Efficacy of Tensed and Straight Free Jejunum Transfer for the Reduction of Postoperative Dysphagia

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**Background:** Free jejunal transfer (FJT) is a standard method of reconstruction after total pharyngo-laryngo-cervical esophagectomy (TPLE) in patients with advanced head and neck cancer. However, it is related to various degrees of postoperative swallowing dysfunction. This study aimed to assess whether the tensed and straight FJT method results in a reduced rate of postoperative dysphagia compared with historical controls.

**Methods:** Patients who were undergoing FJT after TPLE for squamous cell carcinoma of the hypopharynx or cervical esophagus were enrolled. The primary endpoint was the rate of not developing dysphagia within 6 months of the surgery, and we compared this value with that obtained from historical data of patients who underwent FJT. The secondary endpoint was the rate of developing surgical complications.

**Results:** Although 128 patients were registered between August 2012 and July 2015, 7 were excluded based on the exclusion criteria. Of the remaining 121 patients, FJT with the craniocaudally tensed and straight method was performed in all patients. The rate of not developing dysphagia and its 95% confidence interval (CI) were 66.1% and 57.0–74.5%, respectively. The lower limit of the CI was higher than the prespecified threshold value of 50.0%. The rate of developing complications of total necrosis of the jejunum was 3.3%, cervical infection was 9.9%, and major anastomotic leakage was 4.1%.

**Conclusions:** Our findings revealed that the proportion of postoperative dysphagia decreased in patients who underwent tensed and straight FJT. This method may become the standard surgical method in reconstruction of defects after TPLE.

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FJT was performed immediately after TPLE via the celiac trunk or inferior mesenteric artery, depending on the location of the hypopharyngeal defect. The length of the transferred jejunum was decided by measuring the length of the hypopharyngeal defect under anesthesia. The length of the transferred jejunum was divided into 3 groups according to the ratio of the transferred jejunum length to the defect length. Free jejunum tension was defined as high when the ratio was smaller than 66.7%, medium when the ratio was between 66.6% and 80%, and low when the ratio was larger than 80%. Finally, microvascular anastomosis of the jejunal conduit, when a jejunum of less length than half the length of the hypopharyngeal defect is transferred, was performed. Thus, we use a jejunum length that was between half and the full length of the hypopharyngeal defect. The degree of free jejunum tension was divided into 3 groups according to the ratio of the transferred jejunum length to the defect length. Free jejunum tension was defined as high when the ratio was smaller than 66.7%, medium when the ratio was between 66.6% and 80%, and low when the ratio was larger than 80%. Finally, microvascular anastomosis of the jejunal artery and vein to cervical vessels was performed, and skin closure with permanent tracheostomy was performed.

Endpoints
The primary endpoint was the proportion of dysphagia-free patients at 6 months after surgery. The secondary endpoint was the proportion developing surgical complications during the postoperative hospital stay. Dysphagia-free patients had to have met all of the following criteria at 6 months after surgery: (1) never experienced swallowing dysfunction greater than grade 2 in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Table 1), (2) never experienced clinically evident dysphagia, (3) never required balloon dilatation for dysphagia, (4) survived, and (5) never lost to follow-up.

Data Collection
Data were collected via a case report form (CRF). The treating surgeons in each institution sent CRFs to the study secretariat at the National Cancer Center Hospital East at patient registration, during the perioperative period and at 3 and 6 months after surgery. As preoperative data, the patients’ age, sex, primary site, cancer status, preexisting comorbidities, and history of irradiation to the neck were recorded. As surgical factors, the operation time, amount of blood loss, neck dissection, type of the pharyngeal defect, and free jejunum tension were recorded. As postoperative data, the development and symptom of dysphagia and any requirement of balloon dilatation were also recorded. The postoperative complications evaluated were vascular thrombosis, free jejunum necrosis, anastomotic leakage, cervical infection, hematoma, and lymphorrhoea. Furthermore, the development of postoperative ileus was also recorded.
Statistical Considerations

The primary endpoint was decided to have been met if the lower limit of the 95% confidence interval (CI; calculated by the Clopper and Pearson method) exceeded its threshold value of 50%. The threshold value was determined based on a historical survey reporting that dysphagia occurred at a proportion of 49.2% when 715 patients were treated with standard FJT after TPLE. Of note, the eligibility criteria of the historical control survey were almost the same as this study. The expected value of the primary endpoint was 65%. Our primary aim was to evaluate the efficacy of the tensed and straight FJT method in reducing the rate of dysphagia. Patients who were diagnosed with laryngeal cancer, who underwent larynx-preserving surgery, or who underwent resection beyond the upper pole of the tonsil or beyond the cervical esophagus were planned to be excluded in the primary analysis. The primary analysis was planned to be performed approximately 6 months after enrolling 121 patients, giving a 1-sided alpha of 2.5% and power of 90%.

