Convex Probe EBUS-guided Fiducial Placement for Malignant Central Lung Lesions

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Background: **Stereotactic body radiotherapy (SBRT) had become a therapeutic modality in patients with primary tumors, locally recurrent as well as oligometastasis involving the lung. Some modalities of SBRT require fiducial marker (FM) for dynamic tumor tracking. Previous studies have focused on evaluating bronchoscopic-guided FM placement for peripheral lung nodules. We describe the safety and feasibility of placing FM using real-time convex probe endobronchial ultrasound (CP-EBUS) for SBRT in patients with centrally located hilar/mediastinal masses or lymph nodes.**

Methods: **This is a retrospective review of patients who were referred to Beth Israel Deaconess Medical Center's multidisciplinary thoracic oncology program for FM placement to pursue SBRT.**

Results: **Thirty-seven patients who underwent real-time CP-EBUS were included. Patients had a median age of 71 years [interquartile range (IQR), 59.5 to 80.5]. The median size of the lesion was 2.2 cm (IQR, 1.4 to 3.3 cm). The median distance from the central airway was 2.4 cm (IQR, 0 to 3.4 cm). A total of 51 FMs (median of 1 per patient) were deployed in 37 patients. At the time of SBRT planning, 46 (90.2%) were confirmed radiologically in 32 patients. Patients with unsuccessful fiducial deployment (n = 5) underwent a second procedure using the same technique. Of those, 3 patients had a successful fiducial placement via bronchoscopy, 1 patient required FM placement by percutaneous computed tomography-guided approach and 1 patient required FM placement through EUS by gastroenterology.**

Conclusion: **CP-EBUS-guided FM placement for patients with malignant lymph nodes and central parenchymal lung lesions appears to be safe and feasible.**

Key Words: endobronchial ultrasound, bronchoscopy, fiducial marker, mediastinal and hilar metastasis, CyberKnife, stereotactic body radiotherapy

(*J Bronchol Intervent Pulmonol* 2018;25:283–289)

Lung cancer remains the second most common cancer in the United States and the leading cause of cancer mortality in men and women, with an estimated incidence of 224,390 and estimated annual mortality of 158,080 in 2016.[1] Patients with early-stage lung cancer or oligometastasis involving the lung complicated by multiple medical comorbidities, are usually deemed not eligible for surgical therapy. In these cases, stereotactic body radiotherapy (SBRT) may be considered the treatment of choice for definitive therapy.[2,3]

There are multiple platforms for SBRT. Commercially available devices such as CyberKnife with Synchrony (Accuray Robotic Radiosurgery Systems; Accuray Inc., Sunnyvale, CA) and Novalis (Varian, Palo Alto, CA) are integrated photon SBRT delivery systems. Unique to CyberKnife is a patient-implanted fiducial that can be traced by the system, providing real-time dynamic respiratory tracking of tumors.[4,5]

Previous studies have focused on evaluating bronchoscopic-guided fiducial marker (FM) placement for peripheral pulmonary nodules using conventional bronchoscopy, radial probe-endobronchial ultrasound or electromagnetic

Received for publication August 3, 2017; accepted February 23, 2018.
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Disclosure: There is no conflict of interest or other disclosures.
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DOI: 10.1097/LBR.0000000000000497

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navigation bronchoscopy.[6–13] However, the use of convex probe endobronchial ultrasound (CP-EBUS) for deploying FMs under real-time guidance for centrally located lung and mediastinal tumors as well as hilar/mediastinal lymph nodes has been limited to few case reports.[14–16]

The aim of this study was to assess the feasibility and safety of placing FMs using real-time CP-EBUS for SBRT in patients with centrally located hilar/mediastinal masses or lymph nodes.

MATERIALS AND METHODS

Study Design

This was a retrospective review of all patients who were referred to our multidisciplinary thoracic oncology program at Beth Israel Deaconess Medical Center for FM placement to pursue SBRT from October 2011 to December 2016. The study protocol was approved by the institutional review board at the Beth Israel Deaconess Medical Center/Dana Farber Cancer Institute (DFCI IRB protocol number: 13-476). All patients were evaluated by a multidisciplinary thoracic oncology team (medical oncology, thoracic surgery, radiation oncology, thoracic radiology, and interventional pulmonary) before being offered FM placement for SBRT.

