

What have you done for me lately?  
The value added by health-related  
quality of life data to clinical  
oncology research

Neil K. Aaronson, Ph.D.  
Cancer Experiences Collaborative  
Patient Reported Outcome Measures  
in Cancer and Palliative Care  
Manchester, UK, July 6-7, 2010

# Uses of HRQOL information

- Understand the burden of disease
- Demonstrate treatment efficacy
- Facilitate regulatory approval
- Substantiate marketing claims (labelling)
- Raise consumer and clinician awareness
- Improve patient-provider communication and quality of care

# Uses of HRQOL information

- Understand the burden of disease
- Demonstrate treatment efficacy
- Facilitate regulatory approval
- Substantiate marketing claims
- Raise consumer and clinician awareness
- Improve patient-provider communication and patient compliance

# Use of HRQOL outcomes in clinical trials

## An informal, simple-minded literature search

- PubMed search using terms: “quality of life” and “clinical trial”

<u>Year</u>	<u>N of hits</u>
1980	13
1990	131
2000	1084
2007	2524
2008	2658
2009	2890

## Phase III clinical trials where HRQOL outcomes are likely to add value

- adjuvant therapy for patients at risk of recurrence
- disease site is associated with poor prognosis
- comparing different treatment modalities
- comparing treatments with different intensities and/or duration
- survival is expected to be equivalent but HRQOL to differ as a function of treatment (e.g., symptom control and supportive care studies)

# Phase III clinical trials where HRQOL outcomes are likely to add value

- adjuvant therapy for patients at risk of recurrence
- disease site is associated with poor prognosis
- 
- 
- 
- survival is expected to be equivalent but HRQOL to differ as a function of treatment (e.g., symptom control and supportive care studies)
- survival is expected to be marginally (but significantly) better in one arm, and HRQOL to be better in the other

# HRQOL measurement in breast cancer RCTs

Goodwin PJ, Black JT, Bordeleau LJ, Ganz PA. JNCI 2003; 95:263-81

- 46 RCTs reviewed
  - 8 primary management
  - 7 adjuvant therapy
  - 20 metastatic disease
  - 11 symptom control/supportive care

There is some good news and some bad news. First the good news.

# Key conclusions: RCTs in primary management

“...HRQOL measurement provided information that was useful in selecting optimal treatment when two medical treatments were demonstrated to have equivalent medical outcomes.”

...but now the bad news.

# Key conclusions: RCTs of adjuvant therapy

“In general, HRQOL effects were either absent, transient or associated with observed toxicity...HRQOL measures have had little impact on clinical decision making.”

# Key conclusions: RCTs in metastatic disease

“Disappointingly, HRQOL outcomes in these studies have provided little additional information beyond that obtained from traditional medical outcomes...In none of the published studies...did HRQOL measurement provide information that had a clear effect on treatment recommendations.”

