Dynamic Allocation Methods: Why the Controversy?

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TRENDS IN THE APPLICATION OF DYNAMIC ALLOCATION METHODS IN MULTI-ARM CANCER CLINICAL TRIALS

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Outline

1. My interest in DA methods
2. Review of DA methods
3. Why the controversy?
4. Use of DA in oncology
5. Concluding thoughts

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My Interest in DA

- Planned to use minimization for future protocol
- Minimization = specific form of dynamic allocation (DA)
- ~300 patients
- 3 strata; 2 binary and centre (6 centres)
- 300/24 cells ~ 12-13 patients per cell

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My Interest in DA

- Which technique to use?
- Asked colleagues both at OCOG and elsewhere (NCIC, CR-UK, EORTC)
- No consensus, no policy

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Literature Review

- Lee & Feng (2005): Rand. phase II in cancer – 2.3% of trials used DA
- Altman & Dore (1990), all diseases – 1.3%
- Scott et al(2002), 4% in Lancet, NEJM;
- Others 'infrequently used', 'little used' and 'use … limited due to the administrative burden and concerns about the validity…'

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Anecdotally

- Commonly used (NCIC, OCOG, EORTC, CR-UK)?
- Was oncology different?
- What 'concerns' about the validity of DA?
- Aimed to better understand DA

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What is DA?

- method for allocating patients to treatment in multi-arm clinical trials
- minimization – Taves (1974)
- family of DA methods – Pocock & Simon (1975)

- minimize imbalances between treat. arms

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Example of Minimization

- hypothetical 2-arm trial in breast cancer
- 3 prognostic factors (strata), Her2-neu status, menopausal status and disease stage
- 19 patients on study and want to allocate (randomize) 20^{th}

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Summary of first 19 pts

Predictor		Arm A (n=10)	Arm B (n=9)
Her2-neu Status	+ve : -ve	5 : 5	6 : 3
Menopausal Status	Pre-/peri- : Post-	4 : 6	5 : 4
Stage	Early : Late	7 : 3	2 : 7

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Example of Minimization

- 20th patient is Her2-neu positive, post-menopausal with late-stage disease

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Predictor		Arm A (n=10)	Arm B (n=9)
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- If pt 20 allocated to A =>

(5+1)=6 Her2-neu+, (6+1)=7 post-menopausal and (3+1)=4 late stage pts receiving A

- If pt 20 allocated to B =>

(6+1)=7, (4+1)=5, (7+1)=8 pts receiving B

- 6+7+4 = 17 < 20 = 7+5+8

- Allocate to A

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Variations

- different measures of 'imbalance' – range, variance, imbalance score (counts/allocation ratio)
- weight factors
- balanced coin – allocate w/ probability *p*
- minimization is deterministic (p=1)
- vary *p* depending on level of imbalance

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Controversy

- non-random, primarily deterministic
- if 1st 2 patients identical characteristics
- pt 1 randomly assigned to A
- pt 2 allocated to B with prob.=1 (or *p*)

- prob(pts 1 & 2 receive A)=0 (or .5*(1-*p*))

- prob(pts 1 & 2 receive A)=.25 if random

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Controversy

- Statistical tests (Cox, Kaplan-Meier, t-tests) based on *random allocation*
- Effect of non-random allocation is unknown

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Patient ID	Treatment Received	Outcome
1	A	1
2	B	7
3	B	4
4	A	6
5	B	8
6	B	3
7	A	2
8	A	5

70 ways of selecting 4 pts to A

12 outcomes as extreme or more

p-value = 12*1/70*2 = 0.34

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Prognostic Factor	Treatment Received	Outcome
+	A	1
-	B	7
+	B	4
-	A	6
-	B	8
+	B	3
+	A	2
-	A	5

Wilcoxon rank-sum test (p=0.34)

OLS - adjust for PF (p=0.007)

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Prognostic Factor	Treatment Received	Outcome
+	A	1
-	B	7
+	B	4
-	A	6
-	B	8
+	B	3
+	A	2
-	A	5

