Detection of Gastric and Colonic Sentinel Nodes Through Endoscopic Administration of ^{99m}Tc-DTPA-Mannosyl-Dextran in Pigs

Jeanette Méndez, MD[1,2]; Anne M. Wallace, MD[3,4]; Carl K. Hoh, MD[4,5]; and David R. Vera, PhD[2,4]

[1]Division of Gastroenterology, Department of Medicine, University of California, San Diego, La Jolla, California; [2]Department of Radiology, University of California, San Diego, La Jolla, California; [3]Department of Surgery, University of California, San Diego, La Jolla, California; [4]Comprehensive Cancer Center, University of California, San Diego, La Jolla, California; and [5]Division of Nuclear Medicine, Department of Radiology, University of California, San Diego, La Jolla, California

The purpose of this study was to develop a method for the endoscopic administration of a radiopharmaceutical for sentinel node detection and to characterize its uptake by gastric and colonic sentinel nodes. ^{99m}Tc-Diethylenetriaminepentaacetic acid (DTPA)-mannosyl-dextran is a new radiotracer labeled with ^{99m}Tc and composed of multiple units of mannose attached to the polymeric backbone, dextran. **Methods:** Gastric and colonic lymph node detection was studied in 4 fasting and anesthetized pigs. A flexible video endoscope was inserted into the rectum and positioned in the lower colon or advanced down the esophagus into the stomach. A standard endoscopic sclerotherapy needle and sheath filled with 0.9% saline was then loaded with 0.2 mL of a 7.4-MBq 1:1 (v/v) mixture of isosulfan blue and ^{99m}Tc-DTPA-mannosyl-dextran (7.4 MBq, 0.3 nmol). The needle and sheath were passed through the biopsy channel, and the radiotracer/dye solution (0.1 mL) was injected in a tangential fashion into the submucosa. Within 5–10 min after injection, all radioactive or blue lymph nodes were excised, assayed for radioactivity, and noted for color. Distal lymph nodes were also excised, assayed, and noted for color. **Results:** ^{99m}Tc-DTPA-mannosyl-dextran uptake by colonic sentinel nodes (n = 4) ranged from 0.54% to 2.4% of the injected dose; all radioactive nodes were stained blue. The uptake for all (n = 3) distal nodes ranged from 0.001% to 0.005%, and none of these nodes were stained blue. Uptake by gastric sentinel nodes (n = 6) ranged from 0.13% to 4.50%; all radioactive nodes were stained blue. The range for distal nodes was 0.001% to 0.050%; no distal nodes were stained blue. In 2 pigs, each gastric injection produced 2 hot and blue lymph nodes. **Conclusion:** Within 10 min of a gastric and colonic submucosal injection, ^{99m}Tc-DTPA-mannosyl-dextran demonstrated high sentinel node uptake and high concordance with isosulfan blue.

Key Words: sentinel lymph node detection; colorectal cancer; radiopharmaceutical; ^{99m}Tc-DTPA-mannosyl-dextran; Lymphoseek

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There is growing evidence that the sentinel node concept (*1*) can be effectively applied to cancer of the gastrointestinal tract. The strategy (*2*,*3*) is to identify the first lymph node that receives lymph from the cancer and then focus the pathologic examination for a more thorough search through multilevel sectioning, cytokeratin immunohistochemistry (CK-IHC), and reverse transcriptase-polymerase chain reaction (RT-PCR) (*4*). Currently, the technique yields false-negative rates in the 0%–5% range (*5*–*7*). Recently, Kitagawa et al. (*8*) and Bilchik and coworkers (*9*) introduced the use of radioactive colloid for cancer of the gastrointestinal tract.

^{99m}Tc-Diethylenetriaminepentaacetic acid (DTPA)-mannosyl-dextran is a new radiopharmaceutical designed specifically for sentinel node detection (*10*). The radiotracer is a nonparticulate that accumulates in lymphatic tissue by binding to a receptor residing on the surface of reticuloendothelial cells. The receptor, mannose-binding protein (*11*), binds macromolecules with carbohydrate side-chains that terminate with a mannose glycoside. Known also as Lymphoseek (Neoprobe Corp.), ^{99m}Tc-DTPA-mannosyl-dextran is composed of a 10-kDa dextran backbone attached to multiple units of mannose, which serves as the receptor substrate, and diethylenetriaminepentaacetic acid, which serves as attachment sites for labeling the macromolecule with ^{99m}Tc.

