Self-expandable Esophageal Stent Loaded with ^{125}I Seeds Initial Experience in Patients with Advanced Esophageal Cancer[1]

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【 Abstract 】

Objective

To prospectively compare the response to treatment with a self-expandable esophageal stent loaded with iodine 125 (^{125}I) seeds for intraluminal brachytherapy versus the response to treatment with a conventional self-expandable covered stent in patients with advanced esophageal cancer.

Methods

The study protocol was approved by the institutional ethics committee, and informed consent was obtained from each patient. Patients from one institution who had dysphagia caused by inoperable esophageal cancer were randomly assigned to receive treatment with a stent loaded with 125I seeds (irradiation stent group) or a conventional covered stent (control group). After stent implantation, the outcomes were measured in terms of relief of dysphagia, survival time, and complications related to the procedure. Dysphagia was assigned a grade. A P value of less than .05 was considered to indicate a significant difference.

Results

The stent was successfully placed in the diseased esophagus in all 53 patients (27 patients in the irradiation stent group and 26 patients in the control group). The dysphagia grades significantly improved in both groups within the 1st month after stent placement but were better in the irradiation stent group than in the control group after 2 months (P .05). The median and mean survival times were better in the irradiation stent group than in the control group, and the differences were significant (P .001). Hemorrhage occurred in 16 (30%) patients in both groups combined during follow-up.

Conclusions

In patients with advanced esophageal cancer, treatment with an esophageal stent loaded with ^{125}I seeds, compared with that with a conventional covered stent, has potential benefit in that it allows a slightly longer relief of dysphagia and extended survival.

Dysphagia is the predominant symptom of patients with inoperable esophageal cancer. To relieve the dysphagia and improve the quality of life of such patients, brachytherapy has previously been used (1,2). Recently, stent placement has been widely accepted to be an option for palliation of the symptoms caused by esophageal strictures (3–6). However, recurrence of neoplastic stricture remains a challenge after stent placement. To combine the advantages of the immediate relief of esophageal dysphagia with stent placement and radiation therapy with brachytherapy, an esophageal stent loaded with iodine 125 (^{125}I) seeds has been developed. The technical feasibility and safety with this stent have been demonstrated as adequate in a healthy rabbit model (7). Thus, the purpose of our study was to prospectively compare the response to treatment with a self-expandable esophageal stent loaded with ^{125}I seeds for intraluminal brachytherapy versus the response to treatment with a conventional self-expandable covered stent in patients with advanced esophageal cancer.

Materials and Methods

Patients

The study protocol was approved by our institutional ethics committee, and informed consent was obtained from each patient. Patients who had unresectable tumors because their lesions were extensive, because they had metastatic disease, or because they were in poor medical condition (unfit to undergo surgery) were randomly assigned to two groups: those who received the esophageal stent loaded with ^{125}I seeds (irradiation stent

group) and those who received received a conventional covered stent (control group). Patients were randomly assigned to the irradiation stent (control group). Patients were randomly assigned to the irradiation stent group or the control group by using Proc Plan Seed210002. Except for the interventional radiologists, all patients, the nurse following up patients, and the statistician performing the analyses in our study were blinded to the type of stent used. Exclusion criteria were tumor growth within 3.0 cm of the upper esophageal sphincter, deep ulceration, tracheoesophageal fistula, and previous radiation therapy or stent placement. For ethical reasons, patients in both groups were allowed to be treated with chemotherapy or alternative medicine prior to, concurrently with, or following stent placement.

All diagnoses were histopathologically established by using endoscopic biopsy. Dysphagia was assigned a grade as follows: grade 0, the patient had the ability to eat a normal diet; grade 1, the patient had the ability to eat some solid food; grade 2, the patient had the ability to eat semisolid foods only; grade 3, the patient had the ability to swallow liquids only; and grade 4, the patient had complete obstruction (8).

