‘Heat and Destroy’: Bronchoscopic-Guided Therapy of Peripheral Lung Lesions

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Key Words

Interventional bronchoscopy • Electromagnetic navigation • Lung cancer • Radiofrequency ablation • Radiotherapy • Virtual bronchoscopy

Abstract

Although the treatment of choice for stage I lung cancer patients is surgery, a lot of patients have a high comorbidity and are medically inoperable. Bronchoscopy, as a central technique in diagnosing lung cancer, has the potency to apply endoscopic therapy to small lung lesions in a minimally invasive way in patients with high risk for surgery. Unfortunately, bronchoscopy cannot always reach lesions in the peripheral lung, in particular the smaller lesions. Therefore, new guidance techniques like virtual bronchoscopy and electromagnetic navigation are now available and instead of using the systems as a diagnostic tool, these techniques may provide an option for therapeutic interventions to inoperable lung tumor patients. With endoscopic fiducial marker placement for robotic radiosurgery and endoluminal high-dose brachytherapy, local radiotherapy of peripheral lung tumors becomes feasible, reducing radiotherapy-induced toxicity. Radiofrequency tissue ablation through the working channel of a flexible bronchoscope may be a chance of making a diagnosis and a curative treatment in one endo-

scopic session. However, technical improvements of the ablation probes are currently necessary to expand the sizes of ablated areas. Even though the technologies are very attractive and pilot data are extremely encouraging, more studies establishing selection criteria and best utility are needed.

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Introduction

Lung cancer remains the leading cause of cancer death in both men and women, even though the risk factors for this disease are well established. Despite being the most common cancer in the world, it still remains poorly diagnosed at the early stages, and the tragedy of lung cancer is directly associated with its delayed presentation. Most patients with an initial diagnosis of lung cancer have advanced stage diseases. These individuals are often poor surgical candidates with limited therapeutic options [1–3]. On the contrary, individuals with early-stage disease

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can achieve cure through surgical resection [4–6]. With the advances in imaging, both computed tomography (CT) and positron emission tomography are playing an increasing role in lung cancer detection. Most solitary pulmonary nodules, radiologically defined as an intraparenchymal lung lesion <3 cm in diameter, are detected incidentally at chest radiographs or CT scans, that are obtained for other purposes [7]. The majority of lung lesions <1 cm are benign, but each of which could indicate the presence of lung cancer [8]. Therefore, the need to work up and manage pulmonary nodules is encountered with increasing frequency in chest medicine [9, 10].

The treatment of choice for stage I non-small cell lung cancer (NSCLC) is surgery [11, 12]. In patients with peripheral lung lesions who are surgical candidates and presenting a high pretest probability for lung cancer, a biopsy is often not necessary [13]. There are two main reasons for choosing an alternative approach instead of surgical treatment of such a coin lesion. The first is that the patient refuses surgery or only agrees after confirming a diagnosis of lung cancer. The second is that the patient is medically inoperable, but tissue confirmation of malignancy is required before proceeding with treatment. These facts lead to a cascade of further investigations to establish a definitive diagnosis.

However, it is generally assumed that patients with pre-existing pulmonary disease, particularly chronic obstructive pulmonary disease, often combined with cardiovascular disease are at increased risk of surgical morbidity [14, 15]. There is an increasing demand to provide alternatives to the currently invasive surgical therapy of malignant pulmonary nodules. Therefore, attention has turned to non-surgical therapeutic modalities, but technologies like curative external radiotherapy are limited by radiotherapy-induced lung toxicity [16]. These issues should be taken into account when elaborating treatment strategy for lung cancer patients with severe comorbidities.

Actual Role of Bronchoscopy

Bronchoscopy is a central technique in diagnosing lung cancer, but also in different therapeutic approaches. A variety of interventional bronchoscopic techniques combined with surgery, external beam radiation, or chemotherapy are available for treatment for endobronchial malignancies, which may compromise airway lumen diameter, leading to distal lung collapse and post-obstructive pneumonia [17–19]. A multimodality treatment ap-

proach to lung malignancies can potentially avoid or reduce these complications in a palliative intention [20, 21].

