INTRODUCTION
Lung cancer remains the leading cause of death for both men and women in the US (Siegel et al., 2012). Although the results of treatment for early stage non-small cell lung cancer (NSCLC) are encouraging, as many as 40% of patients present with stage III disease (Chang et al., 2005). The standard treatment approach for these patients is concurrent chemoradiation therapy with or without surgery. However, overall survival with this approach is expected to be only 15–35% at 5 years (Edge et al., 2010). Patterns of failure show that both local and systemic relapse are common. Local failure rate of 35–50% is expected with radiation dose escalation has been correlated to the increased biologic equivalent dose (BED) achieved with the radiation dose schema of SBRT. In this study, we evaluated the dosimetric feasibility of using SBRT as a boost to gross disease (primary lung tumor and bulky mediastinal lymphadenopathy) following standard fractionated three-dimensional conformal radiation therapy (3D-CRT) to 50.4 Gy.

METHODS
Anonymized CT data sets from five randomly selected patients with stage III NSCLC undergoing definitive chemoradiation therapy in our department with disease volumes appropriate for SBRT boost were selected. Three-dimensional conformal radiation therapy (3D-CRT) plans to 50.4 Gy in 28 fractions were generated follow by SBRT plans to two dose levels, 16 Gy in two fractions and 28 Gy in two fractions. SBRT plans and total composite (3D-CRT and SBRT) were optimized and evaluated for target coverage and dose to critical structures; lung, esophagus, cord, and heart. Results: All five plans met predetermined target coverage and normal tissue dose constraints. PTV V95 was equal to or greater than 95% in all cases. The cumulative lung V20 and V5 of the combined 3D-CRT and SBRT plans were less than or equal to 30 and 55%, respectively. The 5 cc esophageal dose was less than 12 Gy for all low and high dose SBRT plans. The cumulative dose to the esophagus was also acceptable with less than 10% of the esophagus receiving doses in excess of 50 Gy. The cumulative spinal cord dose was less than 33 Gy and heart V25 was less than 5%. Conclusion: The combination of chemoradiation to 50.4 Gy followed by SBRT boost to gross disease at the primary tumor and involved regional lymph nodes is feasible with respect to normal tissue dose constraints in this dosimetric pilot study. A phase II/II trial to evaluate the clinical safety and efficacy of this approach is being undertaken.

Keywords: NSCLC, SBRT, SAbR
A margin of 2 cm was placed around all gross disease to account for subclinical disease, set up error, and respiratory motion. Elective nodal irradiation was not performed. Dose calculation were performed using Pinnacle version 8.0m (Philips, Madison, WI, USA). Heterogeneity corrections were employed to correct for differences in tissue density; the collapsed cone convolution (CCC) method was used for dose calculation. A dose of 50.4 Gy in 1.8 Gy/fx was prescribed. Isodose plans and dose volume histograms (DVHs) were generated.

SBRT PLANS

Target volumes for SBRT boost consisted of gross tumor only (GTV) with the standard PTV margin. Typically, patients undergoing SBRT in our department are simulated with appropriate immobilization using the BlueBAG BodyFIX system (Elekta, Stockholm, Sweden) and abdominal compression to reduce respiratory excursion. During simulation, respiratory gated image acquisition is performed to determine target tumor motion in order to generate a patient-specific ITV. Because patients were simulated for 3D-CRT treatment without SBRT appropriate immobilization and a respiratory damping device, an accurate SBRT ITV was not available for these patients. A margin expansion of 1 cm in the superior and inferior directions and 0.5 cm in the radial directions was, therefore, used. This margin corresponds well to the typical margin expansion using for ITV and PTV in our SBRT patient population as well as what is reported in the literature (Fakiris et al., 2009). Dose calculation were performed using Eclipse version 8.6 (Varian, Las Vegas, NV, USA). Heterogeneity correction was used to correct for differences in tissue density and the anisotropic analytical algorithm (AAA) was employed for dose calculation. The primary lung tumor and the hilar/mediastinal nodal disease were planned separately. Intensity modulated radiation therapy (IMRT) was used employing an 8–14 non-coplanar beam arrangement. A composite of the two SBRT plans was generated to evaluate for any significant dose overlap and to calculate the volume of low dose spillage. Two prescription doses were evaluated: 16 Gy in two fractions and 28 Gy in two fractions. These doses were selected on a planned dose escalation study with 16 Gy representing the starting dose and 28 Gy representing the maximum target dose. Plans were normalized such that 95% of the PTV was covered by 95% of the prescription dose.

