

Editor's note:

Palliative Radiotherapy Column” features articles emphasizing the critical role of radiotherapy in palliative care. Chairs to the columns are Dr. Edward L.W. Chow from Odette Cancer Centre, Sunnybrook Health Sciences Centre in Toronto and Dr. Stephen Lutz from Blanchard Valley Regional Cancer Center in Findlay, gathering a group of promising researchers in the field to make it an excellent column. The column includes original research manuscripts and timely review articles and perspectives relating to palliative radiotherapy, editorials and commentaries on recently published trials and studies.

Palliative Radiotherapy Column (Review Article)

Incorporation of life expectancy estimates in the treatment of palliative care patients receiving radiotherapy: treatment approaches in light of incomplete prognostic models

Nicholas Chiu¹, Leonard Chiu¹, Stephen Lutz², Na Zhang³, Breanne Lechner¹, Natalie Pulenzas¹, Marko Popovic¹, Carlo DeAngelis¹, Milica Milakovic¹, Ronald Chow¹, Edward Chow¹

¹Department of Radiation Oncology, Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, ON, Canada; ²Department of Radiation Oncology, Blanchard Valley Regional Cancer Center, Findlay, Ohio, USA; ³Liaoning Cancer Hospital & Institute, Shenyang 110042, China

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Correspondence to: Dr. Edward Chow, MBBS, MSc, PhD, FRCPC. Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada. Email: Edward.Chow@sunnybrook.ca.

Abstract: Physician estimates of patients' survival times have historically been inaccurate. In particular, physicians have often been overly optimistic in their predictions. Our review begins by documenting some of the literature addressing these concerns and proceeds to a discussion of prognostic models that have been created to aid physicians in providing more accurate estimates. We then discuss new findings showing survival to be influenced by particular treatment factors. Given such findings, currently existing prognostic models are now incomplete. However, with the abundance of evidence-based treatment options in a wide variety of patient populations, we propose that radiation oncologists need no longer rely so heavily on the precise prognostic capacity of survival models. Patients of different age demographics and survival prognoses benefit from palliative radiation treatment. More specifically, our report documents studies which show that for uncomplicated bone metastases, a single 8 Gy fraction of radiation is an equally effective tool for palliation regardless of whether a patient will have a short or long duration of survival. In addition we discuss evidence-based treatment options for patients with complicated bone metastases, lung and brain metastases. Further research is required to incorporate treatment factors in future survival prediction models.

Keywords: Radiotherapy; survival; prognosis; palliative

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Introduction

For patients with advanced cancer, an estimate of life expectancy is an important consideration. The significance of such a prediction is three-fold: first, patients and family members may wish to plan for their remaining time together and address end-of-life issues; second, medical professionals must make appropriate decisions regarding treatment and the planning of supportive services; and third, the allocation of resources to provide optimal treatment may vary in response to different life expectancy estimates (1). In light of abundant evidence of the persistent inaccuracy of physician estimates of life expectancy (2,3), several prognostic models have been developed to provide more accurate life expectancy estimates in patients with incurable cancers (4). Despite the acknowledgment of practical value in several such models, further research has now led to the recognition that prognosis also depends on choices of treatment (5-7) which have not yet been incorporated in currently existing models. The purpose of this paper is to provide a background on the area of life-expectancy estimates in palliative cancer, and to discuss an appropriate treatment approach moving forward in light of the now incomplete nature of the existing prognostic models.

Inaccuracy of life-expectancy estimates

Physicians are often required to predict survival at times of referral to hospice programs and at enrollment of patients into clinical trials. However, inaccuracy of life-expectancy estimates on the part of physicians has been well-documented (1-3,8-10). In particular, physicians tend to be overly-optimistic in their survival predictions (2,9,10), although the reverse has been found to be true as well (8). In 2000, Christakis *et al.* found that 63% of physician estimates were over-optimistic while 17% were over-pessimistic (9). Another study done in 2005 which examined six radiation oncologists providing survival estimates for 739 patients found that, on average, estimates were more than 3 months greater than actual survival time (2). Overall, the results showed a striking disparity between actual survival times versus those predicted by physicians.