StRS: 6 permutations for +/-, 6*6=36

1/36=0.0278 (2-sided p=0.0556)

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Patient ID	Prognostic Factor	Outcome
1	+	1
2	-	7
3	+	4
4	-	6
5	-	8
6	+	3
7	+	2
8	-	5

min: 4 permutations for +/-, 4*4=16

1/16=0.0625

(2-sided p=0.13)

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Example

- Wilcoxon rank sum, p-value=0.34

OLS, adjusting for PF, p-value=0.007

- permutation test, Stratified RS, p-value=0.056

- Permutation test, minimization, p-value=0.13

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Authorities

- Committee for Propriety Medicinal Products (2003) 'strongly advised' researchers to avoid DA methods

- FDA not adverse, but often (anecdotally) require permutation tests to be performed

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However…

- stratified block sampling (StRS) not random but accepted by authorities
- e.g. blocks of size 4 => allocation of every 4th patient strictly determined
- Can accrual of patients to trial can be considered ‘random’?

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Controversy 2

- can predict treatment of next patient
- true – if know characteristics and treatment of all patients, at all sites, previously enrolled
- Hills et al. '>60% predictability if site included as factor'
- ~50% predictability if site not included

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Solution

- Brown et al – add random element of 0.8
- reduces predictability to 'acceptable rates' (0.50-0.56) even with site as factor

- note that with StRS (block size 4):

every 4th pt deterministic

predictability =0.667

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Controversy 3

- costly, administrative burden
- extensive programming
- CPMP – observed many programming, implementation errors

- careful programming, use internet anyways, little added cost nowadays

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Controversy 4

- can always statistically adjust for prognostic factors => no need for DA

- true – but univariate analysis 'more impactful'
- ease of interpretability

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Why use DA?

- Buyse & McEntegart:

  "The argument is (about) the protection that balance affords the trial from criticism (whether ill-informed or not) … The CPMP (notes) in the case of a 'very strong baseline imbalance, no adjustment may be sufficiently convincing to restore the results.' Such imbalances are unlikely, but this is of little comfort to the trialist who experiences one!"

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Why use DA?

- balance site costs – avoid one site with all pts allocated to expensive treatment
- increased (minimal) power due to balance
- increased persuasiveness of results
- effect of univariate K-M curves

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My dilemma

- should I use DA?
- Con: concerns re: validity / predictability
- infrequently used
- susceptible to mistakes and not needed

- Pro: balanced design
- increased credibility
- balance site costs

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Nagging doubt

- anecdotally accepted and common
- previous reviews older, not cancer-specific, or for RP2 (i.e. relatively smaller sample sizes, possibly less rigor)

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Aha!!!

- co-author on article:

predictors of better journal publication (IF) for large, multi-arm cancer clinical trials 1995-2005

A) review to determine frequency of DA use

B) does use of DA predict publication in higher IF journal?

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a priori hypothesis

- hypothesis:

if balanced trials are more persuasive

=> use of DA => more persuasive results
=> authors submit to higher IF journals
& reviewers more readily accept

- H0: DA use is associated with publication in higher IF journals

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Methods

- multi-arm cancer clinical trials published in 1995-2005 in journal with IF >3
- ≥100 patients / arm
- excluded pediatric (<18 years old), palliative, supportive care, and prevention trials, meta-analyses, overviews, summaries of 2+ previous trials or updates of previous trials

- use of DA or StRS methods & other allocation factors (e.g. # of strata)

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Results

- 476 total trials
- IF<10: Ann Onc, Ann Surg Onc, BJC, Breast Can Res Treat, Clin Can Res, EJC, IJROBP, Leukemia (n=109)
- IF 10-20: JCO, JNCI (n=261)
- IF>20: JAMA, Lancet, and NEJM (n=106)

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Results

- 112 (23.5%) reported using DA
  1 reported full description of methodology
- 103 (21.6%) reported using StRS
  45 reported block size
- 261 (54.8%) reported neither

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Results

- 403 (84.7%) reported ≥1 stratification factor (including site)
- 16 (3.4%) reported using 0 factors
- 57 (12.0%) did not mention stratification

