Radioactive Self-Expanding Stents Give Superior Palliation in Patients With Unresectable Cancer of the Esophagus but Should Be Used With Caution if They Have Had Prior Radiotherapy

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Background. Self-expandable stents loaded with 125I (iodine 125) seeds may combine the advantages of the immediate relief of esophageal dysphagia with stent placement and radiation therapy with brachytherapy. We compared the self-expanding irradiation stent with a conventional self-expandable covered stent in patients with malignant dysphagia due to recurrent esophageal cancer.

Methods. The patients with recurrent esophageal cancer suffering from dysphagia (≥ grade 2) were enrolled and placed with a stent loaded with 125I seeds (irradiation stent group) or a conventional covered stent (traditional stent group). After stent placement, the outcomes were compared in terms of relief of dysphagia, survival time, and complications related to the procedure.

Results. Primary stent placements were successful in 29 of 31 (93.5%) cases in the irradiation stent group and 30 of 32 (93.8%) cases in the traditional stent group. The dysphagia grades significantly improved in both groups within the first month after stent placement but were better in the irradiation stent group than in the traditional stent group after 3 months (p = 0.04). The median survival was 4 months in the radiation stent group and 3 months in the traditional stent group (p = 0.06). Bleeding occurred in 35.5% versus 21.9% patients in the irradiation stent group versus the traditional stent group during follow-up (p = 0.232).

Conclusions. This study indicated that the radiation stent had a potential benefit of a longer dysphagia relief period. However, no significant survival benefits were observed in the radiation stent group and the high incidence rate of massive hemorrhages further limited its application in patients with malignant dysphagia due to recurrent esophageal cancer.

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 (125I) seeds has been developed. The technical feasibility and safety with this stent have been demonstrated as adequate in patients with first diagnosed advanced esophageal cancer [10], and in a healthy rabbit model [11]. Zhongmin and colleagues [12] reported intraluminal radioactive stent loaded with iodine-125 seeds implantation was a feasible and practical management in treating malignant esophageal stricture and was superior to covered stent alone insertion, as measured by survival. However, there is no report of a self-expandable stent loaded with 125I seeds being administered as salvage treatment for recurrent esophageal cancer thus far.

The purpose of our study was to compare the responses and adverse events to treatment with a self-expandable esophageal stent loaded with 125I seeds for intraluminal brachytherapy versus those with a conventional self-expandable covered stent in previously irradiated patients.
with recurrent esophageal cancer. The combination of cisplatin and 5-fluorouracil is also used with palliative intent.

Patients and Methods

Eligibility and Study Design

The eligibility criteria were as follows: (1) confirmation of esophageal recurrence by histology or cytology; (2) previous external radiotherapy with a interval greater than 6 months before recurrence; (3) symptom of grade 2 or greater dysphagia (0 = normal swallowing; 1 = dysphagia for solids only; 2 = dysphagia for semisolids also; 3 = dysphagia for liquids also; 4 = cannot swallow own saliva); (4) no serious medical conditions that would preclude safe administration of treatment. (5) medically or surgically inoperable or unacceptable to surgery. Exclusion criteria included the following: (1) tumor growth within 3.0 cm of the upper esophageal sphincter; (2) evidence of esophageal perforation or deep ulceration to mediastinum; (3) previous brachytherapy or stent placement.

The study protocol was approved by our institutional ethics committees, and informed consent was obtained from each patient. The researchers interpreted the potential benefits and risks of each treatment to all patients and then the patients selected the esophageal stent loaded with $^{125}$I seeds (irradiation stent group) or a conventional covered stent (traditional stent group) on their own. Patients in both groups were treated with chemotherapy after stent placement.

