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REVIEW ARTICLE

Role of Radiation Therapy in Palliative Care of the Patient With Cancer

Stephen T. Lutz, Joshua Jones, and Edward Chow

Stephen T. Lutz, Blanchard Valley Regional Cancer Center, Findlay, OH; Joshua Jones, University of Pennsylvania, Philadelphia, PA; Edward Chow, University of Toronto, Toronto, Ontario, Canada.

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Corresponding author: Stephen T. Lutz, MD, Blanchard Valley Regional Cancer Center, 15990 Medical Dr South, Findlay, OH 45840; e-mail: slutz@bvha.org.

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A B S T R A C T

Radiotherapy is a successful, time-efficient, well-tolerated, and cost-effective intervention that is crucial for the appropriate delivery of palliative oncology care. The distinction between curative and palliative goals is blurred in many patients with cancer, requiring that treatments be chosen on the basis of factors related to the patient (ie, poor performance status, advanced age, significant weight loss, severe comorbid disease), the cancer (ie, metastatic disease, aggressive histology), or the treatment (ie, poor response to systemic therapy, previous radiotherapy). Goals may include symptom relief at the site of primary tumor or from metastatic lesions. Attention to a patient's discomfort and transportation limitations requires hypofractionated courses, when feasible. Innovative approaches include rapid response palliative care clinics as well as the formation of palliative radiotherapy specialty services in academic centers. Guidelines are providing better definitions of appropriate palliative radiotherapy interventions, and bone metastases fractionation has become the first radiotherapy quality measure accepted by the National Quality Forum. Further advances in the palliative radiation oncology subspecialty will require integration of education and training between the radiotherapy and palliative care specialties.

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INTRODUCTION

Radiotherapy has been used to address symptoms caused by cancer for more than a century, with early goals of shrinking skin lesions having expanded to myriad palliative indications today.[1] Radiotherapy is a successful, time-efficient, well-tolerated, and cost-effective intervention that is crucial for the appropriate delivery of palliative oncology care. Palliative care, by contrast, is a relatively new medical specialty whose importance has grown immensely in the twenty-first century.[2] The WHO defines palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual."[3] On the basis of this definition, a large minority or even a majority of patients receiving radiotherapy would benefit from palliative care interventions. And, given that patients often require daily radiotherapy treatments over a period of weeks, this time frame allows the radiation oncology team to evaluate and address palliative goals beyond those addressed by radiotherapy. Radiation oncologists often have an excellent opportunity to involve palliative care professionals, pain medicine providers, and hospice specialists in a patient's life when they are most in need.

Radiotherapy Intent: The Crux of the Matter

Radiation oncologists have traditionally made a binary clinical decision about the goal of radiation therapy as either curative or palliative. In a seminal piece in JAMA in 1964, Parker[4] describes a different set of rules that govern palliative radiotherapy: "When the initial objective of radiation therapy is palliation, new ground rules must be applied. Possible serious complications or even slowly self-limiting adverse effects of treatment are no longer acceptable. Overall treatment time must be short. Cost must be minimized. Convenience of treatment must be considered."

With advances in cancer care, including advances in surgery, radiotherapy techniques, and systemic therapy, the distinction between curative and palliative goals has become blurred in many patients with cancer treated with radiotherapy. Although the goal of therapy in patients with metastatic disease from solid tumors is generally palliative, improved systemic therapies have, in certain circumstances, led to longer overall survival times in select patients. In addition, questions have arisen about the curative potential for patients with oligometastatic disease. In each of these areas, local control of lesions causing

symptoms becomes more important, leading to the study of highly conformal treatment techniques or prolonged dose fractionation schemes. In contrast, patients with unresectable glioblastoma or pancreatic cancer may have a poor prognosis regardless of antineoplastic treatment, again raising the question of radiotherapy intent. Indeed, the challenge of accurate prognostication plays an important role in determining whether a patient's radiotherapy can be described as "curative intent," "palliative intent," or something in between.

Difficulties With Prognostication

Determining the intent of therapy on the basis of prognosis is highly complex. This task is made more complex by existing patient factors such as patient performance status and comorbid conditions. When queried about patient prognosis, physicians commonly overestimate survival by a factor of three or more.[5] Although it is easier to predict the survival of patients with cancer than other classes of palliative patients (eg, those with congestive heart failure or chronic obstructive pulmonary disease), survival uncertainties create challenges when choosing treatment aggressiveness. One existing prognostic tool uses a three-risk factor model, consisting of nonbreast cancer, metastases other than bone, and Karnofsky performance status ≤ 60 (or Eastern Cooperative Oncology Group performance status ≥ 2) to separate palliative radiotherapy patients into three groups with distinct life expectancies.[6] Even though this and other prognostic models require further refinement, their increased use can help direct patient care moving forward.[7-9]