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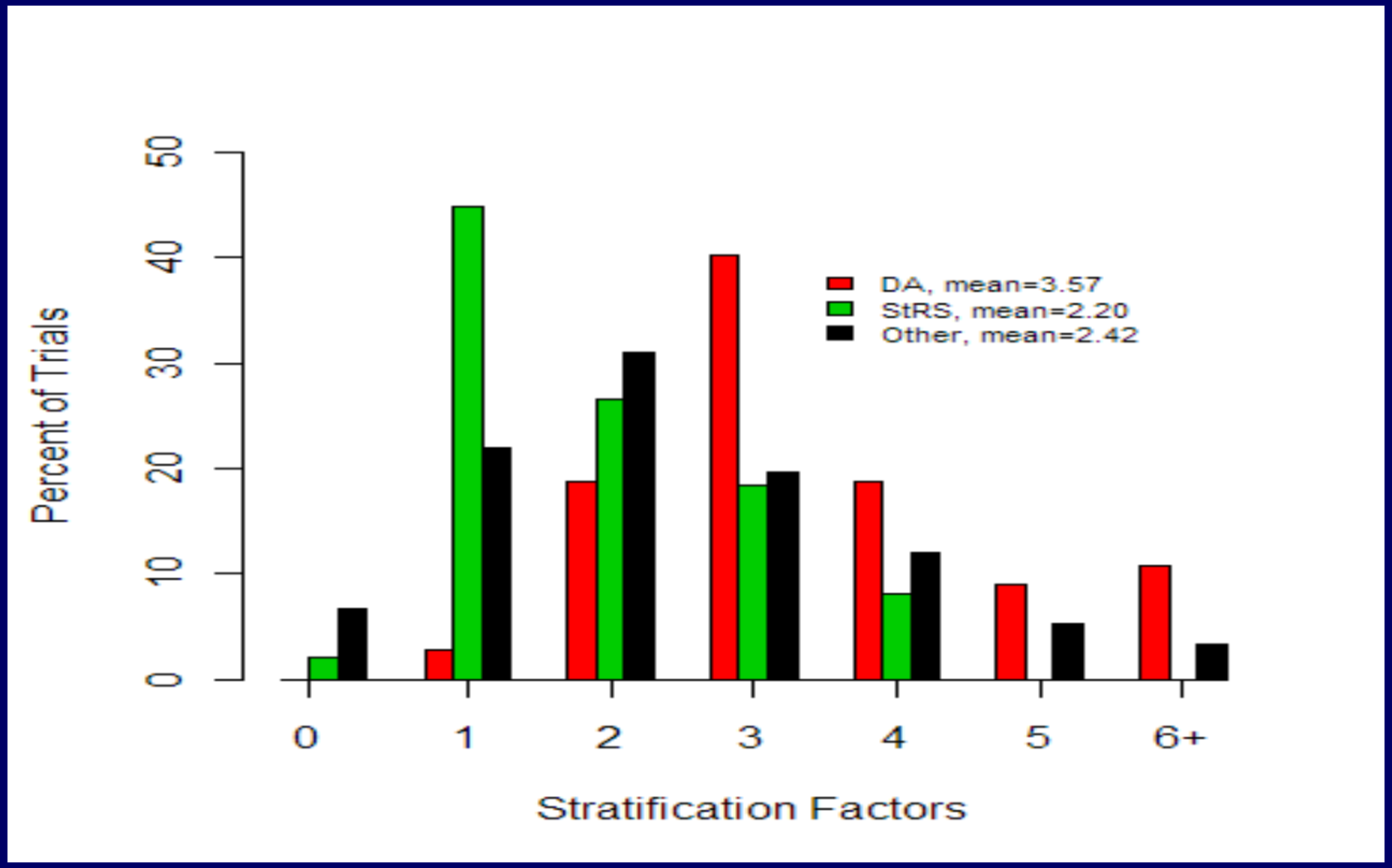