During the last years, several new technologies have been introduced in the field of bronchoscopy. Great potential could be seen in the possibility to apply endoscopic therapy to small lung lesions in patients with high risk for surgery or external beam radiotherapy. The main limitation of flexible bronchoscopy is the difficulty in reaching solitary coin lesions with the accessory tools [7, 22].

Flexible bronchoscopy has a variable and often poor success rate in sampling small pulmonary lesions during a normal endobronchial examination. The sensitivity of bronchoscopy for detecting solitary pulmonary nodule depends on the size of the nodule and the proximity of the nodule to the bronchial tree [22, 23]. Successful transbronchial biopsies (TBB) are mostly achieved with fluoroscopic guidance, but especially nodules <20 mm in diameter are difficult to reach or impossible to visualize. Thus, for these nodules, Schreiber and McCrory [7] found in a meta-analysis an overall diagnostic sensitivity of only 33%. Therefore, new methods for navigation and localization are needed, independent of visualization by fluoroscopy and the technical skills of the bronchoscopist.

Guidance Techniques

Virtual Bronchoscopy

Virtual bronchoscopy (VB) is a CT-based imaging technique that allows a non-invasive intraluminal evaluation of the tracheobronchial tree. Thin bronchoscopes with external diameters <3 mm have been used in clinical practice since 2004 and can be advanced to more peripheral bronchi than conventional bronchoscopes. The challenge is to identify the route to a peripheral lesion under direct vision within the bronchoscopic examination time [24]. However, it is difficult to obtain a three-dimensional (3-D) understanding of the complicated tracheobronchial tree based on axial CT images. While VB can reconstruct helical CT images to display a 3-D reconstruction resembling the bronchoscopic video, it has rarely been used in bronchoscopy for targeting pulmonary peripheral lesions [25, 26]. Today, different virtual bronchoscopic navigation systems are in development (fig. 1).

The usefulness of VB navigation has been reported for CT-guided TBB using an ultrathin bronchoscope [27, 28].

Fig. 1. Typical screen of virtual bronchoscopic navigation system (LungPoint™; Broncus Technologies, Inc., Mountain View, Calif., USA). The blue pathway, leading to a coin lesion in segment RB2, can be seen both in the VB and in the corresponding endoscopic image simultaneously.

However, this procedure has the disadvantages of excessive radiation exposure from CT and of occupying the CT room for approximately 1 h. Combining endobronchial ultrasound (EBUS) guidance by using small-caliber radial probes with VB may overcome the limitations of CT-guided TBB. Asahina et al. [29] could demonstrate the feasibility, safety and efficacy of this endoscopic approach. Diagnostic sensitivities were 44.4% for pulmonary lesions <20 mm and 91.7% for solitary pulmonary nodules 20–30 mm in mean diameter.

Electromagnetic Navigation Bronchoscopy

Electromagnetic navigation-guided bronchoscopy (ENB) is a localization device that enables real-time navigation guidance within the lungs to endobronchially invisible targets [30]. The system (InReach™; SuperDimension, Inc., Minneapolis, Minn., USA) uses low-frequency electromagnetic waves, which are emitted from an electromagnetic board placed under the patient in a supine position. A computer software system converts CT data into multiplanar images with 3-D VB reconstruction. Once the tip of a sensor probe is placed in the electromagnetic field, its position is captured by the electromagnetic system and then displayed on a monitor in real time. The steerable and fully retractable probe is incorporated into a flexible catheter, serving as an extended working channel, which, once placed close to the peripheral lung lesion, creates an easy access for bronchoscopic accessories (fig. 2).

An increasing number of clinical trials demonstrate a successful use and the diagnostic yield has been reported

to be as high as 75.5% for diagnosing peripheral lung nodules both with fluoroscopic guidance and as a stand-alone technique [31–34]. The ENB system lacks a function to directly visualize the lesion before taking biopsies. Combining EBUS and ENB improves the diagnostic yield of flexible bronchoscopy in peripheral lung lesions without compromising safety. In a randomized trial, the combined use of EBUS and ENB overcomes each individual technique's limitation [35]. The diagnostic yield of the combined procedure (88%) was greater than either EBUS (69%) or ENB alone (59%). The diagnostic yield did not differ significantly based on the size of the lesion.

Instead of using the systems as a diagnostic tool, these techniques may provide a means for therapeutic interventions to inoperable lung tumor patients.

