Mini-Review

Proton therapy for post-operative radiation therapy of non-small cell lung cancer

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Abstract: Post-operative radiation therapy (PORT) is typically recommended for patients with locally advanced non-small cell lung cancer (NSCLC) with N2 mediastinal nodal involvement after surgical resection. The routine use of PORT, however, is controversial as older data demonstrated a detriment in overall survival in patients who received PORT. This detriment was thought to be due to older, more toxic radiation techniques. More recent data with modern radiation techniques demonstrates a local-regional and overall survival benefit with PORT in patients with N2 nodal involvement. Due to the competing risks of local-regional recurrence and cardiopulmonary toxicity in patients who are candidates for PORT, methods to widen the therapeutic window are needed. The physical characteristics of proton beam therapy allow for less radiation dose to the heart and lungs. Therefore, proton beam therapy has great potential in patients undergoing PORT. Initial dosimetric and clinical data have been published and are encouraging, but prospective data is needed to further understand the true benefit of proton therapy in patients undergoing PORT.

Keywords: Proton therapy; post-operative radiation therapy (PORT); adjuvant radiation

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Introduction

Lung cancer is the most common cause of cancer related deaths with an estimated 222,500 new cases and 155,870 deaths expected in the United States in 2017 (1). About 20–30% of patients present with stage III disease. Stage III disease includes patients with mediastinal lymph node involvement (N2). There are multiple different ways for approaching patients with stage III disease. Patients who are medically and/or technically inoperable typically undergo definitive chemoradiation. Trimodality therapy, which includes surgical resection, is considered in patients who are medically fit with limited extent of disease. These patients either undergo preoperative concurrent chemoradiation followed by surgical resection or preoperative chemotherapy followed by surgical resection and then post-operative radiation therapy (PORT) for N2 disease. PORT is also recommended in patients who undergo surgical resection for presumed stage I or II disease and are found to have N2 mediastinal lymph node involvement at the time of surgery, which upstages them to stage III.

The rationale and controversy of PORT

While the National Comprehensive Cancer Network (NCCN) guidelines recommend PORT for patients with N2 disease, the use of PORT is controversial.

The PORT meta-analysis, a meta-analysis of nine randomized controlled trials, was published in 1998 and demonstrated a detriment in overall survival in patients undergoing PORT (2). Although PORT reduced the overall rate of local-regional recurrence, it increased mortality in the overall patient population by 7%. Upon analyzing the population by nodal stage, this survival detriment was seen in patients with N0 and N1 nodal involvement. Patients with N2 nodal involvement did not demonstrate a detriment or improvement in overall survival with PORT. The poorer survival associated with PORT was thought to be related to

toxicity from older radiation techniques. For example, most trials included patients treated with Cobalt-60, which is no longer used in the United States for treating extra-cranial disease. Only one trial included patients that were planned with a CT simulator, which has been the standard of care for years. Finally, only five trials included patients who were treated with conventionally fractionated radiation, which is considered standard in the post-operative setting. The other four trials included patients treated with a hypo-fractionated approach, which may increase the risk of toxicity. These older techniques likely administered high radiation doses to normal structures such as the heart and the lung, which increases the risk of cardiopulmonary morbidity and mortality.

After the publication of the PORT meta-analysis, the use of PORT declined (3). Subsequent publications evaluating more modern radiation therapy techniques have demonstrated a clear improvement in overall survival with PORT in patients with N2 nodal involvement (4-9). The ANITA trial, which evaluated the role of adjuvant chemotherapy in patients with resected stage IB–III non-small cell lung cancer (NSCLC), found on subset analysis that PORT improved median overall survival in patients with N2 nodal involvement from 2 to 3.9 years (6). Cancer registry studies from the Surveillance, Epidemiology and End Results (SEER) Database and National Cancer Database (NCDB) also demonstrated a statistically significant benefit in overall survival with PORT in patients with N2 nodal involvement (4,5,8). Finally, a modern meta-analysis evaluating patients with N2 nodal involvement treated with linear accelerators demonstrated that PORT improved overall survival and reduced local recurrence rates from 30% to 10% (9). These studies demonstrate that with more advanced radiation therapy techniques, the benefit in local-regional control with PORT outweighs the toxicity in patients with N2 nodal involvement.

