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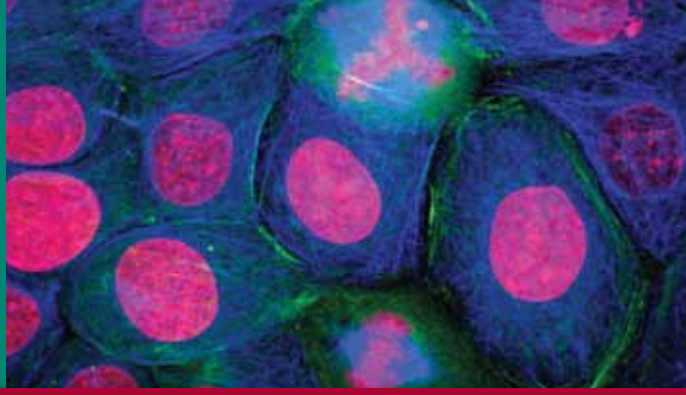

ADVANCES IN CANCER

SEPTEMBER 2009

A Non-surgical, Radiological Approach to the Treatment of Cancer

Peter J. Julien, MD

Cancer has traditionally been approached either systemically with chemotherapy or locally with surgery or radiation therapy. Recent advancements in minimally invasive therapies such as radio-frequency ablation (RFA) are adding another weapon to the anti-cancer arsenal.

Using RFA to treat specific cancers

RFA provides effective local treatment of small tumors of the kidneys, lungs, liver and bones, with very low complication rates and resultant survival data that are often similar to surgery, particularly for small peripheral kidney cancers. Currently, RFA is being used to treat:

- Stage 1 lung cancer in patients who are not eligible for surgery because of co-morbidities, including severe heart and/or lung disease
- Kidney cancer in patients with small tumors, usually under 4 cm in the outer margins of the kidney
- Liver cancer in patients who have tumors that are under 4 cm in size, often with cirrhosis of the liver or limited metastatic disease
- Osteoid osteoma, a benign skeletal neoplasm of unknown etiology which produces intense pain at the tumor site
- Bone pain related to metastatic disease from various cancers

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Figure 1: *Pre-treatment CT scan showing Stage 1 lung cancer in 85-year-old female patient who is not a surgical candidate.*

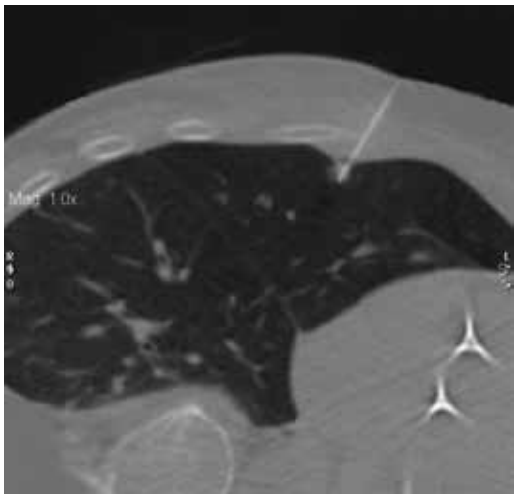

Figure 2: *CT scan showing radiofrequency ablation needle in cancer tissue.*

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Cedars-Sinai Medical Center
Samuel Oschin Comprehensive Cancer Institute
Steven Piantadosi, MD, PhD
Director
(310) 423-8431
steven.piantadosi@cshs.org

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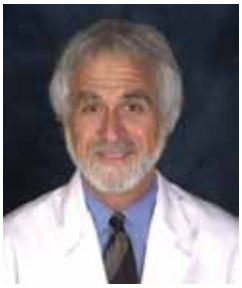
Delivering RFA therapy

During an RFA procedure, an ablation probe is placed directly into the target tissue, usually under computed tomographic (CT) guidance. Once the probe is properly positioned, the generator is turned on. Radiofrequency energy is applied to the tumor tissue, with resultant heat created at the target site ranging from 150 to 180º F. The radiofrequency energy flows through the electrodes, causing ionic agitation and therefore friction, in the nearby tissue. It is this friction that creates heat, with the subsequent destruction of tumor tissue usually completed within 12 minutes.

