

# Major Decision Forks: Arnold Ashley

Adenocarcinoma of Lung; Four Year, No-Evidence-of-Disease Survivor After Multiple Brain Metastases with Immunotherapy

## Decision Fork 1 (10/10/2000)

Bronchoscopy of lung confirms adenocarcinoma partially obstructing left main stem bronchus<sup>1</sup>. What should the initial treatment be?

**Conventional options:** Surgical resection (tumor in main left breathing passage requires resection of entire left lung) versus radiotherapy alone versus radiotherapy with concurrent chemotherapy versus initial (neoadjuvant) chemotherapy prior to subsequent surgical resection.

**Immunotherapeutic approach:** Protect host immunity during primary tumor bulk and clonagen<sup>2</sup> reduction as the over-riding objective. Institute radiotherapy to known tumor mass. Studies have proven pre-op radiotherapy, which allows the radiotherapy to depress immunity by releasing large amounts of tumor specific antigens from dying cancer to accumulate in the blood stream, does not improve survival. Mr. Ashley arrived with the specific request to avoid chemotherapy, traveling 300 miles and selecting as an assertion of his freedom to choose, the immune driven approach we offered. Radiotherapy with concurrent immunotherapy was begun. Initial immunotherapy was cimetidine, selenium, vitamin E, and replacement steroidal hormones.

## Decision Fork 2 (11/10/2000)

Should radiotherapy be further employed after reaching maximum to permit surgery?

**Background:** Treatment had been given at 120 cGy twice daily, and in 29 days elapsed time a dose of 4880 cGy had been delivered to the primary tumor mass. This is approximately 1200 cGy per week, an unusually intense dose rate. The small fraction size,

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<sup>1</sup> The main breathing tube, the trachea, branches into two "main stem bronchi", one to each lung. The main stem bronchi further subdivides to supply air to the entirety of each lung.

<sup>2</sup>Clonagen (definition) A single cell, including a cancer cell, capable of repeated division and expansion as a colony. Normal cells can divide only about 30 times before clonal expansion is curtailed by the telomere. Such cells have reached the limit of normal clonal expansion sometimes known as the Hayflick limit. Cancer cells have evolved adaptive mechanisms, making them uncontrolled by the Hayflick limit. Thus, not only do cancer cells fail to recognize host signals for host needs thereby growing where no cells are needed, but cancer cells are also capable of interminable expansion as a colony. Cancer cells ignore all normal self controls and are renegades. Such renegades must be destroyed by forces applied from without the cell.

however, protected normal tissue repair capacity. The 5-year survival for surgically resected adenocarcinoma of the lung is approximately 33%, and most deaths are cancer specific deaths; i.e., deaths caused by cancer. Surgical excision of resectable disease is the surest way to eliminate the primary tumor.

**Conventional approach:** Deliver more radiotherapy, increasing total dose to soft tissue tolerance level (which precludes surgery).

**Immunotherapeutic approach:** Surgery was chosen, and all gross residual cancer present after initial radiation therapy was resected.

**Result:** The path report describes “moderately differentiated adenocarcinoma with radiation change”.

**Comment:** We believe much of the primary cancer was rendered biologically dead by the preoperative combined concurrent immunotherapy and radiotherapy, in the interest of the patient’s ultimate tumor control and long term survival.<sup>3</sup>

### **Decision Fork 3 (11/11/2000)**

Should a serum carcinoembryonic antigen (CEA), the most important serologic marker for lung adenocarcinoma, be ordered?

**Common convention:** Ignore individual patient tumor markers and treat by “standard protocol”. Change strategy based on evidence of progression other than CEA rise.

**Immunotherapeutic approach:** We ordered the CEA. It was returned significantly elevated to 65.9 (normal: 3.0). We were now in a position to assess the degree of surgically induced tumor body burden reduction by the planned surgical resection in a quantitative way.<sup>4</sup> It is interesting to this researched that patients with lung cancer managed by physicians trained in medical oncology often have this test ignored.

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<sup>3</sup>“Biologically dead”: has a special meaning here. Radiotherapy causes crosslinking of DNA in the nucleus of cancer cells. This condition renders subsequent attempted division of the cancer cell a fatal event. However, the cancer cell must cycle through the cell cycle to division, the M phase or mitosis, for the cell to actually disintegrate. Thus microscopic images of recently irradiated cancer show evidence of disintegrating tumor and ostensibly viable “normal” cancer cells destined to die at the next attempted division. At this point, Mr. Ashley’s tumor was decimated of cancer, and those viable cells that might be released into circulation at surgery faced an activated immune system. In conventional treatment of 180 cGy per day plus chemo, the cancer is also shrunk, but the hematopoietic system is damaged and the lymphocyte mediated anticancer system is incapacitated. The systemic guard is down.

<sup>4</sup>The essence of science is testability. Tests are best when results can be described in a quantitative manner. CEA monitoring gives quantitative information.

## **Decision Fork 4 (1/02/2001)**

After the primary tumor was surgically removed, should post pneumonectomy systemic adjuvant treatment be employed?

**Common convention:** Watch and wait approach. By this time, most conventionally treated patients would have had several cycles of chemotherapy, their quality of life would be depressed, and significant hematopoietic depression would have occurred. Lymphocyte driven anticancer defenses would be in disarray.

**Immunotherapeutic approach:** Mr. Ashley was restarted on his immune stimulating medications that had been terminated one week before pneumonectomy.

## **Decision Fork 5 (11/06/2001)**

What is best treatment for multiple brain metastases?

**Background:** MRI reveals two brain metastases. These metastases seemed to be poor candidates for surgical removal due to significant risk of neurologic damage from surgical excision. Implicit in two metastases recognizable on MRI and CT scan is the high risk for other sub-resolvable micrometastases in other parts of the brain. Treating less than whole brain results in other "fertile soil" metastases in areas of the brain not treated. Remember, the brain has the highest risk of distant metastatic relapse of any organ in patients with adenocarcinoma of the lung.

**Conventional approach:** Critics would have asserted our immunotherapy efforts had failed. Acceptable conventional approaches would include large fraction<sup>5</sup> localized "boost" radiotherapy to recognizable disease. External beam (300 cGy x 10 = 3000 cGy) is a standardized regimen.

If systemic chemotherapy were initiated based on a presumption of generalized systemic failure as evidenced by the brain metastases, we have already discussed the consequence that most standard chemotherapy agents destroy or severely compromise anticancer immunity.

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<sup>5</sup>During radiotherapy, a total dose of treatment is typically divided into individual smaller doses given over several days. These smaller individual doses are called "fractions". Fractions in the 110 cGy to 180 cGy range are gentle on normal tissues. Larger fractions in the 200 cGy to 1000 cGy range become increasingly more destructive to surrounding normal tissues unavoidable encompassed in an irradiated volume. If preservation of normal tissue function and minimal long term side effects are considered important, large fractions usually should be avoided. We prioritize long term quality of life in our management decisions, and seldom use large fractions.

**Immunotherapeutic approach:** The large fraction radiotherapy path would introduce a significant risk of generalized neuronal damage after a few years of survival. Radiotherapy to the brain accelerates brain aging, and we believe neuronal repair functions must be assiduously preserved. Neurons are very sensitive to fraction size, and are protected by small individual treatments. We employed 96 hour 5-FU infusions x 5 during whole brain radiotherapy, and we treated the whole brain to 4980 cGy, mostly at 120 cGy twice daily. This form of chemotherapy has toxicity to normal gut but preserves the blood making systems (hematopoiesis), including natural killer and other lymphocyte systems.

## **Decision Fork 6 (12/12/2001)**

Should the localized tumor deposits receive additional radiotherapy?  
If so, how much?

**Conventional approach:** Cure nihilists might not have boosted at all. There is no question that many medical oncologists would have seized this opportunity to initiate conventional cytotoxic chemotherapy. Physicians who choose to boost localized deposits commonly employ large fraction methods including gamma knife or large fraction radiosurgery<sup>7</sup>. Brain metastases in lung cancer, if destroyed, may result in cure. To accomplish this objective, this cancer's ability to sustain the growth of colonies elsewhere in the body destroyed, and the primary tumor must be destroyed.