Stent Preparation

The esophageal irradiation stent combined a self-expandable covered or uncovered esophageal stent (MTN; Nanjing MicroInvasive Medical, Nanjing, China) and ^{125}I radioactive seeds (Fig 1). In 22 patients, covered stents were used, and in five, uncovered stents were used. Sheaths (4.8 mm long 0.8 mm wide) that contained ^{125}I radioactive seeds (CIAE-6711; Chinese Atomic Energy Science Institution, Beijing, China) were attached to the outer surface of the stent. Five patients with an uncovered irradiation stent were randomly selected from the patients who were in the irradiation stent group. The purpose of using uncovered stents in the irradiation stent group was to permit follow-up endoscopic biopsy. The ^{125}I seed had a half-life of 59.6 days, with a range of x-ray energy of 27.4–31.5 keV and a mean count of gamma ray energy of 35.5 keV. The initial dose rate was 7.7 cGy/h, with effective irradiating distance of 20 mm. The seeds were loaded into the sheaths on the stent immediately before implantation of the stent. The number and dose of the radioactive stent seeds were determined according to the treatment planning system (Syncor, Shanghai, China) on the basis of the size of the individual tumor. The mean radioactivity

administered to each patient was 370.0 MBq <?> 155.4 (standard deviation), with a range of 259–592 MBq. To cover the entire lesion of the tumor with the sheaths containing ^{125}I seeds, at least 2 cm exceeding the tumor margins was required. The distance between the two sheaths was 15 mm. In the control group, conventional self-expandable covered esophageal stents (MTN; Nanjing MicroInvasive Medical) were used.

Stent Placement

Placement of all irradiation stents and conventional stents was performed with fluoroscopic guidance. Before stent placement, barium esophagography was performed to document the site and length of the lesion. The pharynx was anesthetized with topical aerosolized li- docaine (Shanghai Fuxing Zhaohui Pharmaceutical, Shanghai, China). The patient was then placed in a right lateral decubitus position in a C-arm angiographic unit (Innova 3100; GE Healthcare, Waukesha, Wis). A 5-F catheter (H1; Terumo, Tokyo, Japan) was placed through the mouth into the stomach through the segment of the esophageal cancer with a stricture, and then a 0.035-inch guidewire (Amplatz Super Stiff; Boston Scientific, Natick, Mass) was exchanged through the catheter. The stent catheter was then advanced over the guidewire, and the stent was deployed on the lesion. The stent localization was confirmed by means of injection of iodinated contrast medium (iohexol, Omnipaque 300; GE Healthcare, Shanghai, China) via the catheter immediately after deployment.

The technique for placement of an irradiation stent was the same as that for placement of a conventional covered stent in the control group except for the preloading of ^{125}I seeds into the sheaths.

The loading process of ^{125}I seeds into the sheaths on the stent before stent placement was shielded by using a seed-loading gun within a self-made radiation- resistant box. The stent placement procedures were performed by experienced interventional radiologists (J.H.G., G.J.T., and G.Y.Z., with, 17, 20, and 10 years of experience in interventional radiology, respectively). The radiologist who performed the implantation procedure with the irradiation stent always wore lead gloves. After irradiation stent placement, patients stayed in a single room until discharge (5 days or longer). All management related to radiation safety of the irradiation stent was based on criteria recommended by the International Commission on

Radiological Protection (9).

Comparisons, Definitions, and Follow-up

The results that were compared between the two groups were the dysphagia relief period and survival time. The dysphagia relief period was defined as the time from stent implantation to the time at which deterioration of swallowing occurred or a decrease of one or more points in the dysphagia grade was observed. Survival time was defined as the time from stent insertion to death. Complications, which included subjective symptoms such as chest pain and hemorrhage and objective findings such as stent or radioactive seed migration and stent restenosis, were recorded. Severe pain was defined as pain occurring after stent insertion that required narcotic analgesics (bucinnazine hydrochloride injection; Tianjin Jin-Yao Amino Acid, Tianjin, China) for control. Complete stent migration was defined as migration of the stent out of the segment with the stricture, whereas partial migration was defined as partial migration of the stent with the stent remaining partially in the area with the stricture.

