Workshop # 5

Applications of Quality of Life Outcomes in Three Recent NCIC CTG Trials:

What Every New Clinician-Investigator Wants to Know

M. Brundage and H. Richardson

Outline

- Nature of QOL data – a brief review
- Application in practice
- Three RCT Examples
- Prevention, Curative, Advanced Systemic
- Practical Approaches – Formulating a QOL section of a protocol suitable for funding
- Informal and interactive

Back to our Research Question

I'm interested in comparing two treatments: "R" and "M"

I want to evaluate how each treatment affects patients' quality of life.

Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial

Padraig Warde, Malcolm Mason*, Keyue Ding, Peter Kirkbride, Michael Brundage, Richard Cowan, Mary Gospodarowicz, Karen Sanders, Edmund Kostashuk, Greg Swanson, Jim Barber, Andrea Hiltz, Mahesh K B Parmar, Jinka Sathya, John Anderson, Charles Hayter, John Hetherington, Matthew R Sydes†, Wendy Parulekar†, for the NCIC CTG PR.3/MRC UK PR07 investigators*

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See Comment page 2056

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Summary

Background Whether the addition of radiation therapy (RT) improves overall survival in men with locally advanced prostate cancer managed with androgen deprivation therapy (ADT) is unclear. Our aim was to compare outcomes in such patients with locally advanced prostate cancer.

Methods Patients with: locally advanced (T3 or T4) prostate cancer (n=1057); or organ-confined disease (T2) with either a prostate-specific antigen (PSA) concentration more than 40 ng/mL (n=119) or PSA concentration more than 20 ng/mL and a Gleason score of 8 or higher (n=25), were randomly assigned (done centrally with stratification and dynamic minimisation, not masked) to receive lifelong ADT and RT (65–69 Gy to the prostate and seminal vesicles, 45 Gy to the pelvic nodes). The primary endpoint was overall survival. The results presented here are of an interim analysis planned for when two-thirds of the events for the final analysis were recorded. All efficacy analyses were done by intention to treat and were based on data from all patients. This trial is registered at controlledtrials.com as ISRCTN24991896 and Clinicaltrials.gov as NCT00002633.

Results Between 1995 and 2005, 1205 patients were randomly assigned (602 in the ADT only group and 603 in the ADT and RT group); median follow-up was 6·0 years (IQR 4·4–8·0). At the time of analysis, a total of 320 patients had died, 175 in the ADT only group and 145 in the ADT and RT group. The addition of RT to ADT improved overall survival at 7 years (74%, 95% CI 70–78 *vs* 66%, 60–70; hazard ratio [HR] 0·77, 95% CI 0·61–0·98, p=0·033). Both toxicity and health-related quality-of-life results showed a small effect of RT on late gastrointestinal toxicity (rectal bleeding grade >3, three patients (0·5%) in the ADT only group, two (0·3%) in the ADT and RT group; diarrhoea grade >3, four patients (0·7%) *vs* eight (1·3%); urinary toxicity grade >3, 14 patients (2·3%) in both groups).

Interpretation The benefits of combined modality treatment—ADT and RT—should be discussed with all patients with locally advanced prostate cancer.

NCIC CTG PR.3/MRC PR07/SWOG JPR3:
Study Scheme

T3/T4 N0/NX
or
T2 and PSA > 40 µg/L
or
T2 and PSA > 20 µg/L and GS: 8-10

- Continuous Androgen Deprivation Therapy
- Continuous Androgen Deprivation Therapy + Radiotherapy

- Initial PSA Level: < 20 vs 20-50 vs > 50 µg/L
- Hormonal Therapy: orchiectomy vs LHRH analogue+ anti androgen
- Method of lymph node staging: clinical vs radiological vs surgical
- Gleason Score: < 8 vs 8-10
- Prior hormonal therapy: yes vs no
- Centre

	Androgen deprivation therapy (n=602)	Androgen deprivation therapy and radiation therapy (n=603)
Patient characteristics		
Region of recruitment		
North America		
UK		
Prostate-specific antigen		
<20 ng/mL		
20–50 ng/mL		
>50 ng/mL		
Median (IQR)		
Gleason score		
Not available		
<8		
8–10		
Previous hormone therapy		
No		
Yes		
Age at allocation		
<65 years		
≥65 years		
Median (IQR)		
Performance status (ECOG)		
0		
1		
2		
Performance status (ECOG)		
0	474 (79%)	469 (78%)
1	119 (20%)	126 (21%)
2	9 (1%)	8 (1%)
Clinical stage		
Missing	0 (0%)	2 (<1%)
T2	76 (13%)	70 (12%)
T3	499 (83%)	501 (83%)
T4	27 (4%)	30 (5%)
Lymph node staging		
Clinical or radiological	477 (79%)	475 (79%)
Not done	113 (19%)	111 (18%)
Surgical	12 (2%)	17 (3%)
Health-related quality-of-life scores		
FACT-P, global assessment* (n=844)	55·3 (1·4)	58·1 (1·4)
EORTC, global assessment* (n=179)	77·8 (1·9)	77·4 (1·9)
FACT-P, physical function* (n=844)	90·7 (0·5)	90·3 (0·6)
EORTC, physical function* (n=179)	92·5 (1·2)	91·4 (1·7)
EORTC, bowel or rectum† (n=179)	3·6 (1·2)	3·3 (0·9)
EORTC, diarrhoea† (n=179)	4·3 (1·1)	5·8 (1·9)
EORTC, urinary† (n=180)	9·7 (1·7)	11·2 (1·7)
FACT-P, urinary† (n=835)	28·8 (1·4)	29·7 (1·4)

Data are n (%) or mean (SE). EORTC=European Organisation for Research and Treatment of Cancer, quality-of-life

- EORTC QLQ-C30+3 Instrument
- Domain: Global quality of life

How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

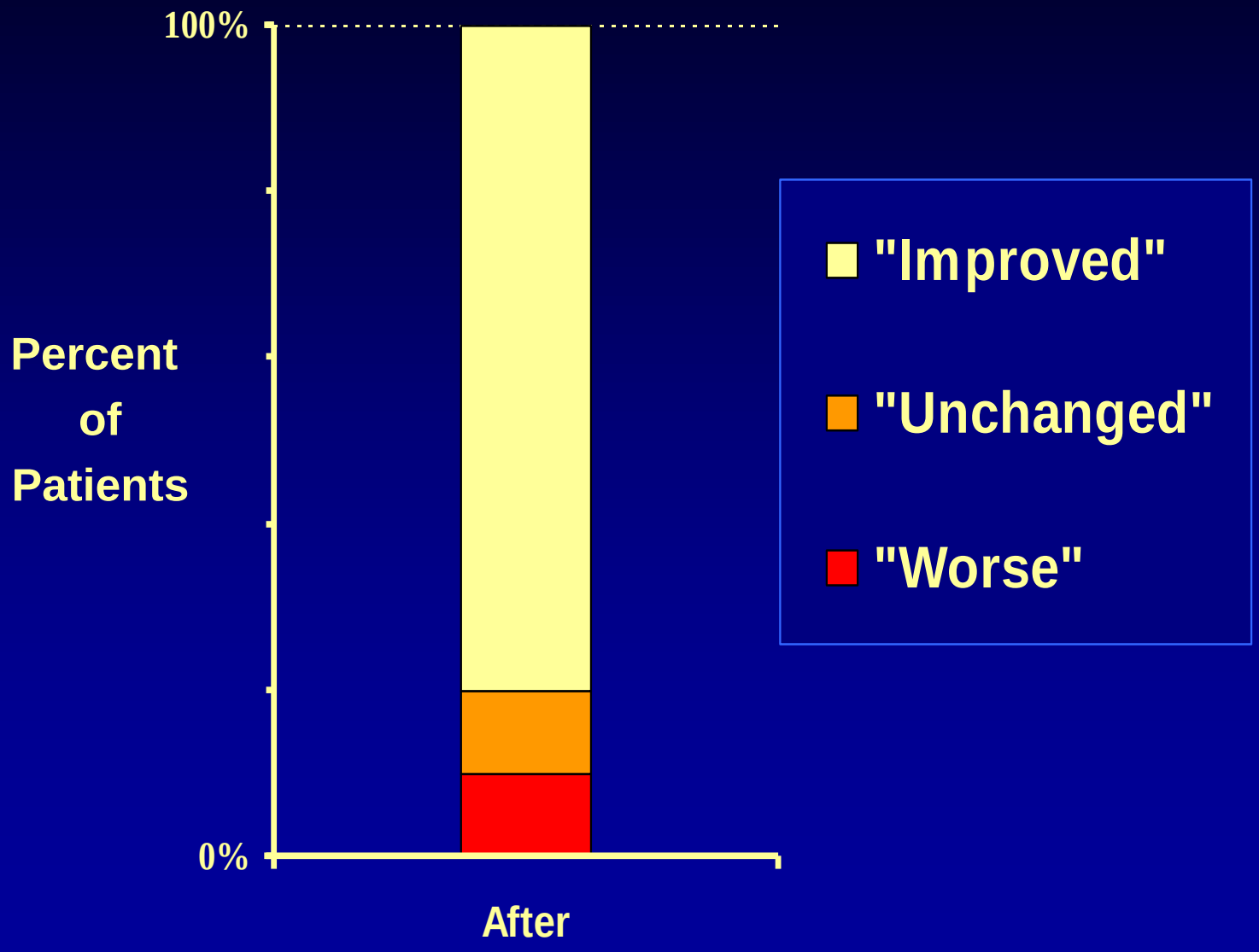
How would you rate your overall quality of life during the past week