Except for in the primary analysis, we evaluated the efficacy of the method in question in both all registered patients and the primary analysis set. The proportion of patients who were dysphagia-free at 6 months and the proportion of patients who developed postoperative complications were presented with their 95% CIs. Fisher’s exact test was used to evaluate the difference in these proportions among subgroups constructed based on the risk factors listed in Tables 4 and 6. Univariate and multivariate logistic regression analyses were performed to estimate the odds ratios and associated 95% CIs. Stepwise variable selection was performed in the multivariate regression model, which included all of the possible risk factors listed in Tables 4 and 6. All P values were calculated as 2-sided, and P < 0.05 was considered to indicate statistical significance. The IBM SAS Statistics software program, version 9.4 (SAS Institute Inc., Cary, N.C.), was used.

RESULTS

Baseline Data

Between August 2012 and July 2015, 128 patients from 10 institutions were registered in this study, and 7 were excluded based on the exclusion criteria. The exclusions were due to a different diagnosis in 2 patients, larynx-preserving surgery in 2 patients, advanced resection in 2 patients, and withdrawal of agreement in 1 patient. As a result, 121 patients were ultimately evaluated. The present and historical patient demographic data are shown in Table 2. Most of the patients had primary hypopharyngeal cancer, and 25% had recurrent cancer after radiation therapy. Preexisting diabetes mellitus was observed in 19 patients (15.7%) in the study group, whereas the rate was 7.6% in the historical controls.

Operative Findings and Surgical Complications

The median length of the hypopharyngeal mucosal defect was 10.0 cm and that of the transferred jejunum was 5.5 cm. FJT was carried out with high tension in 82 cases, me-
were healed with conservative treatment. Among the 40 cases, partial necrosis of the transferred jejunum occurred in 5 cases, requiring immediate second-look laparotomy, and pulmonary alveolar bleeding was observed in 1 case. The patient with pulmonary alveolar bleeding could not resume oral feeding and died during his hospital stay. Postoperative ileus was observed in 2 cases during their hospital stay and was treated conservatively.

**Postoperative Dysphagia**

Postoperative dysphagia was observed in 41 patients at least once during the 6-month follow-up period. Of these, dysphagia had been observed in 28 cases by 3-month follow-up and in 34 cases by 6 months. Continuous dysphagia was observed in 28 cases by 3-month follow-up and in 34 cases by 6 months. Continuous dysphagia was observed in 21 patients from 3 to 6 months postoperatively. Of 41 patients, 3 patients died (2 because of cancer recurrence, and 1 because of respiratory complications), and 10 were lost to follow-up. Five patients required balloon dilation. Ultimately, the proportion not developing postoperative dysphagia within 6 months was 66.1% (95% CI: 57.0–74.5%) among 121 patients. The primary objective of this study was met because the lower limit of the 95% CI was higher than the prespecified threshold value of 50.0%.

**Univariate/Multivariate Analyses**

We conducted subgroup analyses for factors listed in Table 4. Neither preoperative nor intraoperative factors were found to be risk factors for the development of postoperative dysphagia up to 6 months postoperatively. A statistical evaluation revealed that only postoperative radiotherapy was a significant risk factor for the development of dysphagia, both in univariate and multivariate logistic regression analyses, with a P-value of 0.014 calculated by Wald’s test (Table 5).

**Adjuvant Therapy and Cancer Recurrence**

Adjuvant radiation therapy or chemoradiation therapy was administered in 30 patients who were at a high risk of cancer recurrence, such as those with extracapsular spread of lymph node metastasis or positive surgical margins. Cancer recurrence was observed in 9 patients, and 2 patients died during the 6-month follow-up period because of cancer recurrence.

