Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

A review of recently published radiotherapy treatment guidelines for bone metastases: Contrasts or convergence?

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ARTICLE INFO

Article history: Received 5 February 2012 Received in revised form 23 March 2012 Accepted 5 April 2012 Available online 10 May 2012

Keywords: Radiotherapy Bone metastases Treatment guidelines Palliative care Quality measures Fractionation

ABSTRACT

Bone metastases are a common manifestation of malignancy, and external beam radiotherapy (EBRT) effectively and safely palliates the pain caused by this clinical circumstance. The myriad of EBRT dosing schemes and complexities involved with coordinating radiotherapy with other interventions necessitated the need for bone metastases treatment guidelines. Here we compare and contrast the bone metastases radiotherapy treatment guidelines recently published by the American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR). These evaluations acknowledge current controversies in treatment approaches, they evaluate the nuances of ASTRO and ACR task force decision-making regarding standard approaches to care, and they project the upcoming research results that may clarify approaches to palliative radiotherapy for bone metastases. The results of these two dedicated radiotherapy guidelines are compared to the brief mentions of radiotherapy for bone metastases in the National Comprehensive Cancer Network (NCCN) guidelines. Finally, the paper describes how treatment guidelines may influence patterns of care and reimbursement by their use as quality measures by groups such as the National Quality Forum (NQF).

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1. Bone metastases as a clinical problem

Many cancers metastasize to bone, with the most common sites of origin of primary disease being breast, lung, thyroid, kidney, prostate, and malignant melanoma of the skin. The presence of tumor in the bone can lead to local symptoms such as pain, spinal cord compression, and pathologic fracture, as well as systemic effects caused by hypercalcemia. The work-up and treatment of bone metastases requires input and interventions from many medical disciplines, including radiologists, orthopedic surgeons or neurosurgeons, radiation oncologists, medical oncologists, pain medicine specialists, physical medicine and rehabilitation physicians, and palliative care professionals. The delivery of radiation therapy to these patients requires communication and coordination of scheduling with these other specialists. Furthermore, the aggressiveness of treatment must take into account patient factors such as performance status and co-morbidities, tumor factors such as stage and histology, and treatment factors such as sequencing and risks of concurrent therapy [1–3].

2. Radiotherapy for bone metastases

As a palliative intervention, radiotherapy is effective and efficient at treating painful bone metastases, and the side effects associated with its use are manageable and usually self-limiting in nature. Between 50% and 80% of patients gain at least partial relief of their pain following external beam radiotherapy (EBRT), and complete relief may be seen in up to one-third [4]. External beam radiotherapy may be delivered to the same anatomic site of affected bone in the case of recurrent pain. Technological advances have created interest in the possibility that highly conformal therapies may improve either the rates of pain relief or the duration of the results of treatment, especially in cases of tumors located in bones of the spine. These treatments are termed stereotactic body radiation therapy (SBRT), or stereotactic ablative body radiotherapy (SABR), and are given by machines that deliver intensity modulated radiation therapy (IMRT), Cyberknife therapy, Tomotherapy, or proton therapy. Patients with spinal cord compression may receive EBRT primarily or as an adjuvant treatment after surgical decompression. Kyphoplasty or vertebroplasty may be used in cases where there is no spinal cord compression, but where spinal instability is noted and contributes to metastatic bone pain. Furthermore, injectable radiopharmaceuticals such as Strontium 89, Samarium 153, and Radium 223 may be delivered to patients with widespread tumors whose histologies are osteoblastic and therefore easily visualized on



Review Article





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a Technetium 99 bone scan. Finally, the addition of osteoclast inhibiting agents may be considered concurrently or sequentially with EBRT.

3. Emergence of radiotherapy guidelines

The driving forces behind the emergence of radiotherapy guidelines include a desire to maximize pain relief and functional capabilities of an individual patient while minimizing the risks of treatment toxicity. The treatment guidelines are also meant to serve as a means by which to guarantee a minimum standard of care across geographic locales and different practice settings. And, given some areas of incomplete data regarding the proper choice for treatment, one goal of the guidelines is to acknowledge and address the controversies that arise due to that lack of complete data. From a societal standpoint, the guidelines provide a means to assess the best practice patterns as developed countries face an increased number of cancer patients with resource constraints and many developing countries struggle with throughput limitations on antiquated machinery.

