Improved outcomes with "7+3" induction chemotherapy for acute myeloid leukemia over the past four decades: analysis of SWOG trial data

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Abstract

We have previously shown that complete response (CR) rates and overall survival of patients with acute myeloid leukemia have improved since the 1980s. However, we have not previously evaluated how the length of first CR (CR1) has changed over this time period. To address this, we analyzed 1,247 patients aged 65 or younger randomized to "7+3" arms from five SWOG studies: S8600 (n=530), S9031 (n=98), S9333 (n=57), S0106 (n=301), and S1203 (n=261). We evaluated length of CR1 and survival after relapse from CR1 over the four decades that these studies represent. Both length of CR1 and survival after relapse from CR1 have improved over the last four decades. The relative benefit associated with CR1 and the relative detriment associated with relapse have decreased over this period; while achieving CR1 and relapse from CR1 still have strong prognostic associations with outcomes, the magnitude of the association has decreased over time. Possible explanations for these patterns include higher CR rates with salvage therapies after relapse, more frequent use of hematopoietic cell transplant, and better supportive care.

Introduction

We have previously shown that the early mortality, complete remission (CR) rates, and overall survival of patients with acute myeloid leukemia (AML) treated with cytarabine (ara-C) and an anthracycline ("7+3" regimen) have improved since the 1980s.[1] However, we have not previously evaluated how much of the increase in overall survival is due to longer duration of first complete remission (CR1) and how much is due to improved salvage therapies after first relapse, including allogeneic hematopoietic cell transplantation (HCT). Understanding the relative contributions of these two effects should provide insight into the interpretation of past and current studies. This prompted us to evaluate AML clinical trials from the 1980s, 1990s, 2000s, and 2010s to examine whether the length of CR1 and survival after relapse from CR1 have changed over time.

Methods

Study population

We analyzed 1,247 patients randomized to "7+3" arms in five National Cancer Institute National Clinical Trials Network clinical trials conducted by the SWOG Cancer Research Network. We analyzed patients who were aged 65 and younger from SWOG studies (number of cases; enrollment decade): S8600 (n=530; 1980s), S9031 (n=98; 1990s), S9333 (n=57; 1990s), S0106 (n=301; 2000s), and S1203 (n=261; 2010s).[2-6] S9031 and S9333 were analyzed together. In each trial, the "7+3" regimen was given per contemporary standard, which changed over time. In S8600, S9031, and S9333, the ara-C and daunorubicin doses were 200 mg/m^2 and 45 mg/m^2 respectively, in S0106 the doses were 100 mg/m^2 and 60 mg/m^2, and in S1203 the doses were 100 mg/m^2 and 90 mg/m^2. Consolidation chemotherapy varied over time per contemporary practice, with protocols S9031 and S9333 specifying two cycles of consolidation therapy with ara-C and daunorubicin doses of 200 mg/m^2 and 45 mg/m^2, respectively; protocols S0106 and S1203 specified three and four cycles, respectively, of 3,000 mg/m^2 of ara-C and no daunorubicin; protocol S8600 included a consolidation randomization between up to two cycles of the contemporary standard ara-C and daunorubicin doses of 200 mg/m^2 and 45 mg/m^2 *versus* 2,000 mg/m^2 and 30

mg/m^2. HCT was not specified as a component of protocol therapy (with associated data collected) except in the most recent trial S1203. The institutional review boards of the participating institutions approved all protocols, and patients were treated according to the Declaration of Helsinki.

Statistical methods

CR was defined morphologically and required full recovery of absolute neutrophil counts and platelets (>1x10^9/L and >100x10^9/L, respectively).[4] Overall survival was measured from the date of study registration/randomization to date of death due to any cause; patients last known to be alive were censored at the date of last contact. Relapse-free survival was measured for patients who achieved CR from the date of CR to the first of relapse from CR or death from any cause, with patients last known to be alive censored at the date of last contact. Time to relapse was measured for patients who achieved CR1 from the date of CR1 to relapse, with death without relapse considered a competing risk. Endpoints were not censored at the time of a transplant. Overall and relapse-free survival were estimated using the Kaplan-Meier method. Time to relapse was estimated by cumulative incidence curves and multivariable associations were evaluated by Fine and Gray subdistribution hazard models.[7] Among patients who achieved CR1, the percent in CR1 without relapse was summarized at landmark times in 6-month increments between 6 months and 3 years after CR1. Time-dependent Cox regression models for overall survival and relapse-free survival were fitted with CR1 and relapse from CR1 as time-dependent covariates. Multivariable regression models included the following covariates (modeled quantitatively unless otherwise specified): age at study registration, gender (male *vs*. female), cytogenetic risk (favorable *vs*. intermediate *vs*. high *vs*. missing), prestudy white blood cell counts, pre-study platelet counts, pre-study marrow blast percentages, secondary AML (*vs. de novo* AML), indicator of receiving reinduction, and decade/study.

