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Factors Associated With and Characteristics of Patients Receiving Proton Therapy at the End of Life

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A B S T R A C T

Purpose: To identify the characteristics, indications, and toxicities among patients receiving proton beam therapy (PBT) in the final year of life at an academic medical center.

Materials and Methods: A retrospective review of patients who received PBT within the final 12 months of life was performed. Electronic medical records were reviewed for patient and treatment details from 2010 to 2019. Patients were followed from the start of PBT until death or last follow-up. Acute (3 months) toxicities were graded using the Common Terminology Criteria for Adverse Events v5.0. Imaging response was assessed using the Response Evaluation Criteria in Solid Tumors v1.1. The χ^2 test was used to evaluate factors associated with palliative treatment. Simple logistic regression was used to evaluate factors associated with toxicity.

Results: Bet299 patients were treated at the end of life (EOL) out of 5802 total patients treated with PBT (5.2%). Median age was 68 years (19-94 years), 58% male. The most common cancer was nonsmall cell lung cancer (27%). Patients were treated for symptom palliation alone (11%), durable control (57%), curative intent (16%), local recurrence (14%), or oligometastatic disease (2%). Forty-five percent received reirradiation. Median treatment time was 32 days (1-189 days). Acute toxicity was noted in 85% of the patients (31% G1, 53% G2, 15% G3). Thirteen patients (4%) experienced chronic toxicity. Breast and hematologic malignancy were associated with palliative intent χ^2 (1, N = 14) = 17, P = .013; (χ^2 (1, N = 14) = 18, P = .009).

Conclusion: The number of patients treated with PBT at the EOL was low compared to all comers. Many of these patients received treatment with definitive doses and concurrent systemic therapy. Some patients spent a large portion of their remaining days on treatment. A prognostic indicator may better optimize patient selection for PBT at the EOL.

Introduction

Patients with cancer may receive proton beam radiation therapy (PBT) with the aim of reducing acute or long-term toxicities or in the reirradiation setting. PBT deposits little exit dose beyond the intended target, and therefore may offer superior sparing of surrounding tissues. A proportion of patients may receive PBT near the end of life, with either palliative or curative intent. Existing clinical studies have documented the feasibility and efficacy of protons for patients who were reirradiated or treated for symptom palliation in head and neck cancer,[1,2] gastrointestinal (GI) malignancies,[3–5] hepatobiliary and pancreatic cancers,[6,7] sarcoma,[8] nonsmall cell lung cancer,[9,10] and pleural mesothelioma.[11] PBT has also been demonstrated to be effective with acceptable toxicities in palliative regimens such as the QUAD shot[12,13] for head and neck cancer and in craniospinal irradiation.[14,15]

PBT has the potential to reduce toxicities due to its dosimetric advantages, which may be of particular importance when treating patients with incurable diseases and at the end of life to reduce acute toxicity. However, the use of PBT in palliation or near the end of life as a standard remains controversial. First, there is limited randomized data demonstrating clinical benefit to the use of PBT compared to more conventional forms of radiation therapy (RT) in terms of disease control, symptom palliation, or toxicity, and additional randomized data are needed in order to establish PBT as a high-value intervention for patients with cancer in general. PBT remains a higher-cost intervention than traditional photon therapy,[16] and given the equipment and infrastructure required, it is difficult to scale. Finally, planning time required for PBT may lead to delays in treatment, which is of high concern for patients with limited life expectancy. The current coverage guidelines issued by Centers for Medicare & Medicaid Services require the use of protons to be justified by (1) the expectation of a long-term benefit or (2) the expectation of improved safety or duration of control that cannot be achieved with conventional radiation.[17]

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There are no data to describe the factors associated with the use of PBT and the characteristics of patients who receive it near the end of life (EOL). The present study is a retrospective clinical review to identify the characteristics, treatment indications, and toxicities among patients treated with PBT within the final year of life at a tertiary academic medical center between 2010 and 2019. Results from this study will provide a framework for recommendations on the use of PBT in optimal populations near or at the EOL.

