PRO measures: when do they add value?

Examples in Oncology

DIA Workshop
Paris, May 10-11, 2004

Pierre-Philippe Sagnier, MD, MPH
Bayer Health Care

Medline: “Cancer and Quality of Life”

1514 references in the last 12 months...

- Instrument development, analysis, reporting
- Burden of diseases
- Short and long-term evaluation of treatments
    - Surgery
    - Radiotherapy
    - Chemotherapy
    - Adjuvant care
- Prognostic factor of outcome
- Regulatory views

in a wide range of oncology indications

PROs added value in oncology

- Instrument development, analysis, reporting
- Burden of diseases
- Short and long-term evaluation of treatments: “from care to cure”
    - Chemotherapy
    - Adjuvant care
    - Palliative care
    - Psychosocial and rehab. interventions
- Prognostic factor of outcome
- Regulatory views

Chronic Phase of CML

Imatinib vs. IFN+Ara-C: the IRIS trial

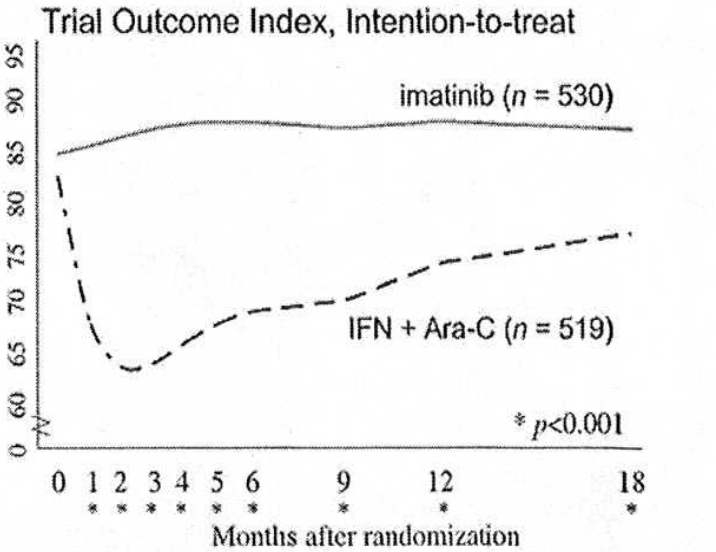


Figure 1. Estimated mean TOI scores by treatment arm, adjusted for missing data (ITT approach). *P* values are for difference in treatment arm means at each scheduled administration of the FACT-BRM.

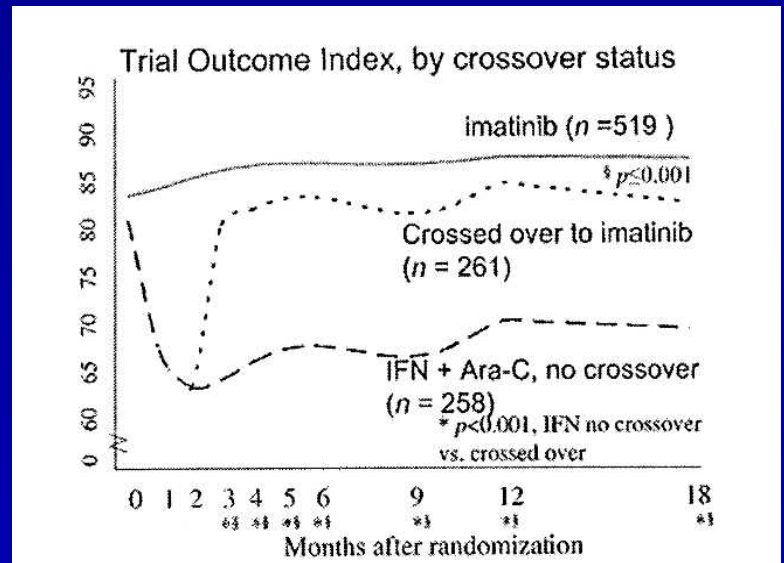


Figure 4. Estimated mean TOI scores by treatment arm and crossover status.*P* values are for difference in means between IFN + LDAC after crossover and §imatinib and *IFN + LDAC as first-line treatment. Results not shown for imatinib crossovers (n = 11) or for IFN + LDAC crossover prior to month 3 (n = 3).

