Comparing Breath Hold and Free Breathing during Intensity-Modulated Radiation Therapy and Proton Therapy in Patients with Mediastinal Hodgkin Lymphoma

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Introduction

In the treatment of mediastinal lymphoma, there has been increased interest over the last 5 years in utilizing proton therapy techniques as well as breath-hold techniques with 3-dimensional conformal radiation therapy (RT) or intensity-modulated RT in an effort to reduce the radiation dose to the organs at risk [1–6]. Combining both breath-hold techniques and proton therapy has been less common owing to concerns about the reproducibility of breath hold, the impact of poor reproducibility when using proton therapy, and the lack of volumetric image-guided RT and real-time diaphragm monitoring of the breath hold. Additionally, the length of treatment may be of concern, especially when matching fields are required due to large treatment volumes. Yet newer RT treatment centers with faster delivery systems and more advanced image-guided RT equipment make the combination of proton therapy and breath hold a more realistic possibility.

In the present report, we investigate the impact of using the breath-hold technique with 3 female patients treated for bulky mediastinal stage II Hodgkin lymphoma with proton therapy, and compare our findings with the free-breathing technique.

Case Report

Three female patients with bulky anterior mediastinal Hodgkin lymphoma who were referred for proton therapy underwent computed tomography simulation using both breath hold with an ABC device and free breathing for a 4-dimensional computed tomography scan on an institutional review board-approved protocol. The breath-hold technique was performed on these 3 patients owing to the distribution of their disease and the expectation of a high cardiac dose with free-breathing proton therapy; therefore, we hoped the breath-hold technique would help reduce the heart dose. Pre-chemotherapy positron emission tomography scans for the 3 patients are shown in Figure 1, demonstrating mediastinal disease extending into the cardiophrenic recess with additional cardiophrenic lymph nodes in patients 1 and 2. With the breath-hold technique, 3 scans were acquired to assess position reproducibility and an involved-site RT internal tumor volume (ITV) plan was developed to ensure coverage of the clinical target volume for all 3 scans. For the free-breathing technique, an ISRT ITV plan was developed based on the 10 phases of the 4-dimensional scan to ensure the clinical target volume was covered throughout the breathing motion. The planned target volume margin was an 8-mm margin on the ITV. Proton plans were developed to treat the patient to 30.6 Gy (RBE), using anterior passive scattering or uniform scanning proton beams, as previously
described [7]. Two intensity-modulated RT (IMRT) plans were developed using the butterfly technique, although no inclined breast board was used [8], for breath-holding and free-breathing techniques respectively. IMRT was chosen for comparison instead of 3-dimensional conformal RT since it has been shown to help reduce the heart dose most significantly with deep inspiration breath hold [9].

Radiation dose to the heart, lungs, esophagus, and breasts, and the body integral dose were assessed for all 3 patients with all 4 plans. Comparisons were made between the free-breathing IMRT and breath-hold IMRT plans, the free-breathing proton therapy and breath-hold proton therapy plans, and the free-breathing proton therapy and breath-hold IMRT plans (Figure 2).

Results

Table 1 reports the mean dose to the organs at risk according to the various treatment plans for the 3 patients. Table 2 reports the difference in mean dose among the different techniques for the 3 patients. Table 3 reports the ITV and lung volumes for the different patients and different breathing techniques. When evaluating free-breathing proton therapy with breath hold proton therapy, the integral dose and esophagus dose were slightly higher with breath hold. On the other hand, the dose to the lungs

Figure 1. Distribution of disease by baseline positron emission tomography scan with the heart contoured in red.

Figure 2. Colorwash dose distribution for Case 1 with (A) free-breathing intensity-modulated radiation therapy, (B) free-breathing proton therapy, (C) breath-hold intensity-modulated radiation therapy, and (D) breath-hold proton therapy.

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was slightly lower with breath hold. The dose to the heart was lower with breath hold in 1 patient, but unchanged in the other 2. The dose to the breast was better in 2 patients with breath hold.

When comparing free-breathing IMRT with breath-hold IMRT, the integral dose and esophagus dose were worse with breath hold. On the other hand, lung dose and breast dose was slightly lower with breath hold. The heart dose in 1 patient was worse with breath hold, while it was similar in the other 2 patients.

Lastly, when comparing free-breathing proton therapy with breath-hold IMRT, the integral dose, esophagus dose, and heart dose were substantially better with free-breathing proton therapy. But the breast dose was better in 2 of the cases with breath-hold IMRT. In 2 cases, the lung dose was better with free-breathing protons than breath-hold IMRT, and it was marginally better with breath-hold IMRT in the 3rd case.

Discussion

The present case series is small but provides some much-needed data regarding the impact of combining both proton therapy and the breath-hold technique for patients with bulky anterior mediastinal Hodgkin lymphoma that draped over the heart. In the series, proton therapy with breath hold compared with proton therapy with free breathing reduced the mean lung dose by 1.6 Gy in 1 patient, while in another patient the mean heart and breast doses reduced by 2.2 and 1.7 Gy, respectively. All other differences for the 3 patients impacted the mean dose to the OAR by 1 Gy. Our findings suggest that although breath hold may improve the dosimetry of an RT treatment, the magnitude of benefit needs to be considered based on the concerns of reproducibility with breath hold and proton therapy. In our case, only case 2 was ultimately treated with the breath hold technique and proton therapy.