Palliative Care Perceptions of Radiation Oncology

Two separate surveys of palliative care professionals revealed their perspectives about radiotherapy and radiation oncologists. Respondents from the National Hospice and Palliative Care Organization described barriers to the provision of radiotherapy for hospice patients, such as cost of treatment, transportation difficulties, short patient life expectancy, and educational lapses between the specialties. Those factors were thought to be the main reasons that less than 3% of hospice patients receive radiation therapy, although cancer remains the most common diagnosis in patients admitted to hospice. The disparity between radiotherapy costs and the hospice per diem of about $120 per day was limiting, as was the perceived unwillingness of radiation oncologists to offer single-fraction treatment to eligible patients with painful bone metastases.[10] In a separate survey, palliative care professionals were much less likely to describe radiation oncologists as "part of the palliative care team" or "good communicators" than were the radiation oncologists themselves.[11] These disparities in perception explain what has, in many locales, remained sequential rather than concurrent and collaborative care of patients common to radiation oncologists and hospice and palliative care professionals (Table 1).

Table 1. Barriers to Collaboration Between the Radiation Oncology and Hospice and Palliative Care Specialties

Factor	Barriers and Limitations
Education	No formal palliative care training for radiation oncology residents
	Lack of radiotherapy training for palliative care professionals
	Minimal protected time at national meetings for palliative oncology topics
Research	Dependence upon patient-reported outcomes in trials
	Missing data points because of declining health or death of accrued patients
	Paucity of experienced research teams in hospice and palliative care programs
	Lack of federal funds dedicated to end-of-life studies
Financial	Hospice capitated payment model differs from radiotherapy model
	Radiotherapy costs several times the average hospice per diem
	Increasing radiotherapy costs due to technologic advances

COMMON CLINICAL CIRCUMSTANCES

Although curative treatment schemes have been developed to deliver daily fraction sizes of 1.8 to 2.0 Gy to doses totaling between 40 and 80 Gy (depending on tumor histology), palliative courses are designed to minimize time and effort spent in travel and treatment for patients approaching the end of life. In addition, although hypofractionated treatments may correlate with a higher risk of late toxicity, careful selection of palliative patients with limited life expectancies minimizes those risks. Thus, palliative treatment courses of 8 to 30 Gy given in 1 to 10 fractions have been shown to be useful for a wide range of scenarios. Furthermore, although it is true that high-dose-per-fraction treatment might yield a higher risk of late toxicity if the same total dose were given, what is often overlooked or ignored is the fact that, according to linear quadratic modeling, a single 8-Gy treatment has lower-risk late effects than 30 Gy in 10 fractions or 40 Gy in 20 fractions. Likewise, there is higher acute toxicity associated with a course of 30 Gy in 10 fractions versus a single 8-Gy fraction.

The selection of palliative radiotherapy dose depends not only on prognosis but also on performance status, comorbidities, risk of acute toxicity, prior treatment, delivery of systemic therapy, and patient wishes.[12] Goals of treatment may be to address symptoms caused by the primary tumor, metastatic disease, or both (Tables 2 and 3). Generally, the variables that correlate with shorter life expectancy include factors related to the patient (ie, poor performance status, advanced age, significant weight loss, severe comorbid disease), the cancer (ie, metastatic disease, aggressive histology), or the treatment (ie, poor response to systemic therapy, previous radiotherapy).

LOCAL SYMPTOMS RESULTING FROM PRIMARY DISEASE

Primary Brain Tumors

The most common primary malignant brain tumors, high-grade astrocytomas, are associated with short life expectancy and cause debilitating symptoms such as seizure, headache, fatigue, personality changes, altered memory, dysphasia, nausea, and focal motor deficit. Even in circumstances in which treatment is delivered with curative intent, palliative care plays a significant role in the care of virtually all of these patients. Patients who successfully complete surgical resection and adjuvant radiotherapy and chemotherapy commonly suffer disease recurrence within or adjacent to the site of initial tumor.[15] External beam radiotherapy in 1.8- to 2.0-Gy fractions to about 60 Gy to partial brain fields is considered standard for the primary treatment of glioblastoma multiforme, whether the patient has or has not undergone surgical resection. In patients older than age 70 years or younger

Table 2. Examples of Prognosis-Dependent Treatment Options for Symptoms of Primary Cancer

Primary Site	Treatment Options	
	Poor Prognosis/Performance Status	Average Prognosis/Performance Status
CNS	• 30 Gy in 10 fractions • Temozolomide alone • Supportive care alone	• 59.4-60 Gy in 30 to 33 fractions
Head and neck	• 14 Gy in four fractions monthly to a total of 42 Gy • 8 Gy in one fraction • Supportive care alone	• 70 Gy in 35 fractions • 50 Gy in 20 fractions
Breast	• 20-30 Gy in four to five fractions • 8-10 Gy in one fraction • Supportive care alone	• 30 Gy in 10 fractions • 50 Gy in 25 fractions
Lung	• 17 Gy in two fractions in 2 weeks • 8-10 Gy in one fraction • Supportive care alone	• > 30 Gy in 10 fraction-equivalents • Endobronchial brachytherapy for endoluminal obstruction
Esophagus	• 30 Gy in 10 fractions • 24 Gy in three fractions • 8-10 Gy in one fraction • Supportive care alone	• 50 Gy in 25 fractions • 50 Gy in 20 fractions
Genitourinary	• 14.4 Gy in four fractions monthly to a total of 43.2 Gy • 8-10 Gy in one fraction • Supportive care alone	• 30 Gy in 10 fractions • 50 Gy in 20 fractions
Gynecologic	• 14.4 Gy in four fractions monthly to a total of 43.2 Gy • 8-10 Gy in one fraction • Supportive care alone	• 30 Gy in 10 fractions • 50 Gy in 20 fractions

