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## PURPOSE / OBJECTIVES

- Increasing data suggest that radiotherapy, particularly ablative radiotherapy, alters the natural history of metastatic disease.
- For patients with metastatic disease enrolled on prospective trials testing systemic therapy, the use of off-protocol radiotherapy to improve clinical symptoms or extend the duration of study systemic therapy may influence study endpoints.
- We sought to evaluate how often off-protocol radiotherapy was permitted among systemic therapy phase III trials, how often off-protocol radiotherapy is utilized, and whether off-protocol radiotherapy correlated with study outcomes.

## MATERIAL & METHODS

- This was a cross-sectional analysis of phase III trials with a superiority, two-arm design testing systemic therapies for metastatic solid tumors with an available protocol.
- Trials were identified on ClinicalTrials.gov.
- Off-protocol RT was defined as RT that was not required by the protocol, that did not require permanent discontinuation of the protocol's systemic therapy, and that did not result in a change in progression status.
- The association of a policy allowing for off-protocol RT and trial success was adjusted in a multivariable logistic regression for the type of primary endpoint (surrogate vs overall survival), based on previous work suggesting a strong association between endpoint type and trial outcome, with Firth's penalized likelihood correction.

## RESULTS

- After screening 1,877 trials, 112 trials enrolling 80,134 patients were included
- Off-protocol RT was allowed, not discussed, or prohibited during study systemic therapy in 52% (N=58), 25% (N=28), and 23% (N=26) of trials, respectively.
- Only 2% (N=2) of the 86 permissive trials reported utilization rates of off-protocol RT.
- No trials evaluated or adjusted for the potential influence from off-protocol radiotherapy on study endpoints.
- Among open-label studies, trials permissive towards off-protocol RT were more likely to meet their primary endpoint (aOR 4.50, 95% CI 1.23 to 20.23, P = 0.04).

Off-protocol RT during systemic therapy may influence the outcomes of phase III trials.

Among 112 published trials, 77% permitted off-protocol RT and continuation of protocol systemic therapy. However, only 2% of trials reported rates of off-protocol RT use. No trials accounted for the potential confounding effects of RT on outcomes. Open-label trials allowing off-protocol were more likely to meet their primary endpoint.

These findings argue for thoughtful integration of off-protocol RT, particularly ablative RT, at the time of trial design for phase III systemic therapy trials.