Negative consequences may be associated with both a patient's and a physician's inaccurate optimistic beliefs about survival time. Choices for appropriate treatment options made on the part of physicians are dependent on accurate approximations of survival time. Furthermore, overly

optimistic survival predictions may lead to inadequate delivery of palliative care or may deter palliative care involvement at an earlier stage (11). Weeks *et al.*, who conducted a study of 917 adults, found that patients who believed they would live for at least 6 months were two times more likely to favor life-extending therapy than comfort care when compared with patients who believed they had at least a 10% chance of dying within 6 months (3). Furthermore, the study found that patients greatly overestimated their odds of surviving 6 months, even when physician estimates were less optimistic and more accurate. Such patients preferring life-extending therapy were more likely to undergo aggressive treatment; however, controlling for known prognostic factors, their 6-month survival was no better (3). Evidently, inaccurate perceptions may lead both patients and physicians toward unrealistic expectations that may direct them to treatment options they would otherwise not have elected to undergo.

Lamont *et al.* investigated physician estimates further and reported that physicians would not communicate any survival estimate to patients 22.7% of the time. Furthermore, they would communicate the same estimate that they formulated 37% of the time, and would communicate a different estimate than the one they personally formulated 40.3% of the time (12). More strikingly, of these consciously altered predictions, 70.2% of them were overly-optimistic (13).

To understand and address the difficulty of predicting survival in advanced cancer patients, Lamont *et al.* divided prognostication into two distinct elements: foreseeing and foretelling (12). The authors defined foreseeing as the physician's silent, cognitive estimate of a patient's illness. On the other hand, foretelling was defined to be the physician's communication of that estimate to the patient. Based on this dichotomy, Lamont *et al.* raised the point that physicians often make unconscious errors in foreseeing patients' prognoses due to an optimism bias; however, they also make conscious errors in foretelling prognoses to patients due in part to the possible belief that reporting unfavorable prognoses may compromise their patients' survival and quality of life. They concluded by re-addressing the importance of providing truthful, accurate estimates to patients and recommended greater reliance on actuarial predictions from prognostic models. This sentiment is echoed by Parkes *et al.* in a commentary recommending that prognosis be based on proven indices rather than intuition (14).

Predictive model for survival

In recognition of the practical use of accurate survival estimates in guiding patient and physician decisions, a predictive model for survival in metastatic cancer patients attending an outpatient palliative radiotherapy clinic was published in 2002 (15). Six prognostic factors were identified as having a statistically significant impact on survival: primary cancer site, site of metastases, Karnofsky performance score (KPS), and fatigue, appetite, and shortness of breath as assessed by the Edmonton Symptom Assessment Scale (ESAS). Risk groups were stratified using two different methods: (I) assigning weights to the prognostic factors based on their levels of significance; and (II) based on the number of risk factors (NRFs) present. The final model generated three different risk groups with different probabilities of survival based on either a weight-assigned Survival Prediction Score (SPS) or based NRFs. This model successfully underwent temporal validation using an independent data set (16).

Due to the difficulty of collecting information for all of the prognostic factors under certain circumstances, a simpler model was developed and validated in 2008. It included only the three readily-available parameters: primary cancer site, site of metastases, and KPS. Both the original and simplified models separated patients into three prognostic groups and predicted their survival similarly using both the SPS and NRF methods. As there was no statistically significant difference in the performance of the models, the use of the three-variable NRF model was favored due to its relative simplicity (16). The NRF model was further validated in another study by Glare *et al.* in 2014 (17).

While the models have received support, the SPS model was critiqued in a Norwegian study by Angelo *et al.* (18). In particular, the study found that while the model performed well in patients ≥ 60 years of age, it was not satisfactory in younger patients. As such, they recommended that the SPS model be used mainly to predict survival of elderly cancer patients.

Treatment-dependent prognosis: a shortcoming for predictive models of survival

Despite the support and validation of prognostic models for predicting survival, emerging evidence that prognosis may also depend on treatment has rendered most predictive models of survival incomplete. Three separate articles

published in the *New England Journal of Medicine* have each found that prognosis depends on type of treatment received. In 2004, Tannock *et al.* found statistically superior survival for patients treated with docetaxel every 3 weeks after given prednisone, when compared with those treated with mitoxantrone and prednisone (6); in 2010, Temel *et al.* found that median survival was longer among patients receiving early palliative care (5); and in 2013, Parker *et al.* showed that Radium-223 significantly improved overall survival when compared with placebo (7).

Given the evidence of treatment-dependent factors influencing survival, it is important to assess whether any existing prognostic models capture such phenomena. In a review published in 2013, Krishnan *et al.* identified models that had been created to aid physicians in predicting prognosis in patients with solid tumors (4)—all of them neglect the treatment factors previously discussed. Similarly, Krishnan *et al.*'s newly developed TEACHH model (19) also neglects the previously mentioned treatment factors.