However, because these data are population-based, aggregated, retrospective or from unplanned subset analyses, the use of PORT for N2 nodal involvement is still considered controversial. The Lung Adjuvant Radiotherapy Trial (Lung ART) trial is an ongoing phase III randomized control trial in Europe randomizing patients with N2 nodal involvement to PORT *vs.* no PORT (10). The results of this trial will hopefully provide level 1 evidence to resolve the controversy of PORT.

Risk of cardiopulmonary toxicity

Cardiac toxicity has been considered a late toxicity from radiation therapy. The risk of cardiac morbidity and mortality from radiation therapy has been of great concern in lymphoma and breast cancer patients given the favorable prognoses and importance of reducing late toxicity (11). In lung cancer patients, however, due to the relatively poor prognosis and the higher rates of pre-existing cardiac pathologies in the patient population, radiation-induced cardiac toxicity was not as clinically relevant until the recent publication of RTOG 0617 (12). RTOG 0617, a randomized controlled trial comparing two radiation dose levels: 60 *vs.* 74 Gy in patients with locally advanced NSCLC undergoing concurrent chemoradiation, demonstrated worse overall survival rates in patients receiving 74 Gy. This study reported cardiac dose as an independent predictor of overall survival on multivariable analysis and speculated that the worse survival seen in the dose-escalated arm may be attributable to cardiac toxicity. Additionally, recent data have demonstrated that cardiac toxicity can occur earlier than initially thought (13). Wang *et al.* analyzed 127 patients with locally advanced NSCLC treated with definitive dose-escalated radiation therapy and found that the rate of symptomatic cardiac events (pericardial effusion, acute coronary syndrome, pericarditis, arrhythmia, and heart failure) was 23% with a median time to the first cardiac event of 26 months (13).

The evolving and emerging cardiac toxicity data in patients treated with definitive radiation for locally advanced NSCLC can be extrapolated to the post-operative setting. As noted above, PORT has been shown to increase mortality in patients with N0 and N1 nodal involvement (2,5). The SEER study, which included patients treated with more modern radiation techniques, also demonstrated an overall survival detriment with PORT in patients with N0–1 nodal involvement (5). PORT is typically centrally directed at the post-operative bronchial stump, ipsilateral hilum, and involved and high-risk lymph node stations. Although the radiation prescription doses for PORT are lower than definitive doses (generally 50–54 Gy in PORT *vs.* 60–70 Gy in definitive cases), given the central target in the thorax, the increased mortality seen with PORT is presumed to be related to cardiopulmonary toxicity. There is, however, limited data on this topic with some studies demonstrating no excessive increase in death from intercurrent disease with PORT (7,14-16). Another SEER analysis indicated that heart disease mortality declined with improvements in technology. In this study, patients diagnosed in 1983–1988 experiencing increased cardiac mortality with PORT, but patients diagnosed in 1989–1993

experiencing less toxicity (17).

While cardiac toxicity is of increasing concern in lung cancer patients, pulmonary toxicity is also important to consider, particularly in those patients undergoing PORT. In general, lung cancer patients have poor lung function due to extensive smoking histories. Patients treated with PORT may be at increased risk for pulmonary toxicity as their lung volume is reduced after surgical resection and their lungs need to heal after surgical intervention. One study from China demonstrated higher rates of radiation pneumonitis (grade 2: 50% *vs.* 38% and grade 3: 16% *vs.* 9%) in patients undergoing PORT compared to patients undergoing definitive radiation, despite lower radiation prescription doses and lower lung doses [volume of lung receiving 20 Gy (V20), mean lung dose and mean heart dose] (18). A study from Duke, however, did not find a difference in radiation pneumonitis rates in patients undergoing surgery *vs.* definitive radiation in locally advanced NSCLC (19).