Stent Placement

The esophageal irradiation stent combined a self-expandable esophageal stent (MTN; Nanjing MicroInvasive Medical, Nanjing, China) and $^{125}$I radioactive seeds (CIAE-6711; Chinese Atomic Energy Science Institution, Beijing, China). Sheaths (4.8 mm long × 0.8 mm wide) that contained $^{125}$I radioactive seeds were attached to the outer surface of the stent. The $^{125}$I seed had a half-life of 59.6 days, with a range of X-ray energy of 27.4 to 31.5 keV and a mean count of gamma ray energy of 35.5 keV. The initial dose rate was 7.7 cGy/hour, 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 on the basis of the size of the individual tumor. To cover the entire lesion of the recurrence with the sheaths containing $^{125}$I seeds, at least 2 cm exceeding the tumor margins was required. The both ends (about 1.5 cm) of the stent were not covered by the membrane. The distance between the 2 sheaths was 15 mm [10]. In the traditional stent group, conventional self-expandable covered esophageal stents were used (MTN; Nanjing MicroInvasive Medical). The radial force of the traditional and the experimental stent had similar radial force according to the measurement by the manufacturer.

Parameters and Follow-Up

The 2 treatment groups were compared for clinical characteristics (age, gender, dysphagia score, tumor length and location, histology), clinical outcome (technical success and dysphagia relief period), complications, and survival.

The dysphagia relief period was defined as the time from stent implantation to the time at which deterioration of swallowing occurred and 1 or more points increase in the dysphagia grade was observed. Survival time was defined as the time from stent insertion.

The patients were asked to return for laboratory and imaging examinations in 1 month after stent and every 2 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 was performed in the patients in the irradiation stent group at 1 and 3 months after stent insertion.

Statistical Analysis

Continuous variables were compared between therapy groups using the nonparametric Wilcoxon rank sum test. Categoric variables were compared between therapy groups using a $\chi^2$ or Fisher exact test. Ranked data were examined with the Wilcoxon 2-sample test. Kaplan-Meier analysis was used for the evaluation of survival time. A $p$ value of less than 0.05 was considered to indicate a significant difference.

Results

Overall, 63 patients with malignant dysphagia due to recurrent esophageal cancer received endoscopic stenting (irradiation stent group, $n = 31$; traditional stent group, $n = 32$) between 2007 January and 2010 May. There were 27 female and 36 male patients with a median age of 65 years (range, 43 to 78 years). Ten patients presented with a recurrence in the proximal esophagus, whereas 27 and 26 patients had recurrence location in the middle and distal esophagus. The histologic type was squamous cell carcinoma in 52 patients, adenocarcinoma in 10 patients, and adenosquamous cell carcinoma in 1 patient. The baseline characteristics of all patients in the 2 groups are listed in Table 1. There were no significant differences in age, gender, location of strictures, histologic type, presence of metastatic disease, and dysphagia grade before stent placement between the 2 groups (Table 1).

The mean and median of follow-up in the irradiation stent group versus the traditional stent group were 3.4 versus 2.7 months, and 3.5 versus 2.0 months, respectively. Two patients in the irradiation stent group and 3 patients in the traditional stent group missed follow-up at 2 months and 3 months, and 1 month, 2 months, and 4 months after the stent placement, respectively.

Technical Success

Primary stent placement was successful in 29 of 31 (93.5%) cases of the irradiation stent group and 30 of 32 (93.8%)
cases of the traditional stent group. The average applied radioactivity is $260.0 \pm 105.6$ MBq. The patients tolerated stent placement well and no $^{125}$I seed loss occurred during the process of irradiation stent insertion and deployment. We were unable to insert a stent in 4 patients with very tight strictures; 2 in the middle and 2 in distal esophagus. Three of these 4 patients underwent endoscopic gastrostomy, whereas 1 patient received total parenteral nutrition.

All patients in the irradiation stent group and traditional stent group were treated with chemotherapy prior to or after the stent placement. One to 4 cycles of chemotherapy with 5-fluorouracil and cisplatin were administered. Altogether 7 patients in the irradiation stent group and 5 patients in the traditional stent group rejected further chemotherapy after stent implantation.

