

Intraluminal brachytherapy in oesophageal cancer: defining its role and introducing the technique

Sebastian Lettmaier, MD, Vratislav Strnad, MD, Prof.

Department of Radiation Oncology, University Hospital Erlangen, Erlangen, Germany

Abstract

Intraluminal brachytherapy plays an important role in the treatment of oesophageal tumours. This article aims to define this role in the curative as well as in the palliative treatment settings drawing on data from the literature, and also emphasizing its potential for harm when used inexpertly. It also provides a short introduction to practical aspects of the treatment procedure and treatment planning.

J Contemp Brachytherapy 2014; 6, 2: 236–241

DOI: 10.5114/jcb.2014.43780

Key words: brachytherapy, curative, oesophageal cancer, palliative, technique.

Purpose

Oesophageal cancer continues to pose a major challenge to the treating physician, and the overall prognosis is poor except for the earliest stages of this disease [1]. Radiotherapy has traditionally played a major role, both as an adjunct as well as an alternative to surgical approaches, but is hampered by the fact that despite the inherent radiosensitivity of these tumours, locally curative doses are difficult to achieve, because of the close proximity of the target volume to vital organs such as the lungs, the heart, and the spinal cord [2,3]. Unsurprisingly therefore, local failure is frequently observed as a result of relative underdosage of the primary tumour site. This has only partially been mitigated by the introduction of treatment regimens incorporating concomitant chemotherapy, designed to differentially enhance radiosensitivity of the tumour tissue [4]. Intraluminal brachytherapy offers an elegant way of delivering high doses to the oesophageal wall with great spatial precision, while avoiding the need to traverse organs-at-risk as would be the case with percutaneous modes of dose delivery. Combined with the ease of access provided by endoscopic procedures, this has led to intraluminal brachytherapy becoming established as an integral part of radiotherapy treatment schedules both in the curative as well as in the palliative treatment settings.

Brachytherapy in the curative setting

In the curative setting, intraluminal brachytherapy has been used both as a sole treatment and as a boost following external beam radiotherapy. There is limited data on its use as sole treatment, and from the data available

it must be assumed that it is only for the earliest disease stages that brachytherapy on its own may offer a realistic chance of a permanent cure, so its use in this setting must be regarded as experimental [5]. The main use of brachytherapy in the curative setting is in the context of definitive treatment schedules as boost following external beam radiotherapy, taking advantage of its capability to deliver high doses to the primary tumour, while effectively sparing the surrounding normal tissues. The use of brachytherapy as boost has been evaluated in a number of clinical trials providing data on feasibility, tumour control, and associated toxicities. Table 1 gives an overview of selected clinical series [6–10].

Okawa *et al.* in 1999 found intraluminal brachytherapy to be superior to external beam radiotherapy when used as boost in a subgroup of patients with small tumours less than 5 cm in length. Patients had been randomly assigned to undergo intraluminal brachytherapy or external beam radiotherapy to deliver a 10 Gy boost to their primary tumour, following a course of external beam radiotherapy up to a total dose of 60 Gy. Tumour-specific survival at 5 years was more than doubled at 64% in the experimental arm as opposed to 31.5% in the control arm ($p = 0.025$). A very similar effect was seen in patients with early stage tumours (T-stages 1 and 2). Of note, these improvements in survival were not accompanied by an increase in treatment-related toxicity [9].

Despite this, it is important to appreciate that dose escalation by means of intraluminal brachytherapy may hold a significant potential for both acute and late toxicity. Clinical data to guide safe practice are owed in large part to Gaspar *et al.* who in the year 2000 reported a very high incidence of fistula formation, following an intra-

Address for correspondence: Sebastian Lettmaier, MD, Universitätsstraße 21-23, 91054 Erlangen, Germany, Department of Radiation Oncology University Hospital Erlangen, Erlangen, Germany, phone: +49 9131 8533419 (office), fax: +49 9131 85-34144, ✉ e-mail: sebastian.lettmaier@uk-erlangen.de

