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Nanotechnology in Thoracic Surgery*

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Abstract

Nanotechnology is an exciting and rapidly progressive field offering potential solutions to multiple challenges in the diagnosis and treatment of lung cancer, with the potential for improving imaging and mapping techniques, drug delivery and ablative therapy. With promising preclinical results in many applications directly applicable to thoracic oncology, it is possible that the frontiers of minimally invasive thoracic surgery will eventually be explored on a nanoscale.

Keywords

Lung cancer; diagnosis and staging; lung cancer surgery; lymph nodes; imaging (all modalities); minimally invasive surgery

Lung cancer is the leading cause of cancer death among both men and women, with 5 year survival rates of only 50–80% after pathologically complete resection of stage I or II disease, respectively. Nodal status is a major determinant of prognosis, with nodal involvement further decreasing the 5 year survival rate by as much as 40% [1]. While nodal involvement is the single most significant factor in predicting outcome, truly accurate nodal staging has proven challenging due to the variable lymphatic drainage of the lung and the prevalence of occult micrometastatic disease within thoracic nodes which may appear benign both radiographically and intraoperatively.

An analysis of survival following resection of stage I non-small cell lung cancer (NSCLC) in 16,800 patients by Ludwig et al in 2005 revealed a statistically significant increase in median survival by 24 months when more than 10 lymph nodes (LN) were also removed [2]. Histopathologic analysis of resected nodes following lobectomy with hilar and mediastinal lymphadenectomy in patients with small (<1.1 cm) adenocarcinomas reveals an incidence of unsuspected nodal disease as high as 17% [3]. Furthermore, in 20–30% of cases, N2 nodes are found to be involved despite negative parenchymal or hilar nodes [1]. The prevalence of subclinical nodal metastasis and the variable anatomy of lymphatic drainage suggest that the prolongation in survival associated with extensive lymphadenectomy may be due to an increased detection of nodal disease or increased removal of nodes harboring occult foci of

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metastatic disease. Lymphatic mapping using standard vital blue dyes and radioisotopes has been attempted by several investigators with limited success due to a number of factors including difficulty visualizing dyes in anthracotic nodes, lack of tracer migration, and risk of radiation exposure to patient and personnel [4,5].

While recent advances in minimally invasive surgical techniques and ablative therapy have decreased the morbidity of lung cancer surgery and increased the treatment options available for the high-risk patient population, reliable methods of identifying and treating nodes at risk for micrometastases remain elusive. Near-infrared (NIR) fluorescence imaging detects light with wavelengths in the 700–900 nm range, just outside of the visible spectrum. Near-infrared optical imaging systems detect NIR fluorescence and can overlay these images on visible video image in real-time. The Fluorescence-Assisted Resection and Exploration (FLARE™) system, developed by Dr. John Frangioni of Beth Israel Deaconess Medical Center, is an NIR optical imaging system developed for intraoperative use which creates a real-time merged NIR/visible spectral image of the operative field, allowing the surgeon to actively identify and manipulate NIR-positive structures in the patient. The real-time use of NIR fluorescent markers as an intra-operative guide is therefore analogous to performing a videoscopic operation with the field visualized on a video monitor.

NIR fluorophore-based contrast agents evaluated in preclinical studies of SLN mapping in lung cancer include semiconductor nanocrystals, often referred to as quantum dots (QD). These nanoscale particles contain a heavy metal core and shell which emit in the NIR spectrum and a hydrophilic outer layer which facilitates lymphatic migration. Clinical use of QD has been hampered however, as the need for heavy metals within the particle poses significant risk of toxicity to the patient and has barred regulatory clearance and clinical application [6]. For this reason, current clinical efforts have been focused on the use of organic NIR fluorophores of which indocyanine green (ICG) and methylene blue are already FDA-approved. Indocyanine Green (ICG), utilized conventionally in angiography and dilution studies, fluoresces within the NIR spectrum at 830 with minimal autofluorescence in situ. Human serum albumin (HSA) has been bound to ICG in order to increase the quantum yield of this organic NIR fluorophore, thus increasing detection at very low ICG doses. HSA:ICG has now been used successfully in large and small animal models for lymphatic mapping of a number of anatomic structures including subcutaneous tissues, esophagus, pleural space and lung [7,8,9]. This approach has also been utilized to identify sentinel lymph nodes (SLNs) in the setting of malignancy as evidenced by the migration of ICG: HSA from a peritumoral injection site to the draining lymph nodes in a swine model of spontaneous malignant melanoma. Histopathologic analysis of NIR-positive nodes demonstrated intranodal micrometastatic deposits whereas NIR-negative nodes in the nearby nodal basins were histologically normal [7]. Similar results have also been reported with the use of ICG in several clinical trials examining lymphatic mapping and SLN identification in patients with breast cancer [10].

