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Transplantation of Mucosa From Stomach to Esophagus to Prevent Stricture After Circumferential Endoscopic Submucosal Dissection of Early Squamous Cell

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Endoscopic submucosal dissection (ESD) in the esophagus is an expert technique for "en bloc" resection of even widespread mucosal cancers of ≥1.5 cm. ESD can provide a quasi-surgical specimen for adequate histopathologic evaluation and significantly reduces the risk of local recurrence compared with conventional widespread endoscopic mucosal resection ("piecemeal" EMR).[1,2] However, secondary stricture formation is the major drawback for resections ≥60% of the esophageal circumference. Multiple dilation sessions may be required, limiting quality of life. Experimental approaches include transplantation of buccal, dermal, or submucosal intestinal cell grafts as well as systemic and local steroid applications.[3–5] However, clinical experience is very limited so far. Since March 2011, we have been performing animal experiments concerning tubular esophageal resection and retransplantation of esophageal and gastric mucosal patches in pigs under an approved protocol with first preliminary but encouraging results when the following clinical case presented.

Case Report and Description of Technology

A 72-year-old man was referred with biopsy-proven high-grade intraepithelial neoplasia, suspicion of an early squamous cell cancer in the cervical esophagus. Prior history included a T2N0 rectal cancer curatively treated with abdominoperineal resection and terminal sigma anus praeter several years ago. High resolution magnifying and chromoendoscopy (EG 590 ZW; Fujifilm, Tokyo, Japan) found a circumferential mucosal tumor spreading within the upper esophageal sphincter area (Paris Type IIab; 17.5-25 cm). A 1 × 10-mm tumor tongue reached cranially to the distal hypopharynx (Figure 1). Staging was UT1a, N0 on endoscopic ultrasonography; computed tomography of the neck, chest, and abdomen was negative. Options were discussed with our interdisciplinary tumor board: Total surgical esophagectomy with cervical saliva fistula/gastric feeding tube; thermoablation with doubtful result owing to a tumor thickness of ≥3 mm; primary chemoradiation; and widespread ESD with an increased risk of stricture formation. Board and patient favored an attempt of ESD en bloc resection. Because the need for repeat postinterventional dilation sessions was most probable, the patient agreed to an experimental approach of ESD plus gastroesophageal mucosal transplant as "compassionate use."

On April 13, 2011, the endoscopic procedure was performed under general anesthesia. After digital chromoendoscopy proximal and distal markings of the resection area were made using a 1.5-mm FlushKnife (Fujifilm) followed by submucosal injection of 6% hydroxyethylic starch (Voluven; 1.5 mL of 0.8% indigo carmine/500 mL; epinephrine, 1:250,000). A circumferential tubular en bloc submucosal dissection was successfully performed from the hypopharynx through the upper esophageal sphincter into the cervical esophagus (17–27 cm aborally). The tubular specimen was retrieved and macroscopically ≥5 mm tumor-free craniocaudal margins confirmed (Figure 1*Ai–vi*). A second, widespread ESD measuring 9 cm in length and 4-6 cm in width followed encompassing the entire anterior wall of the gastric antrum (Figure 1*Bi*). The gastric specimen was retrieved and cut into 3 pieces because isolated mucosa tend to retract to about 30% of its initial size owing to a contraction of the

Abbreviations used in the paper: **EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.**