Received: 26.05.2014

Accepted: 10.06.2014

Published: 26.06.2014

Table 1. Selected clinical series employing brachytherapy as boost

Author	n	EBRT dose	iBT dose	Local control	Overall survival
Mujis <i>et al.</i>	62	60 Gy	12 Gy (2 fractions)	45% (3y)	11% (5y)
Murakami <i>et al.</i> (2011)	87	50-61 Gy	10 Gy (4-5 fraction)	49-75% (5y)	31-84% (5y)
Tamaki <i>et al.</i> (2011)	54	56-60 Gy	10 Gy (2 fractions) 9 Gy (3 fractions)	79% (5y)	61% (5y)
Gaspar <i>et al.</i> ; phase I/II – RTOG 9207 trial (2000)	49	50 Gy	10-15 Gy (2-3 fractions)		49% (1y)
Yorozu <i>et al.</i> (1999)	169	40-61 Gy	8-24 Gy (2-4 fractions)	40-80% (2y)	20-70% (2y)
Okawa <i>et al.</i> ; phase III trial (1999)	103	60 Gy	10 Gy (2 fractions)		20% (5y)
Kumar <i>et al.</i> (1993)	75	40-55 Gy	8-10 Gy 10-12 Gy 12-15 Gy	38% (1y)	39% (1y)

EBRT – external beam radiotherapy, iBT – intraluminal brachytherapy

luminal brachytherapy boost in 49 patients undergoing radiochemotherapy for oesophageal cancer. In their patients, a HDR brachytherapy boost was delivered at doses of 10 to 15 Gy in fractions of 5 Gy, following external beam radiotherapy up to a total dose of 50 Gy. They were able to show that the development of fistulas was strongly associated with a higher boost dose (15 Gy), a smaller applicator diameter (0.6 cm), as well as with chemotherapy being applied concomitantly with the brachytherapy boost [6].

Based on the clinical data available, the ABS has drawn up a set of guidelines to help in the selection of patients who are likely to benefit from an intraluminal brachytherapy boost [11]. These are summarized in Table 2.

Table 2. Guidance on patient selection and clinical implementation of intraluminal brachytherapy as boost with curative intent (modified from recommendations of American Brachytherapy Society)

Indications curative
Unifocal thoracic adeno- or squamous cancers
Maximum length 10 cm
No evidence of intra-abdominal or metastatic disease
Contraindications
Tracheal or bronchial involvement
Cervical esophagus location
Stenosis that cannot be bypassed
Guiding principles
Applicator should have an external diameter of ≥ 10 mm
Avoid giving chemotherapy concurrently
Brachytherapy should follow external beam radiation therapy
Dose recommendations (3-4 weeks after 50-60 Gy EBRT)
HDR 10-12 Gy in two weekly fractions of 5-6 Gy each

HDR – high dose rate brachytherapy

Brachytherapy in the palliative setting

There is now a robust pool of clinical data to support the use of intraluminal brachytherapy in the symptomatic treatment of patients with advanced incurable oesophageal cancer. Table 3 gives an overview of some of the largest trials that have been performed [12-15]. The main advantage of brachytherapy seems to lie in its ability to provide for a more lasting control of tumour-related symptoms than would be possible by other means such as stent insertion or argon plasma coagulation. Its advantage over external beam radiotherapy in this setting is obviously due to its ability to safely deliver large doses of radiation with great spatial precision, making for a rapid tumour response while shortening treatment time and sparing surrounding organs-at-risk, thus minimizing unwanted effects. Two large randomized trials comparing intraluminal brachytherapy with stent insertion have shown more lasting effects on health-related quality of life, and dysphagia scores in patients treated with brachytherapy with a significantly lower overall complication rate in the brachytherapy arm in comparison to sole stent implantation [12,15].

Palliative brachytherapy with or without stent implantation should therefore always be considered in all patients with a life expectancy exceeding 3 months. Stent insertion as sole treatment may be reserved for patients with an extremely short life expectancy, where the immediacy of symptomatic relief offered by this procedure clearly dominates. A summary of indications and dose recommendations for brachytherapy administered in the palliative setting is given in Table 4 [11].