NIR imaging technology offers distinct advantages compared with traditional SLN mapping methods including a high signal-to-noise ratio and low tissue autofluorescence, making detection superior to other methods using vital blue dyes. Furthermore, the imaging system does not use laser light or radioisotopes thus avoiding any exposure hazard for the patient or OR staff, making this technology ideal for intra-operative lymphatic mapping and SLN identification. Therefore, given the low surgical field background and excellent safety profile of ICG:HSA, several investigators have clinically explored this technology and have established safety and feasibility of ICG lymphatic mapping for intra-operative SLN identification in patients with breast cancer [11]. Clinical application of NIR lymphatic mapping is now being expanded to patients with lung cancer in an ongoing NCI-funded trial

at Brigham and Women's Hospital in collaboration with Beth Israel Deaconess Medical Center.

Adjuvant chemotherapy is not currently recommended for patients with surgically resected stage I NSCLC as it has not been shown to significantly decrease recurrence risk or prolong survival in this population. Initially this finding seems somewhat counterintuitive given what we know about the incidence of occult nodal metastasis; however, efficacy of the cytotoxic chemotherapy agents traditionally used in adjuvant therapy for NSCLC is dependent upon concentration and duration of exposure within the target tissue. An inherent limitation of systemic chemotherapy in the treatment of nodal disease is the low drug concentration present within the nodes and the limited duration of exposure at doses within the therapeutic window. Biodistribution studies of paclitaxel show a concentration within lymph nodes at 24 hours of approximately 0.06% of the systemic dose [12]. Similarly, Chen and colleagues assessed intranodal drug levels present in the operative specimen 6–24 hours following systemic or peritumoral (lymphatic) administration of carboplatin in 60 patients with breast cancer [13]. Axillary nodes were then analyzed for the presence of metastatic disease and tissue concentration of carboplatin. Peak levels of carboplatin were detected within the axillary nodes 12 hours after peritumoral subcutaneous injection and were nearly 300 times higher than corresponding intranodal drug levels detected in subjects receiving the same dose of carboplatin via intravenous injection.

Given the encouraging results with direct nodal delivery of chemotherapy together with the challenges inherent in consistently identifying sentinel nodes in lung cancer, methods of effectively delivering chemotherapy to at-risk thoracic lymph nodes during lung cancer treatment are currently being investigated in parallel with SLN mapping studies. Our group is presently evaluating nodal delivery of paclitaxel, a mainstay of adjuvant treatment of NSCLC, via a polymer-based nanocarrier system designed to effect direct intracellular drug delivery. Briefly, a methacrylate-based monomer is polymerized with a pH-sensitive crosslinking group resulting in a 50–100 nm hydrophobic nanoparticle encapsulating 1–5% paclitaxel by weight. Upon endocytosis and exposure to the acidic pH present within the endosome, the hydroxyl crosslinking groups are cleaved resulting in transition of the polymer to a hydrophilic state with resulting expansion and drug release [14]. These paclitaxel-loaded expansile nanoparticles (Pax-eNP) can now be labeled with fluorophore dyes to facilitate fluorescent and/or real-time NIR imaging for real-time evaluation of lymphatic migration and nodal delivery *in situ*. Further studies are planned to evaluate intrathoracic nodal drug delivery and concomitant imaging via this nanocarrier system.

In addition to the identification and treatment of occult locoregional metastasis, nanotechnology-based applications have been studied to improve other commonly-used adjunct techniques in lung cancer diagnosis and therapy. Nanoparticle-mediated administration of gene therapy agents has been explored with the goal of eventually eliminating the need for bioengineered adeno- and retroviral gene therapy, a requirement which has hindered the clinical application of this technology [15]. Antibody-labeled quantum dots have been used to characterize subcellular patterns of biomarker localization in *in vitro* tumor cells expressing epithelial growth factor receptor (EGFR) mutations [16]. Gold and silica nanoshells have been designed to convert NIR-wavelength light to thermal energy and show promise in preclinical studies evaluating their efficacy in tumor ablation [17,18,19].

Nanotechnology is an exciting and rapidly progressive field offering potential solutions to multiple challenges in the diagnosis and treatment of lung cancer, with the potential for improving imaging and mapping techniques, drug delivery and ablative therapy. With promising preclinical results in many applications directly applicable to thoracic oncology, it

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