

**Early Results of a Randomised Trial Comparing
Surgery Alone with Surgery Plus Post-Operative
Radiation Therapy Following Resection of
Melanoma Involving Regional Lymph Nodes -
Results of the TROG 02.01 / ANZMTG 01.02
Intergroup Trial**



**Trans-Tasman
Radiation Oncology Group**



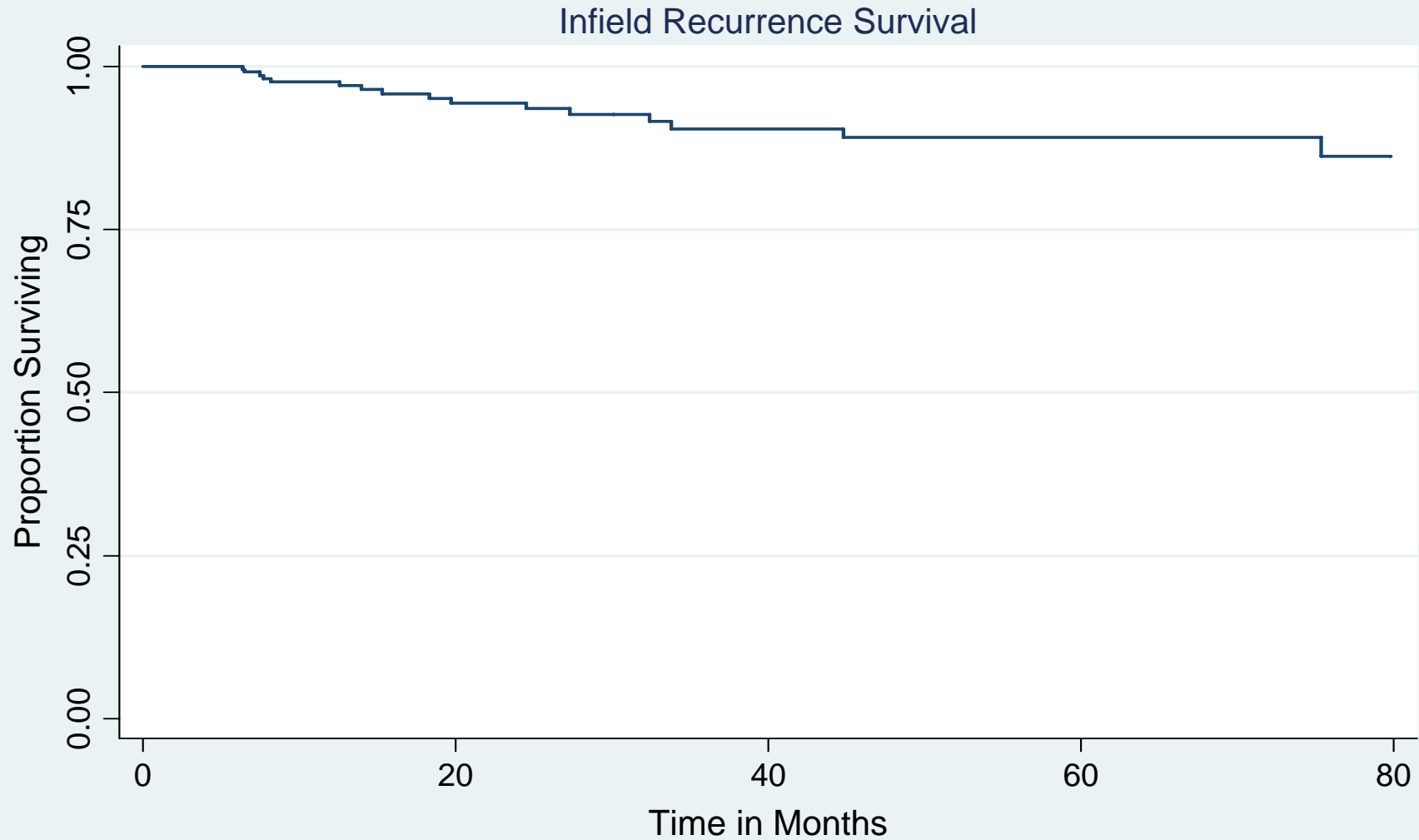
Disclosures

Nil

Background

- **TROG 96.06: single arm phase II trial of adjuvant radiation therapy after lymphadenectomy for lymph node field recurrent melanoma:**
 - 234 patients, 8 centres
 - Radiation therapy: 48 Gy in 20 fraction given 5 days per week
 - Analysis of late toxicity (n=130): *Burmeister et al., ANZ J Surg 72: 344-48; 2002*
 - Final analysis: *Burmeister et al., Radiotherapy and Oncology 81: 136-42; 2006*

TROG 96.06 - Time to in-field recurrence



Primary Objective

Patients with a nodal field relapse which is completely resected but who are at significant risk of further lymph node field relapse:

To compare adjuvant radiation therapy with initial observation with respect to risk of subsequent lymph node field relapse.

Trial Schema

Surgery for Lymph Node Field Recurrent Melanoma

Main Eligibility Criteria

- Completely resected, palpable, nodal metastatic melanoma
- No previous or concurrent local, *in transit* or distant metastatic relapse
- At significant risk for lymph node field relapse

Stratification

Institution
Lymph node field site
Number of positive nodes
Metastatic node size
Extent of extra-nodal spread

RANDOMISATION

**Adjuvant Radiation
Therapy (RT)**

Observation (Obs)

RT for isolated lymph node field relapse

Statistical Considerations

Target sample size	220 patients
Criterion	Nodal field relapse rate difference = 15% (15% versus 30% at 1 year) with 80% power
Statistical methods	Logrank comparison of time to nodal field relapse curves (Kaplan-Meier)
IDMC	Three international experts (surgeon, radiation oncologist, statistician)
Amendment	Sample size increased to 250 to compensate for eligibility infringements

Trial Endpoints

- **Primary Endpoint:**
 - Lymph Node Field Relapse
(as a first relapse)
- **Secondary Endpoints:**
 - Overall survival
 - Relapse-free survival
 - Patterns of relapse
 - Late toxicity
 - Quality of life

Eligibility Criteria

Standard Surgical Procedure

Minimum lymph node numbers harvested:

