Self-expandable stent loaded with ^{125}I seeds: Feasibility and safety in a rabbit model

Guo Jinhe , Teng Gaojun ★, Zhu Guangyu , He Shicheng , Deng Gang , He Jie

Department of Radiology, Zhong-Da Hospital, Southeast University, 87# Dingjiaqiao Road, Nanjing 210009, China

Received 24 April 2006; received in revised form 30 September 2006; accepted 3 October 2006

【Abstract】

Objective

To evaluate technical feasibility and acute and subacute radiotolerance of a self-expandable stent loaded with ^{125}I seeds in the rabbit esophagus.

Methods

A self-expandable stent designed for esophageal application was made of 0.16mm nitinol wire and loaded with ^{125}I seeds (CIAE-6711). Twenty-seven stents with three different radioactive dosages (n = 9 in each dosage group) were implanted in the esophagus of healthy rabbits, while nine stents alone were used as controls. The stents were perorally deployed into the esophagus under fluoroscopic guidance. Radiological follow-up included plain chest film, CT scan, and barium esophagography which were undertaken in all rabbits of each group at 2, 4, and 8 weeks, respectively, which were correlated to histopathological findings. The stented esophageal segments along with their adjacent tissues were harvested for histopathological examinations.

Results

The stent was successfully deployed into the targeted esophageal segment in all rabbits. Neither ^{125}I seeds dislodged from the stent during the deployment, nor they did during the follow-up period. The greatest (16.2 Gy) absorbed dose was found in the tissue 10mm from ^{125}I seeds at 8 weeks.
Slight epithelial hyperplasia on the stent surface and submucosal inflammatory process developed at 2 weeks, which reached the peak at 8 weeks after the procedure. Significant thickness of the esophageal muscular layer was found at 8 weeks only in the groups with ^{125}I seeds. On radiologic follow-up, moderate strictures on both ends of the stents developed at 4 weeks and became severe at 8 weeks after the procedure in all groups. Conclusion: Deployment of a self-expandable stent loaded with ^{125}I seeds is technically feasible and safe within the first 8 weeks. Acute and subacute radiotolerance of the treated esophagus and its adjacent tissues by ^{125}I seeds is well preserved in a healthy rabbit model.

【Key words】 Esophagus; Stent; Irradiation; Intraluminal brachytherapy; ^{125}I seed

Introduction

Although the prognosis of surgical resection for esophageal cancer has been improved, the majority of such patients are nonsurgical candidates and have to undergo palliative treatments because of late stage cancer or metastasis [1,2]. The esophageal stenting has become the treatment of choice for esophageal strictures with inoperable esophageal cancer in many institutes [3–5]. However, recurrence of neoplastic stricture remains a challenge after a tent implacement alone in such patients. The effectiveness of brachytherapy with interstitial implantation of ^{125}I seeds has been recently used in various malignant tumors including prostate cancer, malignant gliomas, liver metastases, etc. [6–9]. Promising results was also reported recently with interstitial brachytherapy using ^{125}I seeds via surgical implantation for palliative management of malignant esophageal stricture [10]. Therefore, it may hold advantages of both mechanical and irradiating approaches to simultaneously maintain lumen patency mechanically and cure tumor by using a self–expanding stent attached ^{125}I seeds. The purpose of this study was to explore a technical feasibility and safety with an esophageal stent loaded with ^{125}I seeds in a healthy rabbit model.

Materials and methods

2.1. Development of radioactive stent

The self-expandable esophageal stent (15mm in length and10mm in diameter) was made of 0.16mm nitinol wire (Fig. 1,Nanjing MicroInvasive Medical Inco., Nanjing, China). Two plastic sheathes (4.8mm×0.8 mm) were attached to the outer surface of the middle portion of the stent, containing ^{125}I radioactive seeds (Chinese Atomic Energy Science Institution, Beijing). The ^{125}I seed had a half-life of 59.6 days, being possessed of energies of 27.4–31.5 meV with X-ray and 35.5 meV with -ray. The initial dose rate was 7.7 cGY/h with effective irradiating distance of 20 mm. The seeds were loaded into the sheathes immediately before the stents were implanted.