Primary endpoint: TOI, a composite index (physical, functional, ttment specific sub-scales) part of the FACT-BRM

E. Hahn et al. Semin Hematol 2003; 40(suppl 2): 31

PSagnier 05/04

Ovarian cancer first line treatment

Cisplatin/Paclitaxel vs. Carboplatin/Paclitaxel

EORTC QLQ-C30

Time point	N	Mean Differences	95% CI
		Between group scores	
Baseline	679	-1.61	-5.15 to 1.93
After 1st cycle	604	-2.59	-5.89 to 0.71
After 3rd cycle	525	-3.67	**-6.97 to -0.37**
End of treatment	226	-13.28	**-18.88 to -7.68**
3-mo follow-up	534	-7.83	**-11.61 to -4.05**
		Intra-individual differences	
After 1st cycle	538	-2.40	-6.12 to 1.32
After 3rd cycle	466	-2.70	**-7.13 to 1.73**
End of treatment	205	-11.70	**-18.80 to -4.60**
3-mo follow-up	474	-6.80	**-12.05 to -1.55**

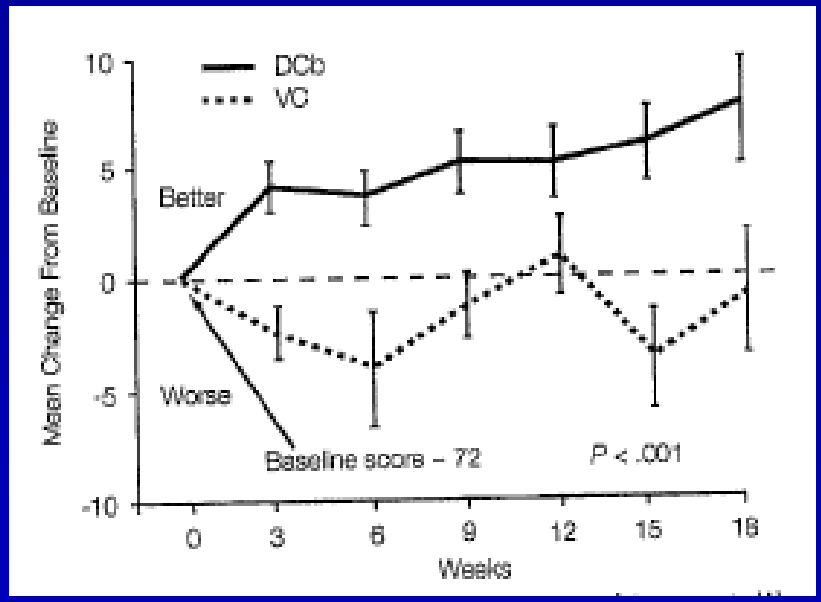
Efficacy: ns Anemia, nausea, vomiting ($p<.01$)

A. du Bois et al. JNCI 2003; 95:1320

PSagnier 05/04

Non-small-cell lung cancer (stage IIIb and IV)
Phase III docetaxel+carboplatin vs vinorelbine+cisplatin

EuroQol scores



Consistent results with Lung Cancer Symptom scale

Median survival (months)

9.4(DCb) 9.9 (VC) p=.66

Toxicity (%)

	DCb	VC	p
Grade III-IV	39.9	48.0	ns
Feb.neutropenia	3.7	4.5	ns
Nausea	6.2	16.4	.01
Vomiting	4.2	16.2	.01

F. Fossella J Clin Oncol 2003; 21:3016

Does HRQ0L measures inform clinical decision making?

The prostate cancer example

- Checklist approach to reporting
- 24 RCTs
- 1/3 of studies were deemed “robust”
- Clear improvement after1998
- 50% of studies on metastatic patients had HRQoL as primary endpoint
- 54% of studies: no difference on traditional endpoints
- 74% of studies: some differences on HRQoL endpoints

Table 4. Level of Reporting According to the Minimum Standard Checklist for Evaluating HRQOL Outcomes in Cancer Clinical Trials

HRQOL Issue	Reports No.*	%
Conceptual		
A priori hypothesis stated	3/23	13
Rationale for instrument reported	7/24	29
Measurement		
Psychometric properties reported	21/24	87
Cultural validity verified	13/16	81
Adequacy of domains covered	21/24	87
Methodology		
Instrument administration reported	6/24	25
Baseline compliance reported	11/24	46
Timing of assessments documented	23/24	96
Missing data documented	13/24	54
Interpretation		
Clinical significance addressed	3/24	12
Presentation of results in general	16/24	67