Parotid & Neck	2 – 25 (depending on type of dissection)
Axilla	10
Groin	6

At 'significant' risk of lymph node field relapse

No of positive lymph nodes, OR

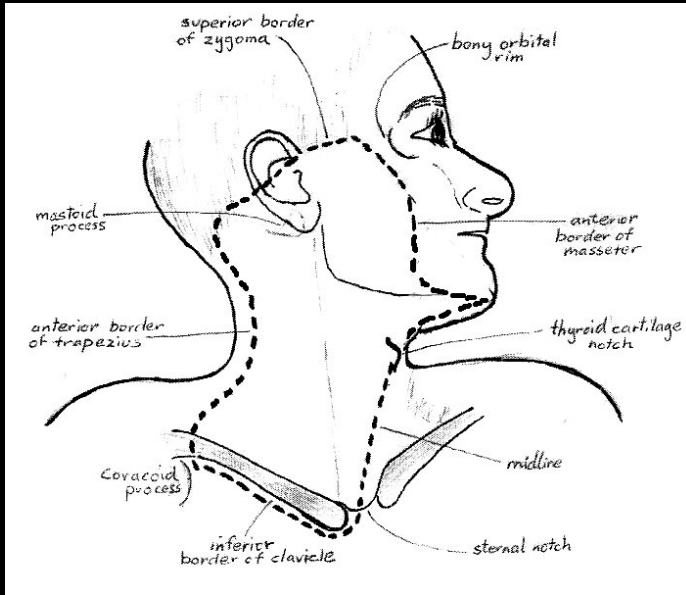
Parotid	≥ 1
Neck, axilla	≥ 2
Groin	≥ 3

Maximum positive lymph node size, OR

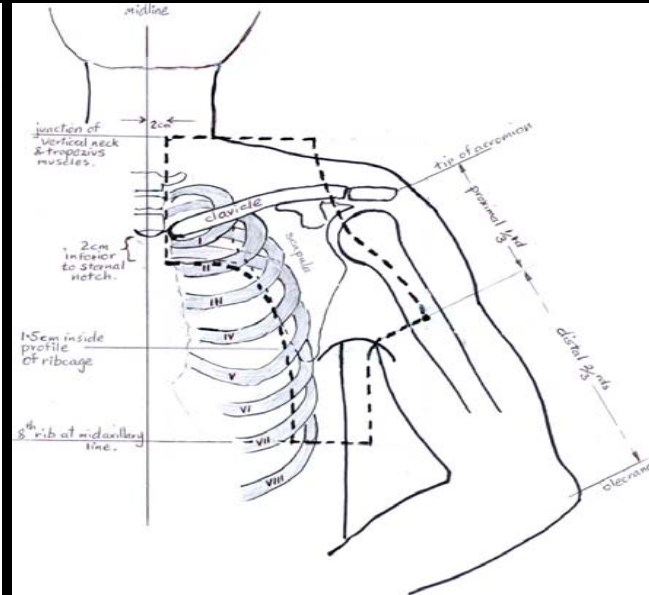
Parotid, Neck + Axilla	≥ 30 mm
Groin	≥ 40 mm

Extra-nodal spread

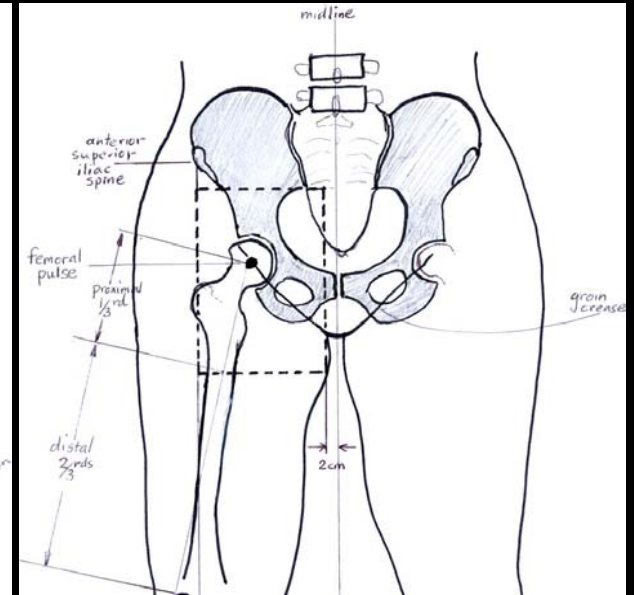
Lymph Node Fields



Parotid & Neck



Axilla



Groin

Radiation Therapy

48 Gy in 20 fractions over 4 weeks

Review of Eligibility Infringements

- **Eligibility infringements noticed during planned QA of data.**
- **IDMC recommended:**
 - **Independent, blinded review of eligibility to identify patients with major eligibility infringements**
 - **Purpose: to establish the most appropriate patient population to be used for the analysis of the primary endpoint.**

Major Eligibility Infringements

41 infringements in 31 patients

Major eligibility infringement	N
Local or <i>in transit</i> disease (prior to or surgery)	19
Non-palpable nodes	12
Disease in two lymph node fields	4
Distant metastasis prior to randomisation	3
Incomplete resection	1
Previous disease in nodal field	1
No melanoma in nodes at lymphadenectomy	1

Patient Populations

Patient subset	All	RT	Obs
Randomised	250	123	127
No follow-up (withdrew consent)	2	1	1
ITT population	248	122	126
Major eligibility infringement	31	13	18
Fully evaluable population	217	109	108