figure 1. number of stratification factors

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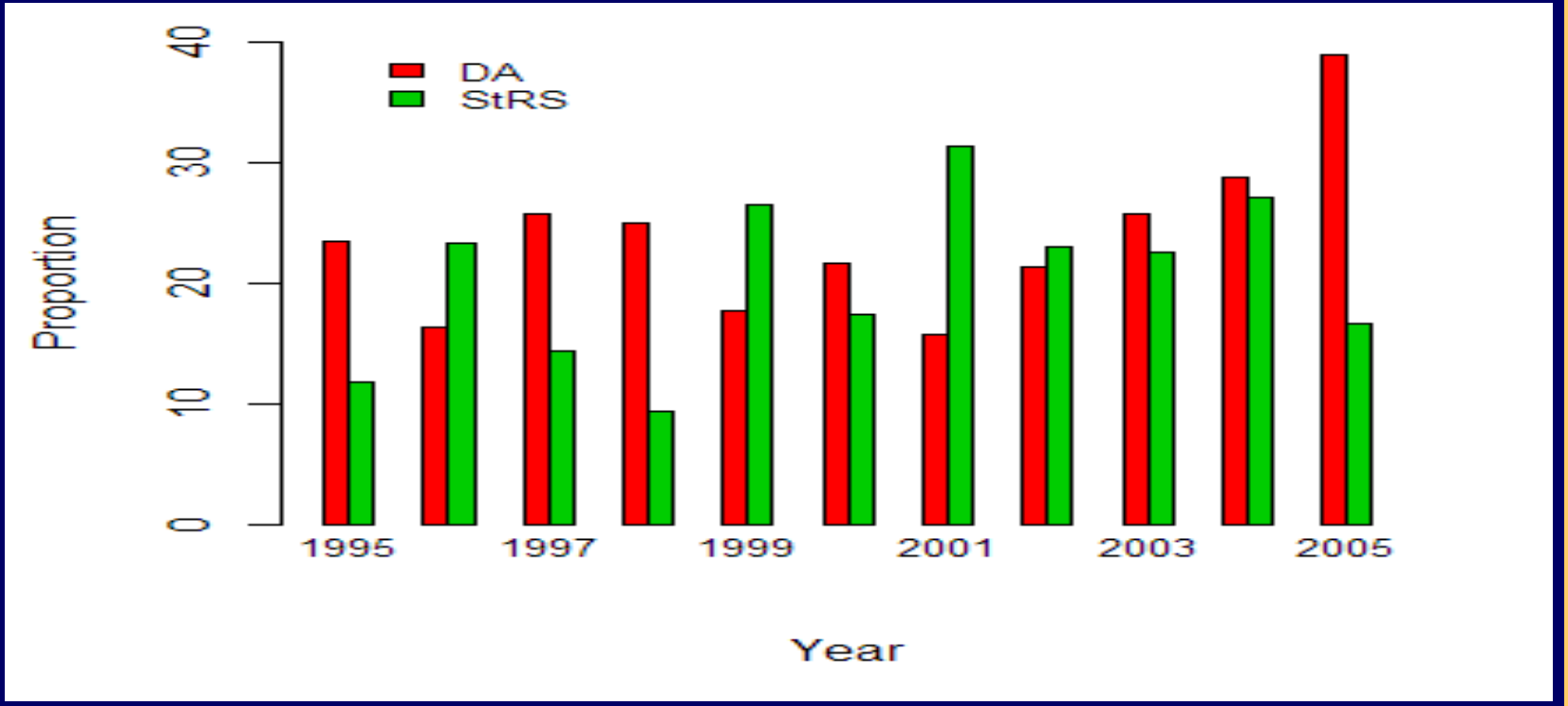

figure 2. frequency of use over time

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Results

- mean number of stratification factors in trials using DA was greater than non-DA trials (3.57 vs 2.36 – $p<0.001$)
- trend towards increased use of DA methods over time ($p=0.071$)
- no association observed between time and reported StRS use ($p=0.23$)