Technique

Nowadays, intraluminal brachytherapy of the oesophagus is usually administered using HDR brachytherapy. Under sedation, the endoscopy is performed to visualize the tumour, and the proximal and distal borders of the tumour are marked with metal clips (Fig. 1). If there is marked stenosis, a dilation procedure should be performed to allow insertion of an applicator of sufficient diameter (≥ 10 mm). If this cannot be achieved in a single

Table 3. Selected clinical series employing brachytherapy as palliative treatment

Author	n	Compared with	iBT dose
Rosenblatt <i>et al.</i> (2010)	219	± EBRT (30 Gy in 10 fractions)	16 Gy (2 fractions)
Rupinski <i>et al.</i> , randomized trial (2011)	87	Photodynamic therapy	12 Gy (1 fraction)
Bergquist <i>et al.</i> , randomized trial (2005)	65	Stent	21 Gy (3 fractions)
Homs <i>et al.</i> , randomized trial (2004)	209	Stent	12 Gy (1 fraction)

iBT – intraluminal brachytherapy

session, the brachytherapy should not be attempted and the patient should be scheduled for a second appointment. Once insertion of an appropriately sized applicator seems practical, the endoscope is removed leaving a guide wire in situ. The applicator is then inserted into the oesophagus over the guide wire, and under fluoroscopy, the radiopaque marker ring at its distal end is made to overlie the metal clip marking the distal border of the tumour. With the applicator position thus defined, it is then secured at the level of the patient's mouth with the help of a bite block to prevent any further shifts in position that would adversely affect the treatment (Fig. 2). Under sedation, the patient is then transferred to the CT scanner with the applicator in situ. Once the CT-based planning process has been completed, the patient is transferred to the treatment room. The source carrying tube is then inserted into the applicator and also secured to avoid displacement. Finally, the afterloading machine is connected by means of transfer tubes and the brachytherapy treatment is performed (Fig. 3).

Treatment planning

We recommend to perform 3D CT-based treatment planning for all patients. This has distinct advantages over applicator-based approaches, where the craniocaudal dimension of the target is the only degree of freedom available to the planner, leading to the generation of a uniform cylinder-shaped target volume that does not take into account individual anatomical relations. Figure 4 illustrates this straightforward technique, where the reference iso-



Fig. 1. Sedated patient undergoing endoscopy to visualize intraluminal tumour extension

Table 4. Guidance on patient selection and dose recommendations for intraluminal brachytherapy as palliative treatment (modified from recommendations of American Brachytherapy Society)

Indications palliative
Unresectable local disease progression/recurrence after definitive radiation treatment
Adeno- or squamous cancers of the thoracic esophagus with distant metastases
Stenosis
Dysphagia
Tumour haemorrhage
Alternative to stent placement
Dose recommendations
HDR 7-28 Gy in fractions of 5-7 Gy

dose is usually placed at 5 mm tissue depth and a 2 cm longitudinal safety, where margin beyond the macroscopic tumour boundaries is added to account for microscopic tumour extension, and the spatial inaccuracy of the applicator position. In CT-based treatment planning,



Fig. 2. Applicator being introduced into the oesophagus and secured at the mouth with a bite block



Fig. 3. Patient with applicator connected to the afterloading machine in the HDR treatment room ready to start treatment

the CTV as well as organs at risk are contoured, and consequently the dose constraints for OARs, D_{90} , and V_{100} for the CTV can be analysed and respected. An example is given in Figure 5. This allows for variation of the shape and size of the reference isodose in all directions, which is particularly useful in larger tumours extending beyond the oesophageal wall, improving tumour coverage, while