Results

(ITT population n= 248)

Accrual	5.5 years	(Mar 2002 – Sept 2007)
Median follow-up	39 months	(range 14 to 75 mo.)
Lost to follow-up	4	(followed 5 – 21 mo.)
Total relapses	161 patients	
Lymph node field relapses (as a first relapse)	62 patients	
Deaths	120	(2 not melanoma related)

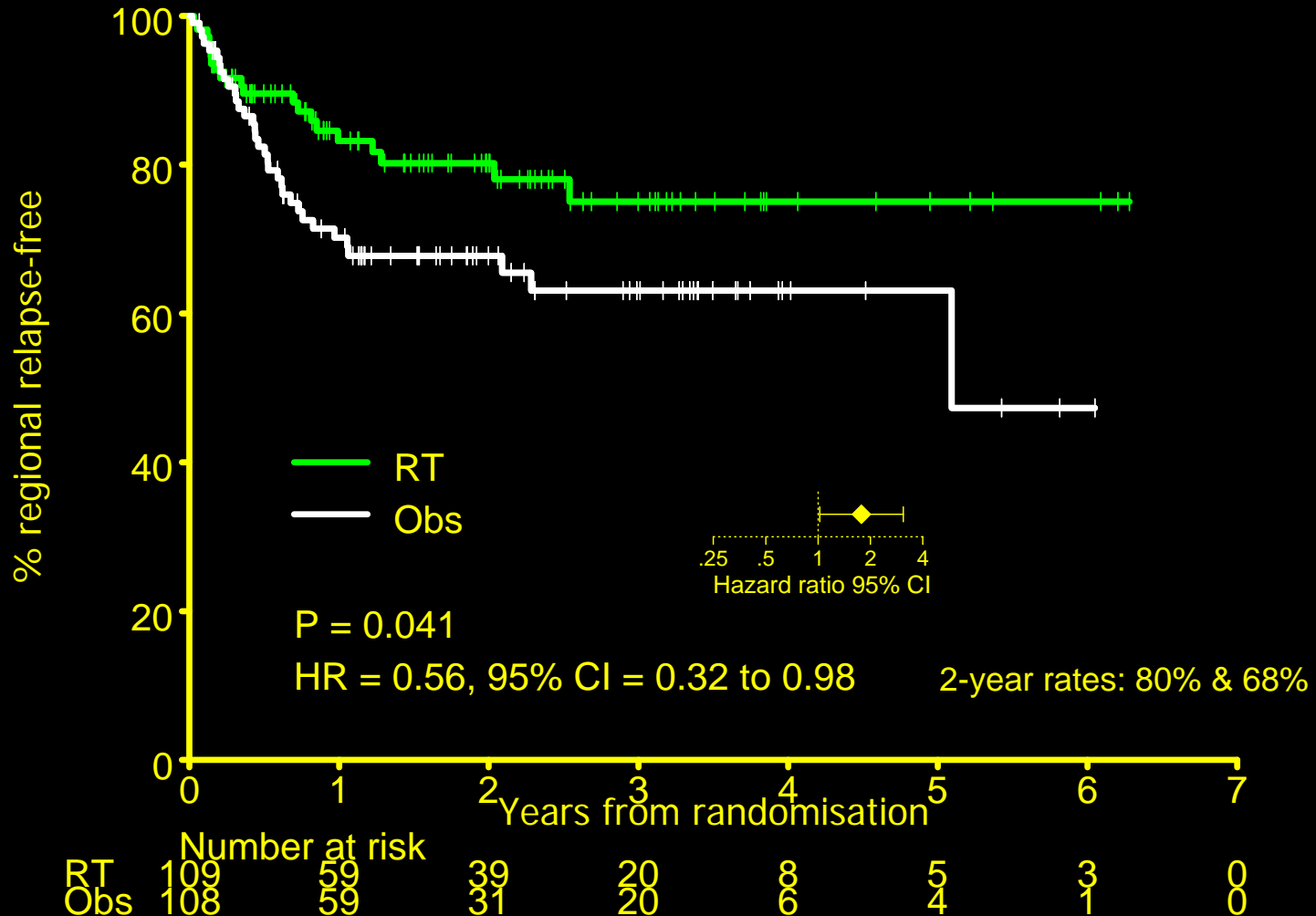
Baseline Characteristics

(ITT population n=248)

