Technology: An estimated 6,400 Canadians were diagnosed with head and neck cancers in 2003. The standard treatment for these cancers is radiation therapy in combination with surgery to remove the tumour. Unfortunately, radiation therapy can damage the salivary glands. This reduces the flow and changes the chemical composition of saliva, causing xerostomia (dry mouth) and its associated side effects, such as dental cavities; gum disease; and problems with speaking, tasting, swallowing and digesting. Xerostomia, which is a common and usually permanent adverse effect of head and neck radiotherapy, affects an individual’s quality of life.

Submandibular gland transfer is a surgical procedure during which one of the submandibular salivary glands is repositioned into the submental space of the lower jaw. As a result, the gland can be shielded from most of the radiation administered during treatment and its salivary function maintained. The operation is also known as the Seikaly and Jha procedure, after the two Edmonton physicians, Dr. Hadi Seikaly and Dr. Naresh Jha, who developed it.

Purpose: Saliva is produced by several glands. The major salivary glands (parotid, submandibular and sublingual glands) occur in pairs, with one of each gland on either side of the head (Figure 1). These glands produce about 90% of the saliva, while minor salivary glands, in the lining of the mouth and throat, produce the remainder. The submandibular and parotid glands produce about 65% and 20% to 25% respectively of unstimulated saliva, while the parotid glands produce about 50% of the stimulated saliva that flows during eating.

Figure 1: Salivary glands

<table>
<thead>
<tr>
<th>Figure 1:</th>
<th>A = Sublingual Gland</th>
<th>B = Submandibular Gland</th>
<th>B₁ = Transferred Submandibular Gland</th>
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<tbody>
<tr>
<td></td>
<td>C = Parotid Gland</td>
<td>D = Subdigastic Nodes</td>
<td>E = Shielding</td>
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As submandibular gland transfer is a surgical procedure, it does not require Health Canada licensing.

Submandibular gland transfer is usually performed during the surgery to remove primary tumours, before the start of radiation therapy. The transfer surgery can also be undertaken in patients who require radiation therapy but not surgical removal of their tumours. Submandibular gland transfer is performed using the salivary gland on the contralateral (opposite) side to that of the primary tumour. Submandibular gland transfer is not an option for patients with cancer of the oral cavity (the mouth) or for those who have bilateral neck lymph node involvement. A selective neck dissection is done first. Suspicious nodes and all level 1 lymph nodes (submental and submandibular) are sent for frozen section evaluation. If cancer is found, the transfer is abandoned and a formal neck dissection is performed. The borders of the transferred gland are marked with 25 mm gauge wire to help identify it during radiotherapy. Submandibular gland transfer is a simple procedure that adds about 45 minutes to the operating time. Dr. Jha estimates that up to three-quarters of patients with head and neck cancers could benefit from the use of this surgical procedure.

A submandibular gland transfer is not listed in provincial physician fee schedules, information on the cost of the procedure is unavailable. If the surgery becomes widely adopted, fee schedules should be revised to reflect the additional surgical time involved. Overall health care costs might be reduced through reduced hospitalization for post-treatment complications (such as dehydration or the inability to eat or drink due to mouth sores and pain) and decreased expenditures on drug and other therapies to treat xerostomia. For example, the manufacturer’s price (excluding dispensing fees and retail markup) for each 5 mg pilocarpine hydrochloride (Salagen®) tablet, a drug commonly used to treat xerostomia, is about C$1. The typical dosage is three or four tablets daily and if the treatment is tolerated by and effective for the patient, it is continued for the rest of his or her life.

Dental costs for the treatment of the tooth decay and gum disease associated with xerostomia could be reduced if submandibular gland transfer can maintain salivary function. This is being investigated as part of the phase III randomized, multicentre study comparing pilocarpine and submandibular salivary gland transfer. A recent US study of drug treatments for radiation-induced xerostomia concluded that “the cost of maintaining and restoring dentition following radiation-induced xerostomia can be tremendous….Given the number of teeth that may be involved and the ongoing nature of the requirement for dental treatment in patients with radiation-induced xerostomia, it is easy to see how the costs of maintaining oral and dental health can escalate rapidly. Periodontal treatment and time lost from work only add to these expenses.”