1 2 3 4 5 6 7

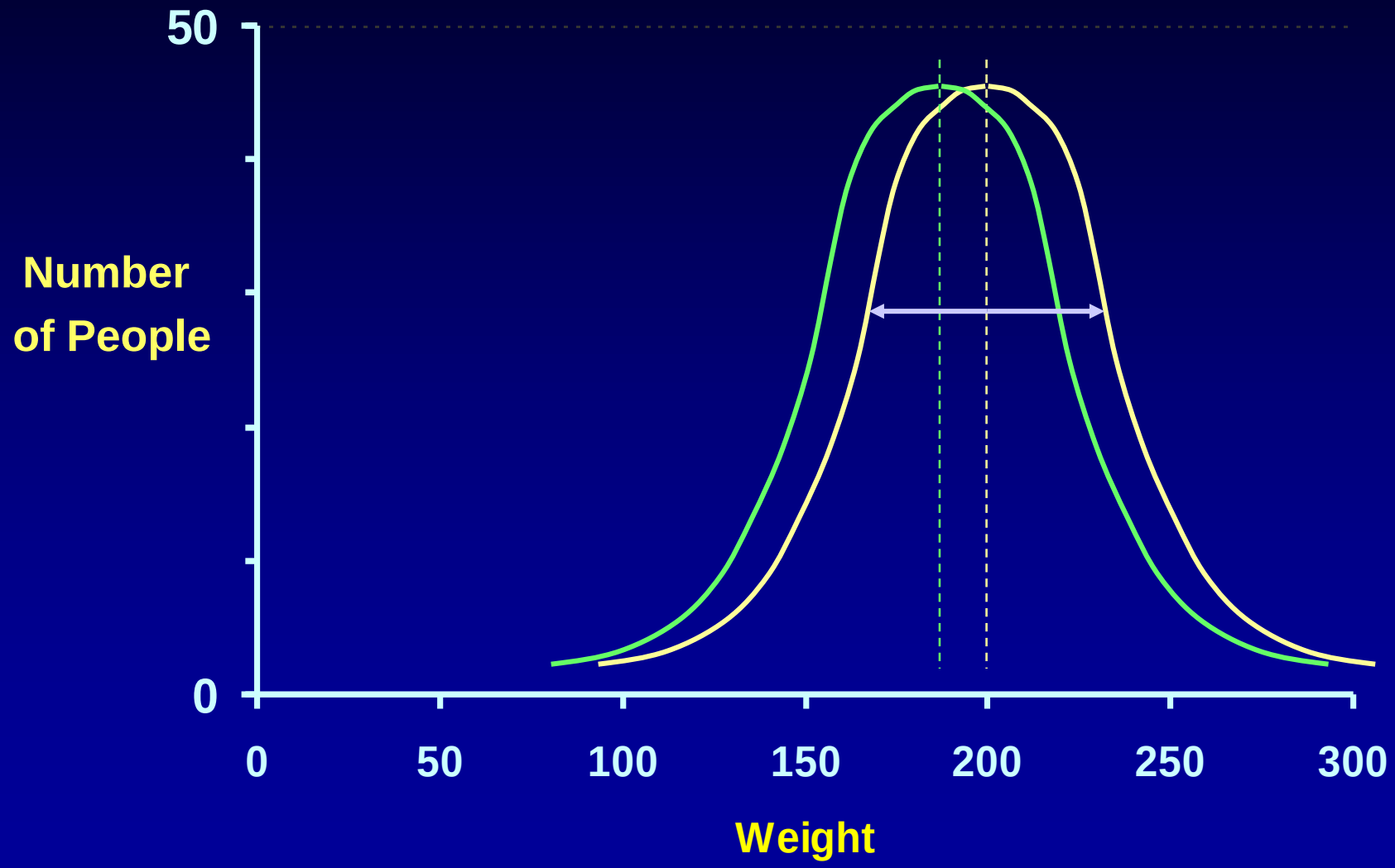
Very poor Excellent

During the past week:	Not at All	A Little	Quite a Bit	Very Much
34. Did you have to pass urine more frequently than normal for you?	1	2	3	4
35. Did you have difficulty passing your urine?	1	2	3	4
36. Did you have pain when you passed urine?	1	2	3	4
37. Did you have blood in your urine?	1	2	3	4
38. Did you have difficulty emptying your bladder completely?	1	2	3	4
39. Did you have difficulty controlling your urination (for example dribbling)?	1	2	3	4
40. Did you have accidental wetting of your underwear?	1	2	3	4
41. Did you have to wear added protection to prevent accidental wetting of your underwear?	1	2	3	4

Treatment Intent: Improve QOL



Treatment Intent: Shed Pounds




MULTI LASER solutions
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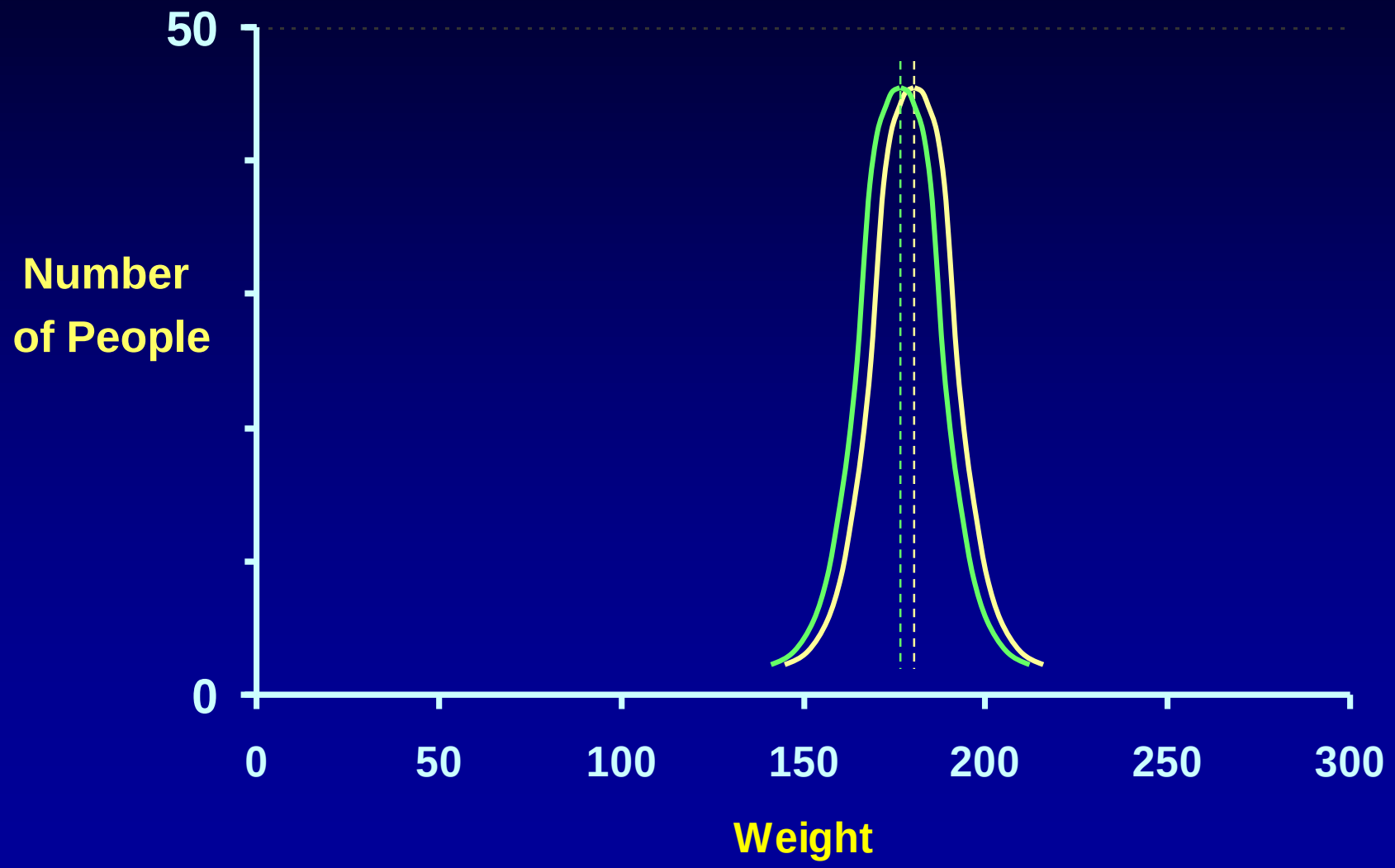
MULTI LASER solutions
www.multilaser.com
TJ Cycle Canadienne
LOOK
MAVIC

Treatment Intent: Shed Pounds



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Volume 41, Number 5, pp 582–592

Point/Counterpoint

Interpretation of Changes in Health-related Quality of Life

The Remarkable Universality of Half a Standard Deviation

GEOFFREY R. NORMAN, PHD,* JEFF A. SLOAN, PHD,† AND KATHLEEN W. WYRWICH, PHD‡

BACKGROUND. A number of studies have computed the minimally important difference (MID) for health-related quality of life instruments.

OBJECTIVE. To determine whether there is consistency in the magnitude of MID estimates from different instruments.

METHODS. We conducted a systematic review of the literature to identify studies that computed an MID and contained sufficient information to compute an effect size (ES). Thirty-eight studies fulfilled the criteria, resulting in 62 ESs.

RESULTS. For all but 6 studies, the MID estimates were close to one half a SD (mean = 0.495, SD = 0.155). There was no consistent relationship with factors such as disease-specific or generic instrument or the number of response options. Negative changes were not associated with larger ESs. Population-based estimation procedures and brief follow-up were associated with smaller ESs, and acute conditions with larger ESs. An explanation for this consistency is that research in psychology has shown that the limit of people's ability to discriminate over a wide range of tasks is approximately 1 part in 7, which is very close to half a SD.

CONCLUSION. In most circumstances, the threshold of discrimination for changes in health-related quality of life for chronic diseases appears to be approximately half a SD.