Materials and methods

Study population and clinical data

Eligible patients were identified from the review of institutional records in the Department of Radiation Oncology at the authors' institution. Patients were included in the study if they were > 18 years of age and received PBT within the final 12 months of life, measured from delivery of first fraction to death, irrespective of the treatment intent. Patients were followed from initial consultation for PBT until death or last follow-up. Electronic medical records were reviewed for patient and treatment details. Patient characteristics extracted from the medical record included demographic data, performance status, diagnosis, histology, stage at the time of treatment, treatment dates, radiation treatment details including treatment intent, systemic therapy details, anatomic region treated, clinical symptoms, toxicities, and imaging response to treatment. Dates of death were confirmed through a public records search of obituaries. This study was reviewed by the Institutional Review Board and a waiver of informed consent was obtained.

Treatment intent was defined from consultation notes and our prospectively collected peer-reviewed chart rounds database as one of the following: treatment for localized disease, isolated local recurrence, oligometastatic disease, durable local control, or palliation of symptoms. Durable local control was defined as treatment for durable control of otherwise incurable disease, while palliation was defined as treatment for symptom palliation only. Toxicities were recorded by visit from the start of treatment until the last follow-up. Acute (< 3 months) and chronic (> 3 months) toxicities were numerically graded using the Common Terminology Criteria for Adverse Events v5.0.

Clinical response was documented for patients treated for symptom palliation. Clinical response was based on patient clinic notes and was graded as progressive (worsening of symptoms), stable (no change in symptoms), partial (some remaining symptoms), and complete (no remaining symptoms). Clinical response was identified by initial clinical response and maximum clinical response. The initial clinical response described the first change in symptoms documented during the study period. Maximum clinical response described the final change in symptoms documented during the study period.

Imaging response was recorded by review of all imaging taken during the follow-up period. Imaging data were extracted from the medical record at 3 to 6-month and 6 to 12-month intervals. Patients were evaluated as having a complete response, partial response, stable disease, progressive disease, or were deemed inevaluable (eg, did not have imaging performed at the specified time point) by the Response Evaluation Criteria in Solid Tumors criteria.

Statistical analysis

Simple percentages were calculated to identify the characteristics, treatment indications, and toxicities among patients who received PBT in the final year of life. Survival analysis was performed using the Kaplan-Meier method. Chi-square testing was used to evaluate factors associated with palliative treatment intent.

All data were collected and stored using RedCap electronic data capture tools hosted by the authors' institution. Statistical analysis was performed in Stata Version 15 (Stata Inc, College Station, Texas).

Results

Descriptive statistics

During the study period from 2010 to 2019, 299 patients were treated in the final year of life out of 5802 patients treated with PBT overall (5.2%). Patient characteristics and descriptive statistics are shown in Table 1. Median age was 68 years (19-94 years) with 58% male. The most common cancers were nonsmall-cell lung cancer (81 patients, 27%), hepatocellular carcinoma (40 patients, 13%), small-cell lung cancer (19 patients, 6%), breast cancer (14 patients, 5%), soft tissue sarcoma (12 patients, 4%), and esophageal adenocarcinoma (10 patients, 3%).

Patients included in the study had stage 1 disease (14 patients, 5%), stage 2 (23 patients, 9%), stage 3 (34 patients, 13%), stage 4 (125 patients, 46%), local or distant recurrence (49 patients, 18%), or unknown or unresectable disease (41 patients, 14%). Twelve patients (0.04%) with small-cell lung cancer had de novo extensive-stage disease, and 1 patient had limited-stage disease, while the remainder had locally recurrent or metastatic disease.

Treatment

Thirty-two patients (11%) were treated for symptom palliation alone; the remainder were treated for durable local control (171 patients, 57%), definitively (48 patients, 16%), an isolated local recurrence (41 patients, 14%), or oligometastatic disease (7 patients, 2%). Patients treated with definitive intent were treated with full course PBT with the goal of cure after multidisciplinary discussion (Table 2).

Forty-five percent of the overall population of patients received PBT for reirradiation. The most common tumor types to receive PBT in the reirradiation setting were nonsmall cell lung cancer (40/79 patients, 51%), glioblastoma multiforme (15/18 patients, 83%), and oral cavity and oropharynx cancers (14/18 patients, 77%).