Results

Characteristics of the cohorts

Table 1 summarizes the patients' characteristics from the studies as analyzed by decade. Trials S9031 and S9333 (completed in the 1990s) were restricted to patients aged 55 and older; the other studies included patients aged 18 and older. The proportion of patients with performance status 2 and higher has decreased over time, particularly comparing studies conducted in the 1980s and 1990s (S8600, S9031/S9333) with those conducted in the 2000s and 2010s (S0106, S1203). Patients with secondary AML

Table 1. Summary of trials included in the analyses.

Factor	S8600 (N=530)	S9031/S9333 (N=155)	S0106 (N=301)	S1203 (N=261)	*P* value
Age in years, median (range)	43 (15-64)	61 (56-65)	45 (18-60)	46 (19-20)	<0.001
Gender, N (%)					
Female	247 (47)	69 (45)	147 (49)	131 (50)	0.65
Male	283 (53)	86 (55)	154 (51)	130 (5)	
Performance status, N (%)					
0-1	374 (73)	113 (75)	255 (85)	221 (85)	<0.001
2-3	140 (27)	38 (25)	44 (15)	40 (15)	
WBCx10^9/L, median (range)	41 (0.4-416)	36 (0.7-274)	114 (7-9300)	110 (4-8500)	0.029
Platelet count x10^9/L, median (range)	78 (2-700)	82 (6-1200)	114 (7-9300)	110 (4-8500)	0.040
Marrow blasts, %, median (range)	67 (0-99)	61 (10-99)	62 (3-100)	57 (0-100)	<0.001
Cytogenetic risk, N (%)					
Favorable	9 (2)	5 (3)	42 (14)	28 (11)	<0.001
Intermediate	56 (11)	67 (43)	126 (42)	168 (64)	
Unfavorable	32 (6)	36 (23)	55 (18)	60 (23)	
Missing	433 (82)	47 (30)	78 (26)	5 (2)	
Secondary AML, N (%)					
De novo	506 (95)	121 (78)	301 (100)	236 (90)	<0.001
Secondary	24 (5)	34 (22)	0	25 (10)	

Note: not all percentages add up to 100 due to rounding. WBC: white blood cells; AML: acute myeloid leukemia.

were not eligible for S0106, which compared “7+3” to “7+3” plus gemtuzumab ozogamicin.

Outcome patterns over time

Overall survival after CR1 increased over the time period analyzed here (Figure 1), as demonstrated also by multivariable regression models (Table 2), with a multivariable hazard ratio (HR) of 0.43 (95% confidence interval [95% CI]: 0.34-0.53, *P*<0.0001) for patients treated since year 2000 compared to patients treated before year 2000. Among patients who achieved CR1, there were fewer relapses and a longer time to relapse among patients treated since 2000 (Figure 2), also in multivariable regression models (Table 2), with a multivariable HR of 0.40 (95% CI: 0.31-0.51, *P*<0.0001) taking before year 2000 as the reference. Among patients who relapsed after CR1, those treated since year 2000 had a significantly longer overall survival after relapse compared to those treated before year 2000 (Figure 3), also in multivariable modeling (Table 2): HR=0.43, 95% CI: 0.34-0.52, *P*<0.0001.

Figure 4 and Table 3 summarize the percentage of patients, from among the patients who achieved CR1, who were in continuous CR1 at the landmark times. In multivariable models (*data not shown*), the probability of being alive without relapse was higher at all landmark times for patients treated since year 2000 compared to patients treated before year 2000.

