2 Mcneill RS. Effect of a β-adrenergic-blocking agent, propranolol, on asthmatics. *Lancet* 1964; 2: 1101–1102.
3 Callaerts-Vegh Z, Evans KL, Dudekula N, *et al.* Effects of acute and chronic administration of β-adrenoceptor ligands on airway function in a murine model of asthma. *Proc Natl Acad Sci USA* 2004; 101: 4948–4953.
4 Lin R, Peng H, Nguyen LP, *et al.* Changes in β_2-adrenoceptor and other signaling proteins produced by chronic administration of ''β-blockers'' in a murine asthma model. *Pulm Pharmacol Ther* 2008; 21: 115–124.
5 Nguyen LP, Omoluabi O, Parra S, *et al.* Chronic exposure to beta-blockers attenuates inflammation and mucin content in a murine asthma model. *Am J Respir Cell Mol Biol* 2008; 38: 256–262.
6 Nguyen LP, Lin R, Parra S, *et al.* β_2-adrenoceptor signaling is required for the development of an asthma phenotype in a murine model. *Proc Natl Acad Sci USA* 2009; 106: 2435–2440.
7 Hanania NA, Singh S, El-Wali R, *et al.* The safety and effects of the β-blocker, nadolol, in mild asthma: an open-label pilot study. *Pulm Pharmacol Ther* 2008; 21: 134–141.
8 Lipworth BJ, Williamson PA. β blockers for asthma: a double-edged sword. *Lancet* 2009; 373: 104–105.
9 Lima DR, Turner P. Propranolol increases reduced β-receptor function in severely anxious patients. *Lancet* 1983; 2: 1505.
10 Lima DR, Turner P. β-blocking drugs increase responsiveness to prostacyclin in hypertensive patients. *Lancet* 1982; 2: 444.

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Endobronchial metallic clips to guide high-dose external-beam radiotherapy in radio-occult lung cancer

To the Editors:

As a result of the increased sensitivity of videobronchoscopy (including narrow-band and video autofluorescence imaging) and a specific interest in surveillance of pre-invasive lesions, an increase in diagnosis of radiographically occult lung carcinoma (ROLC) can be anticipated. Described for the first time in the late 1970s by MARTINI and MELAMED [1] and in the early 1980s by CORTESE *et al.* [2], surgery still remains the treatment of choice for ROLC [3]. However, patients can be functionally inoperable due to comorbidity, advanced age, multiple primary lesions or irresectable, centrally localised tumours, or because they refuse surgery [2]. Therefore, varieties of endoscopic techniques, such as photodynamic therapy, cryotherapy, laser therapy, electrocautery and brachytherapy, were developed as alternatives to surgery [3–5]. The combination of high-dose external-beam radiotherapy (EBRT) with intraluminal radiotherapy (IR) using low [6–8], middle [9] and high dose-rate [10] iridium-192, has been investigated in ROLC with promising results. EBRT has obvious advantages to surgery, as it is less invasive and better tolerated by the patient. A major issue is, however, the localisation of the tumour for the guidance of EBRT, since these tumours are radiologically occult. Previously, in those studies combining EBRT with IR [6–10], localisation of tumour was determined under fluoroscopy using the tip of the bronchoscope. Radiation was given using small anterior–posterior opposed portals. Obviously, this is less reliable, precise and comfortable, as might be anticipated. To overcome this problem, we hypothesised that metallic clips, the same as used in gastroenterology to obtain haemostasis, could be used as beacons to locate the tumour during EBRT. In a post-operative setting, the same principle is often used to orient EBRT in incomplete resections. Radiation fields are collimated using metallic clips placed by the surgeon.