Forty-seven percent of the patients received concurrent systemic therapy, most commonly for nonsmall cell lung cancer (58/81 patients, 72%), small-cell lung cancer (12/19 patients, 63%), breast cancer (8/14 patients, 57%), and gliobastoma multiforme (12/18 patients, 66%). Other common scenarios included split-course proton therapy for hepatocellular carcinoma, reirradiation for liver and lung, and craniospinal irradiation. Patients most commonly received treatment to the thorax (116 patients, 39%), abdomen (79 patients, 26%), central nervous system (CNS) (42 patients, 14%), and head and neck (26 patients, 9%). The median prescribed dose was 50.5 Gy (15-80 Gy) in median 22

Table 1
Baseline characteristics.

N	299
Median age	68.0 (range: 19-94)
Gender	
Male	172 (57.5%)
Female	127 (42.5%)
Malignancy type	
Lung	105 (35.1%)
Hepatobiliary and Pancreatic	60 (20.1%)
GI (non-Hepatobiliary)	26 (8.7%)
CNS	25 (8.4%)
Head and neck	20 (6.7%)
Breast	14 (4.7%)
Hematologic	14 (4.7%)
Sarcoma	12 (4.0%)
Genitourinary	7 (2.3%)
Gynecologic	6 (2.0%)
Skin	4 (1.3%)
Neuroendocrine	4 (1.3%)
Undifferentiated primary	1 (0.003%)
Thyroid	1 (0.003%)

Abbreviations: CNS, central nervous system; GI, gastrointestinal.

Table 2
Treatment details by intent.

Treatment intent	Definitive	Durable local control	Isolated local recurrence	Oligometastatic	Palliation
N	48	171	41	7	32
Median dose (Gy)	53.8	50	66.6	60	30
Median fractions prescribed	26.5	20	33	25	10
On treatment time (Days)	49.5	28	49	36	14

fractions. Median treatment time was 32 days (1-189 days). At the authors' institution, hepatocellular carcinoma and cholangiocarcinoma are sometimes treated with a split-course external beam regimen to minimize toxicity. Seven patients (2%) received split-course proton therapy for hepatocellular carcinoma.

Acute and chronic toxicity

For patients who reported baseline symptoms reported at the start of treatment, these included pain (66 patients, 22%), neurological symptoms (16 patients, 5%), respiratory symptoms (7 patients, 2%), dysphagia (7 patients, 2%), and bleeding (4 patients, 1%). Eighty-five percent of patients reported acute toxicity of any grade after treatment initiation. Acute toxicities tended to be a lower grade (G1 80 patients, 31%, G2 138 patients, 53%, G3 39 patients, 15%). The most commonly experienced acute toxicities were GI (169 patients, 57%), skin (117 patients, 39%), respiratory (72 patients, 24%), and oral cavity/oropharynx (23 patients, 8%). Thirteen patients, 4%, experienced chronic toxicity (toxicity that occurred more than 90 days after the first treatment date). Chronic toxicities were G1 (6 patients, 2%) G2 (4 patients, 1%), and G4 (1 patient, 0.33%). The most common chronic toxicities were GI (4 patients, 1%), oropharyngeal (2 patients, 0.67%), and constitutional (2 patients, 0.67%). The most severe chronic toxicity was a tracheo-esophageal fistula (G4), which occurred in one 58-year-old woman treated to 66 Gy for an isolated local recurrence of a nonsmall cell lung cancer. Fourteen patients experienced toxicity of any grade within 30 days of death.

Median survival from final fraction to death was 139 days (1-363 days). Median survival from first fraction to death was 173 days (1-458 days). On average, patients spent 25% of days from the first fraction until death receiving PBT. Among the 3 most commonly treated malignancies, median survival was longest among patients being treated for CNS malignancies (163 days) followed by lung cancers (139 days), and then hepatobiliary and pancreatic (90 days). In the χ^2/Fischer's exact test, breast and hematologic malignancy were associated with being treated for symptom palliation only (χ^2 (1, N = 14) = 17, P = .013; (χ^2 (1, N = 14) = 18, P = .009).