Bronchoscopic-Guided Treatments

Fiducial Marker Placement for Robotic Stereotactic Radiosurgery

Stereotactic radiosurgery (Cyberknife™; Accuray, Inc., Sunnyvale, Calif., USA) is a treatment option for patients who are medically unfit to undergo lung tumor resection [36]. The system includes a frameless and image-guided 6-MV linear accelerator mounted on a robotic arm. For a precise tumor ablation and compensation of changes of the tumor position during the respiratory cycle, the robotic device requires fiducial marker placement in or near the target tumor. Fiducials can be inserted into intrathoracic tumors via three modalities: transthoracic,

Fig. 2. a Typical screen of an electromagnetic navigation system (InReach™; SuperDimension, Inc.). The locatable guide is navigated to the lesion in the left lower lobe. The distance from the tip to the marked center (navigation error) is 0.5 cm. **b** Corresponding ultrasound image: after removal of the locatable guide an ultrasound probe (UM-S20-17R; Olympus, Tokyo, Japan) is placed within the lung lesion.

intravascular, and bronchoscopic. Fiducial placement under transthoracic CT guidance is associated with a high risk of iatrogenic pneumothorax. The bronchoscopic modality therefore has an excellent side effect profile compared to the other modalities [37–39].

Fiducial placement via standard flexible bronchoscopy using a conventional transbronchial aspiration needle is technically feasible, but its use is limited by a high number of subsequent marker migrations [39, 40]. In contrast, ENB can be safely used as a vehicle to precisely place fiducials into peripheral lung tumors beyond the reach

Fig. 3. **a** Small peripheral lesion suspicious for lung cancer recurrence after pneumonectomy 3 years ago. **b** Inserted brachytherapy catheter with a dummy probe. **c, d** Endoluminal brachytherapy planning was performed on the basis of chest CT scans. The target volume was defined and included the primary tumor and the bronchovascular bundle. The resulting dose distribution is displaced (courtesy of Prof. J. Debus and Prof. W. Harms, Department of Radiooncology, University of Heidelberg).

of standard bronchoscopes. In a prospective feasibility study, a total of 39 fiducial markers were successfully deployed in 8 out of 9 patients (89%) due to undergo stereotactic radiosurgery [40]. Of these 8 successful cases, 7 had fiducials placed directly within the tumor. At radiation planning, 7–10 days after marker placement, 35 of 39 fiducial markers (90%) were still in place and were adequate to allow radiosurgery to proceed. No severe complications associated to bronchoscopy and no pneumothoraces were observed after fiducial placement.

Endoluminal Brachytherapy

Harms et al. [41] reported about a patient with medically inoperable lung cancer. The patient was treated with external beam radiotherapy (50 Gy) first, followed by electromagnetic navigated and EBUS-controlled endoluminal brachytherapy (370 GBq iridium-192). After successful localization of the NSCLC by electromagnetic navigation, EBUS was performed to confirm the exact position in the center of the lesion. A brachytherapy catheter was then placed within the tumor. After that the catheter was fixed at the nose and left in place for treatment planning and endoluminal irradiations. Primary 3-D-planned brachytherapy was applied as a boost 3 times a week (single dose 5 Gy) and provided highly conformal irradiations of the NSCLC including the draining bronchovascular bundle (fig. 3).

In a feasibility and safety trial, 18 patients with inoperable peripheral lung cancer were treated in two centers [42]. The observation showed a complete remission in 9 of 18 patients (50%), the majority of the other 9 patients achieved a partial remission. This new endoluminal treatment was tolerated without major side effects or severe complications. Only one small pneumothorax was observed directly after the procedure. The authors conclude that in future, electromagnetic navigated and EBUS-controlled brachytherapy could become a potentially even curative treatment for inoperable peripheral lung tumors, sparing major damage to radiosensitive surrounding structures. However, further prospective studies are both necessary to confirm these promising results and warranted to evaluate safety, long-time outcome and maximum treatment size of peripheral pulmonary tumors.