Key words: Quality of life; threshold; interpretation; MID; effect size. (Med Care 2003; 41:582–592)

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Planned Treatment

- Androgen Deprivation Therapy
  - Bilateral Orchiectomy

  or

  - LHRH agonist
    - Antiandrogen for 2 weeks, optional to continue
- Radiotherapy
  - 45 Gy/25 F/5 weeks to pelvis
  - 20-24 Gy/10-12 F/2-2.5 weeks to prostate
  - If treating physician felt patient inappropriate for whole pelvis then RT given to prostate only

Locally Advanced Prostate Cancer 1990s

- **Canadian and UK surveys of clinicians revealed substantial uncertainty about the role of radiotherapy**

"These men all have metastatic disease; adding radiotherapy to hormones is unnecessary and unkind"

Locally Advanced Prostate Cancer 1990s

- **Canadian and UK surveys of clinicians revealed substantial uncertainty about the role of radiotherapy**

"These men all have metastatic disease; adding radiotherapy to hormones is unnecessary and unkind"

- **Additional uncertainty about the 'best' instrument for evaluating HRQL in prostate cancer**

Functional Assessment of Cancer Therapy – Prostate **(FACT-P)**
EORTC instrument (**EORTC QLQ C-30** and Prostate-specific check list)

Baseline Characteristics

Characteristic	ADT Alone	ADT+RT
Median Age	69.7 years	69.7 years
T Category		
≤ T2c	11%	10%
T3/T4	89%	88%
Gleason Score		
≤ 7	81%	81%
8-10	18%	18%
PSA ng/ml		
<20	37%	36%
20-50	38%	38%
>50	25%	26%

Performance status (ECOG)		
0	474 (79%)	469 (78%)
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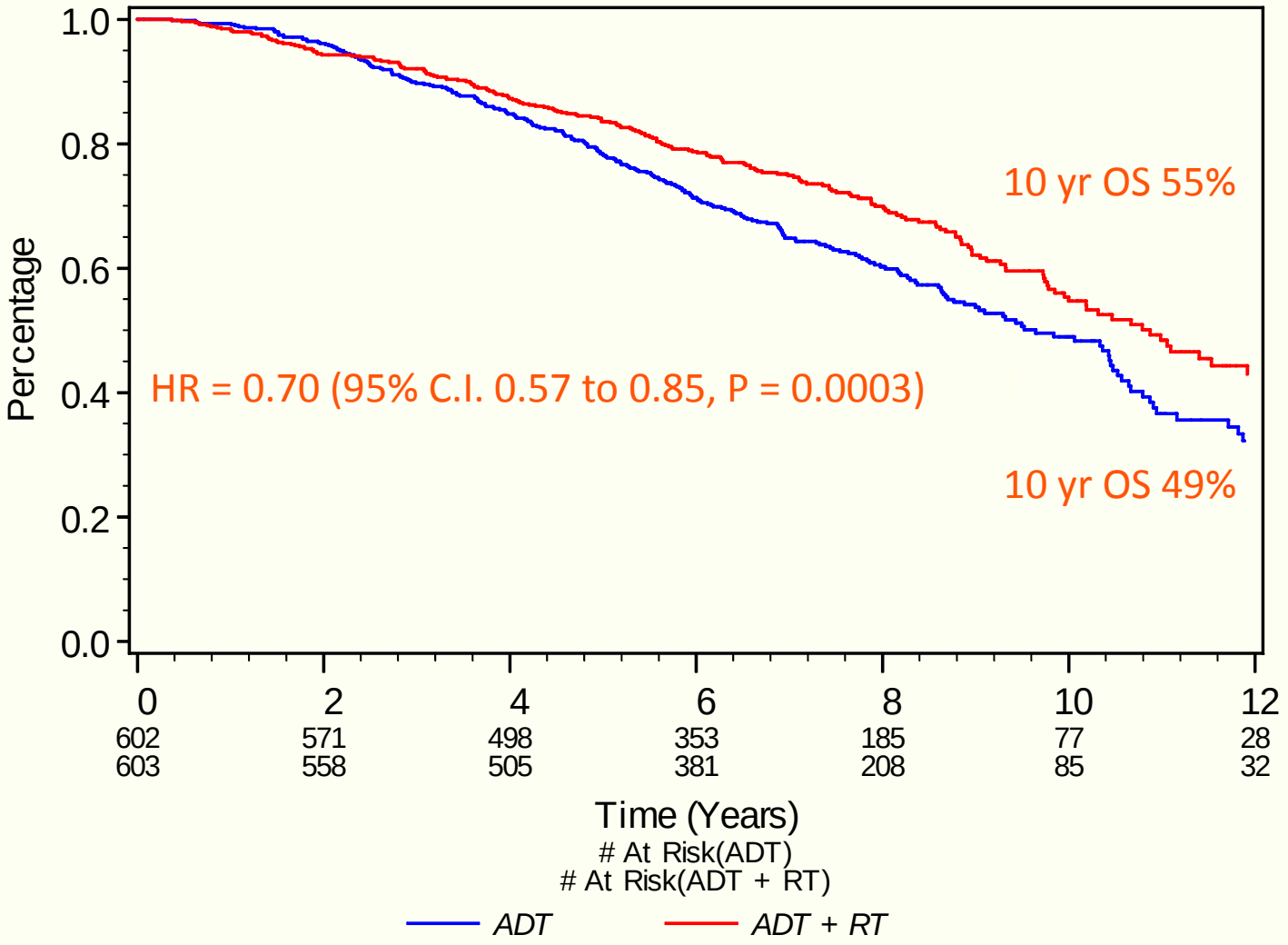
Data are n (%) or mean (SE). EORTC=European Organisation for Research and Treatment of Cancer, quality-of-life questionnaire and the PR-13 prostate module. *High scores represent a high quality of life. †High scores represent a high symptom burden. FACT-P=Functional Assessment of Cancer Therapy–Prostate Module.

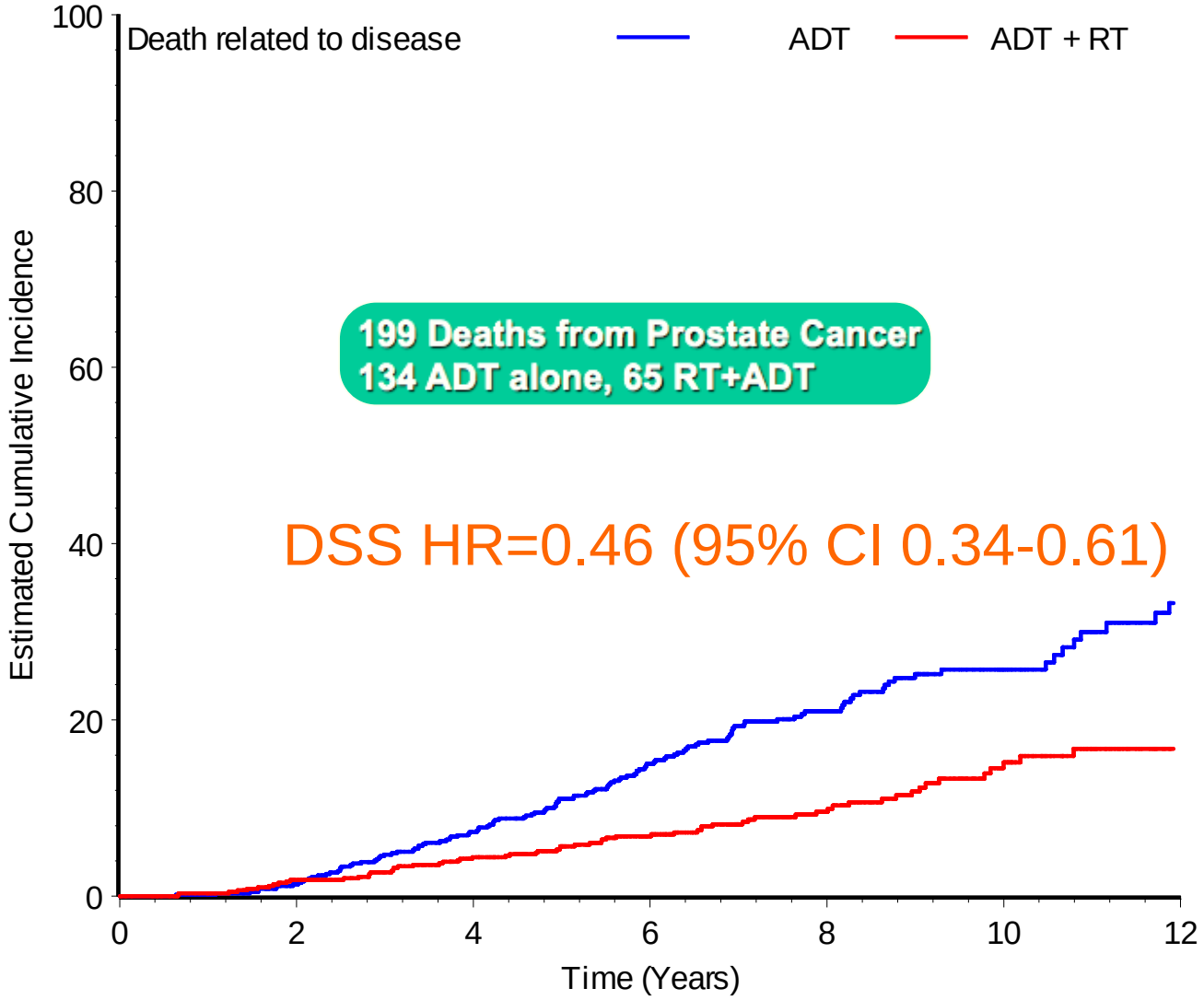
Table 1: **Patients' baseline characteristics at study entry**

	Androgen deprivation therapy alone (n=602)	Androgen deprivation therapy and radiation therapy (n=603)	p value
Reported by toxicity criteria			
Gastrointestinal			
Diarrhoea (grade 1–2)	47 (8%)	81 (13%)	..
Diarrhoea (grade >3)	4 (<1%)	8 (1%)	..
Rectal bleeding (grade 1–2)	30 (5%)	75 (12%)	..
Rectal bleeding (grade >3)	3 (1%)	2 (<1%)	..
Genitourinary (grade 1–2)	252 (2%)	262 (43%)	..
Genitourinary (grade >3)	14 (2%)	14 (2%)	..
By patient-reported outcomes			
Overall score			
FACT-P* (at 6 months; n=716)	4·3 (1·5)	−3·0 (1·6)	0·002
FACT-P* (at 36 months; n=538)	2·5 (2·0)	−1·1 (1·8)	0·2
EORTC* (at 6 months; n=148)	−1·74 (1·7)	−8·98 (2·5)	0·04
EORTC* (at 36 months; n=123)	−9·4 (2·1)	−11·4 (2·4)	0·96
Physical functioning			
FACT-P* (at 6 months; n=721)	−4·1 (0·7)	−7·6 (0·7)	0·01
FACT-P* (at 36 months; n=545)	−6·1 (0·8)	−5·5 (0·8)	0·74
EORTC* (at 6 months; n=151)	−3·5 (1·7)	−3·8 (1·7)	0·72
EORTC* (at 36 months; n=124)	−9·2 (2·3)	−10·2 (2·4)	0·67
Urinary functioning			
FACT-P* (at 6 months; n=706)	−6·1 (1·2)	0·1 (1·2)	0·003
FACT-P* (at 36 months; n=528)	−5·2 (1·3)	−5·5 (1·3)	0·74
EORTC* (at 6 months; n=149)	−1·4 (1·3)	0·1 (1·3)	0·07
EORTC* (at 36 months; n=124)	−0·6 (1·4)	−0·4 (1·4)	0·72
Bowel or rectal			
EORTC† (at 6 months; n=149)	−1·3 (0·8)	3·4 (1·7)	0·02
EORTC† (at 36 months; n=121)	−0·3 (1·3)	1·7 (2·0)	0·54
Diarrhoea			
EORTC† (at 6 months; n=149)	−1·8 (1·4)	7·3 (2·5)	0·001
EORTC† (at 36 months; n=120)	1·1 (2·2)	1·7 (2·4)	0·33