2.2. Animal experiment

The protocol was approved by the Institutional Animal Care and Use Committee in our institute. A total of 36 healthy rabbits weighing 2.0–3.2 kg with an average of 2.5±0.8 kg were randomly assigned to one of four groups (n = 9 in each group): Group A receiving a stent loaded with 0.3 mCi/^{125}I seed, Group B receiving a stent loaded with 0.6 mCi/seed, Group C treated a stent with 0.9 mCi/seed, and Group D treated with a stent alone. There were three rabbits separately at every experimental endpoint of 2, 4, and 8 weeks in each group.

All rabbits were anaesthetized with intraperitoneal injections of 40 mg/kg Phenobarbitol (Shanghai Chemical Reagent Co., Shanghai) and were then placed on an operating table of a portable C-arm unit (Stenoscope 900, GE Healthcare). Barium esophagography was undertaken before stent implantation in each animal. The stent was deployed perorally into the midto low-esophagus where the proximal end of stent leveled with the tracheal carina. After stent implantation, the rabbits were fed with granule diets instead of long-fiber diets to avoid potential intra-stent obstruction that could cause stent migration and even death. During the follow-up, a plain chest radiography, CT scan (High speed CT/i, GE) and barium esophagography were performed in all rabbits of each group at 2, 4, and 8 weeks, respectively, which were correlated to histopathological findings. The animals were euthanized by injection of 10 ml air through the auricular vein immediately after the follow-up study.

The stented esophageal segments along with the adjacent tissues including the lungs, bronchus, and thoracic descending aorta were harvested for pathological examination. The harvested tissues were obtained including a radius of 20mm from the radioactive seeds and the esophageal segments 20mmabove and below the stents. The lumen diameter of the stent and the thickness of the esophageal wall near the seeds were measured. After removal of the stent wire, the esophagus and the adjacent tissues were resected en bloc and immediately fixed in a 4% formaldehyde solution. The specimens were evaluated under a light microscope with hematoxylin and eosin stain. Electronic microscopic examination (H-600, Hitachi)was carried out with fixed, embedded, ultra-sliced, and lead–uranium double stained.

2.3. Radiation dosimetry

Since ^{125}I emits -ray, the following equation was adopted for the measurement of absorbed dose [11–13]. Dγ = 34.6 Δ∑Δi-iC0Teff[1 − e-(0.693/Teff)t]. In the equation, Δi represents balance absorbed dose constant; i represents fraction of energy absorbed in the target which is 0.219 of ^{125}I; C0 is the radiation dosage in the tissue when t=0Ci/g, namely the activity of single ^{125}I seed divided by the mass; and Teff is the physical half-life of ^{125}I (59.4 days).

2.4. Statistical analysis

F test and LSD-t test were used to determine statistical significance of the differences in the intra-stent diameter and the esophageal thickness among the groups. An equal to or less than 0.05 of P value was considered as a statistical significance. Statistical analyses were performed by using statistical software package SPSS 10.5 (SPSS Inc., Chicago, IL).

Results

The stent was successfully implanted into the targeted esophageal segment in all rabbits. None of these ^{125}I seeds was dislodged from the stents during stent deployments.

Stent migration to the distal esophagus ≤10mm was observed in three rabbits at the 2-week follow-up. However, no seed dislodgement from the sheath was found on chest film during 8-week follow-up (Fig. 2). CT scan demonstrated that the adjacent lungs, bronchus and thoracic aorta were within a radius of 2 cm from the seeds.

Barium esophagography showed a slight in-stent stenosis at 2-week follow-up in all groups. The stenosis became severe over the time and reached peak especially at the edges of the stent between 4 and 8 weeks (Fig. 3). Neither esophageal perforation nor fistulas was detected by barium esophagography during the follow-up.

3.1. Histological results

3.1.1. Macroscopic findings

Two weeks after the implantation, the esophagus and its adjacent tissues including the lungs, aorta, and bronchus appeared to be normal in color without the evidence of exudation, hemorrhage and necrosis in all rabbits. Slight epithelial proliferation on the inner surface of the stents presented in all groups, but stents were still readily separated from the esophagus. No visible intra-stent stricture of the esophagus was observed.

