription was per the accepted standards of radiotherapy, and the total dose varied from 50 to 70 Gy, in 2 Gy per fraction, treating once a day, 5 times a week.

DATA COLLECTION

All patients were followed up through the head and neck cancer clinic. All demographic, staging, surgical, radiation, pathologic, and follow-up data and quality-of-life questionnaires were collected and recorded prospectively by a dedicated research nurse (P.B.).

Table 1. Amount and Consistency of Saliva Questionnaire

<table>
<thead>
<tr>
<th>Score</th>
<th>Amount of Saliva</th>
<th>Consistency of Saliva</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>I have a normal amount of saliva</td>
<td>My saliva has normal consistency</td>
</tr>
<tr>
<td>20</td>
<td>I have a mild loss of saliva</td>
<td>My saliva is slightly thicker</td>
</tr>
<tr>
<td>30</td>
<td>I have a moderate loss of saliva</td>
<td>My saliva is moderately thicker</td>
</tr>
<tr>
<td>50</td>
<td>I have no saliva</td>
<td>I have saliva that dries in my mouth or on my lips</td>
</tr>
</tbody>
</table>

Salivary function was evaluated at regular intervals before and after surgery, at the mid point of radiotherapy, at the end of radiotherapy, and 2, 6, 10, 16, and 24 months after radiotherapy. The following 2 evaluation methods were used.

Salivary Flow

Saliva from the anterior floor of mouth was collected by means of an appliance consisting of a micropipette holder (Drummond Scientific, Broomall, Penn) (for use with 20-ml micropipettes) fitted with a 2-ml latex dropper bulb. The procedure involved the initial collection of an unstimulated saliva sample, the patient then had a 3-minute rest interval, and a stimulated saliva sample was collected using 0.2 ml of 6% citric acid solution on the posterior dorsal surface of the tongue every 30 seconds. All collections were made at least 1 hour after the most recent meal, between 9:30 AM and 12:30 PM to reduce possible circadian contributions. The flow rate was calculated as collected volume per collection time.

Salivary Questionnaire

We used sections 7a and 7b of the University of Washington Quality-of-Life Questionnaire to evaluate the patients' subjective symptoms of xerostomia. These sections deal with the amount and consistency of the patient's saliva (Table 1). The lower scores (10 and 20) depict no or minimal change of saliva, while higher scores (30-50) indicate moderate to severe change of saliva (xerostomia).

STATISTICAL ANALYSIS

The study groups and the demographic variables were tested for independence using t test for age and Fisher exact test for the contingency tables. The salivary flow and saliva questionnaires were analyzed with t test and Kruskal-Wallis nonparametric test. All statistical tests were 2-tailed, with P<.05 considered significant.

RESULTS

Ninety-six patients were enrolled in the study, and 38 had a minimum of 2 years' follow-up. The cohort of 38 patients was composed of 2 groups. Twenty-six patients (GP group) had preservation of one submandibular gland through surgical transfer and appropriate postoperative radiation shielding. The remaining 12 patients (NGP group) did not have preservation of the gland because of transfer abandonment or lack of postoperative shielding owing to the presence of disease on pathologic examination (7 on frozen section and 5 on permanent section) in the lymph nodes on the side of the transfer. There was no statistically significant difference between the 2 groups with regard to patient demographics (Table 2), disease site and stage (Table 2), survival status and cause of death (Table 3), or rate and site of recurrence (Table 4).

The stimulated and baseline salivary flow data are seen in Figure 2 and Figure 3. There was preservation of the salivary flow in the GP group compared with the NGP group. This difference was statistically significant at the mid point of radiotherapy, at the end of radiotherapy, and 2, 6, 16, and 12 months after radiotherapy.

The salivary questionnaire data (amount and consistency) are presented in Figure 4 and Figure 5.
There was a statistically significant difference between the 2 groups at 2, 6, 16, and 24 months after the end of radiotherapy. Eighty-three percent (15/18) of patients in the GP group reported a normal amount of saliva (scoring 10 or 20 on the salivary questionnaire) 2 years after radiotherapy, compared with none in the NGP group.

The SJP added a mean of 45 minutes to the surgical procedure. There were no disease recurrences on the side of the transferred gland or in the submental space. There were no surgical complications attributed to the transfer procedure.

Dose-volume histograms were calculated for all parotid and submandibular glands along with the radiation dose ranges. The transferred submandibular gland received 8 to 14 Gy, while the in situ submandibular, left parotid, and right parotid glands were targeted with doses of 50 to 70 Gy.

Table 2. Patient Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>GP (n = 26)</th>
<th>NGP (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>57.7</td>
<td>62.1</td>
<td>.21</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (77)</td>
<td>7 (58)</td>
<td>.27</td>
</tr>
<tr>
<td>Female</td>
<td>6 (23)</td>
<td>5 (42)</td>
<td></td>
</tr>
<tr>
<td>Site of disease, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larynx and pharynx</td>
<td>13 (50)</td>
<td>3 (25)</td>
<td>.21</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>7 (27)</td>
<td>7 (58)</td>
<td></td>
</tr>
<tr>
<td>Skin and unknown primary</td>
<td>6 (23)</td>
<td>2 (17)</td>
<td></td>
</tr>
<tr>
<td>Stage, No. (%)</td>
<td></td>
<td></td>
<td>&gt;.99</td>
</tr>
<tr>
<td>1 and 2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3 and 4</td>
<td>26 (100)</td>
<td>12 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: GP, group with preservation of one submandibular gland with the Seikaly-Jha procedure; NGP, group without preservation of the gland.

