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Proton therapy in the palliative setting※

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Abstract: Given its sharp dose fall off and ability to spare healthy surrounding tissue, proton beam therapy (PBT) has traditionally been used to treat various types of malignancies in the definitive setting, with strong, empirical data supporting its utility and safety. In the palliative setting, however, photon therapy has generally remained the standard of care in radiation treatment delivery due to lower cost, and greater availability. However, recent data suggest that the use of PBT may provide benefit in terms of symptom management and disease control in patients with locally advanced or recurrent disease who do not qualify for definitive therapy or with metastatic disease. Additionally, due to its unique dosimetric properties, PBT may confer less overall toxicity, thus helping preserve or improve the quality of life in this patient population, especially for those who are nearing end of life. While there is a need for further study, initial data analyzed from both retrospective and prospective single-institution and multi-institution trials are promising. This review aims to explore the efficacy and safety of PBT in the palliative setting among adults and to summarize pertinent studies that support its usage. To the authors' knowledge, this is the first review of the literature pertaining to PBT used in the palliative setting across multiple disease sites.

Keywords: End-of-life care; palliative care; palliative radiation therapy; proton therapy; advanced modalities

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Introduction

Proton beam therapy (PBT) is a unique form of external beam radiotherapy (EBRT) that offers several key physical advantages relative to conventional electron or photon-based techniques. First, protons have significantly more mass than electrons or photons, which can result in less scatter and a sharper lateral beam distribution. Second, PBT allows for energy to be deposited at a specific depth within tissues, with considerable energy fall-off beyond this point—exploiting a phenomenon known as the Bragg Peak (1). As such, with its superior lateral and distal dose conformality, in well-selected patient populations, PBT can offer: (I) safer delivery of therapeutic dose radiation to tumors in challenging anatomic locations that can reduce acute toxicities and/or better optimize tumor control; and (II) decreased integral dose (or exposure to low dose radiation) to adjacent normal tissues, potentially reducing the risks of subacute and late toxicities (1). Additionally, recent improvements in the delivery of PBT, such as pencil beam scanning, allow for an even higher degree of conformality, further amplifying its potential clinical benefit in reducing toxicities and improving clinical outcomes (2-4).

While the dosimetric advantages of PBT are clear,

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important considerations including high capital costs and limited randomized clinical data have historically limited widespread use and distribution of proton centers (5). However, the recent emergence of single-room proton units has made this technology more logistically and economically viable, thereby improving access and utilization rates across the United States (6,7). Additionally, the indications for PBT have only continued to grow in the past decade: 2022 National Comprehensive Cancer Network guidelines support PBT use across 43 different cancer types, and numerous ongoing phase III randomized trials are directly comparing proton versus photon therapy for the treatment of breast, lung, esophageal, head and neck, liver, brain, and prostate cancers in the upfront or definitive setting (8). While the true clinical benefit of PBT remains an active area of investigation, ongoing studies measuring potential reductions in treatment-related adverse effects will help to elucidate these controversies.

Importantly, rising use of PBT nationally has coincided with the rapid development of novel targeted agents and immunotherapies for a variety of cancer diagnoses. Consequently, patients with locally advanced, recurrent, and metastatic disease are living longer, deriving benefit from advances in systemic therapy. As such, radiation oncologists have also begun to explore the use of PBT in the palliative setting. By definition, palliative radiation therapy is any course of radiation in which a disease is treated with non-curative intent. This includes management of diffusely metastatic, oligometastatic, or even locally advanced disease (9). There have been several studies demonstrating a benefit to PBT for the palliation of tumor-related symptoms, particularly in cases where low dose radiation from photon-based radiation to surrounding normal tissues could cause considerable toxicity, particularly mucosal structures and bone marrow, thereby posing a significant threat to quality-of-life, even if expected prognosis is 6 months to a year. As such, proton therapy can be particularly beneficial in preserving quality of life in patients with advanced malignancies (10). However, it is important to evaluate the appropriateness of PBT on a case-by-case basis, as PBT may not always offer distinct advantages over photon-based approaches. Moreover, as with any decision to deliver treatment in the palliative setting, the decision to deliver PBT must always carefully balance risk with benefit, ensuring that the use of PBT is in alignment with the patient's goals of care.

Herein, we discuss the use of PBT in the palliative setting across an array of disease sites. We review available data on its overall safety and efficacy, and we explore potential applications for its use, highlighting important limitations as well as considerations for appropriate patient selection when treating with palliative intent.

Lung cancer

Lung cancer is the leading cause of cancer-related mortality, with a 5-year survival rate of only approximately 7% for patients diagnosed with metastatic non-small cell lung cancer (NSCLC). Despite considerable advances in the definitive treatment of localized disease, lung cancer patients have a high recurrence rate of approximately 30–55% (11). Therefore, given that radiation therapy is a primary modality used in the definitive treatment of both early-stage and locally advanced disease, patients with recurrent lung cancer can often benefit from reirradiation (12). Due to its proximity to critical structures such as the heart and spinal cord, reirradiation of the lung can result in significant cardiotoxicity, as well as bone marrow suppression (13). Additionally, the risks of acute and late pulmonary and esophageal toxicities are higher in the reirradiation setting, as the lungs and esophagus have often received high irradiation doses during the initial radiotherapy course. In this setting, the ability of PBT to deliver a conformal reirradiation dose that limits overall radiation to surrounding tissue, may help significantly mitigate these risks (14,15).

In 2017, Chao *et al.* published the current largest multi-center prospective study to date focusing reirradiation for locally recurrent NSCLC cases treated at the University of Pennsylvania, Procure Oklahoma City, and the Northwestern Medicine Chicago Proton Center. Of the 52 patients who completed their full course of PBT reirradiation, locoregional control was 75% and median overall survival (OS) was 14.9 months. One-year OS and progression free survival (PFS) were 59% and 58%, respectively. This intervention, however, resulted in 6 grade 5 toxicities and 24 total grade 3 or greater acute or late toxicities. Grade 5 toxicities were noted to be bronchopulmonary fistula, severe sepsis secondary to neutropenia and radiation-induced bone marrow suppression, as well as hypoxic respiratory failure secondary to pulmonary effusion (*Table 1*). Centrally located tumors that abutted critical structures, such as the mainstem bronchus, were noted at higher risk for developing more significant toxicity (16).

