Supplementary Appendix

Adjuvant whole brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicentre, randomised phase 3 trial

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Table of Contents

Table S1. Recruitment by site **4**

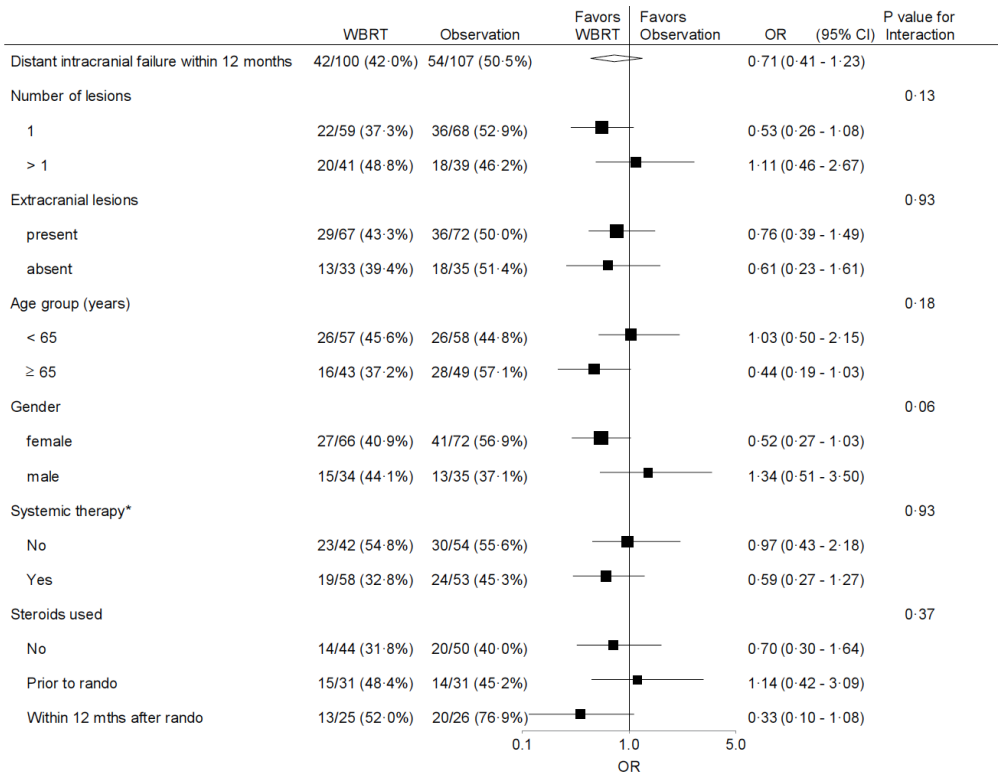
Table 3a. Distant intracranial failure within 12 months stratified by subgroup ... **5**

