Brief update on the use of proton beam therapy for non-small cell lung cancer: Gimmick or Godsend?

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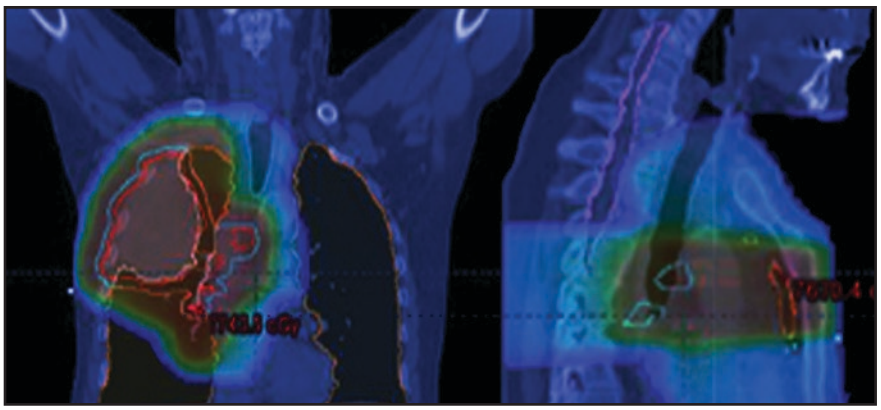
Both photon and proton techniques exist for the treatment of thoracic tumors, in particular non-small cell lung carcinoma (NSCLC). This brief review will explore the strengths and weaknesses of each technique and examine some of the more recent data comparing the most current methods, in particular with a focus on proton beam therapy (PBT). Limitations of the technology will be discussed both in terms of patient immobilization and in terms of beam delivery methodology. Current studies comparing protons to photons are examining if the ability to spare normal tissue superiority of protons will have a significant clinical effect on the treatment of lung cancer.



Lung cancer and radiation therapy

In 2014, approximately 160,000 people are expected to die from lung cancer in the United States. It is estimated that this number is higher than the sum of the deaths due to prostate, pancreas, breast, and colon cancers combined.[1] In many countries, lung cancer is one of, if not the absolute, leading causes of death.[2] The majority of patients are over 65 years of age and have multiple medical problems that limit the ability to use aggressive therapeutic options. It is more common to present with locally advanced disease than with early stage disease. The standard of care for lung cancer is evolving, but surgery, chemotherapy, and radiation therapy all play crucial roles in the disease that vary by stage and patient performance status.

The primary risk matrix with which the radiation oncologist is faced is the toxicity to normal lung and to normal non-lung tissue, such as the esophagus and heart when large volumes of disease are treated. The standard of care for early stage disease is lobectomy if patients can undergo surgery. For those that cannot tolerate surgery for any reason, some form of local radiation therapy has been used, and recent work on stereotactic ablative radiotherapy (SABR), previously called stereotactic body radiation therapy (SBRT), has been promising.[3-5] Caution has been needed and dose has had to adapt from the initial series of SABR to allow for treatment near the main bronchi, mediastinum, and chest wall. Cases where lymph-node spread is known have not typically been treated with SABR.

Perhaps the most challenging group of patients for a lung cancer specialist is the so-called locally advanced group, or stage III group. Despite advances in chemotherapy, radiation delivery ad-

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vances (photons), imaging and staging improvements, and surgical technology, this group of patients still has a 5-year overall survival rate that hovers in the 20% to 25% range.[6,7] Increased side effects with SABR were seen in the early U.S. experience although it was not seen in the early Japanese experience. New agents have been unable to really improve this, despite efforts globally.

The concept that newer technology in radiation therapy that may allow the safe escalation of dose has become a focus in the world of lung cancer. In an effort to improve cure for all non-metastatic patients, while keeping toxicity as low as possible, researchers are currently evaluating multiple dosimetric questions. It is in this context that this review seeks to evaluate and summarize some of the progress that has been made in photon and proton methods. For the sake of simplicity, the complex and controversial aspects of current chemotherapy will not be addressed in depth.