Relative benefit of complete remission and relative detriment of relapse over time

Over the four decades analyzed, achieving CR1 was associated with a large benefit in overall survival (HR=0.06, 95% CI: 0.04-0.10 before year 2000; HR=0.16, 95% CI: 0.11-0.23 since year 2000), although the magnitude of benefit was less extreme for patients treated since 2000 (in other words the HR for since year 2000 was significantly closer to 1 than the HR for before year 2000, interaction *P*=0.001). Similarly, relapsing from CR1 was associated with a large decrement in overall survival across all the decades analyzed (HR=16.6, 95% CI: 11.0-24.1 for before year 2000; HR=10.1, 95% CI: 7.0-14.7 for since year 2000), although there was some evidence that the magnitude of decrement was less for patients treated since 2000 (in other words the HR for after 2000 was significantly closer to 1 than the HR for before 2000, interaction *P*=0.079).

Discussion

In the cohorts of patients studied here, overall survival for AML improved drastically over the last four decades, and this improvement was observed in all the intermediate endpoints we evaluated: early death rates, CR1 rates, length of CR1/time to relapse, relapse rates, and overall survival after relapse from CR1.

Reasons for improved outcomes are plausibly related to higher chemotherapy doses,[8-10] improved antibiotics, more use of allogeneic HCT,[11,12] and incorporation of novel agents (including gemtuzumab ozogamicin and FLT3 inhibitors) in the upfront, refractory, and salvage settings. These same reasons for improved survival may also explain why the relative benefit of achieving CR1 and the relative decrement from relapse from CR1 are less extreme among patients who were treated after year 2000 compared to

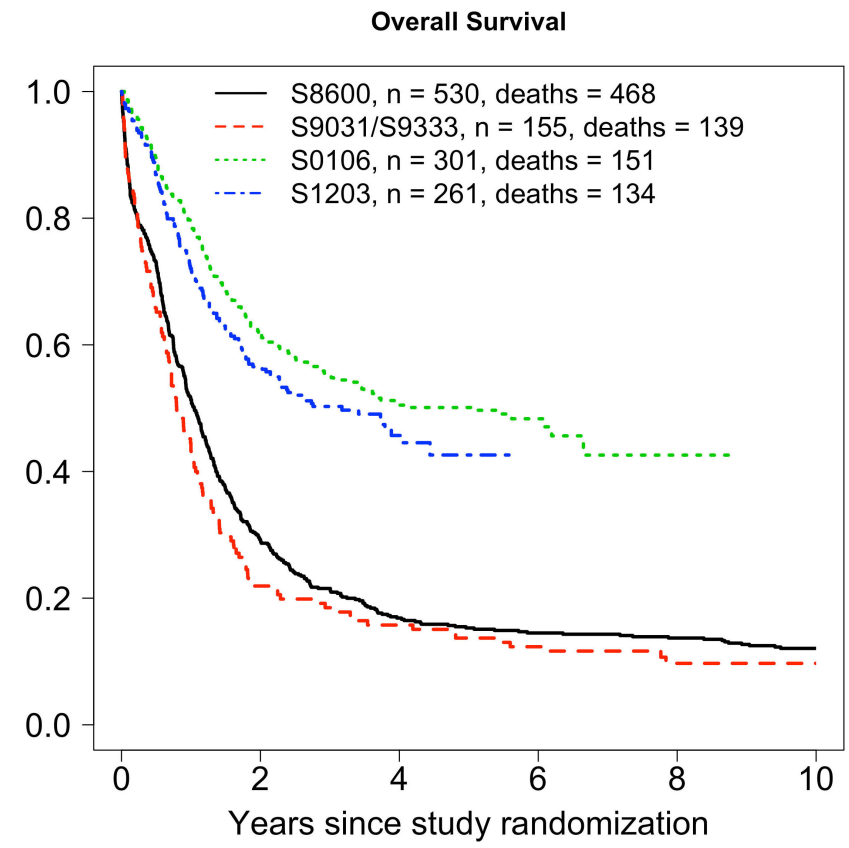

Figure 1. Overall survival after first complete remission by trial/decade.