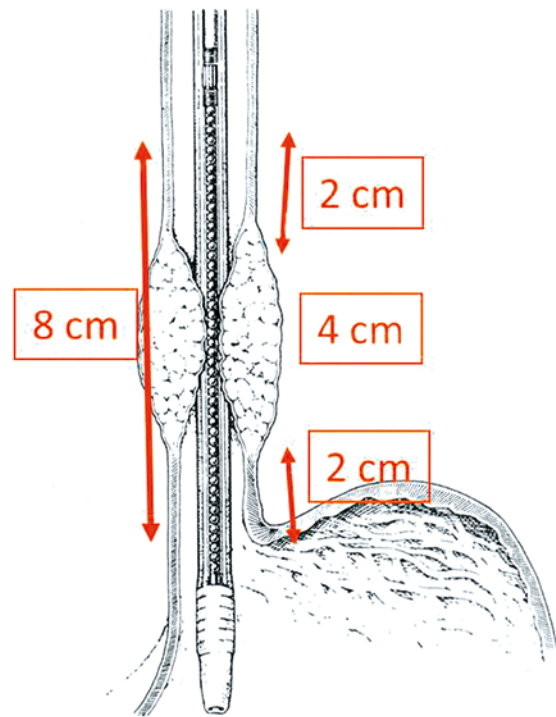


Fig. 4. Diagram showing definition of the target volume using the applicator-based approach to treatment planning

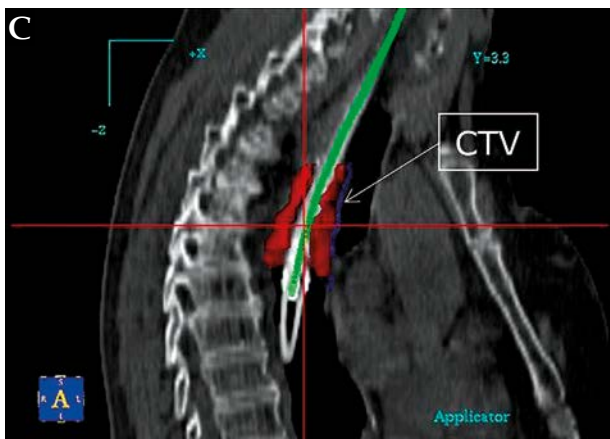
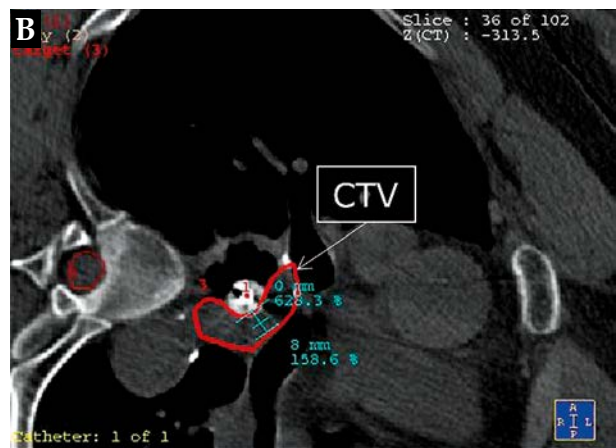
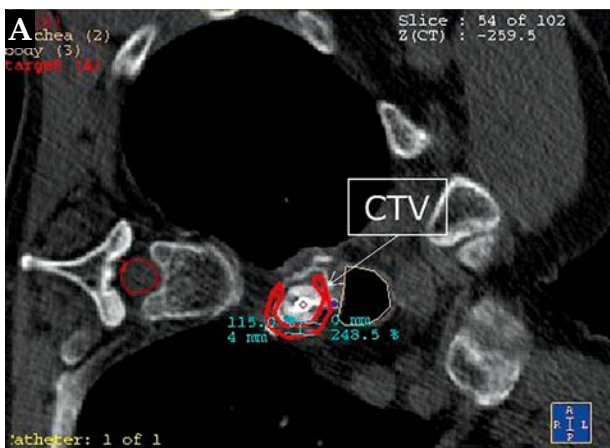


Fig. 5. Planning CT scan with applicator in situ showing anatomical relations and contours of the CTV