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) is a non-profit organization funded by the federal, provincial and territorial governments. (www.ccohta.ca)
Evidence: Several case series reports describe early experiences with submandibular gland transfer. A 2003 paper by Jha et al. reports on 84 patients in a phase II clinical trial. Of these patients, 60 underwent submandibular gland transfer. Nine patients did not subsequently receive radiation therapy and in another eight patients, the transferred gland was not shielded from radiation because of the proximity of the cancer. As a result, 43 patients underwent submandibular gland transfer followed by radiation therapy. The University of Washington quality of life (QOL) questionnaire was used to measure xerostomia before treatment began and at several points post-treatment. Six months after the end of radiation treatment, 71% of patients reported no or minimal xerostomia. Among the patients who had submandibular gland transfer but no shielding from radiation due to the proximity of the cancer and those who did not have submandibular gland transfer, 71% had moderate to severe xerostomia. Similarly, a Dutch study of 39 long-term survivors of head and neck cancers who had undergone standard radiation treatment found that 64% continued to suffer from moderate to severe xerostomia.

An earlier paper reporting on 25 patients in the submandibular gland transfer study found that the amount of saliva after surgery and radiation treatment remained normal. Most patients found that their chewing and swallowing were unchanged, though many reported an alteration in taste. Head and neck cancer patients often suffer from oral mucositis (mouth ulcers) that make eating painful. The patients who underwent salivary gland transfer had less oral mucositis and candidiasis (a fungal infection of the mouth) than head and neck cancer patients undergoing the typical post-treatment experience. Most did not require a liquid diet and their weight remained stable.

A phase II multicentre study of submandibular salivary gland transfer to prevent radiation-induced xerostomia is underway in North America under the auspices of the Radiation Therapy Oncology Group (RTOG). The trial will involve 48 patients and will assess the reproducibility of the submandibular salivary gland transfer procedure, the rate and severity of xerostomia after this procedure, the quality of life of patients and their health outcomes (cancer recurrence and overall survival rates).

A phase III multicentre trial comparing drug therapy (pilocarpine hydrochloride) to salivary gland transfer is ongoing at centres in Alberta, Manitoba, Quebec and Newfoundland. The Cross Cancer Institute, in Edmonton AB has data on over 170 patients treated through various protocols (Naresh Jha, Alberta Cancer Board, Edmonton: personal communication, 2004 Mar 22).
Available Alternative Technologies: Treatments for xerostomia include saliva substitutes (such as the use of artificial saliva) and saliva stimulants (such as the use of sugar-free mints or chewing gum; or drug therapies). Saliva substitutes may temporarily reduce dry mouth, but they have little effect on the maintenance of dental health. Patients reportedly find little difference in comfort between using artificial saliva or water.\textsuperscript{15}

Saliva stimulants may reduce xerostomia and other conditions related to salivary gland dysfunction.\textsuperscript{16} Pilocarpine hydrochloride (Salagen\textsuperscript{8}) is often used to treat xerostomia, but the drug is contraindicated for some patients (for example, asthmatics or those with significant cardiovascular disease).\textsuperscript{17} Moreover, only one- to two-thirds of patients will benefit from pilocarpine hydrochloride and it may take weeks for the treatment to take effect.\textsuperscript{15} The adverse effects, which are considered minor, include sweating, flushing, increased urinary frequency, blurred vision and tachycardia (rapid heart beat).\textsuperscript{2,17}

Amifostine (Ethylol\textsuperscript{9}) is a chemoprotectant that may be given intravenously before each session of radiation therapy to lessen some side effects, including xerostomia. Its adverse effects include nausea and a decrease in blood pressure. Patients receiving amifostine must be monitored for signs of toxicity. Its subcutaneous administration, which appears to be as effective yet less toxic, is being investigated in clinical studies.\textsuperscript{15} A Cochrane Collaboration systematic review of the effectiveness of drug therapies used in the prevention and treatment of salivary gland dysfunction due to radiation therapy is underway.\textsuperscript{16}

Intensity modulated radiation therapy (IMRT) may be used to decrease the exposure of parotid salivary glands to radiation. A study by Lin \textit{et al.} found that this reduces xerostomia and improves the quality of life for patients after treatment.\textsuperscript{18} An international, randomized controlled trial of parotid-sparing IMRT in patients with head and neck cancer is underway.\textsuperscript{19}

Alternative therapies for the treatment of xerostomia, such as acupuncture and electrostimulation, have been used, but there is little evidence of their effectiveness.\textsuperscript{20}

Salivary gland gene therapy is also being investigated. Only data from animal studies are available and the clinical use of this procedure is years away.\textsuperscript{4,21,22}

Commentary: The preliminary study results of submandibular gland transfer look promising. This surgical procedure may improve the quality of life and health of many head and neck cancer patients after radiation therapy. Clinical trials to determine the advantages of the procedure and its effect on other health outcomes, particularly long-term survival, are ongoing.
Emerging Technology List

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