		RT (122)	OBS (126)
Age	Median (years)	58	57
Gender	M	92	92
	F	30	34
Nodal field site	H+N	31	34
	Axilla	52	52
	Groin	39	40
Extra-nodal spread	Present	61	64
	Absent	61	62

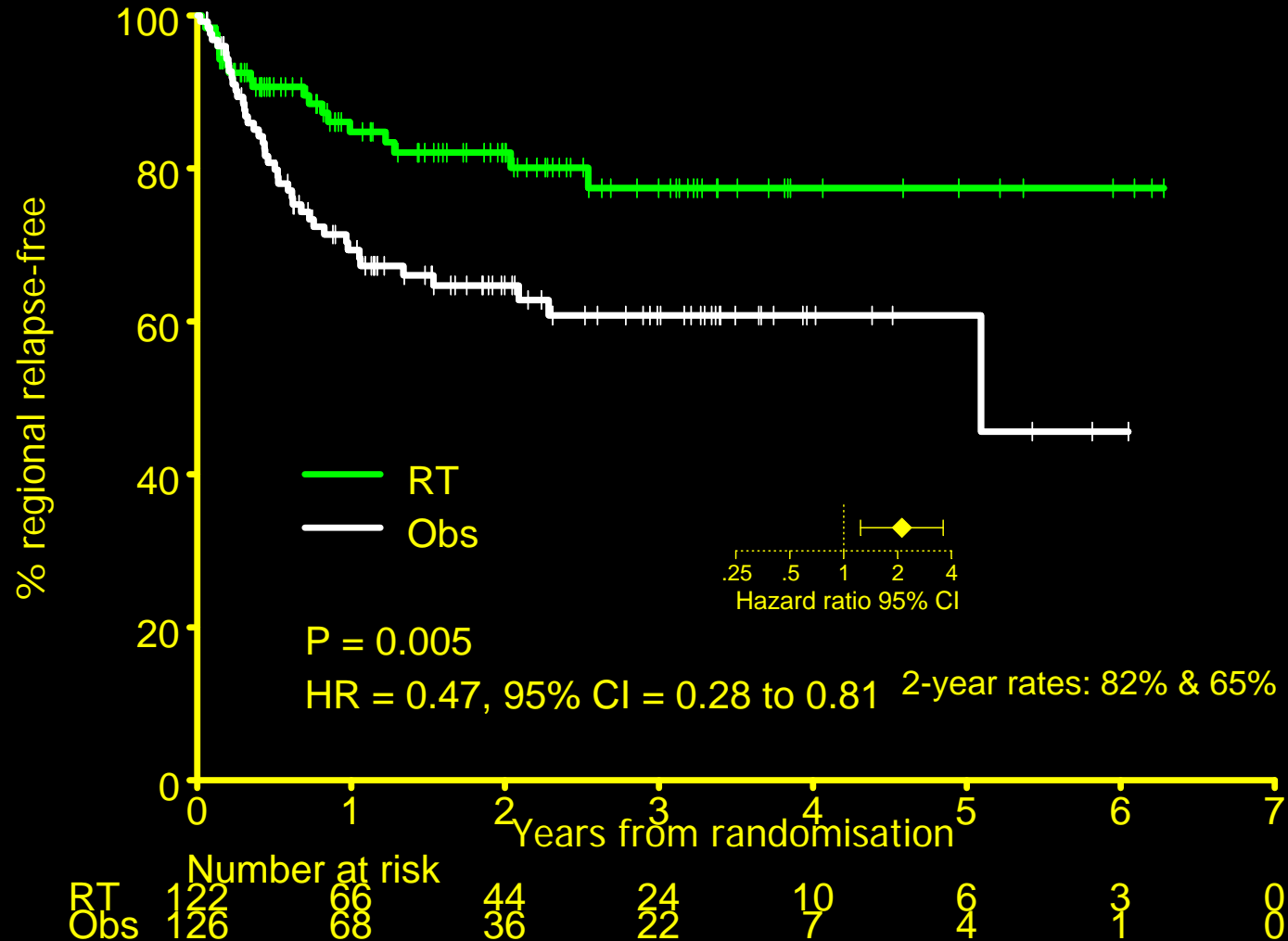
Time to lymph node field relapse by arm

First relapse; fully evaluable patients (217)