patients with poor performance status, significant comorbid conditions, or extracranial spread of disease, shortened courses of 34 to 40 Gy in 10 to 15 fractions are appropriate.[16,17] Patients with locally recurrent disease have at times been reirradiated with palliative intent while paying close attention to neurotoxicity risks, although this approach is not considered standard.[18]

Head and Neck Cancers

Although the category of head and neck malignancy includes tumors from a variety of anatomic sites that represent a diverse number of histologies, its most common diagnoses are squamous cell carcinomas primary to the oral cavity, pharynx, and larynx. Common symptoms include dysphagia, decreased phonation, pain, bleeding, malnutrition, thickened secretions, cough, and shortness of breath. Palliative radiotherapy affords higher response rates with any one of several hypofractionated regimens.[19] Patients with poor performance status or significant comorbid disease can benefit from the so-called "quad shot" regimen of 14 Gy in four fractions over 2 consecutive days with the opportunity to repeat this same dosing twice more at 4-week intervals, for a potential total dose of 42 Gy.[20] Some patients with locally recurrent disease after previous radiotherapy may be reirradiated and may achieve good outcomes, but proper patient selection is critically important.[21]

Locally Advanced and Recurrent Breast Cancer

Breast cancer is the most common and second deadliest cancer in women in developed countries, and radiotherapy plays a key role in the management of both locally advanced and recurrent disease. It is uncommon to encounter patients with unresectable primary cancers in the era of mammography, but older series include outcomes data for radiotherapy as treatment to the primary site in this setting.[22] Still, radiotherapy provides critical relief for women who suffer from symptoms including ulceration, bleeding, arm edema, or brachial plexopathy.[23] The most appropriate palliative dosing regimens for women with locally advanced or recurrent local tumor have not been fully elucidated, although there is a trend toward increased local control with increased total dose. However, total doses greater than 60 Gy correlate with increased risks of toxicity such as fibrosis, necrosis, lymphedema, and brachial plexopathy.[24] Patients with isolated locoregional recurrence of breast cancer following local therapy pose a management challenge; although they are at risk for distant disease, many can still enjoy an extended survival.[25] In cases of chemotherapy-refractory recurrence, there are limited data suggesting that a moderate radiotherapy re-treatment dose can safely be delivered to manage distressing symptoms such as uncontrolled bleeding.[26,27] Hyperthermia has also been studied as an adjuvant therapy in addition to radiotherapy for chest wall recurrence of breast cancer, and improved rates of complete response have been observed with combination therapy.[28]

Non–Small-Cell Lung Cancer

Radiotherapy palliates intrathoracic symptoms caused by locally advanced or metastatic non–small-cell lung cancer, including dyspnea, cough, hemoptysis, chest pain, dysphagia, brachial plexopathy, and superior vena cava syndrome. Despite multiple prospective randomized trials attempting to define the optimal fractionation scheme to aid intrathoracic symptoms in patients with locally advanced or metastatic non–small-cell lung cancer, questions remain.[29] Those studies do suggest that regimens of 30 Gy in 10 or more fractions are associated with small improvements in symptom control and survival at the cost of increased short-term adverse effects such as esophagitis when compared with shorter courses.[30] Still, hypofractionated courses of 20 Gy in five fractions or 17 Gy in two fractions given 1 week apart can effectively palliate intrathoracic symptoms and should be considered for patients with short survival expectations or poor performance status, or for those who have a desire to minimize the number of trips for treatment. There are currently no studies to suggest that

Table 3. Palliative Radiotherapy for Metastatic Cancer as Delineated in American Society for Therapeutic Radiology and Oncology Treatment Guidelines[13,14]

Primary Site and Clinical Circumstances	Recommendations
Bone metastases	
Uncomplicated, painful bone metastases	• Acceptable fractionation schemes: 30 Gy in 10 fractions, 24 Gy in six fractions, 20 Gy in five fractions, 8 Gy in one fraction
Recurrent pain at same skeletal site	• Re-treatment may be attempted, taking into account normal tissue tolerance
Multiple painful osteoblastic metastases	• Consider radiopharmaceutical injection
Spinal cord compression	• Surgical decompression plus postoperative radiotherapy • Radiotherapy alone in those who do not qualify for or desire surgery
Metastases in bones of the spine	• Standard external beam radiotherapy • Stereotactic body radiation therapy may be used, although preferably on a trial
Brain metastases	
Poor prognosis or performance status	• 20 Gy in five fractions • Supportive care alone
Multiple lesions, all < 4 cm in size	• Whole-brain radiotherapy alone • Whole-brain plus radiosurgery • Radiosurgery alone
Multiple lesions, any > 4 cm in size	• Whole-brain radiotherapy alone
Solitary lesion	• If completely resectable, then surgery plus whole-brain or radiosurgery • If not completely resectable and < 4 cm in size, then radiosurgery alone or with whole-brain radiotherapy • If not completely resectable and > 4 cm in size, then whole-brain radiotherapy alone

concurrent chemotherapy should be considered for this patient group, although sequential chemotherapy may be effective.

