

Evolution of the Randomised Controlled Trial (RTC) in Oncology over Three Decades

Authors: Christopher Booth, David Cescon, Lisa Wang, Ian Tannock, Monika Krzyzanowska

National Cancer Institute of Canada Clinical Trials Group, Queen's University
Princess Margaret Hospital, University of Toronto

Background: The RCT is the gold standard for establishing new therapies in clinical oncology. Here we document changes with time in design, results, author conclusions and sponsorship.

Methods: Reports of RCTs evaluating systemic therapy for breast, colorectal (CRC) and non-small cell lung cancer (NSCLC) published 1975--2004 in 6 major journals were reviewed. Two authors independently abstracted data regarding trial design, effect size and author conclusions. Author conclusions were assigned a score from 1 to 7: 4/7 for a neutral statement, 7/7 and 1/7 for strong endorsement of experimental and control arm respectively. For each study the effect size for the primary endpoint was converted to a summary measure: hazard ratio [HR] for survival endpoints and relative risk [RR] for response rate. Descriptive statistics were used to analyze trends over time.

Results: 326 eligible RCTs were included (48% breast, 24% CRC, 28% NSCLC). There was a significant increase in the number and size of RCTs (see Table). Median rate of accrual increased from 7 patients/month in 1975-84 to 14 patients/month in 1995-2004 ($p<0.001$). There was an increase in multicenter (55 to 95%, $p<0.001$), international trials (26 to 52%, $p<0.001$) and for-profit sponsorship over time (6 to 57%, $p<0.001$). There was increasing use of survival (13 to 48%,) and decreasing use of response rate (32 to 14%) as primary endpoint ($p<0.001$). Authors have become more likely to strongly endorse the experimental arm despite no change in relative effect size over time ($p=0.005$). Studies sponsored by for-profit organizations were more likely to strongly endorse the experimental agent than studies not sponsored by for-profit groups (median author score 6/7 vs. 4/7, $p<0.001$).

Conclusions: RCTs in oncology have become more common, larger, and are more likely to be sponsored by industry. Authors of modern RCTs are more likely to strongly endorse novel therapies despite no increase in the relative benefit of interventions. For-profit sponsorship is associated with stronger endorsement of the experimental arm.

Trends in effect size, author conclusions, and sponsorship in RCTs from 1975-2004						
	No. RCTs	No. patients*	Effect size*#: HR	Effect size*#: RR	Author score*	For-profit sponsor
1975-84	47	100	1.4	0.9	4.0	6%
1985-94	108	250	1.2	1.0	4.0	21%
1995-04	171	441	1.2	1.2	6.0	57%
p-value	<0.001	<0.001	0.38	0.12	0.005	<0.001

*Median values are shown.
#Effect size reflects benefit of experimental arm over control for the primary endpoint.