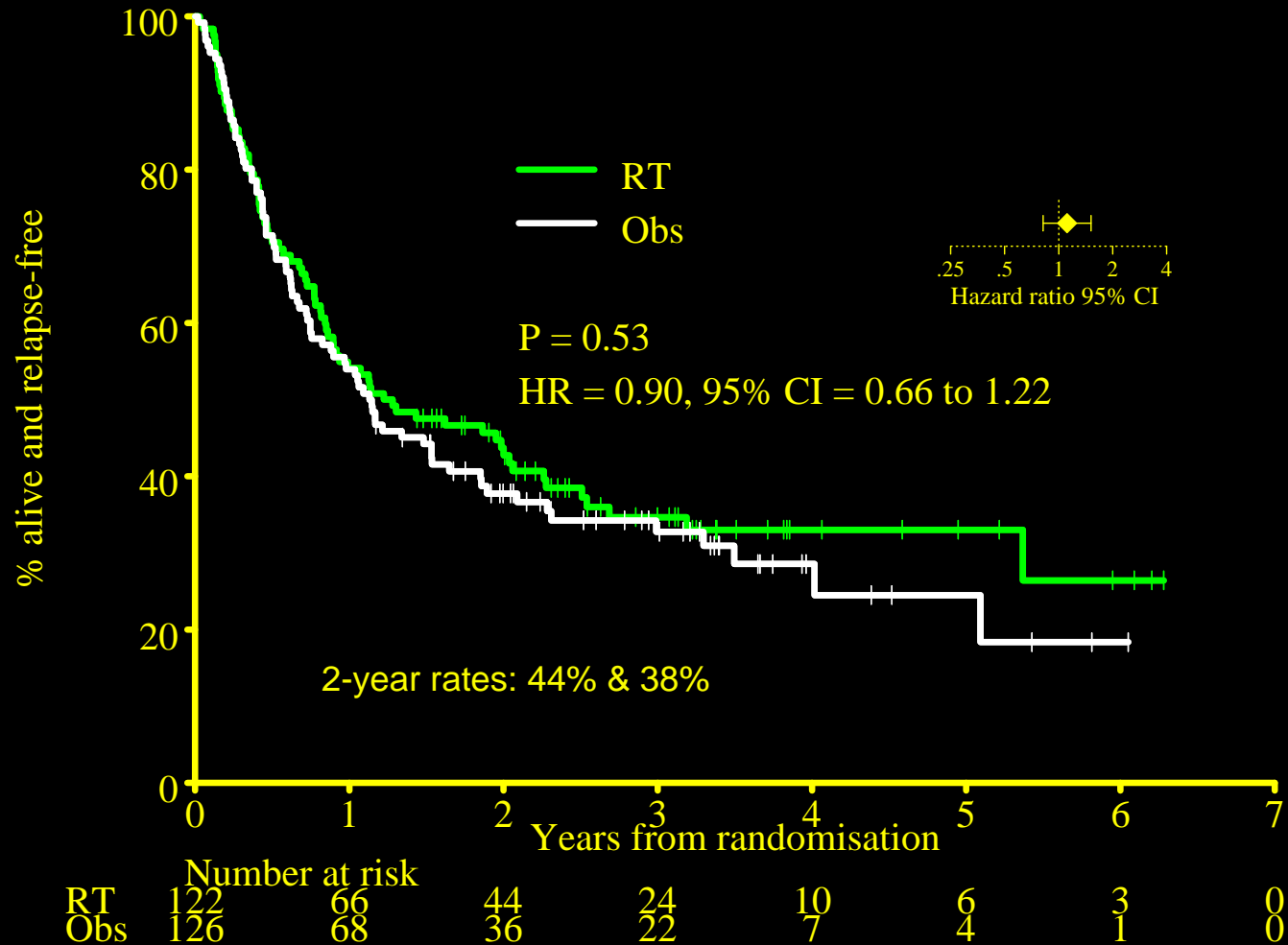
Time to lymph node field relapse by arm

First relapse; ITT patients (248)



