Proton Beam Reirradiation

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The original version of this chapter was revised. An erratum to this chapter can be found at 10.1007/978-3-319-41825-4_78.

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Abstract

Proton therapy is a modality of radiation therapy with unique physical properties relative to photon (X-ray) therapy. Each proton beam is modulated to deposit the maximum radiation dose in the target, with essentially no radiation to tissues beyond the target. Compared to photon treatments, highly conformal treatment plans can typically be developed with fewer proton beams, significantly reducing the overall exposure of nontarget tissues to radiation. Given the narrow therapeutic window of reirradiation, proton therapy is of great interest as a mechanism to potentially avoid or reduce toxicities of reirradiation by limiting the volume of nontarget tissues receiving additional radiation dose. In some diseases, proton reirradiation may improve outcomes by facilitating safer radiation dose escalation to recurrent and potentially radioresistant tumors or providing better target coverage while respecting constraints to critical normal structures. In uncommon cases, proton therapy may permit reirradiation when the dosimetry achieved with other modalities is felt to preclude safe reirradiation. Clinical experience with proton reirradiation is currently limited to relatively small patient series and is highly heterogeneous. To better understand the value of proton therapy in reirradiation relative to other radiation modalities, prospective evaluation with more homogenous patient populations is needed to evaluate predefined end points

Med Radiol Radiat Oncol (2016)
DOI 10.1007/174_2016_71, © Springer International Publishing Switzerland
Published Online: 20 Jul 2016

based on rational clinical hypotheses. In this chapter, the rationale and published clinical results of proton therapy for reirradiation are reviewed for a variety of disease sites, with case examples provided.

1 Background

Proton therapy is a modality of radiation therapy distinguished from photon (X-ray)-based treatments by the unique physical properties of protons. Protons have an energy-dependent finite range in tissue. The rate of energy deposition increases as the protons slow down, yielding a peak in ionization (dose deposition) in the terminal range of the beam, followed by an abrupt falloff to essentially no radiation dose as the protons come to rest. This is known as the Bragg peak of proton therapy (Paganetti 2012; Lomax 2009). Compared to a single photon beam, a single proton beam has a lower entrance dose to normal tissues, puts its maximal energy in the target (rather than near the surface of the patient), and has no meaningful exit dose beyond the target. As a result, highly conformal plans can typically be developed with fewer treatment beams, reducing the overall exposure of nontarget tissues to radiation (Lomax et al. 2004). In addition, compared to photons, proton therapy provides a sharper lateral beam penumbra (dose buildup region) at depths up to about 17 cm in water (Suit et al. 2003).

These physical properties of proton therapy provide unique and heightened opportunities in treatment planning to reduce overall radiation exposure, achieve areas of significant radiation reduction or complete avoidance adjacent to the target, create steep dose gradients adjacent to critical normal structures, and more safely escalate radiation dose to targets adjacent to critical structures. In clinical use since the 1950s, proton therapy has had a rising profile due to technological advancements, continued interest in reducing potential toxicities of radiation therapy, and increased accessibility with a growing number of proton treatment facilities opening globally.

2 Patient Selection for Proton Reirradiation

Reirradiation often has a narrow therapeutic window, and in each case the clinician must balance the clinical benefit of additional radiation for local tumor control against what may be significant risks of toxicity to previously irradiated normal tissues. Anticipated acute toxicities of reirradiation may be deemed excessive or unbearable in heavily pretreated patients. Often of greater concern than acute toxicities are the potential significant late toxicities to normal structures, which may be life altering or even fatal. These concerns must be carefully weighed against the potential benefit of obtaining local control or local palliation. Proton therapy may be selected to reduce radiation exposure to nontarget tissues or achieve regions of complete radiation avoidance in an effort to mitigate the potential toxicities of treatment. In cases where the proximity of critical structures or other constraints would result in significantly compromised target coverage or require significant dose reduction with photon techniques, the dosimetric advantages of proton therapy may facilitate improved target coverage and/or delivery of a higher radiation dose with the intent of improving the likelihood of curative therapy or more durable local control. Proton therapy may therefore be a useful tool to improve the therapeutic ratio of reirradiation and potentially to extend the option of reirradiation to patients otherwise unsuitable for reirradiation with other modalities.

Data-driven patient selection criteria for reirradiation are sparse. Many applications of reirradiation are given with clear palliative intent, and the goals of palliative reirradiation can be met in the great majority of cases with photon techniques. However, practitioners may confront special clinical circumstances where the utilization of more costly palliative proton therapy appears justified. For example, the authors have used palliative proton therapy in a patient with an undefined presumed genetic predisposition that resulted in heightened radiosensitivity. Two prior attempted courses of palliative photon therapy for metastatic osseous spine disease resulted in extraordinary gastrointestinal toxicity requiring hospitalization on both occasions.

Proton therapy was subsequently used to palliate the spine and avoid dose to the viscera anterior to the spine. Outside these uncommon clinical scenarios, there are no substantive clinical data to support the increased economic costs of palliative reirradiation with proton therapy. This application is likely to remain based on the clinical judgment of practitioners facing uncommon scenarios and constrained by restrictions from healthcare payers.

Patients considered for definitive or curative intent reirradiation generally have nonmetastatic disease (or controlled or controllable systemic disease), a good performance status, and a disease process which suggests that successful locoregional therapy could achieve either a long-term disease control or cure (McDonald et al. 2011). As a modality of external beam irradiation, proton therapy may be considered an alternative to photon-based reirradiation with three-dimensional conformal radiation therapy, intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), or stereotactic body radiation therapy (SBRT). Other reirradiation options such as intraoperative radiotherapy (IORT) and brachytherapy have profoundly different dosimetry with unique applications and indications. Practitioners benefit from having access to the broadest array of potential treatment options to tailor therapy to the clinical circumstances. There is no single modality that would be appropriate for every clinical reirradiation scenario.

3 Treatment Planning Considerations in Proton Reirradiation

The distinct physical properties of protons entail special treatment planning considerations and uncertainties (ICRU 2007). These uncertainties and considerations have increased importance in reirradiation, as there are often more organs or structures deemed at risk with more stringent dose constraints and the potential for more significant toxicity should those dose constraints be exceeded.

Although not a unique consideration to proton therapy, patient weight loss (or weight gain), changes in tumor size or morphology, and other potential alterations in tissues within the beam path(s) during retreatment can lead to significant changes in proton dosimetry which could result in unanticipated variations in dose to organs at risk (Mannina et al. 2014). Compared to photon therapy, proton therapy is significantly more sensitive to differences in tissue heterogeneities within the beam path (Paganetti 2012). In situations of anticipated dynamic tissue heterogeneity – such as treatment of the sinuses, where obstructive secretions and inflammatory sinusitis can vary over a treatment course – patients should be frequently reimaged to monitor for dynamic changes that may require adaptive planning. Proton beam arrangements should be selected in a fashion that limit the effect of potential changes in tissue heterogeneity that would risk overdosing critical organs by assessing "worst case" scenarios for plan robustness (Li 2012).

Patients with metal hardware, such as spinal fixation, can pose a tremendous challenge in proton therapy due to the loss of critical CT information needed to accurately calculate proton range, mixed alloy hardware or implants which include materials of varying density, and issues of dose perturbations at the tissue/hardware interface including dose shadowing distal to the hardware. The clinical impact of these uncertainties can be mitigated through the use of metal artifact reduction algorithms for CT simulation (Andersson et al. 2014), incorporating multiple beams with varied angles of incidence relative to the hardware, the use of passive scattered protons rather than pencil beam scanning (Verburg and Seco 2013), and integration of photon therapy for some portion of the total treatment.

Organ motion is an important treatment planning consideration for all radiation modalities and poses special challenges in proton therapy, which are elsewhere reviewed in depth (De Ruysscher et al. 2015). Rigorous patient immobilization and positioning accuracy with pretreatment image verification are essential in proton therapy, both for protection of critical normal structures and also to minimize changes in beam path heterogeneities which can markedly affect dose distributions.

While the majority of clinical experience with proton therapy has been with 3D conformal proton therapy using passive beam scattering techniques, or more recently, uniform scanning, pencil beam scanning (PBS) is the most recent technological advance in the delivery of proton therapy. Older proton techniques provide a uniform dose with a uniform spread-out Bragg peak (SOBP) across the entire treatment field and often require a manual, iterative approach to treatment plan optimization. In contrast, PBS utilizes magnetic steering of a narrow proton beam and can vary the dose distribution across the field and adjust the width of the SOBP across the field so that the dose deposition more closely matches the target geometry. PBS planning techniques include single field uniform dose, in which each treatment field is optimized to deliver a uniform dose to the target, and multifield optimization, in which, similar to photon-based IMRT, inverse optimization is used to create a composite target dose distribution from constituent treatment fields that individually may deliver a highly heterogeneous dose distribution. These newer proton therapy techniques, utilizing a treatment planning objective-based clinical workflow more similar to photon-based IMRT, generally offer improved dose distributions compared to 3D conformal proton plans using passive scattering. They are the focus of significant ongoing work in proton treatment planning optimization, validation, assessments of treatment plan robustness, and adaptive proton therapy in response to dynamic changes through the treatment course.

4 Proton Reirradiation of Radiation-Associated Neoplasms

Benign and malignant neoplasms in patients with prior radiation are uncommon but often devastating complications of prior radiotherapy. Population data from the US Surveillance, Epidemiology, and End Results (SEER) cancer registries suggest the excess risk of a second solid tumor in adult patients is 0.005% at 15 years after radiotherapy (Berrington de Gonzalez et al. 2011). The incidence of second malignancies in children is much higher (Bassal et al. 2006), presumably related to heightened radiosensitivity, more frequent underlying genetic syndromes, and a longer available latency period to develop second neoplasms in children compared to patients treated as adults.