Table S3. Comparison of the toxicity between the two groups **5**

Table S1. Recruitment by site

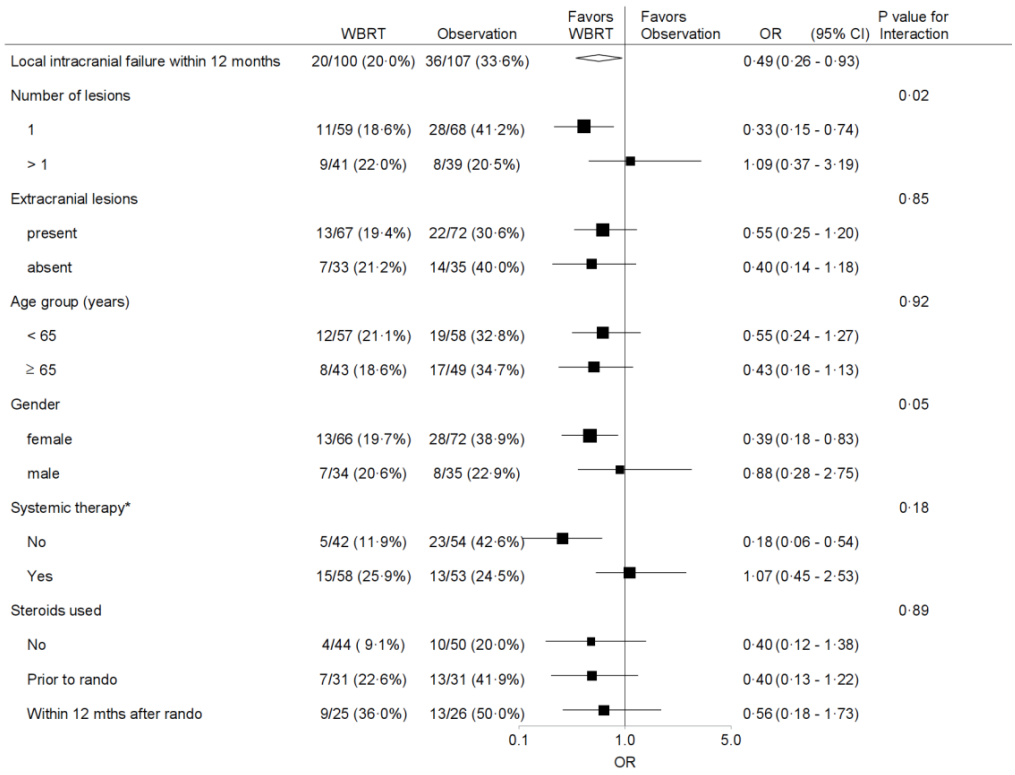
Site	Number of Patients Randomised
Melanoma Institute Australia, Sydney, NSW, Australia	85
Oslo University Hospital, The Radium Hospital, Oslo, Norway	57
Princess Alexandra Hospital, Brisbane, QLD, Australia	21
Peter MacCallum Cancer Centre, Melbourne, VIC, Australia	8
Norfolk and Norwich University Hospital, Norwich, UK	5
Royal Adelaide Hospital, Adelaide, SA, Australia	4
Addenbrookes Hospital, Cambridge, UK	3
Royal Brisbane Women's Hospital, Brisbane, QLD, Australia	3
Royal Hobart Hospital, Hobart, TAS, Australia	3
St James' University Hospital, Leeds, UK	3
St Vincent's Hospital, Sydney, NSW, Australia	3
William Buckland Cancer Centre at The Alfred Hospital, Melbourne, VIC, Australia	3
Genesis Cancer Care Newcastle, NSW, Australia	2
Mount Vernon Cancer Centre, London, UK	2
Nepean Hospital, Sydney, NSW, Australia	2
NT Radiation Oncology, Royal Darwin Hospital, NT, Australia	2
Royal North Shore Hospital, Sydney, NSW, Australia	2
Calvary Mater Hospital, Newcastle, NSW, Australia	1
Churchill Hospital, Oxford, UK	1
James Cook Hospital, Middlesborough, UK	1
Poole Hospital, Dorset, UK	1
Royal Surrey County Hospital, Guildford, UK	1
Townsville Hospital, Townsville, QLD, Australia	1
Westmead Hospital, Sydney, NSW, Australia	1

Table S2a. Distant intracranial failure within 12 months stratified by subgroup



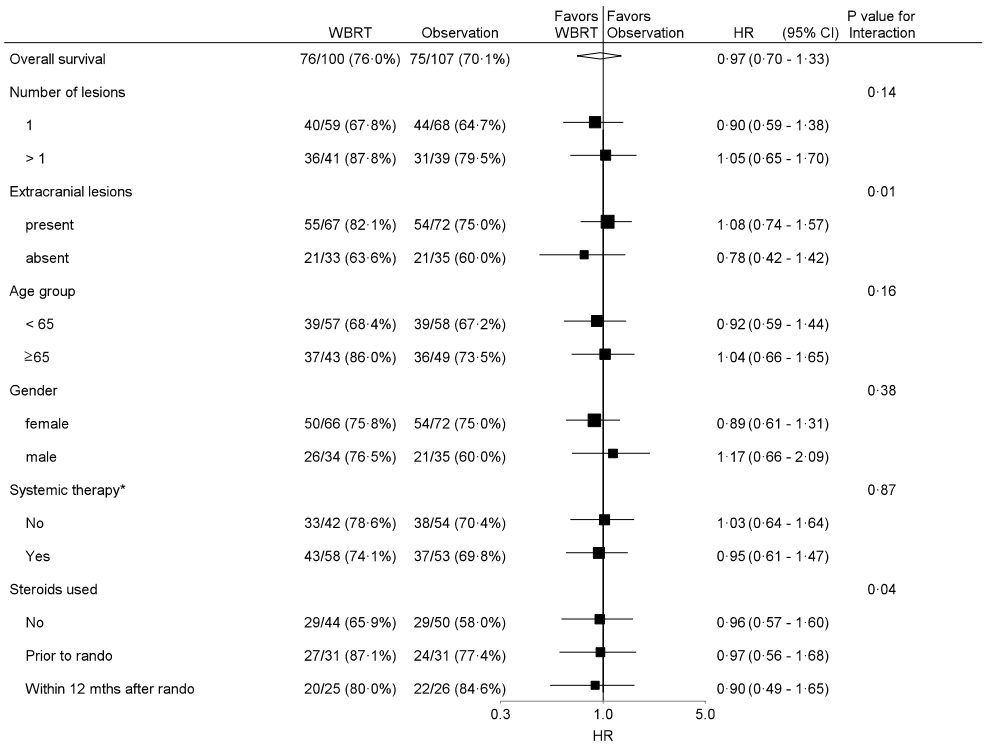
***Systemic therapy at the time of randomisation or prior to reaching primary endpoint.**