Photon therapy

Many excellent reviews exist on the subject of standard radiation therapy in the treatment of lung cancer. For this brief review and as a whole, photon therapy serves as the standard of care for radiation therapy for NSCLC. The first type of photon radiation therapy is fractionated, and standard dose therapy consists of daily fractions of 2 Gy that are delivered in 30 fractions. It can be used for many forms of NSCLC and is the first option for TxN1M0 disease. It is currently used with chemotherapy, unless patients cannot tolerate chemotherapy. The formal developments and studies that lead to this dose are left out of this review and can be found in the current textbooks in radiation oncology and in excellent reviews on the subject.[8,9]

Photon therapy is available in much of the world and is relatively affordable.[10] It is more affordable in terms of equipment costs than proton or other heavy particle therapy at this time.[11] The fractionated methods of external beam photon therapy include 3-dimensional conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT). Image-guidance (IG) and 4-dimensional (4D) motion capabilities have enhanced thoracic therapy capabilities. Treatment planning and CT scanner OEM software can automatically organize organ motion movies into groups called "bins." Software also exists that can automatically contour targets in all motion groups once one group is contoured by the physician. The goal of all of the technical advances in photon radiation therapy is to avoid normal tissue, to decrease normal tissue toxicity, and promote the capacity to increase the dose delivered to the tumor without missing due to motion. It would be impossible to use routine 4D treatment planning without some form of software to help organize the imaging of the target due to the enormous number of images involved. At this point in time, free breathing planning is estimated to underdose the planning target volume (PTV) by up to 5% compared to 4D treatment planning.[12]

Two classes of side effects can be considered primary side effects that the treatment team is trying to mitigate in the planning process for most cases of node positive NSCLC: esophagitis and normal lung damage. Acute NCI grade 3 or 4 esophagitis occurs in 5% to 10% of patients treated with sequential radiation and chemotherapy and perhaps in up to 30% of those treated with concurrent chemotherapy and radiation therapy.[13,14] The treatment physician balances mean esophageal dose, chemotherapy used, hematological status, several dosimetry driven volume cutoffs and the maximum esophageal dose with his or her treatment volume and technique. Those treating NSCLC can use some published models for guidance, but even with those aids it can be complex, if not impossible, to predict how one patient will do relative to the average patient in a treatment regimen.

With better survival now being seen both in the chemotherapy and radiation world and with the use of newer chemotherapy agents, late effects of esophageal stricture are seen in up to 10% of cases and treatment for these can be quite complex and challenging to both the team and the patient.[15-22] Guidelines published as part of a national effort to establish tolerance doses in adults for normal tissue for the esophagus suggest that the mean dose to the structure be kept to <34 Gy and that a V60 be recorded.[13]

Primary lung tissue treated remains the main worry to the treating physician. Knowing what limits we currently face, it is challenging to compare side effects between published series for a number of reasons: patient selection bias, technology employed for treatment delivery, the capacity of any given institution to modulate the side effects via the in-house support system, chemotherapy regimens being employed, and comorbidities that may vary from region to region, such as smoking incidence. Even the scoring systems for toxicity have changed significantly over the years for the Radiation Therapy Oncology Group (RTOG), the European Organization for Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI), and the Common Terminology Criteria for Adverse Events (CTCAE). Many patients have similar side effects in the absence of radiation as well, making it very difficult to be certain that any given side effect is the fault of the radiation therapy.[23]

Because of the pre-existing lung function issues in these patients, it is difficult to measure change accurately. Pneumonitis is short lived and can be intermittent, making it a difficult diagnosis to quantify.[24-26] Severe shortness of breath in a patient population with a significant background of lung disease can be difficult to measure accurately.