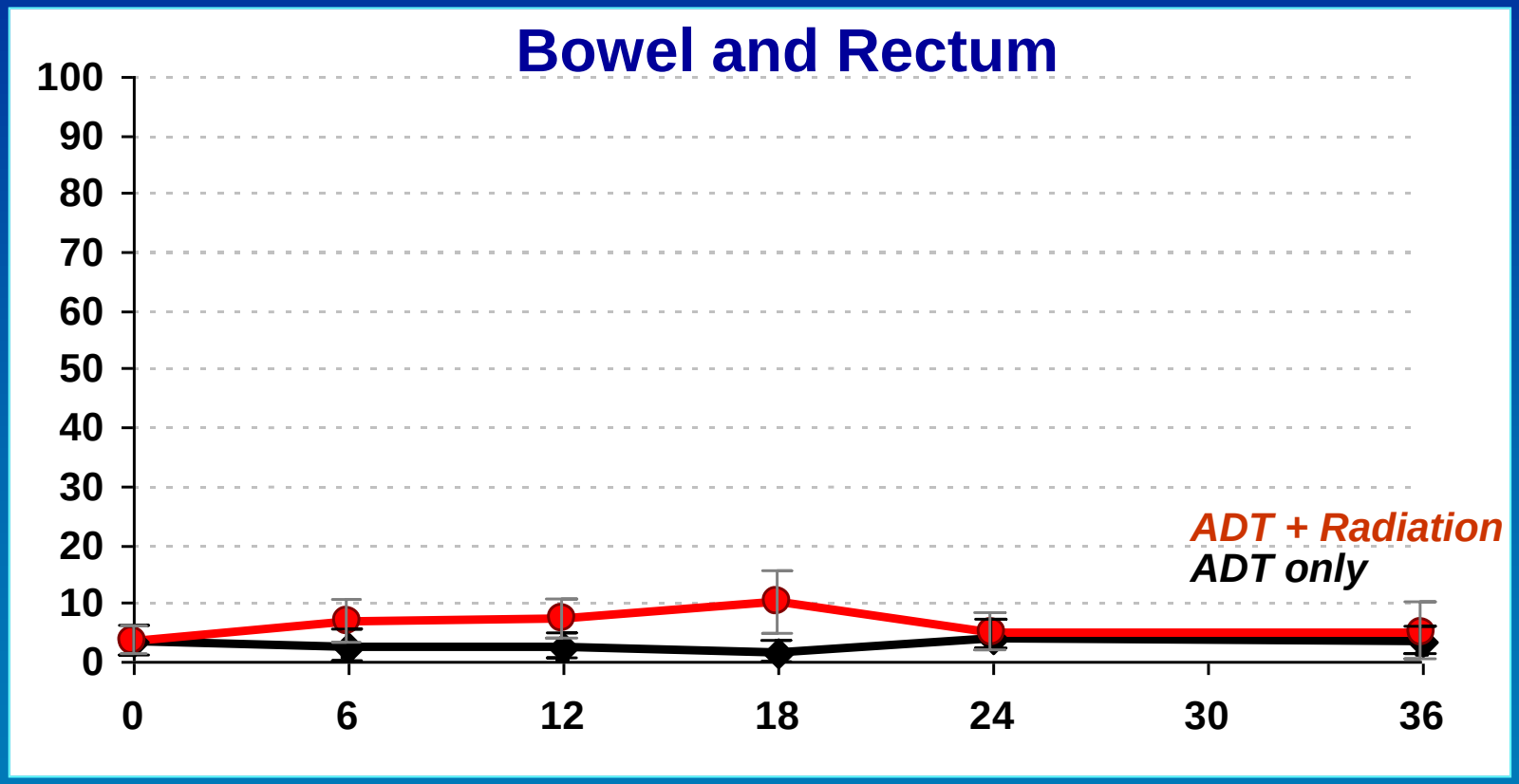
Final Analysis - overall survival



Final Analysis: Cumulative Incidence Probability for Disease-Specific Survival

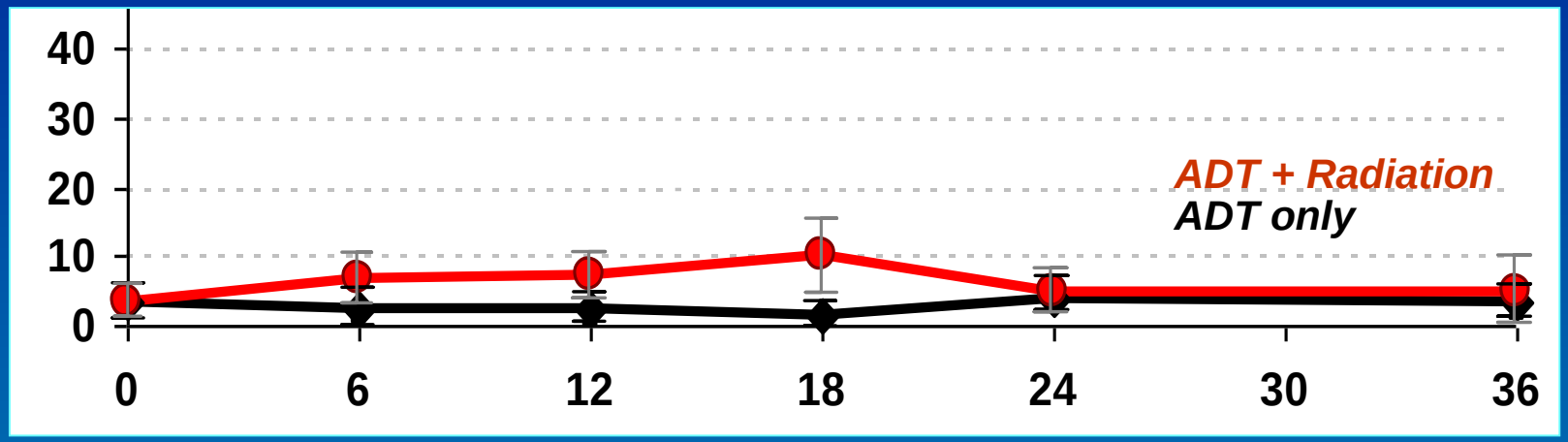


Quality of Life: Bowel Domain (EORTC QLQ)

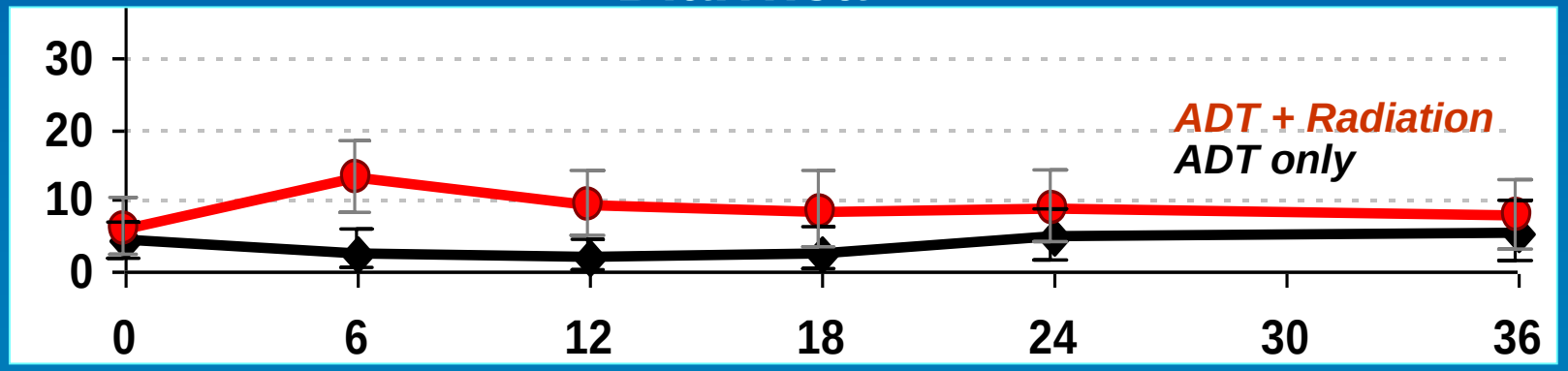


Quality of Life: Bowel Domain (EORTC QLQ)