The primary outcome was relief of dysphagia. The secondary outcome was evaluated by using complications related to the procedure and survival time since the stent placement. Esophagography was performed in all patients 3 days after stent insertion to verify the status of the expansion and position of the stent. Thereafter, follow-up was performed monthly by a research nurse via telephone, and the patient was asked to return for laboratory and imaging examinations every 3 months or whenever dysphagia recurred. Endoscopic examination was employed when abnormal findings were revealed at esophagography. For the purpose of detecting leakage of the radioisotope, emission computed tomography (CT) was performed in the patients in the irradiation stent group at 1 and 3 months after stent insertion. Chest CT examination with transverse scans (HiSpeed CT/i; GE Healthcare) was employed to follow the size of esophageal lesions. Because there were no well-recognized criteria for measuring the exact size of the esophageal cancer on the basis of CT findings, in our study, we set assessment criteria modified from the Response Evaluation Criteria in Solid Tumors (10). The longest distance of the tumor (namely, the longest distance of the lesion in the transverse plane, reducing the diameter of the stent, measured on the CT scans immediately after stent placement) was compared

with that at follow-up by two interventional radiologists (J.H.G. and G.Y.Z.) in consensus. Responses to treatment were categorized as follows: complete response, disappearance of all target lesions; partial response, at least a 15% decrease in the longest distance of target lesions; progressive disease, at least a 10% increase in the longest distance of target lesions; or stable disease, neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease. The longest distance of the target lesion, or tumor, is the largest diameter of the tumor in the longest transverse plane for the tumor on a CT scan.

Statistical Analysis

Statistical analyses were performed with software (SAS, version 9.0; SAS Institute, Cary, NC). Numeric data of the ages were examined with the Student test, whereas other characteristics of the patients before the stent treatment were analyzed with the Fisher exact test. The dysphagia grades were examined with the Kruskal-Wallis test. Comparison of the side effects and complications related to stent placement between the two groups was also analyzed with the Fisher exact test. The onset of stent restenosis was compared by using the Wilcoxon two-sample test. Kaplan-Meier analysis and the log-rank test were used for the evaluation of survival time. A P value of less than .05 was considered to indicate a significant difference.

Results
Patients and Stent Placement

Between April 2004 and April 2006, 60 patients with progressive dysphagia caused by advanced esophageal cancer were equally and randomly assigned to the irradiation stent group or the control group. Seven patients were lost to follow-up; consequently, 27 patients were in the irradiation stent group and 26 patients were in the control group for the analyses. All patients received a histologic diagnosis of adenocarcinoma (n 11) or squamous cell carcinoma (n 42) by using endoscopic biopsy. Because all histologic diagnoses were performed with small specimens obtained endoscopically, the histologic differentiation was not available. The baseline characteristics of all patients in the two groups are listed in Table 1. There were no significant differences in sex, age, histologic type, location of strictures, presence of metastatic disease, and dysphagia grade before stent

insertion between the two groups (Table 1).

The mean, median, and length of follow-up in the irradiation stent group versus the control group were 7.2 versus 3.3 months, 6.0 versus 3.5 months, and 15.0 versus 6.7 months, respectively.

The diameter of the stent used in the irradiation stent and the control groups ranged from 18 to 20 mm, and the length ranged from 80 to 120 mm. Twenty-two covered

Figure 1: Covered self-expandable esophageal stent with plastic sheaths holding ^{125}I seeds fixed on outside of stent (arrows).

and five uncovered esophageal irradiation stents were placed in 27 patients in the irradiation stent group, and 26 conventional covered stents were placed in patients in the control group. The initial stent placement procedure was successful in all 53 patients with 53 stents. An additional conventional covered stent was implanted because of partial stent migration 1 month following insertion of the irradiation stent (covered stent) and the conventional covered stent in one patient each. No ^{125}I seed loss occurred during the process of irradiation stent insertion and deployment(Fig 2a). All patients tolerated stent placement well. Follow-up esophagography 3 days after stent placement showed that all stents expanded fully without stent migration.

No patients in either group were treated with chemotherapy prior to or following the stent placement. However, eight patients in the irradiation stent group and seven patients in the control group had received at least a course of support treatment of traditional Chinese medicine prior to or after stent implantation.