Moving forward in light of incomplete traditional prognostic models

With traditional prognostic models built on patient and tumor factors only, findings that prognosis also depends on treatment-related factors leaves existing models incomplete. New models should take such factors as well as the treatment response into account. However, given the abundance of evidence-based treatment options in a wide variety of patient populations, we propose that radiation oncologists need no longer rely so heavily on the precise prognostic capacity of survival models. Instead, appropriate treatment decisions can be reached without these models based on the evidence-based findings now available.

Historically, deliberation of appropriate treatment in radiation therapy (RT) has concerned itself with the proper choice between single and multiple fraction regimens (20). This choice is of importance: for patients and their families, a single fractionation requires fewer tiring and painful visits to the hospital, and for radiotherapy programs, use of single fractions lowers costs and allows for more economic use of limited resources (20). Various studies are now available to address the aforementioned concerns and to help resolve variations in patterns of practice.

Standard treatment for uncomplicated bone metastases

In terms of treating patients with uncomplicated bone

metastases, the use of single fraction RT has been shown to be equally effective. A 2011 systematic review analyzed all published randomized controlled trials comparing single fraction versus multiple fraction radiotherapy schedules for the palliation of uncomplicated bone metastases (21). In the 25 randomized controlled trials identified, no significant difference was seen in overall or complete response rates. Guidelines by the American Society for Therapeutic Radiology and Oncology have also recommended that single fraction radiotherapy be implemented as the standard of care (21).

The effectiveness of a single fraction has been investigated for uncomplicated bone metastases patients with shorter survival as well. Since the decrease in pain is not immediate after radiotherapy, and may in fact be preceded by an increase in pain (22,23), concerns existed that patients with shorter life expectancies might not benefit as much from radiotherapy in general. In a prospective study, Dennis *et al.* analyzed Brief Pain Inventory (BPI) responses from patients who died within 3 months of radiotherapy (24). The authors found that overall pain response rate was 78% at the 1-month follow up and 83% at the 2-month follow up. In another study examining the shorter-survival patient population, the Dutch Bone Metastasis Study randomized 1,157 patients with uncomplicated painful bone metastases to receive either single fraction (1×8 Gy) or multiple fraction (6×4 Gy) radiotherapy (25). Those patients with a survival of ≤12 weeks after randomization were included for analysis. Between the single fraction and multiple fraction groups, the proportion showing a pain response did not differ. As such, the authors concluded a single fraction should be preferred in patients with short survival.

In addition, the Dutch Bone Metastasis Study also compared the effectiveness of single versus multiple fraction radiotherapy in patients with more favorable prognosis (20). Specifically, of those 1,157 patients studied in the original article, van der Linden *et al.* examined the 320 patients surviving >52 weeks. The study found that responses were 87% after 8 Gy single fractionation and 85% after 24 Gy in 4 fractions. The authors thus concluded that single fraction radiotherapy should be the standard dose schedule even for patients with an expected favorable survival (20).

Another treatment dilemma for RT that has been documented, and which has subsequently been addressed, is whether elderly patients with painful bone metastases should be offered palliative radiotherapy (26,27). Several papers have documented age as a deterring factor in patient referral for palliative radiotherapy due to the fear of inefficacy and

potential toxicities (28-32). In a prospective study, Campos *et al.* found no significant difference in the response rate in patients aged ≥65, ≥70, and ≥75 years compared with younger patients at 1, 2, or 3 months after radiotherapy (26). The authors concluded that elderly patients should indeed be referred for palliative radiotherapy. Another study published in 2014 which grouped patients into three age cohorts, also found no significant difference in pain response between the three cohorts (A: <65; B: 65-74; C: ≥75) (27).

Thus, given the aforementioned evidence-based recommendations, it seems that knowing a patient's true survival prognosis may not be as much of a necessity in guiding treatment decisions as previously believed. We may not need to know the precise prognosis; however, it is important to be able to differentiate patients who may only live for days/few weeks from those expected to live for months with high degree of certainty because this will affect whether we give treatments/radiation or not.