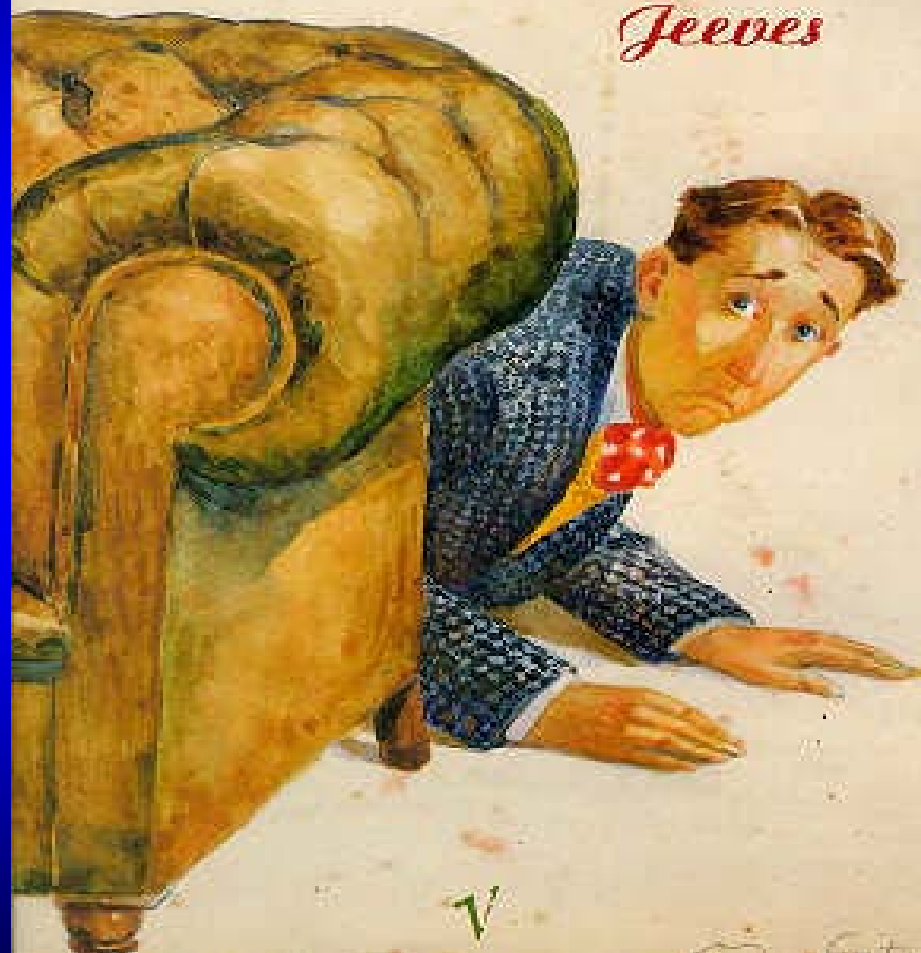
# Key conclusions: RCTs in symptom control

“...measurement of HRQOL adds little if any benefit to traditional medical outcomes in these trials...focus on the specific symptoms being studied rather than selecting general or even cancer-specific HRQOL instruments.”



P.G. WODEHOUSE

*Stiff Upper Lip,  
Jeeves*



# A (relative) success story from early HRQOL investigations: EORTC trial 10801

- RCT comparing radical mastectomy (RM) with breast-conserving therapy (BCT) in stage I and II breast cancer patients (N = 900+ patients)
- Primary endpoint: survival
- Secondary endpoints: local recurrence rate and HRQOL
- No significant differences in survival or local recurrence

# HRQOL hypothesis and measure

- BCT would preserve body image but heighten fear of disease recurrence
- HRQOL questionnaire: 10 items assessing body-image, fear of recurrence, and overall satisfaction with treatment

# HRQOL results and conclusions

- HRQOL data were available for 278 patients approximately 2 years post-treatment
- BCT group reported significantly better body image than RM group
- No significant group differences observed in fear of recurrence

# Amputation vs limb-sparing procedure in soft-tissue sarcoma

Sugarbaker et al. Surgery 91:17-23, 1982

- Small RCT (n = 26) comparing amputation + CT vs. limb-sparing surgery + RT + CT
- HRQOL assessed post-surgery
  - SIP, PAIS, Katz ADL, Barthel Index, clinical assessment of mobility, pain, sexuality
- Hypothesized that limb-sparing procedure would yield better HRQOL

- No significant differences between treatment arms, with exception of sexual functioning, which favoured the amputation group
- Led to improvement in limb-sparing procedure (e.g., better RT shielding)

# HRQOL data can yield unanticipated results

Hopwood P, Stephens R. Lung Cancer 1994; 11 (Suppl 1) S82

- RCT in SCLC (n = 314)
- 3 cycles of etoposide, cyclofosfamide, methotrexate and vincristine vs. 3 cycles of etopsodie en vincristine only
- RSCL and HADS
- No statistically significant differences in survival or tumor response
- 4 drug combination resulted in less distress, fatigue, dyspnea and cough, and better physical functioning

# 3 examples of more recent RCTs with valued-added HRQOL outcomes

What have you done for me lately?