Follow-up Imaging and Endoscopy

Emission CT examinations in the irradiation stent group performed at 1 and 3 months after stent placement showed no radiation seed displacement to other parts of the body (Fig 2b). CT examinations at 3 months after stent placement in the irradiation stent group showed that the size of the esophageal tumor was smaller (partial response) in 13 patients, was stable (stable disease) in 11 patients, and was enlarged (progressive disease) in three patients. At 8 months, marked tumor debulking (partial response) was observed in seven of nine patients.
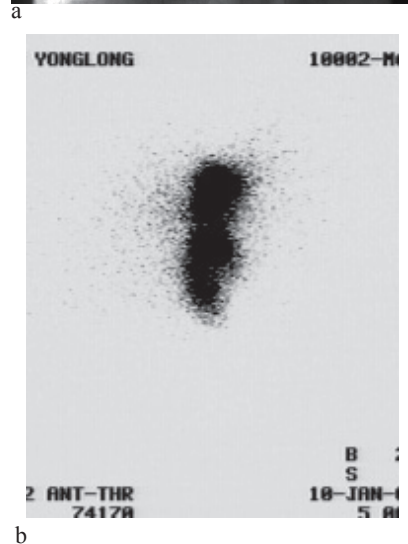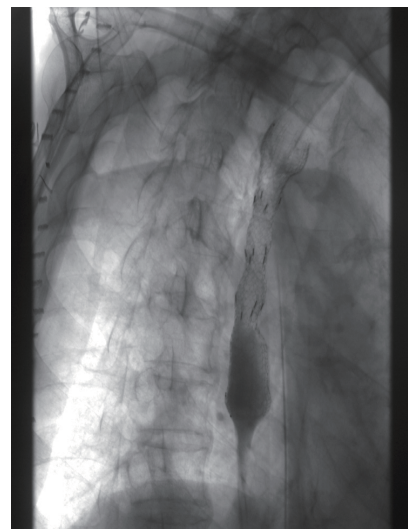

Figure 2: (a) Esophagographic image obtained immediately after deployment of stent shows that stent fully expanded, with visualization of sheaths filled with ^{125}I seeds (arrows). (b) Emission CT scan obtained 1 month after stent insertion in same patient demonstrates dense radiation accumulation within stent and no radioactive seed displacement to other parts of the body.

However, no complete response was obtained in this series of patients. Endoscopy employed for follow- up of the patients with an uncovered irradiation stent at 3 months showed thin and smooth hyperplasia, mainly composed of granulation tissue, instead of tumor overgrowth on the surface of the stents in three of five patients. Hyperplasia

Background Characteristics of Patients before Stent Placement			
	Control Group	Irradiation Stent Group	Improved
Characteristic	(n 26)	(n 27)	P Value*
Age (y)†	69.54 <?> 8.68 (55–82)	72.19 <?> 8.71 (55–84)	.273‡
Sex			.757
Male	20	19	
Female	6	8	
Dysphagia at inclusion			.467
Grade 3	23	21	
Grade 4	3	6	
Histologic type			.744
Adenocarcinoma	6	5	
Squamous cell carcinom	20	22	
Location of stricture			.797
Upper part of thorax	3	4	
Middle part of thorax	14	16	
Lower part of thorax	9	7	
Metastatic disease			》.99
Yes	4	5	
No	14	13	
Unknown	8	9	

* Except where indicated otherwise, the Fisher exact test was used.
† Data are the mean ± standard deviation. Numbers in parentheses are ranges.
‡ The t test was used.

Analysis of Follow-up Period and Stent Restenosis		
Group	Mean Onset (mo)*	Median Onset (mo)†
Irradiation stent (n 8)	4.75 <?> 2.55	4.5 (2,8)
Control (n 6)	2.00 <?> 0.63	2.0 (1,3)

* Data are the mean ± standard deviation.
† Numbers in parentheses are the 95% confidence intervals (CIs) (Wilcoxon rank sum test , T 28.00, P .044).

of granulation tissues was also noted at both ends of the stents, especially the proximal end, in all five patients. Histologic findings obtained at endoscopic biopsy revealed that the tumor tissue near the sites of the radioactive seeds was completely necrotic and was replaced by granulation tissue.