Bowel and Rectum



Diarrhea



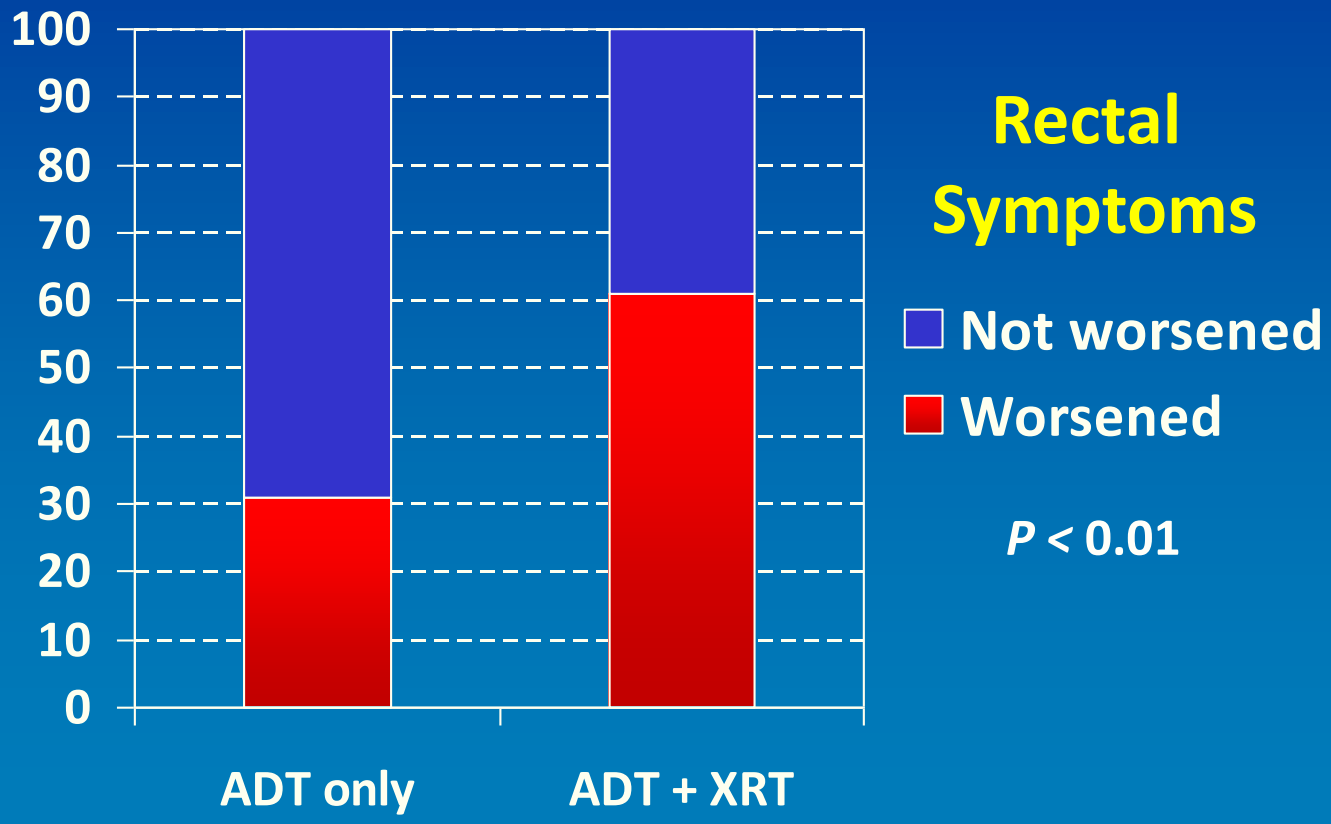
Mean Symptom Scores

← Fewer Symptoms

Months

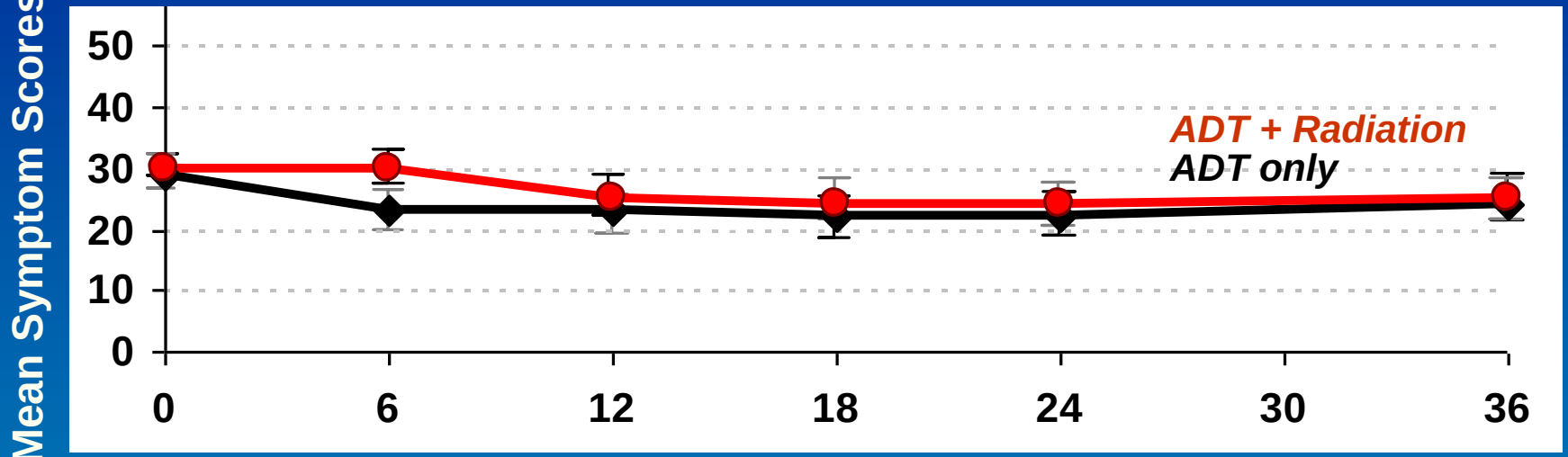
Proportion of Patients Worsening

- Patients deteriorating by 10 points or more at any point up to 3 years



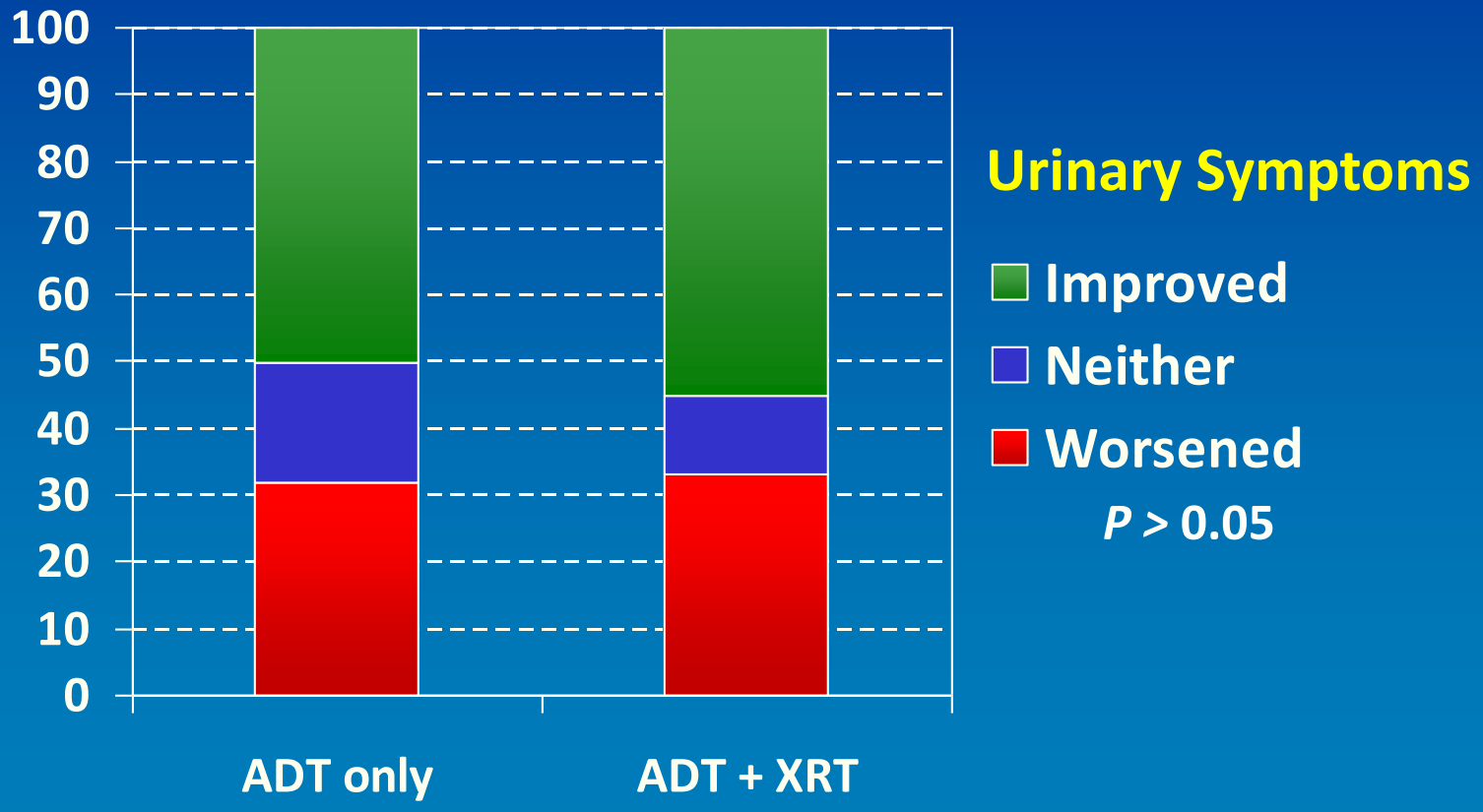
NCIC CTG
NCIC GEC

Quality of Life: Urinary Domain (FACT-P)



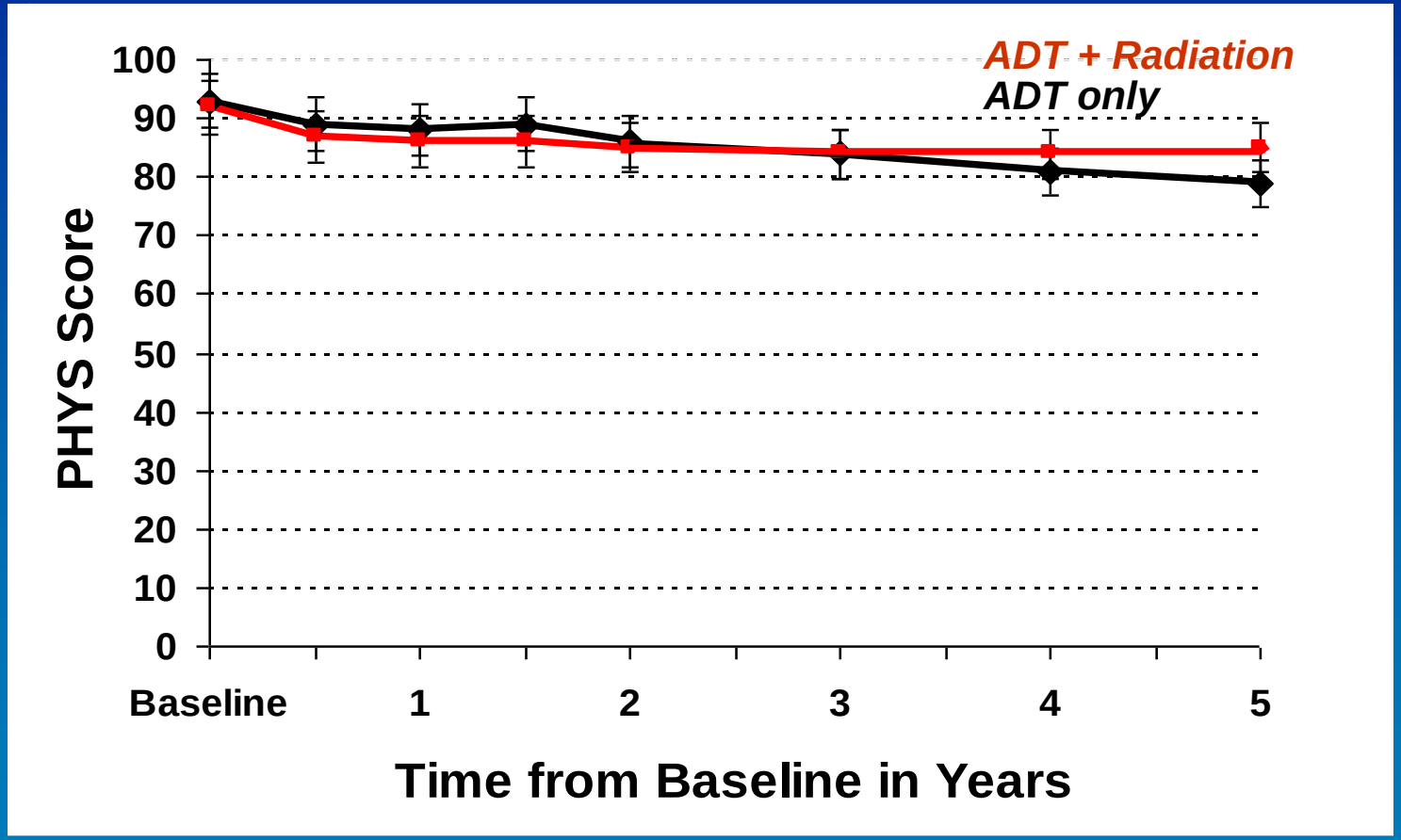
Proportion of Patients changing

- Patients changing by 10 points or more at any point up to 3 years



NCIC CTG
NCIC GEC

Quality of Life: Physical Domain (EORTC)