The macroscopic findings of the esophageal specimens at 8 weeks were similar to those observed at 4 weeks after the implantation, but the intra-stent proliferation and esophagus stricture were more significant. Comparisons of the intra-stent diameter and the thickness of

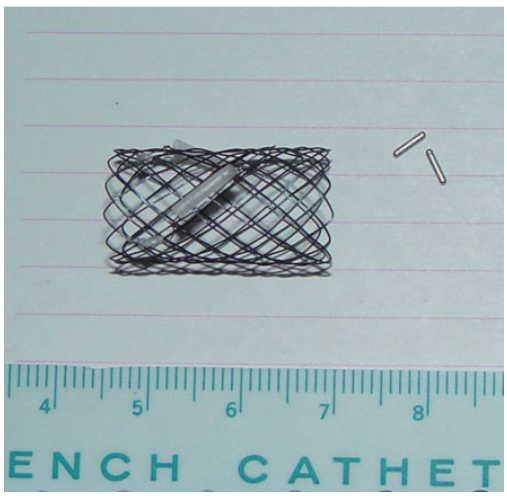

Fig. 1. The bare self-expandable esophageal stent made of 0.16mm nickel–titanium alloy wire in diameter, with 15mm long and 10mm in diameter. Two plastic sheathes as the holder of each ^{125}I seed which was fixed on the out of the stent systemically (arrows). ^{125}I seeds (CIAE-6711) were fixed in a 4.8mm×0.8mm (long×diameter) cylinder alloy container (arrowheads).

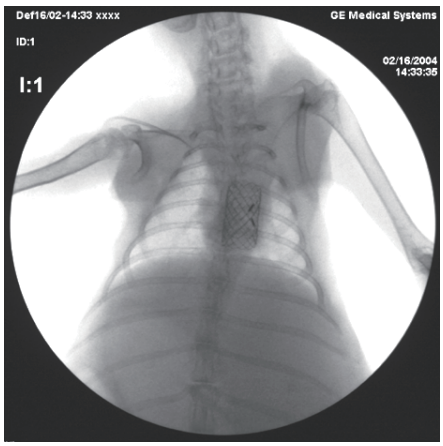

Fig. 2. Chest film showed same location of the stent as the immediately after implantation of the stent at the follow-up of the 8 weeks, with good opacification of the seeds (arrows).

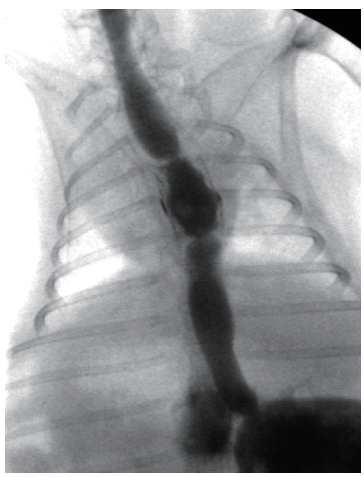

Fig. 3. Barium esophagography at the 8 weeks showed more apparent in-stent stenosis (arrowheads), accompanying with severe stricture at the ends of the stent. Two ^{125}I seeds were seen at the middle of the stent (arrows).

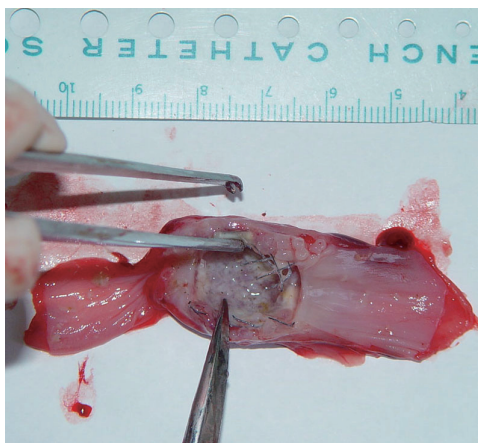

Fig. 4. Hyperplastic proliferation covered the surface of the stent, and the stent was difficult to be dissected from esophagus during the autopsy at 4 weeks after procedure.

