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Letter to the Editor

Exclusion of patients with brain metastases from cancer clinical trials

Historically, cancer clinical trials have excluded patients with brain metastases out of concern for poor life expectancy and intervention tolerability. Given the high incidence of secondary brain metastases across cancer types, excluding these patients in clinical trials may limit generalizability of study results.[1–3] Recent efforts have sought to broaden eligibility criteria in oncologic trials, with more nuanced guidelines for patients with intracranial metastases.[3–5] We therefore sought to characterize the incidence, correlates, and temporal trends of brain metastasis exclusion criteria (BMEC) among phase III cancer clinical trials.

To identify eligible studies, we queried ClinicalTrials.gov using the following search criteria: terms: "cancer"; study type: "all studies"; status: excluded "not yet recruiting"; phase: phase III; and study results: "with results." Of 1239 screen-identified trials, 764 were eligible as cancer-specific phase III randomized multi-arm trials addressing a therapeutic intervention. Trials assessing hematologic malignancies ($N = 157$) and non-metastatic solid tumors ($N = 143$) were excluded; the remaining 464 trials were included in the primary analysis of this study. Total enrollment for the 464 included trials was 250 064 patients. Eligibility criteria were obtained from ClinicalTrials.gov as well as trial publications and study protocols if available. We distinguished between trials that utilized "Complete BMEC," which excluded all patients with any brain metastases, from those that utilized "Conditional BMEC," which excluded patients more selectively. Conditional BMEC excluded patients for any combination of symptomatic, uncontrolled, progressive, or untreated intracranial metastases, as well as intracranial disease requiring steroids or leptomeningeal disease.

Of 464 included trials in this analysis, 169 (36.4%) had complete BMEC. Conditional BMEC was identified for an additional 140 trials (30.2%). Higher incidence of complete BMEC was found among industry-sponsored trials compared with non-industry-supported studies (39.1% vs 26.7%, Pearson's chi-squared $P = 0.02$; Table 1). Complete BMEC utilization was associated with disease site, with higher BMEC rates among genitourinary and gastrointestinal trials ($P < 0.001$; Table 1), and with systemic therapy trials ($P = 0.01$; Table 1). Most notably, complete BMEC utilization rates decrease over time (based on enrollment initiation year), from 45.6% during 2001–2005 to 25.5% during 2011–2015 (binary logistic regression $P = 0.02$; Table 1). On multiple binary logistic regression modeling, industry sponsorship ($P = 0.01$), enrollment start year ($P = 0.03$), disease site ($P < 0.001$), and treatment modality ($P = 0.001$) remained independently associated with complete BMEC utilization. Of note, trials with complete BMEC were not more likely to complete accrual ($P = 0.56$) or meet their primary endpoint ($P = 0.53$).

While complete BMEC rates are decreasing over time, conditional BMEC rates are increasing. Conditional BMEC have risen from 12.5% in 1995–2000 to 18.9% in 2001–2005, 28.7% in 2006–2010, and finally 46.1% in 2011–2015 ($P < 0.001$). The concomitant increase in conditional BMEC utilization as complete BMEC rates fall suggests that efforts to modernize eligibility criteria have been successful. Trials are increasingly nuanced in deciding which patients with brain metastases can participate in studies, consistent with recommendations from national working groups.[3]

It is also noteworthy that higher complete BMEC rates were found among industry-sponsored trials. This subgroup of trials is presently the subject of draft guidance from the FDA specifically recommending inclusion of patients with stable/treated intracranial metastases.[5] Reassuringly, even among industry-supported trials, rates of complete BMEC utilization are decreasing, from 52.4% in 2001–2005 to 26.1% in 2011–2015 ($P = 0.002$).

Taken together, use of complete BMEC in cancer clinical trials remains common and is associated with industry sponsorship. However, complete BMEC utilization is decreasing with time, seemingly being replaced with more nuanced conditional BMEC consistent with national guidelines and working group recommendations. Continued efforts to ensure that patients with brain metastases are appropriately allowed to participate in cancer clinical trials are imperative in order to promote both trial access equity as well as generalizability of study results.

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Table 1 Trial factors associated with complete BMEC

Trial Characteristics		No. Trials with Complete BMEC/Total	Percent	*P*-value[a]
Industry funding of trial	Yes	141/361	39.1	***P* = 0.02**
	No	27/101	26.7	
Cooperative group trial	Yes	35/112	31.3	*P* = 0.20
	No	132/348	37.9	
Enrollment start year	1995–2000	4/8	50	***P* = 0.02**
	2001–2005	41/90	45.6	
	2006–2010	96/258	37.2	
	2011–2015	26/102	25.5	
Disease site[b]	Breast	32/75	42.7	***P* < 0.001**
	Gastrointestinal	43/76	56.6	
	Genitourinary	35/55	65.5	
	Head & Neck	4/23	17.4	
	Melanoma	5/20	25.0	
	Thoracic	18/95	18.9	
Treatment modality[c]	Systemic therapy	137/334	41.0	***P* = 0.01**
	Radiotherapy	1/6	16.7	
	Surgery	1/2	50.0	
	Supportive care	26/112	23.2	
Systemic therapy subgroup[d]	Targeted therapy	106/257	41.2	*P* = 0.88
	Cytotoxic chemotherapy	31/77	40.3	
Completed planned accrual	Yes	90/240	37.5	*P* = 0.56
	No	37/108	34.3	
Trial success (primary endpoint met)	Yes	72/198	36.4	*P* = 0.53
	No	70/177	39.5	

[a] *P*-value reflects Pearson's chi-squared tests for all except enrollment start year, for which *P*-value reflects results of binary logistic regression analysis by year.
[b] Limited to trials with a defined single disease site.
[c] Primary intervention as part of the randomization. Systemic therapy includes cytotoxic chemotherapy, targeted systemic agents, and similar, with primary endpoint aimed at improved disease-related outcomes. Supportive care trials aimed to reduce disease- or treatment-related toxicity.
[d] Systemic therapy trials subdivided further into those assessing a targeted therapy (including small molecule inhibitors, monoclonal antibodies, and similar) and those assessing cytotoxic chemotherapy.

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