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Competing events and costs of clinical trials: Analysis of a randomized trial in prostate cancer

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ABSTRACT

Background: Clinical trial costs may be reduced by identifying enriched subpopulations of patients with favorable risk profiles for the events of interest. However, increased selectivity affects accrual rates, with uncertain impact on clinical trial cost.

Methods: We conducted a secondary analysis of Southwest Oncology Group (SWOG) 8794 randomized trial of adjuvant radiotherapy for high-risk prostate cancer. The primary endpoint was metastasis-free survival (MFS), defined as time to metastasis or death from any cause (competing mortality). We used competing risks regression models to identify an enriched subgroup at high risk for metastasis and low risk for competing mortality. We applied a cost model to estimate the impact of enrichment on trial cost and duration.

Results: The treatment effect on metastasis was similar in the enriched subgroup (HR, 0.42; 95% CI, 0.23–0.76) compared to the whole cohort (HR, 0.50; 95% CI, 0.30–0.81) while the effect on competing mortality was not significant in the subgroup or the whole cohort (HR 0.70; 95% CI 0.39–1.23, vs. HR 0.94; 95% CI, 0.68–1.31). Due to the higher incidence of metastasis relative to competing mortality in the enriched subgroup, the treatment effect on MFS was greater in the subgroup compared to the whole cohort (HR 0.55; 95% CI 0.36–0.82, vs. HR 0.77; 95% CI, 0.58–1.01). Trial cost was 75% less in the subgroup compared to the whole cohort ($1.7 million vs. $6.8 million), and the trial duration was 30% shorter (8.4 vs. 12.0 years).

Conclusion: Competing event enrichment can reduce clinical trial cost and duration, without sacrificing generalizability.

The cost of conducting clinical trials is ever rising due to advancements in therapy, increasing operating costs, and inflation. The average cost of drug development has risen sharply over the past decade, and clinical trial costs are largely responsible for this increase [1–4]. The National Institutes of Health and the National Cancer Institute's fiscal budgets for clinical trials research have not kept pace with rising costs, which has led to chronic underfunding of clinical trials [5–7]. Rising trial costs may also stifle innovation, as investigators are increasingly favoring risk-averse clinical trials in an attempt to avoid costly failures [8,9].

Given the increasing expense of conducting clinical trials and the scarcity of research funding, there is an increasing need for innovation in the conduct and methodology of clinical trials [10,11]. Much attention has focused on enrichment of clinical trial populations as a strategy to increase efficiency, which in turn can permit more optimal resource allocation and rapid advancement of scientific knowledge [12–15]. Enrichment strategies can decrease clinical trial costs by reducing sample size, which is the main driver of trial cost. For example, Stewart et al. [14] used simulated data to show how enriching for high-risk tumor-related characteristics could decrease the cost of a lung cancer trial from $17 million to $2 million, compared to using an unselected cohort of patients.

While considerable attention has been placed on enrichment according to disease-related characteristics, less attention has been given to enrichment according to competing event risk, which also substantially affects the efficiency of clinical trials [16–18]. Increased selectivity of clinical trial populations reduces accrual rates and may delay the completion of clinical trials, with an uncertain impact on a trial's overall cost. We therefore sought to estimate the potential impact of an optimal enrichment strategy on overall trial duration and cost using data from an actual randomized trial.

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Methods

Patient sample

We analyzed data from Southwest Oncology Group (SWOG) 8794, a 425-patient randomized controlled trial of adjuvant radiotherapy in men with high-risk prostate cancer following radical prostatectomy [19,20]. The primary endpoint for the trial was metastasis-free survival (MFS), defined as the time from randomization to the first evidence of metastatic disease or death from any cause. We hypothesized that an optimal enrichment strategy would identify patients with the highest probability of metastasis events relative to competing mortality events, and stratified patients according to separate risk factors for metastasis and competing mortality. Competing mortality was defined as death from any cause in the absence of metastatic disease. We regarded first events contributing to the metastasis-free survival endpoint as mutually exclusive, such that the occurrence of one event (e.g., metastasis) precludes the observation of the competing event. We defined disease-specific enrichment as identifying patients at high risk of developing the outcome of interest (e.g., metastasis) and define competing event enrichment as identifying patients at low risk of developing the competing event (e.g., competing mortality). We used the Welch two-sample t-test and Pearson's Chi-squared test to compare demographic data between subgroups.