In a report with long-term follow-up of 963 patients with hereditary retinoblastoma, patients treated with radiotherapy had almost twice the absolute excess risk of cancer compared to those managed without radiation (Kleinerman et al. 2005). Of interest, the cumulative incidence of second malignancy at 40 years was 32.9% in patients treated with orthovoltage radiation, but for those treated with megavoltage techniques (in which radiation scatter to nontarget tissues was reduced), the cumulative incidence was reduced to 26.3%. These data support the clinical goal of minimizing radiation dose to nontarget tissues, particularly in patients at heightened risk of secondary malignancy.

Radiobiologic modeling predicts a reduced incidence of secondary malignancy in adult and pediatric patients treated with proton therapy compared to photon techniques (Simone et al. 2012; Zhang et al. 2013). Although the risk of second malignant neoplasms is greatest in children and young adults receiving radiation therapy, they are not insignificant in adult patients. For example, meta-analysis of patients receiving radiotherapy for prostate cancer highlights an increased risk of bladder and colorectal cancers following radiation (Wallis et al. 2016). Compared to photon therapy, proton therapy was associated with a reduced risk of second malignant neoplasms in adult patients in a retrospective matched cohort analysis (Chung et al. 2013). We are unaware of any published clinical data on proton therapy in patients with radiation-induced malignancies or second cancers. Due to its reduced radiation exposure to nontarget tissues, proton therapy is an appealing option when radiotherapy is indicated in management of these patients who have a demonstrated heightened sensitivity to radiotherapy.

Figure 1 shows an example of proton therapy in treatment of a patient with a recurrent, clival meningioma in a previously irradiated adult survivor of childhood glioma.

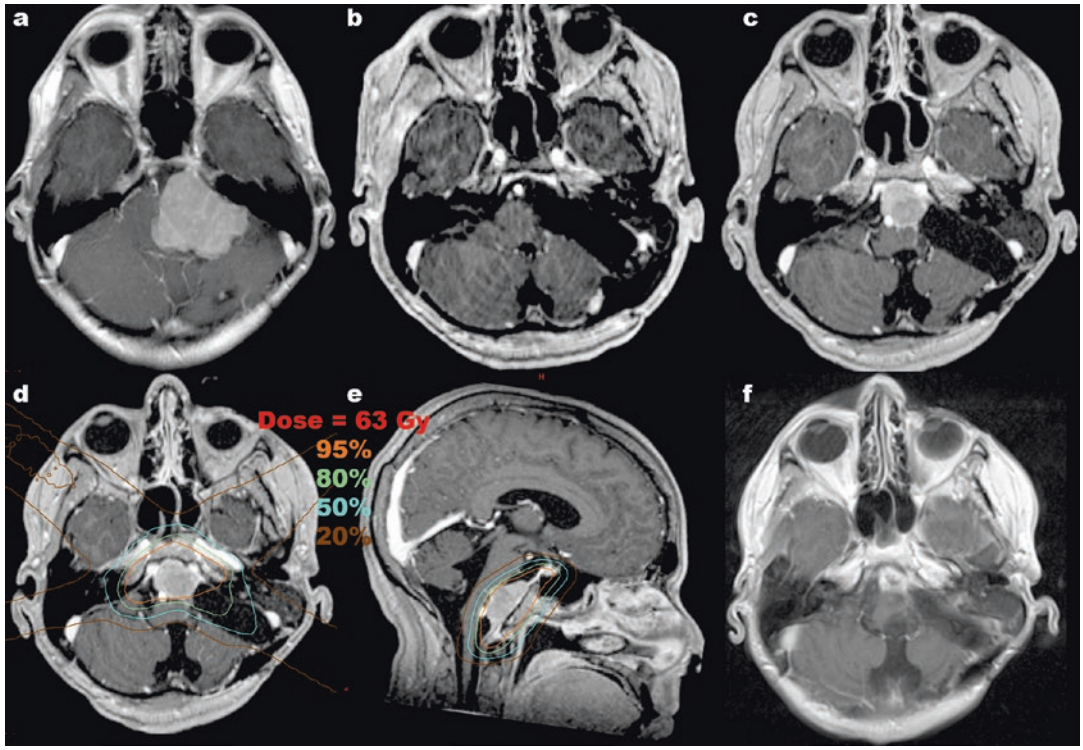


Fig. 1 A 40-year-old male was treated for a radiation-induced atypical clival meningioma. He had a history of a pediatric posterior fossa tumor, reported as a glioblastoma, and had received radiation therapy 30 years prior: 30 Gy to the whole brain and a 55 Gy boost to the posterior fossa with 6 MV photons. Pathology slides from his original tumor had been destroyed. He presented with left-sided hearing loss, dysphagia, and balance disturbance and was found to have a large left cerebellar-pontine angle/posterior clival meningioma with brainstem compression (**a**). Surgical debulking was undertaken via a two-stage approach including lateral suboccipital craniotomy with pathology showing a WHO grade 2 meningioma. A near-total resection of tumor was obtained (**b**). Unfortunately he suffered left cranial nerve VI and VII palsies with neurotrophic keratopathy eventually requiring left eye enucleation and multiple lower cranial nerve palsies with dysarthria and dysphagia requiring permanent tracheostomy and gastrostomy tube feeding. Within 6 months from surgery, his tumor had regrown and was again approximating the brainstem (**c**). No further surgery was advised. He was referred for proton therapy due to concern about brainstem tolerance to additional radiation considering his prior radiation and surgical trauma. A treatment plan was generated using a combination of through and patch fields (keeping the brainstem at the aperture edge) and anterior oblique fields with distal blocking of the brainstem to avoid delivery of any radiation through the brainstem. Two schemas were used of four fields each. The prescription dose was 63 Gy (RBE) in 35 fractions, allowing the surface of the brainstem to receive an additional 50 Gy (RBE) (**d**, **e**). Because of his debilitated condition, daily anesthesia was required to comply with immobilization. The first posttreatment MRI at 6 weeks showed central tumor necrosis and transient enlargement of the tumor without clinical worsening. At 12 months postradiation, his MRI showed significant regression of tumor, volumetrically reduced from 6 to 2.2 cm^3 (**f**). At 37 months from radiation, the patient had continued radiographic regression of tumor

5 Proton Reirradiation of Chordoma

Chordomas are rare primary bone tumors with a high propensity for local recurrence even after aggressive surgery and radiotherapy. For clival chordomas, maximizing tumor debulking and optimizing residual tumor coverage by high-dose radiotherapy are associated with superior outcomes (McDonald et al. 2016a). For patients with recurrent disease after prior radiation, treatment options are limited. While effective targeted

drug therapies are desperately needed in chordoma, local control measures remain the mainstay of treatment.

Salvage surgery alone rarely achieves a durable period of disease stability and has a reported 2-year overall survival of 63 % (Fagundes et al. 1995). Reirradiation options are typically constrained by the prior dose delivered to closely adjacent critical normal structures, particularly the spinal cord for extracranial chordomas and the brainstem and optic apparatus for clival chordomas. Small intracranial recurrences are often amenable to stereotactic radiosurgery (SRS) with satisfactory local control, although there is a not insignificant risk of marginal failure of about 15 % (Kano et al. 2011).

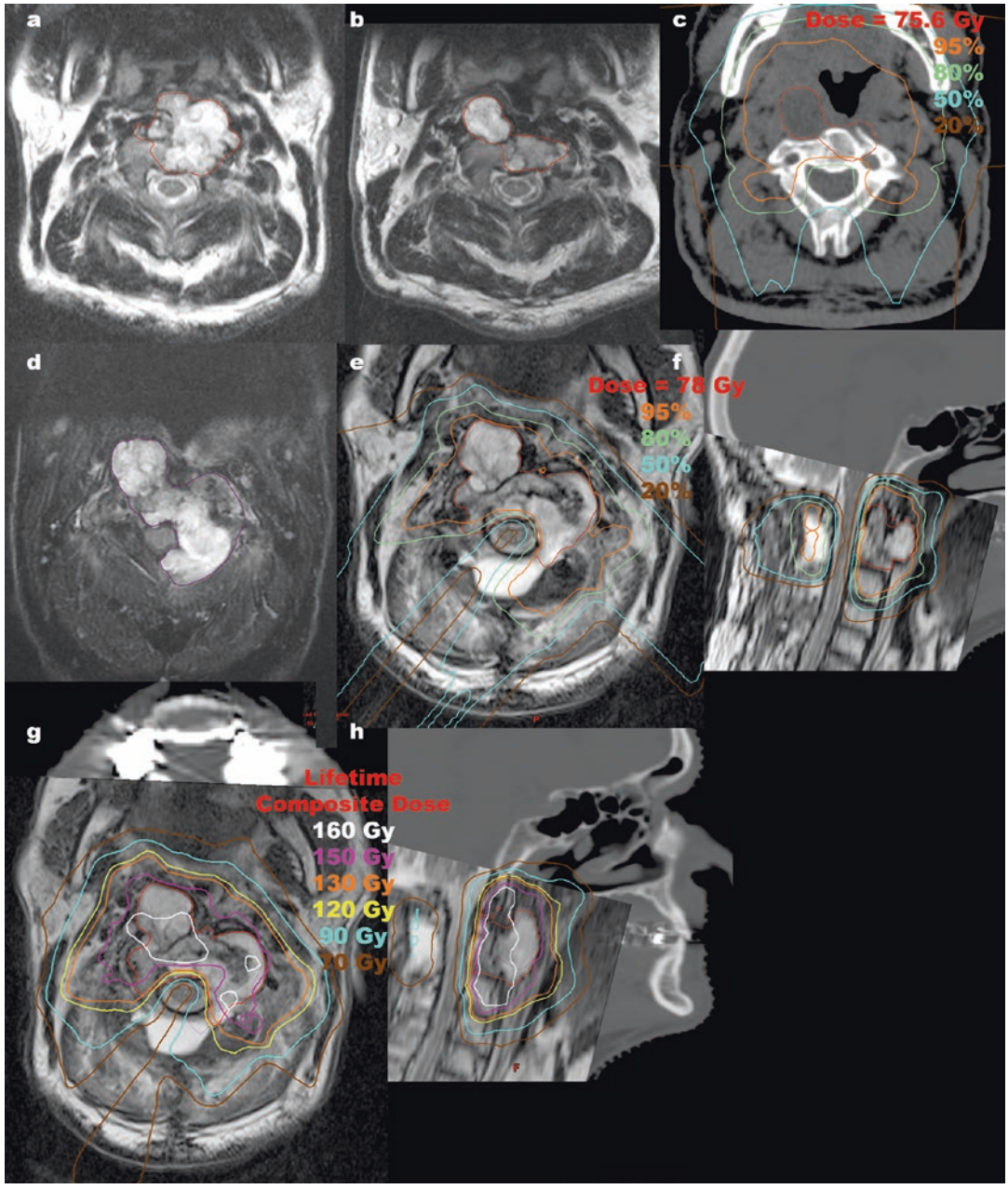
Researchers at the now-closed Indiana University Health Proton Therapy Center reported on 16 previously irradiated patients with recurrent or progressive chordoma (McDonald et al. 2013a). Half the patients underwent salvage surgery in management of their recurrent or progressive disease. At a median of 37 months after a median prior dose of 75.2 Gy, patients were retreated to an additional median dose of 75.6 Gy (RBE). At a median follow-up of 23 months, the 2-year estimate of local control was 85 % and overall survival 80 %. The 2-year estimate of late grade 3+ toxicity was 19 %. The disease control in this experience with aggressive proton reirradiation compares very favorably to other interventions in a population with a historically poor prognosis.