4. International Consensus Conference Bone Metastases treatment recommendations

The prelude to many of the questions posed and answers offered by the existing bone metastases treatment guidelines was contained in previous International Consensus Conference Bone Metastases treatment recommendation publications. The First International Consensus Workshop on radiation in the treatment of metastatic and locally advanced cancer convened in the United States in 1990 [5]. A group of 116 experts evaluated the available palliative radiotherapy data and generated consensus statements for the treatment of bone metastases, amongst other clinical circumstances. Those statements included treatment pathway recommendations, an assessment of international variations in treatment approach, the effects of successful treatment on quality of life, and the role of economic factors in the management of this patient group. The Second Workshop on Palliative Radiotherapy and Symptom Control convened in London in 2000 and confirmed the efficacy of EBRT in controlling pain caused by metastatic bone disease [6]. That group reviewed the efficacy of a single 8 Gy fraction, they better defined the proper use of radiopharmaceuticals for patients with widespread painful disease, and they recommended the standardization of response measurement that led to the development of the International Consensus on Palliative Radiotherapy Endpoints document. Finally, the Third International Consensus Conference Workshop was held in conjunction with the ASTRO meeting with representatives from ASTRO, European Society for Therapeutic Radiology and Oncology (ESTRO), Trans-Tasman Radiation Oncology Group (TROG) and Canadian Association of Radiation Oncology (CARO) in San Diego, California, in 2010 and called for both formal treatment guidelines and a means by which to enhance palliative radiotherapy efforts in developing countries around the world.

5. Formal radiotherapy bone metastases treatment guidelines

The American College of Radiology (ACR) Appropriateness Criteria format employs common clinical circumstances, or "variants", which serve as a means for an expert panel to vote upon the most appropriate interventions for that scenario (Table 1). The panel members collectively base their assessments upon the results of published literature, though the clinical experience of those experts may influence their decision-making, especially in situations where the available data set is incomplete. The bone metastases treatment panel consists of representatives from radiation oncology, nuclear medicine, orthopedic surgery, and medical oncology. The clinical case scenarios allow for recommendations about the best combination of interventions as well as an assessment of the proper radiotherapy treatment set-ups and fractionation schemes. While previous ACR publications have included all types of bone metastases situations in a single manuscript, the increasing complexity of treatment of spine metastases and spinal cord compression led to the division of "spine" and "non-spine" topics. The most recent update of the non-spine topic has just been published, while the spine topic update is still being formulated [7].

The first variant in the non-spine topic describes a patient with an excellent performance status, a favorable life expectancy, and an asymptomatic femur lesion which does not pose an obvious risk for pathologic fracture. While the authors acknowledge that research has begun to determine whether patients with boneonly metastatic disease and otherwise favorable findings may be treated aggressively, they stop short of endorsing curative-intent therapy for patients with "oligometastases" because the available data do not yet prove the usefulness of such an approach [8]. Their recommendations therefore call for an osteoclast inhibitor and a hormone blocking agent, with radiotherapy reserved for an oligometastatic treatment trial. The results of ongoing research may well come to indicate that patients in this most favorable clinical circumstance of metastatic disease should be treated more aggressively than others with less favorable prognostic indicators.

The second variant describes a patient with a good performance status who has a painful lesion in a weight-bearing bone. The task force defined the need for quickly establishing a pain medicine regimen while concurrently consulting an orthopedic surgeon to assess the need for surgical pinning to prevent pathologic fracture [9-11]. Given a low risk of fracture determined by the surgeon, the team recommended external beam radiotherapy (EBRT) based upon CT, fluoroscopic, or clinical simulation, with radiation delivery through anterior and posterior fields sparing a skin strip to minimize the risk of long term lymphedema of the extremity. While the panel detailed the pain relief equivalency between a single 8 Gy fraction and multifraction schedules, they pointed out the data which suggests that the use of fractionated regimens might minimize the risk of subsequent pathologic fracture in this setting [12]. The group essentially declared that pain relief equivalency has been conclusively determined for either single fraction or multi-fraction regimens, obviating the need for further research to examine that question. Finally, the existence of a fairly significant tumor burden in that patient led to recommendations for considering systemic chemotherapy and osteoclast inhibitors.