No positive pathological appearances in the lungs, bronchus and thoracic aorta were demonstrated in all specimens. The radioactive seed sheaths appeared to be intact without any rusty or distortion at all cases.

esophageal wall in each group at 2, 4 and 8 weeks were shown in Table 1. The stents were widely covered by the hyperplastic tissue and were difficult to be separated from the esophagus in all groups (Fig. 4). The whole esophageal wall showed a moderate to severe thickening. There was scattered local necrosis on the inner surface of the stented esophagus, but neither esophageal perforation nor fistulae

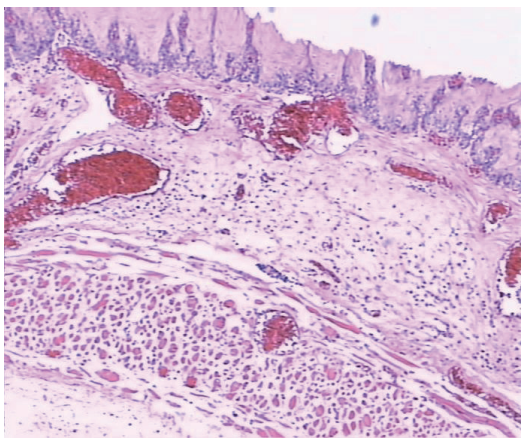

Fig. 5. Subepithelial and submucosal capillary dilatation and congestion were revealed, which were only seen in the experiment groups at 2 weeks (arrows) (HE stain, 100×).

was found.

3.2. Microscopic observation

Inflammatory response characterized with submucosal infiltration of eosinophilic granulocytes and fibroblasts in the stented esophagus was demonstrated at 2 weeks in all groups. Localized erosion under the stent wire was

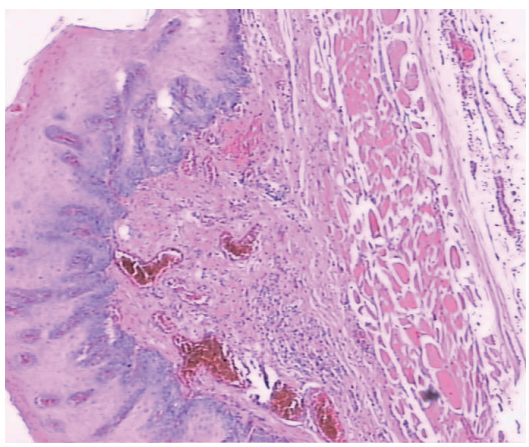

Fig. 6. Proliferation of subepithelial submucosal fibrous tissue, and granulation tissue was the feature in the experimental groups at 4 weeks (arrows), but the muscular layer kept intact (arrowheads) (HE stain, 100×).

detected in all groups. Subepithelial and submucosal capillary dilatation and congestion were only found in the groups with ^{125}I (Fig. 5).At 4 and 8 weeks, it was featured with proliferation of subepithelial/submucosal fibrosis and granulation tissues in this period (Fig. 6). Subepithelial/ submucosal capillary dilatation and congestion were improved in this period. The muscular layer remained intact at 4 weeks, but the increased thickness of the muscular layer was seen at 8 weeks (Fig. 7). The adjacent lungs, trachea and thoracic aorta appeared to be normal microscopically in all groups through the follow-up period. Under electronic microscope, the nucleus, desmosome and tonofilament of epithelia cell in the stented segments of the esophagus showed normal.

The diminished and scaled off microvilli of the type II alveolar epithelial cells, the spaced loose lamellate

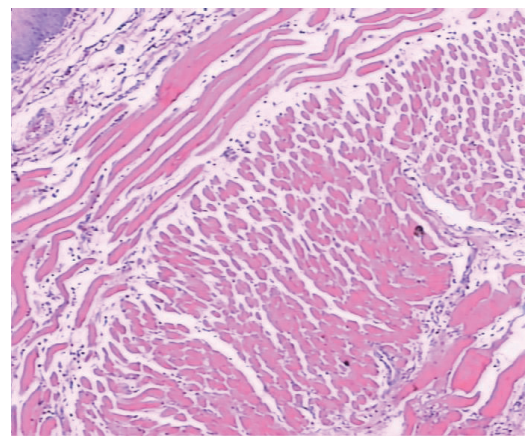

Fig. 7. Subepithelial and submucosal capillary dilation and congestion disappeared, and the muscular layer proliferated greatly in a experimental Group C (arrows), which were not observed in the control group (HE stain, 100×).

bodies, and diminished mitochondria were seen the Group B (0.6 mCi) and Group C (0.9 mCi) at 8 weeks (Fig. 8). The endothelial cells of the visa vasorum supplying thoracic aorta swelled but the basilemma remained intact.