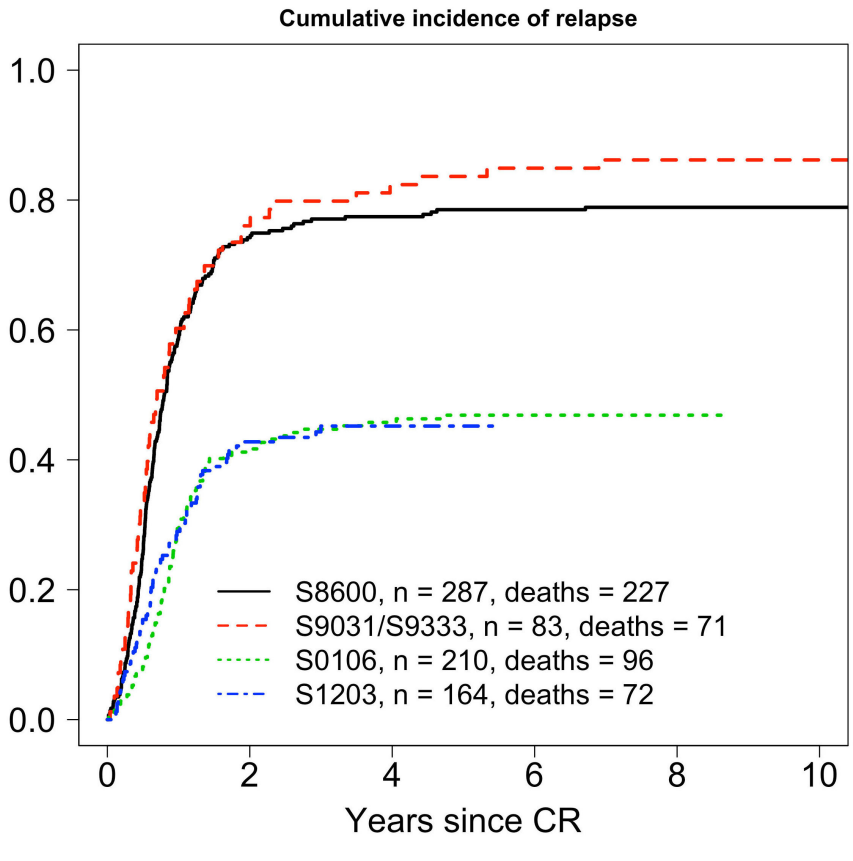

Figure 2. Cumulative incidence of time to relapse by trial/decade. CR: complete remission.

Table 2. Multivariable regression model results.

Cox regression model for OS after CR1 (N=1,181) **Covariate**	**HR**	**95% CI**	***P* value**
S0106/S1203 (ref = S8600/S9031/S9333)	0.42	(0.35-0.49)	<0.001
Age	1.02	(1.01-1.02)	<0.001
Male (ref = female)	1.09	(0.95-1.24)	0.24
PS 2-3 (ref = PS 0-1)	1.23	(1.05-1.45)	0.011
Secondary AML (ref = *de novo*)	1.14	(0.88-1.48)	0.32
Favorable cytogenetic risk (ref = intermediate)	0.42	(0.27-0.65)	<0.001
Unfavorable cytogenetic risk (ref = intermediate)	2.38	(1.93-2.94)	<0.0001
Missing cytogenetic risk (ref = intermediate)	1.09	(0.91-1.30)	0.36
Baseline WBC count	1.10	(0.98-1.23)	0.10
Baseline platelet count	1.01	(0.99-1.03)	0.33
Baseline marrow blast percentage	1.02	(0.99-1.05)	0.19
Subdistribution hazard model for relapse after CR1 (N=710) **Covariate**	**HR**	**95% CI**	***P* value**
S0106/S1203 (ref = S8600/S9031/S9333)	0.40	(0.31-0.51)	<0.001
Age	1.00	(1.00-1.01)	0.33
Male (ref = female)	1.16	(0.96-1.40)	0.13
PS 2-3 (ref = PS 0-1)	1.03	(0.80-1.32)	0.84
Secondary AML (ref = *de novo*)	1.11	(0.72-1.69)	0.64
Favorable cytogenetic risk (ref = intermediate)	0.55	(0.35-0.87)	0.010
Unfavorable cytogenetic risk (ref = intermediate)	1.31	(0.89-1.92)	0.17
Missing cytogenetic risk (ref = intermediate)	0.95	(0.74-1.21)	0.66
Baseline WBC count	1.20	(0.99-1.46)	0.067
Baseline platelet count	1.00	(0.97-1.04)	0.84
Baseline marrow blast percentage	1.01	(0.97-1.05)	0.54
Cox regression model for OS after relapse from CR1 (N=789) **Covariate**	**HR**	**95% CI**	***P* value**
S0106/S1203 (ref = S8600/S9031/S9333)	0.43	(0.34-0.53)	<0.001
Age	1.02	(1.01-1.03)	<0.001
Male (ref = female)	1.05	(0.88-1.25)	0.61
PS 2-3 (ref = PS 0-1)	1.11	(0.89-1.38)	0.36
Secondary AML (ref = *de novo*)	1.17	(0.82-0.66)	0.38
Favorable cytogenetic risk (ref = intermediate)	0.43	(0.27-0.69)	<0.001
Unfavorable cytogenetic risk (ref = intermediate)	1.91	(1.44-2.53)	<0.001
Missing cytogenetic risk (ref = intermediate)	1.07	(0.86-1.35)	0.53
Baseline WBC count	1.15	(0.97-1.36)	0.11
Baseline platelet count	1.01	(0.99-1.03)	0.53
Baseline marrow blast percentage	1.00	(0.96-1.03)	0.82