In the third variant, the patient has suffered a pathologic fracture from a lytic metastasis in a weight-bearing bone that required surgical stabilization. The panel recommended post-operative radiotherapy with 30 Gy in 10 fractions planned by CT, fluoroscopic or clinical simulation, with anterior and posterior opposed fields and a skin strip spared to once again minimize the risk of long term lymphedema. The vignette is valuable in its ability to highlight the need for orthopedic consultation to assess and provide surgical stabilization as well as the need for communication for the patient to receive the necessary post-operative adjuvant radiotherapy. Given a good performance status and significant tumor burden, recommendations were made for considerations of systemic chemotherapy, hormonal ablation treatment, and an osteoclast inhibitor.

The patient in variant number 4 has previously received palliative radiotherapy for a site of painful bony disease with

Table 1

Summary of recommendations regarding radiotherapy for bone metastases in the most recent guidelines from the American College of Radiology, the American Society for Radiation Therapy, and the National Comprehensive Cancer Network.

American College of Radiology Appropriateness Criteria Non-Spine Bone Metastases [7]	
Details of variant	Radiotherapy recommendations
#1—Excellent PS, favorable LE, asymptomatic femur lesion, minimal risk of pathologic fracture	RT only on trial
#2—Good PS, painful lesion in weight-bearing bone, some risk of pathologic fracture	Orthopedic consult, RT alone or post-op depending upon need for surgery
#3—Pathologic fracture in weight-bearing bone, status post surgical pinning procedure	Post-op RT to 30 Gy in 10 fractions, sparing a skin strip to minimize edema risk
#4—Recurrent pain following previous RT to same site of skeleton	Consider re-treatment RT, respect normal tissue tolerance, consider treatment protocol
#5—Short LE, visceral metastases, single site of painful bone metastasis PS=performance status, LE=life expectancy, RT=radiotherapy	RT with a single 8 Gy fraction to minimize patient discomfort and travel time
American Society for Radiation Oncology Bone Metastases Guidelines [2]	Conductors
Clinical question #1—When is single fraction radiotherapy appropriate?	Conclusions Single fraction radiotherapy is a reasonable option for all patients with painful bone metastases
#2—May spine lesions be treated with single fraction therapy?	Single fraction therapy is safe, effective, and convenient for patients with painful spine metastases
#3—Should long-term side effect risks limit the use of single fraction therapy?	
#4—When should patients receive re-treatment with radiation to peripheral bone metastases?	Re-treatment may be effective and safe, though the paucity of published data suggests a need to accrue patients to open trials
#5—When should patients receive re-treatment with radiation to spine lesions causing recurrent pain?	
#6—What role does highly conformal radiotherapy play in the primary treatment of painful bone metastasis?	Stereotactic body radiation therapy (SBRT) holds promise for the treatment of spine metastases, though data regarding its proper uses is still accruing
#7—When should SBRT be considered for re-treatment of painful spine lesions?	Spinal cord-sparing SBRT may be strongly preferable for the re-treatment of painful spine metastases, though data regarding its proper uses is still accruing
#8—Might radiotherapy be omitted in patients who undergo surgery or who receive radionuclides, bisphosphonates or kyphoplasty/vertebroplasty?	Radiotherapy is appropriate and necessary for most patients who undergo surgery or who receive other treatments for painful bone metastases
National Comprehensive Cancer Network Bone Metastases Treatment Recommendations [38–47]	
Clinical disease site	Radiotherapy recommendations
Non-small cell lung cancer	20-30 Gy in 5-10 fractions for metastases with soft tissue mass
Small call lung cancer	8–30 Gy in 1–10 fractions for metastases without soft tissue mass
Small cell lung cancer Kidney cancer	Radiotherapy can provide excellent palliation of painful bone metastases Consider radiotherapy with the goal of long-term progression free survival in patients
Runey Cancer	with single bone metastasis and controlled primary disease
Multiple myeloma	"Low dose" radiotherapy recommended to 10–30 Gy for bone pain, impending
Multiple mycloma	pathologic fracture, or impending spinal cord compression
Prostate cancer	8 Gy in a single fraction to non-spine lesions
	fractionated radiotherapy for spine lesions
	radiopharmaceuticals for widespread metastases
Thyroid cancer	Radiotherapy for painful bone metastases, without any suggestion of proper dose fractionation schema
Breast cancer	No mention of radiotherapy for painful bone metastases
Adult cancer pain guidelines	Radiotherapy should be considered for painful lesions which are likely to respond to antineoplastic therapies
Palliative care guidelines	No mention of radiotherapy for painful bone metastases