Patients of different age demographics and survival prognoses do indeed benefit from palliative radiation treatment. More specifically, in the case of uncomplicated bone metastases, a single 8 Gy fraction of radiation is an equally effective tool for palliation regardless of a patient's duration of survival. However, despite the abundance of evidence, several studies have specifically documented the continued prescription of unnecessary multi-fraction schedules, and have noted continued global reluctance to practice evidence-based medicine in this area (33,34).

Standard treatment for complicated bone metastases

Unlike those with uncomplicated bone metastases, certain patients with complicated bone metastases may benefit from multiple fraction radiotherapy (21). In particular, effective treatment procedures have been investigated in complicated bone metastases patients suffering from associated neuropathic pain, spinal cord compression/cauda equina syndrome, and pathological fracture. As such, distinguishing from uncomplicated and complicated bone metastases cases is an important aim in guiding treatment decisions for the two patient populations.

Neuropathic pain is defined as pain as a result of injury or dysfunction of the nervous system (35). In 2005, Roos *et al.* published a phase III randomized trial comparing the efficacy of 8 Gy in 1 versus 20 Gy in five fractions of radiotherapy in a study population comprised of patients with bone metastases causing neuropathic pain (35). Roos

et al. found that single fractions were not as effective as multiple fractions using point estimates, although these findings were not statistically significant. The authors recommended that multiple fractions be used for this patient population, but cautioned that patients with difficulty making multiple hospital visits could be better served with a single fraction.

Metastatic spinal cord compression (MSCC) is a common and debilitating complication of cancer (36). While hypofractionated radiotherapy is often used as a treatment in MSCC, a phase III randomized trial comparing a short-course of 8 Gy \times 2 to a single 8 Gy found no difference in response between the two RT schedules (37). Another phase III randomized trial investigated the efficacy of short-course RT (8 Gy \times 2 days) versus split-course RT (5 Gy \times 3; 3 Gy \times 5) (38). This study found no significant difference in response, duration of response, survival, or toxicity between the two arms. The authors recommended the use of the short-course regimen due to its advantages in terms of patient convenience and machine time. Other studies have also shown the benefit of direct decompressive surgical resection in the treatment of MSCC (36), and the escalation of radiation dose beyond the common 30 Gy in 10 fractions used as the most frequent schedule worldwide (39). Support for multiple fraction RT for fracture caused by metastatic disease was published early by Townsend *et al.* in 1995 (40). Consequently, post-operative dosing typically continues to be done in multiple fractions.

Radiotherapy treatment for brain metastases

Brain metastases pose as a significant challenge for health care, with 20-40% of cancer patients developing brain metastases during the course of their illness (41). In 2005, Tsao *et al.* published a systematic review of randomized trials on cancer patients with single or multiple brain metastases (41). The authors found no difference in neurologic function improvement or overall survival with the use of altered whole brain dose fractionation schedules when compared with standard fractionation schedules (30 Gy in ten fractions or 20 Gy in five fractions).

Further research into the appropriate palliative treatments for patients with brain metastases arising from non-small cell lung cancer (NSCLC) was conducted by Langley *et al.* (42). In a randomized, non-inferiority, phase III trial, Langley *et al.* investigated the effectiveness of optimal supportive care (including steroids) plus whole

brain radiation therapy (WBRT) compared with optimal support care (OSC) alone. No early evidence of detriment to quality of life, overall survival, or quality-adjusted life years (QALYs) was found for patients allocated to OSC alone.

Studies have also been done to uncover optimal treatment strategies for the palliation of patients with lung cancer. In particular, a randomized phase III trial comparing 10 Gy single-fraction RT with 20 Gy in 5 fractions for the palliation of thoracic symptoms from lung cancer found that patients in the fractionated RT group had greater improvements in symptoms, pain, ability to carry out normal activities, and global quality of life as assessed by the Lung Cancer Symptom Scale (43). A later systematic review of randomized controlled trials published in 2008 by Fairchild *et al.* found a greater likelihood of symptom improvement in patients undergoing schedules of 35 Gy in 10 versus that of lower biologically equivalent doses (BED) (44).

Conclusions

While accurate survival estimates have been documented as an important consideration in the care of end-of-life patients and their families, recent findings of treatment-dependent factors influencing survival have left current prognostic models incomplete. Nevertheless, given the now abundant literature on evidence-based RT treatment strategies, radiation oncologists need not rely as heavily on survival estimates in guiding their treatment decisions. In particular, we echo the collective recommendations laid out by evidence-based studies. More research is required to incorporate treatment factors in future survival prediction models.

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Footnote

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