Subject Population and Study Outcome

Centrally located lung tumors or lymph nodes are defined as lesions residing within the inner third of the lung field by cross-sectional imaging of the chest. The distance to the central airway was determined as the distance from the lesion to "large" airway (trachea or main bronchi). The procedure was considered successful when the FM was placed and the patient subsequently underwent SBRT without the need for additional markers. Baseline demographic, clinical variables, and pulmonary function test were recorded. Both procedure-related as well as anesthesia-related complications and the need for escalation of care were recorded.

FM

FMs currently available in the market come in different shapes, sizes, densities and materials. In our practice, we use a linear gold fiducial seed marker of 0.8×5 mm (model SMG0242-025; Alpha-Omega Services Inc., Bellflower, CA). At the time of placement, we used the front-load method, where a FM is inserted into the outer sheath of the needle with a needle holder that is then secured with bone wax. Release of the FM occurs when the needle pushes the fiducial out of the sheath, at the desired location.

Procedural Technique

The technique of FM placement using CP-EBUS for peribronchial lymph nodes has been previously described by McGuire et al.[17] In our study, all procedures were performed under general anesthesia. Oxygenation and ventilation were provided either with a laryngeal mask airway, an endotracheal tube or a rigid bronchoscope. A flexible Olympus 5.9 mm bronchoscope with a 2.8 mm working channel (Olympus America, Center Valley, PA) was used for complete airway inspection. Thereafter, a CP-EBUS bronchoscope (Olympus BF-UC160F-0L8) was used to identify the target lesion with real-time ultrasound guidance with a Doppler mode to identify surrounding vessels and confirm the absence of vascular structures inside the target lesion. This was followed by several transbronchial needle aspiration passes for cytology using a 21-G Olympus needle.

Once the orifice of the track is well visualized on the airway mucosa (Fig. 1), (1) the sheath is advanced into the airway wall and left in place. (2) A second needle is loaded with a FM (0.8×5 mm); the FM is inserted manually (front-loaded) into the sheath and sealed with bone wax in order to prevent the loss of the marker before the deployment is completed (Fig. 2). (3) The first needle is then removed and the second needle is

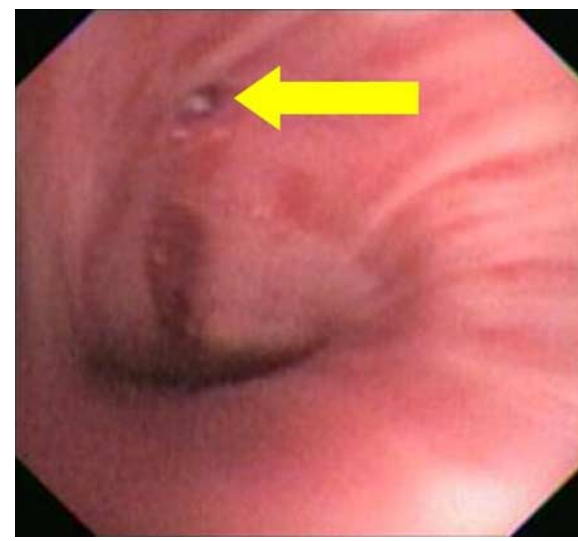

FIGURE 1. Puncture site (arrow) of endobronchial ultrasound–guided transbronchial pathway.