COMPOSITE PLANS

Composite plans between the 50.4 Gy 3D-CRT plan and SBRT boost plan were generated for the five patients using the fusion algorithm of Velocity version 2.5 (Atlanta, GA, USA). Composite DVHs and isodose plans were generated. Plans were optimized to meet dose constraints detailed in Tables 1 and 2. These dose constraints were selected based on commonly used and known dose volume constraints for these organs based on conventional fractionated and SBRT treatments. Cumulative dose limits between the 3D-CRT and SBRT plans were based on BED conversion to take into account differences in biological effect of varying dose per fraction. BED and equivalent dose in 2 Gy fractions (EQD2) calculation were based on the following equations.

$$\text{BED} = n \times d \times (1 + d/(\alpha/\beta))$$

$$\text{EQD2} = n \times d \times (d + 1)/(\alpha/\beta + 2d)$$

An n of 10, 3, and 2 were used for tumor control, late tissue affects, and late affects on spinal cord and neural structures, respectively.

RESULTS

All five plans met predetermined target coverage and normal tissue dose constraints as defined in Tables 1 and 2. PTV V95 was equal to or greater than 99% in all cases. For the five cases studied, the cumulative lung V20 of the combined 3D-CRT and SBRT plans were 17, 30, 28, 18, and 18, 30, 29, 34, 20% for low dose and high dose SBRT, respectively. The cumulative lung V3 was similarly within acceptable limits, less than 55% for all plans. The 5 cc esophageal dose was less than 12 Gy for all low and high dose SBRT plans. The cumulative dose to the esophagus was also low with less than 18% of the esophagus receiving doses in excess of 50 Gy. In addition, heart and spinal cord doses were low.

Table 3 shows target and normal tissue doses for 3D-CRT plans.
Table 3 | Dose statistic for 3D-CRT, SBRT, and composite plans.

| Case 1 | 3D-CRT | Boost PTV | Max dose | Lung V5 | Lung V10 | Lung V20 | Spinal cord max dose (Gy) | Esophagus V50 (%) | Heart V5 (%) | Heart V25 (%) |
|--------|--------|-----------|----------|---------|----------|----------|----------------------------|----------------|-------------|-------------|
|        | 3D-CRT | 99        | n/a      | 117     | 38       | 33       | 28            | 27.4           | 0           | 35.0        | 10.1        |
|        | SBRT 16 Gy | 100      | 97       | 121     | 16       | 5        | 3          | 3.3            | 0           | 5.2         | 0.0         |
|        | Composite (16 Gy) | 100 | 97 | 113 | 44 | 36 | 30 | 30.7 | 5 | 40.2 | 11.1 |
|        | SBRT 28 Gy | 100      | 97       | 121     | 26       | 14       | 3           | 5.7            | 0           | 8.9         | 0.0         |
|        | Composite (28 Gy) | 100 | 97 | 113 | 44 | 36 | 30 | 32.1 | 7 | 43.3 | 32.1 |
| Case 2 | 3D-CRT | 99        | n/a      | 119     | 44       | 35       | 25          | 26.0           | 0           | 20.5        | 22.4        |
|        | SBRT 16 Gy | 100      | 97       | 125     | 15       | 3        | 0           | 4.8            | 0           | 6.8         | 0.0         |
|        | Composite (16 Gy) | 100 | 97 | 118 | 49 | 39 | 28 | 26.6 | 1 | 27.3 | 23.4 |
|        | SBRT 28 Gy | 100      | 97       | 125     | 31       | 12       | 2           | 8.4            | 0           | 11.9        | 0.0         |
|        | Composite (28 Gy) | 100 | 97 | 118 | 53 | 41 | 29 | 31.8 | 4 | 32.4 | 28.4 |
| Case 3 | 3D-CRT | 100      | n/a      | 112     | 40       | 28       | 16          | 23.5           | 3           | 42.6        | 11.1        |
|        | SBRT 16 Gy | 100      | 97       | 129     | 9        | 3        | 0           | 5.0            | 0           | 6.6         | 0.0         |
|        | Composite (16 Gy) | 100 | 95 | 113 | 42 | 30 | 17 | 27.7 | 5 | 49.1 | 13.1 |
|        | SBRT 28 Gy | 100      | 97       | 129     | 14       | 6        | 2           | 8.7            | 0           | 11.5        | 0.0         |
|        | Composite (28 Gy) | 100 | 95 | 113 | 44 | 31 | 18 | 31.2 | 6 | 53.0 | 15.1 |
| Case 4 | 3D-CRT | 100      | n/a      | 113     | 44       | 35       | 275         | 14.7           | 0           | 38.3        | 89.3        |
|        | SBRT 16 Gy | 100      | 95       | 124     | 10       | 2        | 0           | 4.1            | 0           | 4.7         | 0.0         |
|        | Composite (16 Gy) | 100 | 95 | 112.5 | 54 | 42 | 33 | 17.3 | 0.5 | 43.1 | 89.3 |
|        | SBRT 28 Gy | 100      | 95       | 124     | 33       | 8        | 14          | 7.2            | 0           | 8.1         | 0.0         |
|        | Composite (28 Gy) | 100 | 95 | 114 | 61 | 46 | 34 | 19.3 | 1.8 | 46.5 | 93.1 |
| Case 5 | 3D-CRT | 100      | n/a      | 117     | 38       | 28       | 15          | 31.4           | 1.2          | 52.4        | 46.5        |
|        | SBRT 16 Gy | 100      | 95       | 117.7   | 6.2      | 1.3      | 0           | 5.3            | 0           | 5.3         | 14.1        |
|        | Composite (16 Gy) | 100 | 95 | 112 | 41.1 | 31.2 | 19 | 36.9 | 1.7 | 55.9 | 60.6 |
|        | SBRT 28 Gy | 100      | 95       | 117     | 12       | 4.7      | 0.8         | 9.3            | 0           | 9.4         | 20.0        |
|        | Composite (28 Gy) | 100 | 95 | 112 | 42.3 | 31.8 | 20 | 40.0 | 1.7 | 60.1 | 66.5 |
low dose SBRT and high dose SBRT plans, and composite plans. The isodose distribution and DVH for each high dose SBRT boost plan is depicted in Figure 1.