Quality of life in NCIC CTG MAP.3

Menopause-specific and health-related qualities of life among post-menopausal women taking exemestane for prevention of breast cancer

Elizabeth Maunsell, Harriet Richardson

James N. Ingle, José Alés-Martínez (GEICAM), Rowan T. Chlebowski, Carol J. Fabian, Gloria Sarto, Judy E. Garber, Pascal Pujol (UNICANCER), Andrea Hiltz, Dongsheng Tu and Paul E. Goss for the NCIC CTG MAP.3 Study Investigators

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

NCIC CTG MAP.3 Prevention Trial

Double-Blind

Eligible

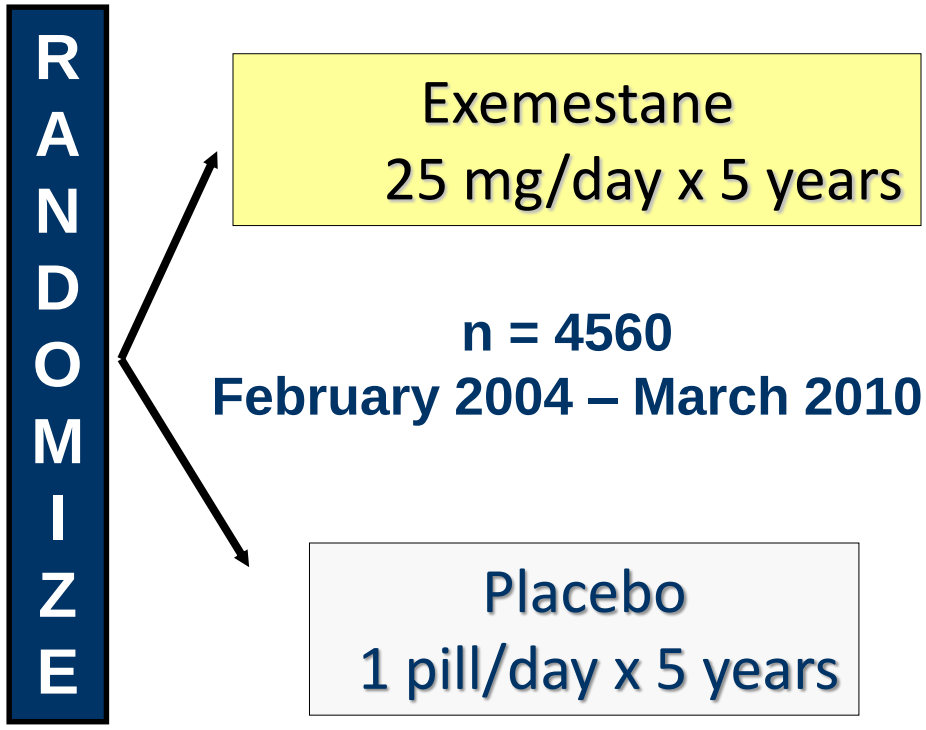
Postmenopausal and ≥ 35 years

At least ONE of the following breast cancer risk factors

- **Age ≥ 60 years**
- **Gail score >1.66%**
- **Prior ADH, ALH, LCIS**
- **Prior DCIS with mastectomy**

Ineligible

- **BRCA 1 and 2 mutation carriers**
- **Prior DCIS with lumpectomy**
- **Women with a history of breast cancer or other malignancies**



n = 4560
February 2004 – March 2010

Stratification

Aspirin use
Gail score (<2.0, ≥ 2.0)

QOL Objectives

- Compare menopause-specific and general quality of life for women while on treatment

- Evaluate extent of any clinically important decline in quality of life while on treatment

MENQOL
Menopause–Specific QOL

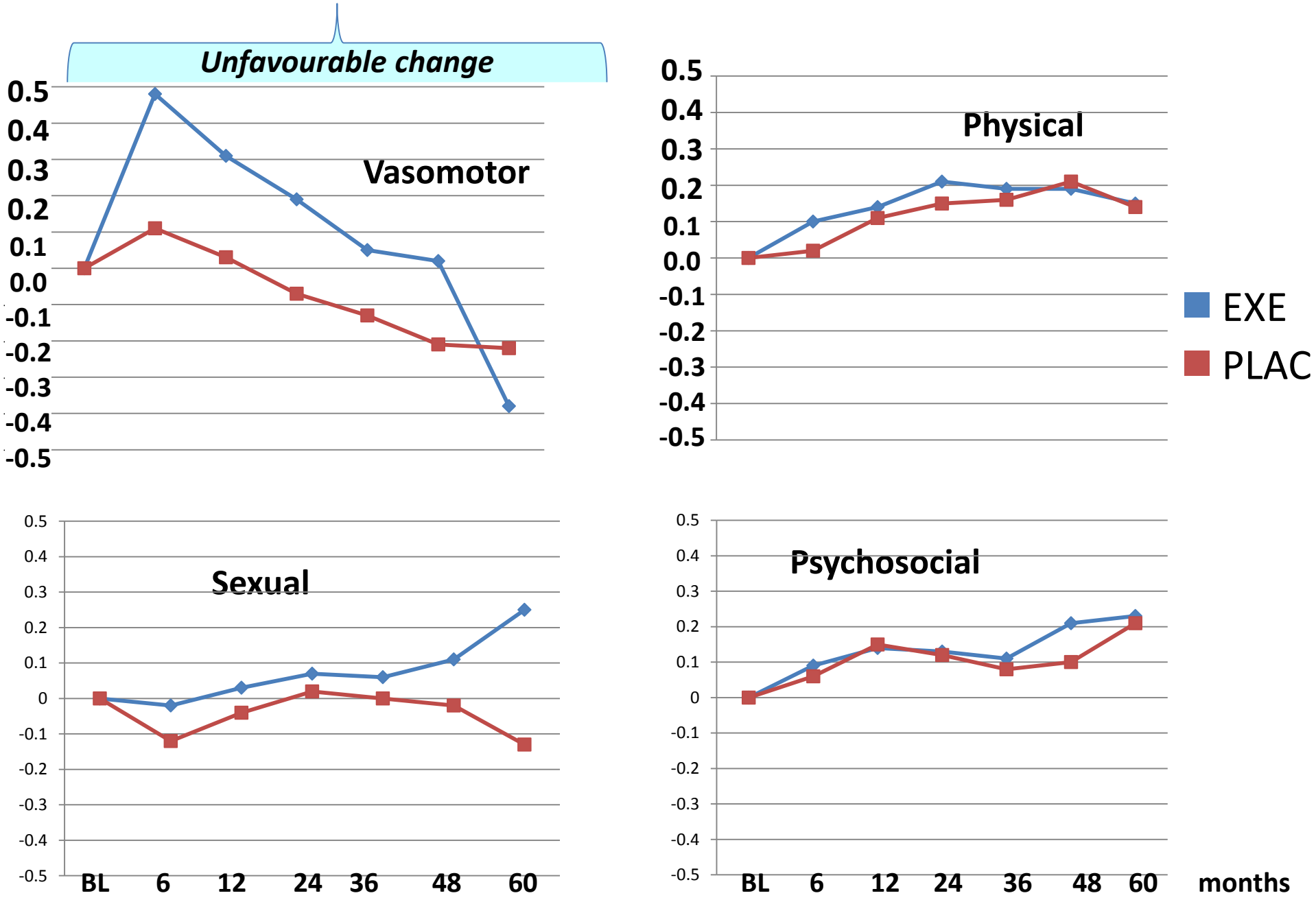
- Four domains: vasomotor, psychosocial, physical, sexual
- Scores can vary between 1 to 8: “symptom absent” to “very bothered by symptom” *[Hilditch et al. 1996]*
- Clinically meaningful worsening in Menopause-specific QOL based on ~ 5% of the scale breadth:
    - MENQOL: 0.5 / 8 points higher from baseline