Other studies have reported lower toxicity rates in the thoracic reirradiation setting. In a retrospective

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Table 1 Potential toxicities of thoracic reirradiation and prospective reported (16) grade 5 events

Toxicity	Cause of death	Attribution to proton reirradiation
Bronchopulmonary hemorrhage	Fatal hemoptysis	Possibly
Neutropenic sepsis	Hypoxic respiratory failure, neutropenic sepsis	Possibly
Anorexia	Failure to thrive and inability to maintain adequate nutrition	Probably
Pneumonitis	Acute respiratory failure	Probably
Hypoxic respiratory failure/pleural effusion	Hypoxic respiratory failure	Possibly
Tracheoesophageal fistula	Hypoxic respiratory failure from recurrent aspiration events	Probably

study from investigators from MD Anderson Cancer Center, 102 patients with locally recurrent NSCLC were treated with reirradiation using either proton or photon therapy. Despite high reirradiation doses [median dose of 60.5 EQD2 (equivalent total dose in 2-Gy fractions) Gy], grade ≥3 toxicities were limited primarily to esophageal (7%) and pulmonary (10%), and higher reirradiation doses were associated on multivariate analysis with improved survival (17). This is notable given that PBT can often allow for safer escalation of radiation dose in the reirradiation setting (18,19). In a prospective registry Proton Collaborative Group multi-center report, proton reirradiation among a cohort of 79 lung cancer patients was generally well tolerated, with only 6% acute grade 3 toxicities and 1% late grade 3 toxicities, although three deaths were determined to be possible related to reirradiation toxicity (20).

Discrepancies in toxicities noted between these studies may be due to a variety of factors. For instance, in one multi-institutional prospective study, participants were stratified into two groups: high-volume [clinical target volume (CTV) ≥250 cm^3] and low-volume (CTV <250 cm^3). Two of the six patients who developed grade 5 toxicities had high-volume disease, with all but one high-volume patients experiencing a grade ≥3 toxicity as a result of their treatment (21). Additionally, more participants in the multi-institutional prospective study received concurrent chemotherapy which may have augmented treatment toxicity, which was associated with higher toxicities rates in both that trial and the MD Anderson report (16,20). Notably, the incidence of grade 5 toxicities waned over time, thus suggesting that refining delivery of radiation can reduce risks of adverse events. To that end, an intensity-modulated approach to proton reirradiation may help prevent high grade toxicities, while still providing a durable response to treatment as was recently demonstrated in an esophageal cancer proton reirradiation report (22).

Head and neck cancers

Head and neck cancer is the sixth most common cancer worldwide, resulting in more than 350,000 deaths every year (23). Most head and neck cancers are squamous cell carcinomas (HNSCC) arising from the mucosal surfaces of the oral cavity. Patients diagnosed with recurrent or secondary head and neck cancers often have poor prognoses, usually surviving less than a year (24). Unfortunately, up to half of patients with locally advanced head and neck cancers develop locoregional recurrences (24), and for most patients, recurrence is associated with significant morbidity, including pain, bleeding, respiratory distress, dysphagia, speech impairment, and negative self-image (25). While salvage reirradiation has the potential to slow further disease progression, in many cases, retreatment may further diminish a patient's quality-of-life, especially among those who already received significant treatment in areas of recurrence.

While there is no consensus regarding the optimal management of patients with recurrent or secondary HNSCC, a Quad Shot (QS) regimen has used to palliate patients who have failed or are unable to tolerate standard-of-care therapies. This treatment paradigm, which requires that radiation be delivered twice daily and at least 6 h apart for 2 consecutive days (for a total of 4 fractions), can be repeated with multiple cycles depending on treatment response (26) As with SRS, QS can be delivered with either photon or proton beams, with emerging data supporting the use of proton QS (pQS) in the palliative setting.

A 2020 study assessed palliative responses of recurrent head and neck cancer patients who received photon QS versus proton QS reirradiation between 2011–2018. Out of 166 patients, 68% achieved palliative benefit, with the most common response being relief from tumor-related pain. On multivariate analysis, patients who had a documented palliative response to pQS therapy had improved OS and

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PFS (27).

Similarly, a 2018 article analyzed 26 patients with recurrent or metastatic HNSCC who received palliative pQS to 3.7 Gy [radiobiological effectiveness (RBE)] twice daily across 2 days. Of note, 88% of patients in this study had prior head and neck radiation. Overall, 73% of patients reported relief from pain interfering with overall quality of life. Pain relief was measured subjectively using a 1 to 10 severity scale and reported at various follow-up intervals after completion of radiation treatment. While 58% of participants experienced a grade 1 toxicity from pQS, none of the participants experienced grade 3 or 4 Common Terminology Criteria for Adverse Events (CTCAE)-designated adverse events or grade 5 toxicity (28).

Collectively, these data support the use of pQS as effective palliative radiation for HNSCC, even among those who received prior photon radiation. Furthermore, the subjective benefit of the proton therapy in this population and the relief from symptoms that these patients achieve generally outweighs the risks of undesired toxicity (27,28).

Proton craniospinal irradiation for leptomeningeal disease (LMD)

LMD is a late-stage sequela of various solid and hematologic malignancies that involves development of multifocal metastases to the leptomeninges. LMD is most common in breast cancer, lung cancer, and malignant melanoma, and it also develops in patients with multiple myeloma, leukemia (most commonly acute lymphoblastic leukemia), lymphoma (most commonly non-Hodgkin's lymphoma), and primary central nervous system (CNS) malignancies. Estimates suggest that between 1–8% of cancer patients develop LMD. Unfortunately, the prognosis for these patients is grim, with an average median OS of 3–6 months with standard treatments and only 4–6 weeks without intervention (29). In this setting, EBRT can be an effective form of palliation, slowing inevitable disease progression and ultimate neurologic demise (30). However, the use of palliative radiotherapy has historically been avoided in patients, as it can cause significant marrow toxicity, thereby precluding patients from receiving further systemic therapies for treatment of their disease (31). As such, there has been growing interest in using proton craniospinal irradiation (pCSI) to deliver biologically effective radiation dose to diseased tissues, while minimizing potential marrow-related toxicity.

In a 2021 systematic review of 13 retrospective studies investigating the use of CSI for LMD in adult patients greater than 18 years of age, 18% of the total aggregate study cohort (N=275) received pCSI. Notably, while the median OS for the entire cohort was 5.3 months, patients treated with proton pCSI had a slightly higher median OS of 8 months. Additionally, the incidence of bone marrow suppression resulting in leukopenia and neutropenia was significantly reduced among patients who received pCSI relative to photon-based techniques/bone marrow suppression can lead to increased risk of bleeding and life-threatening infections, thus deleteriously impacting patient quality of life (32). In addition to minimizing the incidence of dose-limiting cytopenias, studies suggest that pCSI may also reduce the risk of cardiotoxicity, a documented late effect of photon CSI. Owing to its exit dose through anterior structures, photon-based CSI delivers a small, yet often significant, amount of radiation to the heart. In contrast, pCSI offers virtually zero exit dose, and thus normal cardiac tissue is spared (33). This may provide benefit to younger patients with limited sites of intracranial disease and more favorable performance statuses and prognoses.