Figure 2 is an example of proton therapy in reirradiation of a recurrent cervical spine chordoma.

6 Proton Reirradiation of Gliomas

Recurrent or progressive infiltrative glioma develops in almost all patients after initial therapy. In the absence of high-quality data on optimal management, patients with recurrent glioma are typically evaluated for further resection, chemotherapy, reirradiation, and other interventions based on tumor histology, genetic factors, size, location, and patient performance status, among other factors (Stupp et al. 2014). For glioblastoma, the most common malignant primary brain tumor in adults, the standard of care for initial management is maximal safe surgical

Fig. 2 A 67-year-old man was reirradiated for a cervical spine chordoma. He presented with dysphagia and imaging showed a destructive mass at C2 extending into the prevertebral space (**a**; tumor outlined in *red*). He underwent transoral partial resection with pathology showing chordoma and was observed. Imaging one year later showed a bulky recurrence (**b**; tumor outlined in *red*). After neurosurgical evaluation, the morbidity of re-resection was felt to be too great and he was referred for proton therapy. He was treated to 75.6 Gy (RBE) in 42 fractions by another physician (**c**, gross tumor volume outlined in *red*). Due to concern for potential surgical seeding, a large treatment volume was defined which covered the soft palate, resulting in permanent xerostomia and dental caries. Three years after proton therapy, the tumor remained stable in size but he developed a solitary supraclavicular nodal metastasis, which was completely excised. At 38 months from radiation, imaging showed progression of the primary tumor. A 6-month trial of imatinib was undertaken with repeat imaging showing further tumor progression now encroaching upon the cervical spinal cord (**d**; tumor outlined in *magenta*). He was referred for neurosurgical decompression and posterior spine stabilization, which achieved clearance around the spinal cord, although complete surgical resection was not possible. He was then retreated with proton therapy to 78 Gy (RBE) in 38 fractions, 4 years after his prior radiation therapy (**e**, **f**; gross tumor volume outlined in *red*). A CT myelogram was performed in the immobilization devices to define the cervical spinal cord. CT simulation was performed with an orthopedic metal artifact reduction algorithm in light of his spine stabilization hardware and dental amalgam artifacts. He was treated with two complex alternating schemas of through and patch fields, the first schema involving six fields and the second involving five fields. The spinal cord was blocked by all beams to keep the spinal cord surface dose at the 50 % isodose line. His lifetime dose distribution is shown (**g**, **h**). The maximum spinal cord point dose was 54.9 Gy from his initial course, 46.5 Gy from his reirradiation and cumulative lifetime maximum point dose 97.5 Gy (75.4 Gy to 0.5 cm^3). He did not develop any oral mucositis during reirradiation and had only grade 1 odynophagia and grade 1 dermatitis. Three months after reirradiation, he started planned adjuvant therapy with erlotinib which was stopped after 1 month due to skin toxicity. At 6 months after reirradiation, he had a focus of posterior oropharyngeal wall soft tissue necrosis treated with hyperbaric oxygen. Unfortunately, the soft tissue necrosis progressed, leading to exposure of bone and required tracheostomy and gastrostomy tube feeding. He survived for two years after reirradiation without evidence of tumor progression or spinal cord myelopathy but died from a sudden carotid artery rupture, highlighting the significant risks of high dose retreatment


a
b
c
Dose = 75.6 Gy
95%
80%
50%
20%
d
e
f
Dose = 78 Gy
95%
80%
50%
20%
g
h
Lifetime
Composite Dose
160 Gy
150 Gy
130 Gy
120 Gy
90 Gy
20 Gy

resection followed by radiotherapy with concurrent and adjuvant temozolomide (Stupp et al. 2009). The median progression-free survival is approximately 7 months. The Radiation Therapy Oncology Group is currently enrolling patients in a randomized phase II trial for patients with recurrent or progressive glioblastoma in which patients are randomized to bevacizumab alone or bevacizumab plus hypofractionated reirradiation to 35 Gy in 10 fractions. This trial should provide valuable prospective evidence to evaluate the potential benefit of early incorporation of reirradiation.

One of the most significant clinical concerns with reirradiation of gliomas is the risk of brain radiation necrosis. Proton therapy is theoretically appealing because highly conformal reirradiation can be delivered with lower dose to adjacent nontarget brain tissue. However, this would not reduce the risk of central radiation necrosis occurring within the reirradiation target. Furthermore, modern photon techniques of hypofractionated reirradiation for high-grade gliomas have been associated with no discernable or very low risk of radiation necrosis (Fogh et al. 2010). This is presumably due at least in part to the limited survival time of patients. For these reasons, the routine application of proton therapy in reirradiation of high-grade gliomas may not translate into measurable clinical improvements in toxicity.

If prognostic tools improve to accurately identify better prognosis patients (whose longer survival time would presumably place them at greater risk of radiation necrosis and neurocognitive effects of reirradiation), proton reirradiation may be of benefit in these select patients. Proton therapy may be a useful tool in prospective dose-escalation trials of reirradiation. A similar strategy is being employed in an open phase I/II trial at the University of Heidelberg evaluating the role of carbon ion therapy in recurrent gliomas (grades 2–4). The phase I component is designed to establish a recommended carbon ion dose via dose escalation from 30 to 48 Gy equivalent (GyE) in 3 GyE fractions, while the phase II component will compare 12-month survival against photon reirradiation to 36 Gy in 2 Gy fractions (Combs et al. 2010).

Researchers at the now-closed Indiana University Health Proton Therapy Center reported on 20 patients with recurrent gliomas who were treated with proton reirradiation (Galle et al. 2015). Three had grade I or II gliomas, 4 grade III, and 13 grade IV. The patient population was heterogeneous in terms of prior therapy and utilization of concurrent chemotherapy. Additionally, the dose of reirradiation varied from hypofractionated regimens to full dose reirradiation in conventional fractionation. Protracted fractionation was generally used in patients with a long time interval from prior radiation therapy (up to 12 years) based on a belief that such patients may be longer-term survivors. The median dose of reirradiation was 59.4 Gy (RBE) (range 37.5–60) for grade III tumors and 54 Gy (RBE) (range 30–60) for grade IV tumors. The median survival after reirradiation was 10.2 months for grade III tumors and 8.2 months for grade IV tumors. With reference to prior radiation dosimetry, efforts were made to direct proton reirradiation beams to minimize the volume of reirradiated brain. There was a 10 % crude incidence of radiation necrosis. It is difficult to derive any conclusions from such heterogeneous data, but it is quite uncommon to deliver full course reirradiation, and the apparent reasonably low risk of radiation necrosis is provocative even if the benefit of full dose reirradiation is unknown.

Figure 3 illustrates an example of proton therapy in reirradiation of a patient with a recurrent WHO grade III anaplastic astrocytoma.