Competing risk model

We used stepwise Fine-Gray competing risks regression to stratify patients according to metastasis and competing mortality risk and variables with $p < 0.10$ were retained in the model [18,21]. The risk score for competing mortality (R_{CM}) was calculated as:

$$R_{CM} = 0.0591 * (\text{age}) + 0.643 * (\text{CCI} \geq 1) + 0.356 * (\text{PS} \geq 1) \quad (1)$$

where age is the mean-centered age in years, and Charlson Comorbidity Index (CCI) $\geqslant 1$ and performance status (PS) $\geqslant 1$ indicate the presence (value = 1) or absence (value = 0) of the indicated condition. Mean centered age was calculated as: age – mean age, which can result in negative values. Competing mortality risk scores ranged from −1.23 to 1.78 with a median score of 0.22 and standard deviation of 0.54.

The risk score for metastasis (R_M) was calculated as:

$$R_M = 0.692 * (\text{PSA} \geq 0.2) + 1.085 * (\text{SVI}) + 0.522 * (\text{GS} \geq 8) \quad (2)$$

where prostate specific antigen (PSA) $\geqslant 0.2$, seminal vesicle invasion (SVI), and Gleason score (GS) $\geqslant 8$ indicate the presence (value = 1) or absence (value = 0) of the indicated condition. The entire dataset was used for the generation of risk scores in Eqs. (1) and (2), and the coefficients for these equations were taken from the competing risks regression models. 188 patients had a metastasis risk score of 0 and the remaining 237 patients had metastasis risk scores ranging from 0.52 to 2.30. The 237 patients with metastasis risk scores greater than 0 were selected for the disease-specific enrichment strategy. The 20% of patients with the highest competing mortality risk scores were further removed, yielding a subgroup of 188 patients at high risk for metastasis and low risk for competing mortality. The complement of the enriched subgroup was defined as those with either a metastasis risk score below the cutoff or a competing mortality score above the cutoff. For the regression analysis and development of risk scores, the variables were dichotomized, and missing values from the clinical trial database were imputed to a value of 0. There were 6 patients (1.4%) with missing performance status, 47 patients with missing PSA (11.1%), and 47 patients (11.1%) with missing Gleason score. There were no missing data on age, comorbidity, or SVI.

Internal model validation was conducted using bootstrap split-sample methods. Random sampling with replacement was used to obtain a 75% training subsample. The remaining unused data were compiled into the testing cohort. All variables were used in the internal model validation. Estimates of the risk score coefficients were obtained from 100 repeated bootstrap 75% samples without replacement from the training cohort. Three variables (tumor stage, body mass index, and race) were dropped from the internal validation model based on their 95% confidence intervals (Supplementary material, Tables S1 and 2). Results of the regression analysis from the training cohort were used to develop risk scores in the testing cohort. Patients in the test cohort were divided into high and low metastasis risk groups and high, medium, and low competing mortality risk groups, based on risk score cutoffs. The risk scores predicted the cumulative incidence of metastasis and competing mortality in the test cohort (Supplementary material, Table S3).

Power analysis

The effect of radiotherapy was estimated using the Cox proportional hazards model. Due to a statistically significant imbalance in competing mortality risk score favoring the radiotherapy arm, we adjusted treatment effects for competing mortality risk scores. Power and sample size estimates for the competing risk setting were obtained using Pintilie's method [22]. For the power and sample size analysis, we assumed exponential event distribution, 6-year accrual, 6-year follow-up, equal sized arms, evaluation at 10 years, two-sided type I error (α) of 0.10, and type II error (β) of 0.20.

