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Randomization failure in palliative care RCTs

In an ambitious randomized clinical trial (RCT), the Danish Palliative Care Trial (DanPaCT)[1] compared early integrated specialist palliative care against usual care in 297 patients with advanced cancer. Acknowledging the challenges of implementing large palliative care trials, DanPaCT should be lauded for its large sample size, follow-up duration of nearly three years, and patient-centeredness, uniquely tailoring the primary outcome to each patient's primary need.

These strengths notwithstanding, DanPaCT was potentially pessimistically biased against the early integrated palliative care group due to randomization failure. Relative to the palliative care group, controls were more likely to have cancers of the breast or digestive system (35% v 48%, P=.02), which are potentially less aggressive. There was a trend for the palliative care group to have more patients with lung cancer (39% *v* 30%, P=.10), which is often more aggressive. There were no differences in "other" cancers. Essentially, the deck was stacked against the early integrated palliative care group because – despite randomization – the patients likely had more aggressive diagnoses.

Unfortunately, this critique is not unique to DanPaCT, as two other large RCTs[2,3] of outpatient palliative cancer care have also fallen victim to randomization failure and yielded null findings. In a cluster RCT of 146 patients in the U.S.,[2] the palliative care group included 56% with lung cancer, relative to 0% of controls (P<.0001). Similarly, in a cluster RCT of 434 patients in Norway,[3] there was a trend for patients in the palliative care group to be more likely than controls to have lung cancer diagnoses (46% *v* 37%, P=.058), as opposed to less aggressive cancers. In each case, these were null findings, and the direction of the effect was actually negative.

To avoid these issues, it would be helpful for investigators to consider confounding prospectively when planning palliative care RCTs, especially when including patients with heterogeneous cancer diagnoses. Methodologically, stratification by diagnosis, stage, or performance status can help to ensure that groups are comparable with respect to baseline quality of life and expected prognosis.[4] Statistically, analytic plans should prespecify relevant confounders and control for them as covariates.[5] This can correct for potential imbalance, and even when imbalance is negligible, this can provide for greater precision in estimating intervention effects.[5]

With the American Society of Clinical Oncology guidelines[6] now recommending early integrated palliative care for all patients with advanced cancer, clinicians are more aware of palliative care research findings. Negative trials can discourage the earlier integration of palliative care, even when trials have flaws. Greater attention to methodology is needed to avoid unwarranted pessimism about palliative care.

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References

1. Groenvold M, Petersen MA, Damkier A, et al. Randomised clinical trial of early specialist palliative care plus standard care versus standard care alone in patients with advanced cancer: the Danish Palliative Care Trial. *Palliat Med*. Epub ahead of print 1 May 2017. DOI: 10.1177/0269216317705100.
2. McCorkle R, Jeon S, Ercolano E, et al. An advanced practice nurse coordinated multidisciplinary intervention for patients with late-stage cancer: a cluster randomized trial. *J Palliat Med* 2015; 18: 962–969.
3. Jordhøy MS, Fayers P, Loge JH, et al. Quality of life in palliative cancer care: results from a cluster randomized trial. *J Clin Oncol* 2001; 19: 3884–3894.
4. Suresh KP. An overview of randomization techniques: an unbiased assessment of outcome in clinical research. *J Hum Reprod Sci* 2011; 4: 8–11.
5. Kahan BC, Jairath V, Doré CJ, et al. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials* 2014; 15: 139.
6. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2017: 35: 96–112.

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