### Minor Complications

Most patients underwent mild chest pain after implantation of the stent and this diminished after 24 hours with only short-term analgesic therapy needed. However, 8 patients in the irradiation stent group and 9 patients in the traditional stent group complained of severe chest pain, which was palliated with narcotic analgesics more than 3 days. The degree of chest pain between the irradiation stent group and the traditional stent group was not significantly different. Gastroesophageal reflux occurred in 9 of 31 (29.0%) patients in the irradiation stent group and 7 of 32 (21.9%) patients in the traditional stent group ($p = 0.514$). Temperature increased higher than 38 °C from the second day after stent insertion in 6 patients in the irradiation stent group and in 4 patients in the traditional stent group, all of whom recovered after treatment with indomethacin.

### Major Complications

Bleeding occurred in 18 patients (11 in irradiation stent group and 7 in traditional stent group; 35.5% vs 21.9%, $p = 0.232$) and 66.7% (12 of 18) bleeding episodes were hemodynamically significant and transfusions were required. Among them, 8 (5 of irradiation stent group and 3 of traditional stent group, 16.1% vs 9.4%, $p = 0.474$) occurred within 72 hours and 10 (6 of irradiation stent group and 4 of traditional stent group, 19.4% vs 12.5%, $p = 0.509$) occurred in 11 days to 6 months after stent placement. Seven patients (4 patients in the irradiation stent group and 3 patients in the traditional stent group) died from acute massive hemorrhage ($p = 0.482$). The sources of massive bleeding included tumor and adjacent blood vessel invasion. Two of them presented with a recurrence in the proximal esophagus, whereas 3 and 2 patients had recurrence location in the middle and distal esophagus, respectively. Four patients in the irradiation stent group died at 1 month, 3 months, 3 months, and 6 months; 3 patients in the traditional stent group died at 1 month, 2 months, and 5 months; and the remaining 11 patients (7 patients in the irradiation stent group and 4 patients in the traditional stent group) survived the bleeding. There was no significant difference in the incidence of hemorrhage between the 2 groups.

Perforation into the right mediastinum was detected by computed tomographic scan in 2 patients; 1 of the irradiation stent group at 1 month and 1 of the traditional stent group at 2 months after stent placement, and both patients died from septic complications. Tracheoesophageal fistulas were found in 2 patients in the irradiation stent group and 1 patient in the traditional stent group.

Aspiration pneumonia caused by laryngeal nerve paralysis demonstrated by using laryngoscope occurred in 5 patients (2 patients in the irradiation stent group and 3 patients in the traditional stent group) 1 to 6 months after stent insertion. All patients recovered with medical treatment.

Stent migration as a major complication occurred in 7 patients (3 patients of irradiation stent group and 4 patients of traditional stent group) during follow-up. Among them, the stents passed the gastrointestinal tract without causing symptoms of obstruction in 2 patients of the traditional stent group; the devices were retrieved successfully by endoscopic approach and replaced by conventional covered stent. Partial stent migrations were detected in 5 patients (3 patients in the irradiation stent group and 2 patients in the traditional stent group) and no additional stent needed. All complications during follow-up are presented in Table 2.

### Relief of Dysphagia

Within the first month after stenting, the mean dysphagia score decreased significantly from baseline in the irradiation stent group from 3.1 to 1.7 ($p < 0.01$) and in the
traditional stent group from 3.0 to 1.6 \((p < 0.01)\) without significant difference between the 1 treatment groups \((p = 0.91)\). At 3 months after stent, mean dysphagia grade in the irradiation stent group was significantly lower than the traditional stent group \((2.1 \text{ vs } 2.6, p = 0.03)\). The stent restenosis occurred later in the irradiation stent group than in the traditional stent group \((3.5 \text{ vs } 2.5 \text{ months})\). There was a significant difference in the onset of stent restenosis between the 2 groups \((p = 0.04)\) (Fig 1).

Survival

The mean and median survival in the irradiation stent group was 3.7 months \((95\% \text{CI, 3.1 to 4.3 months})\) and 4.0 months \((95\% \text{ CI, 3.5 to 4.5 months})\), while the mean and median survival in the traditional stent group was 3.1 months \((95\% \text{ CI, 2.6 to 3.6 months})\) and 3.0 months \((95\% \text{ CI, 2.4 to 3.6 months})\), respectively. The survival differences between the 2 groups were not significant \((p = 0.064)\) (Fig 2).