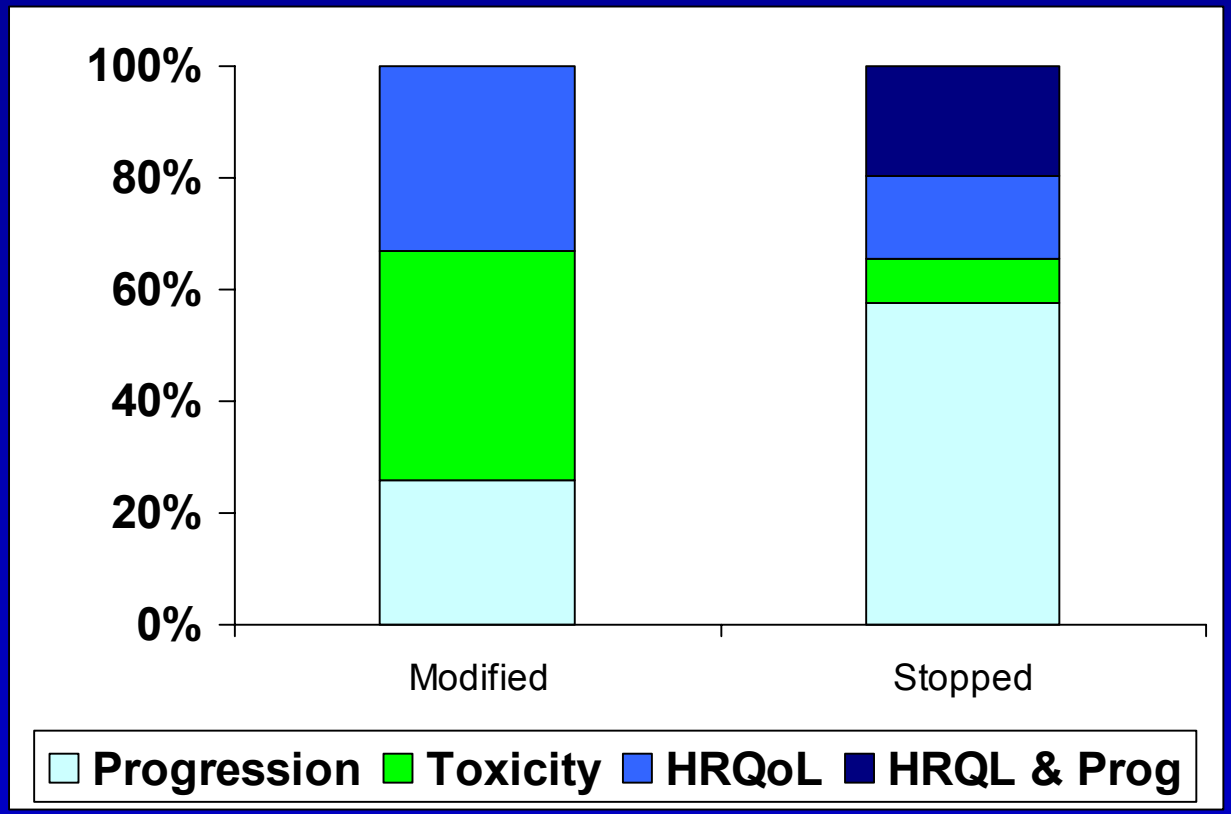
Abbreviation: HRQOL, health-related quality of life.
*Number of articles reporting item/number of articles to which item is applicable.

F. Efficace et al. J Clin Oncol 2003, 21:3502

Treatment decisions in palliative care

Qualitative analysis of 203 patients, 4 consultations

Primary reason for treatment modification (n=54)
or discontinuation (n=40)