Clinical response to treatment

Among the 243 patients who described clinical symptoms at the start of treatment, 176 reported changes in their symptoms during the course of treatment. Three patients (1%) reported a complete clinical response (no residual symptoms); 40 (16%) reported a partial response (some remaining symptoms) 65 patients (27%) reported stable symptoms, and 68 patients (28%) reported progressive symptoms. Of these patients, 169 reported a change in symptoms toward the end of treatment. Eight patients (3%) reported a complete clinical response, 28 patients (12%) reported a partial response, 34 patients (14%) reported stable symptoms, and 99 patients (40%) reported progressive symptoms.

Imaging response to treatment

The imaging response was based on routine surveillance imaging. Given that 1-month and 3-month imaging evaluations were often not completed, we report imaging results at 2-time intervals: 3 to 6 months, and 6 to 12 months. Imaging response was graded based on the response evaluation criteria in solid tumors version 1.1.[18]

Among 125 patients who had imaging available at 3 to 6 months, 3 patients (4%) had a complete response, 3 patients (4%) had a partial response, 47 patients (36%) had stable disease, and 50 patients (39%) had progressive disease. Twenty-five patients (20%) were not evaluable.

Among 64 patients who had imaging available at 6 to 12 months, 1 patient (3%) had a complete response, 1 patient (3%) had a partial response, 19 patients (29%) had stable disease, 29 patients (45%) had progressive disease, and 14 patients (22%) were not evaluable.

Discussion

The efficacy of radiation therapy at the end of life is an area of active investigation.[19] The existing literature demonstrates that more aggressive therapy is used in those treated with curative intent,[20] and supports limited treatment regimens among those nearing the end of life.[21] Currently, there is no established study on the use of proton beam therapy in the palliative setting or near the end of life in eligible populations despite its potential for being a less toxic alternative to photons.[22] We find that the number of patients treated with PBT in the final year of life was low compared to the total population treated with PBT at our center. Nearly half of these patients were treated with definitive intent and concurrent systemic therapy, but experienced disease progression and died within one year of receiving treatment. It can be inferred that the clinicians treating with definitive intent anticipated a good prognosis. Nearly half of the patients in the cohort received PBT in the reirradiation setting. Grade 3 or higher toxicity was moderate, though relatively few patients experienced chronic toxicity or any toxicity in the final 30 days of life. Despite toxicities, patients reported clinical symptom improvement: 17% of the patients who reported any initial clinical response reported complete or partial resolution of symptoms and 27% had stable symptoms. However, patients spent on average one-quarter of their remaining days of life receiving treatment.

An important application of PBT is in the reirradiation setting: 45% of the patients in this study had prior radiation to the same site. Importantly, the selection of patients for proton reirradiation is the subject of ongoing investigation. During this study period, several reirradiation clinical trials were open, including studies in pancreatic,[7] esophageal,[4] and nonsmall cancer.[23] During the study period after the publication of these small trials, practices in patient selection for definitive or durable local control reirradiation evolved. These included, for example, excluding patients from lung re-RT if they exhibited signs of active infection, or excluding patients from treatment to the abdomen with recurrent disease less than 1 year after prior RT. It is the subject of ongoing research to highlight these relative contraindications and allow for better patient selection in the reirradiation setting, as these considerations continue to inform practice.

Radiation offers a unique, noninvasive option that is well-validated in the palliative setting. While there is a paucity of clinical data to support more resource-intensive or costly modalities such as PBT, it is critical to investigate their potential to limit toxicity in the palliative setting. Protons are a costly intervention and a limited resource, and costs of care tend to increase at the end of life.[24] As more institutions

acquire the technological capabilities to deliver PBT, there may be both a clinical and a value-based rationale for this modality in appropriately selected patients. Because we can achieve good symptom control at a lower cost with conventional photon therapy, it is not clear that protons would be of benefit to these patients treated exclusively with the goal of symptom palliation (11% of the patients in this study). It may be of higher utility to predict which patients carry a prognosis long enough to expose them to acute and chronic toxicity that may impact quality of life and thus may benefit from PBT.