Dosimetric guidelines have taken shape for photon tolerance and are part of the set of QUANTEC papers published

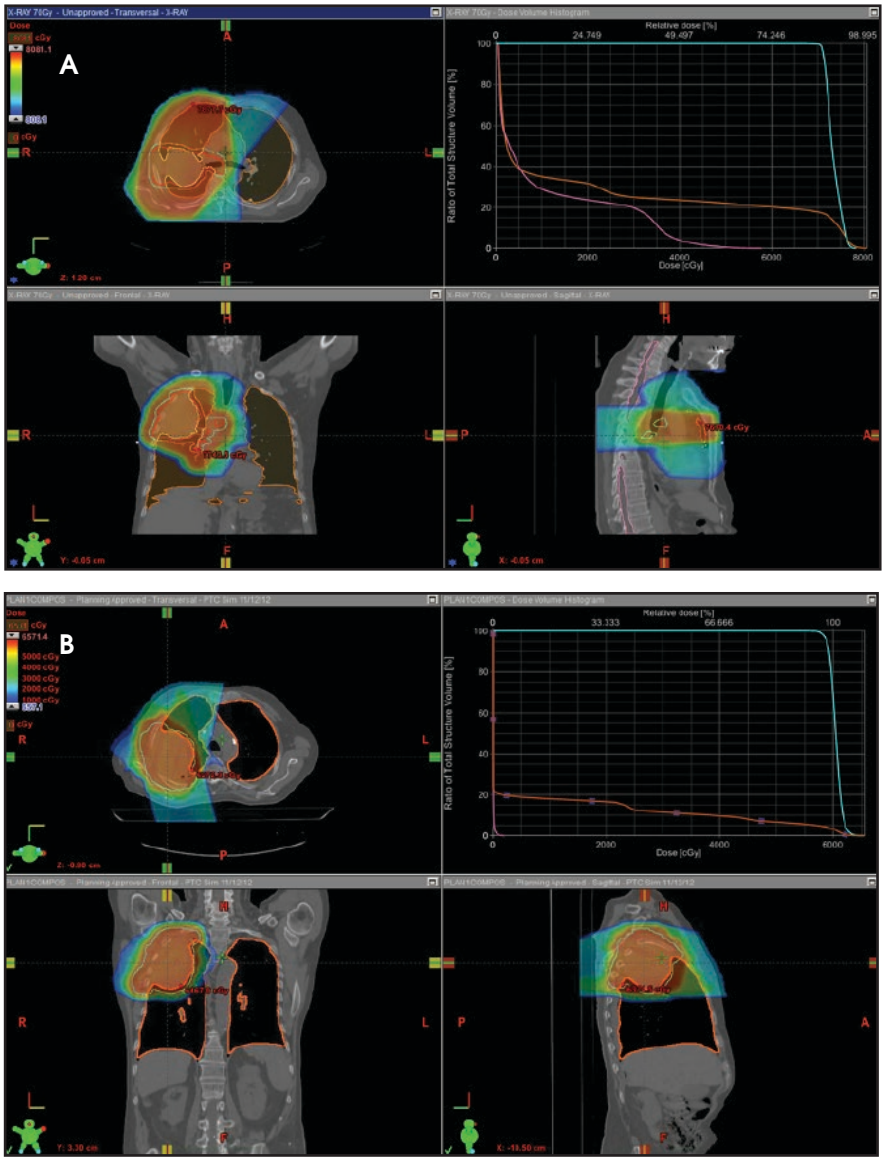

FIGURE 1. *The patient shown initially had 70 Gy delivered at 2 Gy per fraction via 3DCRT (photon) to his stage IIB NCSLC (T3N0M0) as shown in panel (A). The lesion persisted and grew back to the same size it started as proton therapy was delivered at 2.5 Gy CGE x 24 fractions for a total dose of 60 Gy CGE. This is shown in panel (B). V_{20} for the lung is approximately half that of the photon plan. In both images, orange represent V_{20}, pink the spinal cord, and orange the total of both lungs. Treatment in both cases was well tolerated.*

in 2010.[27] In that paper, a review of the literature suggested that it was prudent to limit the volume of lung, seeing a dose of 20 Gy or higher (V_{20}) to <30% to 35% and to keep the mean lung dose (MLD) <20 to 23 Gy if one wants to limit the risk of radiation pneumonitis to <20%.