OS: overall survival; CR1: first complete remission; HR: hazard ratio; 95% CI: 95% confidence interval; PS: performance status; AML: acute myeloid leukemia; WBC: white blood cell.

patients treated before year 2000. We recognize that the lack of HCT data from older studies confounds these analyses, in particular the length of CR1. Without HCT data we cannot separate out the specific role of HCT in these changing trends over time.

The characteristics of patients treated with the “7+3” regimen on these trials changed over time, even though eligibility criteria were stable across time with the exception of age (as noted above in the Methods section) and secondary AML patients being ineligible for S0106. On average the proportion of lower-risk patients increased, possibly reflecting the availability of less intense therapies, in particular azacitidine and decitibine after year 2000 and introducing the possibility of increased selection bias in later years. Al-

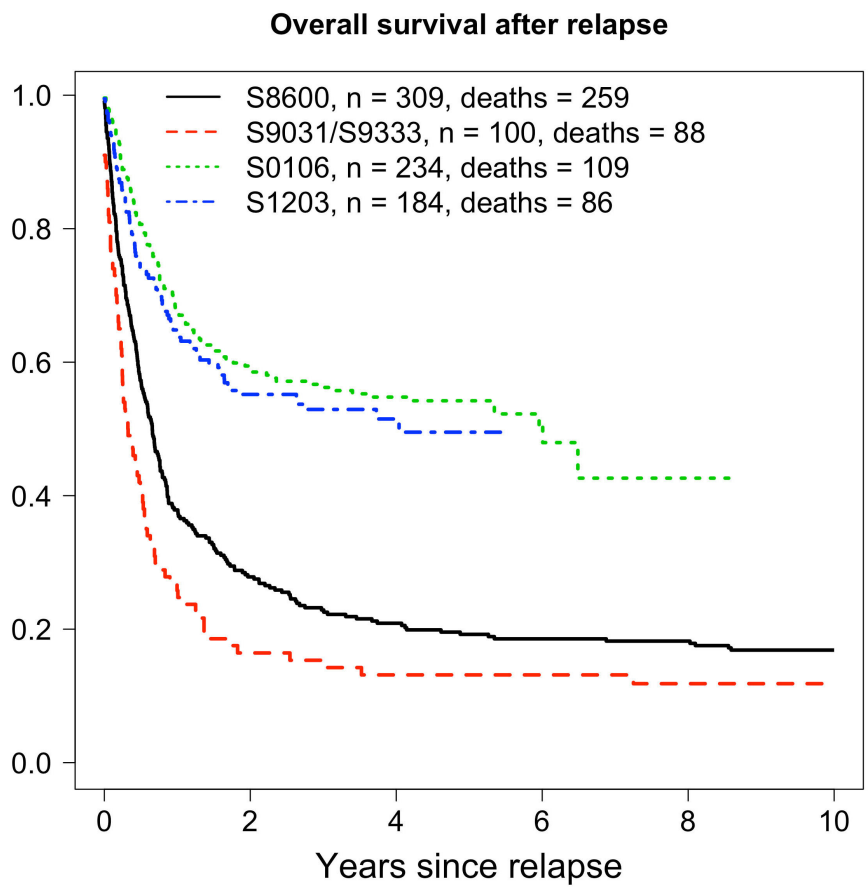

Figure 3. Overall survival after relapse by trial/decade.