Table 3. Survival Status and Cause of Death

<table>
<thead>
<tr>
<th>Category</th>
<th>GP (n = 26)</th>
<th>NGP (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>19 (73)</td>
<td>7 (58)</td>
<td>.46</td>
</tr>
<tr>
<td>Dead</td>
<td>7 (27)</td>
<td>5 (42)</td>
<td></td>
</tr>
<tr>
<td>Cause of death, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease related</td>
<td>3</td>
<td>4</td>
<td>.29</td>
</tr>
<tr>
<td>Other causes</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: See Table 2.

Table 4. Incidence of Disease Recurrence and Second Primaries

<table>
<thead>
<tr>
<th>Category</th>
<th>GP (n = 26)</th>
<th>NGP (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local recurrence</td>
<td>0</td>
<td>2</td>
<td>.42</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Second primary</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: See Table 2.
The Seikaly-Jha procedure; NGP, group without preservation of the gland; GP indicates the group with preservation of one submandibular gland with the Seikaly-Jha procedure. Although the trial was not randomized, we believed that a comparison of the salivary function between the 2 groups would be useful and informative, as the NGP group is representative of patients managed with the standard combined modality treatment of surgery and postoperative radiotherapy.

The long-term results of the phase 2 trial continue to be encouraging. Xerostomia was prevented in 83% of patients in the GP group. These results are clinically and statistically significant when contrasted with the development of xerostomia in all the patients in the NGP group. The procedure appears to be oncologically sound and safe, as there were no changes in the pattern of disease recurrence or recurrences in the submental space. The transfer added 45 minutes to the surgical procedure and required no special surgical skills.

Several other strategies, ranging from radiation delivery modification to acupuncture, have been used in the prevention of radiation-induced xerostomia. The most clinically applicable methods to date are chemoprevention and 3-dimensional radiation. Chemoprevention attempts to preserve salivary gland function through systemic administration of various protective compounds. The 2 most commonly used agents are pilocarpine hydrochloride and amifostine. Pilocarpine results have been inconsistent, but studies have demonstrated its effectiveness at reducing the rate of long-term xerostomia after radiotherapy. Its main disadvantage is the anticholinergic adverse effects, which limit its use in a considerable number of patients. Amifostine has shown some efficacy in clinical trials at reducing short-term and long-term xerostomia after radiotherapy. Its main disadvantages are the need for daily intravenous infusions, prohibitive price, and associated systemic effects, which result in treatment discontinuation in 21% of patients. There is also the theoretical concern that the compound through its radioprotective properties will decrease the effectiveness of radiation on cancer cells. A direct comparison of the SJP and chemoprevention outcomes is difficult based on the variable methods of reporting.

Three-dimensional radiation techniques, such as conformal, intensity modulated (IMRT), and tomotherapy, have recently been described. In theory, they permit more selective delivery of radiation to defined targets in the head and neck, preserving normal tissue and the parotid glands. The early results have been encouraging, resulting in parotid gland preservation when the total dose to the gland is less than 2600 cGy, but the local recurrence rate was disappointingly high (21%). The results, however, continue to improve with further development and standardization of the technologies and the increased familiarity of radiation oncologists with the new treatment protocols.

The SJP and 3-dimensional radiation techniques, specifically IMRT, have been proven effective at preventing xerostomia by preserving one submandibular or one parotid gland. The 2 methods have similar indications and can be used interchangeably in most situations, but we be-
lieve that there are theoretical and practical advantages to the SJP. Sparing of the submandibular gland is notionally preferable to the parotid gland, because it is responsible for most of the resting state salivary volume. The parotid glands normally contribute about 20% of the total volume of unstimulated saliva, while the submandibular salivary glands contribute 65% and the sublingual salivary glands contribute 7% to 8%. At the high flow rates produced during eating (approximately 54 min/d), the parotid becomes the dominant gland, contributing 50% of salivary volume. We believe that the unstimulated saliva flow (resting state) is far more important in the subjective symptoms of xerostomia and in preservation of oral homeostasis, as demonstrated by our study. The SJP is safe, does not change the pattern of recurrence, and has been associated with low local recurrence rates. The procedure does not require special radiation equipment or technologies and does not change the standard radiation prescription. The main disadvantage of the SJP is that it is contraindicated in oral cavity malignancies.

We are involved in the phase 2 multicenter Radiation Therapy Oncology Group trial 0244 evaluating the SJP and another randomized multicenter phase 3 trial comparing the SJP and chemoprevention. Future directions should include a phase 3 trial comparing the SJP with IMRT and the use of IMRT in simultaneously preserving a transferred submandibular gland and parotid gland.

The SJP prevented xerostomia in 83% of the study patients. The procedure required no special surgical skills and appears to be oncologically sound and safe.

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Correspondence: Hadi Seikaly, MD, Division of Otolaryngology–Head and Neck Surgery, University of Alberta, Suite 401, 11044 82nd Ave, Edmonton, Alberta, Canada T6G 0T2 (hseikaly@shaw.ca).

REFERENCES