In our institutional experience, a number of patients were treated with definitive intent, but experienced disease progression and died within 1 year of starting treatment. Thus it is critical to identify the patients with poorer prognosis, potentially by incorporating factors such as performance status, medical comorbidities, third or fourth-line systemic therapy, or the kinetics of disease progression. A number of tools have been proposed in the palliative care literature, and among patients with advanced cancer, incorporating clinical variables such as decline in functional status, cachexia and weight loss, or dyspnea.[25] More recently, efforts to develop a prognostic tool have incorporated machine-learning algorithms and used population-level data to indicate the anticipated survival of cancer patients,[26] and to assess the spending that occurs late in life.[27] For example, Manz et al demonstrated that a machine-learning-based prognostic indicator can be applied to nudge clinicians toward serious illness conversations and thereby decrease aggressive end-of-life interventions in outpatients with cancer.[28] Other prognostic tools (eg, PiPS-A, PPI, PPS, or PaP) may prove useful to predict which patients are best suited for PBT near the end of life, allowing us to better direct treatment intent, limit toxicity, and mitigate cost-of-care escalation in those for whom comfort or less costly modalities should be prioritized.

Limitations

There are several important limitations to this study. First, this is a retrospective study and the study population is subject to selection bias. Patients with good performance status, prior response to RT, or those already receiving aggressive pain management may have been selected for PBT despite passing away within one year, expectedly or unexpectedly. Moreover, the findings reflect the practices at one institution, and our approach may not be generalizable to a broader population. Furthermore, clinical response was documented by Common Terminology Criteria for Adverse events and arguably patient-reported outcomes are the most clinically pertinent with regard to symptom reporting in this population. There are several possible confounders in any patient's clinical response to treatment, such as concurrent systemic therapy, toxicity from RT, and comorbid conditions.

Conclusion

The number of patients treated with PBT at the EOL was low compared to all comers in our institution. Many of these patients received treatment with definitive doses and concurrent systemic therapy, indicating an opportunity for optimization of prognostication and incorporation of enhanced patient-specific factors for selection of definitive doses near the end of life. High-grade toxicity was moderate. Some patients spent a large portion of their remaining days of life receiving treatment. Incorporation of a prognostic indicator in clinical practice may further optimize the use of PBT near the end of life, which is likely limited to scenarios where the benefit of palliation exceeds the risk of toxicity with standard photon radiation, or in re-irradiation in patients with good prognosis. Moreover, recent clinical studies and published expert guidelines provide a data-driven approach to selecting the appropriate patient for proton reirradiation.[29] Further studies comparing protons to photon use in eligible populations will better characterize the optimal treatment regimen for those nearing the end of life.

Author Contributions

Mina Bakhtiar: Conceptualization, Methodology, Data curation, Analysis, Writing - review and editing. **Anish A. Butala**: Conceptualization, Methodology, Data curation, Analysis, Writing - review and editing. **Eva E. Berlin**: Conceptualization, Methodology, Data curation, Analysis, Writing - review and editing. **James M. Metz**: Writing - review and editing. **Jeffrey D. Bradley**: Writing - review and editing. **Joshua A. Jones**: Writing - review and editing. **John Nicholas Lukens**: Writing - review and editing. **Ima Paydar**: Conceptualization, Methodology, Data curation, Analysis, Writing - review and editing. **Neil K. Taunk**: Conceptualization, Methodology, Data curation, Analysis, Writing - review and editing.

Declaration of Conflicts of Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Neil K Taunk reports a relationship with Varian Medical Systems Inc that includes: consulting or advisory and funding grants. Neil K Taunk reports a relationship with Therapanacea AI that includes: funding grants. Neil K Taunk reports a relationship with Radiological Society of North America that includes: funding grants. Neil K Taunk reports a relationship with POINT Biopharma Global Inc that includes: consulting or advisory. Neil K Taunk reports a relationship with Telix Pharmaceuticals Limited that includes: consulting or advisory. Neil K Taunk reports a relationship with Boston Scientific Corp that includes: consulting or advisory. James M Metz reports a relationship with Varian Medical Systems Inc that includes: speaking and lecture fees. James M Metz reports a relationship with IBA Dosimetry US that includes: speaking and lecture fees. Jeffrey D Bradley reports a relationship with Varian Medical Systems Inc that includes: consulting or advisory. Jeffrey D Bradley reports a relationship with AstraZeneca Pharmaceuticals LP that includes: board membership and consulting or advisory. Jeffrey D Bradley reports a relationship with Mevion Medical Systems that includes: board membership. Jeffrey D Bradley reports a relationship with Genentech that includes: board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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