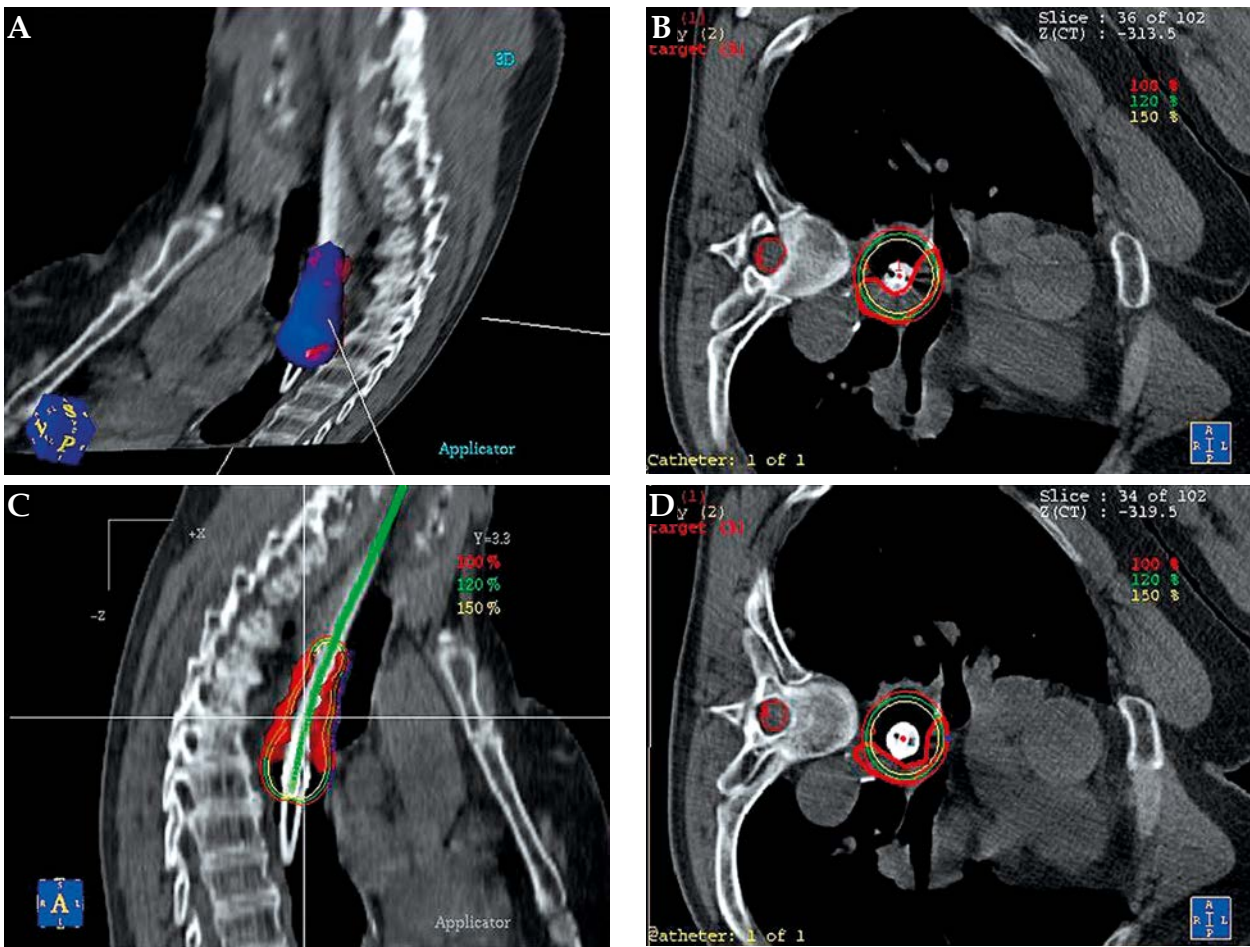


Fig. 6. Treatment plan showing high conformity of isodose lines to the CTV with good sparing of adjacent normal tissues