Cost function

The cost of a clinical trial is assumed to be composed of fixed and variable costs. Fixed costs include startup costs and maintenance costs. Variable costs include accrual and follow-up costs, which are dependent on the number of patients enrolled and the duration of follow up. The startup cost is fixed and independent of time, whereas we assume a linear relationship of maintenance cost with time. The fixed costs (C_{fix}) of a clinical trial are given as a function of time (t):

$$C_{fix}(t) = C_s + C_m t \quad (3)$$

where C_s is the startup cost, C_m is the fixed cost per year, and t is the trial duration in years.

Assuming a constant accrual rate and an exponentially distributed survival function, the cost function for accrual and follow up costs (C_{var}) is given as a function of time (t) by Piantadosi and Patterson [23]:

$$C_{var}(t) = \beta C_a \tau + \beta C_f (\lambda\tau - e^{-\lambda t}(e^{\lambda\tau} - 1))/\lambda^2 \quad (4)$$

where β is the accrual rate, C_a is the cost per individual of accrual, τ is the length of accrual in years, C_f is the cost per patient-year of follow up, and λ is the event hazard.

Combining Eqs. (3) and (4) yields the overall clinical trial cost (C) as a function of time (t):

$$C(t) = C_{fix}(t) + C_{var}(t) = C_s + C_m t + \beta C_a \tau + \beta C_f (\lambda\tau - e^{-\lambda t}(e^{\lambda\tau} - 1))/\lambda^2 \quad (5)$$

Inputs to the cost function were based on cost estimates cited in the literature, including start-up costs of $8000, annual maintenance costs of $80,000, per-patient treatment costs of $5000, and annual per-patient follow-up costs of $200 [5,6,24,25].

Stochastic variability was introduced to the cost analysis by randomly varying the effect on MFS in the enriched subgroup versus the whole cohort. The effect on metastasis (Θ_1) was estimated

from the Cox proportional hazards model and the effect on competing mortality (Θ_2) was assumed to be null and fixed. The effect on MFS (Θ) was computed according to the following equation [26,27]:

$$\Theta = \omega * \Theta_1 + (1 - \omega) * (\Theta_2) = \omega * \Theta_1 + (1 - \omega) \quad (6)$$

where ω represents the ratio of the cause-specific hazard for metastasis to the overall hazard for metastasis-free survival. The mean and standard error of ω at 10-years was estimated from the sample. For each iteration, the values of Θ_1 and ω were randomly drawn from a truncated normal distribution within ±2 standard errors of the respective mean. 5000 simulations were performed and the calculated MFS was entered in the power function to estimate the corresponding sample size, which was passed to the cost function.

Trial duration in the whole cohort was fixed at 12 years with 6 years of accrual and 6 years of follow up, in compliance with original SWOG power calculation. Accrual rate in the enriched subgroups was a proportional fraction of accrual rate in the whole cohort. Accrual duration in the enriched subgroups was calculated as sample size divided by accrual rate. Follow up in the enriched subgroups was fixed at 6 years. For the cost calculation in the whole cohort, variation in sample size with a fixed trial duration of 12 years was used for each of the 5000 iterations. To calculate trial cost in the enriched subgroups, variation in both sample size and trial duration was imputed into the cost function for each of the 5000 iterations.

Results

Demographic data for the whole cohort and the subgroups are given in Table 1. The enriched subgroups had higher prostate cancer specific risk factors compared to the whole cohort. Enrichment according to competing mortality risk resulted in younger patients, with lower performance status and less comorbidity. The race distribution was similar across the subgroups ($p = 0.83$).

Compared to the whole cohort, both enriched subgroups had a higher 10-year cumulative incidence of metastasis, but only the subgroup enriched on competing mortality had a lower 10-year incidence of competing mortality (Table 2, Supplementary material Fig. S1). The effect of therapy on metastasis was similar between the whole cohort and subgroups while the effect of therapy on MFS varied widely due to variations in the incidence of metastasis relative to competing mortality. Combined disease-specific and competing event enrichment resulted in the highest proportion of metastasis events comprising the MFS endpoint, which led to the largest treatment effect and smallest sample size estimate (Table 2).