**Table 2. Patient Characteristics**

| Variables                   | Present Study (n = 121) No. Patients | Historical Control (n = 764) No. Patients |
|-----------------------------|--------------------------------------|------------------------------------------|
| Age (y)                     | 68 (median)                          | 63.8 (average)                           |
| Sex                         |                                      |                                          |
| Male                        | 108 (89.3%)                          | NA                                       |
| Female                      | 13 (10.7%)                           | NA                                       |
| Primary site                |                                      |                                          |
| Hypopharynx                 | 199 (90.1%)                          | NA                                       |
| Cervical esophagus          | 12 (9.9%)                            | NA                                       |
| Cancer status               |                                      |                                          |
| Primary cancer              | 90 (74.4%)                           | 612 (80.1%)                              |
| Recurrent cancer            | 31 (25.6%)                           | 85 (11.1%)                               |
| Unknown                     | —                                    | 67 (8.8%)                                |
| Prior irradiation           |                                      |                                          |
| Yes                         | 32 (26.4%)                           | 217 (28.4%)                              |
| No                          | 89 (73.6%)                           | 523 (68.5%)                              |
| Unknown                     | —                                    | 24 (3.1%)                                |
| Diabetes mellitus           |                                      |                                          |
| Yes                         | 19 (15.7%)                           | 58 (7.6%)                                |
| No                          | 102 (84.3%)                          | 676 (88.5%)                              |
| Unknown                     | —                                    | 4 (0.5%)                                 |

Historical control data extracted from Sugiyama et al.*

**Table 3. Overall Results of the Present Study in Comparison with Historical Data**

| Variables                        | Present Study (n = 121) | Historical Control (n = 764) |
|----------------------------------|-------------------------|-----------------------------|
| Data collection                  | 2012–2015               | 1996–2005                   |
| Study design                     | Prospective             | Retrospective               |
| No. FJT                          | 121 (100%)              | 715 (93.6%)                 |
| Average operating time (range)   | 534.5 min (237–822)     | 573 min (482–878)          |
| Average bleeding (range)         | 349.6 ml (50–1858)      | 611 ml (413–955)           |
| Overall complications            | 47/121 (38.8%)          | 114/420 (27.1%)            |
| Vascular thrombosis              | 5/121 (4.1%)            | 27/674 (4.0%)              |
| Postoperative infection          | 12/121 (9.9%)           | 163/581 (28.1%)            |
| Anastomotic leakage (fistulas)   | 11/121 (9.1%)           | 105/640 (16.4%)            |
| Postoperative dysphagia*         | 41/121 (33.9%)          | 123/250 (49.8%)            |

*P = 0.0002; statistical significant difference between studies, binominal test.
DISCUSSION

This multi-institutional prospective study aimed to assess whether patients who received tensed and straight FJT experienced better subsequent swallowing function than historical controls. Postoperative dysphagia was observed in 41 patients (33.9%), and the proportion of no dysphagia was 66.1% in the study group, versus 50.2% in the historical control study. Therefore, tensed and straight FJT was associated with a significantly better swallowing function than the technique used with the historical controls. To our knowledge, this trial is the first prospective multi-institutional study to evaluate the proportion of postoperative dysphagia based on the method of FJT reconstruction. Furthermore, the subjects were restricted to those who underwent FJT after TPLE for squamous cell carcinoma of the hypopharynx or cervical esophagus.

Carlson et al. reported a lower proportion of functional failure with FJT (20%) than with musculocutaneous reconstruction (40%) or colon reconstruction (42%). Although their report indicated a lower functional failure proportion, the result was based on a small sample, and feeding tube dependence was the only criterion for swallowing dysfunction. Reece et al. retrospectively evaluated the swallowing function of 91 patients who underwent FJT for circumferential defect of the hypopharynx. They also reported that only 20% of patients had some degree of dysphagia and required supplemental tube feeding.
Table 6. Subgroup Analysis of Complications (Univariate Logistic Regression Analysis)

| Variables (Baseline) | Evaluation | Odds Ratio (95% CI) | Wald P Value |
|----------------------|------------|---------------------|--------------|
| Age (median or older, ≥68) | Age < 68 | 0.982 (0.301–3.204) | 0.9762 |
| Sex (male) | Female | 1.139 (0.340–3.824) | 0.8326 |
| Primary site (HPC) | CE | 1.699 (0.744–3.882) | 0.2085 |
| Cancer status (initial Ca) | Recurrent Ca | 0.687 (0.241–1.953) | 0.4809 |
| Diabetes mellitus (no) | Yes | 1.572 (0.693–3.562) | 0.2788 |
| Previous irradiation (no) | Yes | 1.851 (0.872–3.842) | 0.1098 |
| Operating time (<531) | Operating time ≥531 | 1.642 (0.783–3.442) | 0.1890 |
| Bleeding (<290 ml) | Bleeding ≥290 | 1.875 (0.467–7.526) | 0.2447 |
| Neck dissection (no) | Unilateral | 0.952 (0.317–2.865) | 0.3852 |
| | Bilateral | 0.797 (0.357–1.779) | 0.5790 |
| Pharyngeal defect (horizontal) | Oblique | 1.152 (0.509–2.604) | 0.8711 |
| | Medium | 1.097 (0.173–6.934) | 0.9814 |
| | Low | 2.196 (0.234–20.613) | 0.6510 |

