INTRODUCTION:
Adhesion formation following flexor tendon repair is still a significant clinical problem that hinders hand function. The strategies of adhesion reduction have been studied in many aspects including low frictional surgical repair techniques (1), early postoperative rehabilitation(2), physical barriers (3), tendon surface lubricants (4), and antiadhesive reagents (5). The purpose of this study was to investigate the effects of 5-fluorouracil (5-FU), a pharmacological agent, on tendon repairs subject to early postoperative rehabilitation in a canine model in vivo. We hypothesized that with a short exposure of the repaired tendon to topical 5-FU, 5-FU would not penetrate to affect the cells below the tendon surface, so that the use of 5-FU could result in decreased adhesions without an adverse effect on tendon healing.

METHODS:
Study Design: The project was reviewed and approved by our Institutional Animal Care and Use Committee, and all NIH animal care guidelines were followed. Sixty Mixed-breed dogs weighing 20 to 25 kg were used. Each dog was randomly assigned to either the repair treated with 5-FU (n=30) or repair without 5-FU (control group, n=30). The contralateral normal tendons served as the uninjured normal base treated with 5-FU (n=30) or repair without 5-FU (control group, n=30). The 2nd and 5th flexor digitorum profundus (FDP) tendons from three survival groups, 10 days (n=10), 21 days (n=10), and 42 days (n=10). The 2nd and 5th flexor digitorum profundus (FDP) tendons from each dog were fully lacerated at the zone II-D area, and then repaired with a modified Pennington technique with 3/0 Ethibond (Ethicon, Inc., Somerville NJ). A simple running circumferential epitendon suture of 6/0 nylon (Ethicon Inc., Somerville, NJ) was used to reinforce the repair. The therapy started at day 5 postoperatively and continued daily until the dogs were sacrificed. Following sacrifice, the repaired tendons were evaluated for work of flexion (WOF), gliding resistance (GR), or repair strength (RS) testing.

Measurement of Digit Work of Flexion (WOF): To quantitatively evaluate digit function, work of flexion was measured. Briefly, the FDP tendons (n=10 at each time point) were carefully exposed at the proximal metacarpal level, transected, and sutured to a cable connected to a load transducer. The repaired tendon within Zone II was kept intact. A K-wire was inserted longitudinally through the metacarpal bone to fix the metacarpophalangeal MCP joint in extension. “T” shaped hardware mounted with two reflective markers (2mm diameter) was pinned to the proximal, middle, and distal phalanges, respectively. The prepared digit was then mounted on the testing device by fixing the proximal K-wire to a custom jig. The actuator pulled the tendon proximally at a rate of 2 mm per second causing digit flexion against a weight of 50 grams that was attached to the extensor tendon. During testing, digit motion was recorded simultaneously (from extension to flexion) by a Motion Analysis System (Motion Analysis Corporation, Santa Rosa, CA). Work of flexion data were calculated from the tendon displacement vs loading curve during digit flexion, and then normalized (divided) by total PIP and DIP joint motion angle at the point when the DIP reached 40 degrees, named nWOF (6).

Tendon Gliding Resistance (GR) Measurement: After measuring WOF the repaired tendons were further dissected, keeping the proximal pulley intact. The gliding resistance between the tendon graft and proximal pulley was the measured using a custom tendon-pulley friction testing device, as previously described (7).

Measurement of Repair Strength (RS): To measure breaking strength, 10 tendons at each time point were secured in a servohydraulic testing machine and distracted to failure at a rate of 20 mm/min. A differential variable reluctance transducer (DVRT, Microstrain, Williston, VT) was attached to the tendon spanning the repair site to measure gap formation during testing. Tensile force, grip-to-grip displacement, and gap displacement measured by the DVRT transducer were collected at a rate of 20 Hz. Maximum breaking force was recorded. In addition, a regression line was fit to the linear region of the force versus gap formation (as measured by the DVRT) to measure the resistance to gap formation.

Statistical Analysis: Two-way ANOVA was used to analyze the difference among normal FDP tendons, repaired FDP tendons with 5-FU treatment, and repaired tendon without 5-FU treatment at all three timing points regarding WOF, GR, and RS. A significance level of p<0.05 was used.

RESULTS:
For all tendons in the series of animals, the rupture rates (n=2 in the control (3.3%) and n=3 in 5-FU (5%)) and the incidence of large gapping (3 mm or greater) were similar between the two groups (n=10 for control tendons (16.7%) and n=12 in 5-FU tendons (20%)). The 5-FU group had a higher number of tendons with a small gap (1-2 mm) (n=7; 12% versus n=3; 5%) compared to the control, though this difference did not reach statistical significance.

At 10 days, the nWOF of control tendons was significantly higher than the normal and 5-FU tendons (p < 0.05). There was no significant difference between normal and 5-FU tendons at 10 days. At 21 days and 42 days, nWOF of the normal tendons was significantly lower than either 5-FU or control repaired tendons (p < 0.05). There was no significant difference between the 5-FU and control tendons at 21 or 42 days. In the 5-FU group, the nWOF significantly increased with time (p < 0.05). In the control group, the nWOF at 42 days was significantly higher than that at 10 or 21 days (Figure 1). There was no significant difference between 5-FU and control tendons in gliding resistance, maximal failure strength, or stiffness of repaired tendons at any time point.

DISCUSSION:
5-FU, an antimetabolite, suppresses cell proliferation through the blockade of DNA synthesis. However, this effect seemed not to affect the flexor tendon intrinsic healing in our canine model up to 42 days after repair. The anti-adhesion effect of the 5-FU was apparent in the short term postoperatively, but 5-FU had no effect on adhesions beyond 21 days after tendon repair.

Figure 1. nWOF of three groups in different timing period. Means with the same letter are not significantly different.

REFERENCES: