Helical TomoTherapy for Lung Cancer Radiotherapy: Good Science Pays Clinical Dividends

The Challenge
Lung cancer kills more people each year in the US than prostate, breast, colon, liver, melanoma and kidney cancers combined. It kills three times as many men as prostate cancer and twice as many women as breast cancer. According to the American Cancer Society, 30% of cancer deaths each year in men and 26% in women are from lung cancer. This is despite lung cancer accounting for just 15% and 14% of all cancer cases in men and women respectively. An overall five-year survival rate of approximately 15% represents the poorest prognosis of any of the common cancers. By comparison, prostate cancer accounts for just 9% of cancer-related deaths but 25% of cases in men and breast cancer represents 15% of deaths and 27% of cases in women.

Up-to-date facts and figures can be found at the American Cancer Society website, cancer.org.

Why are the statistics for lung cancer so miserable? Partly because lung cancer discovered at any stage of disease – and especially at a later stage as is most common – is hard to control with the usual combinations of surgery, drugs and radiation. Lung tumors are resistant to treatment and the collateral damage to normal tissue, often termed toxicity, is always a limiting factor when considering more aggressive treatments. In the case of radiotherapy, the dose-limiting toxicities are mostly radiation pneumonitis (inflammation of the lungs) and esophagitis (inflammation of the esophagus). Keeping these toxicities low is a major consideration as this brings with it the potential to increase dose and improve the chance of eradicating the primary tumor (often termed local control). Although in many instances the primary tumor metastasizes to other parts of the body, local control has been shown to be a strong factor in overall survival [1]. Metastases are sometimes irradiated as well as the primary disease site, especially when there is a possibility that the visible lesions represent the limit of metastatic disease. In other words, if these metastases are all there is, it is worth trying aggressively to eradicate them. Oligometastases is the term for such metastases that are limited in number and location. Ascertaining the status of visible metastases as oligometastases is significant as it means that a treatment with curative intent may be an option, rather than a palliative regimen intended to improve quality of life but not realistically expected to rid the patient of all disease. Advances in imaging and diagnosis with technologies, such as positron emission tomography (PET) and other forms of molecular imaging, are the key here. There is a strong link between improvements in the ability to accurately target cancerous regions with radiation therapy technology and improvements in ability to accurately detect and delineate them with imaging technology.

About 85% of lung cancers are of the non-small cell type (NSCLC) with the rest being small cell (SCLC). Tumors detected at an early stage can often safely and effectively be removed surgically and for these cases the prognosis is relatively good – the five-year survival rate for patients diagnosed with stage I NSCLC is at least 50%. The trouble is that a small proportion of newly-diagnosed tumors fit this category. Less than 20% of cases in the US are diagnosed when the cancer is confined to the primary site. A further 20% or more of cancers have spread as far as regional lymph nodes and over 50% have also metastasized to distant sites. Average five year-survival drops precipitously to around 5%, and average life expectancy to less than one year, for disease diagnosed at a late stage. Cases are categorized into stages according to the size and spread of the cancer. This helps define the strategy for managing the disease. See the Surveillance Epidemiology and End Results database for further details of survival statistics in terms of disease stage (http://seer.cancer.gov/faststats/selections.php?series=cancer).

Radiation-based alternatives to surgery for early stage disease are in increasingly wide clinical use.
and showing great promise. Stereotactic body radiotherapy (SBRT) is being performed at many centers worldwide, including a growing number of TomoTherapy centers [2]. It is becoming clear that both surgery and SBRT are effective means of treatment for early stage lung cancer, and that a huge part of the battle for improved outcomes is to detect more tumors at a stage when these options are still viable. Clearly, early detection so that disease is more manageable with surgery and focused radiation has the potential for a major impact on overall prognosis for lung cancer sufferers. This article focuses mostly on later stage lung cancer however, which constitutes the overwhelming majority of cases for which radiation is used.

The Dose Dilemma

It has been established that increased dose improves control of disease in the irradiated region [3]. It has also been shown that delivering a higher dose to organs such as lung, esophagus and spinal cord increases the rate of radiation-induced complications. Consequently, “dose escalation” with the goal of improving local control has been practiced very cautiously in clinical trial environments. The optimal dose in terms of balancing local control and complications is as-yet unknown, and indeed is dependent on the ever-improving technology used for treatment. Furthermore, it is not just the total dose delivered that determines local control: the duration of the treatment course (days from start to finish) also plays a part. In particular, it has been observed that increasing dose while extending the treatment course can result in reduced effectiveness of the radiation from what would be expected from the increase in dose alone [4]. Prolonging the course means extra tumor cell repopulation during treatment, so increasing the dose by simply adding more treatment days is analogous to “swimming against the current” in terms of tumor cell killing.

A more effective method of increasing the radiation effect may be to deliver a higher dose per day, thereby not increasing total duration of the treatment course. In fact, increasing the dose per day allows a reduction in the total dose and in total number of treatment days. Following this strategy can make the overall radiation effect on the tumor cells greater than with a smaller dose per day, longer treatment course and higher total dose [5]. Such a strategy is known as hypofractionation. Stereotactic body radiotherapy (SBRT), mentioned earlier as an alternative to surgery for early stage lung cancer, is an extreme form of hypofractionation since the number of fractions is typically reduced to 5 or less.

Radiation and Chemotherapy

It is normal to administer both chemotherapy and radiotherapy in treatment of lung cancer, either sequentially or concurrently. The most potent treatment option in terms of survival has been shown to be concurrent chemo-radiation, but at a cost to side effects such as lung pneumonitis and esophagitis [6,7]. A clear goal for the radiation oncologist is to increase the benefit of the radiation component in terms of tumor control, but also to minimize the radiation-related toxicity so that the overall toxicity from radiation and chemotherapy is minimized. Ideally, from the point of view of survival, concurrent radiation and chemotherapy would be used and high quality radiotherapy can help make this more tolerable for the patient.

IMRT and IGRT

Techniques and technologies that allow delivery of higher tumor dose without exceeding normal tissue tolerances play an important role in improving outcomes. Two recent technological advances in radiation therapy are intensity-modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT).

The purpose of IMRT is to create a dose distribution that conforms to the shape of the target volume defined by the physician and minimizes dose to surrounding organs. More traditional conformal radiation therapy (CRT) attempts to do this by simply creating beam shapes that match the shape of the tumor as viewed from each beam direction. Each CRT beam has a uniform intensity of x-rays within its boundaries. IMRT is different in that beams have an optimized, non-uniform intensity according to target shape, its
geometrical relationship to healthy organs, required target dose and organ tolerance doses.

An example of the benefit of IMRT for lung cancer comes from an MD Anderson Cancer Center study where radiation toxicity in patients treated with IMRT was retrospectively compared with that in patients treated undergoing standard 3D conformal radiotherapy [8]. Both sets of patients were prescribed the same dose (63 Gy) but the IMRT patients had larger tumors. Despite the larger treatment volumes, the rate of grade 3 or higher pneumonitis (severe cough, not responding to narcotic drugs) in the IMRT patients was 8% compared to 32% for the conformal therapy patients. The difference comes from IMRT being able to keep the high-dose volume better confined to the tumor. TomoTherapy is an especially effective form of IMRT because of the much larger number of beam angles used than in most other forms of IMRT such as that used in the MD Anderson study.

IGRT is complementary to IMRT in that its role is to make sure that the planned dose distribution is actually delivered to the correct location within the patient on each day of treatment. The most common forms of IGRT involve x-ray imaging either in 2D mode or 3D computed tomography (CT) mode. 2D images can be used to visualize bony anatomy in one or more projections through the body, i.e. a traditional x-ray image. This is useful as long as bones, or other radio-opaque objects such as implanted metal markers, provide a good reference for the location of the actual target volume. CT allows visualization of bony and soft tissue anatomy in a 3D volumetric image, so it is a more informative means of finding the true location of the target volume at treatment time. CT-based image guidance is preferable as long as its use is practical in terms of time and additional dose incurred in the image acquisition process. The megavoltage CT (MVCT) scans used by TomoTherapy are typically acquired in 1-3 minutes and have been found to deliver a very low dose to patients—typically 1-2 cGy, or less than 1% of the prescribed daily treatment dose [9].

Clearly, given the motivation behind IMRT—keeping a prescribed high dose level restricted to the boundaries of the target volume—its use almost demands the concomitant use of IGRT to make sure that the target volume is properly covered by the intended dose level. Specifically, IGRT allows the use of a smaller high dose volume because of the reduced “margin for error” needed to account for uncertainties in patient setup. IGRT thus further reduces the amount of normal tissue receiving a high dose. The combined use of IMRT and IGRT is often referred to as IG-IMRT.

A Recap
It is worth recapping some of the important points to consider in lung cancer radiotherapy:

1. Cure rates for lung cancer are low, partly because of the difficulty in safely administering enough dose of either radiation or chemotherapy. In lung radiotherapy, it is critical to keep side effects such as radiation pneumonitis and esophagitis low so that dose, and thus local tumor control, can be maximized.
2. Local control of the primary tumor improves survival. Higher dose improves local control, but can increase side effects, so “dose escalation” has been done very cautiously.
3. Dose escalation by extending the course of treatment over more days incurs extra tumor cell repopulation during the course of treatment, lessening the benefit of the extra dose.
4. Another way of effectively escalating dose is to increase dose per day, while reducing the number of treatment fractions and duration of the treatment course. This is called hypofractionation, and if the course is shortened to just a few fractions, it is called stereotactic body radiotherapy (SBRT).
5. Less uncertainty in the extent of disease helps reduce the total volume needing to be irradiated. Accurate determination of extent of disease is helped by newer imaging techniques such as positron emission tomography (PET).
6. A dose that conforms more tightly to the target volume means less normal tissue irradiated. Highly conformal doses can be achieved using intensity-modulated radiotherapy (IMRT) such as provided by TomoTherapy.
7. Less uncertainty in patient setup for treatment helps reduce the total volume needing to be irradiated. Uncertainty in patient setup is reduced using image-guided radiotherapy (IGRT).

**Success with a Dose-escalated, Hypofractionated Treatment Protocol**

As outlined above, there are some clearly understood factors that affect the success of a lung cancer radiotherapy strategy, some posing a considerable dilemma to the physician. A treatment protocol should offer maximal chance of controlling the tumor while not incurring too many adverse side effects, especially those of higher grade. As with all radiation therapy, treatment of lung cancer involves this tradeoff, but the unusually high resistance of lung tumors to radiation means that doctors have to be especially inventive in finding ways to safely escalate the dose.

Thanks to many years spent gaining an understanding of what leads to side effects such as radiation-induced pneumonitis, and figuring out how to minimize these effects, researchers at the University of Wisconsin in Madison have come up with a protocol for treatment of NSCLC that has shown remarkable success. Technology has played a key role in the successful execution of these treatments and this is where TomoTherapy comes in.

The overall goal of the UW protocol is a common one—to deliver as much dose to the tumor as possible while respecting normal tissue tolerances. The difference is in the scientific manner used to arrive at this dose. All patients receive the same number of treatment fractions (25 in this case) and a safe dose per fraction is determined using radiobiological calculations that take account of dose to healthy lung relative to tumor dose. A higher lung dose to tumor dose ratio means that a lower dose per fraction should be used. This is because research has shown the average dose to healthy lung to be a strong factor in whether lung-related complications will occur.

“Binning” Patients

A characteristic of the UW protocol is that patients are categorized into one of 5 bins, essentially according to the ratio of mean lung dose to tumor dose. A larger ratio means a higher bin number (1-5), indicating that there is likely to be a higher risk of lung toxicity. In fact the method used for binning each patient uses the ratio of the mean normalized tissue dose to healthy lung ($NTD_{mean}$) to the normalized prescription target dose $NTD_{ref}$. The ratio is called $r_{NTD_{mean}}$ and this generally increases with the volume of the target relative to the volume of healthy lung, so larger tumors put the patient in a higher bin number. Normalized dose, in this instance, means the equivalent total dose in 2 Gy fractions. Normalization is necessary because, as mentioned above, the dose per fraction is not the same for all patients—it is chosen based on their bin number—and the cell-killing effect of radiation is dependent not just on total dose delivered but on the dose per fraction. In particular, a higher dose per fraction has a greater killing effect for a given total dose because cells are less able to repair themselves between fractions.

Each bin implies a different relationship between probability of lung pneumonitis and dose per fraction, where patients in a higher number bin have a greater probability of pneumonitis for a given fraction dose. Since the study aims to keep the grade 2 pneumonitis rate below a certain level (in this case approximately 20%), patients in a higher bin nominally receive a lower dose. Once a starting dose per fraction is chosen based on bin number, other limiting factors such as esophagus and spinal cord dose may require that the dose is reduced to the next level down.

The range of fraction doses used in the protocol is 2.28-3.22 Gy, equating to 57-80.5 Gy total dose over 25 fractions. Note that these doses are all larger than the standard dose per fraction of 2.0 Gy or less, and the number of fractions is lower than that traditionally used (typically 30 or more), qualifying the protocol as hypo-fractionated.
As mentioned earlier, for a given total dose, larger doses per fraction are more lethal to both cancer and normal cells. Radiobiological calculations reveal that the 57–80.5 Gy delivered to patients in this protocol is equivalent to 60–100 Gy in 2 Gy fractions in terms of tumor cell killing effect. Studies using 2 Gy fractions have shown a significant increase in patient survival with an increase in tumor dose over this range [3], but with the suggestion that the benefit of dose escalation is somewhat nullified by the associated extension of the treatment course [4]. The UW protocol specifically addresses this issue: some patients receive a higher dose than others, but by increasing dose per fraction rather than by increasing the number of fractions [5].

The table below shows the strategy for binning patients and determining the starting dose per fraction. An example for a “bin 2” patient is indicated via the blue shading. Note that the goal is to arrive at a dose per fraction that gives a grade 2 pneumonitis rate of less than 20%. For a bin 2 patient, this means choosing the 12–16% level since the next highest level includes a range exceeding 20%. Following this row across to the left we arrive at 3 Gy per fraction as a starting dose.

**Bin assignments according to rNTD\(\text{mean}\) (top), corresponding probability in percent of grade 2 or greater pneumonitis (middle) and starting dose levels (left).**

<table>
<thead>
<tr>
<th>Dose level (Gy per fraction)</th>
<th>Total Dose (Gy)</th>
<th>Equivalent Dose in 2 Gy fractions</th>
<th>rNTD(\text{mean}) = NTD(\text{mean})/Normalized PTV Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bin 1 0 – 0.119</td>
</tr>
<tr>
<td>2.28</td>
<td>57</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>2.53</td>
<td>63.25</td>
<td>70</td>
<td></td>
</tr>
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<td>2.77</td>
<td>69.25</td>
<td>80</td>
<td></td>
</tr>
<tr>
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<td><strong>75</strong></td>
<td><strong>90</strong></td>
<td><strong>12-16</strong></td>
</tr>
<tr>
<td>3.22</td>
<td>80.5</td>
<td>100</td>
<td>0-13</td>
</tr>
<tr>
<td>3.42</td>
<td>85.5</td>
<td>110</td>
<td>10-21</td>
</tr>
<tr>
<td>3.62</td>
<td>90.5</td>
<td>120</td>
<td>15-23</td>
</tr>
</tbody>
</table>

Grey shaded areas: ~ 20% grade 2 pneumonitis risk level
Blue shaded areas: Example of a bin 2 patient, showing rNTD\(\text{mean}\) (0.12–0.179), probability of grade 2 pneumonitis (12–16%) and starting dose level (3.00 Gy per fraction).

**Other Aspects of the Protocol**

Here, the science of working out the maximum safe dose per fraction, given the volume of lung involved, is coupled with the TomoTherapy system’s job of keeping this volume as small as possible. As discussed earlier, creating a conformal dose in the treatment plan - via IMRT - and making sure this planned dose is delivered to the right volume at treatment time - via IGRT - is crucial.

One key fact in this study is that chemotherapy during the course of radiation (concurrent chemo-radiation) was not allowed. Chemotherapy administered either before (induction chemo) or after (adjuvant chemo) radiotherapy was used in some patients however. Part of the study was to determine the differences in toxicity between these different groups.

Another important aspect is that only the primary tumor and nodal regions with proven or suspected cancer involvement were irradiated. *No elective nodal irradiation* was performed. The rationale behind elective nodal irradiation is to irradiate regions that might contain cancer cells, so as to avoid possible progression in these areas. But because elective nodal irradiation increases the total volume of tissue irradiated, a smaller tumor dose can be tolerated and there is therefore a greater chance of progression of the primary tumor. It has been shown in other studies that there is usually more benefit in increasing the dose to the known tumor volume (and regions known or strongly suspected to contain cancer cells) than in irradiating a larger volume with a lower dose [10].
An example of the dose distribution and dose-volume histograms for a bin 2 patient with stage III disease is shown below. Note that the prescribed target dose is 75 Gy = 25 x 3 Gy, as indicated for a bin 2 patient in the table on the previous page.

Results Presented and Published
Preliminary outcomes were shared at the 2007 ASTRO meeting by Dr. Jarrod Adkison, a UW radiation oncologist [11]. At that stage 41 patients with NSCLC in stages I-IV had been enrolled. No patient had experienced toxicities of greater than grade 2 to either lung or esophagus, with grade 1 (minor symptoms) being more common than grade 2 (cough, difficulty swallowing requiring analgesics). Adkison reported a complete tumor response of 21% and a partial response of 42%.

In a subsequent paper providing more details of the study, published in the journal Technology in Cancer Research and Treatment in December 2008, results were updated and preliminary survival statistics included [12]. Data for 46 patients, now with longer follow-up than for the ASTRO presentation, revealed excellent results in terms of survival and toxicity.
Patients included in the published study fell into the stages and bins in the following table. It can be seen that the majority of patients were stage III. Note that a pilot phase of 5 patients was included in the study, all of whom received the lowest dose per fraction (2.28 Gy).