GI Cancer

Cancers of the esophagus, stomach, biliary tree, and rectum can be successfully palliated with external beam radiotherapy. Common tumor-induced symptoms include pain, bleeding, ulceration, compression, or obstruction. In general, the goals of palliative treatment for GI cancer often focus on maintaining the patency of a luminal structure. Patients with esophageal cancer symptoms may be well treated with a combination of external beam radiotherapy, brachytherapy, or both, with consideration given to adding chemotherapy, laser treatment, or stent placement.[31] External beam radiotherapy can help minimize bleeding and other symptoms caused by locally advanced and unresectable stomach cancer.[32] Patients with biliary obstruction from bile duct cancer might gain relief from stent placement plus external beam radiotherapy, intraluminal brachytherapy, or a combination of both.[33] Patients with rectal cancer who are unable to or unwilling to undergo palliative resection can be treated with aggressive palliative dose regimens totaling 40 to 60 Gy, although those with poor performance status or prognosis can gain relief with courses as short as 30 Gy in six fractions over 3 weeks with concurrent fluorouracil chemotherapy.[34]

Urologic Malignancies

Urologic malignancies are a diverse set of diseases that originate in a similar anatomic region of the body but that differ in biology and symptom constellations. In general, they may cause difficulties including bleeding, pain, urinary tract infection, urinary frequency, dysuria, hematuria, pyelonephritis, urinary retention or obstruction, bowel obstruction, or lower extremity edema. Systemic treatments, such as hormonal ablation for prostate cancer or chemotherapy for bladder cancer, play a major role in the control of local manifestations of these illnesses. Palliative radiotherapy can also add greatly to the improvement of bleeding, pain, and obstruction. A randomized trial of 35 Gy in 10 fractions versus 21 Gy in three fractions for patients with local symptoms caused by bladder cancer showed effective but equal symptom control rates, suggesting that higher-dose therapy adds little to the palliative care of these patients.[35] Patients with local manifestations of castration-resistant prostate cancer can achieve good symptom relief with radiotherapy courses between 45 and 60 Gy at 2.0 Gy to 2.5 Gy per fraction.[36]

Gynecologic Malignancies

Patients with locally advanced or unresectable gynecologic cancer may suffer symptoms including bleeding, pain, dyspareunia, colon or bladder obstruction, ureteral obstruction with renal dysfunction, lower extremity edema, or fistulae. Either external beam radiotherapy or brachytherapy can provide hemostasis for patients with unresectable, locally advanced, or recurrent cervix or endometrial cancer.[37] Patients with low performance status may benefit from symptom relief after hypofractionated courses of therapy. Radiation Therapy Oncology Group (RTOG) research has shown good efficacy and adverse effect profiles following delivery of four 3.7-Gy external beam fractions over 2 days with repeat 14.8-Gy courses twice more at 2- to 6-week intervals for a total dose of 44.4 Gy.[13] The intervals between these four-fraction courses allow for the patient's body to declare symptom response and changes in performance status. A more recent phase I study confirmed good palliative relief and tolerance of twice-per-day dosing up to a total of 18 Gy given over 2 days.[38]

Patients who suffer pelvic recurrence of their gynecologic disease can undergo palliative treatment on the basis of the existence of previous pelvic radiotherapy. Although radical hysterectomy or pelvic exenteration may be theoretical options for the treatment of these patients, in practice, their use in this setting is fairly rare. In those who have not had previous radiotherapy, salvage treatment by using external beam treatment plus brachytherapy to curative-type doses is indicated. In those who have undergone previous pelvic radiotherapy, reirradiation is limited to small volumes of disease anatomically located outside the previous high-dose areas.

SYMPTOMS RESULTING FROM METASTATIC DISEASE

Bone Metastases

The propensity of many primary tumor types to spread to the skeleton is high, especially for those that arise in the breast, lung, thyroid, kidney, prostate, or plasma cells of the bone marrow. Symptoms from bone metastases may commonly include pain,

pathologic fracture, or spinal cord compression. When combined with the appropriate use of other measures such as a pain medicine regimen, surgical stabilization, systemic treatments including bone-strengthening agents, and radiopharmaceuticals, external beam radiotherapy constitutes the most effective and well-tolerated treatment for painful bone metastases.[39] Numerous prospective randomized trials have documented partial pain relief of 60% to 80% and complete pain relief of 30% to 50% in patients 3 to 4 weeks after initiation of external beam palliative radiotherapy.[40] Results from a recent trial also confirm that reirradiation to a previously treated skeletal site of bone pain can provide pain relief in about half of patients.[41]