Analyzing current RFA outcomes

Because this procedure does not surgically remove tumors, its success depends on radiologic follow-up, including the use of CT, PET and/or MR scans. Add introductory sentence:

- When RFA is used on small peripheral renal cell cancers, the data suggests that the results are equivalent to surgical removal.
- Radiofrequency ablation results for primary cancer of the liver and limited metastatic disease under 4 cm are very encouraging – approaching surgical results, particularly in cirrhotic patients
- RFA is the current accepted standard of care for osteoid osteoma
- For bone pain associated with metastatic disease, the results of local treatment with RFA are excellent. Many patients who have become narcotic-dependent to treat their pain and who have been unresponsive to radiation therapy have responded to local pain control using RFA.
- Lung cancer and limited metastatic disease to the lungs from various malignancies have encouraging preliminary results. However, since this is the newest use of RFA, final outcomes have not been followed long enough to make a definitive conclusion as to the long-term success of this therapy.



Dr. Julien is Chief of Thoracic Imaging and Director of the Radiofrequency Ablation Program at Cedars-Sinai.
JulienP@cshs.org

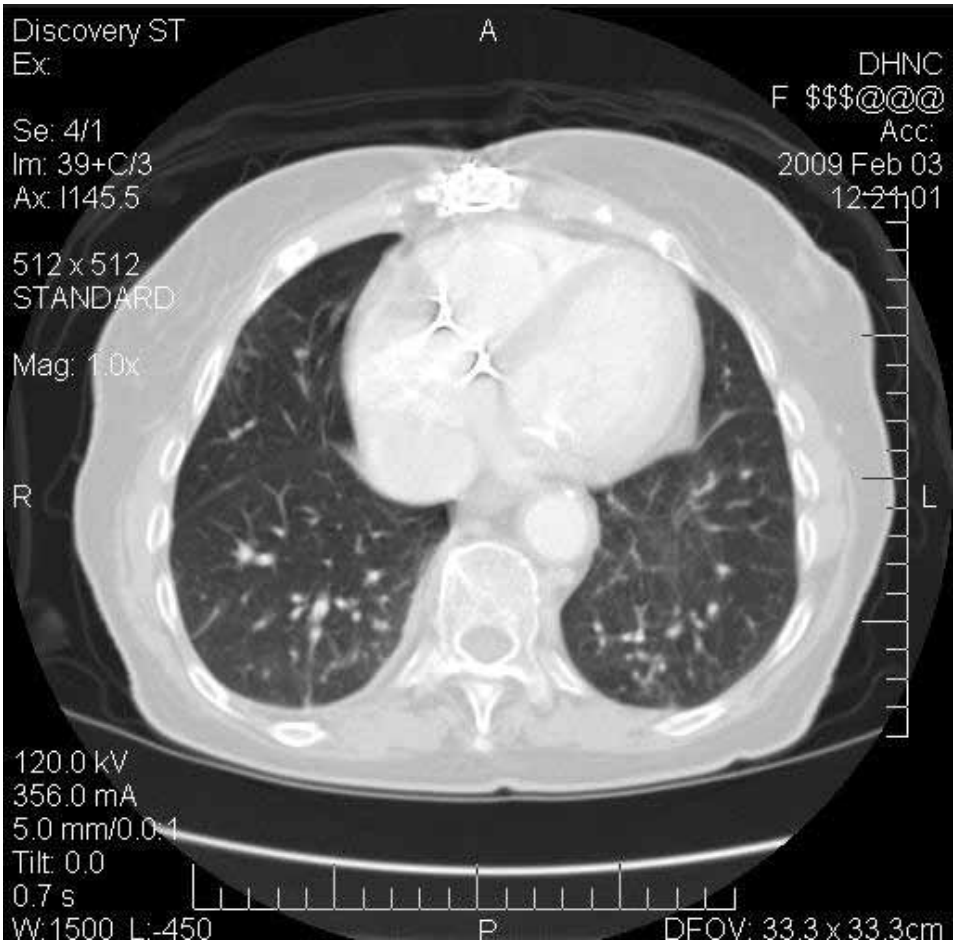


Figure 3: *CT scan one year post-treatment showing disappearance of cancer in 85-year-old female patient.*

Case Study: Minimally Invasive Lung Cancer Surgery

Robert McKenna, Jr., MD

A 72-year-old woman presented with persistent coughing and severe shortness of breath that required oxygen. X-rays showed a collapsed right lung, and bronchoscopy revealed a tumor obstructing her right main stem bronchus. A biopsy of the tumor mass identified a Stage 1 squamous cell carcinoma.