a good initial response, though their pain has recurred and the panel was tasked with evaluating the safety and efficacy of EBRT re-treatment to the same painful site. The panel described the available re-treatment data as being of low quality because it was mostly retrospective, single-institutional, and dated [13–18]. Given those limitations, the group recommended caution when treating volumes containing normal tissue structures which might suffer side effects from the combined palliative doses. The brachial plexus was found to be one normal tissue at risk in this particular case, and the team also reminded the reader to reevaluate the affected long bone for risk of pathologic fracture before offering re-irradiation. The panel therefore recommended treatment planned by CT, fluoroscopic, or clinical simulation, with anterior and posterior opposed fields sparing a skin strip to minimize the risk for upper extremity edema. Given limited data regarding the best dose to use in this setting, the panel recommended placing the patient on an available re-treatment protocol [19]. When completed, the results of that trial will need to serve as a template for the appropriateness of re-treatment to the same painful site, given the lack of prospective data available at this time. While the use of systemic chemotherapy was not thought to be wholly inappropriate, the patient's poor performance status and prognosis led the group to suggest that the patient be seen by a palliative care team and be given the option to choose hospice care.

The final variant deals with a patient who has a poor prognosis due to visceral metastases and who suffers from a single site of painful bone disease. The purpose of the case was to evaluate the panel's views of supportive care with analgesic medications plus or minus EBRT. The group did recommend EBRT for the patient, but they were specific in their belief that the dose should be limited to a single 8 Gy fraction in an effort to decrease time spent in treatment and discomfort from being transferred on and off the treatment table [20]. The likelihood of an increased need for retreatment to the same site in this patient is diminished by his short expected lifespan. It was recommended that CT, fluoroscopic, or clinical simulation may be used while preparing treatment through AP and PA directions while sparing a skin strip. Anti-inflammatory medicines were described as the best method to manage any temporary flare reaction that might occur

In its text, the ACR Appropriateness Criteria Bone Metastases Group suggested several general statements applicable to most or all five variants. First, EBRT was re-defined as an effective means to palliate the pain caused by metastatic bone disease, with rates of relief of 50%-80% and equivalence for fractionation schemes including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction [4,22,23]. The preferred treatment set-up and prescription points should follow those defined in the International Consensus on Palliative Radiotherapy Endpoints [24]. The group determined that the use of highly conformal therapy with intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), or proton therapy have not been proven for this subset of patients without spine disease. Lastly, the need for concurrent pain medicine dosing and palliative care was seen to be imperative, with hospice admission not viewed as being mutually exclusive with the delivery of palliative radiotherapy for bone pain.

6. American Society for Radiation Oncology (ASTRO) bone metastases guidelines

The American Society for Radiation Oncology (ASTRO) has only recently begun creating clinical treatment guidelines, especially when compared to the longstanding existence of the ACR Appropriateness Criteria. In 2009 the ASTRO Board of Directors tasked the Health Services Research Committee to create bone metastases treatment guidelines. The ASTRO group consisted of a neurosurgeon and palliative medicine expert as well as radiation oncologists from academic, private practice, and residency settings. The group was asked to create guidelines that were applicable to patients as well as healthcare providers, with one of the main themes being the integration of radiotherapy with other treatment modalities useful in the care of patients with painful bone metastases. The original literature search covered the most recent ten years of citations in the National Library of Medicine's PubMed database and yielded over 4000 publications. Within that group of papers were found 25 randomized clinical trials, 20 prospective single-arm studies, and 4 meta-analyses or systematic reviews. Given the complexity of the clinical situations involved in the care of these patients, the task force was divided into subgroups to concentrate on those issues that fit each individual's own expertise. The results of the subgroups' work were subsequently presented to the entire group, made available online for public comment, and approved by the ASTRO board of directors prior to publication [2].

