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Pathways in Cancer

Clinical insight and analysis in advanced cancer care

Updates from the Mercy Cancer Institute

Costanzo Di Perna, MD

The five-year survival rate for lung cancer patients across all stages continues to be quoted at a dismal 15%. Does this make sense for patients whose lung cancers have been found and staged as IA?

Clearly physicians across the board would agree that lung cancer is curable in the majority of cases that are found early. Lung cancer screening continues to be controversial—at least in the public forum. Interestingly, when physicians are questioned regarding this crucial topic "behind the scenes," their responses are almost unanimously in favor of screening.

Surgery continues, and in my opinion will continue, to be the best treatment choice for early lung cancer—either lobectomy or wedge resection. Lung surgery is exceedingly safe and effective including for high-risk patients. Lung surgery is well-known and familiar; we clearly know its morbidity and know its effectiveness. When compared to SBRT or stereotactic radiation, lung surgery happens in one day, and sometimes patients go home that same day. Surgery offers not only resection (extracting the tumor) but also offers cancer staging, which SBRT does not. Classic and immutable oncologic principles include (1) complete R0 resection and (2) lymph node dissection versus lymphadenectomy; both of these principles do not occur with SBRT.

That being said, SBRT is an effective and excellent modality and other option for lung cancer in those patients who cannot undergo surgical resection. In this edition of *Pathways in Cancer*, Ellen Wiegner, MD, will discuss SBRT and lung cancer. It is a privilege to have Dr. Wiegner in our Sacramento community of radiation oncologists. She is truly an exceptional clinician and will make a great impact on lung cancer in Sacramento for years to come.

Parimal Bharucha, MD, now having joined Mercy Medical Group, will discuss lung cancer biological markers, as well as novel chemotherapeutics in this issue of *Pathways in Cancer*. As we are learning, lung cancer is being characterized far more accurately these days than before. Non-small cell lung cancer is highly complex and not just one type, but likely many.

In November—Lung Cancer Awareness Month—the Mercy Cancer Institute (MCI) will be producing and airing a lung cancer documentary on News 10. The documentary, 30 uninterrupted minutes, will air at 7:30 p.m. on Thursday, November 29 and replay in its entirety Sunday, December 2. It will present lung cancer patients, all non-smoking women, who underwent surgery for lung cancer with excellent results.

Also in November, the MCI and American Lung Association will be hosting a lung cancer panel discussion with experts in the field at the Mercy Cancer Center in Sacramento. These efforts are happening in November with the sole purpose of underscoring the problem and recognizing cancer's number one killer.

Please enjoy this issue of *Pathways in Cancer*. We encourage all physicians to recognize November as Lung Cancer Awareness Month—with both our aforementioned activities and in your clinical practices.

"SBRT is an effective and excellent modality and other option for lung cancer in those patients who cannot undergo surgical resection."

Mercy Cancer Institute of Greater Sacramento
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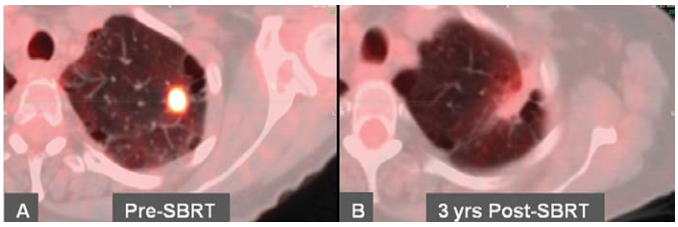
Stereotactic Body Radiotherapy in Stage I Non-Small Cell Lung Cancer

Ellen Wiegner, MD

While surgery remains the standard treatment for patients with stage I non-small cell lung cancer (NSCLC), a significant proportion of these patients have medical co-morbidities which preclude them from undergoing an operation. Additionally, a substantial number of patients who are technically operable will decline surgery. Until recently, these patients were offered a course of conventionally fractionated external beam radiotherapy delivered over five to seven weeks. However, patients treated with conventional radiotherapy fare much worse than those treated with surgery, with poor local tumor control and dismal long-term survival. In the last decade, stereotactic body radiotherapy (SBRT) has revolutionized the treatment of patients with stage I NSCLC. Advances in imaging and radiation techniques now allow radiation oncologists to non-invasively deliver highly conformal ablative radiation doses to the tumor in three to five treatments, while minimizing dose to adjacent normal tissues. For patients with stage I NSCLC who are unable to undergo surgery, SBRT is a highly effective and curative treatment option. The landmark Radiation Therapy Oncology Group (RTOG) 0236 study published in JAMA in 2010, demonstrated a remarkable three-year local tumor control rate of 98% in medically inoperable patients with stage I NSCLC treated with SBRT. Additionally, three-year overall survival was 56%, despite multiple competing causes of death in this highly selected patient population. In addition to being highly effective, RTOG 0236 also demonstrated that, in properly selected patients, this treatment was well tolerated with low risk of severe late toxicity.



A. PET-CT demonstrates a hypermetabolic left upper lobe NSCLC before SBRT treatment

B. PET-CT 3 years after SBRT treatment demonstrates complete metabolic response with mild treatment related lung fibrosis

"Our new Mercy Cancer Center facilitates such multidisciplinary care, and we have a thriving thoracic oncology SBRT program led by a team of radiation oncologists and thoracic surgeons."