Multiple prospective randomized trials have evaluated fractionation schemes for bone metastases, with pain relief equivalency for schedules including 30 Gy in 10 fractions, 24 Gy in six fractions, 20 Gy in five fractions, and a single 8-Gy fraction.[39] Re-treatment rates to the same site are approximately 8% in patients who receive multiple fractions and approximately 20% in those who receive a single fraction, although the convenience advantages of single-fraction therapy are clear. A single 8-Gy fraction has not shown any obvious deleterious effects, even when assessing late spinal cord tolerance in those who received treatment to bones of the spine.[42] Furthermore, evaluation of a group that survived a minimum of 1 year suggested no inferiority in pain control after a single 8-Gy fraction versus lengthier courses.[43]

The special circumstance of spinal cord compression caused by extraosseous extension of tumor from bones of the spine is an oncologic emergency that deserves special attention and management. Although pain nearly always predates spinal cord compression by days to months, the onset of neurologic dysfunction, such as weakness, sensory deficit, and bowel and bladder incontinence, requires prompt recognition and intervention to maximize the chances for long-term functional preservation.[44] The first step in management is initiation of corticosteroids that diminish edema, and they should soon be followed by a discussion about the choice between surgical decompression followed by radiotherapy and radiotherapy alone. Patients undergoing surgical decompression are more likely to maintain ambulation, although that advantage diminishes with increasing patient age.[45] The choice to recommend surgery must also be balanced with limitations suggested by poor performance status or limited prognosis due to tumor extent and biologic behavior. Patients treated with primary radiotherapy generally respond to multitreatment regimens such as 30 Gy in 10 fractions, although recent studies have suggested that patients with short life expectancy might fare well with a single 8-Gy dose.[46]

Brain Metastases

Brain metastases are both a common manifestation of neoplastic disease and a significant cause of cancer morbidity and mortality. Numerous prognostic indices have been developed to predict survival for patients with brain metastases, including in recent years the Graded Prognostic Assessment instrument. It scores patients with different primary cancer types on a scale of 0 to 4 based on the summation of prognostic criteria including age, Karnofsky performance score, number of brain metastases, and presence or absence of extracranial metastases.[14,47] Each of these tools is used not only to predict survival but also to aid practitioners in recommending care. Given survival ranges from 2.8 to 25.3 months depending on these prognostic factors, thoughtful palliative care is paramount for these patients.

A variety of clinical approaches may be used in managing patients with brain metastases, and the American Society for Therapeutic Radiology and Oncology (ASTRO) has issued a guideline on this topic.[48] Whereas there is no clear evidence of the uniform superiority of using any of the combinations of local modalities (surgery and radiosurgery) and whole-brain radiotherapy, care must be taken to consider the ideal combination for a given patient. It should also be appreciated that the addition of whole-brain radiotherapy to surgery or radiosurgery does not confer a survival advantage and has been observed to cause detrimental effects on cognitive function and quality of life in randomized studies.[49,50] For patients with poor prognostic factors and a limited life expectancy, the use of whole-brain radiotherapy might be limited in its usefulness. Given that no differences in overall survival or symptom control have been proven between a course of 30 Gy in 10 fractions or 20 Gy in five fractions, the shorter course seems more reasonable for optimizing convenience in patients with limited life expectancy. For some patients with poor prognosis, supportive care, including dexamethasone and use of pain medication, is sensible.[51]

INNOVATIVE CLINICAL APPROACHES

Just as academic radiation oncology clinical practices have been subdivided into teams that care for patients with specific diagnoses, some institutions have pioneered palliative radiotherapy teams that address end-of-life needs in a comprehensive fashion. These services are further defining palliative radiotherapy as a distinct and necessary subspecialty. Many sites have instituted rapid response clinics to efficiently provide consultation, simulation, treatment planning, and initiation of radiotherapy in the same day to expedite palliative response and minimize time investment and transportation on the part of patients and their caretakers.[52] These clinics also improve communication with referring physicians.[53] Some sites have established routine, ongoing weekly or more frequent meetings between palliative care and radiation oncology teams, allowing comprehensive palliative care evaluations in patients receiving radiotherapy and expedited referrals for palliative radiotherapy among patients followed by the palliative care team. Other sites have established unique interactions between hospice teams and radiotherapy centers, allowing rapid triage and reduced-cost radiotherapy treatment among patients receiving hospice care.[54]

Table 4. Future Directions for Radiation Oncology and Palliative Care Collaborations

Factor	Initiative
Residency training	Formalized role of palliative care training in radiation oncology residency
Board certification	Expanded role of radiotherapy in hospice and palliative medicine boards
Clinical teams	Dedicated academic palliative radiotherapy services
Referral patterns	Early palliative care referral for appropriate radiotherapy patients
Course length	More hypofractionated courses for end-of-life radiotherapy patients
Prognosis	Further development and use of accurate prognostic instrument
Overuse measures	Formation of more radiotherapy overuse guidelines and quality measures

