Proton therapy for Hodgkin lymphoma: does a case report make the case?

David C. Hodgson & Lei Dong

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DAVID C. HODGSON & LEI DONG

It is now well established that historically used treatments for Hodgkin lymphoma (HL) can increase the risk of heart disease among long-term survivors. In particular, 35–45 Gy mantle or extended-field radiation therapy (RT) is associated with an increased risk of cardiac morbidity and mortality [1,2]. The adoption of doxorubicin-based chemotherapy as standard treatment for virtually all patients may make cardiac morbidity, rather than second cancers, the dominant late effect of modern HL therapy, particularly among those also treated with mediastinal RT. One feature of many adjuvant cancer treatments is that most patients do not actually benefit from them: the majority would have been cured without adjuvant therapy, or relapse in spite of receiving it. This is the case for adjuvant RT following doxorubicin-based chemotherapy for HL, which reduces the risk of relapse by approximately 7–20% depending on stage, disease bulk, intensity of chemotherapy, and other clinical features [3]. Several recently completed or ongoing clinical trials have been undertaken with the goal of improving the therapeutic ratio of HL treatment by more judiciously selecting patients for RT, and by reducing the radiation dose and volume among patients receiving it.

Proton therapy is a relatively new technology that potentially allows significant reductions in RT-related toxicity by decreasing the normal tissue dose adjacent to the target tissue. Unlike conventional high-energy photons, which penetrate beyond the targeted lymph nodes and expose normal tissues to the ‘exit dose,’ protons will stop after they deposit all their energy near the end of their range, a phenomenon known as the Bragg peak [4]. A good example of this phenomenon is displayed in Figure 1 of the case report by Hoppe et al. [5]. Because the proton beam is stopped within the posterior aspect of the heart, the dose to the left ventricle and the anterior branch of the left coronary artery should be significantly lower than seen with the photon plan, which requires both anterior and posterior beams. The case is illustrative of the potential for proton therapy to provide a unique advantage in sparing normal tissues distal to the target.

However, the accurate delivery of proton radiation is an evolving and complex undertaking. It is critical to know the radiological path length in the beam direction to determine where the proton beam will actually stop, and this in turn requires the precise estimation of tissue density, based on computed tomography (CT) imaging. Unfortunately, CT images do not provide such information as accurately as was originally hoped. Small imaging artifacts influence the precision of estimating the proton range. Notably, these imaging artifacts do not affect the diagnostic use of CT images, since they are almost undetectable by human eyes. In addition, day-to-day variation in patient position and organ motion also affect the range of protons, and the accurate estimation of where they stop in the patient. Due to these uncertainties regarding where the prescribed radiation dose is actually being deposited in the patient, proton therapy plans usually require a slightly larger margin of normal tissue around the tumor target than do photon RT plans, in order to be certain that the tumor is not under-dosed. As a
result, the volume of tissue receiving the prescribed (high) dose is often larger in proton therapy. However, due to proton stopping, the volume of tissue exposed to intermediate and low doses (and often the total body dose) is decreased with proton therapy. It is also unknown what effect the potentially high dose and uncertain relative biologically effective (RBE) dose of the stopping protons will have on the normal tissues at the end of the proton beam, in this case the posterior wall of the heart [6]. There may be unexpected shortcomings of the technology if, for example, the stopping proton dose is found to carry high RBE value.

Patient selection will also play a major role in determining who might benefit from proton therapy. A previous study by the same group reported that proton therapy did not provide significant sparing for the heart when patients did not have any disease in or below the hila, although it did reduce the breast and lung dose [7]. The case presented by Hoppe et al. was highly selected: recurrent disease in the posterior mediastinum of a patient who declined salvage chemotherapy. Proton therapy indeed demonstrated advantage in sparing a large volume of the heart despite the use of a large treatment margin, and appeared to be a good option for this patient. Whether it would be applicable to a broader population of patients with HL remains to be determined.

It is hard to ignore a dose distribution that appears to deliver dose to the desired target while avoiding most normal tissues. However, several clinical issues regarding proton therapy have yet to be clarified [8]. How accurately can we estimate where a proton beam will stop and how much treatment margin is safe? How will patients be selected for protons (or any RT) and what impact would the adoption of involved node RT (INRT) have on the relative merits of proton therapy? What are the clinical benefits of reducing low-dose exposures? The case described by Hoppe et al. illustrates the remarkable promise of proton therapy to reduce late effects of RT. No doubt the authors are more aware than most of the hard work that lies ahead to make that promise a reality.

References