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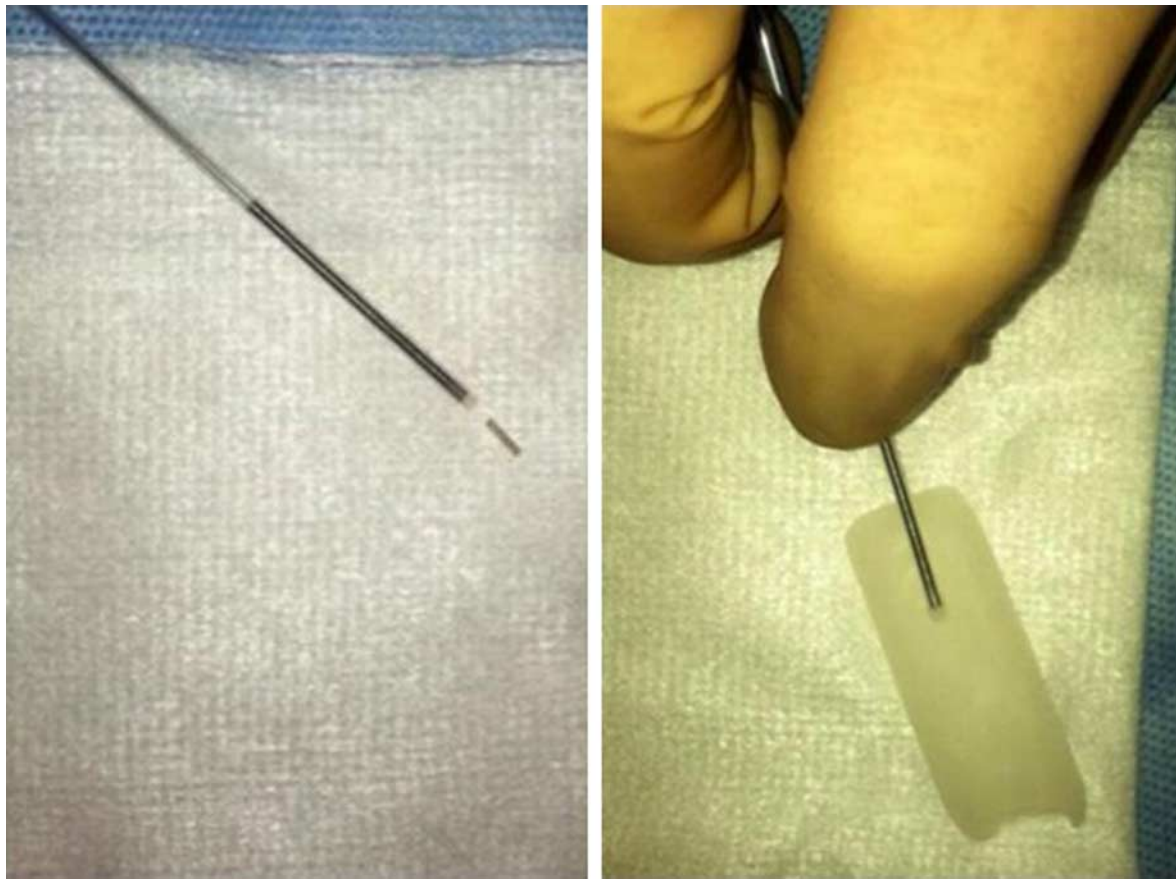

FIGURE 2. Fiducial marker inserted manually (front-loaded) into the sheath and sealed with bone wax.

introduced into the working channel. (4) Once the tip is visualized through the bronchoscope, the sheath of the needle is introduced into the existing track and advanced into the lesion. The time interval between the removal of the first needle and introduction of the second one is kept at a minimum in order to prevent spontaneous closure of the track. (5) Using the ultrasound view, position of the sheath inside the airway wall is confirmed, (6) the sheath adjuster is secured and the needle is advanced to the desired depth using US and fluoroscopic guidance. This last step deploys the FM into the target lesion (Figs. 3, 4). All patients underwent chest x-ray after bronchoscopy to rule out pneumothorax and confirm adequate fiducial placement.

Statistical Analysis

Statistical analysis was performed using SPSS version 21 (IBM Corp., Armonk, NY), with a *P*-value of <0.05 defined as significant.