7 Proton Salvage Craniospinal Irradiation

Salvage craniospinal irradiation has been reported, primarily in children, in treatment of recurrent and disseminated ependymoma (Merchant et al. 2008), recurrent medulloblastoma after prior CSI (Massimino et al. 2009), and for other histologies with neuroaxis dissemination after prior focal radiation (Wei et al. 2012). Researchers at St. Jude Children's Research Hospital reported on varied techniques of salvage reirradiation for recurrent ependymoma. For those treated with

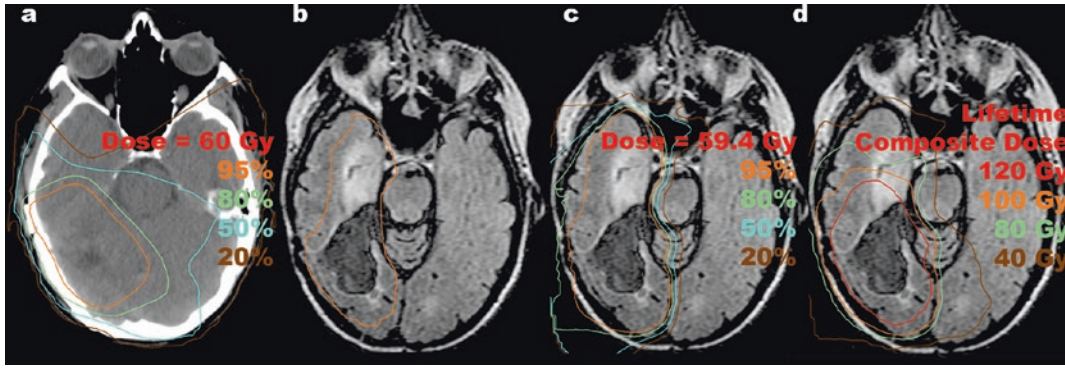


Fig. 3 A 48-year-old woman was reirradiated for a recurrent glioma. She had a history of a complete resection of right posterior temporal anaplastic astrocytoma (grade III) and received adjuvant radiation therapy to 60 Gy in 30 fractions (**a**) without chemotherapy. Seven years later she developed episodes of confusion prompting MRI scan that revealed local recurrence of non-enhancing tumor with progression of FLAIR abnormality into the anterior ipsilateral temporal lobe highly suspicious for tumor. She underwent radical subtotal resection guided by functional MRI, confirming recurrent grade III astrocytoma, IDH-1 intact, with residual inoperable tumor. She was offered reirradiation with proton therapy to 59.4 Gy (RBE) in 33 fractions with concurrent temozolomide. The residual tumor and the target volume for reirradiation are shown in *orange* (**b**). Proton therapy was used to avoid radiation to the contralateral hemisphere and to minimize dose to the brainstem (**c**). The previous tumor region received a cumulative dose of 120 Gy between the two courses separated by 7 years (**d**). She developed bone marrow suppression requiring dose de-escalation of temozolomide in the later course of therapy. Within 1 year, the patient developed brain parenchymal radiation necrosis that was treated with bevacizumab and hyperbaric oxygen treatment. She developed a sustained contralateral hemiparesis with dysarthria. Eighteen months after reirradiation, the patient was alive with no radiographic evidence of tumor progression

salvage CSI, standard photon technique with opposed lateral brain fields was used, with custom blocking designed to limit the brainstem and spinal cord to a maximum cumulative radiation dose of 55.8 Gy. While effective at shielding critical structures and limiting cumulative radiation dose, lateral blocks also shield a volume of cerebrospinal fluid and leptomeningeal space potentially harboring microscopic disease. This could theoretically reduce the effectiveness of salvage CSI and allow for reseeding. Others have used IMRT to attenuate dose to previously irradiated critical structures while maintaining coverage of the surrounding target volume (Wei et al. 2012), but this cannot achieve complete sparing in the same way as lateral blocks.

Using the finite distal range of proton therapy, researchers at the now-closed Indiana University Health Proton Therapy Center reported a novel technique to block a critical structure on lateral fields and then fill in or "plug" dose to cover the target volume lateral to the structure. The resulting plan created a "donut" hole of complete dose avoidance surrounding the critical structure. Two example cases were highlighted in which critical structures were felt to require complete sparing from additional radiation dose: one child receiving salvage CSI for recurrent and disseminated medulloblastoma in which the optic chiasm was spared, and one adult with recurrent and disseminated anaplastic meningioma in which the previously irradiated portion of the lateral brainstem was spared. Compared to lateral photon fields with blocks and with IMRT, this proton technique improved coverage of the planning target volume while reducing the mean and maximum dose to the critical organs at risk (McDonald et al. 2013b).

Similarly, a case report from researchers at the University of Pennsylvania reported on the use of pencil beam scanning proton therapy to deliver salvage craniospinal irradiation with brainstem sparing (Hill-Kayser and Kirk 2015). The case involved a child with a posterior fossa ependymoma whose prior radiation delivered a maximum brainstem dose of 60 Gy (RBE). Ten

months later, spinal dissemination was detected and salvage CSI to 36 Gy (RBE) followed by focal tumor boosts was offered, using pencil beam scanning to limit the surface of the brainstem to an additional 5 Gy (RBE).

In addition to the ability to create regions of complete dose avoidance if necessary around previously irradiated critical structures, proton therapy offers the advantage of no exit dose to viscera anterior to the spine during CSI, which is expected to reduce both acute and late toxicity by complete radiation avoidance. Retrospective cohort analysis supports reduced acute gastrointestinal and hematologic toxicities with proton CSI compared to photon CSI in adult patients treated for medulloblastoma (Brown et al. 2013). Additionally, retrospective cohort analysis found that, compared to photon CSI, proton CSI was associated with fewer late endocrine abnormalities in children treated for standard risk medulloblastoma (Eaton et al. 2015). Radiobiologic modeling predicts that proton CSI is associated with a reduced risk of secondary malignancies compared to photon techniques (Zhang et al. 2013). These data support the role of proton therapy in craniospinal irradiation for patients of all ages.

8 Proton Reirradiation of Ocular Melanomas

Proton therapy is an established modality of treatment for ocular melanomas with a very high rate of local control and favorable toxicity profile (Dendale et al. 2006; Desjardins et al. 2012). In addition to close collaboration with a specialized ophthalmologist, the treatment requires a dedicated patient setup, planning software, and expertise which may not be available at every proton treatment center. However, the shallow beam range and therefore low proton energy required for treatment means that proton therapy for ocular melanomas is also available at a number of centers with low-energy cyclotrons unsuitable for treatment of broader indications. A systematic review and meta-analysis suggested charged particle therapy for uveal melanoma was associated with lower rates of local recurrence, retinopathy, and cataract formation than plaque brachytherapy (Wang et al. 2013).

Choroidal melanomas arising in proximity to the optic disk (juxtapapillary) may be inappropriate for plaque brachytherapy due to inability to properly position the plaque for adequate tumor coverage. Stereotactic radiosurgery (SRS), hypofractionated stereotactic radiation therapy (SRT), and proton beam therapy have been used for posterior choroidal melanomas with success. A comparative treatment planning study of SRT and proton beam therapy for choroidal melanomas arising near the optic disk or fovea centralis found superior dosimetry with proton therapy in the majority of cases (Hocht et al. 2005). Clinical data from the Clatterbridge Cancer Centre and Sheffield Ocular Oncology Service compared outcomes for patients treated with SRS compared to proton therapy for choroidal melanomas (Sikuade et al. 2015). SRS and proton therapy were selected for patients with tumors considered either too large for plaque brachytherapy or for those located too close (<2.5 mm) to the optic disk for plaque placement. While tumor control was very high with both treatments, their analysis found a statistically significant lower rate of severe vision loss with proton therapy compared to SRS for patients whose tumors touched the optic nerve and for those >3 mm from the fovea. It may be that the fractionation used for proton therapy in this series (53.1 Gy (RBE) in 4 fractions) conferred fewer late effects compared to SRS (35 Gy at the 50 % isodose line in 1 fraction) or that other confounding factors were related to the difference in visual preservation.

Researchers at the Massachusetts General Hospital (MGH) reported on 31 patients with recurrent uveal melanoma who received a second course of proton therapy (Marucci et al. 2006). Nearly all the patients had received 70 Gy (RBE) in 5 fractions for both the initial course and the salvage course of proton therapy. At a mean follow-up of 50 months, the 5-year estimate of local control after salvage proton therapy was 69 %. The 5-year eye retention rate was 55 %, with 27 % of those who retained their eye having useful vision of 20/200 or better. Of the nine patients undergoing enucleation, five were due to local recurrence and four due to intractable pain.

Researchers at the Helmholtz-Zentrum Berlin reported on 48 patients with recurrent uveal melanoma after a variety of prior treatments (54 % previously irradiated) who received salvage proton beam radiation, with most receiving 60 Gy (RBE) in 4 fractions. At a mean follow-up time of 81 months, the 10-year estimate of local tumor control after proton reirradiation was 92.1 %. One patient required enucleation for local recurrence. At 5 years after salvage proton therapy, 24 % had useful vision of 20/200 or better. Compared to the MGH experience, the improved tumor control and lower rate of enucleation may be related to fewer patients having had prior radiation treatment or differences in other confounding variables such as tumor size. Together these data suggest that salvage proton reirradiation yields eye preservation in the majority of patients and preservation of useful vision in about a quarter of patients.

While overall survival is not compromised by local therapy with plaque brachytherapy compared to enucleation for choroidal melanomas (Diener-West et al. 2001), it is unclear whether further local therapy provides comparable survival to enucleation for recurrent disease. The MGH group compared survival outcomes for their 31 patients receiving salvage proton therapy to a cohort of 42 patients undergoing enucleation. Patients selected for enucleation had, on average, larger tumors than those selected for reirradiation. The 5-year survival estimate for those treated with reirradiation was 63 % compared to 36 % for those enucleated ($p = 0.040$) suggesting that survival is not compromised by salvage proton therapy compared to enucleation (Marucci et al. 2011).