Previous preclinical and phase I clinical studies demonstrated the properties required for sentinel lymph node imaging. In vitro binding studies (*10*) demonstrated high affinity for the receptor; the equilibrium binding constant, K_D, was 0.12 nmol/L. In women with breast cancer, ^{99m}Tc-DTPA-mannosyl-dextran exhibited (*12*) significantly faster injection site clearance and lower distal-node uptake than did filtered ^{99m}Tc-sulfur colloid. Measurements obtained from sentinel nodes excised within 4–7 h after administration demonstrated equivalent accumulation.

In this article, we present a method for the endoscopic administration of ^{99m}Tc-DTPA-mannosyl-dextran into gas-

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For correspondence or reprints contact: David R. Vera, PhD, Department of Radiology, 200 W. Arbor Dr., San Diego, CA 92103-8756.
E-mail: dvera@ucsd.edu

tric and colonic submucosa and describe its uptake by gastric and colonic lymph nodes shortly afterward.

MATERIALS AND METHODS

Preoperative Preparation and Anesthesia of Animals

Four adolescent pigs (20–22 kg) were used in this study, which was approved by the Animal Subjects Committee of the University of California, San Diego. For cleansing before colonoscopy, the pigs were kept without food for 18 h preoperatively (*13*). A preanesthetic cocktail of ketamine (33 mg/kg) and atropine (0.05 mg/kg) was given intramuscularly. A 22-gauge angiocatheter was inserted percutaneously into a large ear vein, and anesthesia was induced with thiopental (10 mg/kg). The animals were then intubated, and general anesthesia was maintained by 1%–2% halothane with 60% nitrous oxide and oxygen (1–2 L/min). A drip infusion of lactated Ringer's solution (~10 mL/kg) into the ear vein was used to maintain hydration. Cephalosporin (20 mg/kg) was given intramuscularly on the day of surgery for prophylactic antibiotic coverage.

Preparation of Injectate

DTPA-mannosyl-dextran was synthesized as previously described (*10*). Pharmaceutical grade dextran (Amersham-Pharmacia Biotech), having an average molecular weight of 10,500 g per mole, was used as the molecular backbone for the agent. The average molecular weight of the DTPA-mannosyl-dextran preparation used in this study was 28,200 g per mole. The average DTPA and mannose densities were 2.1 and 42 mol of DTPA and mannose per mole of dextran. The mean molecular diameter was 7.0 nm. Formulation, ^{99m}Tc-labeling, and quality control were performed as previously described (*14*). The radiochemical purity exceeded 98%. The radiopharmaceutical was administered within 1 h of radiolabeling.

The injectate was prepared immediately before the endoscopic procedure by combining 0.5 mL each of ^{99m}Tc-DTPA-mannosyl-dextran and isosulfan blue (Lymphazurin 1%; U.S. Surgical Corp.) in a 2-mL multidose vial fitted with a 2-mm-thick Teflon septa (Varian, Inc.). The final DTPA-mannosyl-dextran molar concentration was 15 nmol/mL, with a typical activity of 37 MBq. A fraction of the injectate that represented 1/50 of the amount administered was placed in a plastic scintillation vial and used as a counting standard.

Preparation of Injectors

Two disposable injectors (model NM-201L-0623; Olympus America Inc.) were loaded with 0.2 mL of the radiopharmaceutical and blue dye. The male end of a 3-way stopcock was connected to the injection port at the proximal end of the injector (6-mm × 23-gauge needle). One- and 20-mL syringes, both filled with 0.9% saline of injection, were then placed onto the 2 female ends of the 3-way stopcock. All air was removed from the system by first flushing 0.5 mL of saline from the 1-mL syringe and then turning the stopcock to allow flushing of the entire length of the injection needle tubing with saline from the 20-mL syringe.