Other areas of toxicity are important to measure and can significantly add to the complexity of any given case in NSCLC. For standard fractionation, the location of the brachial plexus, the spinal cord, and the heart are crucial. In addition to these organs at risk (OARs), the chest wall, central airways, and great vessels are of concern in SABR.[28,29]

The most critical data to date for photon irradiation in the lung are those from the recently reported national (USA) phase III trial looking at 74 Gy versus 60 GY with chemotherapy, RTOG 0617.[30] In that study, no advantage was seen going to the higher dose, in part due to the increase in toxicity seen by the higher dose. It was hypothesized that any improvement in disease control was balanced by increased toxicity, in particular cardiac toxicity. The cardiac DVH constraints of RTOG 0617 were based on historic data not fully understood to apply to doses above 60 Gy. Had cardiac constraints been different, the outcome of the study may have been more promising for dose escalation with photons.

Because of this study, the standard of care for photon radiation of lung cancer in stage III patients remains 60 Gy if conventional fractionation and chemotherapy are employed.

Proton beam therapy

Although proton beam therapy (PBT) has a much shorter history for use in lung cancer than other forms of radiation therapy, it has been considered. One of the earliest papers concerning PBT for lung cancer was a dosimetric feasibility study comparing photons to protons many years before protons were in use at the institution presenting the paper, MD Anderson Cancer Center.[31] In that paper, 260 historical patients were treated with photon SABR for lung cancers within 2.5 cm of the chest wall (CW) of which 23 had chronic CW pain. They found that in their series, PBT plans offered significantly improved avoidance of the CW, with proton dosimetry creating a CW V_{20} that was less than half that of conventional therapy. They concluded that PBT may be beneficial for the treatment of lesions close to critical structures. It should be noted that this was a purely *in-silico* study, meaning performed via computer simulation, and patients were not actually treated with proton plans.

Many investigators have since looked at PBT because of the promise it

offers of OAR sparing, given the complex thorax anatomical environment. Dosimetrically, both PBT and photon-based therapy have improved since the 1994 paper by the MD Anderson group, but repeated studies to date have demonstrated superiority of PBT in stage I to III patients. Change et al looked at 3DCRT, IMRT, and passive-scattered PBT and concluded that the PBT option was superior in every aspect evaluated: lung dose, cardiac dose, esophageal dose, and spinal cord dose.[32] The integral dose was also lower across all the studies evaluated. Even in a lopsided comparison with 63 Gy dosing with photons compared to 74 Gy cobalt Gray equivalent (CGE) with protons, the V_{20} lung was lower with protons (34.8% versus 31.6%).

In a more recent dosimetric, *in-silic*o study from 2012, evaluating a possible dose escalation, passive-scattered PBT, the least complex current form of PBT, had the lowest mean lung dose significantly across all plans and patients. When the study criteria were tested regarding dose escalation, 3DCRT, IMRT, and passive-scattered PBT all allowed 10 of 25 patients to have dose safely escalated to 87 Gy (CGE) if a set of arbitrary study guidelines were followed. If the target were limited to a dose of 70 Gy (CGE), mean lung dose across the three modalities was 18.9 Gy, 16.4 Gy and 13.5 Gy (CGE), respectively.[33]

A similar trend exists for SABR planning comparison papers for stage I and selected stage II cases.[32] The dosimetry of protons may allow increased local control rates in these patients with less toxicity to normal structures—felt to prevent the use of large photon fractions.[28,29] When 87.5 Gy (CGE) was delivered to a series of stage IA, IB, and some IIB (T3N0M0) patients, a 16-month local control rate of 89% was seen.[34] Other series have looked at larger fractions to a similar biologic equivalent dose with similar results. A case of this is shown in Figure 1.