The rate of clinical pneumonitis is generally less than 20% after SBRT, and other self-limited side effects including fatigue, cough and chest wall pain are relatively uncommon. An important caveat, however, is that patients with centrally located lung tumors adjacent to mediastinal structures were excluded from participation in RTOG 0236 because initial pilot studies had demonstrated higher rates of severe late toxicity in this patient population. Since the publication of RTOG 0236, though, a number of prospective and retrospective institutional studies have demonstrated that using lower doses of radiation or more protracted SBRT courses in this patient cohort results in acceptable toxicity and durable tumor control. Based on the results of RTOG 0236 and other institutional studies, SBRT is now the standard treatment for patients with medically inoperable stage I NSCLC.

While the role of SBRT in medically inoperable stage I NSCLC patients is clearly established, the use of SBRT in patients who are medically fit to undergo either lobectomy or a more limited sublobar resection remains under active investigation in large national and international cooperative group trials. As we await the results of these trials, SBRT is a promising treatment choice for patients who are borderline operable

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Lung Cancer Molecular Characteristics

Parimal Bharucha, MD

Treatment of patients with lung cancer depends upon the cell type (non-small cell lung cancer [NSCLC] versus small cell lung cancer), tumor stage, molecular characteristics and an assessment of the patient's overall medical condition.

The focus recently has shifted towards targeted therapy for advanced NSCLC. It is recommended that whenever possible, therapy should be individualized based upon molecular and histologic features of the tumor.

Abnormalities in several cell-signaling pathways have been identified in NSCLC. Tumor growth and progression are dependent upon the activity of cell surface membrane receptors that control the intracellular signal transduction pathways regulating proliferation, apoptosis, angiogenesis, adhesion and motility. One such family is receptor tyrosine kinase (TK) which includes an epidermal growth factor receptor (EGFR – HER1 or ErbB1). TK activity is tightly controlled in normal cells, though in malignant cells, the genes encoding these receptors have escaped from usual intracellular inhibitory mechanisms. Another novel fusion oncogene is echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK).

"Tumor growth and progression are dependent upon the activity of cell surface membrane receptors that control the intracellular signal transduction pathways regulating proliferation, apoptosis, angiogenesis, adhesion and motility."

Assessment of EGFR mutations is usually carried out on a biopsy of the primary tumor, though analysis of DNA from other sources may be feasible. Erlotinib and Gefitinib are small molecule EGFR – TK inhibitors that were initially developed for use as second-line therapy after failure with chemotherapy regimens. Multiple studies including phase III randomized trials have identified adenocarcinoma, women, non-smokers and Asians to have more favorable prognoses and be more responsive when treated with this agent. The presence of activating mutations in the EGFR receptor (deletions in exon 19, L858R in exon 21) is predictive of responsiveness. Primary resistance to these agents is associated with mutations in K-ras. Acquired resistance is due to the substitution of methionine for threonine at position 790 (T790M), or amplification of mesenchymal epithelial transition growth factor oncogene (MET). Agents blocking the EGFR TK pathway have been associated with cutaneous, gastrointestinal, pulmonary and hepatic toxicity. Active smoking increases the metabolism of Erlotinib, thereby decreasing exposure to that drug.

Clinical features associated with EML4-ALK oncogene are non- or light-smoking history, younger age and adenocarcinoma with signet ring or acinar histology. Overall incidence of ALK gene rearrangement is about 4%. Cancer cell lines harboring this translocation are effectively inhibited by small molecule inhibitors that target the ALK tyrosine kinase-Crizotinib. This can be detected in tumor specimens using gold standard fluorescence in situ hybridization, immunohistochemistry or reverse transcriptase polymerase chain reaction of cDNA.

Crizotinib is a multitargeted small molecule tyrosine kinase inhibitor that inhibits ALK phosphorylation and signal transduction. This inhibition is associated with G1-S phase cell cycle arrest and induction of apoptosis. The combined objective (complete plus partial) response rate was 55%, the majority of which was achieved during the first eight weeks of treatment. One- and two-year survival rates from a nonrandomized retrospective analysis were 74% and 54% respectively. Acquired resistance can develop after an initial response. LDK378 is a newer agent that is more potent and selective than Crizotinib and may overcome acquired resistance. Common side effects include visual disturbances and gastrointestinal side effects. Hepatotoxicity, fatal pneumonitis, QTc prolongation has been reported.

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Stereotactic Body Radiotherapy in Stage I Non-Small Cell Lung Cancer continued

candidates or for patients who decline surgery. For this patient population, multidisciplinary care involving both a thoracic surgeon and radiation oncologist is imperative for optimal patient management. Our new Mercy Cancer Center facilitates such multidisciplinary care, and we have a thriving thoracic oncology SBRT program led by a team of radiation oncologists and thoracic surgeons. With both SBRT and surgery in our armamentarium, we now can offer highly effective, safe and potentially curative treatment to nearly all patients with stage I NSCLC.

Lung Cancer Molecular Characteristics continued

American College of Oncology recommends patients should have tumor tissue assessed for the presence of a somatic mutation in the EGFR and ALK fusion oncogene. For patients whose tumor contains an ALK fusion oncogene, initial treatment with Crizotinib (Grade 1B) and those with characteristic mutation of EGFR, initial monotherapy with EGFR-TK inhibitor (Grade 1A) is recommended. Treat with chemotherapy, if neither mutation is present (Grade 1B).