To load the injectate, the needle was extended, and the 1-mL syringe was pulled back 0.1 mL to draw a small amount of air into the distal end of the tubing, creating a small air bubble. A small hemostat was used to clasp the injector tube at the end of the injection needle. Behind a lead-lined barrier shield, the vial containing the injectate mixture was inverted and the injection needle was inserted into the vial septum. With the 1-mL syringe, 0.2 mL of the injectate was drawn into the injector tubing. After withdrawal of the needle from the septum, the injectate vial was set upright and the injector needle was retracted into the injector tubing. The injector tip was then placed inside a syringe barrel for sterile storage. Loading 0.2 mL of the injectate solution into the injector produced a 5.1-cm (2 in.) column of the blue injectate between the needle tip and the air bubble. The injector contained 7.4 MBq, 0.30 nmol, of ^{99m}Tc-DTPA-mannosyl-dextran. The remainder of the system contained nonradioactive sterile saline. Each coiled injector was stored and transported with the distal tip within the sterile syringe barrel placed inside a lead-lined syringe holder (16.5 cm [6.5 in.] × 2.0 cm [0.8 in.] internal diameter; Biodex).

Placement of Endoscope

Once intubated, the pigs were placed in the left lateral recumbent position for insertion of the flexible endoscope (model GIFT130; Olympus America). For colonic placement, the endoscope was inserted into the colon and, under direct video visualization, positioned in the lower colon about 20 cm from the anal verge. For gastric placement, the endoscope was advanced through the mouth, down the esophagus, and into the stomach without repositioning of the pig, and a suitable injection site was found in the lesser curvature.

Administration of Injectate

Once the target site was identified through the endoscope, the needle injection system was inserted into the rubber port and advanced down the biopsy channel of the endoscope port. The needle could be seen on the video screen as it exited the distal end of the scope. The needle tip was extended and introduced into the submucosal layer in a tangential approach so as to avoid a transmural puncture to the serosal surface. Administration of the mixture (3.7 MBq, 0.15 nmol, of ^{99m}Tc-DTPA-mannosyl-dextran) proceeded by a method in which the 1-mL syringe plunger was lightly pumped at approximately 1-s intervals to gently administer 0.1 mL of injectate into the submucosa. The sheath was made of transparent plastic, so once the distal end of the sheath was out, the blue injectate could be seen as it was advanced beyond the sheath toward the needle. Once the administration was completed, the needle was retracted into the distal end of the tube, the sheath and needle were removed from the endoscope, and the endoscope was withdrawn from the pig. After colonic administration, a new injector was used for gastric administration.

Detection and Assay of Sentinel Node

Before administration of the ^{99m}Tc-DTPA-mannosyl-dextran/isosulfan blue injectate, a generous midline abdominal incision was made to expose the gastric and colonic lymph node basins. This step permitted visualization of the sentinel node via the blue dye, which typically occurred within 2 min of injection. The lymph nodes were mapped using a hand-held γ-detector (model 1000; Neoprobe). Within 5–10 min after injection, all radioactive or blue lymph nodes were excised. The relationship of the radioactive lymph nodes to the administration site and to each blue lymph node was noted. At least one lymph node distal to the radioactive nodes was also excised. These distal lymph nodes were typically within 2 cm of the sentinel node and the closest node to the radioactive nodes. Each node was placed in a plastic vial for scintillation counting.

The percentage injected dose (%ID) was calculated as the amount of activity in the sentinel node divided by the total activity

administered, which was calculated as 50 times the activity of the injectate counting standard. The activities of the injectate sample and the sentinel node were assayed to within a relative error of 1% in an automated well counter (Gamma 8000; Beckman Instruments) using a 100- to 200-keV energy window.

Statistical Methods

The Wilcoxon rank sum test of statistical significance was performed using JMP software (SAS Institute Inc.). A probability value of less than 0.05 was considered statistically significant. Discordance between ^{99m}Tc-DTPA-mannosyl-dextran and isosulfan blue was tested by calculation of κ, the proportion of chance-expected disagreements, as outlined by Cohen (*15*).