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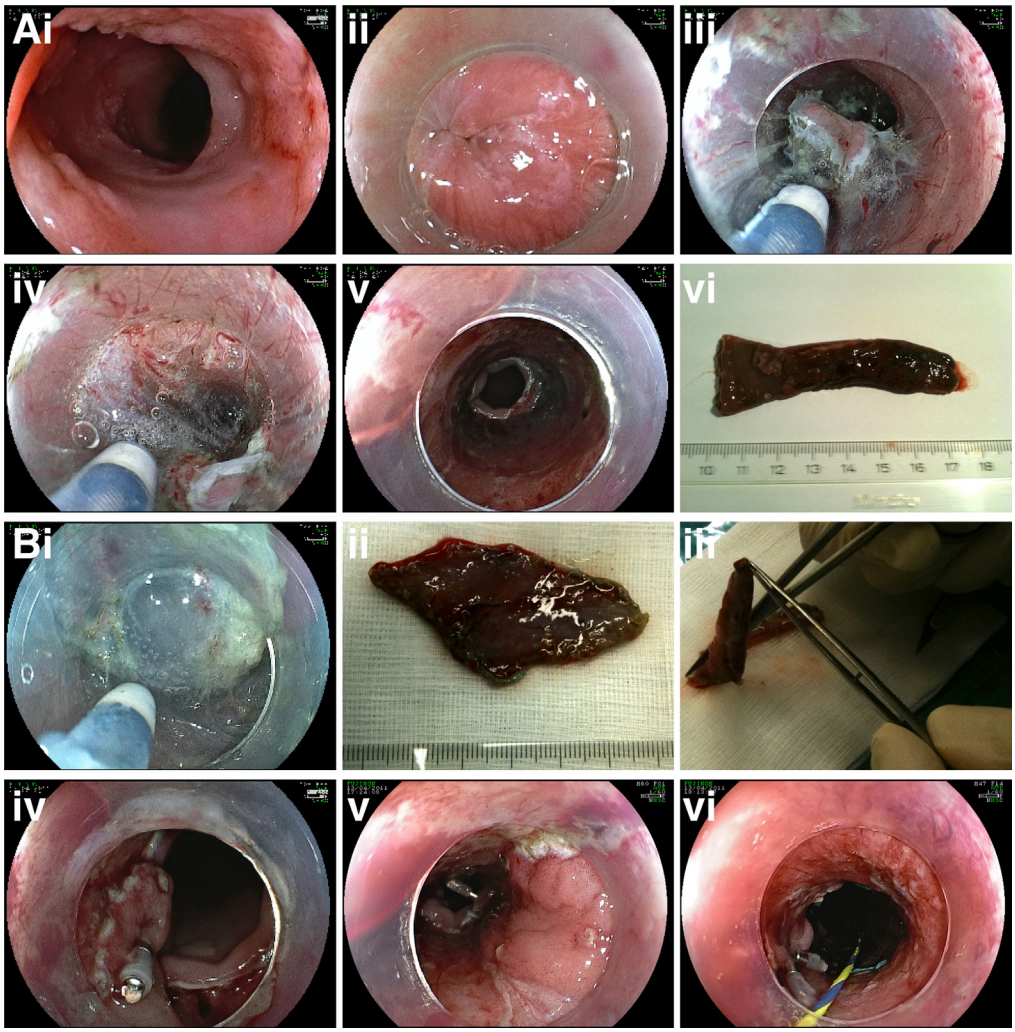

Figure 1. *A*, *i–vi*, Mucosal squamous cell cancer in the cervical esophagus with circumferential spread and extension through the sphincter area to the hypopharynx (*Ai*, ii). Tubular craniocaudal endoscopic en bloc resection of the infiltrated mucosa over 11 cm using the submucosa dissection technique (ESD; *Aiii*, *iv*, *v*) and retrieval of the contracted specimen (*Avi*). (*Bi-vi*) Second 9 × 4- to 6-cm, widespread ESD resection in the gastric antrum to provide a mucosal specimen, which is cut into 3 slices using a surgical pair of scissors (*Bi*, *ii*, *iii*). The gastric transplant is then attached to the denuded muscular esophageal wall by means of endoscopic clips and a noncovered, self-expanding metal stent to allow luminal nutrition of the mucosal specimen (*Biv*, *v*, *vi*). The cervical sphincter area had to be spared to avoid severe pain and potential larynx compression.

"muscularis mucosae" (Figure 1*Bii*, *iii*). Antral mucosa was chosen owing to a thick muscular layer of the antrum and a low quantity of acid-secreting parietal cells.

The 3 mucosal patches were first attached to the "muscularis propria" by hemoclips and then fixed by means of an uncovered metal mesh stent (Ultraflex; Boston Scientific, Natik, MA) to allow the absorption of fluid and nutritional components from the luminal side (Figure 1*Biv*, *v*, *vi*). Because of the risk of laryngeal compression and potential severe pain after stent placement, the esophageal sphincter area was spared for a span of 1.5-2.0 cm. The stent was removed on post-procedure day 20. Stripes of vital gastric mucosa could be seen on EGD before discharge on day 24.

Histopathologic evaluation of the esophageal tumor specimen revealed a pT1a, G2, V-, L-, R0 early squamous cell cancer invading the "lamina propria" of the mucosa to a depth of 150 μm (m2), but not the submucosa with histologically tumor-free cranial, caudal, and basal margins. Therefore, the risk of lymph node metastasis was judged $<$2%.

Within 5 months after the intervention, the area of mucosal transplant had grown nearly circumferentially in the cervical esophagus (Figure 2*A*, *C*). Biopsies confirmed gastric antral mucosa, HP negative (Figure 2*B*). However, the patient had initial problems with repeat stricture formation of a 1-cm segment in the upper sphincter region that, owing to technical issues, had not been treated with the autologous tissue transplant (see above) and served quasi as "natural" control in our patient. Meanwhile, the patient has been followed for $>$32 months without further complaints.

Perspective of Mucosal Transplantation With Regard to Widespread Mucosal Resection for Early Neoplasia in the Esophagus

Worldwide, esophageal cancer is the 8th most common cancer, with squamous cell cancer being the most common subtype. In the Western world, the rate of adenocarcinoma of the esophagus (Barrett's cancer) has increased 10-fold within the last 20 years.[6] Surgical treatment is still highly invasive and in current multicenter studies may even reach a mortality of 6.7%–13.1%, an early morbidity of 15%–32%, and a late morbidity of 47%.[7] Endoscopic