Table S2b. Local intracranial failure within 12 months stratified by subgroup



***Systemic therapy at the time of randomisation or prior to reaching primary endpoint.**

Table S2c. Overall survival stratified by subgroup



***Systemic therapy at the time of randomisation or prior to reaching primary endpoint.**

Table S3. Comparison of the toxicity between the two groups

Type	Severity	Observation (N = 107)	WBRT (N = 100)	P-value
Anorexia				
Baseline				0·4128
	Grade-1	2/102 (2·0%)	1/90 (1·1%)	
	Grade-2	0/102 (0·0%)	2/90 (2·2%)	
2-month				0·4100
	Grade-1	10/89 (11·2%)	13/85 (15·3%)	
	Grade-2	3/89 (3·4%)	6/85 (7·1%)	
	Grade-3	1/89 (1·1%)	0/85 (0·0%)	
4-month				<·0001
	Grade-1	3/60 (5·0%)	24/75 (32·0%)	
	Grade-2	2/60 (3·3%)	10/75 (13·3%)	
6-month				0·0341
	Grade-1	1/51 (2·0%)	8/64 (12·5%)	
	Grade-2	4/51 (7·8%)	9/64 (14·1%)	
	Grade-3	0/51 (0·0%)	2/64 (3·1%)	
8-month				0·1800
	Grade-1	0/42 (0·0%)	1/51 (2·0%)	
	Grade-2	0/42 (0·0%)	4/51 (7·8%)	
	Grade-3	2/42 (4·8%)	1/51 (2·0%)	
10-month				0·4202
	Grade-1	0/28 (0·0%)	3/44 (6·8%)	
	Grade-2	1/28 (3·6%)	1/44 (2·3%)	
	Grade-3	0/28 (0·0%)	2/44 (4·5%)	
12-month				0·5081
	Grade-1	1/29 (3·4%)	5/47 (10·6%)	
	Grade-2	1/29 (3·4%)	1/47 (2·1%)	
	Grade-3	0/29 (0·0%)	2/47 (4·3%)	
14-month				0·1752
	Grade-1	0/22 (0·0%)	5/34 (14·7%)	
	Grade-2	1/22 (4·5%)	1/34 (2·9%)	
16-month				1·0000
	Grade-1	1/17 (5·9%)	3/33 (9·1%)	
	Grade-2	0/17 (0·0%)	1/33 (3·0%)	
18-month				0·1156
	Grade-1	0/17 (0·0%)	1/32 (3·1%)	
	Grade-2	2/17 (11·8%)	0/32 (0·0%)	
20-month				0·1453
	Grade-1	0/16 (0·0%)	3/24 (12·5%)	
	Grade-2	1/16 (6·3%)	0/24 (0·0%)	
22-month				1·0000
	Grade-1	0/13 (0·0%)	1/22 (4·5%)	
	Grade-2	0/13 (0·0%)	1/22 (4·5%)	
24-month				1·0000
	Grade-1	1/17 (5·9%)	2/18 (11·1%)	
Nausea				
Baseline				1·0000
	Grade-1	5/102 (4·9%)	5/90 (5·6%)	
2-month				0·0024
	Grade-1	6/89 (6·7%)	22/85 (25·9%)	
	Grade-2	8/89 (9·0%)	6/85 (7·1%)	
4-month				0·1865
	Grade-1	5/60 (8·3%)	13/75 (17·3%)	