PALLIATIVE RADIOTHERAPY RESEARCH

Despite the number of palliative oncology patients in the United States each year as well as the severity of their symptoms, a small percentage of the national research budget has historically been spent on palliative care trials. Although the RTOG has completed several pivotal palliative trials, most notably reporting on the best care of patients with bone and brain metastases, several forces limit a more robust approach to these issues.[55,56] In a general sense, palliative care outcome measures are hard to define and difficult to measure. Patient reported, validated measures are the most useful outcome variables, although many of the most commonly used instruments have not been fully validated.[57] Furthermore, nearly all palliative radiotherapy trials suffer from missing data points because patients are unable to fulfill follow-up appointments as a result of declining function or death.

EDUCATION

Hospice and Palliative Care has been formalized as a medical specialty by the American Council on Graduate Medical Education.[58] However, given that many radiation oncologists had no formal training in hospice and palliative care during their medical school training and residency, it is imperative that high-quality palliative radiotherapy topics be presented at radiotherapy clinical meetings.

GUIDELINES AND QUALITY MEASURES

End-of-life care constitutes a significant portion of Medicare expenditures in the United States, so it is predictable that numerous efforts have been initiated to couple treatment patterns with published data and to measure cost-effectiveness of palliative interventions. The radiotherapeutic treatment of painful bone metastases has been stringently evaluated, given significant high-quality data about fractionation but variability in practice patterns typified by 101 different fractionation schemes prescribed worldwide.[59] Despite several prospective randomized studies showing pain relief equivalency between single- and multifraction regimens for bone metastases, only 3.3% of Medicare beneficiaries with prostate cancer from bone metastases receive a single fraction.[60] A bone metastasis guideline developed by ASTRO confirmed equivalency between regimens, including 30 Gy in 10, 24 Gy in six, 20 Gy in five, or 8 Gy in one fraction, with the National Quality Forum subsequently developing a quality indicator to measure the behavior of radiation oncologists in this clinical setting.[61] To date, three of the first six ASTRO guidelines deal with palliative radiotherapy questions, confirming the belief that these clinical circumstances are important and are needed for uniform, quality care.

FUTURE DIRECTIONS

Technological advances provide exciting new possibilities for the support and treatment of palliative care patients, especially in the form of stereotactic radiosurgery for brain metastases; stereotactic body radiation therapy for metastases of the spine, liver, or lung; and ablative treatments for highly selected patients with oligometastases. The specifics of those newer treatment approaches are covered elsewhere in this issue of the *Journal of Clinical Oncology*. These promising advances in radiotherapy must be applied while keeping general palliative care approaches in mind.

One landmark study typified the potential usefulness of early palliative care intervention.[62] Patients with newly diagnosed non–small-cell lung cancer were randomly assigned to early palliative care intervention versus standard palliative care, in which palliative care was offered only at the request of the patient on advisement of the treating physician. Patients who received early palliative care showed improved quality of life, lower rates of depression, and longer survival. Of note, this patient group was less likely to choose aggressive end-of-life care as defined by chemotherapy given in the final 2 weeks of life, hospice care for less than 3 days duration, or no hospice care at all.

ASCO has issued guidelines suggesting that palliative care be considered early in the course of illness for patients with significant symptoms or metastatic spread of cancer.[63] Furthermore, ASCO recommends a "hospice informational visit" for any patients felt to have a survival of 3 to 6 months. The radiation oncology specialty must now meet the needs of its patients and the initiatives of its colleagues by dedicating effort to palliative care education, research, and advocacy (Table 4).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: Edward Chow
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Lutz S, Korytko T, Nguyen J, et al: Palliative radiotherapy: When is it worth it and when is it not? Cancer J 16:473-482, 2010
2. Seymour J, Clark D, Winslow M: Pain and palliative care: The emergence of new specialties. J Pain Symptom Manage 29:2-13, 2005
3. World Health Organization: WHO definition of palliative care. http://www.who.int/cancer/palliative/definition/en/
4. Parker RG: Palliative radiation therapy. JAMA 190:1000-1002, 1964
5. Christakis NA, Lamont EB: Extent and determinants of error in physicians' prognoses in terminally ill patients. West J Med 172:310-313, 2000
6. Chow E, Abdolell M, Panzarella T, et al: Predictive model for survival in patients with advanced cancer. J Clin Oncol 26:5863-5869, 2008
7. Krishnan MS, Epstein-Peterson Z, Chen YH, et al: Predicting life expectancy in patients with metastatic cancer receiving palliative radiotherapy: The TEACHH model. Cancer 120:134-141, 2014
8. Tseng YD, Krishnan MS, Sullivan AJ, et al: How radiation oncologists evaluate and incorporate life expectancy estimates into the treatment of palliative cancer patients: A survey-based study. Int J Radiat Oncol Biol Phys 87:471-478, 2013
9. Krishnan M, Temel JS, Wright AA, et al: Predicting life expectancy in patients with advanced incurable cancer: A review. J Support Oncol 11:68-74, 2013
10. Lutz S, Spence C, Chow E, et al: Survey on use of palliative radiotherapy in hospice care. J Clin Oncol 22:3581-3586, 2004
11. McCloskey SA, Tao ML, Rose CM, et al: National survey of perspectives of palliative radiation therapy: Role, barriers, and needs. Cancer J 13:130-137, 2007
12. Bruera E, Kuehn N, Miller MJ, et al: The Edmonton Symptom Assessment System (ESAS): A simple method for the assessment of palliative