<table>
<thead>
<tr>
<th>Stage</th>
<th># Pts.</th>
<th>Pilot</th>
<th>Bin 1</th>
<th>Bin 2</th>
<th>Bin 3</th>
<th>Bin 4</th>
<th>Bin 5</th>
</tr>
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<td>IIB</td>
<td>4</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
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</tr>
<tr>
<td>IIIA</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td></td>
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<td>1</td>
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<tr>
<td>IV</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>8</td>
<td>24</td>
<td>2</td>
</tr>
</tbody>
</table>

A summary of findings from the paper is given below:

For the 46 patients having been enrolled in the study at that time, overall survival rate 2 years after treatment was 46.8% and median survival 18 months. Note that about 80% of patients had stage III disease (relatively advanced). Stage-for-stage, this compares with a 2-year survival rate of 21.5% from a database representing all clinical, surgical-pathologic, and follow-up information for a large number of patients treated for NSCLC [13].

- A complete tumor response was seen in 17% of patients, a partial response in 43% and stable disease in 26%. Only 6.5% had progressive disease immediately after completion of radiotherapy. Disease ultimately progressed in the lung/thoracic area in 13% of patients and 28% of patients developed distant metastases. Some failures can be attributed to lack of disease control locally (mostly radiotherapy responsibility) and some due to existing metastatic spread (mostly chemotherapy responsibility).

- No patient experienced grade 3 or higher pneumonitis. Grade 2 pneumonitis occurred in only 13% of patients in this study. This illustrates one of the major safety parameters of the study and validates the scientific technique for determining a safe dose per fraction based on tumor volume and likelihood of pneumonitis.

- Statistical analysis showed that mean dose to normal lung is a predictor of the rate of lung pneumonitis, but that dose prescribed to the tumor is not. This indicates that the methodology for safe dose prescription based on predicted normal tissue toxicity is valid. In other words, the strategy of allowing higher doses for small tumors works, and these patients can take advantage of the better tumor control that comes with higher dose.

- As well as being correlated to mean lung dose, the rate of lung toxicity is correlated to whether or not chemotherapy was given after the course of radiation (adjuvant chemo). The majority of the 13% of patients experiencing grade 2 pneumonitis underwent adjuvant chemotherapy.

- No patients experienced grade 3 esophagitis. For those developing esophagitis of grade 1 (24% of patients) or grade 2 (13%) an average weight loss of under 3% occurred indicating minimal problems with swallowing. In a University of Michigan dose-escalation study utilizing 3-D radiotherapy, and a non-hypofractionated approach to dose-escalation, grade 1, 2, and 3 esophagitis
occurred in 39.5%, 16.5% and 2.7% of patients respectively [14]. The esophageal dose constraints used in the protocol have since been relaxed, given the low incidence of significant esophagitis. Relaxing this constraint will result in fewer patients being assigned a dose per fraction less than the starting dose and should further enhance overall tumor response.

An overall survival curve shown below indicates the median survival of 18 months, and 24-month survival of 46.8%, found in this study.

Pneumonitis rates for patients with (i) no chemotherapy, (ii) neoadjuvant chemo (before radiation) and (iii) adjuvant chemo (after radiation) are shown in the plot below. It can be seen that grade 2 toxicity is only a significant factor for patients undergoing adjuvant chemo. Adjuvant chemo and increased mean lung dose are the only significant factors affecting pneumonitis.

The authors conclude that higher doses of radiation than are conventionally administered (typically ~60 Gy in 2 Gy fractions) may be delivered safely in a hypofractionated schedule with TomoTherapy. Reported lung and esophageal toxicities are lower than expected from previous dose escalation studies using conventional
radiotherapy technology. The maximum tolerated dose has not been reached in this dose escalation study, considering that toxicity was found in statistical analysis not to correlate with prescribed dose. This means that the strategy of increasing dose for situations where the tumor is small relative to the volume of healthy lung has not resulted in increased toxicity for these patients. Larger doses per fraction for this 25-fraction scheme may be practical, especially for small tumors.

Given the demonstrated low rates of toxicity incurred due to the radiation therapy in this study, the inclusion of concurrent chemotherapy may be feasible, with the corresponding benefits to overall survival seen in other studies.

This study does not yet draw conclusions on the correlation between overall survival and dose level, but a strong relationship would be expected given that (i) higher dose is known to improve local control, and (ii) smaller tumors—which are more easily controlled anyway—generally receive a higher dose under this protocol.

The protocol continues to accrue patients and will give us new insights into the benefits and potential of highly-conformal, accurately-delivered radiotherapy for lung cancer.

References