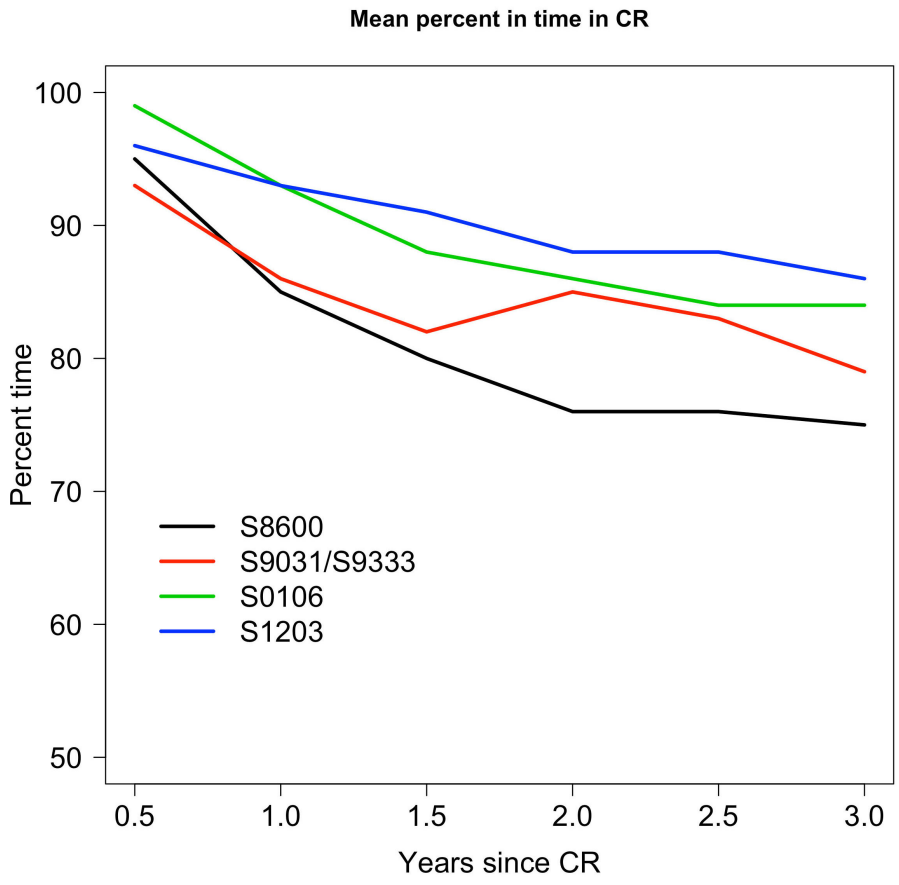

Figure 4. Percentages of patients in continuous first complete remission over a 3-year period. CR: complete remission.

though we present regression results from multivariable models, these models can only account for the covariates that are available in the datasets analyzed. Notably, HCT rates increased over the period analyzed and this post-remission therapy could not be analyzed statistically because rates of HCT were so low in the trials before year 2000 and data on HCT were not collected in the established trial forms. It should also be noted that “7+3” therapy changed over time; doses of both drugs changed over time as noted in the Methods section. The multivariable analysis cannot adjust for factors perfectly confounded with study/decade, such as changes in doses of therapy, to tease out individual contributions.

Table 3. Percentages of patients in continuous complete remission at landmark times after achieving first complete remission.

	S8600	S9031/ S9333	S0106	S1203	*P* value
6 months	82	77	95	88	<0.001
1 year	57	62	75	82	<0.001
1.5 years	50	66	69	77	0.007
2 years	51	63	72	74	0.026
2.5 years	57	61	71	78	0.041
3 years	58	64	72	76	0.11

Only since the 2000s have response criteria such as CR with incomplete platelet recovery, CR with incomplete hematologic recovery, morphological leukemia-free state, and CR with partial hematologic recovery been introduced and it will be interesting to examine their effects on survival relative to that of CR as contemporary trials mature and longer-term analysis of their outcomes becomes feasible.[13]

Disclosures

No conflicts of interest to disclose.

Contributions

MO designed research, analyzed the data, and wrote the paper. GGM, JEG, JKW, FRA, HPE, and EHE designed research and wrote the paper.

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Data-sharing statement

The analyzed dataset can be requested following SWOG data-sharing procedures: https://www.swog.org/sites/default/files/docs/2019-12/Policy43_0.pdf. Questions may be directed to the author for correspondence.

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