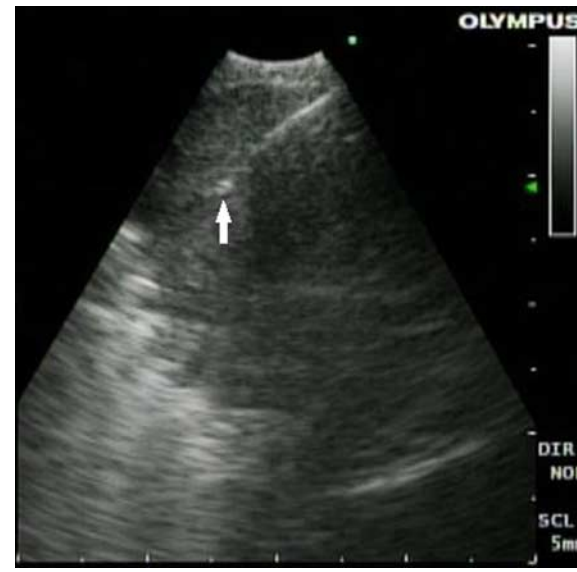

FIGURE 3. Endobronchial ultrasound–guided deployment of fiducial marker (arrow).

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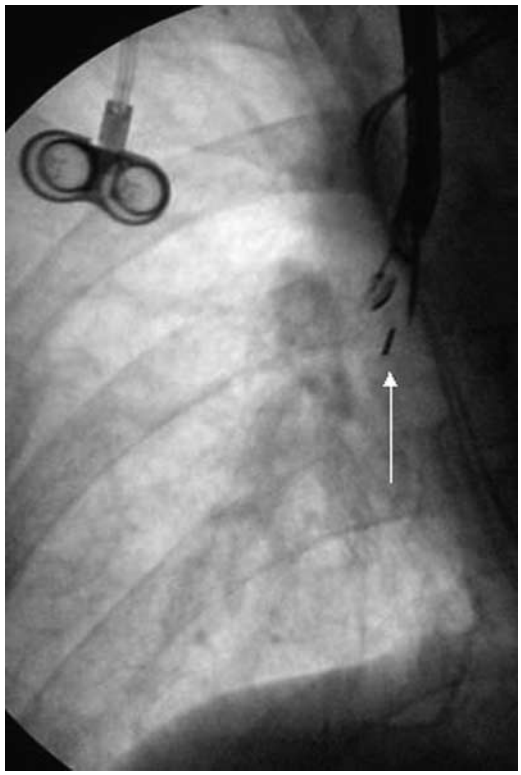

FIGURE 4. Fluoroscopy: deployed fiducial marker (arrow).

Descriptive statistics including mean, median, range, and percentage were utilized to describe patient demographics and outcomes.

TABLE 1. Demographics, Clinical Characteristics, and Patient Comorbidities

Age [median (IQR)] (y)	71 (59.5-80.5)
Men [N (%)]	21 (57)
BMI [median (IQR)]	26.2 (22.2-30.4)
American Society of Anesthesiologists [N (%)]	
I	0
II	3 (8.1)
III	24 (64.9)
IV	10 (27)
Smoking status [N (%)]	
Current smoker	4 (10.8)
Ex-smoker	24 (64.9)
Never smoker	9 (24.2)
Comorbidities [N (%)]	
Chronic obstructive pulmonary disease	13 (35)
Diabetes mellitus	8 (22)
Coronary artery disease	6 (16)
Asthma	3 (8)
Stroke	3 (8)
Obstructive sleep apnea	2 (5)
Congestive heart failure	2 (5)
Chronic kidney disease	2 (5)

IQR indicates interquartile range.

RESULTS

Thirty-seven consecutive patients who underwent real-time CP-EBUS were included in the study. Patients had a median age of 71 years [interquartile range (IQR), 59.5 to 80.5]. Ninety-two percent of patients had an ASA score of at least 3. The baseline demographic, clinical characteristics and medical comorbidities of the patients are shown in Table 1.

Twenty-eight patients had primary lung tumor. Of those, 27 (96.5%) had non–small cell lung cancer and 1 (3.5%) had limited-stage small cell lung cancer. Nine patients had other primary malignancies with oligometastasis to the lung. Of those, 4 (44.5%) had renal cell carcinoma, and 1 (11.1%) had melanoma, esophageal adenocarcinoma, ovarian carcinosarcoma, and leiomyosarcoma, respectively. Nine lesions were located on the left, 15 were on the right, 5 were at the carina, 4 were pretracheal, and 4 were metastasis to hilar/mediastinal lymph nodes. The median size of lesion was 2.2 cm (IQR, 1.4 to 3.3 cm). Distance from the central airway was 2.4 cm (IQR, 0 to 3.4 cm). Tumor characteristics with histologic diagnosis are described in Table 2.