Comment

Recurrent malignant esophageal strictures after radiotherapy are frequently encountered by gastroenterologists and esophageal stent is a reasonable alternative to maintain patency, especially for the patients medically or surgically inoperable or unacceptable to surgery. However, stent placement alone does not offer therapeutic effects on esophageal cancer itself. Brachytherapy is another reasonable alternative for the palliation of dysphagia. Dysphagia improved more rapidly after stent placement than after brachytherapy, but long-term relief of dysphagia was better after brachytherapy \([13, 14]\). Guo and colleagues \([10]\) reported that esophageal stent loaded with \(^{125}\text{I}\) seeds combined the advantages of the immediate relief of esophageal dysphagia with stent placement and radiation therapy with brachytherapy in the palliative treatment of advanced esophageal cancer. Theoretically, the stent placements are more challenging for the recurrent malignant esophageal strictures because of the friability and vulnerability of esophagus after radiotherapy.

In the current study, the dysphagia score in the irradiation stent group was significantly lower than the traditional stent group \((2.1 \text{ vs } 2.6, p = 0.03)\) at 3 months after stent placement although the dysphagia grades improved at the first month after stent placement in both groups. The dysphagia relief period in the irradiation stent group was significantly longer than the conventional covered stent group. This is the direct evidence supporting our main hypothesis that irradiation stent ensures longer patency.

The radiation stent group also had a very weak median survival improvement \((4.0 \text{ months in irradiation stent group versus 3.0 months in traditional stent group})\). The median survival in our series of patients was higher compared with that of 67 days in progressive and recurrent esophageal cancers reported by Sumiyoshi and colleagues \([15]\). These indicate the therapeutic advantages of the irradiation stent.

On the other hand, no complications directly related to radiation were found in the current study. Esophageal perforation or tracheoesophageal fistula occurred in 3 \((9.7\%\) patients in the irradiation stent group and 2 \((6.3\%\) patients in the traditional stent group; no significant difference was observed between the 2 groups \((p = 0.672)\). Esophageal perforation or tracheoesophageal fistula occurred in 3 \((9.7\%\) patients in the irradiation stent group and 2 \((6.3\%\) patients in the traditional stent group; no significant difference was observed in the 2 groups.
These may be due to counteract of protective effect on perforation from tumor control and the radiation damage on the esophageal wall.

Bleeding is the most important complication in our study. There are 35.5% (11 of 31) patients in the irradiation stent group who had bleeding during follow-up, and 4 (12.9%) of them died from acute massive hemorrhage at 1 month, 3 months, 3 months, and 6 months after stent placement. While there are 21.9% (7 of 32) of patients in the traditional stent group who had hemorrhage, three of them died at 1 month, 2 months, and 5 months. There is no statistically significant difference in bleeding between the patients with or without radioactive seeds (35.5% vs 21.9%, \( p = 0.232 \)).

In our series of patients, the stent loaded with \(^{125}\text{I}\) seeds was almost as safe as a conventional self-expandable covered stent in previously irradiated patients with recurrent esophageal cancer. This finding, however, must be interpreted with extreme caution because of the non-randomized nature of the study and the small number of patients in the study. A 35.5% risk of major bleeding in the radioactive stent group, compared with 21.9% in the conventional stent group is potentially a very sobering difference, particularly in light of the fact that 12.9% of the patients in the radioactive stent group experienced lethal bleeding. The bleeding incidence of the irradiation stent group (35.5%) in our study also seems higher than the 30% in advanced esophageal cancer reported by Guo and colleagues [10]. This may be related to previous radiation therapy history and the recurrent characteristic of our patients. Another reason may be the high dose rate of the \(^{125}\text{I}\) seeds loaded in the stents.

In conclusion, our study findings indicate that a radiation stent had the potential benefit of a longer dysphagia relief period in patients with recurrent esophageal cancer. However, no significant survival benefits were observed in the radiation stent group and the high incidence rate of massive hemorrhages further limited its application in patients with malignant dysphagia due to recurrent esophageal cancer.

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References


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Notice From the American Board of Thoracic Surgery

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