The format of the ASTRO guidelines was based upon the task force answers to several questions posed by the board of directors. The first several questions dealt with the most appropriate external beam radiation therapy (EBRT) fractionation scheme to use for the treatment of painful bone metastases. While the rates of pain relief following EBRT appear to be similar across a wide array of dose fractionation schemes, one recent worldwide survey revealing that more than 101 fractionation schemes are used for this one clinical circumstance [25]. The first goal of the task force was therefore to narrow the list of acceptable fractionation schemes to those which have been sufficiently studied in adequately-powered trials. Similar to the ACR group, they documented that several prospective, randomized trials have evaluated different dose-fractionation schedules, with the results suggesting equivalence in pain relief after schedules including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction [2,4]. The advantage of single fraction radiotherapy was seen to be increased convenience and decreased expense for the patient and their caregivers, while multiple fraction therapy was advantageous because it is associated with a lower incidence of re-treatment to the same painful site than in single fraction treatment (8% versus 20%, respectively) [4]. In answer to concerns raised about the safety of a single 8 Gy fraction to anatomic sites historically considered to be sensitive to hypofractionated doses, the task force evaluated the literature but could not find any long term side effect risks that should deter clinicians from using a single dose to spine fields that contain the spinal cord or cauda equina [26].

The re-treatment of metastatic bone disease causing recurrent pain after an initial course of EBRT was seen to be feasible with a reasonable rate of symptom relief [13–19]. In echoing the ACR findings, the task force noted that the available data was derived from studies where re-treatment was not the primary endpoint studied, and that many of the descriptions of re-treatment were based upon small numbers of patients. Additionally, the authors cautioned that re-treatment may only be considered when taking into account the normal tissue tolerance of structures included in the treated volumes. The spinal cord and cauda equina were specifically mentioned as structures whose tolerance to the combined dosing must be taken into account when delivering a second course of EBRT to the spine.

Given significant interest in newer technologies amongst radiation oncologists and neurosurgeons, the ASTRO task force enthusiastically recognized the promise for improvements in care with highly conformal therapy which includes all technologies that can deliver higher doses to metastatic bone disease with a steep dose gradient to spare adjacent normal structures. The team focused their analysis on the potential benefits of stereotactic body radiation therapy (SBRT) for metastases in spine bones, though they described that the available data for this intervention has to this point been accrued in single institutional studies with small numbers of patients whose responses have been measured with novel treatment outcomes. As such, the task force suggested that patients who receive SBRT should strongly be considered for the available treatment protocols to better accrue data about efficacy and toxicity measures. The theoretical advantage of SBRT for sparing spinal cord or cauda equina in the re-treatment of recurrent, painful spine lesions was documented in much greater detail than was true in the ACR Appropriateness Criteria [27–32].

In an attempt to clarify confusion regarding the use of radiotherapy with other available interventions for painful metastatic bone disease, the ASTRO task force clearly stated that EBRT is still necessary in situations where patients receive surgery for spinal cord compression or long bone stabilization, intravenous radiopharmaceuticals for widespread bone disease, osteoclast inhibitors, or kyphoplasty or vertebroplasty for lytic lesions causing spinal instability [33-36]. Surgery was only recommended for patients with spinal cord compression who have a favorable prognosis and sufficient performance status to warrant the surgical risks and post-operative rehabilitation required for that degree of intervention. Radiopharmaceuticals were deemed most appropriate in patients with widespread, painful osteoblastic metastases that are apparent on a technetium-99 bone scan. While the use of osteoclast inhibitors was seen as being a reasonable means by which to palliate bone pain and promote re-ossification, the task force pointed out that there are no data to suggest that the palliation of a single site of metastatic bone pain is superior with osteoclast inhibitors plus EBRT versus EBRT alone. Finally, the task force described the theoretical advantage of using kyphoplasty or vertebroplasty for spinal instability caused by lytic metastases, though they shared the belief that the data proving those assumptions was mostly derived from retrospective, single institutional studies. In its conclusions, the ASTRO group suggested that future bone metastases treatment trials should be made uniform by the measurement of consistent variables as defined by the International Consensus on Palliative Radiotherapy Endpoints while also assessing functional domains and quality of life with validated instruments such as the European Organization for Research and Treatment of Cancer bone metastases quality-of-life questionnaire [24,37].

7. National Comprehensive Cancer Network (NCCN) and bone metastases treatment recommendations

The National Comprehensive Cancer Network is made up of experts from cancer centers of excellence around the United States who designate representatives to committees that evaluate data and provide treatment options for most common cancers [38]. While there is no specific NCCN group designated to evaluate the use of radiotherapy for bone metastases, the topic is dealt with to varying degrees in the publications which deal with primary diagnoses that are most likely to metastasize to bone. The NCCN Guidelines also include a wider variety of author specialty types for each clinical site than do the ACR and ASTRO guidelines. Furthermore, while radiation oncologists make up the majority of panel members on the ACR and ASTRO committees, radiation oncologists generally make up a distinct minority, or are a singular member, of the NCCN committees. As such, the NCCN guideline recommendations regarding radiotherapy for bone metastases are likely to result from less vigorous conversations and voting criteria than might be true for those offered by the ACR and ASTRO groups.

