

## Brain metastases, end-of-life medical policies, and controversies surrounding the term “do not resuscitate”

Charles B. Simone II

Department of Radiation Oncology, Hospital of the University of Pennsylvania, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

Correspondence to: Charles B. Simone II, MD. Department of Radiation Oncology, Hospital of the University of Pennsylvania, Perelman School of Medicine at the University of Pennsylvania, 3400 Civic Center Blvd., PCAM, 2 West, Philadelphia, PA 19104, USA.

Email: charles.simone@uphs.upenn.edu.

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The October 2016 issue of *Annals of Palliative Medicine* features several notable publications on brain metastases. Brain metastases occur in approximately half of all patients with advanced cancer during the course of their disease (1). While brain metastases are often associated with a poor prognosis, intracranial disease can also be associated with a significant symptomatic burden. Patients with brain metastases commonly present with headaches, fatigue, and nausea, and they may also suffer from visual symptoms, focal weakness, difficulty with balance or ambulation, and seizures.

In an original report by Wong *et al.*, investigators analyzed 1,660 patients with brain metastases to determine the prognostic significance of pretreatment baseline symptoms (2). Fatigue and appetite loss were found to be most predictive symptoms of short overall survival. Following treatment with whole brain radiation therapy, which is one of the standard treatment options for intracranial metastases along with stereotactic radiosurgery, neurosurgical resection, and palliative measures alone (3,4), Wong and colleagues found that worsened difficulty with concentration, fatigue, nausea, and headaches were predictors of poor survival (2). These findings are in keeping with prior studies in patients with brain metastases that have reported an increase in symptom burden correlates with worse quality of life and overall survival (5,6).

A second original report by investigators from Odette Cancer Center, Sunnybrook Health Sciences Centre at the University of Toronto is the first to assess if whole brain radiation therapy treatment time impacts overall survival (7).

It is known that circadian rhythm affects cell cycle progression, and that radiosensitivity differs in differing phases of the cell cycle (8,9). In fact, in a prior report of stereotactic radiosurgery delivered with Gamma Knife for metastatic non-small cell lung cancer, better local control and survival were achieved when treatment was given earlier in the day versus later in the day (9). However, other studies have not found that time of treatment has significantly impacted survival on multivariate analysis (10).

Little data exist regarding how conventionally fractionated radiotherapy time of day impacts outcomes. Given the generally poor prognosis of patients treated with whole brain radiation therapy for brain metastases, this patient population is ideal for exploring therapeutic strategies such as chronotherapy that can potentially improve outcomes. Chan *et al.* retrospectively assessed a cohort of 755 patients treated with whole brain radiation therapy and found time of day in which treatment was delivered impacted overall survival among elderly females. When controlling for such factors as age and performance status, which can impact the time of day a patient is treated, the time of day did not significantly affect survival across the entire cohort (7). The current findings, however, underscore a need for prospective studies assessing how treatment time of day affects both clinical outcomes and treatment toxicities following external beam radiation therapy.

Also among patients with brain metastases, following the recent publication of the landmark N0574 randomized trial showing less cognitive deterioration and similar overall

survival among patients with 1 to 3 brain metastases treated with stereotactic radiosurgery alone compared with patients treated with stereotactic radiosurgery combined with whole brain radiation therapy (11), in this issue of *Annals of Palliative Medicine*, Ojerholm *et al.* author an insightful brain metastases commentary (12). They discuss the pros and cons of both stereotactic radiosurgery and whole brain radiation therapy and address how each radiotherapy modality effects intracranial disease control, overall survival, and neurocognitive toxicities. They also discuss the existing treatment guidelines for brain metastases, detail the strengths and limitations of N0574, and make recommendations for which patients are best served by being treated with each modality.

Also in this issue of *Annals of Palliative Medicine*, Weeks *et al.* quantitatively assess how end-of-life policy changes in France have impacted in-hospital death rates (13). Recent advances and interventions in France have been implemented in an attempt to reduce the high rate of inpatient deaths, including improving access to community-based palliative care, passing a “Patient’s Rights and End-of-life Care” act that clarifies end-of-life medical practices, changing reimbursement to discourage the use of inpatient palliative care beds, and establishing palliative care networks that coordinate home care (13,14). The investigators found declines in both cancer and neurological disease inpatient death rates, although notable differences were seen by department location within France. These findings are encouraging and suggest that deploying palliative care into the community can be successful and that efforts to reduce inpatient death rates among patients with cancer or neurological disease diagnoses can be effective. Given that the effectiveness of such efforts differed geographically, the authors suggest that targeted efforts to improve lower performing departments might provide the most substantial performance improvements.