Interestingly, when free-breathing proton therapy was compared with breath-hold IMRT, a substantial benefit (>6 Gy or >75 Joules) in dose reduction to the heart and esophagus and the integral dose were observed for all patients. Additionally, in 2 of the 3 patients, the lung dose was lower with free-breathing proton therapy (2.5 and 4.1 Gy difference), while only 1 patient had an improvement in lung dose with breath-hold IMRT (0.6 Gy difference). On the other hand, the breast dose improved in 2 of the 3 patients with breath-hold IMRT (a 2.7 and 1.7 Gy difference). These findings suggest that, for our patients with bulky mediastinal lymphoma that extends anterior to and drapes over the heart, free-breathing proton therapy still substantially improves the dosimetry of RT treatment.

**Table 1.** The dose to the organs at risk according to various treatment plans.

| Organ                  | IMRT-FB | IMRT-BH | PT-FB | PT-BH | IMRT-FB | IMRT-BH | PT-FB | PT-BH | IMRT-FB | IMRT-BH | PT-FB | PT-BH |
|------------------------|---------|---------|-------|-------|---------|---------|-------|-------|---------|---------|-------|-------|
| Heart, Gy (RBE)        | 20.6    | 24.9    | 15    | 15    | 25.7    | 26      | 19.9  | 17.7  | 14.8    | 14.6    | 7.3   | 7.5   |
| Lung, Gy (RBE)         | 15.7    | 13      | 8.9   | 7.3   | 14.4    | 12.8    | 13.4  | 12.7  | 12.3    | 11.3    | 8.8   | 8.2   |
| Breast, Gy (RBE)       | 6.6     | 6.6     | 6.6   | 7.1   | 9.5     | 8       | 10.7  | 9     | 7.4     | 6.8     | 8.5   | 7.6   |
| Esophagus, Gy (RBE)    | 19.9    | 23.7    | 16.2  | 16.3  | 21.6    | 25      | 13.9  | 15.5  | 19.9    | 21.2    | 11.5  | 12.6  |
| Body, Joules           | 146     | 148.2   | 70.8  | 75.2  | 182.3   | 195.2   | 113   | 122   | 144     | 155     | 70.6  | 79.8  |
| LAD, Gy (RBE)          | 29.3    | 30.2    | 32.6  | 32.7  | 31      | 31.3    | 33.8  | 34.4  | 8.4     | 5.8     | 4.7   | 0.1   |
| Left ventricle, Gy (RBE)| 15.7  | 20.6    | 5.4   | 2.9   | 23.6    | 23.1    | 11.5  | 7.5   | 9.3     | 8.8     | 3.6   | 0.6   |
| Aortic valve, Gy (RBE) | 18.8    | 22.4    | 20.8  | 29.4  | 23.5    | 24.1    | 19.7  | 14.5  | 28.1    | 27.6    | 23.7  | 20    |

**Abbreviations:** BH, breath holding; FB, free breathing; Gy, Gray; IMRT, intensity-modulated radiation therapy; LAD, left anterior descending artery; PT, proton therapy; RBE, relative biological effectiveness.

**Table 2.** The difference in dose among different radiation techniques.

| Organ                  | IMRT FB vs IMRT BH | PT FB vs PT BH | PT FB vs IMRT BH |
|------------------------|---------------------|----------------|------------------|
| Heart, Gy (RBE)        | -4.3                | 0              | -9.9             |
| Lung, Gy (RBE)         | 2.7                 | 1.6            | 0.1              |
| Breast, Gy (RBE)       | 0                   | -0.5           | 1.7              |
| Esophagus, Gy (RBE)    | -3.8                | -0.1           | -7.5             |
| Body, Joules           | -2.2                | -4.4           | -77.4            |

**Abbreviations:** BH, breath holding; FB, free breathing; Gy, Gray; IMRT, intensity-modulated radiation therapy; PT, proton therapy; RBE, relative biological effectiveness.
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Table 3. Calculated volumes of the ITV and lung for the 3 patients.

| Structure | Patient 1 | Patient 2 | Patient 3 |
|-----------|-----------|-----------|-----------|
| ITV (ml)  | 344       | 505       | 466       |
| Lung (ml) | 2,405     | 2,166     | 1,969     |

Abbreviations: BH, breath holding; FB, free breathing; IMRT, intensity-modulated radiation therapy; ITV, internal target volume; PT, proton therapy.

improved the heart, esophagus, and integral doses compared with breath-hold IMRT and can also improve the lung dose in some patients with the trade-off of a minor increase in breast dose. In contrast, Rechner et al observed no statistically significant dose to the heart or lungs when comparing breath-hold IMRT with free-breathing proton therapy [10]. As the Rechner study was presented as an abstract, we do not know the planning techniques for proton therapy nor the case distribution of patients. Nevertheless, it is possible that only a few of the patients included in their analysis had extensive disease draped over the heart, where we see the greatest dosimetric benefit for using proton therapy.

Conclusion

Breath-hold proton therapy appears to help further reduce the dose to the organs at risk compared with the free-breathing technique in patients with bulky anterior mediastinal disease draping over the heart; however, the degree of benefit should be considered before determining the treatment technique to be used. Although technology is rapidly advancing, further investigation and quality measures need to be considered when implementing breath hold with proton therapy. A prospective treatment planning study with more patients to help determine which technique is optimal for varying distributions of disease is warranted.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts of interest to disclose.

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