A 2021 prospective phase I study by Yang *et al.* examined the role of hypofractionated pCSI in the management of patients with solid tumors who developed LMD. The study's primary endpoint was to characterize treatment-related toxicity, while secondary endpoints included CNS PFS and OS. Of the 24 patients enrolled, only 2 patients experienced dose-limiting toxicities (DLTs), notably grade 4 lymphopenia, grade 4 thrombocytopenia, and/or grade 3 fatigue; all DLTs were self-limiting, resolving without further medical intervention. While the median CNS PFS was 7 months, 4 patients had extended periods of freedom from CNS progression for 12 months or longer. The study concluded that hypofractionated pCSI is a safe option for patients with LMD, with some patients experiencing durable disease control (34).

In a recently published subsequent Phase II trial by investigators at Memorial Sloan Kettering Cancer Center exploring pCSI versus photon involved-field radiotherapy (IFRT) for patients with solid tumor LMD, 63 patients were randomized to either IFRT or pCSI. The study's primary endpoint was CNS PFS, and secondary endpoints included OS and treatment-related adverse events. The study found a significant improvement in PFS in patient's receiving pCSI *vs.* IFRT (7.5 *vs.* 2.3 months). Interestingly, the study also concluded that there was a significant OS benefit to pCSI (9.9 *vs.* 6.6 months) with no significant increased toxicity (35).

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While further investigation with phase III trials are warranted, collectively, these data suggest that pCSI may not only be safe and effective but may also confer a potential survival benefit to patients with this difficult to manage condition. Thus, pCSI should be considered in patients with LMD who have good performance statuses and thus stand to gain a reasonable benefit from this technology.

Brain metastasis and primary CNS malignancies

It is estimated that 10–20% of patients with cancer will develop brain metastasis over the course of their disease (36). Similar to LMD, cancers of the lung, breast, colon, kidney and skin (melanoma) generally tend to have the greatest propensity to metastasize to the brain (37). The treatment intent for patients with brain metastases is largely palliative. In the last decade, there have been a number of immunotherapy options and targeted therapies approved by the FDA that have significant blood-brain barrier activity and. As such, these drugs have been incorporated into the treatment paradigm for brain metastases. Additionally, rising use of highly focused forms of radiation, namely, stereotactic radiosurgery (SRS), have proven effective in the management of brain metastases, improving intracranial disease control and, in many instances, survival (38). In contrast to whole brain radiotherapy (WBRT), which indiscriminately delivers conventional doses of radiation to all brain tissue, SRS is a newer and more advanced modality that allows for the delivery of highly conformal, high-dose radiation to much smaller targets at discrete points throughout the brain (39). Technologic advances in its delivery (e.g., improved image guidance and immobilization), increasing familiarity and comfort among U.S. practitioners, as well as purported neurocognitive advantages over WBRT have led to its widespread use in the treatment of multiple brain metastases, with some centers having the capacity to treat far more than the standard 1–5 lesions (40). In the setting of reirradiation, SRS is particularly useful, even in patients who have previously received WBRT (41). However, as the brain is an inherently radiosensitive organ (42), reirradiation with SRS is associated with the potential risk of radionecrosis (43). Historically, the risk of symptomatic radionecrosis is approximately 20% in patients who have already received radiation to the brain, especially in patients with high-risk features such as large gross tumor burden (44). Although the vast majority of SRS is performed using photon beams, it has been postulated that proton SRS could reduce the risk of radionecrosis in patients with brain metastases or primary CNS malignancies requiring reirradiation (45). Radionecrosis can significantly impact a patient's overall quality of life and can often be difficult to manage. Treatment of radionecrosis may involve initiation of long-term steroids, bevacizumab, surgery, or a combination of these therapies (46). However, steroids have unfavorable side effects when used long-term, including weight gain, hyperglycemia, mood issues, adrenal insufficiency and increased risk of bone fracture, and bevacizumab has a myriad of contraindications including anticoagulant use or recent bleed (47,48). Additionally, surgery for radiation necrosis has potential morbidity, with some patient developing new or worsening neurologic deficits following surgery (49).

Studies have been conducted comparing overall the quality of plans between proton and photon therapy using the conformity index (CI), the ratio between a fraction of the tumor volume and the volume covered within a certain isodose line. A lower CI generally means that there is less dose administered to normal tissue. In a study published in 2018 evaluated the CI of proton based and photon-based plans across multiple disease sites in both adult and pediatric malignancies, PBT displayed better conformity with a reduction in the integral non-target dose (50).

In a large retrospective 2018 study, Atkins and colleagues from Massachusetts General Hospital reviewed a large single-institution cohort of 370 patients treated with proton SRS between April 1991 and November 2016 for recurrent brain metastasis or primary gliomas or glioblastomas (N=815 brain lesions) who were previously treated with WBRT or photon-based SRS. Median OS was 12.4 months, and estimates of 6-month and 12-month local failure, distant brain failure, and OS were 4.3% and 8.5%, 39.1% and 48.2%, and 76.0% and 51.5%, respectively. Approximately 40.5% of patients experienced treatment-related toxicities, most of which were grade 1 (N=109, 72.7%), and none of which were grade 4 or 5. The common mild to moderate adverse events included fatigue, weakness, and dizziness. Significant symptomatic radionecrosis, confirmed through neuroimaging, was only reported in 3.6% of patients at one year following their initial surgery. The 3.6% rate of radionecrosis reported in this study is notably lower than the historical average of approximately 20%. Overall, this study demonstrates that proton SRS is well-tolerated and provides similar local control when compared to traditional photon SRS. Moreover, proton SRS may prolong OS in patients with aggressive, advanced tumors of the brain not

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amenable to curative surgery (51).

Similarly, a 2015 study examined the role of proton reirradiation in patients diagnosed with recurrent gliomas or glioblastomas. Between 2005–2012, 20 patients with recurrent gliomas were irradiated with PBT at the Indiana University Health Proton Therapy Center. Median survival from completion of reirradiation was 24.9 months for grade 3 gliomas and 7.8 months for glioblastomas. While most patients tolerated treatment well, 2 patients experienced radiation necrosis following radiation requiring further treatment with hyperbaric oxygen and steroids. Given the high doses of radiation received by these patients previously, the 10% rate of radiation necrosis was deemed modest by the study authors and, once again, was noted to be half that of the reported historic average of approximately 20%. Thus, it was concluded that proton reirradiation for primary CNS tumors is relatively safe and associated with favorable long-term survival outcomes (52).

Informed by positive findings from earlier studies, there are ongoing trials to further evaluate the safety of efficacy of PBT in patients with high grade gliomas or brain metastases, as compared to standard photon-based approaches. An ongoing phase III randomized study conducted by the University Hospital Heidelberg in Germany (NCT04752280) is seeking to evaluate the safety of PBT versus photon beam therapy as standard of care palliative therapy. The primary endpoint of the study is to evaluate overall toxicity, defined as CTCAE grade 2 or higher, within 4 months of treatment. Secondary endpoints include overall and PFS, as well overall quality of life (QoL) scores and neurocognitive ability following treatment (53).