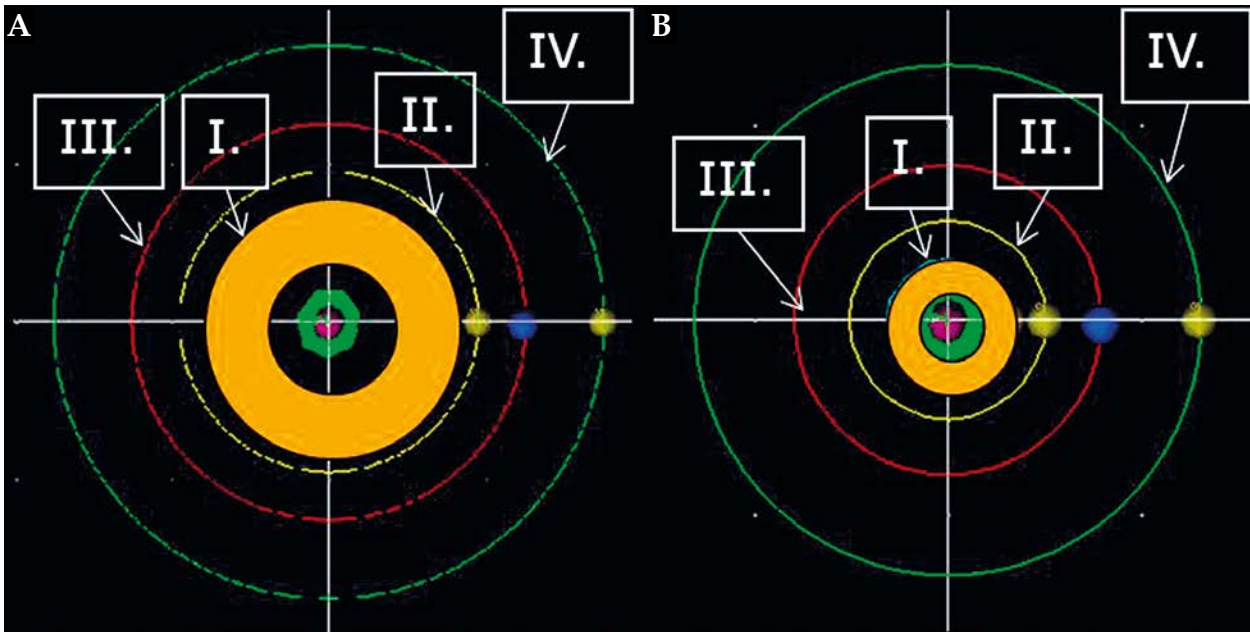


Fig. 7. Dose distribution in relation to applicator diameter. A) Diameter 15 mm. Isodoses I – surface of applicator 175% (8.75 Gy), II – 3 mm 136% (6.8 Gy), III – 5 mm 100% (5.0 Gy), IV – 10 mm 68% (3.4 Gy). B) Diameter 6 mm. Isodoses I – surface of applicator 265% (13.25 Gy), II – 3 mm 160% (8.0 Gy), III – 5 mm 100% (5.0 Gy), IV – 10 mm 58% (2.9 Gy)

at the same time sparing the adjacent organs-at-risk (Fig. 6). The crucial effect of applicator diameter on the dose distribution is shown in Figure 7. This provides a dosimetric explanation for the clinical observation that smaller applicator diameters are associated with a higher risk of serious side effects such as the development of fistulas. For a given reference dose specified in relation to the applicator surface in the case of the smaller applicator, the dose gradient will be steeper, leading to higher doses at the oesophageal mucosa that touches the surface and lower doses in the oesophageal wall beyond the reference isodose. This highlights once more the need to use applicators of sufficient size.

Summary

In experienced hands, brachytherapy offers an elegant way to safely deliver relatively large doses of radiation to tumours in the oesophagus with minimal exposure of adjacent organs-at-risk. In the curative setting, this may be used to escalate the dose absorbed by the tumour tissue to improve local control and to increase the number of patients who will achieve a definitive cure. In the palliative setting, a relatively small number of treatment sessions can offer sustained symptomatic relief with minimal side effects, which makes brachytherapy the treatment of choice in patients with a life expectancy greater than 3 months.

3D CT-based treatment planning offers all the advantages of an individualized treatment to achieve the optimum therapeutic index, and allows one to derive DVH parameters for the target as well as the relevant organs-at-risk, which play a crucial role in quality assurance.