# Clinical trials where HRQOL outcomes are likely to result in value-added

- adjuvant therapy for patients at risk of recurrence
- disease site is associated with poor prognosis
- comparing different treatment modalities
- comparing treatments with different intensities and/or duration
- survival is expected to be equivalent but HRQOL to differ as a function of treatment

# EORTC Protocol 30893

## HRQOL in hormone-resistant prostate cancer

- RCT comparing flutamide vs prednisone in symptomatically progressing, hormone-resistant prostate cancer (N = 201)
- Primary endpoints:
  - Time to progression (TTP) based on physician-rated pain score, analgesic use, need for other pain treatment (e.g., RT), declining performance status
  - Overall survival
- Secondary endpoint:
  - HRQOL

# Clinical findings

- No significant group differences observed in TTP (3.4 months for prednisone vs 2.3 months for flutamide) or overall survival (10.6 vs 11.2 months)
- No significant group differences in “subjective response” based on physician-ratings of pain and performance status (56% vs 45%)

# HRQOL assessment

- QLQ-C30 + 3 questions on analgesic use
- Data collection schedule and compliance
  - Baseline (90%)
  - 3 weeks following start of treatment and every 6 weeks thereafter until subjective progression (~ 70%)

# Key HRQOL results and conclusions

- Overall, statistically significant differences favoring prednisone for pain, emesis, diarrhea, constipation and overall QL
- Prednisone group exhibited significantly less fatigue at 6 weeks and better role functioning, and less appetite loss at 3 months.
- Conclusion: in patients with symptomatic, metastatic HRPC, prednisone is superior to flutamide in reducing pain and fatigue, based on patient (but *not* physician) generated data

# Clinical trials where HRQOL outcomes are likely to result in value-added

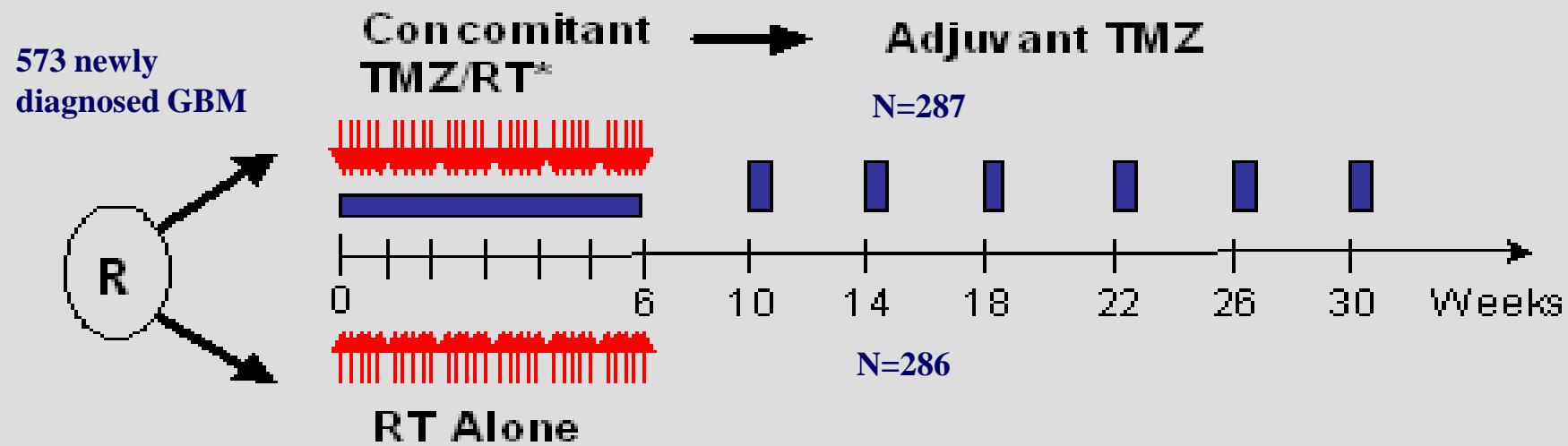
- adjuvant therapy for patients at risk of recurrence
- 
- 
- comparing treatments with different intensity and/or duration
- survival is expected to be equivalent but HRQOL to differ as a function of treatment