As in LMD, proton therapy for brain metastases and primary high-grade gliomas could prove to minimize toxicity, better preserve quality of life, and potentially even confer an overall PFS benefit (51,52). Additional studies are necessary, however, to better support this postulation (54).

Liver cancer

Primary liver cancers are notoriously difficult to manage. As many patients with liver cancer also have some degree of liver damage or cirrhosis, curative options are often limited. Liver transplantation remains the gold standard in the treatment of localized, unresectable disease (55). However, there are finite livers available for transplantation, and many patients may be on transplant lists for extended periods of time oftentimes exceeding 1 year (56). Additionally, a patient's Model for End-Stage Liver Disease (MELD) score, which is reflective of underlying liver dysfunction, may preclude them from liver transplantation candidacy (57). Given these treatment challenges, there is a clear need for palliative approaches that could both help prolong a patient's life expectancy while preserving overall quality-of-life. For patients with unresectable, locally advanced, or metastatic disease, chemotherapy has been a mainstay in the palliative management of liver cancer (58). In contrast, in decades prior, radiation therapy historically was not used in overall management of this disease due to concern for unacceptable toxicities (59).

Like the brain, the liver is considered a highly radiosensitive organ (60). As such, patients who receive radiation to the liver are at risk for developing radiation-induced liver disease (RILD)—a clinically diagnosed radiation-induced hepatitis associated with right upper quadrant pain, ascites and significant transaminitis (61). Researchers have postulated that using protons as opposed to photons can help mitigate the risk of developing RILD, while offering a safe and effective modality with which to palliate symptoms and prevent further disease progression.

In a 2020 prospective study of 63 patients with unresectable primary liver cancers diagnosed with either intrahepatic cholangiocarcinoma (ICC) or hepatocellular carcinoma (HCC), participants received a median prescribed PBT dose of 58.05 Gy (RBE) in a median of 15 fractions. Overall, treatment was well-tolerated, with 17 patients (39.5%) experiencing grade 2 toxicities, most commonly fatigue, anorexia, nausea, or vomiting. No patients experienced a grade ≥3 toxicity. Additionally, none of the patients who received proton therapy developed RILD. This approach offered excellent local control at 1 year, with rates of 91.2% and 90.9% for HCC and ICC, respectively. OS estimates at 1-year were 65.6% for HCC and 81.8% for ICC. Although further assessment of late toxicities is pending longer follow-up, study authors concluded that hypofractionated PBT offers excellent local control, with significant organ sparing and a favorable acute toxicity profile relative to what can be achieved with photon therapy (62).

Similarly, a 2016 phase II, multi-institutional study by Hong *et al.* evaluated 92 patients with biopsy-confirmed HCC or ICC determined to be unresectable by multidisciplinary review with a Child-Turcotte-Pugh score (CTP) of A or B, ECOG performance status of 0 to 2, no extrahepatic disease, and no prior radiation. These patients received 15 fractions of PBT to a maximum total dose of 67.5 Gy (RBE). The study determined that the LC rate was

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94.8% for HCC and 94.1% for ICC. In terms of OS, 63.2% of HCC patients were alive at 2 years, as were 45% of ICC patients (63).

A 2014 study published by Makita and his colleagues examined 28 patients with various forms of cholangiocarcinoma treated with PBT. Six patients had ICC or peripheral cholangiocarcinoma (CC), 6 had hilar cholangiocarcinoma, 3 had distal extrahepatic CC, 3 had gallbladder carcinoma, and 10 patients had local or lymph node recurrent tumors. Eight patients had a palliative stent placed prior to PBT initiation, while 3 patients received concurrent platinum-based therapy (either cisplatin or carboplatin). The study found that OS at 1 year was 50%, while LC and PFS rates were 68% and 30%, respectively. In regards to toxicity, gastrointestinal toxicities of grade 2 or higher were observed in 7 patients within 12 months after PBT; these toxicities included development of a duodenal or gastric ulcer and duodenal stenosis. Additionally, 11 patients enrolled in this study developed cholangitis, treated with intravenous antibiotics, and three developed biliary stent strictures. No patient, however, experienced Grade 3 or higher toxicities, thus suggesting this regimen to be relatively safe (64).

Comparative data between proton and photon therapy have emerged for advanced hepatocellular carcinoma. In a single institution retrospective study from Massachusetts General Hospital, 133 patients with unresectable HCC were treated with ablative protons (n=49) or photons (n=84). Proton therapy was associated with an improved OS (HR =0.47, P=0.008) and more than doubling of median OS (31 *vs.* 14 months), driven by a reduction in risk of radiation-induced liver disease (OR =0.26, P=0.03) (65). Similarly, among inoperable HCC cases in the National Cancer Database, PBT was an independent predictor for longer survival (HR =0.48) despite being delivered to HCC patients with multiple poor prognostic factors relative to photon stereotactic body radiation therapy (SBRT) (66).

Overall, these studies suggest that PBT is safe and provides durable local control for patients with liver cancer who are not candidates for resection or liver transplantation. Additionally, PBT has a reduced overall incidence of RILD, allowing providers the ability to palliate symptoms and prevent further tumor proliferation while minimizing overall toxicity. Although these results are promising, further additional prospective studies are needed to further explore the safety and efficacy of PBT, especially in larger cohorts, with studies ongoing in the management of both primary liver cancer and metastatic disease to the liver. An enrolling NRG Oncology phase III trial (NCT03186898) for patients with unresectable or locally recurrent HCC seeks to directly compare OS of patients with HCC treated with protons versus those treated with traditional photon therapy (67).

Sarcoma

Sarcomas are an uncommon, heterogeneous group of cancers that develop in the bones, cartilage and soft tissues, accounting for only approximately 1% of cancer diagnosed annually (68). While localized sarcoma is often treatable with surgery and adjuvant radiation, the 1-year survival rate for patients diagnosed with metastatic sarcoma is only 15% (69). Common sites of metastatic disease include the thorax and abdomen, often with direct abutment of critical structures. Moreover, most sarcomas are high-grade and highly radioresistant, often resulting in a poor clinical response to traditional photon-based cEBRT (70). To that end, PBT not only offers many potential physical and anatomic advantages, but also potential radiobiological advantages as well owing to the energy and charge properties of protons, with an estimated RBE of at least 1.1 (71). Although this remains an active area of research, available data suggest that PBT is at least as biologically effective as photon therapy, if not greater, thus adding to its appeal in the treatment of metastatic sarcoma.