3.3. Radiation dosimetry

The absorbed radioactive dosages of the tissues adjacent to the esophagus at a distance of 10 and 20mmfrom ^{125}I seeds were summarized in Figs. 9 and 10. The largest absorbed dosage was found at 8 weeks, indicating 16.2 and 2.02 Gy at a distance of 10 and 20mm from ^{125}I seeds, respectively.

Discussion

Intraluminal brachytherapy using ^{60}Co and ^{192}Ir has been established as a standard care for patients with esophageal cancer. Tolerance for these radioisotopes on esophagus and its adjacent tissues have been extensively investigated [2,13–15]. As for interstitial brachytherapy, ^{125}I seeds are the most frequently used in the treatment of prostate cancer, malignant gliomas, and liver metastases without significant complications associated with irradiation [6–9]. However, it is not comparable in dosimetry involved intraluminal brachytherapy using ^{60}Co and ^{192}Ir or interstitial brachytherapy using ^{125}I seeds to the technique here using a stent impregnated with ^{125}I seeds due to their differentways of placement of the radioactive source. Therefore, it is important to know its biological tolerance before a clinical application. To our best knowledge, it has not been reported in literature to use a ^{125}I seeds loaded metal stent in the esophageal application.

Although ^{125}I seeds have been proven to be safe on several malignancies such as prostate cancer, it does not seem to be applicable for esophageal application because of its tubular structure that makes retaining an isotope seed difficult if not impossible. However, radiation risks in the esophagus have been reported after intracavitary and external-beam radiotherapy [16]. Such a radiotherapy could cause a variety of pathological changes in the treated esophagus including epithelial denudation, mucosal erosion, shallowulceration, granulation, and fibrosis. Recently, ±-ray emitter of ^{166}Ho was used by impregnating it into a polyurethane membrane of a covered esophageal stent [17]. In the animal study with different radioactive doses in a healthy canine model, the use of 194–383 Gy caused esophageal strictures accompanied with mucosal ulceration, while a dose of 23–90 Gy resulted in only mild to moderate histological changes such as glandular atrophy, submucosal inflammation, and submucosal fibrosis. Compared to the pathological changes in that study [17], a less extent of mucosal ulceration and more significant esophageal stricture at the edges of the stent occurred in our series. These differences in pathological changes might reflect different physical properties of the emitter sources used in the experiments: a -ray can travel through the tissues at longer distance than a ±-ray. As an ideal radioactive source for esophageal brachytherapy, its penetration capability should be sufficient to reach the neoplastic tissues in the esophageal walls. ^{125}I with

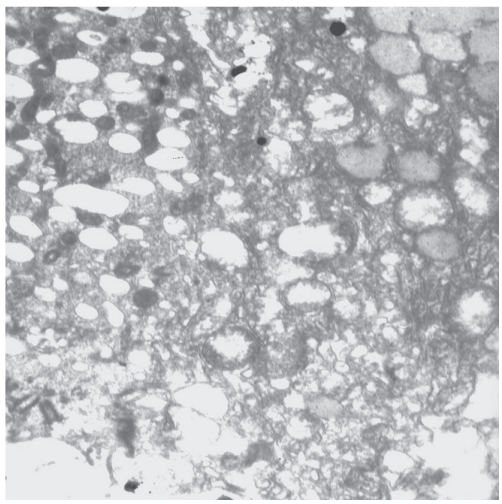

Fig. 8. Cilia on the surface of tracheal mucosa were showed scaled and sparse. Vacuolated mitochondria were noted at 8 weeks in the Group C (0.9 mCi) (1200×).

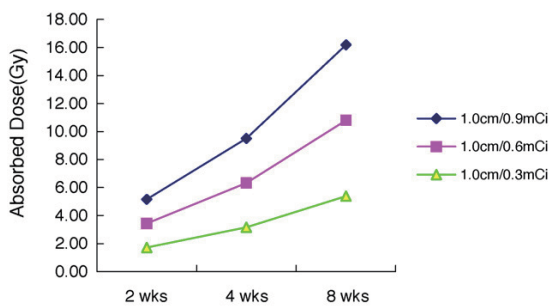

Fig. 9. Graph of accumulative absorbed dose of the tissues adjacent to esophagus at 10mm from the ^{125}I seeds in 2–8 weeks among the different groups.