In a prospective pilot series (June–October 2008) we assessed the feasibility and safety of EZ-Clips HX 610-090 (Olympus, Aartselaar, Belgium) in inoperable patients with ROLC to guide high-dose EBRT. The standard length of these clips is 6 mm when deployed, and when opened the angle of the jaws is 90° (fig. 1). Patient characteristics and tumour locations are summarised in table 1. All four patients were male, smokers with a median age of 68 yrs and fitted the criteria for ROLC as described by the Japan Society of Lung Cancer [8]. They underwent white light and autofluorescence video bronchoscopy (fig. 1) because of haemoptysis (case 1), persistent infiltrate (case 2), screening for second primary (case 3) and persistant cough (case 4). Pathology of the endobronchial biopsies was invasive squamous cell carcinoma for all patients. One was staged cT2N0M0 and three were cT1N0M0. Staging was performed according to the 6th edition of the TNM (tumour, nodes, metastasis) Classification of Malignant Tumours [11]. Patients 1, 2 and 4 received brachytherapy with one fraction of 10 Gy at 1 cm from the catheter. Patient 3 did not receive endobronchial brachytherapy because of a concurrent supraglottic tumour. Before EBRT, the patients underwent a second bronchoscopy to place two endobronchial metallic clips: one on the proximal carina and one on the distal carina, relative to the ROLC (fig. 1). This was performed under local anaesthesia and was well tolerated by all patients. The time needed to place the clips was estimated to be no longer than an ordinary flexible bronchoscopy with biopsies. Although one clip loosened immediately after placement, it could be removed using biopsy forceps. No other complications occurred. As can be seen in figure 1, the clips are radiographically identifiable. The clips were used for delineation of the clinical target volume on the treatment planning system (fig. 1). In addition, the clips served as beacons facilitating the correct positioning of the patient with cone-beam computed tomography (CT) during hypofractionated radiation therapy (8×7.5 Gy EBRT).

3–4 weeks after EBRT, the patients underwent another bronchoscopy to remove the endobronchial clips by means of biopsy forceps. In cases 1 and 4, both clips were easily retrieved. In case 2, one of the clips was missing, and in case 3 both clips had disappeared. Thorough examination of all