In the first study of its kind, Lee *et al.* examined the use of proton QS in the palliative management of 28 patients with 40 sites of metastatic or recurrent sarcoma. The most common histologies were gastrointestinal stromal tumor and leiomyosarcoma, and 67.5% of disease sites were in the abdomen or pelvis. Seventeen (42.5%) treatments involved concurrent systemic therapy and 13 (32.5%) patients received further systemic therapy following proton therapy. Overall, 70% of patients reported a subjective palliative response to treatment. The most common distressing symptom was pain at the tumor site for patients in this cohort, which significantly improved in 67.7% of patients following PBT. While seven grade 3 toxicities were observed, notably intraabdominal infection and colonic obstruction, there were no grade 4 or grade 5 toxicities noted. Also, as this regimen proved effective in palliating symptoms and thus improving overall performance status, 33% of patients were subsequently able to pursue additional systemic therapy for disease management, which was associated with improved OS (72).

A prospective study assessed proton reirradiation as an

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alternative to systemic therapy or amputation in 23 patients with soft tissue sarcoma who had recurred following prior surgical resection and radiation therapy. Only one grade 3 toxicity (acute dysphagia) was seen, and no grade 4–5 acute or late toxicities were reported. The 3-year cumulative incidence of local failure was 41%, median OS was 44 months, and median PFS was 29 months. Quality of life was also well preserved, with 7/10 (70%) extremity patients being spared an amputation (73).

Limitations to PBT in the palliative setting

Overall, PBT can be a safe and effective palliative treatment modality for advanced solid tumors of varied histologies. However, there are certain limitations to PBT in the palliative setting that must also be considered, along with potential scenarios in which the ultimate risk of PBT outweighs its benefits.

It is important to be cognizant of a patient's performance status as well as their medical comorbidities prior to initiating palliative PBT. While protons may confer more favorable dosimetric properties compared to photons, these advantages cannot completely mitigate all treatment toxicity, as evidenced by the studies above. Therefore, providers considering PBT for patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater should exhibit caution. In patients who are chronically deconditioned, any palliative radiotherapy—including PBT—may confer greater harm than benefit. For instance, patients with recurrent lung cancer who have significant chronic obstructive pulmonary disease may benefit more from medical analgesic therapy and bronchodilators than they would radiation therapy, as PBT can result in radiation pneumonitis (RP) rates approaching or comparable to rates seen with photon therapy (74,75).

It is also imperative to note that most clinical trials evaluating the safety and efficacy of PBT have stringent inclusion and exclusion criteria, with most excluding patients with poor performance status (i.e., ECOG ≥2). This proves to be a limitation of many oncologic trials (76). Pragmatic studies are still needed to assess the safety of PBT in a frail, older adult population. Additionally, while many patients with advanced cancer are able to tolerate PBT, for some, the process of planning for and undergoing additional therapy may be daunting. Like photon-based radiation, initiating PBT involves a consultation with a radiation oncologist and treatment consent, along with a simulation CT scan to plan treatment, followed by the treatment itself. While each treatment is only a few minutes in length, patients are expected to present to their radiation oncology facility on a daily basis for the duration of their treatment. Treatment length may be a few days to a few weeks depending on tumor type and extent of disease, as well as the radiation technique employed (77). Patients who are deconditioned, have highly symptomatic disease burden, and/or have high pain levels may have difficulty tolerating lying flat on a hard surface while radiation is administered. This is also true for patients with serious comorbidities, including severe congestive heart failure or degenerative joint disease. Intrafractional patient motion in such cases may be more challenging to mitigate with proton therapy than photon therapy. Similarly, many patients such as those with significant ambulatory dysfunction or those with extreme fatigue as a result of either their disease or prior cancer-directed treatments may be less able to come to a radiation oncology facility on a daily basis for treatment. For these patients, either single-fraction photon-based treatment (78) or hospice services, either in-home or facility-based, may be the best option. Additionally, it is important to note that although not widely employed, patients under hospice care may still elect to pursue palliative radiation therapy, whether proton or photon based, to help alleviate their symptoms (79).

Ultimately, these decisions are personal and multifactorial, and they are unique to each patient. Therefore, it is important for providers to appropriately assess their patient's performance status, and tailor their treatment recommendations accordingly. Additionally, and perhaps most importantly, prior to the initiation of any palliative treatment, it is of the utmost importance to fully understand a patient's expectations and directives regarding their cancer treatment. Fully understanding and respecting a patient's desires regarding end-of-life care can help practitioners make informed, shared decisions with their patients in order to implement the most appropriate treatment course (80).

Future directions

Although patients with locally advanced and metastatic cancer historically had limited treatment options and relatively short life expectancies, the advent and continued development of targeted therapies allow patients to live longer with their disease (81). Therefore, new and advanced treatment modalities are needed to help preserve overall quality of life in these patients and better manage symptoms

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Table 2 Summary of benefits of PBT in the reirradiation setting across disease sites

Malignancy type	Study	Benefit of PBT
CNS	Atkins *et al.* Proton Stereotactic Radiosurgery for Brain Metastases: A Single-Institution Analysis (32)	• Reduced incidence of symptomatic radionecrosis
Soft tissue sarcoma	Guttmann *et al.* A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma (62)	• Low incidence of Grade 3 toxicities • No reported Grade 4–5 toxicities
Lung	Badiyan *et al.* Clinical Outcomes of Patients With Recurrent Lung Cancer Reirradiated With Proton Therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies (72)	• Decreased dose to heart and spinal cord • Low incidence of grade 3 toxicities • No definitive Grade 4–5 toxicities
Lung	Chao *et al.* Multi-Institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer (68)	• Durable local control • Prolonged overall survival
Head & neck	Ma *et al.* Proton Radiotherapy for Recurrent or Metastatic Head and Neck Cancers with Palliative Quad Shot (43)	• No reported Grade 3–5 toxicities • Improved symptom management and decreased pain

PBT, proton beam therapy; CNS, central nervous system.

that may arise due to progression of their disease.

While PBT typically has been thought to be more expensive than traditional photon-based plans, new solutions are helping make PBT more affordable for patients. First, since its nascence in the 1990s, the infrastructure required to administer PBT has drastically shrunk. The weight of proton linear accelerators has been effectively reduced from hundreds of tons to less than twenty tons. Furthermore, superconducting magnets have the ability to confine protons to a smaller space. This has led to the advent of single-room proton centers which have significantly fewer overhead costs when compared to large proton centers, thus reducing the overall cost of care for the patient (5,6).

Similarly, in the past, PBT has been denied by insurers given its greater costs when compared to photon-based therapy. However, as health policy continues to evolve and governing bodies continue to affirm the utility and benefit of PBT, insurance coverage for PBT will likely continue to improve. In 2014, the American Society for Radiation Oncology (ASTRO) composed a list of diagnoses that its leaders recommended insurers should cover. Based on the interval data reported supporting this modality, the 2023 update to the ASTRO Model Policy on Proton Beam Therapy has significantly expanded the recommended indications for proton therapy, including for many of the advanced, incurable, and recurrent tumors discussed above. Additionally, for patients on Medicare, PBT is already considered medically appropriate and necessary for a number of cases, including unresectable malignant CNS tumors, advanced stage and unresectable malignant lesions of the head and neck and unresectable peritoneal sarcomas (82).