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			DA	StRS	Neither	p-value
Tumour Type	Hematological	34	6 (17.7)	2 (5.9)	26 (76.5)	0.053
	Other	158	41 (26.0)	39 (24.7)	78 (49.4)	
	Common	284	65 (22.9)	62 (21.8)	157 (55.3)	
Therapy	Chemo +/- MTA	292	71 (24.3)	59 (20.2)	162 (55.5)	0.60
	Non-chemo	184	41 (22.3)	44 (23.9)	99 (53.8)	
Purpose of Therapy	Adjuvant	207	52 (25.1)	62 (30.0)	93 (44.9)	<0.001
	Non-adjuvant	269	60 (22.3)	41 (15.2)	168 (62.5)	
Sponsor	Industry	183	44 (24.0)	36 (19.7)	103 (56.3)	0.72
	Non-industry	293	68 (23.2)	67 (22.9)	158 (53.9)	
Region	North America	132	26 (19.7)	24 (18.2)	82 (62.1)	0.32
	European	252	66 (26.2)	58 (23.0)	128 (50.8)	
	Multinational/Other	92	20 (21.7)	21 (22.8)	51 (55.4)	
Primary Outcome	Overall survival	221	66 (29.9)	34 (15.4)	121 (54.8)	<0.001
	Other	255	46 (18.0)	69 (27.1)	140 (54.9)	
Independent Review	No	338	75 (22.2)	76 (22.5)	187 (55.3)	0.52
	Yes	138	37 (26.8)	27 (19.6)	74 (53.6)	
Sample Size	Included	406	101 (24.9)	95 (23.4)	210 (51.7)	0.004
	Not included	70	11 (15.7)	8 (11.4)	51 (72.9)	
Analysis Method	ITT	360	92 (25.6)	88 (24.4)	180 (50.0)	<0.001
	Non	116	20 (17.2)	15 (12.9)	81 (69.8)	
Blinding	Yes	44	13 (29.6)	12 (27.3)	19 (43.2)	0.28
	No	432	99 (22.9)	91 (21.1)	242 (56.0)	
Outcome of Study	Positive	162	32 (19.8)	44 (27.2)	86 (53.1)	0.073
	Not positive	283	72 (25.4)	52 (18.4)	159 (56.2)	
Trial Sample Size	<300	128	32 (25.0)	23 (18.0)	73 (57.0)	0.006
	300-499	171	28 (16.4)	36 (21.1)	107 (62.6)	
	500-749	81	20 (24.7)	19 (23.5)	42 (51.9)	
	750-999	36	7 (19.4)	12 (33.3)	17 (47.2)	
	1000+	60	16 (26.7)	22 (36.7)	22 (36.7)	

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Table 2. Summary of trial-specific characteristics

Results

- allocation method associated with:

- purpose of therapy (adjuvant vs non-adj)
- primary outcome (OS vs other)
- SS calculation reported (yes vs no)
- analysis method (ITT vs other)
- trial SS

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Results

- Better written trials associated with higher reported use of DA
- If used OS as primary outcome, SS calculation described, used ITT => more likely to report using DA
- positive trials less likely to report using DA & more likely StRS (p=0.073)