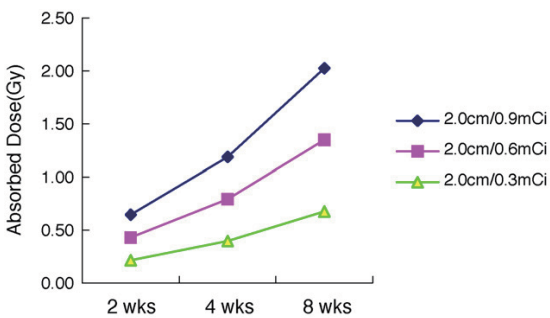

Fig. 10. Graph of accumulative absorbed dose of the tissues adjacent to esophagus at 20mm from the ^{125}I seeds in 2–8 weeks among the different groups.

penetration depth from 15 to 20mm appears to be desirable source compared to the maximum depth of 8.7mm (average 2.2 mm) with 166Ho reported by others [17]. However, it raises concern over the risks of radiation injuries on the adjacent esophagus and other organs. The results of this study in an animal model indicate that the placement of a metal esophageal stent loaded with ^{125}I causes little tissue damages associated with radiation in the adjacent organs. Focal shallow ulcerations were observed in the esophageal mucosa where the stent wires set against. These changes were found in both the control group and the groups with ^{125}I seeds, therefore, unlikely to be associated with the use of ^{125}I seeds. These ulcerations are probably attributed to the ischemic changes resulting from compressio by the stent wires. However, significant esophageal stricture at the edges of stents was revealed in all groups with ^{125}I seeds at 4 and 8 weeks. It appeared to be associated with the use of radioactive agent, since there is the lack of the finding in the control group. The finding seems to be similar to "candy wrapping" phenomenon in vascular application of brachytherapy. In addition, proliferative responses of the muscular layer of the esophagus were found only in Group B (0.6 mCi/seed) and Group C (0.9 mCi/seed) at 8 weeks after the implantation. Minimal injuries in the adjacent tissues such the lungs and aorta were noted under electronic microscope in these groups with ^{125}I seeds. Different dosimetric properties with various isotopes and irradiation techniques may result in diverse types of tissue reaction [18–20]. The use of ^{125}I has several advantages over other - or ±-emitting isotopes in esophageal application. ^{125}I seed has an effective emitting radius of 15–20 mm, which is an ideal for the penetrating esophageal neoplasm as it is usually surrounding a narrowing esophageal lumen. The half-life of 60 days of ^{125}I provides an optimal period for continuous irradiation treatment.

For the sake of safety, ^{125}I seeds should be encapsulated in a titanium alloy sealed apparatus and the plastic chambers are mounted on the strut of the stent, holding only one seed in each chamber. This design has three advantages: (1) easy to fill seeds in, which consequently reduced the radiation exposure to the operators and (2) easy to release the stent, and (3) preventing dislodgement or migration of the seed sheath during and after placement.

There are several limitations of this study. Firstly, only two radioactive seeds were attached to the stent whereas the stent itself covers a much larger area, which results in a poor dose homogenity. Furthermore it may have been difficult to attach the seeds in exactly the same place on each of the stents. So the dose distribution in the esophagus may have been different for each rabbit. Secondarily, since the animal was sacrifice at 8 weeks due to the high late mortality happened, only acute and subacute radiation effects on the esophagus and its adjacent organs were evaluated. However, most humans with inoperable esophageal cancer live beyond 8 weeks. The long-term effects on tissues with this device need to be answered before a clinical application. In addition, the esophageal stent used in this study is not as same as in humans. In order to reduce the delivery sheath of the stent, bare esophageal stent is used here. However, it is common to use a covered esophageal stent for malignant stricture.

In conclusion, it is technically feasible and safe within the first 8 weeks to place an esophageal stent with ^{125}I seeds as an adjunct therapy. The device proves to be mechanically stable and biologically tolerable by the recipients. Efficacy of the device on esophageal neoplasm and optimal dosimetry of ^{125}I in human warrant further investigation.