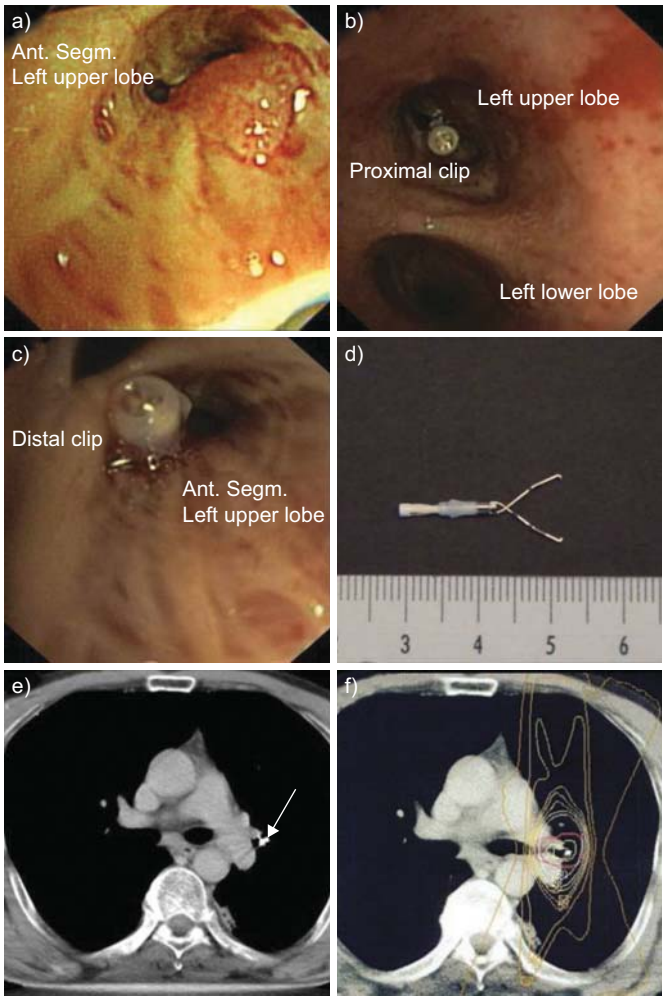

FIGURE 1. a) An endoluminal lesion in the anterior segment of the left upper lobe. b) Clip placed on the carina proximal of to the radiographically occult carcinoma (ROLC). Image taken from the left main bronchus. The carina seen is the secondary carina, with the upper part being the left upper lobe. c) Clip placed on the carina distal to the ROLC. Procedure performed after brachytherapy. The endoluminal lesion seen in a) has vanished. d) Close-up of an EZ clip. Scale is in cm. e) Visualisation of the distal endobronchial clip as seen in c) on computed tomography images. Arrow shows endobronchial clip. f) Planning of external-beam radiotherapy with the field collimated using the EZ clips.

cone-beam computed tomography imaging revealed that one clip was already lost at the time of treatment planning, while two were lost during radiation therapy.

During the removal procedure, we also reassessed the mucosa and, interestingly, the macroscopic aspect of the tumour was unchanged in two cases, while in the other two, the tumour was no longer endoscopically identifiable (fig. 1). More importantly, endobronchial biopsies taken showed only inflammatory changes in all patients without signs of malignancy.

At follow-up, the patient treated with EBRT alone did very well, while the others treated with brachytherapy and EBRT developed either airway stenosis, infection or haemoptysis. The patient with haemoptysis succumbed 10 months after therapy. These complications fit with the data from FURUTA *et al.* [10]. Therefore, we think the adverse events experienced

TABLE 1 Patient characteristics

Case	Age yrs	Sex	Histology	Clinical TNM	Site	Findings before RT		Reason for nonsurgical treatment	Position of the clips	
						WL	FB		Proximal	Distal
1	74	Male	Squamous carcinoma	cT1N0M0	Distal part of bronchus intermedius	Thickened carina	Negative	Patient refusal	Right secondary carina	Tertiary carina RML and RLL
2	62	Male	Squamous carcinoma	cT1N0M0	Anterior segment of LUL	Endoluminal lesion	Positive	Cardiac and pulmonary comorbidity	Tertiary carina lingula and LUL division	Quaternary carina LUL (anterior segment)
3	71	Male	Squamous carcinoma	cT2N0M0	Dorsal site right main bronchus, 2 cm from carina	Pathological mucosa	Positive	Chemotherapy treatment head and neck cancer	Main carina	Right secondary carina
4	65	Male	Squamous carcinoma	cT1N0M0	Apex LLL	Pathological mucosa	Positive	Cardiac and pulmonary comorbidity	Tertiary carina superior and basal segments LLL	Quaternary carina apical segments LLL

RT: radiotherapy; WL: white light bronchoscopy; FB: fluorescence bronchoscopy; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe.

were due to the effects of brachytherapy and not to the use of metallic clips or EBRT.

In conclusion, although surgery remains the first choice to treat ROLC, a considerable number of patients are inoperable. EBRT is an alternative, but is hampered since the ROLC is effectively invisible. We report that the use of metallic clips placed during bronchoscopy can make ROLC visible for the radiation oncologist. The clips appear to be safe, well tolerated and removable in inoperable patients with ROLC who are candidates for EBRT. In the future, this technique could facilitate EBRT or even stereotactical beam radiotherapy in patients with ROLC. Prospective studies further investigating this technique are warranted.