We applied a cost function to examine the differences in cost between a trial conducted in the enriched subgroups compared to the whole cohort. Disease-specific enrichment reduced the estimated cost of the trial by 65% and the trial duration by 25% compared to the whole cohort. The addition of competing event enrichment reduced the cost of the trial by 75% and the trial duration by 30% compared to the whole cohort (Table 2).

Table 1
Patient and tumor characteristics according to enrichment strategy.

	Disease-specific enrichment ($n = 237$)	Combined disease-specific and competing event enrichment ($n = 188$)	Complement of combined enrichment ($n = 237$)	Total ($n = 425$)	P^*
Mean age, years	64.7	63.4	65.0	64.3	.01
Ethnicity, *n* (%)					.83
White	156 (65.8)	122 (64.9)	173 (73.0)	295 (69.4)	
Black	48 (20.3)	37 (19.7)	46 (19.4)	83 (19.5)	
Asian	1 (0.4)	1 (0.5)	2 (0.8)	3 (0.7)	
Missing	32 (13.5)	28 (14.9)	16 (6.8)	44 (10.4)	
Mean body mass index	27.7	28.1	27.4	27.7	.10
Performance status, *n* (%)					<.001
0	181 (76.4)	163 (86.7)	158 (66.7)	321 (75.5)	
1	48 (20.3)	22 (11.7)	69 (29.1)	91 (21.4)	
2	6 (2.5)	1 (0.5)	6 (2.5)	7 (1.6)	
Missing	2 (0.8)	2 (1.1)	4 (1.7)	6 (1.4)	
Charlson comorbidity index, *n* (%)					<.001
0	192 (81.0)	175 (93.1)	174 (73.4)	349 (82.1)	
1	30 (12.7)	11 (5.9)	43 (18.1)	54 (12.7)	
2	10 (4.2)	2 (1.1)	13 (5.5)	15 (3.5)	
3	4 (1.7)	0	6 (2.5)	6 (1.4)	
4	1 (0.4)	0	1 (0.4)	1 (0.2)	
Seminal Vesicle Invasion, *n* (%)					<.001
Present	139 (58.6)	115 (61.2)	24 (10.1)	139 (32.7)	
Absent	98 (41.4)	73 (38.8)	213 (89.9)	286 (67.3)	
Gleason score, *n* (%)					<.001
⩽6	100 (42.2)	81 (43.1)	139 (58.6)	220 (51.8)	
7	66 (27.8)	52 (27.7)	56 (23.6)	108 (25.4)	
8–10	50 (21.1)	37 (19.7)	13 (5.5)	50 (11.8)	
Missing	21 (8.9)	18 (9.6)	29 (12.2)	47 (11.1)	
Prostate specific antigen, *n* (%)					<.001
<0.2 ng/ml	70 (29.5)	57 (30.3)	122 (51.5)	179 (42.1)	
⩾0.2 ng/ml	149 (62.9)	117 (62.2)	82 (34.6)	199 (46.8)	
Missing	18 (7.6)	14 (7.4)	33 (13.9)	47 (11.1)	
Adjuvant radiotherapy (%)	121 (51.1)	103 (54.8)	111 (46.8)	214 (50.4)	.13

* Comparison between combined enrichment and its complement.

Table 2
Treatment effect, sample size, cost, and trial duration according to enrichment strategy.