RESULTS

Loading the injector with the radioactive injectate required approximately 60 s and could be performed by a single person. With the needle withdrawn in the injector sheath, the injector could be transferred from shielded storage and threaded down the biopsy channel to the proximal end of the endoscope in less than 20 s. Table 1 lists the lymph node uptake of ^{99m}Tc-DTPA-mannosyl-dextran and isosulfan blue by all excised lymph nodes. ^{99m}Tc-DTPA-mannosyl-dextran uptake by colonic lymph nodes ($n = 4$) ranged from 0.54 to 2.4 %ID; the mean ± SD was 1.48 ± 0.91 %ID. Uptake for all excised ($n = 3$) distal nodes ranged from 0.001 to 0.005 %ID; the mean ± SD was 0.0023 ± 0.0023 %ID. The difference between primary-node and distal-node uptake was significant, with a probability value of 0.049. No distal lymph nodes were stained blue. Uptake by blue gastric lymph nodes ($n = 6$) ranged from 0.13 to 4.5 %ID; the mean ± SD was 1.47 ± 1.64 %ID. The range for nonblue distal nodes ($n = 6$) was 0.001–0.05 %ID; the mean ± SD was 0.018 ± 0.025 %ID. The difference between primary-node and distal-node uptake was significant, with a probability value of 0.0049. In 2 pigs, each gastric injection produced 2 hot and blue lymph nodes. During the second occurrence, a single blue lymph channel was observed to bifurcate approximately 3 cm from the injection site; celiac and periaortic sentinel nodes were detected and excised. No discordance was found between ^{99m}Tc-DTPA-mannosyl-dextran and isosulfan blue.

DISCUSSION

This study demonstrated the feasibility of sentinel node mapping with a submucosal injection of a lymph node–specific radiopharmaceutical. We developed a facile method for loading the injection catheter with the radiotracer and demonstrated rapid lymph node uptake with high isosulfan blue concordance and low distal-node uptake.

Colorectal cancer is currently understaged. Systemic disease develops in up to approximately 30% of patients with stage I or II cancer. The hypothesis is that these patients actually have stage III disease. It is for this reason that sentinel node imaging, the standard for staging of melanoma (*1*) and breast cancer (*16*), is being applied to colorectal cancer. Whereas in breast cancer the aim is to limit the area of resection, the goal of sentinel node mapping in colorectal cancer is to accurately stage the cancer and give the appropriate patients the benefit of adjuvant therapy. Three factors contribute to understaging. First, conventional lymph node harvesting, which removes the mesentery and fat surrounding the segment of bowel containing the primary tumor, may miss the diseased lymph node. This prob-

TABLE 1
^{99m}Tc-DTPA-Mannosyl-Dextran and Lymphazurin Uptake

	Colon			Stomach			
Pig no.	Lymph node status	TcDTPA-man-Dx (%ID)	Blue	Lymph node status	Location	TcDTPA-man-Dx (%ID)	Blue
1	S	2.4	+	S	Celiac	2.1	+
	D	ND		D		0.05	−
2	S	0.54	+	S	Celiac	0.9	+
	D	0.001	−	D		0.05	−
3	S	2.1	+	S	Celiac	0.13	+
	D	0.001	−	D		0.005	−
				S	Periaortic	0.27	+
				D		0.002	−
4	S	0.89	+	S	Celiac	4.5	+
	D	0.005	−	D		0.001	−
				S	Periaortic	0.92	+
				D		0.002	−
Mean ± SD	S	1.48 ± 0.91		S		1.47 ± 1.64	
	D	0.002 ± 0.002		D		0.018 ± 0.025	
P	S vs. D	0.049		S vs. D		0.0049	

TcDTPA-man-Dx = ^{99m}Tc-DTPA-mannosyl-dextran; S = sentinel; D = distal; ND = not detected.

lem can occur when the lymph drainage pattern is abnormal. Second, sampling of the submitted specimen is problematic, with a probability of missing small lymph nodes (*17*). Solving this problem requires increased time during the gross examination or use of fatting clearing techniques with liquids that are potentially toxic (*18*). Last, successful staging by conventional resection and lymph node harvesting requires at least 10 lymph nodes (*19*). Consequently, meticulous multilevel sectioning with CK-IHC and RT-PCR techniques to detect micrometastases is impractical. With sentinel node mapping, the appropriate lymph node can be identified, removed, and submitted for greater pathologic scrutiny by detailed molecular ultrastaging techniques. Recent applications (*5,6*) of sentinel node mapping in colorectal cancer have allowed upstaging of 11%–24% of patients originally designated as having stage I or II. Many of these patients were found to have micrometastases with serial sectioning at IHC evaluation. Although the significance of micrometastases has not been established, these values approach the percentage of colon cancer recurrence.