9 Proton Reirradiation of Head and Neck Cancers

Despite aggressive therapy, locoregional disease failure remains common in many head and neck cancers. Reirradiation is a potentially curative treatment option for appropriately selected patients, although only a small percentage of patients achieve long-term survival (McDonald et al. 2011). The toxicities of head and neck reirradiation can be significant. A prospective multi-institutional trial using an accelerated hyperfractionated reirradiation regimen interdigitated with chemotherapy reported early grade 3 or higher toxicities in 77 % of patients. While many were hematologic, radiation mucositis occurred in 16 % and gastrointestinal toxicity in 48 %. Grade 3 or higher late radiation toxicities were reported in 37 %. In total, treatment-related deaths occurred in 8 % (Langer et al. 2007). These results drive the desire to improve the therapeutic ratio of reirradiation. Proton therapy may be advantageous in reducing the volume of previously irradiated tissues receiving additional radiation dose, potentially reducing toxicities of retreatment. Proton therapy may also enable the option of retreatment for patients whose prior radiation dose distribution is felt to preclude the safe delivery of additional radiation using other modalities.

Researchers from the now-closed Indiana University Health Proton Therapy Center reported on 61 adult patients with recurrent, progressive, or second primary head and neck malignancies after prior radiotherapy (McDonald et al. 2016b). The most frequent histologies were squamous cell (54.2 %), adenoid cystic (11.0 %), and undifferentiated (8.2 %) carcinoma. The great majority of cases (90.2 %) involved skull base tumor sites, and 45 % had macroscopic intracranial perineural spread or direct intracranial tumor extension. These patients had been referred from over 30 separate institutions and practices, most often because there were felt to be no appropriate photon-based reirradiation treatment options. The patients were heavily pretreated; 18 % had received two to four prior courses of radiotherapy, 52.5 % had undergone two or more prior surgeries, and 59 % had received prior chemotherapy.

Patients were treated to a median dose of 66 Gy (RBE) for microscopic residual disease and 70 Gy (RBE) for gross residual disease. Concurrent chemotherapy was used in a minority of patients (29.5 %). With a median follow-up time of 15.2 months (28.7 months in those alive), the 2-year estimate of overall survival was 32.7 % and median survival 16.8 months. In a competing risk analysis with death as a competing risk, the

2-year cumulative incidence estimate for local failure was 19.7 % and distant metastasis 38.3 %. Acute toxicity of maximum grade 2 occurred in 47.5 %, grade 3 in 13.1 %, and grade 5 in 1.6 %. Late toxicity of maximum grade 2 occurred in 22.6 %, grade 3 in 15.1 %, grade 4 in 5.7 %, and grade 5 in 3.8 %. There were a total of three treatment-related deaths.

Given the heterogeneity and complexity of this patient population, it is difficult to assess the relative merits of proton reirradiation. Outcomes appear comparable to series of patients treated with photon-based reirradiation, despite a patient population with more adverse risk factors and largely felt ineligible for additional photon therapy. For many of these patients, proton therapy was used to extend a reirradiation option to those who would otherwise likely have received supportive care alone or palliative chemotherapy in a minority. Compared to historical expectations of survival outcomes with supportive care and palliative chemotherapy, the patient survival outcomes appear favorable.

Investigators at the Northwestern Medicine Chicago Proton Center and the ProCure Proton Therapy Center in Somerset, New Jersey, reported a pooled analysis of 92 patients who received proton therapy as reirradiation for recurrent or metachronous head and neck cancers (Romesser et al. 2016). The most frequent histologies were squamous cell carcinoma (56.5 %), adenocarcinoma (9.8 %), and sarcomas (5.4 %). The most common tumor site was the oropharynx (85.5 %), followed by the nasal cavity and paranasal sinuses (13 %), with 8.7 % being skull base tumors. Patients were heavily pretreated: 17.4 % had two or more prior course of radiotherapy and 48.9 % had prior chemotherapy.

The median dose of reirradiation was 60.6 Gy (RBE) and 47.8 % of patients received concurrent chemotherapy. With a median follow-up time of 10.4 months (13.3 months in those alive), the 1-year estimate of overall survival was 65.2 %. In a competing risk analysis with death as a competing risk, the 1-year cumulative incidence estimate for local failure was 25.1 %. The Kaplan-Meier estimate of distant metastasis at 1 year was 16 %. There were no reported acute grade 4 or 5 toxicities. Late toxicities of grade 4 occurred in 7.2 % and grade 5 in 2.9 % with two treatment-related deaths.

Figures 4 and 5 illustrate the use of proton therapy in patients with recurrent head and neck cancer.

10 Proton Reirradiation of Lung Cancer

Researchers from MD Anderson Cancer Center (MDACC) reported on 33 patients treated with proton therapy for intrathoracic recurrence of non-small cell lung cancer (McAvoy et al. 2013). After a median prior dose of 63 Gy, patients received a median reirradiation dose of 66 Gy (RBE) at a median time of 36 months from prior radiation. Relative to the initial tumor, the retreatment was infield in 57.5 %, marginal in 6 %, and out of field for 36 %. For the majority (85 %), reirradiation was given for a centrally located tumor. Roughly half had received chemotherapy prior to reirradiation and 24 % received concurrent chemotherapy with reirradiation. After a median follow-up time of 11 months (21 months in those alive), the 1-year Kaplan-Meier estimate of overall survival was 47 %, locoregional control 54 %, and freedom from distant metastases 39 %. Grade ≥3 esophageal toxicity occurred in 9 %, grade ≥3 pulmonary toxicity in 21.2 %, and there was 1 grade 3 cardiac toxicity. Toxicity was similar to other experiences with retreatment of NSCLC. Locoregional control remained problematic and the risk of distant metastasis was high. While these data cannot provide insight into the relative merit of proton therapy compared to other modalities for reirradiation of NSCLC, they do provide clinical experience with the feasibility and tolerance of proton reirradiation.

Subsequently, the MDACC researchers reported their combined experience of reirradiation with proton therapy and IMRT (McAvoy et al. 2014). They found no association between treatment technique and pulmonary or esophageal toxicity but did note a correlation between grade ≥2 pulmonary toxicity and increasing volume of lung receiving 10 Gy (V10) during