# EORTC / NCIC CTG phase III trial evaluating HRQOL in glioblastoma patients

- RCT comparing radiotherapy alone (RT) with RT plus temozolomide (RT + TMZ)
- Primary endpoint: survival
- Secondary endpoint: HRQOL



# Treatment Schema



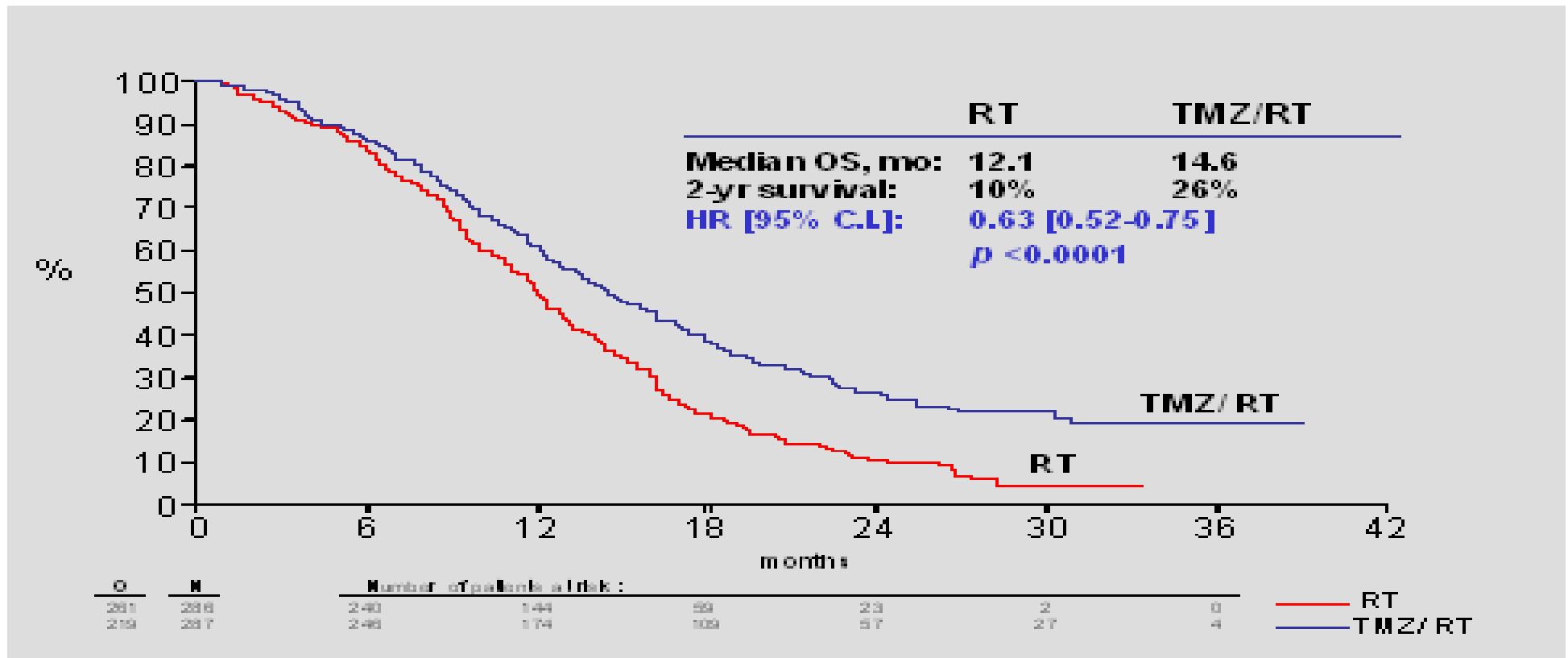
-  **Temozolomide** 75 mg/m<sup>2</sup> po qd for 6 weeks, then 150-200 mg/m<sup>2</sup> po qd d1-5 every 28 days for 6 cycles
-  **Focal RT** daily — 30 x 200 cGy  
Total dose 60 Gy

\*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.