care patients. J Palliat Care 7:6-9, 1991

13. Spanos W Jr, Guse C, Perez C, et al: Phase II study of multiple daily fractionations in the palliation of advanced pelvic malignancies: Preliminary report of RTOG 8502. Int J Radiat Oncol Biol Phys 17:659-661, 1989

14. Sperduto PW, Kased N, Roberge D, et al: Summary report on the graded prognostic assessment: An accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol 30:419-425, 2012

15. Wallner KE, Galicich JH, Krol G, et al: Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. Int J Radiat Oncol Biol Phys 16:1405-1409, 1989

16. Roa W, Brasher PM, Bauman G, et al: Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. J Clin Oncol 22:1583-1588, 2004

17. Malmström A, Gronberg BH, Marosi C, et al: Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: The Nordic randomised, phase 3 trial. Lancet Oncol 13:916-926, 2013

18. Fuller CD, Choi M, Forthuber B, et al: Standard fractionation intensity modulated radiation therapy (IMRT) of primary and recurrent glioblastoma multiforme. Radiat Oncol 2:26, 2007

19. Chen AM, Vaughan A, Narayan S, et al: Palliative radiation therapy for head and neck cancer: Toward an optimal fractionation scheme. Head Neck 30:1586-1591, 2008

20. 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 77:137-142, 2005

21. McDonald MW, Lawson J, Garg MK, et al: ACR appropriateness criteria retreatment of recurrent head and neck cancer after prior definitive radiation expert panel on radiation oncology: Head and neck cancer. Int J Radiat Oncol Biol Phys 80:1292-1298, 2011

22. Price A, Kerr GR, Rodger A: Primary radiotherapy for T4 breast cancer. Clin Oncol (R Coll Radiol) 4:217-221, 1992

23. Bedwinek JM, Lee J, Fineberg B, et al: Prognostic indicators in patients with isolated local-regional recurrence of breast cancer. Cancer 47: 2232-2235, 1981

24. Sheldon T, Hayes DF, Cady B, et al: Primary radiation therapy for locally advanced breast cancer. Cancer 60:1219-1225, 1987

25. Schmoor C, Sauerbrei W, Bastert G, et al: Role of isolated locoregional recurrence of breast cancer: Results of four prospective studies. J Clin Oncol 18:1696-1708, 2000

26. Würschmidt F, Dahle J, Petersen C, et al: Reirradiation of recurrent breast cancer with and without concurrent chemotherapy. Radiat Oncol 3:28, 2008

27. Harkenrider MM, Wilson MR, Dragun AE: Reirradiation as a component of the multidisciplinary management of locally recurrent breast cancer. Clin Breast Cancer 11:171-176, 2011

28. Zagar TM, Oleson JR, Vujaskovic Z, et al: Hyperthermia combined with radiation therapy for superficial breast cancer and chest wall recurrence: A review of the randomised data. Int J Hyperthermia 26:612-617, 2010

29. Rodrigues G, Videtic GM, Sur R, et al: Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. Pract Radiat Oncol 1:60-71, 2011

30. Fairchild A, Harris K, Barnes E, et al: Palliative thoracic radiotherapy for lung cancer: A systematic review. J Clin Oncol 26:4001-4011, 2008

31. Javle M, Ailawadhi S, Yang GY, et al: Palliation of malignant dysphagia in esophageal cancer: A literature-based review. J Support Oncol 4:365-373, 2006

32. Kim MM, Rana V, Janjan NA, et al: Clinical benefit of palliative radiation therapy in advanced gastric cancer. Acta Oncol 47:421-427, 2008

33. Mosconi C, Renzulli M, Giampalma E, et al: Unresectable perihilar cholangiocarcinoma: Multimodal palliative treatment. Anticancer Res 33:2747-2753, 2013

34. Janjan NA, Breslin T, Lenzi R, et al: Avoidance of colostomy placement in advanced colorectal cancer with twice weekly hypofractionated radiation plus continuous infusion 5-fluorouracil. J Pain Symptom Manage 20:266-272, 2000

35. Duchesne GM, Bolger JJ, Griffiths GO, et al: A randomized trial of hypofractionated schedules of palliative radiotherapy in the management of bladder carcinoma: Results of medical research council trial BA09. Int J Radiat Oncol Biol Phys 47:379-388, 2000

36. Gogna NK, Baxi S, Hickey B, et al: Split-course, high-dose palliative pelvic radiotherapy for locally progressive hormone-refractory prostate cancer. Int J Radiat Oncol Biol Phys 83:e205-e211, 2012