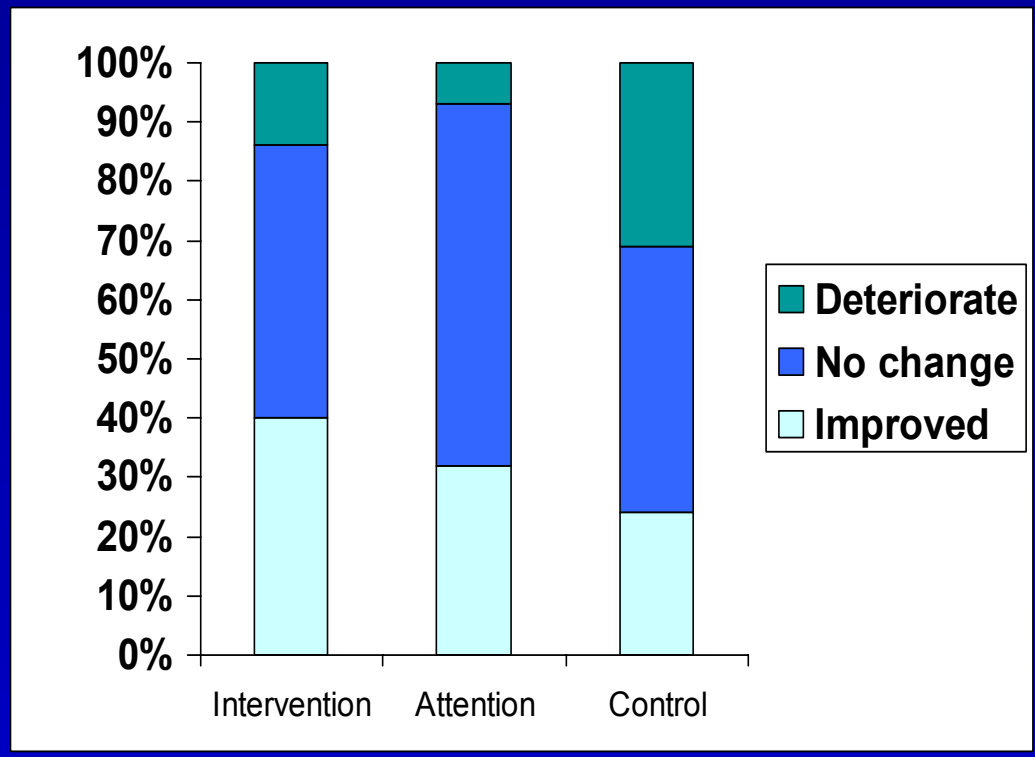


S. Detmar et al. J Clin Oncol 2002, 20:1056

Measuring HRQoL in routine oncology practice tend to improve communication and well-being of patients

- RCT ; n=286
- Regular EORTC-C30 with vs. without physican feed-back vs. control
- 4 encounters
- Qualitative analysis of patient-physician communication
- Improvement linked to:
  - Use of HRQoL data (p=.016)
  - Discussion of pain and role function (p=.046)

FACT-G
% achieving meaningful change (7 points)



G. Velikova et al. J Clin Oncol 2004, 22:714

Depression linked to shorter survival post stem-cell transplantation, even after adjusting on confounders

Variable	Relative Risk	95% CI	P	
Nondepressed*		1.00		
Depressed ≤ 12 months after transplantation	2.99	1.07-8.30	.04	✸
Depressed > 12 months after transplantation	0.80	0.29-2.21	.67	
Other significant variables				
Disease stage at transplantation				
Good/early		1.00		
Intermediate/advanced	3.35	1.21-9.22	.02	
Disease type			.002†	✸
AML/ALL/other leukemia		1.00		
NHL/HD	0.09	0.03-0.34	< .001	
CML	0.42	0.17-1.07	.07	
CLL	0.14	0.03-0.62	.009	
MM	0.16	0.05-0.51	.002	
Others	0.11	0.02-0.54	.007	
Age at transplantation				
Age > 40 years		1.00		
Age ≤ 40 years	0.35	0.14-0.87	.02	✸

* Model stratified by type of transplantation (autologous *v* allogeneic).
† Five-degree of freedom test.

F. Loberiza et al. J Clin Oncol 2002, 20:2118

Will a pharmacological or psychological intervention improve survival and/or HRQoL?

So far no...

Active management of QOL after treatment
Example in colo-rectal cancer

- RCT
- Home exercice vs. control
- n=69 vs. 33
- Patients under adjuvant therapy
- Primary endpoint: FACT-C

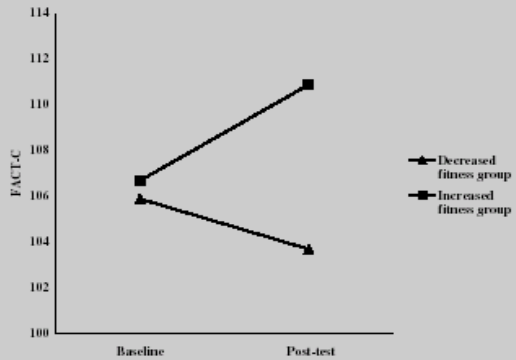


Figure 2. Significant change in quality of life as measured by the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) scale.