# Clinical findings



## Overall Survival



# HRQOL Hypotheses

- Baseline HRQOL would be impaired
- HRQOL would deteriorate more severely during intensive treatment (RT + TMZ) compared to standard treatment (RT)
- HRQOL would improve more slowly following RT + TMZ compared to RT alone
- At longer term follow-up HRQOL profiles of the two treatment arms would converge

# HRQOL assessment

- 7 scales of the EORTC QLQ-C30 and BN20
- Data collection schedule and compliance
  - Baseline (85%)
  - week 4 of radiotherapy (73%)
  - week 4 following radiotherapy (78%)
  - During 4 subsequent follow-ups (65% to 87%)

# Key HRQOL results and conclusions

- Baseline HRQOL was similar for the two treatment arms
- During early follow-up, significant differences favoring RT alone were noted for social functioning, fatigue, emesis, and constipation, but these were transient
- Over time, HRQOL outcomes were similar for the two groups
- Conclusion: Combination of RT + TMZ significantly increases survival without a sustained negative effect on HRQOL

# Phase III clinical trials where HRQOL outcomes are likely to add value

- adjuvant therapy for patients at risk of recurrence
- disease site is associated with poor prognosis
- comparing different treatment modalities
- comparing treatments with different intensities and/or duration
- survival is expected to be equivalent but HRQOL to differ as a function of treatment

# Making tradeoffs explicit

## Treatment of early stage prostate cancer

Holmberg L et al. NEJM 2002; 347:781-789

- RCT of radical prostatectomy vs watchful waiting in early stage prostate cancer (N = 695)
  - 100% follow-up survival (6 yrs), 87% follow-up HRQOL (4 yrs)
- Prostatectomy - decrease in prostate-specific death rates (9% versus 5%; RR 0.50, 0.27 to 0.91, p = 0.02)
- Prostatectomy – trend for reduced all-cause mortality (18% versus 15%; p = 0.31)

# Making tradeoffs explicit

Steineck G et al. NEJM 2002; 347: 7980-796

- Sexual dysfunction
  - 45% waiting; 80% prostatectomy
- Urinary leakage
  - 21% waiting; 49% prostatectomy
- Urinary obstruction (weak stream)
  - 44% waiting; 28% prostatectomy
- Bowel function, anxiety, depression, well-being did not differ

# Added value spin-off

## Baseline HRQOL predicts survival

Gotay CG et al. J Clin Oncol 2008; 26:1355-1363

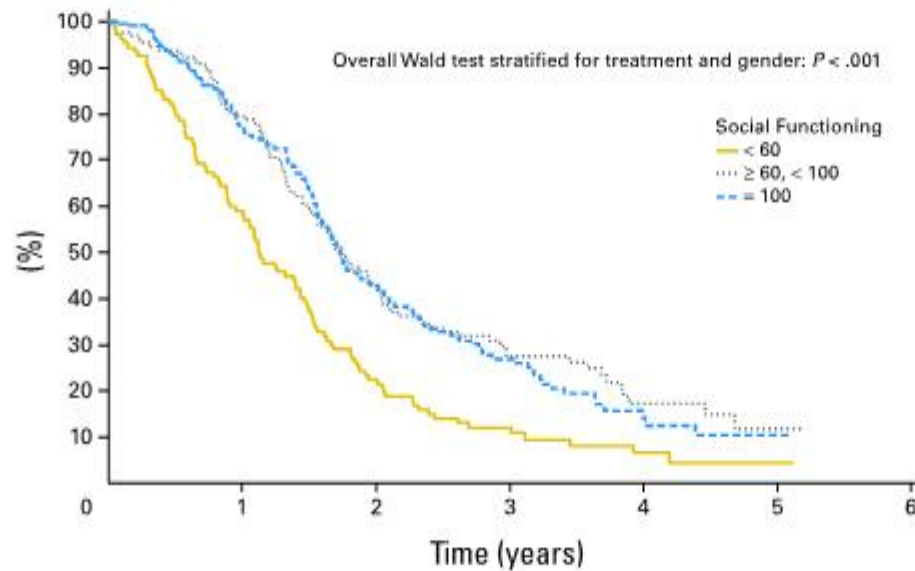
- Review of 39 studies including ~ 14,000 patients with diverse cancer diagnoses
- Studies employed a range of HRQOL measures (single symptom, multidimensional, global QL)
- Analyses typically accounted first for known sociodemographic and clinical prognostic factors (e.g, performance status, weight loss)