A total of 34 patients received general anesthesia, of those 16 patients (43.2%) were ventilated using a laryngeal mask; 9 patients (24.3%) using a

TABLE 2. Tumor Characteristics

No. tumors	37
Size [median (IQR)] (cm)	2.2 (1.4-3.3)
Distance from central airway [median (IQR)] (cm)	2.4 (0-3.4)
Tumor location [N (%)]	
Right upper lobe	8 (21.6)
Right middle lobe	2 (5.4)
Right lower lobe	5 (13.5)
Left upper lobe	4 (10.8)
Left lower lobe	5 (13.5)
Station 11	1 (2.7)
Station 7	5 (13.5)
Station 4R	6 (16.2)
Station 4L	1 (2.6)
Tumor histology [N (%)]	
Adenocarcinoma	12 (32.4)
Squamous cell	12 (32.4)
Large cell	2 (5.4)
Small cell	1 (2.7)
Renal cell	4 (10.8)
Melanoma	1 (2.7)
Esophageal	1 (2.7)
Ovarian	1 (2.7)
Pancreatic	1 (2.7)
Colon	1 (2.7)
Leiomyosarcoma	1 (2.7)

IQR indicates interquartile range.

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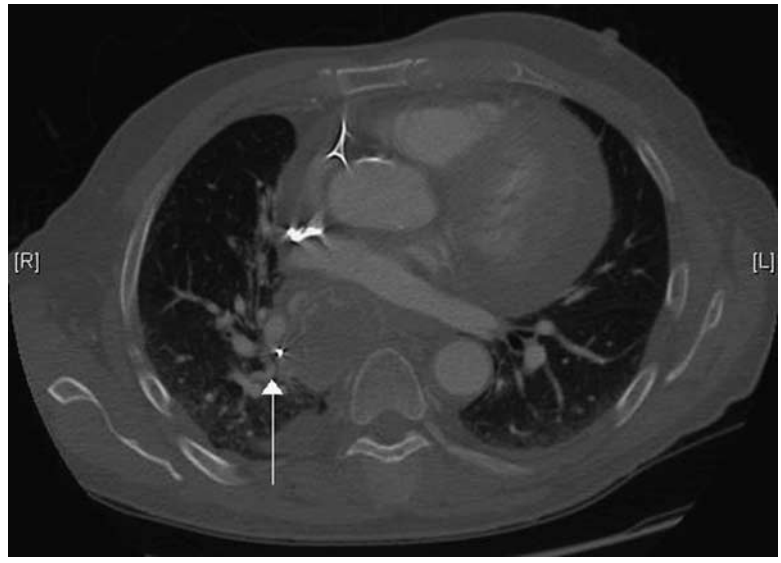

FIGURE 5. Cyberknife planning. Fiducial marker in satisfactory location (arrow).

rigid bronchoscopy, 7 patients (18.9%) using an endotracheal tube, and 2 patients (5.4%) using the tracheostomy tube. Three patients (8.1%) underwent the procedure under light sedation. Fifty-one FMs (median of 1 per patient) were deployed in 37 patients and 46 (90.2%) were identified radiologically in 32 patients when the SBRT planning chest computed tomographic (CT) scan was performed 2 weeks later (Fig. 5). One patient coughed up the FM. Patients with unsuccessful fiducial deployment (n = 5) underwent a second fiducial placement using the same technique. Of those, 3 patients had a successful fiducial placement in the second bronchoscopy, 1 patient required FM placement by percutaneous CT-guided approach, and 1 patient required transesophageal FM placement by gastroenterology using EUS. The medial total time of bronchoscopy (scope-in-scope-out) was 66 minutes (IQR, 44.5 to 95). In total 14 (37.8%) patients underwent other procedures including: 6 (16.2%) tumor debridement, 4 (10.8%) electrocautery, 3 (8.1%) cryotherapy, and 3 (8.1%) stent placement.

Two patients had FMs fall into the airway during the procedure. Both had their FMs successfully removed followed by adequate placement of other FMs. There were no anesthetic-related complications or hospital readmissions in the interval time before SBRT began. Real-time CP-EBUS results are described in Table 3.