Nevertheless, it is important to realize that this treatment modality also holds the potential for devastating side effects, and to be carried out safely requires input from an experienced multidisciplinary team made up of a radiation oncologist, a physician as well as medical physicists and radiographers. Also, there is a need for high quality clinical data to better define dose schedules both in the palliative and the curative settings. For example, there is still, no clear treatment standard to optimally weight the relative dose contributions of intraluminal brachytherapy and external beam radiotherapy in the setting of definitive treatments. A sufficiently high powered trial to address this question is seriously needed.

Conclusions

Intraluminal brachytherapy should always be considered as a treatment option in patients suffering from oesophageal cancer. However, the demands it makes on the team delivering the treatment should limit its use to centres of excellence where sufficient clinical experience has accumulated to allow its safe application. In order to better define dose schedules, more clinical trials are needed.

Disclosure

Authors report no conflict of interest.

References

1. Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol* 2013; 19: 5598-5606.
2. Sykes AJ, Burt PA, Slevin NJ et al. Radical radiotherapy for carcinoma of the oesophagus: an effective alternative to surgery. *Radiother Oncol* 1998; 48: 15-21.
3. Gignoux M, Roussel A, Paillot B et al. The value of preoperative radiotherapy in esophageal cancer: results of a study of the E.O.R.T.C. *World J Surg* 1987; 11: 426-432.
4. Fietkau R. Definitive and neoadjuvant radiochemotherapy of squamous cell carcinoma of the oesophagus. *Onkologie* 2004; 27: 39-44.
5. Liu H, Wang Q, Jia X et al. Early-stage esophageal squamous cell carcinoma treated with californium-252 neutron brachytherapy: clinical report on 16 cases. *Tumori* 2013; 99: 172-175.
6. Gaspar LE, Winter K, Kocha WI et al. A phase I/II study of external beam radiation, brachytherapy, and concurrent chemotherapy for patients with localized carcinoma of the esophagus (Radiation Therapy Oncology Group Study 9207): final report. *Cancer* 2000; 88: 988-995.
7. Kumar MU, Swamy K, Supe SS et al. Influence of intraluminal brachytherapy dose on complications in the treatment of esophageal cancer. *Int J Radiat Oncol Biol Phys* 1993; 27: 1069-1072.
8. Murakami Y, Nagata Y, Nishibuchi I et al. Long-term outcomes of intraluminal brachytherapy in combination with external beam radiotherapy for superficial esophageal cancer. *Int J Clin Oncol* 2012; 17: 263-271.
9. Okawa T, Dokiya T, Nishio M et al. Multi-institutional randomized trial of external radiotherapy with and without intraluminal brachytherapy for esophageal cancer in Japan. Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group. *Int J Radiat Oncol Biol Phys* 1999; 45: 623-628.
10. Tamaki T, Ishikawa H, Takahashi T et al. Comparison of efficacy and safety of low-dose-rate vs. high-dose-rate intraluminal brachytherapy boost in patients with superficial esophageal cancer. *Brachytherapy* 2012; 11: 130-136.
11. Gaspar LE, Nag S, Herskovic A et al. American Brachytherapy Society (ABS) consensus guidelines for brachytherapy of esophageal cancer. Clinical Research Committee, American Brachytherapy Society, Philadelphia, PA. *Int J Radiat Oncol Biol Phys* 1997; 38: 127-132.
12. Homs MY, Steyerberg EW, Eijkenboom WM et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. *Lancet* 2004; 364: 1497-1504.
13. Rosenblatt E, Jones G, Sur RK et al. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: a prospective multi-centre randomized trial of the International Atomic Energy Agency. *Radiother Oncol* 2010; 97: 488-494.
14. Rupinski M, Zagorowicz E, Regula J et al. Randomized comparison of three palliative regimens including brachytherapy, photodynamic therapy, and APC in patients with malignant dysphagia (CONSORT 1a) (Revised II). *Am J Gastroenterol* 2011; 106: 1612-1620.
15. Bergquist H, Wenger U, Johnsson E et al. Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. *Dis Esophagus* 2005; 18: 131-139.