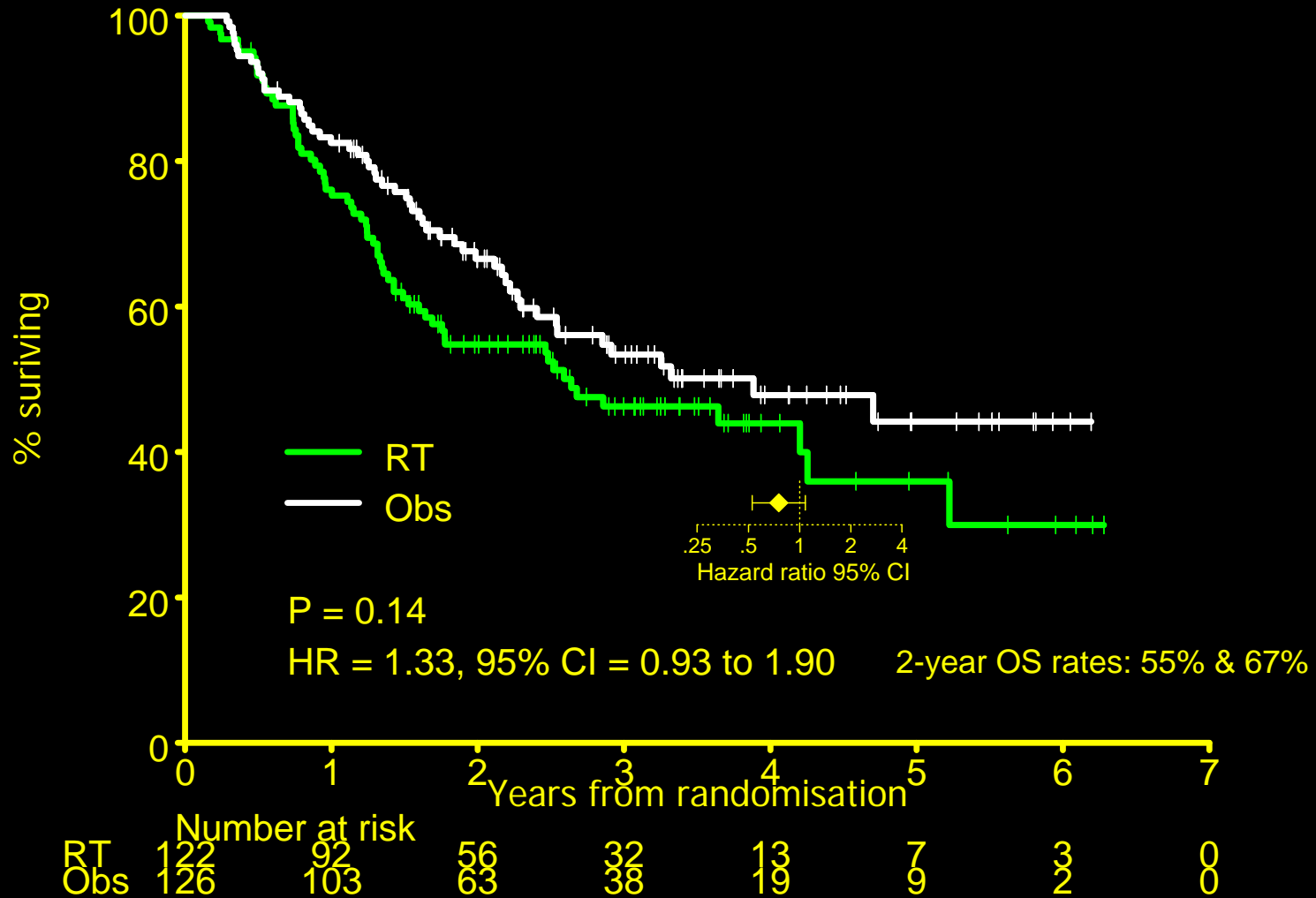
Relapse-free survival by arm

ITT population (248)



Overall survival by arm

ITT population (248)



Cumulative incidence (observed first relapses) at 2 years by site(s) of relapse

Sites	RT	OBS
Lymph node field ± local or <i>in transit</i>	5.0%	20%
Lymph node field + distant ± local or <i>in transit</i>	10%	11%
Distant ± local or <i>in transit</i>	35%	29%
Local or <i>in transit</i> only	5.0%	2.5%
All sites	55%	62%

Grade 3 Early Radiation Therapy Toxicities (RT arm)

H&N (n=31)

Axilla (n=50)

Groin (n=34)

2 weeks post-RT

Radiation dermatitis

3

10

5

Pain

-

2

-

6 weeks post-RT

Radiation dermatitis

-

5

-

Pain

-

1

1

Fatigue

-

1

-

No grade 4 early RT toxicities

Radiation Therapy Quality Assurance

- 54 patients (44.6%) selected for central review, including first 5 patients from each centre
- Review actually occurred in 28 patients randomised to the RT arm and 5 who were randomised to Obs but crossed over after developing regional recurrence
- Overall compliance rate was 79.2%
- Main deviations were doses to reference points and exceeding doses to critical structures

Conclusions

In patients with lymph node field recurrent melanoma at significant risk of relapse after lymphadenectomy:

