# Nitinol stents loaded with a high dose of antitumor 5-fluorouracil or paclitaxel: esophageal tissue responses in a porcine model

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**Background:** A poor prognosis associated with esophageal cancer leads to surgical resection not suitable for most patients. Nitinol stents loaded with 50% 5-fluorouracil (5-FU) or paclitaxel (PTX), functioning both as a stent and local chemotherapy, could provide a new therapy modality for these patients.

**Objective:** To investigate esophageal tissue responses to nitinol stents loaded with 50% 5-FU or PTX implanted in the esophagus of healthy pigs.

**Design:** Twenty-three healthy Bama mini-pigs were randomly divided into 4 groups for stent implantation: group A (PTX stent, n = 13), group B (5-FU stent, n = 8), group C (blank film–covered stent, n = 1), and group D (bare stent, n = 1). Tissue responses were observed by endoscopy or pathologic analyses, and 5-FU or PTX concentrations were measured in the esophagus at the stent implantation site at different time points.

**Setting:** Animal laboratory.

**Interventions:** Endoscopic placement of esophagus stent.

**Main Outcome Measurements:** Endoscopic examination, histology, and drug concentration analysis.

**Results:** In general, the esophageal tissue responses varied according to different parts of 5-FU or PTX stent (middle part [drug-containing part] and bare ends [drug-free part]). Severe tissue responses at the bare ends of the stent included inflammation, ulceration, and granulation. However, the tissue responses were greatly reduced in the middle part of the stent. The drug concentrations in the esophagus that had contact with the 5-FU stent or PTX stent were very high, especially for the first period after implantation, which did not cause obvious tissue damage.

**Limitation:** Some subjects had incomplete follow-up because of unexpected deaths and stent migration.

**Conclusion:** The nitinol stents loaded with 50% 5-FU or PTX did not cause severe esophageal tissue responses, although there was a large concentration of the drug in these tissues.

Nitinol stents are widely used for palliation of dysphagia.[1] However, they cannot hinder esophagus restricture because of tumor ingrowth.[2,3] Drug-eluting stents are used for benign esophageal strictures[4,5]; however, their antitumor effects are limited because their drug loadings are generally too low to effectively treat tumors.[6,7]

Our group has been working on antitumor drug-loaded esophagus stents for a dozen years.[8-13] We have developed a new approach to preparing nitinol stents loaded with a high dose of 5-fluorouracil (5-FU) or paclitaxel (PTX). The stents can provide unidirectional, sustained, and prolonged drug release toward stent-touching tissue, and

*Abbreviations: 5-FU, 5-fluorouracil; EVA, ethylene-vinyl acetate; H&E, hematoxylin and eosin; PTX, paclitaxel.*

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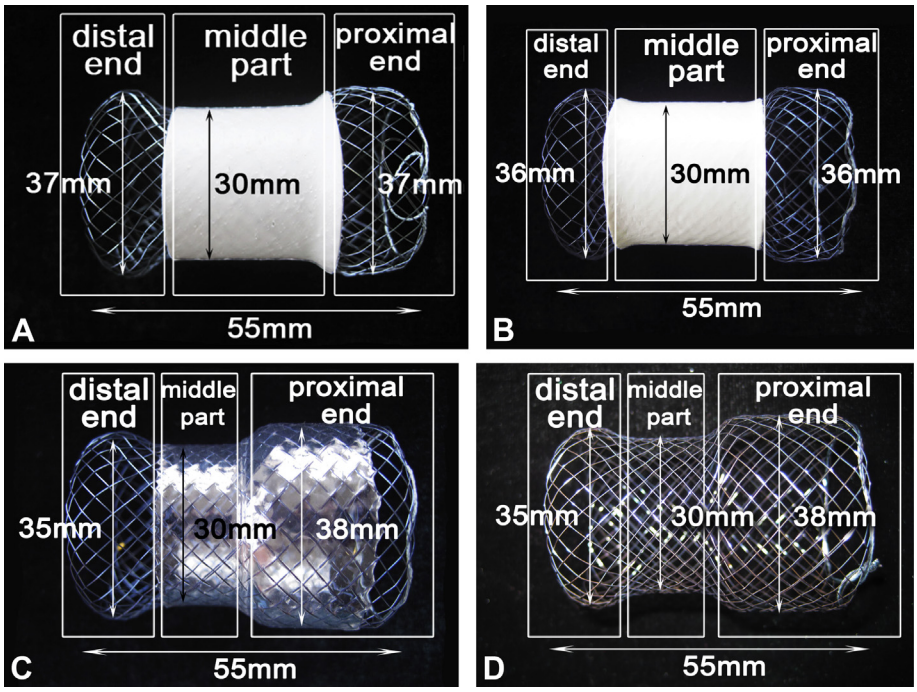