37. Mishra SK, Laskar S, Muckaden MA, et al: Monthly palliative pelvic radiotherapy in advanced carcinoma of uterine cervix. J Cancer Res Ther 1:208-212, 2005

38. Caravatta L, Padula GD, Macchia G, et al: Short-course accelerated radiotherapy in palliative treatment of advanced pelvic malignancies: A phase I study. Int J Radiat Oncol Biol Phys 83:e627-e631, 2012

39. Lutz S, Berk L, Chang E, et al: Palliative radiotherapy for bone metastases: An ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 79:965-976, 2011

40. Chow E, Harris K, Fan G, et al: Palliative radiotherapy trials for bone metastases: A systematic review. J Clin Oncol 25:1423-1436, 2007

41. Chow E, van der Linden YM, Roos D, et al: Single versus multiple fractions of repeat radiation for painful bone metastases: A randomised, controlled, non-inferiority trial. Lancet Oncol 15:164-171, 2014

42. Howell DD, James JL, Hartsell WF, et al: Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases: Equivalent efficacy, less toxicity, more convenient—A subset analysis of Radiation Therapy Oncology Group trial 97-14. Cancer 119:888-896, 2013

43. van der Linden YM, Steenland E, van Houwelingen HC, et al: Patients with a favourable prognosis are equally palliated with single and multiple fraction radiotherapy: Results on survival in the Dutch Bone Metastasis Study. Radiother Oncol 78:245-253, 2006

44. Byrne TN: Spinal cord compression from epidural metastases. N Engl J Med 327:614-619, 1992

45. Chi JH, Gokaslan Z, McCormick P, et al: Selecting treatment for patients with malignant epidural spinal cord compression: Does age matter? Results from a randomized clinical trial. Spine (Phila Pa 1976) 34:431-435, 2009

46. Maranzano E, Trippa F, Casale M, et al: 8 Gy single-dose radiotherapy is effective in metastatic spinal cord compression: Results of a phase III randomized multicentre Italian trial. Radiother Oncol 93:174-179, 2009

47. Gaspar LE, Scott C, Murray K, et al: Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys 47:1001-1006, 2000

48. Tsao MN, Rades D, Wirth A, et al: Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2:210-225, 2012

49. Chang EL, Wefel JS, Hess KR, et al: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: A randomised controlled trial. Lancet Oncol 10:1037-1044, 2009

50. Soffietti R, Kocher M, Abacioglu UM, et al: A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: Quality-of-life results. J Clin Oncol 31:65-72, 2013

51. Langley RE, Stephens RJ, Nankivell M, et al: Interim data from the Medical Research Council QUARTZ Trial: Does whole brain radiotherapy affect the survival and quality of life of patients with brain metastases from non-small cell lung cancer? Clin Oncol (R Coll Radiol) 25:e23-e30, 2013

52. Pituskin E, Fairchild A, Dutka J, et al: Multidisciplinary team contributions within a dedicated outpatient palliative radiotherapy clinic: A prospective descriptive study. Int J Radiat Oncol Biol Phys 78:527-532, 2010

53. Barnes EA, Chow E, Andersson L, et al: Communication with referring physicians in a palliative radiotherapy clinic. Support Care Cancer 12:669-673, 2004

54. Wilson D, Sheng K, Yang W, et al: STAT RAD: A potential real-time radiation therapy workflow. http://www.intechopen.com/download/get/type/pdfs/id/34239

55. Hartsell WF, Scott CB, Bruner DW, et al: Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 97:798-804, 2005

56. Murray KJ, Scott C, Zachariah B, et al: Importance of the mini-mental status examination in the treatment of patients with brain metastases: A report from the Radiation Therapy Oncology Group protocol 91-04. Int J Radiat Oncol Biol Phys 48:59-66, 2000

57. Bruner DW: Should patient-reported outcomes be mandatory for toxicity reporting in cancer clinical trials? J Clin Oncol 25:5345-5347, 2007

58. Lutz S, Lupu D, Johnstone P, et al: The influence of the newly formed hospice and palliative medicine subspecialty on radiation oncology and end-of-life care. J Am Coll Radiol 5:1102-1105, 2008

59. Fairchild A, Barnes E, Ghosh S, et al: International patterns of practice in palliative radiotherapy for painful bone metastases: Evidence-based practice? Int J Radiat Oncol Biol Phys 75:1501-1510, 2009

60. Bekelman JE, Epstein AJ, Emanuel EJ: Single- vs multiple-fraction radiotherapy for bone metastases from prostate cancer. JAMA 310:1501-1502, 2013

61. National Quality Forum: NQF endorses cancer measures. https://www.qualityforum.org/News_And_Resources/Press_Releases/2012/NQF_Endorses_Cancer_Measures.aspx

62. Temel JS, Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733-742, 2010

63. Smith TJ, Temin S, Alesi ER, et al: American Society of Clinical Oncology provisional clinical opinion: The integration of palliative care into standard oncology care. J Clin Oncol 30:880-887, 2012