While current data with more advanced radiation therapy techniques demonstrates a benefit with PORT in patients with N2 nodal involvement, there is still a risk for toxicity. Due to the competing risks of local-regional recurrence and cardiopulmonary toxicity in patients who are candidates for PORT, methods to widen the therapeutic index are needed.

Rationale for protons for PORT

Proton therapy, with its characteristic physical properties, may be a good option for minimizing the risk/benefit ratio of PORT. The proton beam can deposit most of its energy at a specific depth in the patient with a characteristic peak, called the Bragg peak. Beyond this Bragg peak, the energy or radiation exit dose is negligible. Due to the negligible exit dose with proton beam therapy, less radiation dose can be delivered to surrounding normal structures.

Because the proton beam is sensitive to changes in tissue density, accounting for target motion is critical when designing proton beam therapy plans. Motion management is particularly important with considering proton therapy treatment with intensity-modulated proton therapy (IMPT) (20). The radiation volume target in PORT cases is typically the bronchial stump, ipsilateral hilum and high-risk mediastinum. These structures are centrally located and are less susceptible to motion uncertainties compared to lesions in the lung parenchyma. Because of the limited motion of the PORT target, proton therapy is well suited for PORT.

Dosimetric data has demonstrated that targeting PORT volumes with proton beam therapy reduces radiation dose to organs at risk, such as the lung, heart and spinal cord (21). Berman *et al.* evaluated dosimetric data from ten patients treated with PORT, planned with intensity-modulated photon radiation therapy (IMRT), passive-scatter proton therapy and IMPT (21). IMPT demonstrated the greatest reduction in dose to the organs at risk. For example, compared to IMRT, IMPT reduced the lung V5 (46.2% *vs.* 26.9%), lung V20 (22% *vs.* 14.4%), mean lung dose (10.8 *vs.* 6.7 Gy), and mean heart dose (10.2 *vs.* 6.9 Gy). Of note, the PORT volumes in this study were slightly larger than standard as they were contoured with older techniques that targeted the entire mediastinum. A common current standard is to target PORT volumes according to the Lung ART trial, which is more selective for high-risk nodal stations. With smaller PORT target volume definitions, proton beam therapy may further reduce radiation doses to the lung and heart.

The University of Pennsylvania also recently published their clinical data using proton beam therapy for PORT (22). The authors identified 27 patients treated with proton therapy and 34 patients treated with IMRT. They demonstrated that proton beam therapy is well tolerated with similar grade 3 pneumonitis (3.7% proton *vs.* 2.9% IMRT, 1 patient in each group) and possibly lower grade 3 esophagitis (3.7% proton *vs.* 11.8% IMRT, P value not given) rates. Proton therapy also resulted in similar 1-year overall survival (85.2% proton *vs.* 82.4% IMRT) and local recurrence-free survival (92.3% proton *vs.* 93.3% IMRT) rates.

Although these initial dosimetric and clinical data are encouraging, prospective data is needed to further understand the true benefit of proton therapy in patients undergoing PORT.

Conclusions

In conclusion, PORT should be recommended for patients with N2 nodal involvement in order to decrease local-regional recurrence and improve overall survival. There are potential cardiopulmonary toxicity risks associated with PORT, however, as seen in patients with N0–1 nodal involvement treated with PORT (2,5). Due to the physical characteristics of the proton beam, proton beam therapy has great potential to widen the therapeutic window in patients undergoing PORT.

There are challenges, however, in implementing proton beam therapy for PORT, such as access to proton

centers and cost of treatment. In order to overcome these challenges, studies to prove the benefit of proton therapy for PORT are needed. Studying this patient population, however, can also be challenging due to the variability of practice patterns for stage III NSCLC and the controversy regarding the true benefit of PORT, which can result in reduced referrals for PORT. Therefore, a multi-center study randomizing patients to PORT with proton therapy *vs*. photon therapy with a cardiopulmonary toxicity endpoint would be a good approach to understanding the benefit of proton therapy in patients undergoing PORT. The Proton Collaborative Group is currently exploring the feasibility of this study.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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