The authors thank Dr. Zhong Qian (New Orleans) and Dr. Ho-Young Song (Seoul, Korea) for their revision and valuable comments on this article.

References

1. Stein HJ, Siewert JR. Improved prognosis of resected esophageal cancer. World J Surg 2004;28:520–5.

2.Churn M, Jones B, Myint AS. Radical radiotherapy incorporating a brachytherapy boost for the treatment of carcinoma of the thoracic esophagus: results from a cohort of patients and review of the literature. Clin Oncol 2002;14:117–22.

3. Song HY, Do YS, Han YM, et al. Covered, expandable esophageal metallic stent tubes: experiences in 119 patients. Radiology 1994;193:689–95.

4. Christie NA, Buenaventura PO, Fernando HC, et al. Results of expandable metal stents for malignant esophageal obstruction in 100 patients: shortterm and long-term follow-up. Ann Thorac Surg 2001;71:1797–802.

5. Sabharwal T, Hamady MS, Chui S, Atkinson S, Mason R, Adam A. A randomised prospective comparison of the Flamingo Wallstent and Ultraflex stent for palliation of dysphagia associated with lower third oesophageal carcinoma. Gut 2003;52:922–6.

6. Blank LECM, Gonzalez DG, Reijke TMD, Dabhoiwala NF, Koedooder K. Brachytherapy with transperineal 125Iodine seeds for localized prostate cancer. Radiother Oncol 2000;57:307 – 13.

7. Nag S. Brachyherapy for prostate cancer: summary of American brachytherapy society recommendations. Semin Urol Oncol 2000;18:133 – 6.

8. Gaspar LE, Zamorano LJ, Shamsa F, Fontanesi J, Ezzell GE, Yakar DA. Permanent 125Iodine implants for recurrent malignant gliomas. Int J Radiat Oncol Biol Phys 1999;43:977 – 82.

9. Martinez-Monge R, Nag S, Nieroda CA, Martin EW. Iodine-125 brachytherapy in the treatment of colorectal adenocarcinoma metastatic to the liver. Cancer 1999;85:1218–25.

10. Luo KY, Mao WY, Li B, et al. Iodine-125 interstitial brachytherapy for malignant tumor. Chin J Surg 2003;41:122–4.

11. Snyder WS, Ford MR,Warner GG, Fisher HL. Estimates of absorbed fractions for monoenergetic photon sources uniformly distributed in various organs of a heterogeneous phantom. J Nucl Med 1969;3(Suppl):7–52.

12. Stabin MG, Tagesson M, Thomas SR, Ljungberg M, Strand SE. Radiation dosimetry in nuclear medicine. Appl Radiat Isotopes 1999;50:73–8.

13. Homs MYV, Eijkenboom WMH, Coen VLMA, et al. High dose rate brachytherapy for the palliation of malignant dysphagia. Radiother Oncol 2003;66:327–32.

14. Yorzon, Dokiya T, Oki Y, Suzuki T. Curative radiotherapy with high-doserate brachytherapy boost for localized esophageal carcinoma: dose-effect relationship of brachytherapy with the balloon type applicator system. Radiother Oncol 1999;51:133–9.

15. Tak VM, Naunheim KS. Current status of multimodality therapy for esophageal carcinoma. J Surg Res 2004;117:22–9.

16. Berry B, Miller RR, Luoama A, Nelems B, Hay J, FloresAD. Pathologic findings in total esophagectomy specimens after intracavitary and externalbeam radiotherapy. Cancer 1989;64:1833–7.

17. Won JH, Lee JD, Wang HJ, et al. Self-expandable covered metallic esophageal stent impregnated with beta-emitting radionuclide: an experimental study in canine esophagus. Int J Radiat Oncol Biol Phys 2002;53:1005–13.

18. Jhon M, Shroff S, Farb A, et al. Local arterial responses to 32P <?>-emitting stents. Cardiovasc Radiat Med 2001;2:143–50.

19. Amols HI. Review of endovascular brachytherapy physics for prevention of restenosis. Cardiovasc Radiat Med 1999;1:64–71.

20. Virmani R, Farb A, Carter AJ, Jones RM. Pathology of radiationinduced coronary artery disease in human and pig. Cardiovasc Radiat Med 1999;1:98–101.