As demonstrated by the results of the studies outlined above, PBT has been demonstrated to have a favorable toxicity profile in the palliative management across a wide variety of tumor types. Owing to its various physical and biologic advantages, PBT allows radiation oncologists the ability to deliver radiation safely and effectively to tumors in the palliative setting. In the setting of reirradiation, PBT is particularly beneficial in reducing toxicities, providing durable tumor control, and palliating tumor-related symptoms (83), with generally more favorable outcomes and toxicities relative to photon reirradiation (84) (*Table 2*). Ultimately, the decision to treat with PBT proves dependent on appropriate patient selection and stratification. Capital costs should ultimately not hinder providers from offering less toxic therapies, such as PBT, that can help preserve patients' overall quality of life while adequately managing their cancer.

Lastly, proton therapy has recently had a prominent role in the experimental palliative treatment of patients with metastatic disease when delivered as ultra-high-dose-rate FLASH therapy. Increasing preclinical data over the past few years (85) has demonstrated that radiation therapy, when delivered at an ultra-high dose rate, better spares normal tissues without impairing anti-tumor activity (86).

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The first in human clinical trial of ultra-high-dose-rate FLASH was delivered with proton therapy in patients with symptomatic bone metastases (87). That recently published trial demonstrated that proton FLASH was clinically feasible with high levels of treatment efficacy and few adverse events (88). Currently, proton therapy is the optimal radiotherapy modality for delivering FLASH (89), as existing proton accelerators can more readily deliver ultra-high-dose-rate deliveries and as proton FLASH can allow for the treatment of deeper and larger tumors than FLASH delivered with other modalities (90). Should such ultra-high-dose-rate radiotherapy delivered with protons prove to reduce toxicities in future clinical trials, this would allow for the safer delivery of radiotherapy in patients with advanced and metastatic disease, and thus would result in an event larger role for proton therapy in the palliative setting.

Conclusions

Despite these encouraging results, more research on PBT in the palliative setting is needed. Most available studies are limited by their retrospective study design and small sample size. This may be due, in part, to limitations in access to PBT: currently, there are only 41 proton centers operational in the United States, and most are located in large metropolitan cities (91). Additionally, PBT is generally more expensive, with photon therapy generally considered to be the more economical option (92). However, as more proton centers (and especially single-room proton therapy centers) open, and as the cost of PBT continues to decline, prospective studies will prove more logistically feasible and thus, will help generate further robust data on PBT for patients who have exhausted all other treatment options. In the interim, the studies that have been conducted to date demonstrate that proton therapy may be a safe, well-tolerated option for patients with unresectable or metastatic cancer across various disease sites and histologies.

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References

1. Simone CB 2nd, Rengan R. The use of proton therapy in the treatment of lung cancers. Cancer J 2014;20:427-32.
2. Kaiser A, Eley JG, Onyeuku NE, et al. Proton Therapy Delivery and Its Clinical Application in Select Solid Tumor Malignancies. J Vis Exp 2019;(144):e58372.
3. Gjyshi O, Xu T, Elhammali A, et al. Toxicity and Survival After Intensity-Modulated Proton Therapy Versus Passive Scattering Proton Therapy for NSCLC. J Thorac Oncol 2021;16:269-77.
4. Tian X, Liu K, Hou Y, et al. The evolution of proton beam therapy: Current and future status. Mol Clin Oncol 2018;8:15-21.
5. Maillie L, Lazarev S, Simone CB 2nd, et al. Geospatial Disparities in Access to Proton Therapy in the Continental United States. Cancer Invest 2021;39:582-8.
6. Contreras J, Zhao T, Perkins S, et al. The world's first

© Annals of Palliative Medicine. All rights reserved.

single-room proton therapy facility: Two-year experience. Pract Radiat Oncol 2017;7:e71-6.
7. Forsthoefel MK, Ballew E, Unger KR, et al. Early Experience of the First Single-Room Gantry Mounted Active Scanning Proton Therapy System at an Integrated Cancer Center. Front Oncol 2020;10:861.
8. Butala A, Williams G, Doucette A, et al. Developing an Algorithm to Identify Palliative Radiation Treatments: A Single-Institution 10-year Experience. Int J Radiat Oncol Biol Phys 2020;108:E54-5.
9. Ganz PA, Greendale GA, Petersen L, et al. Breast cancer in younger women: reproductive and late health effects of treatment. J Clin Oncol 2003;21:4184-93.
10. Verma V, Simone CB 2nd, Mishra MV. Quality of Life and Patient-Reported Outcomes Following Proton Radiation Therapy: A Systematic Review. J Natl Cancer Inst 2018;110:341-5.
11. Nguyen QN, Ly NB, Komaki R, et al. Long-term outcomes after proton therapy, with concurrent chemotherapy, for stage II-III inoperable non-small cell lung cancer. Radiother Oncol 2015;115:367-72.
12. Cancer of the lung and bronchus - cancer stat facts. SEER. n.d. [cited 2023 Feb 7] Available online: https://seer.cancer.gov/statfacts/html/lungb.html
13. Uramoto H, Tanaka F. Recurrence after surgery in patients with NSCLC. Transl Lung Cancer Res 2014;3:242-9.
14. Troost EGC, Wink KCJ, Roelofs E, et al. Photons or protons for reirradiation in (non-)small cell lung cancer: Results of the multicentric ROCOCO in silico study. Br J Radiol 2020;93:20190879.
15. Vyfhuis MAL, Rice S, Remick J, et al. Reirradiation for locoregionally recurrent non-small cell lung cancer. J Thorac Dis 2018;10:S2522-36.
16. Chao HH, Berman AT, Simone CB 2nd, et al. Multi-Institutional Prospective Study of Reirradiation with Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer. J Thorac Oncol 2017;12:281-92.
17. McAvoy S, Ciura K, Wei C, et al. Definitive reirradiation for locoregionally recurrent non-small cell lung cancer with proton beam therapy or intensity modulated radiation therapy: predictors of high-grade toxicity and survival outcomes. Int J Radiat Oncol Biol Phys 2014;90:819-27.
18. Lazarev S, Rosenzweig K, Samstein R, et al. Where are we with proton beam therapy for thoracic malignancies? Current status and future perspectives. Lung Cancer 2021;152:157-64.
19. Fischer-Valuck BW, Robinson CG, Simone CB 2nd, et al. Challenges in Re-Irradiation in the Thorax: Managing Patients with Locally Recurrent Non-Small Cell Lung Cancer. Semin Radiat Oncol 2020;30:223-31.
20. Badiyan SN, Rutenberg MS, Hoppe BS, et al. Clinical Outcomes of Patients With Recurrent Lung Cancer Reirradiated With Proton Therapy on the Proton Collaborative Group and University of Florida Proton Therapy Institute Prospective Registry Studies. Pract Radiat Oncol 2019;9:280-8.
21. Ohnishi K, Nakamura N, Harada H, et al. Proton Beam Therapy for Histologically or Clinically Diagnosed Stage I Non-Small Cell Lung Cancer (NSCLC): The First Nationwide Retrospective Study in Japan. Int J Radiat Oncol Biol Phys 2020;106:82-9.
22. DeCesaris CM, McCarroll R, Mishra MV, et al. Assessing Outcomes of Patients Treated With Re-Irradiation Utilizing Proton Pencil-Beam Scanning for Primary or Recurrent Malignancies of the Esophagus and Gastroesophageal Junction. J Thorac Oncol 2020;15:1054-64.
23. Duvvuri U, Myers JN. Cancer of the head and neck is the sixth most common cancer worldwide. Curr Probl Surg 2009;46:114-7.
24. Mehanna H, Kong A, Ahmed SK. Recurrent head and neck cancer: United Kingdom National Multidisciplinary Guidelines. J Laryngol Otol 2016;130:S181-90.
25. Nayak SG, Pai MS, George LS. Self-image of the Patients with Head and Neck Cancer: A Mixed Method Research. Indian J Palliat Care 2016;22:331-4.
26. Corry J, Peters LJ, Costa ID, et al. The 'QUAD SHOT'--a phase II study of palliative radiotherapy for incurable head and neck cancer. Radiother Oncol 2005;77:137-42.
27. Fan D, Kang JJ, Fan M, et al. Last-line local treatment with the Quad Shot regimen for previously irradiated head and neck cancers. Oral Oncol 2020;104:104641.
28. Ma J, Lok BH, Zong J, et al. Proton Radiotherapy for Recurrent or Metastatic Head and Neck Cancers with Palliative Quad Shot. Int J Part Ther 2018;4:10-9.
29. Nayar G, Ejikeme T, Chongsathidkiet P, et al. Leptomeningeal disease: current diagnostic and therapeutic strategies. Oncotarget 2017;8:73312-28.
30. El Shafie RA, Böhm K, Weber D, et al. Palliative Radiotherapy for Leptomeningeal Carcinomatosis-Analysis of Outcome, Prognostic Factors, and Symptom Response. Front Oncol 2019;8:641.
31. Green DE, Rubin CT. Consequences of irradiation on bone and marrow phenotypes, and its relation to disruption of hematopoietic precursors. Bone 2014;63:87-94.