# Baseline HRQOL predicts survival

- In 36 of 39 studies, HRQOL proved to be a significant predictor of survival, above and beyond known prognostic factors
- Effect sizes (hazards ratios) tended to be small to moderate

# Baseline social functioning predicts survival in metastatic colorectal cancer

(Efficace F et al. JCO 2008, 26:2020-6)



**Fig 1.** Overall survival curves in the three groups defined by Social Functioning scale of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) by tertiles. N, number of patients; O, number of observed events (ie, deaths).

Social Functioning	O	N
< 60	99	107
≥ 60, < 100	98	128
= 100	155	205

No. of patients at risk						
	0	1	2	3	4	5
< 60	63	24	10	3	1	
≥ 60, < 100	101	52	25	11	2	
= 100	155	84	32	9	2	

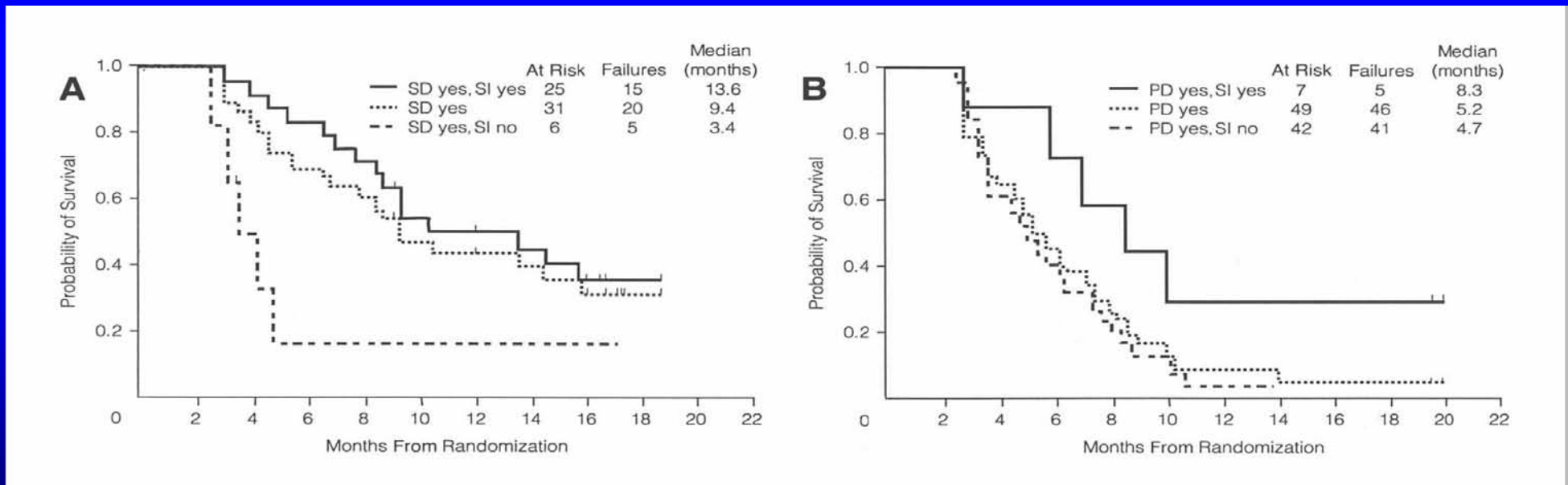
Social Functioning Scale by the EORTC QLQ-C30	Hazard Ratio (95% CI)	Median Survival (months; 95% CI)	2-Year Survival (%) (95% CI)
< 60	1.00	13.47 (12.06 to 17.58)	22.43 (15.07 to 30.70)
≥ 60, < 100	0.50 (0.38 to 0.67)	20.90 (18.20 to 24.41)	41.91 (33.20 to 50.36)
= 100	0.55 (0.43 to 0.71)	20.83 (19.58 to 24.44)	43.15 (36.25 to 49.85)