- **Radiation Therapy improves lymph node field control.**
- **There is no evidence for a difference in overall survival between RT and Observation groups.**
- **Early radiation therapy toxicity appears minimal**

Acknowledgements

Trial Personnel

Chairpersons

Bryan Burmeister
Michael Henderson
John Thompson
(Jill Ainslie)

Statistician

Richard Fisher

Trial Co-ordinator

Juliana Di Iulio

Pathologist

Richard Scolyer

Funding

NHMRC
ANZMTG
CCV

Participating Centres

Site / Hospital	Investigator	Data Manager
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East Coast Cancer Centre Qld	David Christie	Thai Le
Groningen University Hospital Netherlands	Harald Hoekstra	
Hospital do Cancer, Sao Paulo Brazil	Joao Duprat	
Mater, Brisbane	Michael Poulsen	Kacy Baumann
Mater, Newcastle	Chris Wratten	Sarah Gallagher
Mater, Sydney	Gerald Fogarty	Kin Sheather
Princess Alexandra Brisbane	Bryan Burmeister Mark Smithers	Brenda Rosser Janelle Meakin
Peter MacCallum Cancer Center Melbourne	Michael Henderson Jill Ainslie	Monique Robinson Melanie Evans
Royal Prince Alfred Sydney / Sydney Melanoma Unit	John Thompson Angela Hong	Julie Coffee Sandie Grierson
Royal Perth WA	Yvonne Zissiadis	Elizabeth Kearney
Wellington NZ	Carol Johnson	Maureen Blakemore
Westmead NSW	Colin Bull	Marivic Lagleva