Type	Severity	Observation (N = 107)	WBRT (N = 100)	P-value
	Grade-2	4/60 (6·7%)	8/75 (10·7%)	
6-month				0·0516
	Grade-1	2/51 (3·9%)	11/64 (17·2%)	
	Grade-2	1/51 (2·0%)	2/64 (3·1%)	
	Grade-3	0/51 (0·0%)	1/64 (1·6%)	
8-month				1·0000
	Grade-1	2/42 (4·8%)	3/51 (5·9%)	
	Grade-2	0/42 (0·0%)	1/51 (2·0%)	
	Grade-3	1/42 (2·4%)	1/51 (2·0%)	
10-month				1·0000
	Grade-1	1/28 (3·6%)	3/44 (6·8%)	
	Grade-2	0/28 (0·0%)	1/44 (2·3%)	
12-month				0·4306
	Grade-1	2/29 (6·9%)	5/47 (10·6%)	
	Grade-2	0/29 (0·0%)	3/47 (6·4%)	
14-month				0·1502
	Grade-1	0/22 (0·0%)	3/34 (8·8%)	
	Grade-2	0/22 (0·0%)	3/34 (8·8%)	
16-month				0·4615
	Grade-1	0/17 (0·0%)	2/33 (6·1%)	
	Grade-2	0/17 (0·0%)	3/33 (9·1%)	
18-month				0·7878
	Grade-1	1/17 (5·9%)	1/32 (3·1%)	
	Grade-2	0/17 (0·0%)	2/32 (6·3%)	
20-month				1·0000
	Grade-1	0/16 (0·0%)	1/24 (4·2%)	
	Grade-2	1/16 (6·3%)	1/24 (4·2%)	
22-month				0·5193
	Grade-1	0/13 (0·0%)	2/22 (9·1%)	
24-month				0·4857
	Grade-1	1/17 (5·9%)	0/18 (0·0%)	
Vomiting				
2-month				0·4492
	Grade-1	2/89 (2·2%)	5/85 (5·9%)	
	Grade-2	2/89 (2·2%)	1/85 (1·2%)	
4-month				0·3410
	Grade-1	2/60 (3·3%)	5/75 (6·7%)	
	Grade-2	1/60 (1·7%)	0/75 (0·0%)	
6-month				1·0000
	Grade-1	1/51 (2·0%)	2/64 (3·1%)	
	Grade-2	0/51 (0·0%)	1/64 (1·6%)	
	Grade-3	0/51 (0·0%)	1/64 (1·6%)	
8-month				0·8395
	Grade-1	0/42 (0·0%)	1/51 (2·0%)	
	Grade-2	1/42 (2·4%)	0/51 (0·0%)	
	Grade-3	0/42 (0·0%)	1/51 (2·0%)	
10-month				1·0000
	Grade-1	1/28 (3·6%)	1/44 (2·3%)	
	Grade-3	0/28 (0·0%)	1/44 (2·3%)	
12-month				1·0000
	Grade-1	1/29 (3·4%)	1/47 (2·1%)	
14-month				1·0000
	Grade-1	1/22 (4·5%)	1/34 (2·9%)	
	Grade-2	0/22 (0·0%)	1/34 (2·9%)	
16-month				0·5420