When non-small cell lung cancers are detected at an early, localized stage, surgery has the highest cure rate. Accordingly, I recommended photodynamic therapy to break up the tumor followed by a minimally invasive lobectomy. No radiation or chemotherapy was required for this Stage 1 cancer.

Photodynamic therapy has proven an effective technique for debulking endobronchial tumors over an acceptably short period of time. The therapy involves combining photoactivate medication with laser-generated light to destroy tumor cells. In the first phase of this patient's treatment, she was injected with Photofrin® and underwent laser surgery via bronchoscopy two days later.

After her photodynamic treatment, there was no longer evidence of the tumor in the right main stem bronchus. With the bronchus now opened, the right middle and lower lobes regained function, and the patient no longer experienced shortness of breath or needed supplemental oxygen. Both her breathing and her pulmonary function test returned to normal.

For the second phase of this patient's surgical treatment, I used a staging mediastinoscopy to remove the lymph nodes, which were found to be negative. Next, I employed video-assisted thoracoscopy (VATS) to perform a sleeve lobectomy, in which the main stem bronchus and the intermediate bronchus were incised, the upper lobe was removed, and the intermediate bronchus was re-implanted to the trachea. With visualization on a monitor, both lymph node sampling and dissection could be performed through an incision of approximately 5 cm without spreading the ribs. Currently, the patient is doing well with no evidence of recurrence.

Moving from open lobectomy to VATS

Sleeve resection is at present the surgical treatment of choice when anatomically feasible. Lobectomy using VATS, while it offers substantial patient benefits, is a technically challenging procedure – and only 10 to 20 percent of lobectomies in the United States are currently accomplished using minimally invasive techniques. The remainder are performed as open procedures.

Although many VATS lobectomies have been performed over the 18 years since its introduction, some physicians have remained concered about the procedure's safety and associated morbidity and mortality. To address this issue, my colleagues and I published a retrospective review of 1,100 consecutive patients who underwent a standard VATS lobectomy with lymph node dissection at Cedars-Sinai (IRB #4267). The data showed VATS lobectomy for bronchogenic carcinoma provides the same survival rates as expected for lobectomy done via the traditional invasive thoracotomy incision.

Over time, we expect the percentage of VATS procedures to increase as more thoracic surgeons receive specialized training in the technique.

Dr. McKenna is Medical Director of Thoracic Surgery and Trauma, Surgical Director of the Women's Guild Lung Institute and Program Director of the General Thoracic Surgery Fellowship at Cedars-Sinai.
Robert.McKenna@cshs.org

Targeting Inoperable Lung Cancer with Stereotactic Body Radiation Therapy

Amin J. Mirhadi, MD

Early stage non-small cell lung cancer (NSCLC) is ideally managed with surgical resection. However, a large number of patients with NSCLC are determined to be inoperable based on pulmonary function tests, performance status, or other factors. Also, many of them have sought to explore other options given the potential morbidity and pain associated with surgical resection, particularly in the elderly population.

Historically, patients who elected not to have surgery were managed with standard fractionated radiation therapy. However, this proved to be cumbersome, given that a typical treatment course was six to seven weeks and generally had very poor outcomes.

Stereotactic body radiation therapy (SBRT) offers a possible alternative for radiation therapy of NSCLC. SBRT is an extension of the approach successfully used in stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) to deliver precisely targeted radiation to intracranial, orbital and cranial-base tumors, as well as benign conditions that can use the skull as a reference system.

The development of SBRT has required significant technical advances in imaging, patient immobilization and conformal radiation delivery techniques. Like SRS and SRT, the technique utilizes precisely targeted radiation to a tumor while minimizing radiation to adjacent normal tissue. This targeting allows treatment of small- or moderate-sized tumors in extracranial sites in either a single or limited number of dose fractions.

