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Reply to Serin et al

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Dear Dr. Portenoy

We thank Serin et al. for their probing questions about our study¹ and appreciate this opportunity to respond and to clarify our results. We agree that age is an important consideration, as associated comorbidities and physiology may impact functional reserve and, potentially, tolerance to radiation therapy (RT). Indeed, epidemiologic data demonstrating 60% of cancer diagnoses, and 70% of all cancer deaths, occur in individuals age 65 or older.^{2,3} In our study, we did not exclude patients based on age. Though our mean age is 58.6, we report a standard deviation of 12.6 in Table 1, reflecting at least 30% of patients to be age 65 or older. Importantly, as shown in Table 1, there was no statistically significant association between age and use of radiotherapy, thus, not meeting our criteria as a statistical confounder that would need to be accounted for in our modeling of quality of life outcomes.

The majority of retrospective studies on radiation as a single modality do not reveal significant differences in tolerance to radiation between elderly and younger patients;⁴ however, the combination of radiation and chemotherapy has been shown to increase acute toxicity in the elderly.⁵ Current ASTRO guidelines recommend against combining palliative RT with chemotherapy, as there is no evidence to demonstrate improved outcomes.⁶ With appropriate patient selection and utilization of palliative RT, patients experience benefit regardless of age. We would like to point out that the pivotal trials assessing benefit of palliative RT enrolled patients with median age of 65 or older,^{7,8,9,10} or mean age of 64,^{9,10} and showed tolerability and pain control in the entire patient cohort. At present, advanced age in and of itself should not be used as an exclusion criteria for palliative RT; better selection criteria are needed.

Accurate evaluation of pre-existing comorbidities is also important when selecting patients for palliative therapy. The Charlson comorbidity index (CCI), originally published in 1987, was selected for several reasons. Though not perfect, it is the most commonly utilized index,

validated in numerous studies, including cancer and elderly patients.^{11,12} Thus, the reported CCI in our patient cohort can be readily compared to measurements from other studies. We strived to define comorbidity as the burden of illness unrelated to the cancer diagnosis, to avoid confounding. As such, it is preferable that hematological parameters are not taken into account. In addition, the CCI was significantly associated with other measures of physical dysfunction and disability such as the ECOG performance status score and the McGill measures of symptom burden and quality of life (data not shown), and neither CCI or ECOG status were significantly associated with RT use. Thus, our results are unlikely to have changed if we had used other measures of physical dysfunction.

Though Serin et al. argue that CCI has limitations in discriminating mild versus moderate comorbidity, the papers cited are not relevant to our particular study for two reasons; first, the Nakaya et al. publication focuses exclusively on a Japanese subset of patients, validating the CCI in a non-Western patient cohort; Yurkovich et al. point out flaws in use of CCI in administrative health dataset and acknowledge that a limitation in their study is their specific focus on administrative data alone, without evaluation on chart reviews or patient-reported data.¹³ Our study did not use an administrative health dataset, but extracted records from medical charts.

To establish guidelines, the American Society of Radiation Oncology (ASTRO) provided measures of quality palliative RT, supporting use of short RT regimens ranging from 1 to 10 treatments total.⁶ Advanced techniques such as intensity modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT) and use of concurrent chemotherapy are not recommended except within the confines of a clinical trial.^{6,14} Palliative RT takes weeks to months to take effect,¹⁵ and yields the most benefit when delivered early during the disease trajectory, when patients live long enough to benefit. Administered appropriately, RT can reduce pain, shrink tumors and even, as we found in our study,¹ improve overall quality of life in patients with advanced cancer. However, when RT is administered close to death in patients with poor performance status, we find it lacks efficacy,¹ consistent with studies demonstrating that approximately 50% of patients experiencing worsening symptoms despite treatment.¹⁶ Though shorter course regimens may have need for retreatment, this is likely not a relevant consideration in patients with short life expectancy, who will not live long enough to experience recurrence of pain. Studies finding retreatment rates to be higher with single fraction radiation note at least 3 month follow up was required to assess need for additional RT. The median life expectancy of our patient cohort was 3.8 months.

Clearly, the decision to deliver palliative RT requires careful evaluation of a combination of factors, including prognosis, comorbidities, performance status, concurrent systemic therapy, as well as overall impact on patient's quality of life. We agree that lack of RT details in our study is a limitation, but we hope to address this in the future by collecting this in our currently ongoing studies.

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