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32. Maillie L, Salgado LR, Lazarev S. A systematic review of craniospinal irradiation for leptomeningeal disease: past, present, and future. Clin Transl Oncol 2021;23:2109-19.
33. Welch GD, Lin KY, Fisher MJ, et al. Cardiac Toxicity After Craniospinal Irradiation: A Late Effect That May be Eliminated With Proton Therapy. J Pediatr Hematol Oncol 2018;40:e330-3.
34. Yang TJ, Wijetunga NA, Yamada J, et al. Clinical trial of proton craniospinal irradiation for leptomeningeal metastases. Neuro Oncol 2021;23:134-43.
35. Yang JT, Wijetunga NA, Pentsova E, et al. Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis. J Clin Oncol 2022;40:3858-67.
36. Lauko A, Rauf Y, Ahluwalia MS. Medical management of brain metastases. Neurooncol Adv 2020;2:vdaa015.
37. Amsbaugh MJ, Kim CS. Brain Metastasis. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Feb 7].
38. Ma L, Wang L, Tseng CL, et al. Emerging technologies in stereotactic body radiotherapy. Chin Clin Oncol 2017;6:S12.
39. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol 2017;18:1049-60.
40. Hughes RT, Masters AH, McTyre ER, et al. Initial SRS for Patients With 5 to 15 Brain Metastases: Results of a Multi-Institutional Experience. Int J Radiat Oncol Biol Phys 2019;104:1091-8.
41. Yomo S, Hayashi M. The efficacy and limitations of stereotactic radiosurgery as a salvage treatment after failed whole brain radiotherapy for brain metastases. J Neurooncol 2013;113:459-65.
42. Wong CS, Van der Kogel AJ. Mechanisms of radiation injury to the central nervous system: implications for neuroprotection. Mol Interv 2004;4:273-84.
43. Pan M. Radionecrosis and Complete Response After Multiple Reirradiations to Recurrent Brain Metastases From Lung Cancer Over 10 Years: Is There a Limit? Adv Radiat Oncol 2021;6:100733.
44. Donovan EK, Parpia S, Greenspoon JN. Incidence of radionecrosis in single-fraction radiosurgery compared with fractionated radiotherapy in the treatment of brain metastasis. Curr Oncol 2019;26:e328-33.
45. Foote RL, Stafford SL, Petersen IA, et al. The clinical case for proton beam therapy. Radiat Oncol 2012;7:174.
46. Patel U, Patel A, Cobb C, et al. The management of brain necrosis as a result of SRS treatment for intra-cranial tumors. Transl Cancer Res 2014;3:373-82.
47. Buchman AL. Side effects of corticosteroid therapy. J Clin Gastroenterol 2001;33:289-94.
48. Hershman DL, Wright JD, Lim E, et al. Contraindicated use of bevacizumab and toxicity in elderly patients with cancer. J Clin Oncol 2013;31:3592-9.
49. Loganadane G, Dhermain F, Louvel G, et al. Brain Radiation Necrosis: Current Management With a Focus on Non-small Cell Lung Cancer Patients. Front Oncol 2018;8:336.
50. Feuvret L, Noël G, Mazeron JJ, et al. Conformity index: a review. Int J Radiat Oncol Biol Phys 2006;64:333-42.
51. Atkins KM, Pashtan IM, Bussière MR, et al. Proton Stereotactic Radiosurgery for Brain Metastases: A Single-Institution Analysis of 370 Patients. Int J Radiat Oncol Biol Phys 2018;101:820-9.
52. Galle JO, McDonald MW, Simoneaux V, et al. Reirradiation with Proton Therapy for Recurrent Gliomas. Int J Part Ther 2015;2:11-8.
53. Glioblastoma Radiotherapy Using IMRT or Proton Beams (GRIPS). NCT04752280. Updated April 20, 2021.
54. Press RH, Chhabra AM, Choi JI, et al. Proton therapy for newly diagnosed glioblastoma: more room for investigation. Neuro Oncol 2021;23:1980-1.
55. Liu CY, Chen KF, Chen PJ. Treatment of Liver Cancer. Cold Spring Harb Perspect Med 2015;5:a021535.
56. Samuel D, Coilly A. Management of patients with liver diseases on the waiting list for transplantation: a major impact to the success of liver transplantation. BMC Med 2018;16:113.
57. Wedd JP, Harper AM, Biggins SW. MELD score, allocation, and distribution in the United States. Clin Liver Dis (Hoboken) 2013;2:148-51.
58. Kane RC, Farrell AT, Madabushi R, et al. Sorafenib for the treatment of unresectable hepatocellular carcinoma. Oncologist 2009;14:95-100.
59. Munoz-Schuffenegger P, Ng S, Dawson LA. Radiation-Induced Liver Toxicity. Semin Radiat Oncol 2017;27:350-7.
60. Stryker JA. Science to practice: why is the liver a radiosensitive organ? Radiology 2007;242:1-2.
61. Kim J, Jung Y. Radiation-induced liver disease: current understanding and future perspectives. Exp Mol Med 2017;49:e359.
62. Parzen JS, Hartsell W, Chang J, et al. Hypofractionated proton beam radiotherapy in patients with unresectable