Analysis

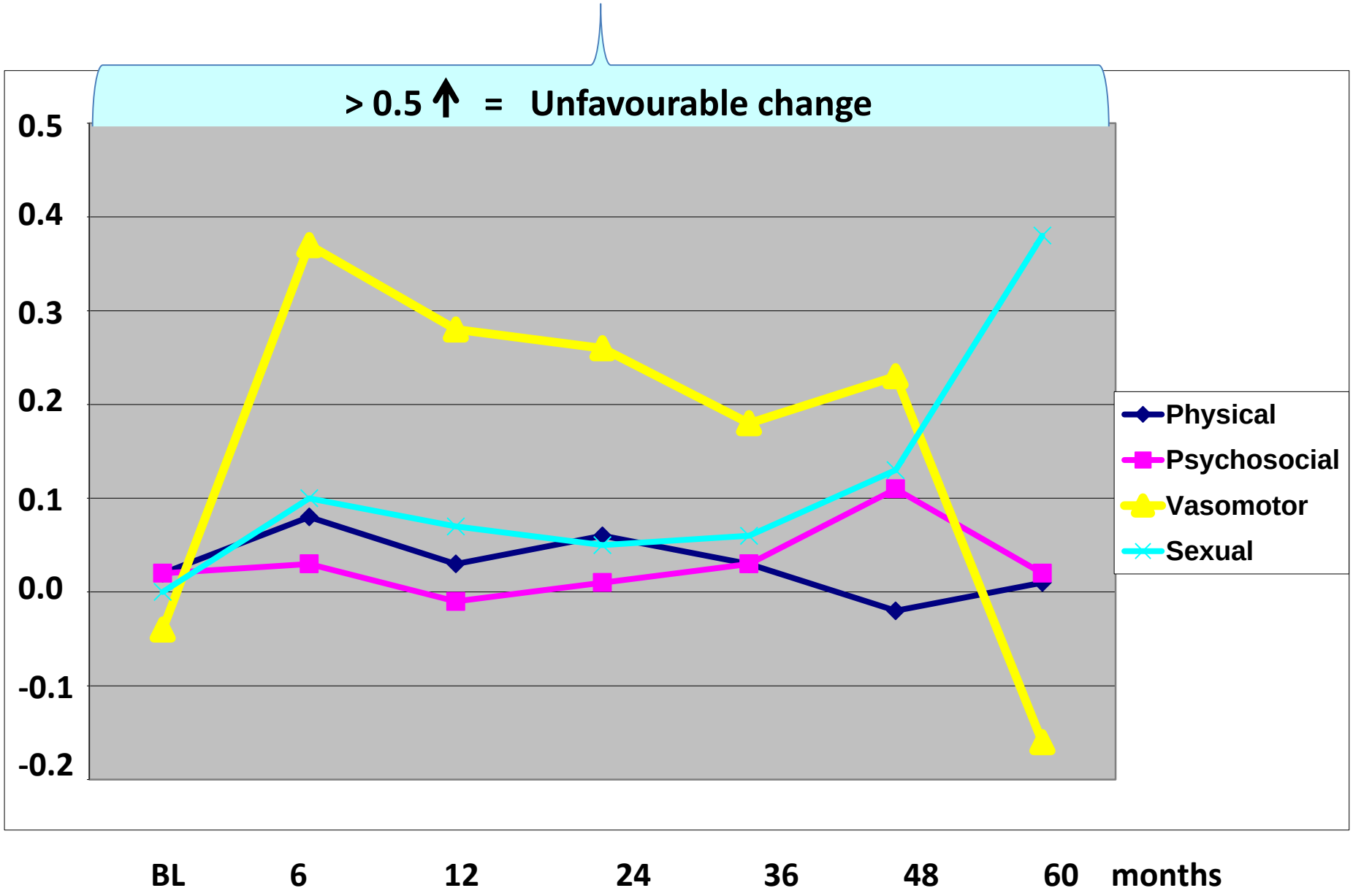
- Net effects of exemestane on QOL:
  - Difference in mean change score from baseline between exemestane and placebo (*Rank-sum test*)
- Clinically meaningful worsening in QOL defined as:
  - MENQOL scores increased by > 0.5 points
  - SF-36 scores decreased by ≥5 points
- Proportion with meaningful decline ≥ 1 visit while on study medication (*Chi square test)*
- Proportion with bothersome menopause-specific symptoms (scores 6-8) (*Chi square test)*

[Osoba et al. European J Cancer, 2005]

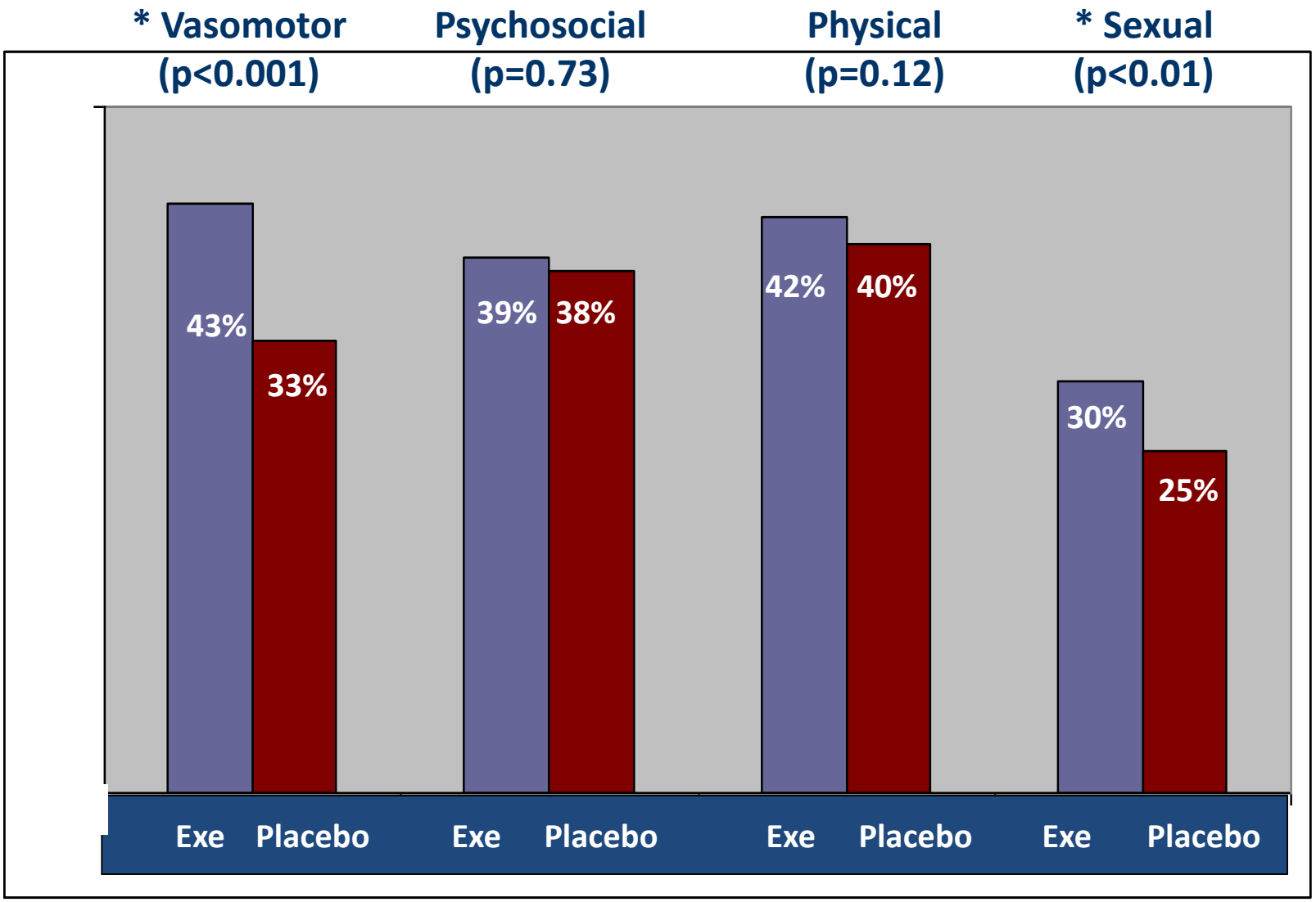
Clinically unimportant changes in menopause-specific QOL



No clinically important differences



Proportion of women with worsened domains of MENQOL at least once while on treatment



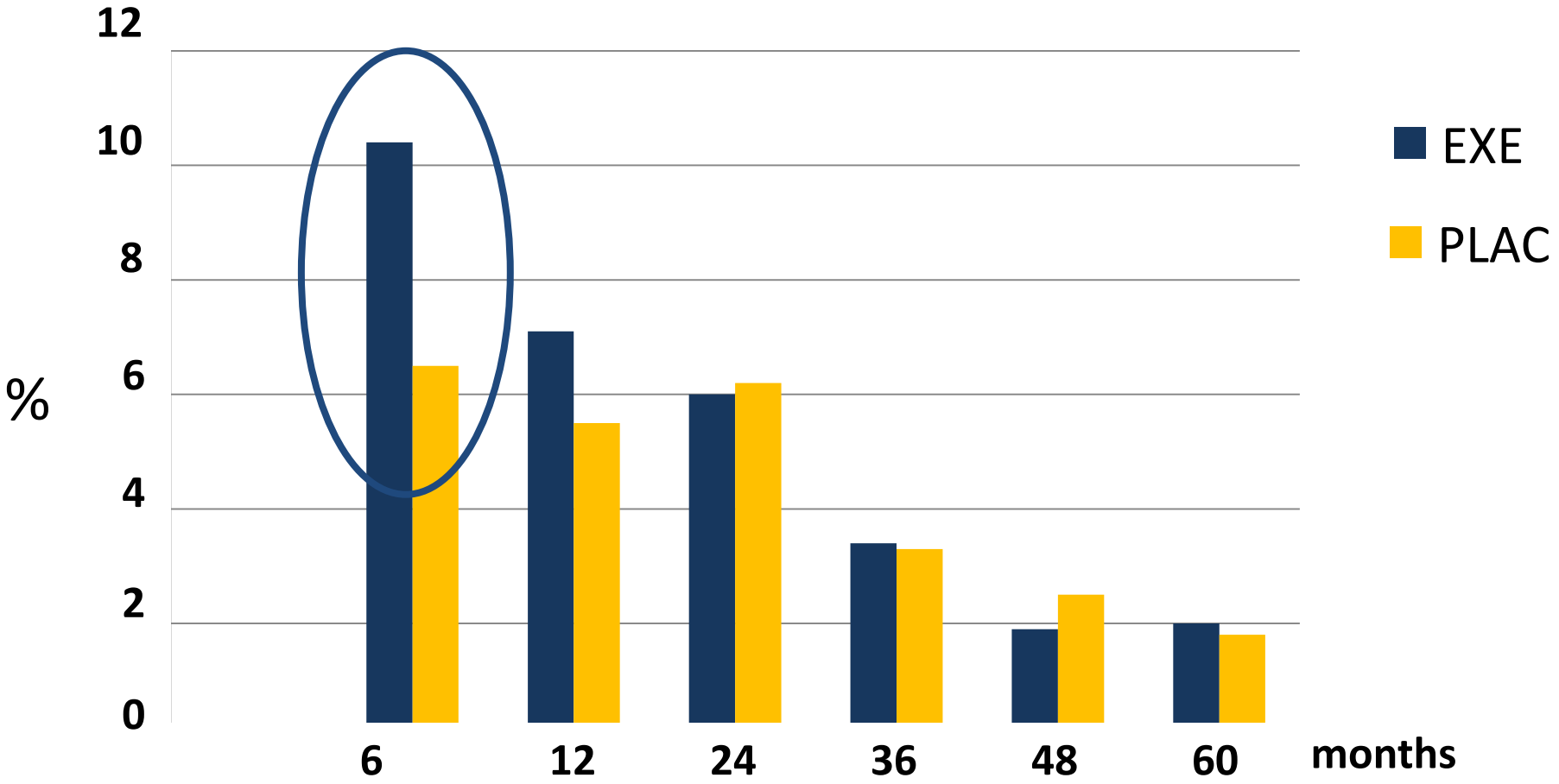
Goss et al. ASCO, 2011

Incidence of *bothersome MENQOL symptoms at 6 months, or ever, while on treatment