Stent restenosis was demonstrated by using esophagographic and/or endoscopic examinations in eight patients in the irradiation stent group and in six patients in the control group. These patients had recurrent dysphagia after stent placement during follow-up. The stent restenosis occurred later in the irradiation stent group than in the control group (4.75 vs 2.00 months) (Table 2). There was a significant difference in the onset of stent restenosis between the two groups (P .044, Wilcoxon rank sum test). Histologic examination of the specimens obtained at endoscopic biopsy revealed that thepredominant tissue of the restenosis was granulation-like tissue, with smooth muscle cell proliferation and matrix deposition, in seven patients (six patients from the irradiation stent group and one patient from the control group) and tumor overgrowth in the other seven patients (two patients from the irradiation stent group and five patients from the control group).

Dysphagia Grades

The dysphagia grades (Fig 3) improved greatly in both the irradiation stent group (mean, 1.07 ± 0.27) and the control group (mean, 1.04 ± 0.20); 3 days after stent placement, there was no significant difference between the two groups (P >.99, Kruskal-Wallis test). The dysphagia was equally well palliated within the 1st month after stent placement in both groups; for the irradiation stent group, the mean grade was 1.22 ± 0.42, and for the control group, the mean grade was 1.17 ± 0.38 (P =.732, Kruskal-

Wallis test). Thereafter, the dysphagia grades increased in both groups, but more substantially in the control group than in the irradiation stent group. After 2 months, there was a significant difference (P < .05). Although the dysphagia returned slowly, beginning at 1 month after stent placement in the irradiation stent group, the dysphagia grades indicated that the patients were able to eat without serious difficulty during the follow-up of 6 months.

Side Effects and Complications

No severe procedure-related complications occurred in any case. The side effects and complications during follow- up are presented in Table 3.

All patients experienced dull chest pain after stent insertion, and most of them tolerated the pain well without medication. However, 15 patients (eight patients in the irradiation stent group and seven patients in the control group) complained of severe chest pain, which was palliated with narcotic analgesics. The degree of chest pain between the irradiation stent group and the control group was not significantly different. Temperature increased higher than 39°C from the 2nd day after stent insertion in one patient in the irradiation stent group and in three patients in the control group, all of whom recovered after treatment with indomethacin (Tungshun Enterprises Group, Shashi, Hubei, China).

Tracheoesophageal fistula occurred at the site 2 cm upward from the proximal end of the stent in one patient 3 months after stent placement in the irradiation stent group. No tracheoesophageal fistula was found in the control group.

Aspiration pneumonia caused by laryngeal nerve paralysis demonstrated by using laryngoscopy occurred in three patients (one patient in the irradiation stent group and

two patients in the control group) 2–3 months after stent insertion. All patients recovered with medical treatment. Hemorrhage occurred in 16 (30%) patients (nine patients
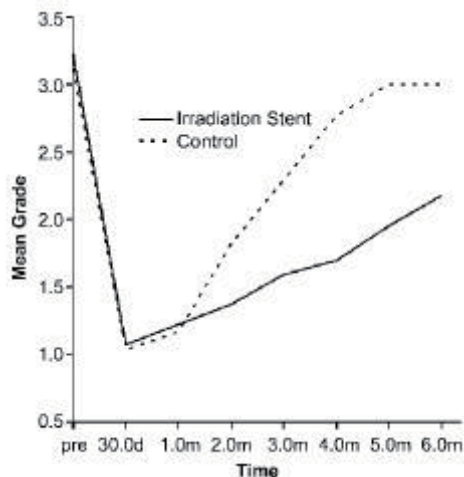