DISCUSSION

SBRT has a well-established role as a treatment option for patients with early-stage lung cancer who are medically unfit, who refuse to undergo surgery or opted for nonsurgical treatment as well as patients with oligometastasis involving the lung.[2,18] Furthermore, such therapy has also been increasingly used in patients with locally advanced or recurrent lung cancer.[2] In addition, thoracic radiation with concurrent chemotherapy has shown favorable 5-year survival rate in patients with limited-stage small cell lung cancer. However, in this cohort the patient with small cell lung cancer died 8 months after started cyber knife therapy.[19]

The efficacy of SBRT for treatment of tumors depends on precise beam delivery of high biological dose. However, centrally located lesions might be difficult to treat with such high dosing without causing damage to surrounding radiosensitive organs such as heart, esophagus, major vessels, and tracheobronchial tree due to their proximity. SBRT can be achieved with various methods that include respiratory gating,

TABLE 3. Convex Probe Endobronchial Fiducial Marker Placement Results

No. fiducial marker per patient [median (range)]	1 (1-4)
Fiducial markers identified during chest CT for SBRT [N (%)]	46 (90.2)
Complications [N (%)]	
Anesthesia related	0
Procedure related	2 (5.4)
Escalation of care	0

CT indicates computed tomography; SBRT, stereotactic body radiotherapy.

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body frame or real-time target and motion tracking. The real-time target and motion tracking are thought to allow for smaller treatment margins and avoidance of patient immobilization devices, while delivering highly conformal dose distributions with rapid dose fall off.[20–22] This treatment approach (ie, shortening treatment sessions) appears to enhance radiobiological response against the tumor in an attempt to reach curative intent.[23]

Recent reports have also described the advantages of fiducial placement under guided bronchoscopy compared with percutaneous placement by CT-guidance for peripheral lung tumors. The most striking reported difference was the rate of iatrogenic pneumothoraces (18% with CT-guided placement vs. 0% when FMs were placed under guided bronchoscopy).[20]

The use of CP-EBUS FM placement for central lesions offers several advantages as it (1) allows direct visualization as well as precise placement during deployment, (2) seems to decrease the risk of FM embolization, (3) avoids any vascular structures within the target lesion with use of Doppler US, (4) appears to lower the risk of pneumothorax that that accompanies the transthoracic approach, and (5) offers the potential for a combined approach of diagnosis, staging, and providing initial step therapy (ie, FM placement) for patients with multiple medical comorbidities that cannot undergo surgery, but require SBRT as definitive treatment.

To the best of our knowledge, this is the largest case series addressing the feasibility and safety of CP-EBUS-guided FM placement in centrally located lesions. Our study shows that real-time CP-EBUS-guided FM placement, using a very simple technique, into centrally located lung lesions or lymph nodes for SBRT is safe and feasible. This supports the growing literature about the utility of CP-EBUS as a therapeutic tool in such population. It is important to emphasize that the retention rate for FMs in our current study was 90.2% and 3 patients required repeated EBUS procedure prior to SBRT. This is probably due to the fact that we used seed markers rather than coils where the latter have demonstrated durability following implantation.[24] As such; we are changing our practice to implement coils instead of seed markers in peripheral tumors due to a high migration rate. However, for centrally located lesions we still using the seeds as migration and cost remain low.

This study has a number of limitations: retrospective case series, relatively small sample size, and the procedures were performed from a single institution with high expertise in advanced therapeutic and diagnostic bronchoscopic techniques. With SBRT becoming a widely adopted treatment for primary, locally recurrent or oligometastatic lung tumors, the incorporation of FM placement during CP-EBUS diagnosis and staging in selected population might expedite treatment care as well as reduce cost. Further prospective trials are needed to address such combined approach.

In conclusion, placement of FMs using CP-EBUS for centrally located parenchymal lung tumors and mediastinal/hilar lymph node metastasis for SBRT is safe and feasible.

ACKNOWLEDGMENT

The authors would like to take this opportunity to acknowledge Dr Robert Berger who passed away 2 years ago for the time and effort devoted to this manuscript.

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