MENQOL Domains		Exemestane (n=2015)		Placebo (n=2096)	
Vasomotor:	6 months	184	9.5 %	104	5.2 %
	Ever	285	14.1 %	195	9.3 %
Psychosocial:	6 months	43	2.2 %	29	1.4 %
	Ever	89	4.4 %	73	3.5 %
Physical:	6 months	24	1.2 %	16	0.8 %
	Ever	61	3.0 %	40	1.9 %
Sexual:	6 months	78	4.0 %	79	3.9 %
	Ever	171	8.5 %	179	8.5 %

**Bothersome = MENQOL scores 6-8*

Proportion of women on exemestane discontinuing early - greatest at 6 months



MAP.3 QOL Conclusions

Exemestane had few clinically important effects on quality of life as measured by either the MENQOL or SF-36

Specifically:

- **No clinically important worsening in symptoms over time, based on mean change scores**
- Excess of vasomotor symptoms due to exemestane most pronounced at 6 months
- Excess of early discontinuation in the exemestane arm at 6 months only
- Small to no differences observed on other dimensions of menopause-specific or general quality of life

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ORIGINAL REPORT

Health-Related Quality of Life in Patients With Advanced Colorectal Cancer Treated With Cetuximab: Overall and *KRAS*-Specific Results of the NCIC CTG and AGITG CO.17 Trial

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ABSTRACT

Purpose

National Cancer Institute of Canada Clinical Trials Group CO.17 demonstrated the antiepidermal growth factor receptor (anti-EGFR) monoclonal antibody cetuximab improves overall and progression-free survival in patients with advanced, chemotherapy-refractory colorectal cancer (CRC), particularly in patients with wild-type *KRAS* tumors. This article reports the health-related quality-of-life (HRQL) outcomes from CO.17.

Patients and Methods

Patients (N = 572) with pretreated EGFR-detectable advanced CRC were randomly assigned to cetuximab and best supportive care (BSC) or to BSC alone. HRQL primary end points assessed by the EORTC QLQ-C30 were physical function (PF) and global health status (GHS); mean changes from baseline to 8 and 16 weeks were assessed. Post hoc analysis by *KRAS* mutation status was performed.

Results

Questionnaire compliance was 94% at baseline, but it declined differentially (67% *v* 47% for cetuximab *v* BSC at 16 weeks). PF change scores were −3.9 for cetuximab and −8.6 for BSC

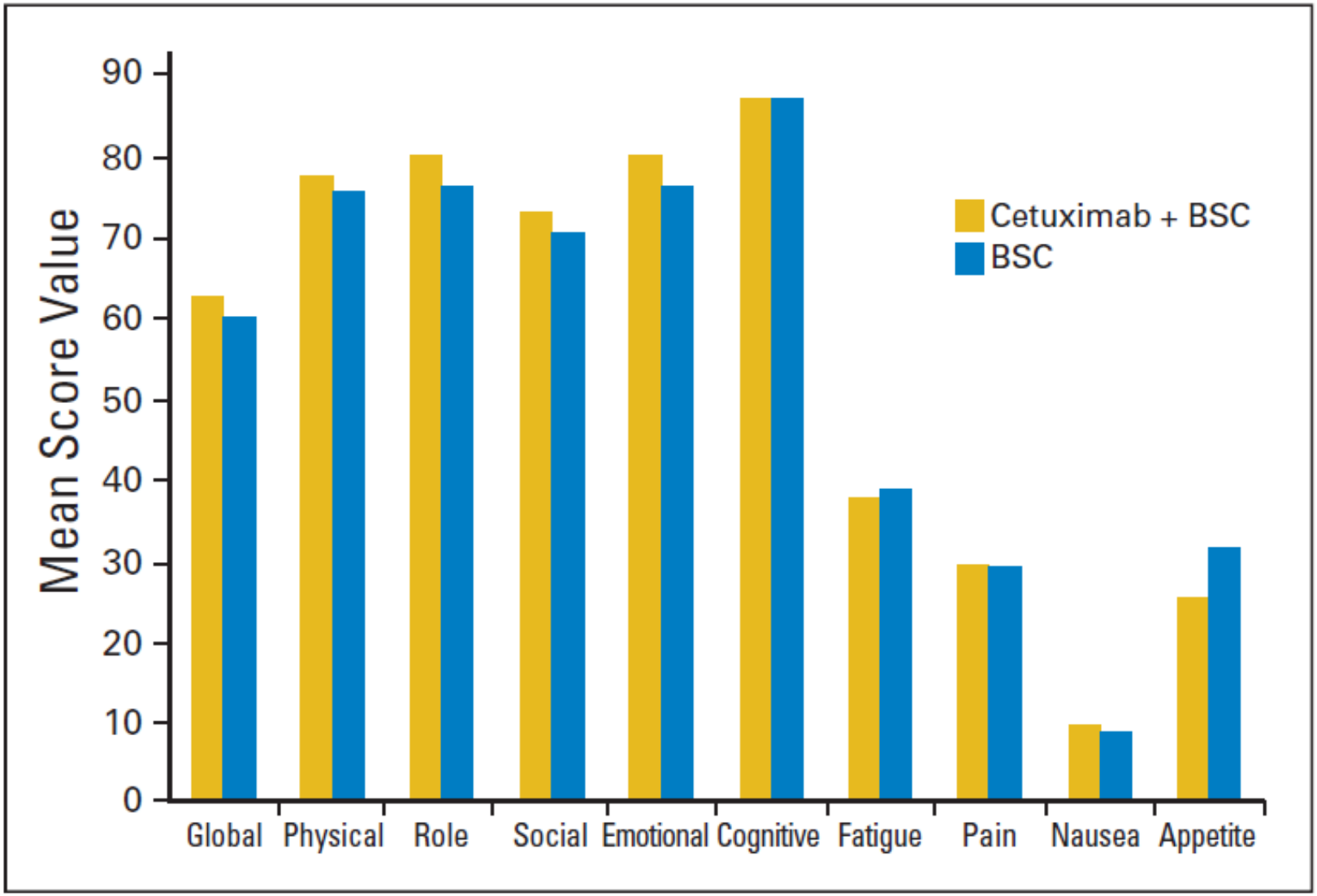
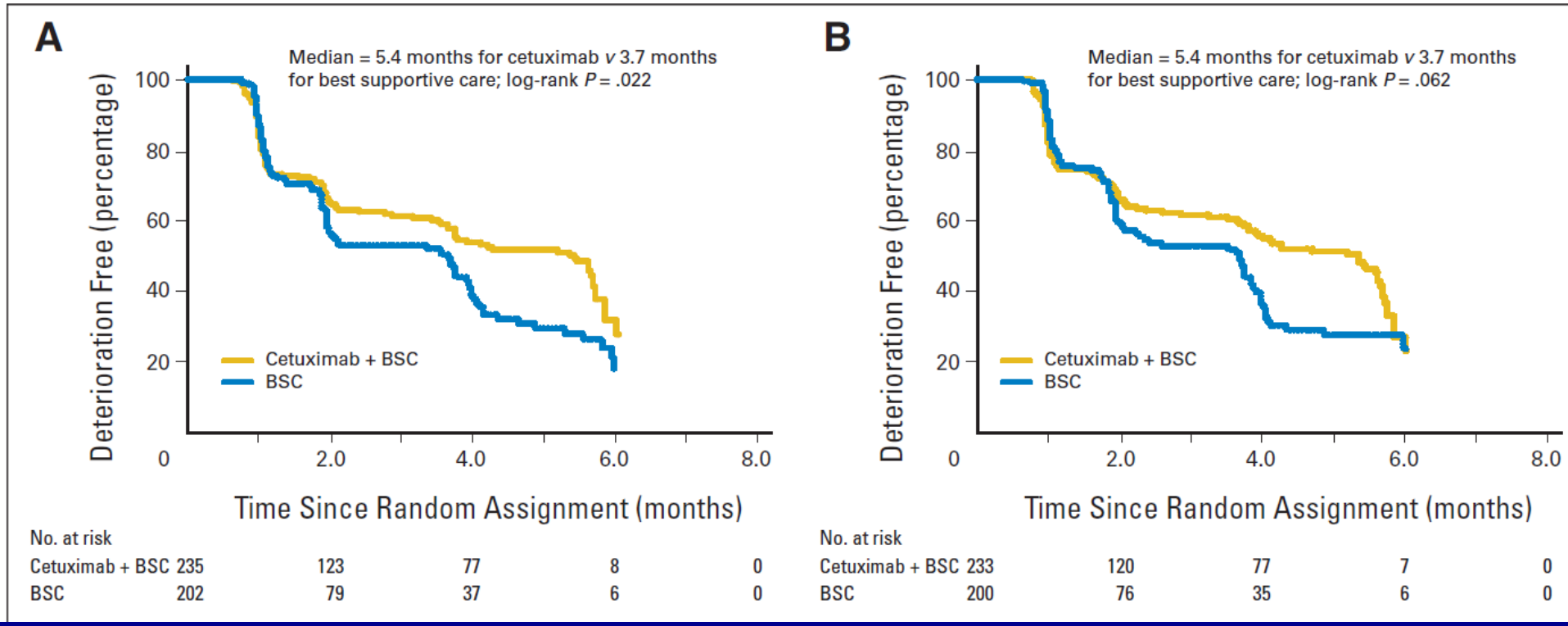


Fig 1. Mean health-related quality-of-life scores at baseline. No statistical differences were seen between arms for any scales or items. (Data for single items of dyspnea, sleep disturbance, constipation, and diarrhea are not shown).


A
Median = 5.4 months for cetuximab v 3.7 months for best supportive care; log-rank P = .022
Deterioration Free (percentage)
100
80
60
40
20
0
2.0
4.0
6.0
8.0
Cetuximab + BSC
BSC
Time Since Random Assignment (months)
No. at risk
Cetuximab + BSC 235 123 77 8 0
BSC 202 79 37 6 0
B
Median = 5.4 months for cetuximab v 3.7 months for best supportive care; log-rank P = .062
Deterioration Free (percentage)
100
80
60
40
20
0
2.0
4.0
6.0
8.0
Cetuximab + BSC
BSC
Time Since Random Assignment (months)
No. at risk
Cetuximab + BSC 233 120 77 7 0
BSC 200 76 35 6 0