Type	Severity	Observation (N = 107)	WBRT (N = 100)	P-value
	Grade-1	0/17 (0·0%)	2/33 (6·1%)	
18-month				0·5374
	Grade-1	0/17 (0·0%)	2/32 (6·3%)	
20-month				0·4000
	Grade-1	1/16 (6·3%)	0/24 (0·0%)	
22-month				0·3714
	Grade-3	1/13 (7·7%)	0/22 (0·0%)	
Alopecia				
Baseline				0·6667
	Grade-1	2/102 (2·0%)	3/90 (3·3%)	
2-month				<·0001
	Grade-1	2/89 (2·2%)	6/85 (7·1%)	
	Grade-2	2/89 (2·2%)	47/85 (55·3%)	
4-month				<·0001
	Grade-1	1/60 (1·7%)	12/75 (16·0%)	
	Grade-2	6/60 (10·0%)	29/75 (38·7%)	
6-month				0·0068
	Grade-1	1/51 (2·0%)	8/64 (12·5%)	
	Grade-2	6/51 (11·8%)	17/64 (26·6%)	
8-month				0·7170
	Grade-1	2/42 (4·8%)	5/51 (9·8%)	
	Grade-2	4/42 (9·5%)	5/51 (9·8%)	
10-month				0·3033
	Grade-1	1/28 (3·6%)	6/44 (13·6%)	
	Grade-2	0/28 (0·0%)	1/44 (2·3%)	
12-month				0·2059
	Grade-1	0/29 (0·0%)	4/47 (8·5%)	
	Grade-2	0/29 (0·0%)	1/47 (2·1%)	
14-month				0·5143
	Grade-1	0/22 (0·0%)	2/34 (5·9%)	
16-month				0·7921
	Grade-1	0/17 (0·0%)	2/33 (6·1%)	
	Grade-2	1/17 (5·9%)	1/33 (3·0%)	
18-month				1·0000
	Grade-1	0/17 (0·0%)	1/32 (3·1%)	
20-month				1·0000
	Grade-1	1/16 (6·3%)	2/24 (8·3%)	
22-month				1·0000
	Grade-1	0/13 (0·0%)	1/22 (4·5%)	
24-month				0·4857
	Grade-2	1/17 (5·9%)	0/18 (0·0%)	
Dermatitis				
2-month				0·0006
	Grade-1	0/89 (0·0%)	9/85 (10·6%)	
	Grade-2	0/89 (0·0%)	1/85 (1·2%)	
4-month				1·0000
	Grade-1	0/60 (0·0%)	1/75 (1·3%)	
6-month				1·0000
	Grade-1	0/51 (0·0%)	1/64 (1·6%)	
14-month				0·3929
	Grade-1	1/22 (4·5%)	0/34 (0·0%)	
22-month				1·0000
	Grade-1	0/13 (0·0%)	1/22 (4·5%)	
Fatigue				
Baseline				0·9403

Type	Severity	Observation (N = 107)	WBRT (N = 100)	P-value
	Grade-1	23/102 (22·5%)	23/90 (25·6%)	
	Grade-2	8/102 (7·8%)	6/90 (6·7%)	
	Grade-3	1/102 (1·0%)	0/90 (0·0%)	
2-month				<·0001
	Grade-1	13/89 (14·6%)	38/85 (44·7%)	
	Grade-2	12/89 (13·5%)	20/85 (23·5%)	
	Grade-3	2/89 (2·2%)	1/85 (1·2%)	
4-month				0·0017
	Grade-1	11/60 (18·3%)	24/75 (32·0%)	
	Grade-2	9/60 (15·0%)	25/75 (33·3%)	
	Grade-3	2/60 (3·3%)	2/75 (2·7%)	
6-month				0·3821
	Grade-1	7/51 (13·7%)	13/64 (20·3%)	
	Grade-2	7/51 (13·7%)	14/64 (21·9%)	
	Grade-3	1/51 (2·0%)	2/64 (3·1%)	
	Grade-4	0/51 (0·0%)	1/64 (1·6%)	
8-month				0·5987
	Grade-1	7/42 (16·7%)	10/51 (19·6%)	
	Grade-2	7/42 (16·7%)	9/51 (17·6%)	
	Grade-3	2/42 (4·8%)	0/51 (0·0%)	
10-month				0·2503
	Grade-1	5/28 (17·9%)	5/44 (11·4%)	
	Grade-2	3/28 (10·7%)	13/44 (29·5%)	
	Grade-3	1/28 (3·6%)	1/44 (2·3%)	
12-month				0·6055
	Grade-1	7/29 (24·1%)	7/47 (14·9%)	
	Grade-2	3/29 (10·3%)	10/47 (21·3%)	
	Grade-3	2/29 (6·9%)	2/47 (4·3%)	
	Grade-4	0/29 (0·0%)	1/47 (2·1%)	
14-month				0·2779
	Grade-1	2/22 (9·1%)	9/34 (26·5%)	
	Grade-2	4/22 (18·2%)	6/34 (17·6%)	
	Grade-3	0/22 (0·0%)	1/34 (2·9%)	
16-month				1·0000
	Grade-1	4/17 (23·5%)	8/33 (24·2%)	
	Grade-2	3/17 (17·6%)	6/33 (18·2%)	
	Grade-3	0/17 (0·0%)	1/33 (3·0%)	
18-month				0·6577
	Grade-1	3/17 (17·6%)	5/32 (15·6%)	
	Grade-2	5/17 (29·4%)	5/32 (15·6%)	
	Grade-3	0/17 (0·0%)	1/32 (3·1%)	
20-month				0·7861
	Grade-1	2/16 (12·5%)	4/24 (16·7%)	
	Grade-2	3/16 (18·8%)	6/24 (25·0%)	
	Grade-3	1/16 (6·3%)	0/24 (0·0%)	
22-month				0·7787
	Grade-1	1/13 (7·7%)	3/22 (13·6%)	
	Grade-2	4/13 (30·8%)	5/22 (22·7%)	
	Grade-3	1/13 (7·7%)	0/22 (0·0%)	
	Grade-4	0/13 (0·0%)	1/22 (4·5%)	
24-month				0·3237
	Grade-1	4/17 (23·5%)	1/18 (5·6%)	
	Grade-2	3/17 (17·6%)	5/18 (27·8%)	
	Grade-3	1/17 (5·9%)	0/18 (0·0%)	
Pain				