Figure 3: Mean dysphagia grade during follow-up and before stent placement. Within 1st month after stent placement, dysphagia was equally well palliated in both groups: For irradiation stent group, mean grade was 1.22±0.42; for control group, mean grade was 1.17±0.38 (P+ .732, Kruskal-Wallis test). Thereafter, dysphagia grades increased in both groups but more substantially in control group than in irradiation stent group. After 2 months, there was a significant difference (P<.05).
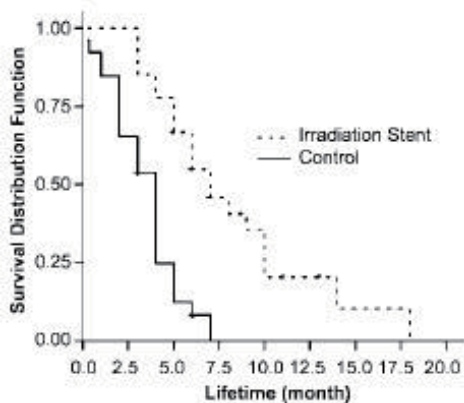

Figure 4: Median and mean overall survival period with stent placement. In irradiation stent group, median overall survival period was 7 months (95% CI: 5.0, 10.0) and mean overall survival period was 8.3 months (95% CI: 6.36, 10.21). In control group, median overall survival period was 4 months (95% CI: 2.0, 4.0) and mean overall survival period was 3.5 months (95% CI: 2.72, 4.16).

in the irradiation stent group and seven patients in the control group) during follow-up. Eleven (21%) patients (six patients in the irradiation stent group and five patients in the control group) died from acute massive hemorrhage. Six patients in the irradiation stent group died at 3, 3, 4, 7, 7, and 10 months; five patients in the control group died at 8 days, 10 days, 1 month, 2 months, and 2 months; and the remaining five patients (three patients in the irradiation stent group and two patients in the control group) survived the bleeding. There was no significant difference in the incidence of hemorrhage between the two groups.

No complete migration of stents was demonstrated, but partial stent migration was detected in five patients (two patients in the irradiation stent group and three patients in the control group) at 1 month following stent insertion. In two of them (one in each group), one additional conventional covered stent was implanted.

Survival

Forty-five (21 patients in the irradiation stent group and 24 patients in the control group) of 53 patients died of hemorrhage, metastases, cachexia, or multiorgan failure during the follow-up of 1–18 months. The median survival in the irradiation stent group was 7 months (95% CI: 5.0, 10.0), with a mean of 8.3 months (95% CI: 6.36, 10.21), versus a median survival in the control group of 4 months (95% CI: 2.0, 4.0), with a mean of 3.5 months (95% CI: 2.72, 4.16). The differences between both measures of survival in the two groups were significant (P < .001, log-rank test) (Fig 4).

Discussion

Stent placement alone does not offer therapeutic effects on esophageal cancer itself. Intraluminal brachytherapy with cobalt 60 and iridium 192 has been widely used in patients with esophageal cancer, with the achievement of palliation and few complications (2,11,12). Findings in a multicenter randomized trial performed by Homs et al (11) indicated that better long-term relief of dysphagia was observed with brachytherapy than with covered stent insertion, although better improvement of the dysphagia within 1 month after stent insertion was obtained with the covered stent. Technically, deployment with x-ray guidance of a self-expandable stent loaded with ^{125}I seeds was successful without difficulties in all procedures in our series, and no ^{125}I seed loss was found during or after deployment of the stent, which indicated an adequate mechanical design of the stent and stent delivery system.

Theoretically, interstitial brachytherapy with implantation of ^{125}I seeds may be better than conventional intraluminal brachytherapy because of their different means of placement of the radioactive source in proximity to the tumor. Interstitial brachytherapy provides closer, longer treatment with continuous irradiation of tumors. However, the radiation dosimetry with such a stent in the esophageal lumen is difficult to precisely measure and plan. Therefore, a proper dose of ^{125}I seeds is important. The average applied radioactivity of 370.0 MBq in our study was determined by taking into account data in our own previous experiments in rabbits (7), as well as experiences with intraluminal brachytherapy. There were no severe complications related to the radiation dose in our series of patients, and the tumors improved with therapy, suggesting that the selected dose was appropriate.