## RESULTS

Figure 1. Trial screening strategy

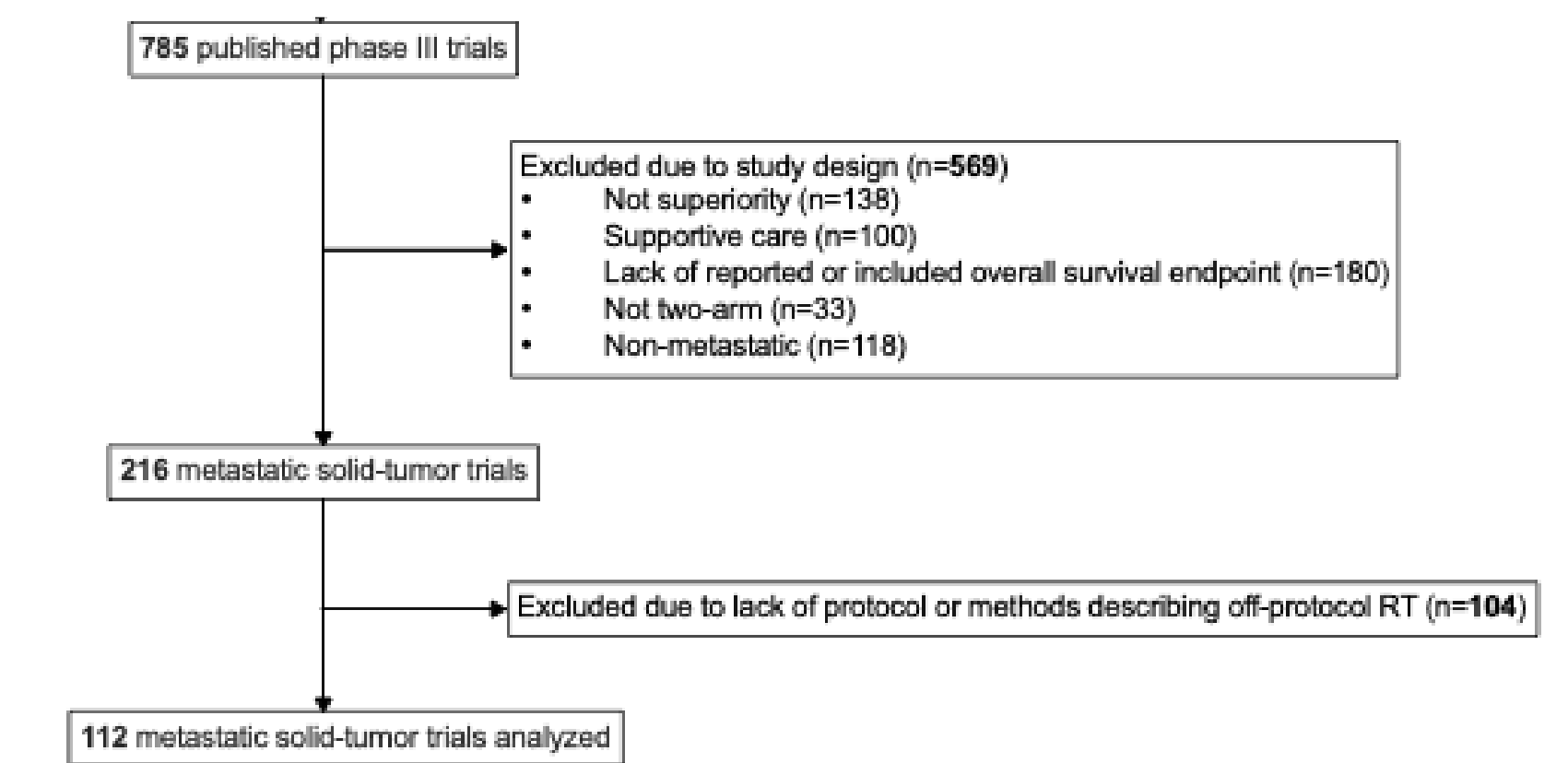
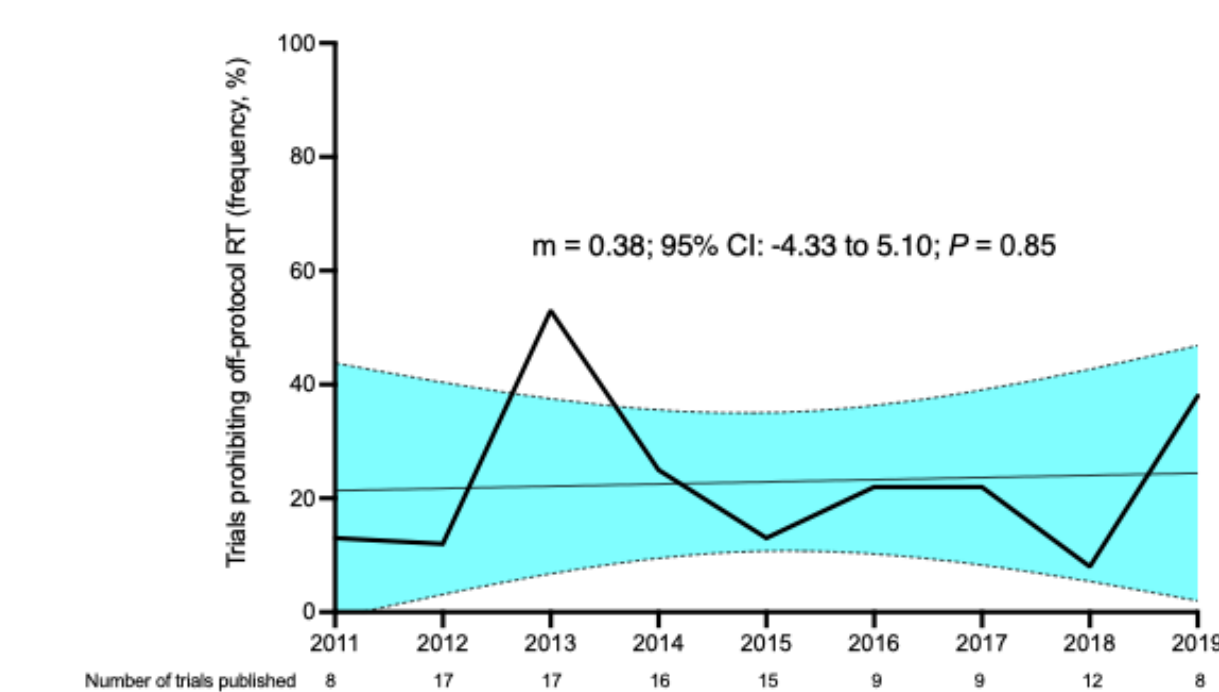


Figure 2. No change over time in trials prohibiting off-protocol RT.



## SUMMARY / CONCLUSION

While most phase III trials allowed off-protocol radiotherapy during the receipt of the study systemic therapy, the influence of off-protocol radiotherapy, especially ablative radiotherapy, on study outcomes is under-reported and under-evaluated among phase III systemic therapy trials.

## ACKNOWLEDGMENTS & CONTACT

- Cancer Center Support (Core) grant P30CA016672 & Sabin Family Foundation
- Full-text manuscript has been published by the Red Journal (*IJROBP*)
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