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REFERENCES

1 Martini N, Melamed MR. Occult carcinomas of the lung. *Ann Thorac Surg* 1980; 30: 215–223.
2 Cortese DA, Pairolero PC, Bergstralh EJ, *et al.* Roentogenographically occult lung cancer. A ten-year experience. *J Thorac Cardiovasc Surg* 1983; 86: 373–380.
3 Kennedy T, McWillians A, Edell E, *et al.* Bronchial intraepithelial neoplasia/early central airways lung cancer. ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007; 132: 221S–233S.
4 Sutedja TG, van Boxem AJ, Postmus PE. The curative potential of intraluminal bronchoscopic treatment for early-stage non-small-cell lung cancer. *Clin Lung Cancer* 2001; 2: 264–270.
5 Vonk-Noordegraaf A, Postmus PE, Sutedja TG. Bronchoscopic treatment of patients with intraluminal microinvasive radiographically occult lung cancer not eligible for surgical resection: a follow-up study. *Lung Cancer* 2003; 39: 49–53.
6 Saito M, Yokoyama A, Kurita Y, *et al.* Treatment of roentogenographically occult endobronchial carcinoma with external beam radiotherapy and intraluminal low dose rate brachytherapy: second report. *Int J Radiation Oncology Biol Physic* 2000; 47: 673–680.
7 Fuwa N, Ito Y, Matsumoto A, *et al.* The treatment results of 40 patients with localized endobronchial cancer with external beam irradiation and intraluminal irradiation using low dose rate ^{192}Ir thin wires with a new catheter. *Radiotherap Oncol* 2000; 56: 189–195.
8 Fuwa N, Kodaira T, Tachibana H, *et al.* Long-term observation of 64 patients with roentgenographically occult lung cancer treated with external irradiation and intraluminal irradiation using low-dose-rate iridium. *Jpn J Clin Oncol* 2008; 38: 581–588.
9 Fuwa N, Matsumoto A, Kamata M, *et al.* External irradiation and intraluminal irradiation using middle-dose-rate iridium in patients with roentgenographically occult lung cancer. *Int J Radiat Oncol Biol Phys* 2001; 49: 965–971.
10 Furuta M, Tsukiyama I, Ohno T, *et al.* Radiation therapy for roentogenographically occult lung cancer by external beam irradiation and endobronchial high dose rate brachytherapy. *Lung Cancer* 1999; 25: 183–189.
11 Silvestri GA, Gould MK, Margolis ML, *et al.* Noninvasive staging of non-small cell lung: ACCP evidenced-based clinical practice guidlines (2nd edition). *Chest* 2007; 132: 178S–201S.

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Iloprost-induced thrombocytopenia: a case proven by rechallenge

To the Editors:

A 63-yr-old female underwent aortic and mitral valve replacement surgery (ATS 18 and 29 mm, respectively; ATS Medical, Inc., Minneapolis, MN, USA) for aortic stenosis and mitral incompetence in August 2009. Pre-operatively, she was in New York Heart Association class III and exhibited comorbid hypertension, obstructive sleep apnoea (managed with night-time continuous positive airway pressure), obesity (body mass index of 42 kg·m^{-2}) and hypercholesterolaemia. Pre-operative right and left heart catheter investigation demonstrated a normal left ventricular ejection fraction, mean aortic valve gradient of 42 mmHg (normal 0–10 mmHg), valve opening area of 0.7 cm^2 (normal >2 cm^2), mean pulmonary arterial pressure of 48 mmHg (normal 12–16 mmHg), pulmonary vascular resistance of 225 dyn·s·cm^{-5} (normal 100–200 dyn·s·cm^{-5}), pulmonary capillary wedge pressure of 34 mmHg and cardiac output of 4.97 L·min^{-1}. Her medication included an angiotensin-converting enzyme inhibitor, diuretics and aspirin.

Her post-operative course was complicated by a sternal wound infection, mediastinitis, pneumonia and renal failure requiring continuous high-flow haemodiafiltration. On the 14th post-operative day, she developed right heart failure (central venous pressure (CVP) of 25 mmHg, mean arterial pressure ($\bar{P}$a) of 60 mmHg and severely impaired right ventricular function on echocardiography) due to sepsis- and pneumonia-related exacerbation of her initially mild post-capillary pulmonary hypertension. She required mechanical ventilation in a spontaneously breathing mode and circulatory support with noradrenalin and dobutamine. Treatment with inhaled iloprost (Ilomedin®; Bayer Schering Pharma, Berlin, Germany) was commenced in order to reduce pulmonary arterial pressures and right ventricular work. A total of 10 μg iloprost