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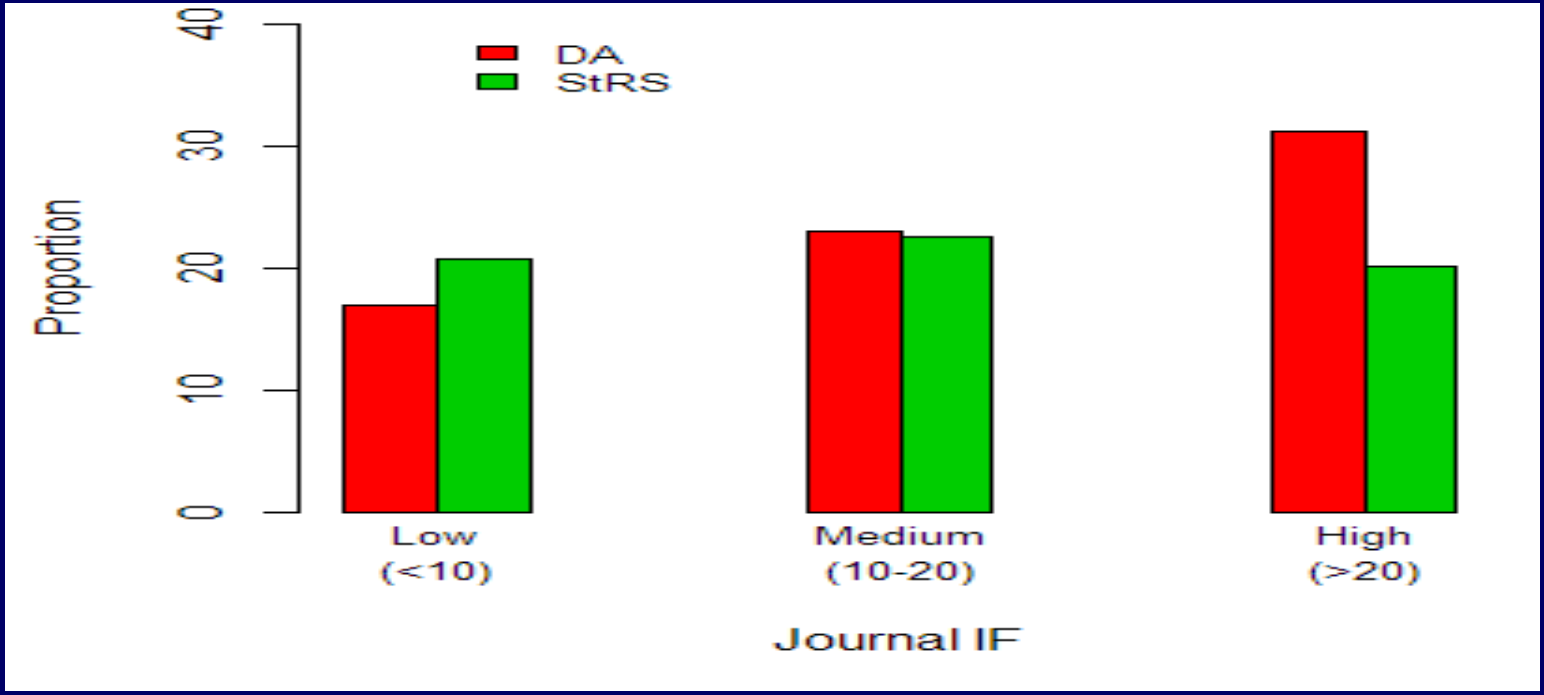

figure 3. frequency of use by journal IF

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Results

	Low (IF <10)	Middle (IF 10-20)	High (IF >20)
N	*106*	*261*	*109*
DA StRS Neither	18 (17.0%) 22 (20.8%) 66 (62.3%)	60 (23.0%) 59 (22.6%) 142 (54.4%)	34 (31.2%) 22 (20.2%) 53 (48.6%)

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- allocation method significantly associated with journal IF (p=0.039)
- OR was 1.75 (95% CI: 1.14-2.68) for DA versus no allocation method (p=0.024)
- OR was 1.16 (95% CI: 0.74-1.79) for StRS versus no allocation method (p=0.54)

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- adjusted for study outcome, SS, ITT, geographic region, purpose of therapy, time to publication, tumor type and SS calculation described
- allocation method remained significant as predictor of journal IF (p=0.039)
- OR: 1.55 (95% CI: 0.94-2.55) for DA versus no allocation method (p=0.015)
- OR: 0.72 (95% CI: 0.42-1.21) for StRS vs no allocation method (p=0.033)

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Conclusions

- DA methods frequent in cancer trials
- manuscripts in higher IF journals reported DA methods more frequently
- other measures of quality also associated with reporting of DA use
- adjusting for other measures, reported DA use remained a predictor of publication in higher IF journals

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Personal Opinion

- DA appears acceptable
- need better reporting of methodology
- using DA ≠ higher IF journal publication
- better written article => more likely to describe allocation method & be positively reviewed

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Why?

- StRS negatively associated w/ journal IF
- positive trials reported using DA less often, and StRS more often
- Does it relate to impact of results?

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