**DISCUSSION**

The results of definitive treatment for stage III NSCLC are disappointing with an expected 5 year survival of only 15–35% (Edge et al., 2010). RTOG 9410 help establish concurrent chemoradiation as the current standard treatment approach for these patients (Curran et al., 2011). Patterns of failure from this study have been reported and show that local-regional control with cisplatin-based chemotherapy and concurrent radiation therapy to 63 Gy in standard fractionation was only 69%. Furthermore, 23% of patients experience in-field local failure only without distant metastasis (Curran et al., 2011). The addition of surgery to improve upon suboptimal local control was evaluated in INT/INT/RTOG 0139 (Albain et al., 2009). This trial showed improved 5 year progression-free survival from 11 to 22%, but overall survival was not improved. The lack of overall survival benefit has been attributed to early treatment related morbidity and mortality of the tri-modality arm particularly in patients who required pneumonectomy. Many high volume and academic centers still favor a tri-modality approach for select patients based on evidence that the morbidity and mortality rates at these centers is low with this approach (Allen et al., 2008). Nonetheless, many patients are not ideal candidates for surgery due to concurrent cardiac and/or pulmonary disease or due to the requirement for pneumonectomy. Attempts to improve upon local disease control with radiation dose escalation have thus been undertaken. This approach is grounded soundly in the fundamental principles of radiation biology. The higher the radiation dose, the larger the fractional cell kill, and hence the greater the probability of tumor control. Kong et al. (2005) reported on the results of a dose escalation trial which showed improved overall survival with concurrent chemotherapy, a maximum tolerated dose of only 74 Gy, and with cetuximab. This trial unexpectedly showed 3 year survival was 18%. RTOG 9311 showed feasibility of dose escalation to 83.8 Gy (Bradley et al., 2005). However, with concurrent chemotherapy, a maximum tolerated dose of only 74 Gy could be achieved in RTOG 0117 (Bradley et al., 2010). Fartridge et al. (2011) performed a systematic review and modeling analysis of published trials of dose escalation. They found a clear dose–response relationship for improved disease-free survival. Reported 3 year survival was 18%. RTOG 9311 showed feasibility of dose escalation to 83.8 Gy (Bradley et al., 2005). However, with concurrent chemotherapy, a maximum tolerated dose of only 74 Gy could be achieved in RTOG 0117 (Bradley et al., 2010). Fartridge et al. (2011) performed a systematic review and modeling analysis of published trials of dose escalation. They found a clear dose–response relationship for improved disease-free survival. Interestingly, the best outcomes were seen in hypofractionated regimens. RTOG 0617/CALGB 30609, a phase III randomized trial, was designed to evaluate the efficacy of dose escalation using concurrent chemoradiation for stage III NSCLC (Bradley et al., 2011). This trial consists of a 2 by 2 factorial design comparing 60 vs. 74 Gy with and without cetuximab. This trial unexpectedly was closed early for futility after enrolling 450 patients. No difference in the primary endpoint of overall survival was seen between the high and low dose arms. Several explanations can be postulated for why this study failed to show a benefit from dose escalation. First, failure to control systemic disease may be overshadowing any benefit from improvements in local disease control. Second, toxicity from dose escalation using conventional 3D-CRT may limit any benefits gained. Third, 74 Gy is not a high enough dose to result in a high rate of local disease control. And lastly, accelerated tumor repopulation that typically begins after 4 weeks of treatment may be mitigating any tumor cell kill gained from dose escalation using a protracted standard fractionated regime.

