Radiation de-intensification for patients with glioblastoma and poor prognostic features—how much do we really know?

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The effect of radiation dose on survival for patients with glioblastoma has been investigated since the first clinical trials demonstrating the benefit of adjuvant radiation therapy (RT) were reported.¹ It is important to note that radiation dose, in a radiobiological sense, depends on several factors (including dose per fraction and total treatment time) in addition to total radiation dose. Courses of radiation shorter than “standard fractionation” (60 Gy in 30 fractions over 6 wk) may represent either intensification or de-intensification of radiation dose, depending on the dose per fraction. For patients with older age or poor performance status, there has been interest in shorter, de-intensified courses of radiation with the hypothesis that these patient populations may not benefit from more aggressive therapy. Shorter courses of RT (or omitting RT altogether) would perhaps offer better quality of life and conservation of resources in that context.

As a foundation for determining the value of radiation in older patients, Keime-Guibert et al² showed that radiation offers a survival benefit versus supportive care alone for patients ≥ 70 years old with KPS ≥ 70 (median 29.1 versus 16.9 wk, hazard ratio [HR] 0.47, $P = .002$). The survival curve separated almost immediately, suggesting that people with the worst prognosis in this population still had some benefit. But there is some evidence that shorter, de-intensified courses of RT may be equivalent to or better than standard fractionation. The Nordic trial suggested a survival benefit to 34 Gy in 10 fractions versus standard fractionation in a subgroup analysis of patients ≥ 70 years old,³ and Roa et al⁴ reported that 40 Gy in 15 fractions over 3 weeks was not worse than an absolute survival decrement of 13.7% at 6 months compared with standard fractionation. Recently reported were the results of the International Atomic Energy Agency's (IAEA) E33033 trial, which randomized “elderly” (≥ 65 y) or “frail” (KPS 50–70) patients to 40 Gy in 15 fractions (with a different target volume than the prior study) versus 25 Gy in 5 daily fractions over one week in an attempt to further de-intensify therapy.⁵

The IAEA trial found no differences in overall survival, progression-free survival, or health-related quality of life between the two arms.⁵ How these data are interpreted will likely depend more on the semantics used to characterize them than on the data themselves, however. The authors describe the

study as a “phase III, randomized, international, multicenter, prospective, *non-inferiority* trial” (emphasis mine). If the take-away is that a 1-week course of dose de-intensified RT is “non-inferior” to 3 weeks, as the authors claim, it would follow that 1-week courses of RT can be given to “elderly” or “frail” patients with confidence that survival is not adversely impacted. But is E33033 a non-inferiority trial and can the data be easily interpreted and applied to individual patients?

Non-inferiority trials seek to determine whether a treatment is not worse than a reference treatment *by a prespecified amount* related to a clinically meaningful efficacy difference, an essential component given that proving exact equality is impossible.⁶ The null hypothesis is inferiority, and operating characteristics are reported to reject inferiority at the specified level with larger sample sizes needed to exclude smaller effect differences.⁶ Is E33033 a non-inferiority study by these criteria? Does it matter?

In the Methods section, the authors state that they assumed that going from 1 week to 3 weeks of radiation would be associated with an improvement in survival of 15% and that 144 events would be needed to detect an HR of 1.61 with a “power of 80% and a significance level of 5%.” These are the methods of a superiority trial: defining operating characteristics to detect a hypothesized effect size with a null hypothesis that there is no difference in treatments. Similarly, the results reported only that the median overall and progression-free survival times were “not inferior,” citing *non-significant* P -values of .988 and .716, respectively, implying nonrejection of a null hypothesis more suitable for superiority trials. Furthermore, an interim analysis was planned once two thirds of the expected patients enrolled, which seems to be when the study was terminated. Why would the study stop when enrollment of the intended cohort would have improved our confidence in the degree of non-inferiority? Based on the authors' description of the design, conduct, and results of the trial, E33033 can be more accurately characterized as a negative superiority trial.

Does it matter what we call it or how the data are presented? It does, in at least two ways. The first is that a positive non-inferiority trial is more attractive than a negative superiority trial, so there is potential for publication bias and acceptance

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without more critical evaluation. The second is that there are not enough data presented to determine what efficacy differences could be excluded by the data. There are no estimates of hazard ratio and, more importantly, no confidence intervals so that readers may judge whether a clinically significant effect difference might be still possible. For example, in the prior trial reported by Roa et al, readers may decide for themselves whether a 13.7% absolute survival difference at 6 months is a small enough effect size to claim non-inferiority, more of a values-based judgment than a statistical one. The data from E33033 are not similarly presented and do not allow the reader the same value judgment.

Furthermore, in the era of precision medicine, the study and reporting of hypothesized biomarkers require additional scrutiny. Age and performance status, in their suggested capacity to interact with treatment effect, can be considered biomarkers in the same vein as immunohistochemical analysis or genotyping. By including age and performance status as an “either/or” entry criterion, E33033 implies equivalence in terms of their predictive capacity. Is this equivalence justified? Probably not—age is associated with tumor biology, for example, and while advancing age may be associated with worse prognosis generally, biological similarities (or differences) in how tumors respond to radiation may mitigate (or enhance) this relationship. KPS is also subjective and varying. It is true that sufficiently bad prognostic markers can serve as predictive markers by swallowing potential therapeutic signals in poor prognosis noise, and this was perhaps the intent. But going forward, we should be more explicit in investigating the possible linkages between individual biomarkers and treatment effects rather than assuming a broad linkage based on eligibility criteria. The relationships between varying levels of radiation dose intensification and potential biomarker categories are not well understood and more data are needed.

Clinical decision making involves tradeoffs. Efficacy and toxicity are commonly considered tradeoffs, but so too should confidence in data to be applied. In the case of the E33033 study, there was nothing beneficial for patients in terms of improvements in health-related quality of life, and the reduction in health resource utilization is likely to be small and addressable by other means (such as reference pricing or bundling). Given the limited potential benefit, we should demand a high degree of confidence that survival is not impacted, and E33033 does not provide such confidence or the data to make a values-based judgment on a claim of non-inferiority. Certainly there are patients for whom prognosis is poor enough to limit benefit from more aggressive courses of radiation—but

which clinical characteristics or other biomarkers define such a group are not clear. A 65-year-old patient with a KPS of 100 is likely not the same as an 85-year-old patient with a KPS of 50, and limited confidence in the available data regarding radiation dose de-intensification may lead to variability in applying the results.⁷ Additionally, many of the studies that report radiation dose de-intensification do so in the absence of temozolomide. Taken together, there are data to support radiation dose de-intensification for older patients, but applying data to individual patients remains challenging, and treatment with standard fractionation RT with concurrent and adjuvant temozolomide or enrollment on clinical trials for select older patients are still very reasonable options. Furthermore, future trials of radiation intensification or de-intensification in glioma should take into account the molecular profile of the tumor, which will be increasingly used to define the disease and through which individual associations between biomarkers and treatment effects may be hypothesized.

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