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liver tumors: multi-institutional prospective results from the Proton Collaborative Group. Radiat Oncol 2020;15:255.
63. Hong TS, Wo JY, Yeap BY, et al. Multi-Institutional Phase II Study of High-Dose Hypofractionated Proton Beam Therapy in Patients With Localized, Unresectable Hepatocellular Carcinoma and Intrahepatic Cholangiocarcinoma. J Clin Oncol 2016;34:460-8.
64. Makita C, Nakamura T, Takada A, et al. Clinical outcomes and toxicity of proton beam therapy for advanced cholangiocarcinoma. Radiat Oncol 2014;9:26.
65. Sanford NN, Pursley J, Noe B, et al. Protons versus Photons for Unresectable Hepatocellular Carcinoma: Liver Decompensation and Overall Survival. Int J Radiat Oncol Biol Phys 2019;105:64-72.
66. Hasan S, Abel S, Verma V, et al. Proton beam therapy versus stereotactic body radiotherapy for hepatocellular carcinoma: practice patterns, outcomes, and the effect of biologically effective dose escalation. J Gastrointest Oncol 2019;10:999-1009.
67. Radiation Therapy with Photons or Photons in Treating Patients with Liver Cancer. NCT03186898. Last updated August 12, 2022.
68. Choi JH, Ro JY. The 2020 WHO Classification of Tumors of Soft Tissue: Selected Changes and New Entities. Adv Anat Pathol 2021;28:44-58.
69. Sarcomas, Soft Tissues: Statistics. Cancer.Net. 2022 Jun [cited 2023 Feb 7]. Available online: https://www.cancer.net/cancer-types/sarcomas-soft-tissue/statistics
70. Vezeridis MP, Moore R, Karakousis CP. Metastatic patterns in soft-tissue sarcomas. Arch Surg 1983;118:915-8.
71. Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer. Phys Med Biol 2014;59:R419-72.
72. Lee A, Kang JJ, Bernstein H, et al. Proton radiotherapy for recurrent or metastatic sarcoma with palliative quad shot. Cancer Med 2021;10:4221-27.
73. Guttmann DM, Frick MA, Carmona R, et al. A prospective study of proton reirradiation for recurrent and secondary soft tissue sarcoma. Radiother Oncol 2017;124:271-6.
74. Mohan R. A Review of Proton Therapy - Current Status and Future Directions. Precis Radiat Oncol 2022;6:164-76.
75. Liao ZX, Komaki RR, Thames HD Jr, et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2010;76:775-81.
76. Abi Jaoude J, Kouzy R, Mainwaring W, et al. Performance Status Restriction in Phase III Cancer Clinical Trials. J Natl Compr Canc Netw 2020;18:1322-6.
77. Maani EV, Maani CV. Radiation Therapy. Treasure Island (FL): StatPearls Publishing; 2023. Retrieved February 6, 2023.
78. Shuja M, Elghazaly AA, Iqbal A, et al. Efficacy of 8 Gy Single Fraction Palliative Radiation Therapy in Painful Bone Metastases: A Single Institution Experience. Cureus 2018;10:e2036.
79. Lutz S, Spence C, Chow E, Janjan N, Connor S. Survey on use of palliative radiotherapy in hospice care. J Clin Oncol 2004;22:3581-6.
80. Pautex S, Herrmann FR, Zulian GB. Role of advance directives in palliative care units: a prospective study. Palliat Med 2008;22:835-41.
81. Dal Maso L, Panato C, Guzzinati S, et al. Prognosis and cure of long-term cancer survivors: A population-based estimation. Cancer Med 2019;8:4497-507.
82. ASTRO Model Policies 2023 [cited June 29, 2023]. Available online: https://www.astro.org/ASTRO/media/ASTRO/Daily%20Practice/PDFs/ASTROPBTModelPolicy.pdf
83. Simone CB 2nd, Plastaras JP, Jabbour SK, et al. Proton Reirradiation: Expert Recommendations for Reducing Toxicities and Offering New Chances of Cure in Patients With Challenging Recurrence Malignancies. Semin Radiat Oncol 2020;30:253-61.
84. Verma V, Rwigema JM, Malyapa RS, et al. Systematic assessment of clinical outcomes and toxicities of proton radiotherapy for reirradiation. Radiother Oncol 2017;125:21-30.
85. Zhang H, Wu X, Zhang X, et al. Photon GRID Radiation Therapy: A Physics and Dosimetry White Paper from the Radiosurgery Society (RSS) GRID/LATTICE, Microbeam and FLASH Radiotherapy Working Group. Radiat Res 2020;194:665-77.
86. Zou W, Zhang R, Schueler E, et al. Framework for Quality Assurance of Ultra-High Dose Rate Clinical Trials Investigating FLASH Effects and Current Technology Gaps. Int J Radiat Oncol Biol Phys 2023. [Epub ahead of print]. doi: 10.1016/j.ijrobp.2023.04.018.
87. Daugherty EC, Mascia A, Zhang Y, et al. FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01): Protocol for the First Prospective Feasibility Study. JMIR Res Protoc 2023;12:e41812.
88. Mascia AE, Daugherty EC, Zhang Y, et al. Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone

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Metastases: The FAST-01 Nonrandomized Trial. JAMA Oncol 2023;9:62-9. Erratum in: JAMA Oncol 2023;9:728.
89. Kang M, Wei S, Choi JI, et al. A Universal Range Shifter and Range Compensator Can Enable Proton Pencil Beam Scanning Single-Energy Bragg Peak FLASH-RT Treatment Using Current Commercially Available Proton Systems. Int J Radiat Oncol Biol Phys 2022;113:203-13.
90. Wei S, Lin H, Choi JI, et al. A Novel Proton Pencil Beam Scanning FLASH RT Delivery Method Enables Optimal OAR Sparing and Ultra-High Dose Rate Delivery: A Comprehensive Dosimetry Study for Lung Tumors. Cancers (Basel) 2021;13:5790.
91. The National Association for Proton Therapy: Proton Therapy Centers in the U.S. 2023 [cited 2023 Feb 7]. Available online: https://www.proton-therapy.org/map/.
92. Verma V, Shah C, Rwigema JC, et al. Cost-comparativeness of proton versus photon therapy. Chin Clin Oncol 2016;5:56.

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