Radiofrequency-Induced Tissue Ablation

Tumor cells are generally more sensitive to heat than normal cells [43]. Radiofrequency-induced tissue ablation (RFA) uses an electromagnetic wave with a frequency band and a radiofrequency interchange electric current. RFA is a new approach offered as a minimally inva-

sive treatment and is most commonly used to treat patients with liver tumors, kidney cancers and lung cancer [44–46]. The number of reports on the application of RFA with primary and secondary lung tumors that were not considered to be surgical candidates is growing [47–50].

Schneider et al. [51] investigated in a prospective trial the early histopathological changes following RFA in an open thoracotomy setting. Immunostaining revealed a complete ablation in 7 of 18 patients and an ablation more than 90% in 9 of 18 patients. Therefore, tumor devitalization sufficient for local tumor control could be achieved in 89% of patients with peripheral metastatic tumors in the lung.

RFA has been more widely used than percutaneous imaging-guided therapy. The highly resistant air-filled lung tissue surrounding a low resistant intraparenchymal tumor affords an isolating effect and traps heat within the targeted tumor [52, 53]. However, complications following percutaneous treatment like pain, hemothorax, pneumothorax and pleural effusion occur in 16–35% [52, 54].

Tsushima et al. [43] could demonstrate the feasibility of fiberoptic bronchoscopy-guided radiofrequency-induced tissue ablation using normal sheep lungs [43]. One limitation for endoscopic RFA was that coagulated necrotic tissue was formed around the electrode tip and tissue impedance increased rapidly. As a result, an adequate tissue necrosis could not be achieved. An internally cooled probe may overcome this drawback (fig. 4).

In a recent study [55], the authors could confirm the feasibility and safety of bronchoscopic RFA in humans using a cooled ablation probe. The group used an electrode catheter with a power output of 20 W through the working channel of a video-bronchoscope in inoperable patients with lung cancer. The probes were attached to a monopolar radiofrequency generator and a steel mesh dispersive electrode was attached to the patient's leg. The RFA applications were repeated 3 times in each patient.

Improvement of the RFA effect was achieved according to the catheter tip used and prolongation of ablation time. Histological analysis indicated that the extent of the maximal ablated area was 12×10 mm, when using a 10-mm catheter tip with 5 beards. The ablated area showed destruction of the alveolar space and coagulation necrosis. Even though the size of destroyed tissue is small, bronchoscopic RFA has the potency as a therapeutic tool, especially for local control in medically inoperable patients. The advantages of bronchoscopic RFA could include the ability to administer non-surgical treatment as well as a shorter hospital stay for the patients. However,

Fig. 4. **a, b** Prototype of a non-cooled, bipolar flexible radiofrequency ablation probe. **c** CT scan of an 83-year-old, medically inoperable patient with an adenocarcinoma in the right lower lobe. **d** Corresponding CT scan 6 weeks after endoscopic radiofrequency tissue ablation with an incomplete remission (courtesy of Prof. C.P. Heussel, Department of Radiology, Thoraxklinik, University Heidelberg).

the role of RFA in lung cancer is not sufficiently clear. RFA seems to be inferior to surgical resection, but in the future it can become a therapeutic option for pulmonary cancer patients who are not surgical candidates.

Conclusions

VB and ENB can be performed safely in humans and can easily be incorporated into a flexible bronchoscopy practice. Coupled with a new generation of steerable instruments, a much more reliable means of approaching

peripheral lung lesions endoscopically finally seems within reach. Such systems would not only provide a reliable means of establishing a tissue diagnosis but may also open the door for bronchoscopic-guided fiducial marker placement for robotic stereotactic radiosurgery and ENB-guided endoluminal brachytherapy for endoscopic therapeutic management and minimal-invasive radiotherapy in selected patients. An early application of endoscopic radiofrequency ablation of small pulmonary nodules or the curative treatment of peripheral lung lesions in non-surgical lung cancer patients is giving the treatment back in the hands of pulmonologists. In future, the goal should

be to diagnose and to treat early stages of lung cancer endoscopically in the same procedure.

With the newest available prototype techniques, we may improve the treatment options of inoperable patients with peripheral lung cancer. A minimally invasive application of interventional techniques in the management of

these patients, in collaboration with oncologists and radiotherapists, will most probably have a larger impact on quality of life and maybe also on survival. Even though the technologies are very attractive and pilot data are extremely encouraging, more studies establishing selection criteria and best utility are needed.

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