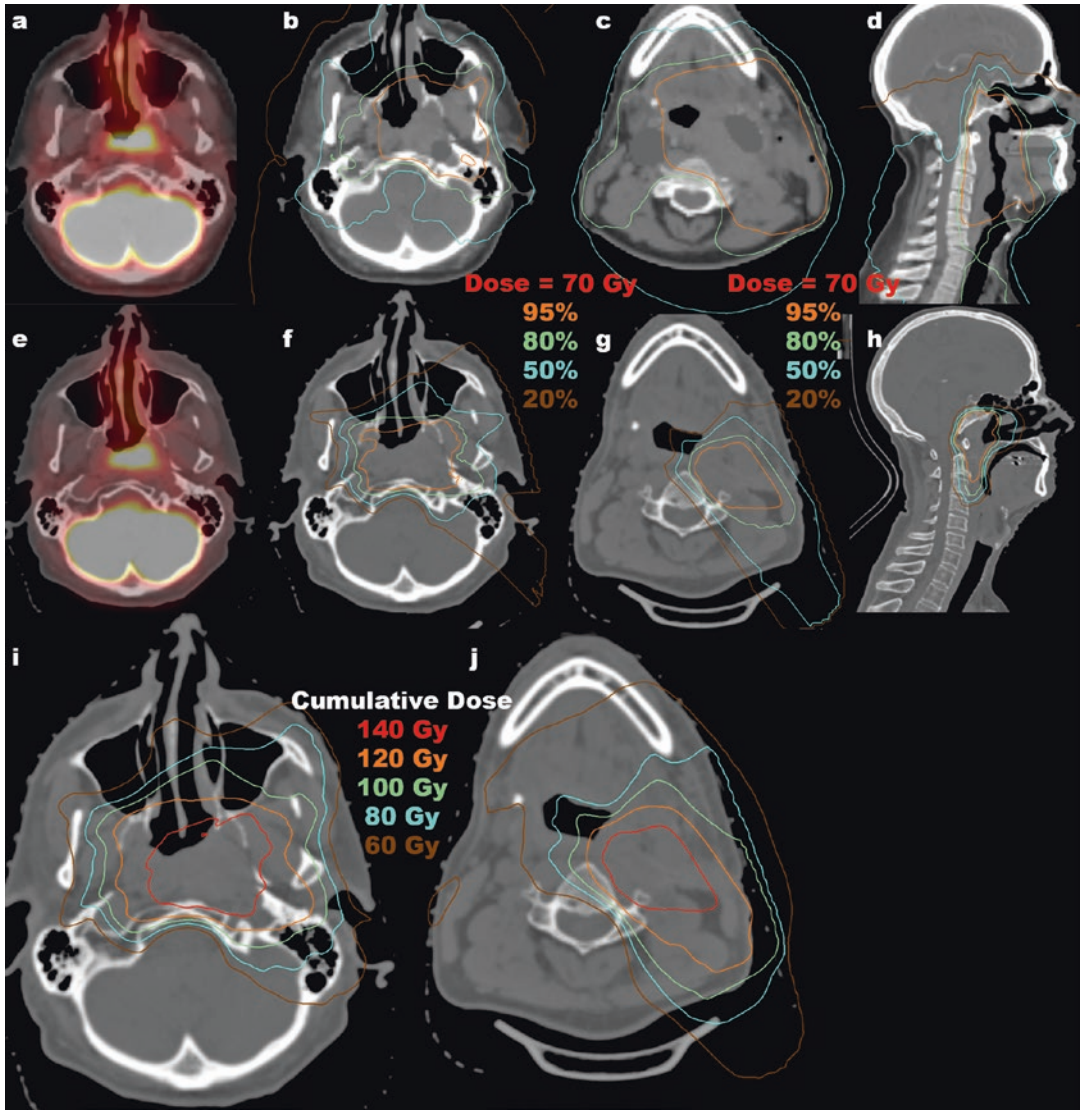


Fig. 4 A 48-year-old man was reirradiated for recurrent nasopharyngeal squamous cell carcinoma. He presented with headaches, left-sided otalgia, and a serous otitis media and was found to have a nasopharyngeal mass (**a**) extending down the oropharyngeal wall to the level of the larynx with associated ipsilateral necrotic neck adenopathy. His pathology was negative for p16. He was treated with tomotherapy to 70 Gy in 35 fractions (**b**–**d**) with three cycles of 100 mg/m^2 cisplatin chemotherapy (third cycle dose reduced). He had profound xerostomia and dysphagia with over 70 lb of weight loss and remained gastrostomy tube dependent 9 months after radiation. Follow-up PET/CT showed resolution of hypermetabolic uptake but with residual centrally necrotic nodal adenopathy. Six months after radiation, an FNA of the nodal mass confirmed residual viable neck disease and a repeat PET/CT 7 months after radiation showed recurrent disease in the nasopharynx (**e**), biopsy proven. Given the short time interval from prior radiation and persistent disease in the neck, further radiation was not offered. Palliative chemotherapy was recommended. After seeking a second opinion, he was referred for an opinion on salvage proton reirradiation. At the time of our evaluation, he has a KPS of 80 %, his weight had been stable over the past 3 months, and a PET/CT scan showed no evidence of distant metastatic disease. He was offered reirradiation to 70 Gy in 35 fractions (**f**–**h**) and received concurrent weekly cetuximab, carboplatin, and paclitaxel. He developed no oral mucositis during treatment and gained 12 lb during the course of reirradiation with improved oral intake. He continued to gain weight after reirradiation although he still required a gastrostomy tube. Cumulative lifetime dose distribution is shown (**i**, **j**). A PET/CT scan 3 months after reirradiation showed a complete response. Unfortunately, he later developed intracranial tumor progression and died at 8 months from reirradiation

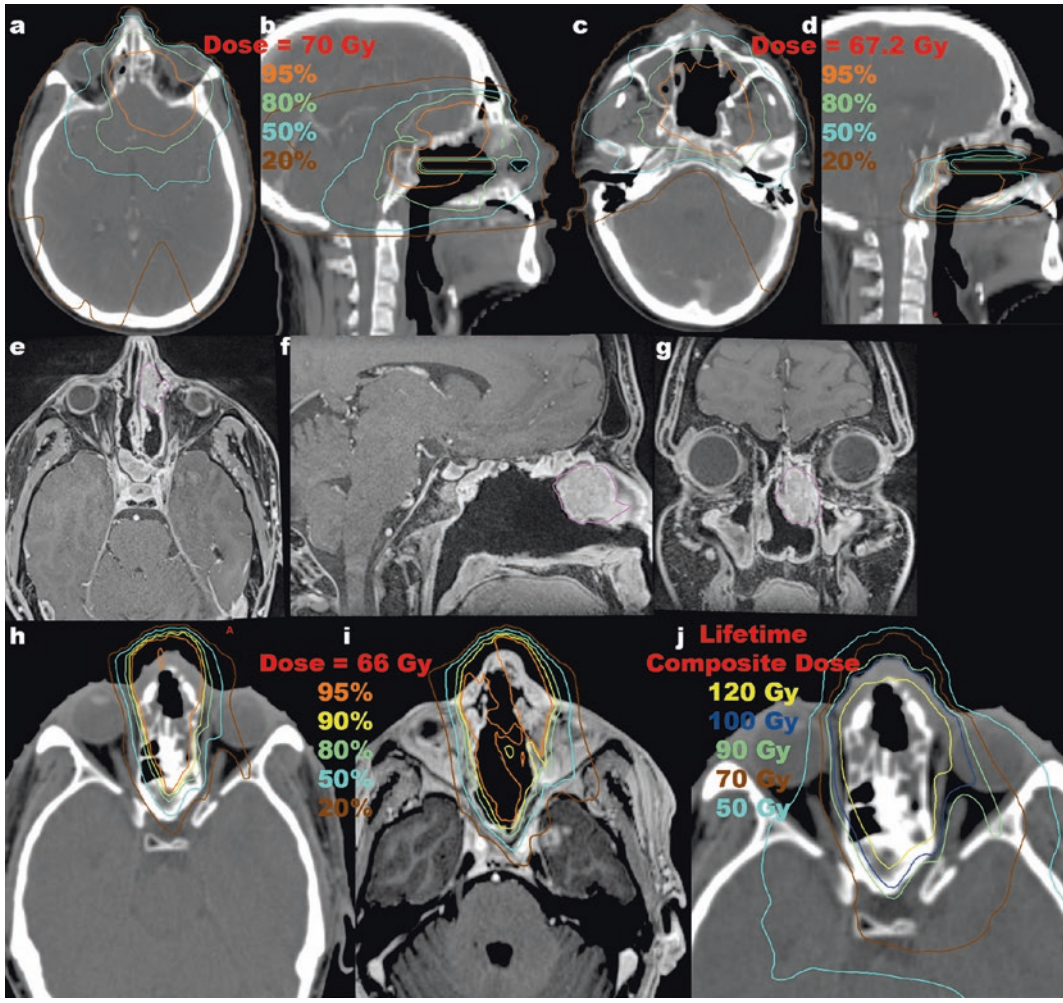


Fig. 5 A 34-year-old man was treated for a recurrent sinonasal poorly differentiated adenocarcinoma. He originally presented with a sphenoid sinus primary with left orbital extension. The pathology was felt consistent with sinonasal undifferentiated carcinoma. He underwent induction chemotherapy followed by concurrent chemoradiation therapy to 70 Gy using IMRT (**a**, **b**). Imaging suggested a complete response and endoscopic exploration and resection identified no residual tumor. He developed radiation retinopathy of the left eye with loss of useful vision. Three years later, he developed recurrent disease versus a second primary in the left nasal cavity (within the prior radiation volume) involving the sphenopalatine foramen and pterygoid canal and abutting the infraorbital nerve. It was biopsied as an intermediate grade adenocarcinoma. He was then reirradiated with concurrent cisplatin, receiving 67.2 Gy in 1.4 Gy fractions given twice daily with IMRT (**c**, **d**). He had another complete response to therapy and went on to develop moderate trismus as well as a focus of grade 1 (asymptomatic) radiation necrosis in the left temporal lobe. Ten months after reirradiation, there was concern for recurrent disease in the anterior nasal cavity on PET/CT scan, and an MRI 14 months after reirradiation showed enhancing tumor in the anterior left nasal cavity (**e**–**g**), biopsy confirmed as a poorly differentiated adenocarcinoma. This was largely outside of his reirradiation volume but within the 80% isodose line of his original radiation volume. He underwent an endoscopic endonasal craniofacial resection with involved surgical margins and both perineural and angiolymphatic space invasion. Tumor involved the crista galli and the lamina papyracea, which was removed, but did not grossly invade the periorbita. He sought evaluation at two major academic centers for further reirradiation, but in light of his two prior courses of treatment, the risk: benefit ratio of further radiation was deemed unfavorable. He was then referred for consideration of reirradiation with proton therapy. A recent postoperative PET/CT scan and a repeat MRI showed no evidence of recurrence or distant metastatic disease, and proton therapy was offered. He declined concurrent chemotherapy with repeat reirradiation. Proton therapy was used to maximize sparing of his right eye (**h**), which had his only useful vision, and to minimize additional dose to the area of his preexisting left temporal lobe radiation necrosis (**i**). The lifetime cumulative dose is shown (**j**). Unfortunately, he developed distant metastatic disease to the liver and lung at 4 months and succumbed to metastatic disease