**Immunotherapeutic approach:** Focal functional loss as a consequence of focal brain damage at the site of high dose radiotherapy arises almost immediately after large fraction radiation therapy. This is akin to the loss of good tissue when a "margin" of normal tissue is excised around a cancerous mass to increase the likelihood that none is left behind. Most people, however, need all the brain they were born with. You make focal deletions in the memory of a computer with considerable risk of malfunction. We continued the two brain masses to 6480 cGy, using fractions of 150 cGy twice daily. This dose was intended to cause total destruction of these 5-FU sensitized masses. We kept our "eye on the ball"; i.e., preserving immunity through all adversity unless convincing evidence of dissemination was present. We perceived in an immunotherapeutic approach protective of normal structures was not shaken. To further enhance immunity, we started IL-2 as belly plaque technique.

<sup>7</sup>The association of "knife" and "surgery" with these strictly radiotherapeutic methods has a political meaning. In large centers, neurosurgeons often are consulted for any type of brain tumor, including metastases. The surgeon becomes the gatekeeper for further triage. Gamma knife and radiosurgery methods are carried out with the stereotactic techniques developed by the surgical community, and the surgeon's presence can generate large fees for the surgeon's participation. The methods do not eliminate the need to get "margins" around the cancer, and methods akin to surgery destroy normal tissue.

<sup>8</sup>Tumors have characteristic sites to which they metastasize. It is characteristic of adenocarcinoma of the lung to relapse in the brain without evidence of cancer elsewhere.

## Decision Fork 7 (2/26/2002)

Should immunotherapy be sustained after patient enters serologic remission?

**Conventional approach:** Presume the tumor has been adequately treated, stop all immune stimulating efforts, and let the patient's "normal" immune physiology return.

**Immunotherapeutic approach:** In view of the very poor long term survival of adenocarcinoma of the lung in clinical remission after "standard" treatment, should we presume a heightened immune state was of critical importance and should we maintain immune stimulation and persevere with IL-2 and a multiple agent immune restoration and immune stimulating program?

**Background:** The CEA had risen prior to brain relapse and fallen as follows (also see graph):

<u>DATE</u>	<u>CEA</u>
3-15-2001	1.7
10-03-2001	3.8
10-23-2001	4.51
11-06-2001	MRI brain - The patient has an enhancing mass within the anterior portion of the right occipital lobe measuring 1.2 cm in diameter. There is surrounding edema that involves the posterior upper portion of the right parietal lobe and the upper portion of the right occipital lobe. There is a second lesion present within the medial portion of the left occipital lobe measuring 8 mm. There is surrounding edema that involves most of the left occipital lobe. There is compression of both occipital horns of the lateral ventricles.
11-12-2001	6.4
11-12-2001	start radiotherapy to brain
11-12-2001	start IL-2
11-16-2001	6.0
12-14-2001	5.6
12-19-2001	complete radiotherapy
01-22-2002	3.5
01-25-05	stop IL-2
02-26-2002	1.7

We chose the latter course of action.

**Result:** Excellent quality of survival, an ability to return to work, and persistent freedom from all evidence of disease for over 4 years.

## **Decision Fork 8 (Jan. 2005)**

Continue or stop IL-2?

This important decision was really open to Mr. Ashley's discretion. At this time his insurance company changed its policy and curtailed reimbursement for IL-2. In view of the protracted clinical and serologic remission, a CEA monitored cessation of IL-2 treatment seemed prudent enough.

The dosage of IL-2 was cut in half, from a once a day dosage to every other day, but other immune agents continued. Based on our experience, NK cell levels will probably fall significantly after the IL-2 decrease takes effect and belly plaque resolves over a few weeks.

**Comment:** We do not at present know how long IL-2 belly plaque treatment should be continued during immunotherapy treatment. We do know that high quality 4-year survival after multiple brain metastases is quite unusual.