Although the dysphagia grades improved immediately after the stent placement in both groups, they remained in the range of grade 0–2 significantly longer in the patients with the irradiation stent than in the patients with a conventional covered stent. The main goals of ensuring longer patency of the stent and effective treatment of the tumor were accomplished. Moreover, the significant improvement in survival, with a median survival of 7.0 months in the patients with the irradiation stent versus 4.0 months in those with the conventional covered stent, indicates the therapeutic advantages of this stent. Our survival data in the control group are similar to those in a multicenter trial (155 days for single-dose brachytherapy vs 145 days for the stent alone) (11). In addition, endoscopic examinations in five patients with the uncovered irradiation stent in our series histologically demonstrated the therapeutic effects on tumors around the ^{125}I seeds. The CT examinations showed the debulking of the entire tumor, including the tumor outside of the esophageal lumen.

Hemorrhage is the most important late complication. The incidence of late hemorrhage varies from 9.7% to 12.3% (11,13). The incidence in our series of patients was higher compared with that reported in the literature; 16 (30%) patients had hemorrhage during follow-up, and 11 (21%) of them died from acute massive hemorrhage at 8 days to 10 months after stent placement. However, the incidence of hemorrhage between the two groups was not significantly different. Although the actual mechanism of hemorrhage with esophageal stent placement is

uncertain, it is believed that hemorrhage may be caused by the exertion of pressure by the stent on the tumor, on the normal mucosa of the esophagus, or on both (14). Animal experimental data indicate that ischemic changes that result from compression by the stent wires may cause esophageal ulcerations (7). The hemorrhage may be related to previous radiation therapy, different types of stents used, or different sites of stent placement (4,13,15,16). It is interesting that there is no significant difference in hemorrhage between the patients with or without radioactive seeds, although the patients with radioactive seeds survived longer. This result may be due to a protective effect on bleeding from the tumor through tumor debulking and an injury effect on the tumor vasculature by the radiation of brachytherapy, as well as the increasing risk caused by the expanding force of a stent. However, two patients in the control group died of massive hemorrhage in 8 and 10 days after placement, compared with no deaths within 3 months in the irradiation group. These two patients had sudden uncontrolled hematemesis. Our best explanation for the deaths is aortic perforation caused by stent meshes, although autopsy was not performed in these patients. There has been a report of a case caused by perforation of the aorta from stent penetration (16).

Esophageal perforation or tracheoesophageal fistula occurs in 2.7%–7.3% of patients after esophageal stent placement (4,13,15,16). Such a complication may be increased with an irradiation stent because of the radiation effect on the esophageal wall. However, tracheoesophageal fistula occurred in only one patient in our series. An irradiation stent was used in this patient, but the site of the fistula was at least 2.0 cm away from the proximal end of the stent. Therefore, we do not think this complication is related to the irradiation stent.

Radiation safety protection measures should be taken by physicians, patients, and anyone who approaches the patient with the irradiation stent. Several protection measures for radiation safety were taken in our study. Because it is difficult tomeasure the absorbed dose in the lumen of an organ such as the esophagus, we did not obtain the exact dosimetry in the patient with an irradiation stent or in people approaching that patient in our study. However, the safety of radiation with the implantation of ^{125}I seeds has been accepted in brachytherapy for cancers such as prostate cancer. Moreover, no complications related to radiation were found in our series of patients.

Our study had certain limitations. First, accurate measurement of the dosimetry of the irradiation stent loaded with ^{125}I was not possible because of the lack of sophisticated measuring

Complications after Conventional and Irradiation Stent Placement			
Complication	Conventional Stent (n 26)	Irradiation Stent (n 27)	P Value*
Fever	3	1	.351
Severe pain	7	8	>.99
Fistula formation	0	1	>.99
Aspiration pneumonia	2	1	.610
Hemorrhage	7	9	.767
Stent migration	3	2	.669
Restenosis	6	8	.757

Note.—Some patients had more than one complication.
* Fisher exact test.

techniques dedicated to esophageal cancer. Therefore, we could not provide quantitative data related to radiation therapy. Second, the quality of life, which is an important measure of outcomes for the palliative treatment of malignancies such as inoperable esophageal cancer, was not measured in our study. In conclusion, with increased survival combined with decreased dysphagia grades, our study findings indicate that therapy with an irradiation stent loaded with ^{125}I seeds has potential benefit in patients with advanced esophageal cancer. We believe further investigation of this treatment modality is indicated.

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