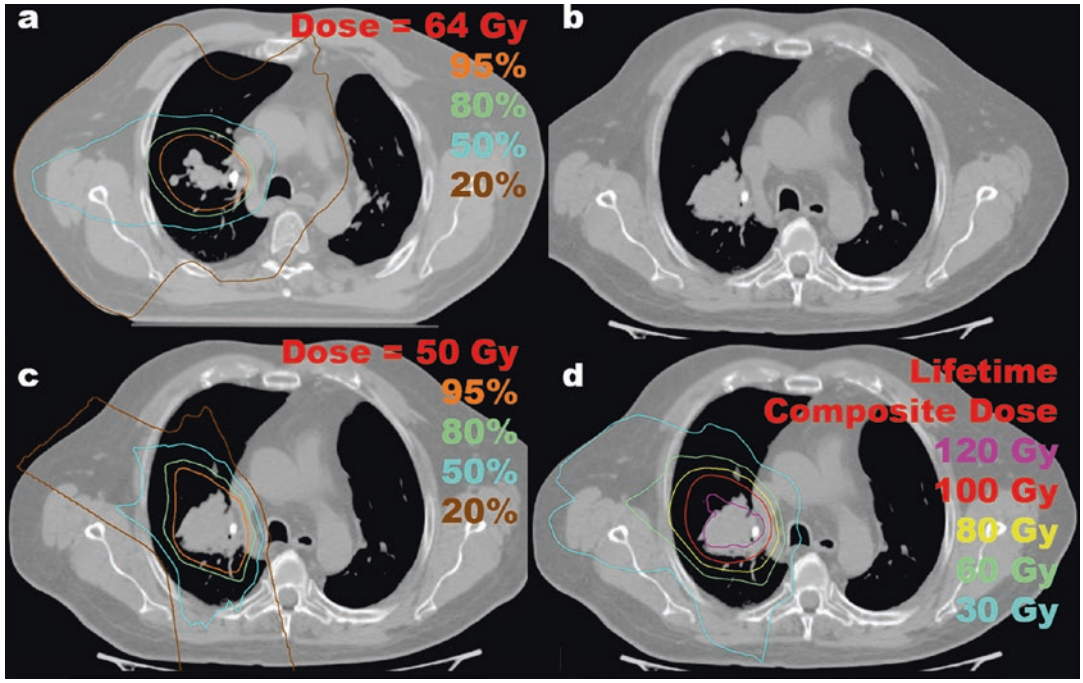


Fig. 6 An 80-year-old man was treated for recurrent solitary lung metastasis from colon adenocarcinoma. Five years after surgery for a pathologic T3 N0 colon adenocarcinoma, he developed hemoptysis and was found to have a solitary right perihilar metastasis, biopsied as adenocarcinoma consistent with his colon primary. Given his advanced age and medical comorbidities including hypertensive cardiomyopathy, and obstructive pulmonary disease from asbestosis with poor pulmonary function tests, he was not a candidate for surgical metastasectomy. He then received thoracic radiotherapy with IMRT to 64 Gy (**a**) with concurrent capecitabine. Eighteen months later he developed recurrent hemoptysis, and a CT (**b**) showed recurrence of the previously treated right perihilar metastasis, now measuring just over 5 cm in size, without evidence of other distant disease on PET/CT. He was not felt to be a candidate for additional external beam radiation or stereotactic body radiotherapy in light of his prior radiation and tumor size. He was then referred for salvage proton therapy. He was treated with a field-in-field technique, delivering 30 Gy (RBE) in 10 fractions to a larger volume and 50 Gy (RBE) in 10 fractions at the 80% isodose line to the gross tumor volume with more limited margin (**c**). In the absence of 4D CT capability and gated delivery, a respiratory compression belt was used to minimize respiratory excursion, and a slow CT was acquired to create an average image over several respiratory cycles. Beam angles were selected to treat through lung which had previously been irradiated to significant dose and avoid increasing the lifetime lung V20. Three beam angles were used: a right anterior oblique, left posterior oblique, and a PA. His lifetime dose distribution is shown (**d**). His hemoptysis resolved with reirradiation and he had no acute toxicities of treatment. In follow-up imaging, he had a persistent right hilar mass that could represent fibrosis or residual tumor but without clear progression. He did later develop intrabronchial progressive disease outside of the reirradiation field. At 45 months after reirradiation, he was alive off therapy

reirradiation, as well as V20, mean lung dose, and composite (lifetime) mean lung dose. These findings support a planning objective of minimizing nontarget lung exposure to additional radiation using the most conformal modality available.

Figure 6 shows an example of a patient treated with proton therapy for reirradiation of a solitary lung metastasis.

11 Proton Reirradiation of Esophageal Cancer

Putative advantages of proton therapy in reirradiation of esophageal cancer include reduced cardiac and lung dose, potentially reducing the risk of cardiopulmonary complications. Esophageal mucosal toxicity would not be anticipated to be different from other external beam modalities but likely

lower than with brachytherapy, which has been associated with a fairly high risk of stricture, ulceration, and perforation (Sharma et al. 2002).

Researchers at the University of Pennsylvania reported on 14 patients receiving proton reirradiation for esophageal cancer who had been treated on a prospective study of proton reirradiation (Fernandes et al. 2015). Patients were retreated to a median dose of 54 Gy at a median interval of 32 months from their initial radiation treatment course, which had delivered a median prior dose of 54 Gy. One patient was deemed infeasible due to development of a pleural effusion which necessitated that 30 % of the reirradiation dose be delivered with IMRT due to the increased proton range uncertainties in the setting of the pleural effusion. One grade 5 and one grade 3 esophageal ulceration occurred, both thought to be related to persistent tumor rather than radiation. Of the ten patients presenting with dysphagia, 70 % had partial or complete improvement. The median survival after reirradiation was 14 months. Nine patients developed further infield tumor progression and six developed distant metastatic disease.

12 Proton Reirradiation of Rectal Cancer

Prior to total mesorectal excision (TME), locally recurrent rectal cancer was estimated to occur in up to one-third of patients, and approximately one-half of these recurrences arose without evidence of distant metastatic disease (Moriya 2006). Following preoperative short-course radiotherapy and TME, long-term data from a randomized controlled trial reported a 10-year local recurrence risk of 5 % (van Gijn et al. 2011), which still yields a large number of cases given the high incidence of colorectal cancer.

A common approach in previously irradiated patients selected for curative intent salvage therapy is preoperative reduced dose reirradiation with concurrent chemotherapy followed by reassessment for radical resection and IORT (Konski et al. 2012). Compared to more favorable locations such as anastomotic recurrences, presacral and posterolateral recurrences are associated with a low likelihood of radical surgical resectability, significant rates of morbidity and mortality, and poorer outcomes (Kusters et al. 2009). The dose of reirradiation has typically been limited, with 30 Gy in conventional fractionation being a common prescription, because of the risk of toxicity to previously irradiated bowel and neurovascular tissues. Because these low doses are extremely unlikely to eradicate gross disease, reirradiation is generally a palliative treatment when surgery is not a component of treatment.

Proton therapy may be considered for preoperative reirradiation in an effort to reduce the dose to previously irradiated bowel and bladder. Through improved avoidance of pelvic viscera, proton therapy may be hypothesized to reduce the risk of urinary toxicity, small bowel obstruction, or fistula compared to less conformal treatments. Improved target conformality and normal tissue avoidance may allow for dose-escalated preoperative proton reirradiation, which may be hypothesized to improve the likelihood of tumor response and subsequent R0 resection.

For patients managed without surgery, proton therapy also offers the possibility of dose escalation and treatment with radical intent. Other modalities which may be considered for radical reirradiation include SBRT (Defoe et al. 2011) and interstitial brachytherapy (Bishop et al. 2015). Potential advantages of proton therapy in radical reirradiation include the ability to target recurrences that are not anatomically accessible or otherwise unsuitable for interstitial therapy (e.g., encasement of neurovascular structures) or are too large or poorly defined to be suitable targets for SBRT. Clinical outcomes data of proton reirradiation are too sparse to judge the merits of any of these hypotheses.

Figures 7 and 8 are examples of the application of radical proton therapy with concurrent chemotherapy in patients with recurrent rectal cancer.

Researchers from the University of Pennsylvania reported outcomes for seven patients with locally recurrent rectal cancer treated on a prospective study of proton reirradiation (Berman et al. 2014). At a median of 39 months after a median prior dose of 50.4 Gy, patients received an additional 45–64.8 Gy