The rationale to use SBRT boost as a method of dose escalation addresses the later three postulates. The conformal nature of an SBRT approach limits the amount of normal tissues receiving radiation thereby allowing the potential for safer radiation dose escalation. By delivering the boost in just two fractions, the detrimental effect of accelerated tumor repopulation is eliminated. And finally, the dose of radiation can be significantly elevated using an SBRT approach. Although the optimal dose which results in high likelihood of tumor control is not known for locally advanced NSCLC, one can extrapolate from the dose–response data gained from early stage NSCLC. Onishi et al. (2004) reported on the correlation between the BED and local tumor control using several SBRT dose and fractionation regime. They showed that at a BED of greater than 100 Gy results in a 92% likelihood of local control compared to 74% for BED less than 100 Gy. This resulted in a statistically significant improvement in 3 year overall survival of 88 vs. 69%, respectively.

In this study, we evaluate the dosimetric feasibility of chemoradiation therapy using standard fractionation to 50.4 Gy to control microscopic disease and systemic disease followed by an SBRT boost to gross tumor. We evaluated two SBRT dose levels, 16 and 28 Gy in two fractions. This study shows that at both the low and high dose levels, lung, heart, esophagus, and spinal cord dose can be kept low and within reasonable accepted dose constraints. The lung V20 and V3 for our cases was less than 30 and 55%, respectively. These are below the doses at which a high risk pulmonary toxicity is expected. Equally, the doses to other organs are within acceptable limits (Timmerman, 2008; Marks et al., 2010).

This study has potential limitations. The sample size is small. Although a variety of disease locations and distributions is represented by the evaluated patients (Figure 1). Not all possible disease distributions are represented. Thus, some patients who meet the inclusion criteria defined in Section "Methods" may not be able to meet the dose constraints set forth in this study. Furthermore, the dose constraints selected are based on currently accepted dose constraints used for SBRT and conventional fractionation. Some of these dose constraints were established empirically or were based on conversions using the linear-quadratic model. This model although useful has limitations especially when using large dose per fraction. Thus, the dose constraints used in this study may or may not be optimal constraints. Nonetheless, the present study does support that at least some patients with stage III lung cancer can be treated with this approach and achieve reasonable dosimetric constraints to critical organs, and thus supports further clinical evaluation of this approach.

We therefore are planning a phase I dose escalation study to evaluate the clinical feasibility and any potential dose limiting toxicity of SBRT boost for stage III lung cancer. A starting dose of 16 Gy in two fractions will be used. The dose will then be increased...
FIGURE 1 | Orthogonal isodose distribution and DVH of SBRT boost plan to 28 Gy in two fractions. Three separate cases are depicted in (A–C).
by 2 Gy per fraction increments until a maximum dose of 28 Gy in two fractions or dose limiting toxicity is reached. Table 4 shows the relative BED10 of each dose level. The initial dose level is roughly equivalent to the BED10 of a standard conventional fractionation treatment to 70 Gy. The dose escalation goal is to reach a BED10 of greater than 100 Gy. The maximum dose level was selected to be at a cumulative BED10 of less than 151 Gy, since toxicity for centrally located tumors has been reported at these doses (Timmerman et al., 2006). The maximum tolerated dose will then be evaluated for efficacy in a follow-up phase II trial.

CONCLUSION

The combination of chemoradiation to 50.4 Gy followed by SBRT boost to gross disease at the primary tumor and involved regional lymph nodes is feasible with respect to normal tissue dose constraints in this dosimetric pilot study. A phase II/III trial to evaluate the clinical safety and efficacy of this approach is being undertaken.

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Table 4 (Biological equivalent dose (BED) and equivalent dose in 2 Gy per fraction (EQD2) for tumor control at each dose level.

| Levels | Dose EST | BED10 | Cumulative* | EQD2 | BED10 | Cumulative* | EQD2 |
|--------|---------|-------|-------------|------|-------|-------------|------|
| 1      | 16 Gy (8 Gy x 2) | 28.8 | 88.3 | 24 | 73.6 | |
| 2      | 20 Gy (10 Gy x 2) | 40 | 99.5 | 33.3 | 82.9 | |
| 3      | 24 Gy (12 Gy x 2) | 52.8 | 112.2 | 44 | 93.6 | |
| 4      | 28 Gy (14 Gy x 2) | 67.2 | 126.7 | 56 | 105.6 | |

*Combined with 50.4 Gy (BED 127.6). **Combined with 50.4 Gy (BED 124.0).
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