Numerous assessment tools have been developed for palliative care, but no uniform consensus exists as to which tool is optimal among patients without neurocognitive failure admitted to a palliative care unit. In an original report (15), Gonçalves and colleagues performed a validation study demonstrating good reliability on one such tool that is relatively easy to administer and was previously selected for used by international experts in palliative care (16).

Next, Brugnoli authors a report on the use of clinical hypnosis for palliative relief of symptoms in patients with severe chronic diseases (17). He reviews the existing

literature on how clinical hypnosis can improve pain, anxiety, muscular contractions, tremors, rigidity, dyspnea, dysphasia, constipation, nausea, decreased appetite, sleep difficulties, and depression (18,19). He also details multiple hypnotic techniques that can be employed to attempt to achieve the mind-body and spiritual positive effects of hypnosis and improve quality of life (17). This manuscript serves as the foundation for a planned focused issue on clinical hypnosis in palliative care that will be featured in *Annals of Palliative Medicine* in 2017.

In the Palliative Radiotherapy Column, Tsao *et al.* report on an original study retrospectively assessing 47 patients with Kaposi sarcoma treated with radiation therapy in 1–10 fractions at a single cancer center (20). An 87% response rate was achieved with therapy, including a complete response in 30%. Reirradiation for progressive lesions was less successful, however, with no complete responses seen and half of these patients having continued disease progression. It should be noted that most of these patient (n=43) had classic Kaposi sarcoma, and so the results may not be completely generalizable to patients with Kaposi lesions associated with AIDS. This study does, however, significantly add to the previously limited literature on how Kaposi lesions respond to radiation therapy.

The new ethics column of *Annals of Palliative Medicine* makes its debut in the October 2016 journal issue. The ethics subcommittee chairman, Blair Henry, a senior ethicist at Sunnybrook Health Sciences Center in Toronto, Canada, authors a provocative and very interesting argument on why the classic use of term “do not resuscitate” (DNR) should be abolished (21). Dr. Blair discusses the controversies surrounding the three-lettered acronym and how this term has resulted in cases of legal disputes, distrust in medicine, and moral distress. Instead of the term DNR, he advocates replacing it with more precise terminology such as “no cardiopulmonary resuscitation”. He describes multiple studies in which the DNR order has impacted mortality rates of patients admitted to hospitals for a variety of causes and demonstrates that a DNR status can result in differences in treatments offered to patients (22,23). Dr. Blair also offers steps that can be taken to manage conversations regarding code status, and he underscores the importance of structure conversations between providers and patients and their families in order to best implement a patient’s wishes and values (21).

In a related article by Bradford, the relationship between DNR status and mortality is further described and put into

the context of palliative care research. He also differentiates early (within 24 hours of admission) and late DNR orders, with an early decision for DNR potentially more likely to represent a patient with significant baseline comorbidities and a late DNR order more likely to represent treatment failure for the presenting diagnosis. The article also champions improve documentation of limitations of care beyond DNR to reduce the ambiguity of the term itself, and to account for patient limitations of care when conducting and interpreting comparative effective research (24).

Also in this issue of *Annals of Palliative Medicine*, Kissane authors an interesting editorial on the challenge of family-centered care in palliative medicine (25). It is well described that advanced disease affects both the patient and their family. Family caregivers have distress over emotionally coming to terms with disease progression, managing caregiving, coping with uncertainty, and responding to suffering of their loved ones (26,27). This editorial addresses who is considered family, knowing when a family is in need, and psychosocial interventions to support caregivers. The article also provides recommendations for structured models of family-centered care (25).

This issue of *Annals of Palliative Medicine* also features two case reports. The first is a report on the use of palliative care in a patient with Lambert-Eaton myasthenia syndrome, a rare autoimmune idiopathic paraneoplastic syndrome (28). In the second, a case highlighting a potential role of aprepitant, a substance P antagonists, to treat radiation-induced nausea and emesis is presented (29).

The issue is concluded by a report on the exciting news that *Annals of Palliative* is now indexed in Emerging Sources Citation Index (ESCI) and in Scopus (30). Following the news that *Annals of Palliative Medicine* became indexed in PubMed in early 2015 (31), these new milestones for the journal are critical for the continued growth and success of the journal that we hope will allow for the journal to become indexed in Science Citation Index Expanded (SCIE) and achieve an official impact factor, which we hope will occur before the end of 2017.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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