**Change in HRQL  
(not just baseline score)  
predicts outcome**

# Survival of NSCLC patients as a function of tumor status and symptom improvement

Cella D et al. J Clin Oncol 2005; 23: 2946-54

Patients were treated with gefitinib  
(epidermal growth factor receptor tyrosine kinase inhibitor)



Symptom improvement =  $\geq 2$  point increase in symptom index score for  $\geq 28$  days without worsening at any interim weekly assessment

# How would you rate your overall health?

excellent    good    fair    poor

---

In general population studies, self-rated health is one of the most consistent, independent predictors of:

- use of medical and mental health services
- morbidity
- 5 and 10 year mortality

# HRQOL as prognostic factor: clinical trial applications

- stratification prior to randomization
  - help ensure pretreatment group equivalence
  - increase efficiency of trial
  - facilitate planned subgroup analyses

# Summary and conclusions

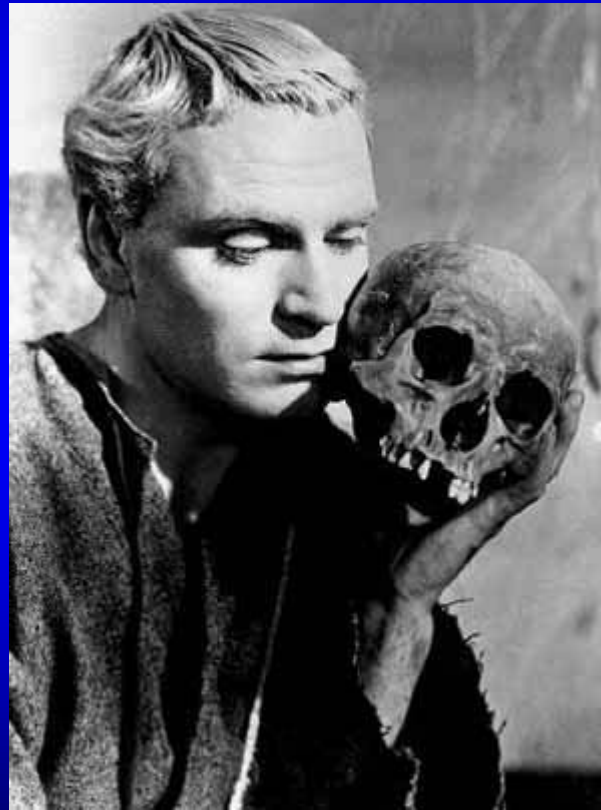
## Phase III clinical trials where HRQOL outcomes are likely to add value

- ✓ adjuvant therapy for patients at risk of recurrence
- ✓ disease site is associated with poor prognosis
- ✓ comparing different treatment modalities
- ✓ comparing treatments with different intensities and/or duration
- ✓ survival is expected to be equivalent but HRQOL to differ as a function of treatment (e.g., symptom control and supportive care studies)

# Conclusions

- Need to be selective in deciding in which trials to invest additional time, energy and resources
- In most cases, HRQOL data will confirm clinical impressions and expectations

If you're looking for drama,  
catch a Shakespeare play



Laurence Olivier

However, occasionally...





**17<sup>th</sup> Annual ISOQOL Conference**  
**October 27 – 30, 2010**  
**London, United Kingdom**



*visit [www.isoqol.org](http://www.isoqol.org) for details!*