The outcome data from a promising phase II PBT-based study[35] with 74 Gy (CGE) and concurrent weekly carboplatin and paclitaxel may prove to be superior to that seen in the RTOG 0617 74-Gy arm. Median overall survival on the study was 29 months, and no grade 4 or 5 toxicity was reported on the study. Twenty-one percent (9 of 44) had local recurrence. This phase II study forms the basis of a randomized study currently underway at MD Anderson Cancer Center. The formal endpoints of the study are local control and grade 3 esophagitis/pneumonitis. It may prove that in a phase III study, without the same inherent biases of the phase II study, that no advantage exists for the higher dose.

Proton treatment planning uses the same normal structure constraints as used in photon treatment planning. Field number is driven by skin toxicity to some degree because the proximal dose of a proton beam can be higher than that of a photon beam. Computer optimization seen in the photon treatment planning does not exist in the proton planning world to nearly the same degree, so proton plans are almost all forward planned much like photon 3DCRT planning. That is changing, but not rapidly.[36,37]

Immobilization for proton beam therapy in the thorax is more complex than for photon therapy. The typical body-frame devices used for photon SABR and even routine treatment machine tabletop can introduce proton range issues and dose uncertainty for PBT that make these devices impossible to use. New methods and devices are being introduced for proton therapy in the thorax. Our center has a unique version of uniform active scanning and has, along with some other centers, the capacity to gate to motion, a capability that may turn out to be crucial to the delivery of protons to moving targets. Centers have developed methods to achieve lung immobilization for PBT with the complexity of proton dosimetry.[38-40] The use of intensity-modulated PBT via newer devices, and even breath coaching much like photon breath coaching, simply need to be created with PBT in mind.

Finally, technology has moved forward to some degree and the historic data for PBT has been based on passive scattering. One of the older center, my center, has uniform active scanning which is both faster in the delivery of beam and less neutron producing. Other centers either have or are developing new spot canning nozzles that allow for intensity modulated proton therapy (IMPT). It is not clear that IMPT is actually superior to the other methods in that it can be slow to deliver beam as the SOBP is modulated in overall shape in real time. Thus, it may turn out that the ultimate version of proton beam therapy for lung cancer is a hybrid between passive scattering and spot scanning: uniform active scanning along with gating. This is currently under research at multiple institutions.

Conclusion

At the present time, 2 areas of external beam therapy are employed in curative NSCLC treatment: SABR with localized disease that can be treated safely to high local doses and fractionated therapy to control very large lesions or disease involving lymph nodes. In both circumstances, PBT clinical studies suggest that further dose escalation is likely achievable, in cases where photon therapy has possibly achieved the maximum tolerated dosing that the current technique allows.

The outcome from RTOG 0617 is not fully understood at this time. It is possible that the extended time used for 74 Gy at 2 Gy per fraction was biologically less effective than one would expect. It is also possible that the toxicity of the photon therapy trades off the advantage in cell death offered by the higher dose of 74 Gy relative to 60 Gy. If this latter suggestion is the root cause of the failure of RTOG 0617 to show an

advantage of 74 Gy, PBT for locally advanced NSCLC may prove to be the method required to achieve safety at this higher dose regime.[41] The randomized trial from MD Anderson and similar ongoing trials at other centers will help to gain the insight. Ultimately, randomized, multicentric, prospective trials using protons at these dose levels will be needed to see if there is an advantage to using 74 Gy (CGE) over 60 Gy (CGE), in proton and photon treatment, that is reproducible across centers.

Proton therapy is neither simpler nor less expensive than its photon sibling, on first glance, but if it can allow more of these patients to achieve disease control with decreased toxicity, then it may prove far less expensive in the long run.[42] The final form of optimal therapy for NSCLC is not currently known, but proton data show tremendous promise relative to the photon data in hand. In addition, the price of admission for proton therapy is not going to remain as high relatively for much longer.

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