Type	Severity	Observation (N = 107)	WBRT (N = 100)	P-value
Baseline				0·9229
	Grade-1	11/102 (10·8%)	9/90 (10·0%)	
	Grade-2	5/102 (4·9%)	3/90 (3·3%)	
	Grade-3	1/102 (1·0%)	0/90 (0·0%)	
2-month				0·1472
	Grade-1	11/89 (12·4%)	16/85 (18·8%)	
	Grade-2	14/89 (15·7%)	6/85 (7·1%)	
4-month				0·1112
	Grade-1	5/60 (8·3%)	11/75 (14·7%)	
	Grade-2	3/60 (5·0%)	10/75 (13·3%)	
	Grade-3	1/60 (1·7%)	0/75 (0·0%)	
6-month				0·0062
	Grade-1	4/51 (7·8%)	8/64 (12·5%)	
	Grade-2	1/51 (2·0%)	12/64 (18·8%)	
	Grade-3	0/51 (0·0%)	1/64 (1·6%)	
8-month				0·7679
	Grade-1	4/42 (9·5%)	6/51 (11·8%)	
	Grade-2	2/42 (4·8%)	4/51 (7·8%)	
	Grade-3	1/42 (2·4%)	0/51 (0·0%)	
10-month				0·6718
	Grade-1	4/28 (14·3%)	9/44 (20·5%)	
	Grade-2	2/28 (7·1%)	5/44 (11·4%)	
12-month				0·4506
	Grade-1	4/29 (13·8%)	12/47 (25·5%)	
	Grade-2	3/29 (10·3%)	6/47 (12·8%)	
	Grade-3	0/29 (0·0%)	1/47 (2·1%)	
14-month				0·7796
	Grade-1	5/22 (22·7%)	6/34 (17·6%)	
	Grade-2	2/22 (9·1%)	6/34 (17·6%)	
16-month				0·1132
	Grade-1	4/17 (23·5%)	2/33 (6·1%)	
	Grade-2	0/17 (0·0%)	5/33 (15·2%)	
	Grade-3	1/17 (5·9%)	1/33 (3·0%)	
18-month				0·4368
	Grade-1	4/17 (23·5%)	3/32 (9·4%)	
	Grade-2	1/17 (5·9%)	3/32 (9·4%)	
20-month				0·4854
	Grade-1	3/16 (18·8%)	1/24 (4·2%)	
	Grade-2	1/16 (6·3%)	3/24 (12·5%)	
22-month				0·8760
	Grade-1	2/13 (15·4%)	5/22 (22·7%)	
	Grade-2	2/13 (15·4%)	2/22 (9·1%)	
24-month				0·8625
	Grade-1	2/17 (11·8%)	2/18 (11·1%)	
	Grade-2	2/17 (11·8%)	4/18 (22·2%)	
	Grade-3	1/17 (5·9%)	0/18 (0·0%)	