CE, cervical esophagus; HPC, hypopharynx.

However, only 59% of the patients could tolerate a regular diet in their report. In our study, patients who required changes to their food intake were also defined as having dysphagia. Furthermore, we also included dysphagia data from patients who died during the study period or were lost to follow-up. Despite our severe criteria for dysphagia, our results were comparable to those of previous reports.

Sugiyama et al. conducted a retrospective, multi-institutional study to evaluate the reconstructive results after TPLE in a Japanese population and found the incidence of dysphagia to be 49.2%. Although their report was retrospective, the number of the patients was large enough (764 cases) to perform statistical evaluations. We therefore selected their report as the historical control for comparison. However, although those authors examined patients who had undergone a number of different procedures for free jejunum suturing, such as end-to-side anastomosis, mechanical suture anastomosis, and suturing without cranio-caudal tension, only the tensed and straight FJT method was used in our study protocol. We hypothesized that the tensed and straight method would result in a significantly improved swallowing function compared with other methods. Our data showed that the lower limit of the 95% CI exceeded the prespecified threshold value of 50% (1-sided binomial test, \( P = 0.0002 \)), which met the primary endpoint. As a result, the tensed and straight FJT was concluded to be effective in reducing the proportion of swallowing dysfunction. We therefore believe that free jejunum grafts should be transferred using the tensed and straight method. However, the degree of tension was not found to have a statistically significant effect on the swallowing outcomes in the subgroup analysis (Table 4). This is because of the small number of patients in the low-tension group.

Many risk factors affecting the postoperative swallowing function have been reported, such as high age, history of irradiation, radical neck dissection, and postoperative radiotherapy. However, neither the preoperative nor intraoperative factors were defined as risk factors for the development of postoperative dysphagia in this study. A statistical evaluation revealed that only postoperative radiotherapy was a significant risk factor for the development of dysphagia. The negative effects of postoperative radiation therapy on the postoperative swallowing function have been well documented in previous reports. This may be due to postoperative mucosal edema of the transferred jejunum or stiffness of the surrounding cervical soft tissue or scar formation caused by irradiation. The effects of irradiation will change according to the time of follow-up; as such, a longer follow-up is required to evaluate the exact effects of radiation therapy.

The rate of developing postoperative complications was the secondary endpoint. Although previous irradiation, diabetes mellitus, recurrent cancer, and wider resection are well-known risk factors for postoperative complications, they were not defined as risk factors in this study. In addition, among these risk factors, the free jejunum tension was not related to the development of postoperative complications (Table 6). Furthermore, the proportion of surgical complications in this study tended to be lower than in the historical control study. Theoretically, the tensile strength at the enteric anastomosis can exacerbate the development of wound dehiscence and anastomotic leakage. Although it did not reach statistical significance, the frequency of anastomotic leakage was lower in this study than in the historical study (9.1% vs 16.4%, Table 3). Given these findings, we believe that the tensed and straight FJT method will not increase the risk of postoperative complications.

Several limitations associated with this study warrant mention. First, this was a nonrandomized study, and the results were not obtained from a direct comparison between the tensed method and nontensed methods. Second, the appropriate degree of tension for FJT was not clear in this study. These points should be clarified in a future randomized prospective study. In addition, our definition of the tension of the FJT inset tended to be a subjective evaluation. However, it is impossible to obtain 100% objective data in the evaluation of surgical procedures. We therefore measure the length of defect and the jejunum intraoperatively to evaluate the FJT tension as objectively as possible. Although our data are not perfectly objective, we believe that our evaluation still has some important scientific merit.

**CONCLUSIONS**

The frequency of postoperative dysphagia was significantly lower in our study group than in the historical
controls. The frequency of complications was not increased with the tensed and straight method of FJT. Given these findings, we believe that free jejunum transfer should be performed with the tensed and straight method.

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