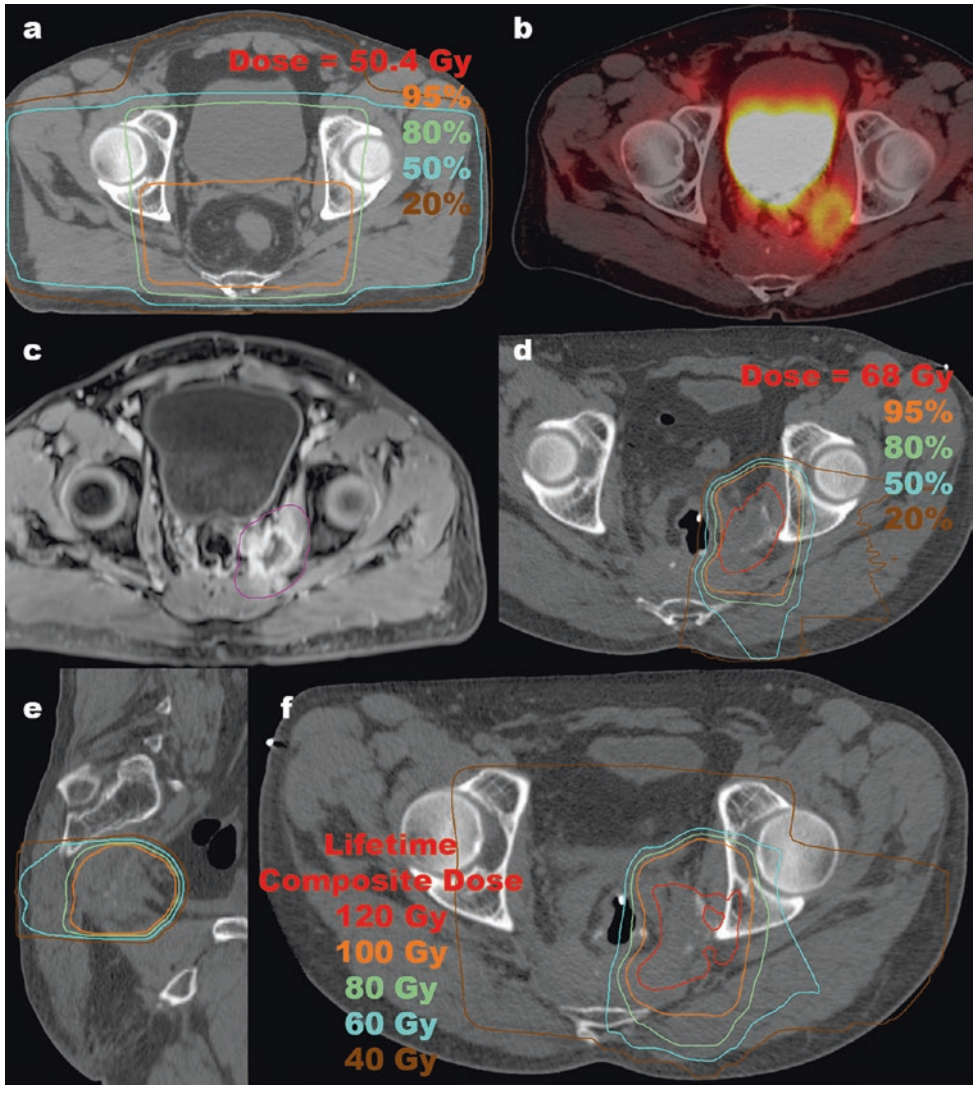


Fig. 7 A 63-year-old man was reirradiated for a posterolateral pelvic side wall recurrence of rectal adenocarcinoma. He originally presented with a T2 N2 rectal adenocarcinoma, KRAS wild type, and was treated with preoperative radiation therapy to 50.4 Gy with continuous infusion 5-fluorouracil (**a**). He then underwent a low anterior resection with a pathologic complete response, with 0/3 lymph nodes being involved. He had poor tolerance of planned adjuvant capecitabine and so received no adjuvant therapy. Four and a half years after surgery, he developed a rising CEA with a PET/CT showing a hypermetabolic (SUV 4.2) mass at the left pelvic sidewall (**b**), with a CT-guided FNA showing recurrent adenocarcinoma consistent with his rectal primary. He was not felt to be a candidate for radical surgical resection due to tumor location. He was referred for salvage proton therapy, which was initially denied by insurance. He received FOLFOX4 plus bevacizumab for 4 months while awaiting insurance approval, with stabilization of disease. Oxaliplatin was stopped early due to acute reaction. Pelvic MRI was obtained to assess the extent of disease (**c**). He was then treated with salvage proton therapy, planned to 70 Gy (RBE) in 38 fractions (he elected to stop at 68 Gy (RBE) due to travel arrangements) with continuous infusion fluorouracil (**d**, **e**). It was decided to allow the lateral rectal wall to receive an additional 50 Gy (RBE), assuming some interval normal tissue recovery in the intervening years since prior radiotherapy. The lifetime cumulative dose distribution is also shown (**f**). A PET/CT scan at 3 months after reirradiation showed a complete response and his CEA had normalized. Three years after reirradiation, he had a rising CEA again, and a PET/CT scan showed a solitary focus of osseous metastatic disease in the left ischium, biopsy proven, at which point he elected observation. He remains alive 4 and a half years after reirradiation without rectal bleeding, ulceration, or colostomy

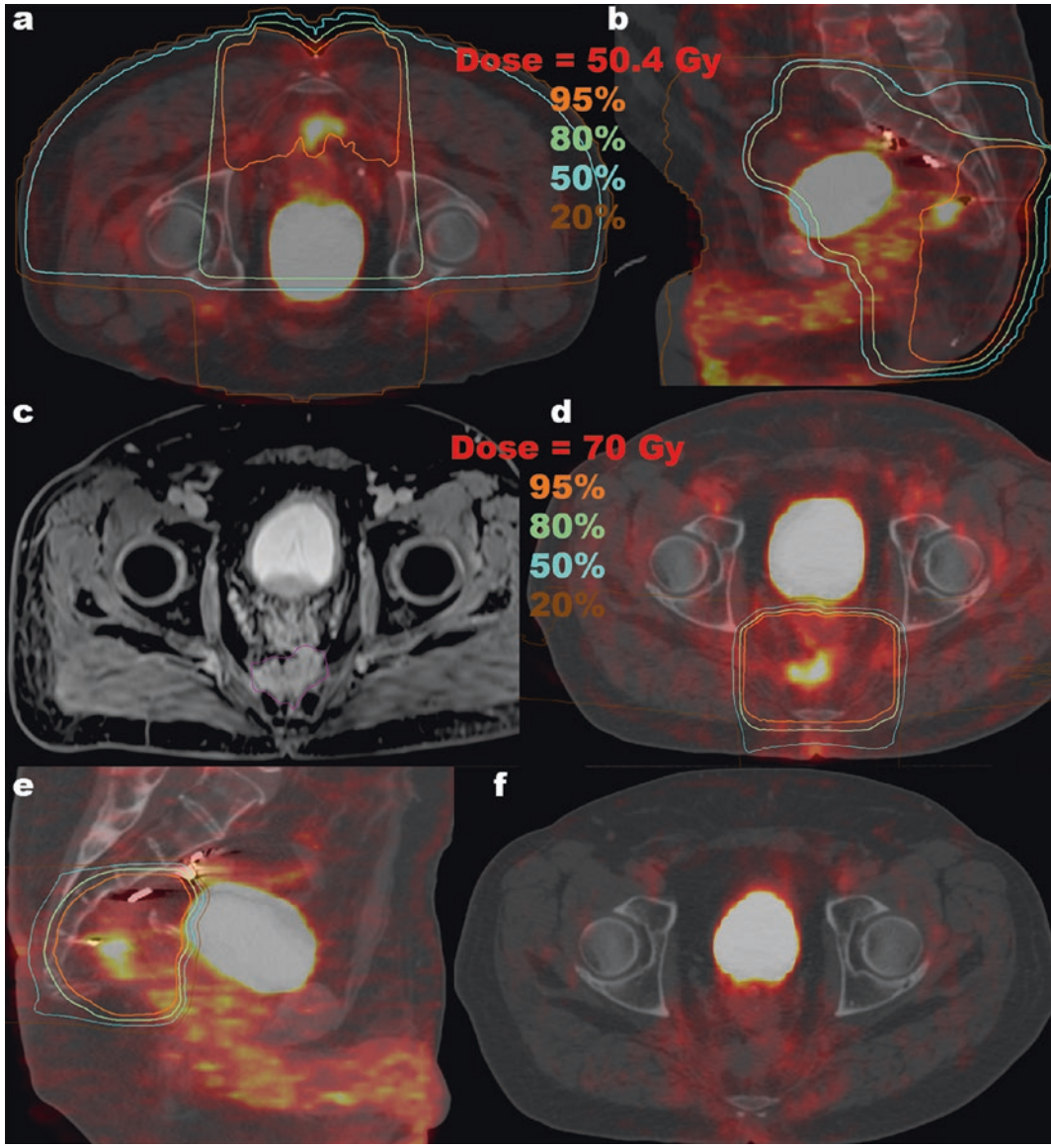


Fig. 8 A 63-year-old man was treated for a presacral recurrence of rectal adenocarcinoma. His original treatment was an abdominal perineal resection (APR) for a pathologic T2 N0 rectal adenocarcinoma with uninvolved surgical margins and no lymphovascular space invasion. No adjuvant therapy was indicated. Two years later, a rising CEA prompted a PET/CT scan which showed a hypermetabolic focus in the presacral space, biopsied by fine needle aspiration which confirmed locally recurrent adenocarcinoma, without evidence of regional or distant metastatic disease. It was not felt to be surgically resectable without significant morbidity. He was treated with 3DCRT to 50.4 Gy (**a**, **b**: dose shown on PET/CT scan) with concurrent capecitabine with a complete response on subsequent PET/CT scan. One year later, his CEA was rising again and PET/CT and MRI (**c**) showed recurrence of the previously treated lesion without evidence of regional or distant metastatic disease. He was then referred for salvage therapy with protons and again received concurrent capecitabine. On exam he had fairly pronounced radiation fibrosis of the sacral skin (bolus had been applied over the buttocks during prior radiation). He was reirradiated with proton therapy to 70 Gy (RBE) with three fields: a PA and steeply angled left and right oblique fields to improve skin sparing during reirradiation (**d**, **e**). Proton therapy was readily able to avoid the bladder and a small amount of bowel in the cranial portion of the field which was not in close proximity to the target. At 3 months postradiation, his CEA had normalized and a CT scan showed stability of the presacral thickening. At 5 months postradiation, a repeat PET/CT scan showed a complete response (**f**). At 32 months from completion of reirradiation, he remains without evidence of recurrent disease

(mean 61.2 Gy) with proton therapy. Most (6/7) received concurrent 5-FU-based chemotherapy and two patients had R2 (macroscopically incomplete) surgical resections as part of management. At a median follow-up of 14 months, there had been one complete response, one patient with progressive disease, and five partial responses, two of whom later developed another local recurrence. In dosimetric comparison to alternate prospectively developed treatment plans using IMRT, proton therapy was associated with reduced dose to bowel. There were three acute (and transient) grade 3 toxicities and three late grade 4 toxicities (two bowel obstructions and one enterovaginal fistula thought due to progressive tumor).

Researchers from the Hyogo Ion Beam Medical Center have also reported on three cases of particle reirradiation of recurrent rectal cancer (two proton, one carbon ion) (Mokutani et al. 2015). Treatment was given with radical intent (proton dose 74 Gy in 34 fractions) without concurrent chemotherapy and achieved durable control of the treated tumor in two of the cases with the third developing another local re-recurrence approximately 30 months after reirradiation.

Conclusions

Clinical experience with reirradiation using proton beam therapy is increasing. The rationale for proton reirradiation is often to avoid or reduce toxicities of reirradiation by limiting the volume of nontarget tissues receiving additional radiation dose. In some diseases, proton reirradiation may improve outcomes by facilitating safe dose escalation or providing better target coverage while respecting constraints to critical normal structures. In uncommon cases, proton therapy may permit reirradiation when the dosimetry achieved with other modalities is felt to preclude safe reirradiation. The existing data on proton reirradiation is limited to small series and is highly heterogeneous. To better understand the value of proton therapy in reirradiation relative to other radiation modalities, prospective evaluation with more homogenous patient populations is needed to evaluate predefined end points based on rational clinical hypotheses.

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