The sentinel node technique has been applied to gastrointestinal cancer by various groups (*7*), using isosulfan blue in North America, patent blue V in Europe, and indocyanine green in Japan. The drawback with using a dye is that its rapid transit through the lymph node chain limits the mapping to the time of surgery. The dyes do not bind to the sentinel node and consequently drain into the distal nodes, diminishing the advantage of the sentinel node technique. In areas such as the stomach and rectum, with high concentrations of fat, visualization is difficult (*20*). Finally, direct visualization of lymphatic channels and lymph nodes in the esophagus and rectum require mobilization (*3*), which disrupts lymphatic flow.

A radiopharmaceutical with the appropriate biologic and physical qualities will facilitate sentinel node mapping based on γ-detection. Radiodetection, which does not require direct visualization, permits extension of the method to other cancers. The esophagus and rectum can be mapped by an endoscopic administration followed by radiodetection of the sentinel node. A γ-detector can easily pick up lymph nodes in areas with aberrant lymphatic drainage. This situation has been reported in 4%–8% (*21–23*) of colorectal cancer cases and 30% of gastric cancer cases (*8*). Lymphatic drainage of the colon is thought to proceed in an orderly progression from the submucosa to the epicolic nodes to the paracolic nodes and on to nodes at the inferior and superior mesenteric arteries. Kitagawa et al. (*7*), using intraoperative γ-detection of radiolabeled colloid, observed intermediate lymph nodes in 20% of the cases. Of these paracolic nodes, 14% were at greater distances from the cancer than typically expected. γ-Detection of nodes in areas, such as the stomach, where there is a high density of fat around the tumor can guide the surgeon intraoperatively before direct visualization. In addition, a radioguided procedure would permit the surgeon to confirm complete removal of sentinel nodes within a basin. Radiopharmaceutical injection by the endoscopic technique is complementary to other laparoscopic surgical techniques. The endoscopic technique also permits direct injection into the submucosa, which is the site of lymphatic drainage.

Our demonstration of rapid lymph node uptake by ^{99m}Tc-DTPA-mannosyl-dextran overcomes one of the challenges in using particulate radiotracers for sentinel node mapping of gastrointestinal cancer. Rapid uptake will permit transmucosal administration during open surgery or an endoscopic injection after induction of anesthesia. In contrast, radiolabeled particles do not exhibit adequate lymph node uptake at 5 min after injection. Therefore, they must be administered endoscopically many hours before surgery, thus requiring additional sedation and procedure time. A second challenge is the reluctance to administer radioactivity in the operating room. Uptake of ^{99m}Tc-DTPA-mannosyl-dextran is 100-fold higher than typical uptake of unfiltered sulfur colloid by breast sentinel nodes (*24*). These studies used 37 MBq. It is therefore reasonable to expect that a 1.85-MBq dose would be more than adequate for ^{99m}Tc-DTPA-mannosyl-dextran mapping of a gastrointestinal sentinel node. A typical procedure would consist of a 2.78-MBq dose drawn into an injection catheter by a technologist in a nuclear medicine department. The injector would be coiled into a small lead-lined carrier and transported to the operating room. When the surgeon or gastroenterologist has positioned the endoscope, the injector would be removed from the carrier and immediately passed down the therapeutic channel and into the patient. At that point, the endoscope would effectively shield the patient and staff.

Although rapid uptake by the sentinel node is a requirement for successful mapping of gastrointestinal tract cancer, other attributes are needed for reliable application of a radiotracer. Long retention in the sentinel node and low uptake in distal nodes would be highly desirable. These properties would permit endoscopic administration with next-day laparoscopic surgery. Additionally, rapid clearance from the injection site would greatly facilitate intraoperative detection by reducing primary and scattered radiation into the γ-probe when the sentinel node is near the primary lesion. Although ^{99m}Tc-DTPA-mannosyl-dextran has demonstrated these properties in sentinel node mapping of breast cancer (*12*), they must be demonstrated for the gastrointestinal tract.

CONCLUSION

In less than 10 min after gastric and colonic submucosal injection, ^{99m}Tc-DTPA-mannosyl-dextran demonstrated sentinel node accumulation, low distal-node uptake, and a high concordance with isosulfan blue. A radiotracer with these properties, combined with recent technologies such as side-viewing laparoscopic γ-detectors, should increase the ease, availability, and flexibility of sentinel node mapping in patients with gastrointestinal cancer.

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