	Disease-specific enrichment (n = 237)	Combined disease-specific and competing event enrichment (n = 188)	Complement of combined enrichment (n = 237)	Total (n = 425)
10-Year cumulative incidence (95% CI)				
Metastasis	30% (22–38%)	33% (23–43%)	11% (7–18%)	20% (15–26%)
Competing mortality	22% (15–30%)	14% (8–23%)	24% (16–31%)	20% (15–26%)
Cox hazard ratio (95% CI)				
Metastasis	0.43 (0.25–0.75)	0.42 (0.23–0.76)	0.58 (0.25–1.36)	0.50 (0.30–0.81)
Competing mortality	0.85 (0.54–1.33)	0.70 (0.39–1.23)	1.08 (0.72–1.62)	0.94 (0.68–1.31)
Metastasis-free survival	0.64 (0.45–0.91)	0.55 (0.36–0.82)	0.96 (0.67–1.38)	0.77 (0.58–1.01)
Sample size	301	191	42,781	1063
Trial cost	$2.35 million	$1.71 million	$271.3 million	$6.78 million
Trial duration	9.0 years	8.4 years	431.3 years	12 years

Abbreviation: CI, confidence interval.

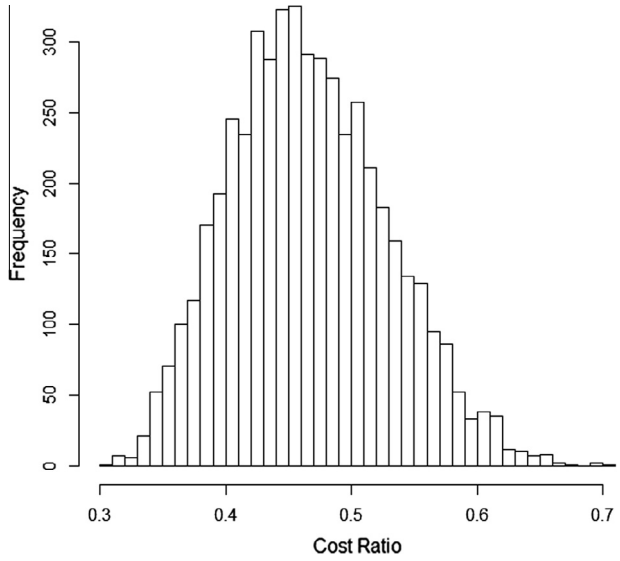

Fig. 1. Cost ratio in the disease-specific and competing mortality enriched subsample compared to the whole cohort.

In the stochastic model, combined disease-specific and competing event enrichment was less costly in 100% of simulations compared to the whole cohort (Fig. 1). Combined enrichment was less costly than disease-specific enrichment in 99.9% of simulations (Supplementary material, Fig. S2).The median trial cost was smallest in the combined enriched subgroup followed by the disease-specific subgroup and the whole cohort (Table 3). Combined disease-specific and competing event enrichment was more likely to result in a shorter trial duration in 81% of simulations compared to the whole cohort (Fig. 2) and combined enrichment resulted in a shorter trial duration compared to disease-specific enrichment in 92% of simulations (Supplementary material, Fig. S3).

Discussion

Enriching trial populations based on both disease-specific and competing events provides an opportunity to maximize efficiency. In this study, we applied an enrichment strategy and cost function to data from a large clinical trial, with consideration given to accrual rate, trial duration, and generalizability. Our study is novel in that enrichment decreased cost and trial duration without loss of generalizability. While perhaps counterintuitive, stricter selection criteria would have decreased the trial duration, despite slowing accrual, due to the high probability of disease-specific events, and smaller overall sample size required. These results indicate the potential for large cost savings in cancer clinical trials, which can in turn improve the efficiency of resource allocation.

We also found that the treatment significantly reduced metastasis, without a significant adverse effect on competing mortality. This interpretation holds across the subgroups, and tests for the interaction between treatment and subgroup assignment were not significant. While some caution should be used in interpreting effects within subgroups that are defined post hoc [28], it is evident that the observed differences in the effect on MFS across

Table 3
Sample size, cost, and trial duration estimates according to enrichment strategy in the stochastic analysis.