The authors of the NCCN non-small cell lung cancer guidelines provide the most guidance about radiotherapy dosing for painful bone metastases of any of the primary sites evaluated [39]. Bone metastases due to non-small cell lung cancer are separated into those "with soft tissue mass" versus those "without soft tissue mass", with recommendations for 20–30 Gy in 5–10 fractions for the former circumstance and 8–30 Gy in 1–10 fractions for the latter. The small cell lung cancer guidelines go so far as to only state that radiotherapy may provide excellent palliation of painful bone lesions [40].

The kidney cancer guidelines hint at the notion of radiotherapy for oligometastases, describing that long-term progression-free survival has been noted in patients treated with radiotherapy for a single bone metastases and controlled primary disease [41]. The multiple myeloma guidelines recommend a "low dose" of radiation therapy to between 10 and 30 Gy for bone pain, impending pathologic fracture, or impending spinal cord compression. The multiple myeloma authors caution clinicians to limit the volume of irradiated fields to minimize the impact upon bone marrow given the potential for additional chemotherapy or stem cell harvest [42]. The prostate cancer guidelines suggest that a single 8 Gy dose should be used to treat painful bone disease, though in contradistinction to the ACR and ASTRO guidelines, the NCCN prostate cancer authors suggest that vertebral metastases should receive a fractionated rather than single fraction dose. They also offer a recommendation to use radiopharmaceuticals such as strontium 89 or samarium 153 for widespread bony metastases [43]. Similarly, the thyroid cancer group only mentions EBRT in the setting of optimization of dosimetry for Iodine 131 for treatment of painful bone metastases [44]. The NCCN adult cancer pain guidelines suggest that radiotherapy be considered for painful lesions which are "likely to respond to antineoplastic therapies" [45]. Lastly, neither the breast cancer treatment guidelines nor the palliative care guidelines mention the use of radiotherapy for painful bone disease [46,47].

8. Implications of bone metastases guidelines

The publication of treatment guidelines may cause angst for practitioners, given justifiable concerns that their decision-making autonomy may be threatened by a need to pigeon-hole clinical circumstances into pre-determined bins. It is certainly true that third party payers and the Centers for Medicare and Medicaid Services are interested in using guidelines to reward literature-based patterns of care while questioning treatment patterns that deviate sharply from those data. Still, the advantages for the use of treatment guidelines include the provision of a minimum standard of care and a delineation of those topics which remain controversial enough to spur additional clinical trials to reach consensus on outcomes. The interest for the bone metastases treatment guidelines has been high, as is evidenced by the fact that the ASTRO bone metastases treatment guidelines were the most frequently downloaded articles in 2011 from the International Journal of Radiation Oncology, Biology, and Physics website [48]. One might foresee that ongoing interest in guidelines, in general, will spur more formal comparisons of formatting and content that will aid in standardization across the publications from different societies. This convergence of guidelines would most certainly decrease any discrepancies that currently exist in recommendations offered by the task force groups.

The National Quality Forum (NQF) has been tasked with measuring quality of care for specific clinical circumstances, to analyze reports of how frequently those quality measures are employed, and to provide guidance that improves patterns of care [49]. The Affordable Care Act requires that the NQF provide annual input to the Department of Health and Human Services regarding a National Quality Strategy that provides measures and tracks progress toward fulfilling those goals. The NQF Cancer Endorsement 2011 group will evaluate EBRT dose fractionation schemes for bone metastases treatment as its first potential measure of radiation oncology quality. If the NQF Cancer Committee and Board of Directors accept that measure, then the full implications of bone metastases guidelines will be ascertained.

Finally, virtually all of the guidelines products provide a disclaimer stating that the ultimate appropriateness of therapy relies on the judgment of treating physician while taking into account their experiences, the available clinical data, and the specific circumstances of the patient who is undergoing that care. Similarly, the details of the guidelines evaluated in this manuscript are available online and should be read in detail prior to making conclusive comments about their content and recommendations.

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