Special Cases for Proton Beam Radiotherapy: Re-irradiation, Lymphoma, and Breast Cancer

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The dose distributions that can be achieved with protons are usually superior to those of conventional photon external-beam radiation. There are special cases where proton therapy may offer a substantial potential benefit compared to photon treatments where toxicity concerns dominate. Re-irradiation may theoretically be made safer with proton therapy due to lower cumulative lifetime doses to sensitive tissues, such as the spinal cord. Proton therapy has been used in a limited number of patients with rectal, pancreatic, esophageal, and lung cancers. Chordomas and soft tissue sarcomas require particularly high radiation doses, posing additional challenges for re-irradiation. Lymphoma is another special case where proton therapy may be advantageous. Late toxicities from even relatively low radiation doses, including cardiac complications and second cancers, are of concern in lymphoma patients with high cure rates and long life expectancies. Proton therapy has begun to be used for consolidation after chemotherapy in patients with Hodgkin and non-Hodgkin lymphoma. Breast cancer is another emerging area of proton therapy development and use. Proton therapy may offer advantages compared to other techniques in the setting of breast boosts, accelerated partial breast irradiation, and post-mastectomy radiotherapy. In these settings, proton therapy may decrease toxicity associated with breast radiotherapy. As techniques are refined in proton therapy, we may be able to improve the therapeutic ratio by maintaining the benefits of radiotherapy while better minimizing the risks.
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PROTON THERAPY FOR TOXICITY REDUCTION

There has been much controversy surrounding proton-beam therapy. The dose distributions that can be achieved with protons are usually superior to those of conventional photon external-beam radiation. Their principle benefit is in the potential sparing of normal tissue and the promise of reduced side effects from radiation. The chief criticism is with an emphasis on its cost and the relative paucity of clinical data suggesting any measurable benefit, or cost-effective benefit, compared to conventional photons. Most critics have centered their arguments on the use of proton therapy for prostate cancer, where it has become a symbol of the US healthcare system's inability to control costs. It is true that prostate cancer has been the disease most commonly treated with proton therapy, and the debate rages on whether the additional costs are worth the questionable toxicity benefit in this group of patients.

For the enthusiasts of proton therapy, the treatment of pediatric cancers represents a clear case of this modality's promise. Unlike x-ray therapy, proton-beam therapy has no exit dose, allowing for smaller volumes and vastly reduced or zero dose to normal organs that are beyond the tumor targets (Figure 1). When treating tissues of young patients, especially with curable diseases, why would one want to deposit *any* additional dose outside the target region? Even low doses to normal tissues can stunt growth, compromise intellectual development, and stimulate second cancers.

Although this concept is obvious for children with cancer, this principle holds in many adult malignancies. This is especially the case where the use of radiotherapy in general is questioned due to the concern for excessive toxicity. Radiotherapy is a potent tool to obtain and maintain local and regional control of cancers, but the risk/benefit ratio often

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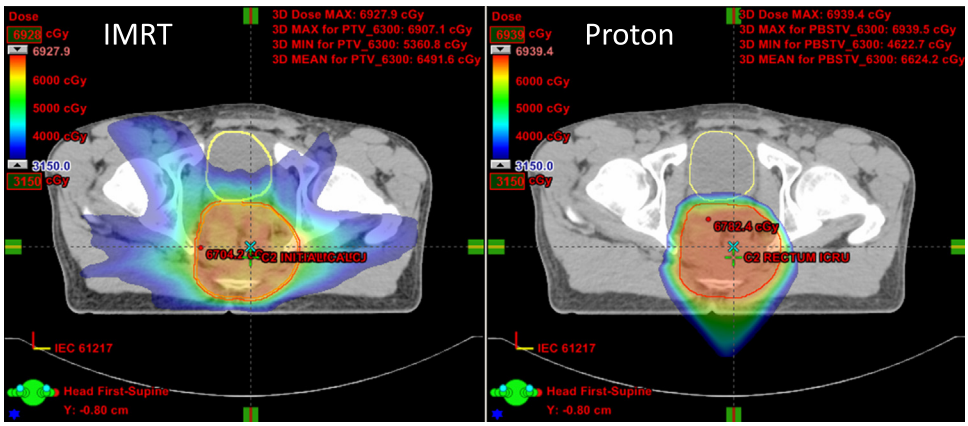

Figure 1. Comparative radiation planning for locally recurrent rectal cancer. This patient developed a locally recurrent rectal adenocarcinoma. Compared to an IMRT photon plan (left), the pencil-beam scanned proton therapy plan (right) delivers less dose to the bladder (yellow contour), femoral heads, and bowel (not shown).

teeters close to the center. Proton-beam therapy may offer a tool to help tip that balance more favorably.

As more proton therapy centers have opened, more physicists and clinical researchers have set their attention to developing proton therapy for cancers other than prostate and pediatric tumors. In this exciting explosion of translational research, other special cases for proton therapy are being developed. This review will focus on 3 such cases where toxicity concerns dominate the use of radiotherapy: re-irradiation, lymphoma, and breast cancer.

RE-IRRADIATION

Side effects from radiotherapy can be divided generally into acute toxicities and late toxicities. Acute toxicities occur during the course of fractionated radiotherapy, generally peak shortly after the completion, and resolve on their own in the weeks following radiotherapy. Hollow viscous organs are rapidly renewing tissues and manifest toxicity by transiently exhausting their usual process of continuous cell division before recovery. Dermatitis, cytopenias, enteritis, and mucositis generally resolve once the relevant stem cells start to divide and repopulate the tissue. Late toxicities are different. They occur months to years after radiotherapy and are characterized by cell loss, atrophy, and replacement with scar tissue. It is thought that the cumulative lifetime radiation doses are the most important determinants of late toxicities, although it is thought that some tissues may "forget" at least part of prior radiation doses.

When the need arises to use radiation a second time to the same part of the body, concern about these late effects loom large in the minds of treating physicians. The principle of "primum non nocere" is likely at the heart of radiation oncologists' reluctance to re-irradiate. A survey of Canadian radiation oncologists demonstrated this reluctance, with less than two-thirds of practitioners willing to re-irradiate lung, rectal, and breast cancers.[1] More than 95% were willing to re-irradiate the vaginal vault, possibly due to the teaching that the vaginal mucosa is one of the most radioresistant normal tissues in the body. In addition, patients who need re-irradiation are usually very complicated, and their clinical management and radiotherapy planning consume a lot of time. The frequency and severity of the risks from retreatment are perceived to be high and uncertain. The success rate in cure or palliation of symptoms is generally estimated to be low. Refusing to re-irradiate is frequently the easiest answer when a consulting physician asks about treatment options.

Optimizing the Risk/Benefit Ratio in Re-irradiation

Several advances in oncology have potentially opened the door to more effective re-irradiation. Much research in radiation biology has explored ways to widen the therapeutic ratio. Modifiers of radiotherapy, such as radiation sensitizers and protectants may have a role in the re-irradiation setting. For example, hyperthermia, a proven radiosensitizer, has been used to improve outcomes in breast cancer re-irradiation.[2] Cetuximab, a proven radiosensitizer in squamous cell carcinoma of the head and neck, has been investigated in the re-irradiation setting both with fractionated radiotherapy and with stereotactic body radiation therapy (SBRT).[3–6] The early results from a multi-institutional phase II study of cetuximab/SBRT re-irradiation for patients with recurrent head and neck squamous cell carcinoma are encouraging, with a 1-year overall survival rate of 47.5% and disease control rate of 91.7%.[3]

The use of advanced imaging, in particular magnetic resonance imaging and fluorodeoxyglucose