	Disease-specific enrichment (n = 237)	Combined disease-specific and competing event enrichment (n = 188)	Complement of combined enrichment (n = 237)	Total (n = 425)
Sample size				
Median	695	449	3409	1141
IQR	449–1272	279–821	2177–6072	733–2070
Cost				
Median	$4.8 million	$3.4 million	$21.9 million	$7.2 million
IQR	$3.5–7.7 million	$2.5–5.3 million	$15.8–35.3 million	$5.2–11.8 million
Trial duration				
Median	12.6 years	11.3 years	37.4 years	12.0 years*
IQR	11.9–13.3 years	10.8–11.8 years	33.3–42.3 years	

Abbreviation: IQR, interquartile range.
* Fixed.

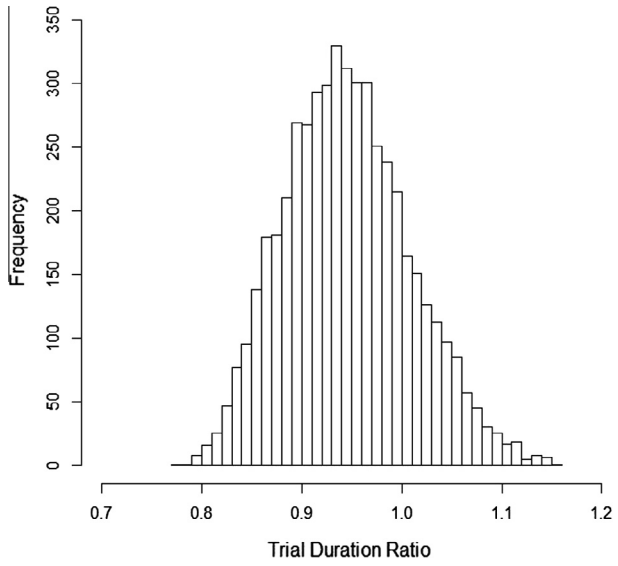

Fig. 2. Trial duration ratio in the disease-specific and competing mortality enriched subsample compared to the whole cohort.

subgroups are strongly influenced by differences in the relative probability of metastasis versus competing mortality. Because the effect of treatment on metastasis is similar across subgroups, the conclusions drawn from the enriched subgroups are generalizable to the whole cohort, and little additional information was gained about the treatment effects studying the complement of the enriched population.

The data set in this study was unusually well-suited for this type of analysis because of the long follow-up, high incidence of both disease-specific and competing events, detailed data regarding patient and tumor characteristics, significant treatment effect, and randomization to provide unbiased estimates of the treatment effect. The factors we identified for our risk models have been previously associated with metastasis and competing mortality in prostate cancer [29–32]. While the post hoc nature of the algorithm developed in this study may limit inference, the value of this study is the novelty of the findings and the potential significance of the approach. External validation of competing event enrichment strategies in prospective studies is needed.

A common concern regarding enrichment strategies is the potential for reduced generalizability of the results. However, there is substantial evidence already that patients enrolled in clinical trials are not representative of the general population, because trials often accrue disproportionately at academic centers, patient participation is voluntary, informed consent is required, and stringent inclusion and exclusion criteria deliberately narrow the study sample [33–35]. Despite these differences, evidence that outcomes differ based on participation in cancer clinical trials is lacking [36]. Implicit in the conduct of efficacy clinical trials is the principle that they are designed to estimate treatment effects under idealized conditions. Physicians in turn use knowledge of these effects to estimate the net benefit to patients given their individual circumstances, including their relative probability of competing events [37]. Enrolling patients in trials who are unlikely to benefit from treatment increases costs and risks missing true treatment effects when they are present, while not necessarily improving the generalizability of the results [38].

As treatments improve, competing events will become an increasingly significant problem confronting the design and interpretation of clinical trials. Given the current funding climate, heightened attention to the efficiency of trials is needed. Identifying factors that place individuals at high risk for competing events that preclude a therapeutic benefit would improve efficiency of resource allocation for clinical trials. Here we found that enrichment based on competing event risk resulted in substantial potential for cost savings and reduced study duration, while still yielding effect estimates applicable to the broader population. These principles could be applied to other trials to improve efficiency and reduce costs.

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Conflict of Interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.03.018.

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