**Figure 1.** Self-expandable nitinol stents. **A,** Stent A was covered with a bilayered EVA film consisting of 1 drug layer containing 50% PTX and 1 drug-free layer. **B,** Stent B was covered with a bilayered EVA film consisting of 1 drug layer containing 50% 5-FU and 1 drug-free layer. **C,** Stent C was covered with EVA film. **D,** Stent D was a bare nitinol stent. (The proximal end of the stent is denoted as the end toward the oral cavity after implantation.)

these stents avoid washout of the drug by esophageal fluids and systematic administration. However, whether the stents damage the stent-contacting esophagus wall is of concern. Herein, we investigated the esophageal tissue responses to the stents with high doses of 5-FU or PTX implanted in the esophagus of healthy pigs.

## METHODS

### Materials

Nitinol stents were purchased from Micro-Tech Co, Ltd (The city and country of manufacturer is correct. Nanjing, China). 5-FU and PTX were provided by Nantong Jinghua Pharmaceutical Co, Ltd and Xi'an Haoxuan Biological Technology Co, Ltd (Xi'an, China), respectively. Ethylene-vinyl acetate (EVA) copolymer was purchased from the Shanghai Research Institute of Chemical Industry (Shanghai, China). All other reagents were of analytical grade and used as received.

### 5-FU stent and PTX stent preparations

A PTX or 5-FU stent (hereafter referred to as *stent A* or *stent B*, respectively; Fig. 1) was fabricated by coating 1 bilayered EVA film around the outside surface of a nitinol stent with its drug-free EVA layer facing the lumen of the stent. The bilayered EVA films were prepared by pressing together one 50% 5-FU– or PTX-loaded EVA layer (300 μm) and one drug-free EVA layer (100 μm) for 5 minutes.[10]

*Stent C* was prepared by coating 1 blank EVA film around the outside surface of the stent with a thickness of 400 μm.

### Experimental animals and stent insertion

The experimental procedures in this study were approved by the Shanghai Jiao Tong University Ethics Committee for Animal Experiments. Twenty-three healthy Bama mini-pigs with an average weight of 20.1 ± 3.0 kg (Provided by Shanghai Jiao Tong University School of Agriculture and biology, Shanghai, China, license no. SCXK [Hu]2007-0013) were randomly divided into 4 groups: group A received stent A (n = 13), group B received stent B (n = 8), group C received stent C (n = 1), and group D received a bare stent (stent D; n = 1).

After the pigs were fasted for 48 hours, an intramuscular injection of 250 mg ketamine-HCl for sedation was followed by an injection of 3% pentobarbital (1 mL/kg) into the abdominal cavity. The pigs were positioned in a left lateral decubitus position. Endoscopy (GIF-2TQ260 M; Olympus, USA) was used to insert a guidewire (Terumo, Tokyo, Japan) into the esophagus through the mouth, and an 8-mm (~24F) undeployed stent delivery system (Micro-Tech) was introduced along the guidewire to the esophagus. The stent was released under fluoroscopic guidance. After placing the stent, a hanging string tied to the proximal side of the stent was pulled out from the nasal cavity and sutured to the alae of the pig's nose to avoid stent migration. Endoscopy was performed on the 7th or 13th day post-implantation.