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Exploring the Role of Circadian Rhythms in Lung Tumorigenesis

H. Phillip Koeffler, MD

Circadian rhythms are endogenous biological clocks of about 24 hours that regulate biological and behavioral activities in almost all organisms. In mammals, the circadian system affects a variety of physiological processes including metabolic pathways, homeostatic function of steroid hormones and their receptors, cell cycle progression, and aging. In fact, between two and 10 percent of genes in any given tissue are under circadian control.

Recent data have demonstrated that major biological pathways, including those critical to cell division, are controlled by circadian rhythms – and that disruption of these rhythms may be involved in pathological conditions, including human tumorigenesis. Recent studies have also shown that the silencing of tumor suppressor genes as a result of epigenetic alterations is an early event in many malignancies, including non-small cell lung cancer (NSCLC).

A potential tumor suppressor

In the normal 24-hour circadian rhythm cycle, mammals express Clock and Bmal genes beginning in the early morning and Cry and Per genes in the early evening. In some cancer patients, these genes are markedly deregulated. Particularly, Per genes are downregulated, and these may contribute to uncontrolled cell proliferation, a hallmark of malignant transformation.

At Cedars-Sinai, investigators are looking at the important role of circadian rhythm genes in the proliferation of cancer cells, including NSCLC (IRB #3017). More than 22,000 genes have been screened from lung cancer tissues, and adjacent normal lung tissues obtained from a library of lung cancer surgical specimens. From these samples, the period 1 (Per1) circadian clock gene was identified as a potential tumor suppressor in NSCLC. Using real-time polymerase chain reaction (PCR), the investigators determined that Per1 levels were low in 70 percent of the NSCLC patient samples and cell lines compared to normal lung tissue. Forced expression of Per1 in NSCLC cell lines led to significant growth reduction and loss of clonogenic survival.

Looking to the future

Our research has helped underscore the link between circadian epigenetic regulation and cancer development by determining that DNA hypermethylation and histone H3 acetylation are potential mechanisms for silencing Per1 expression in NSCLC. Further work is underway to increase our understanding of how the circadian clock regulates pathways that are crucial for the suppression of malignant growth and to identify specific genes and pathways that are deregulated in NSCLC.

Dr. Koeffler is Director of the Division of Hematology/Oncology and holder of the Mark Goodson Chair in Oncology Research at Cedars-Sinai's Samuel Oschin Comprehensive Cancer Institute.
H.Phillip.Koeffler@cshs.org

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Exploring advantages of SBRT

Early results suggest that SBRT offers important advantages in a number of settings. The technology is evolving rapidly, and the optimal dose, schedule and technique remain to be determined. Previous experience with conventional external beam radiation therapy showed that control of the primary lesion is directly related to the dose of radiation, suggesting that higher doses might offer better local control.

SBRT dosing is influenced by a number of parameters, including the size of the tumor and the number of fractions. Ultimately, the goal is to deliver the maximum amount of radiation to the tumor while limiting the exposure of surrounding normal lung tissue to safe levels. Although it seems counter-intuitive, fewer fractions is considerably more cytoxic than multiple small fractions because cells have the ability to repair themselves when small dose fractions are given. This applies to both normal and cancerous cells. When very little normal tissue is irradiated, the necessity to fractionate becomes diminished and much larger doses can be delivered.

In the largest reported experience, 257 patients with Stage 1 NSCLC were treated at multiple institutions with varying doses and schedules, ranging from 18 to 75 Gy in 1 to 22 fractions (note 1). The rate of local recurrence was 15 percent, and a dose-response relationship was found for a biological equivalent dose (BED) ≥100 Gy versus <100 Gy (recurrence rate, 8 versus 43 percent). Among medically operable patients, five-year survival was significantly higher in those treated with BED ≥100 Gy compared to a BED <100 Gy (71 versus 30 percent).

SBRT may be a valuable therapeutic option in patients who are not candidates for surgery, either for small primary lung cancers or for carefully selected patients with lung metastases. Radiofrequency ablation may be another option in institutions with appropriate expertise.

Dr. Mirhadi is a radiation oncologist at the Samuel Oschin Cancer Center and a member of the Saul and Joyce Brandman Breast Center at Cedars-Sinai's Samuel Oschin Comprehensive Cancer Institute.
Amin.Mirhadi@cshs.org

Note 1: Onishi et al, J Thorac Oncol., 2007 Jul;2(7 Suppl 3):S94-100