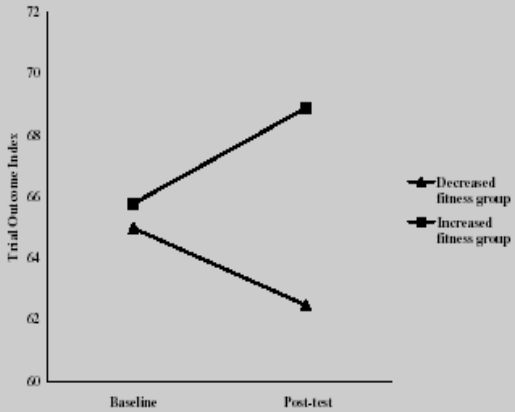


Figure 4. Significant change in the trial outcome index.

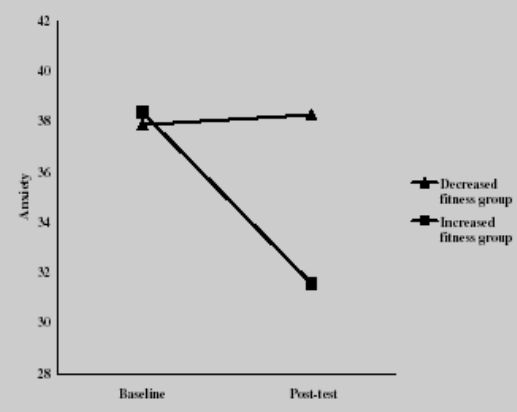


Figure 3. Significant change in anxiety.

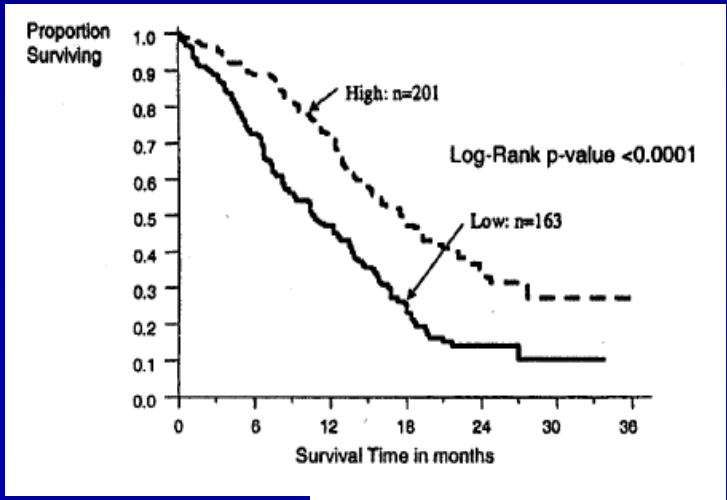
K. Courneya. Eur J Cancer Care 2003, 12:347

PROs added value in oncology

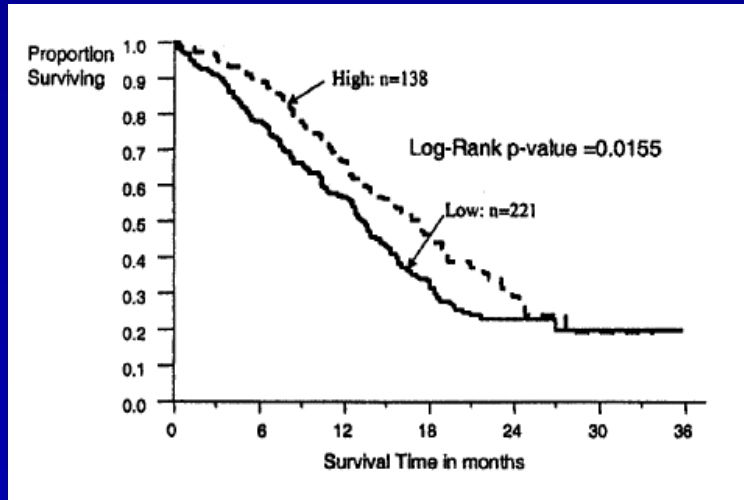
- Instrument development, analysis, reporting
- Burden of diseases
- Short and long-term evaluation of treatments: “from care to cure”
- Prognostic factor of outcome
- Regulatory views

Advanced bladder cancer

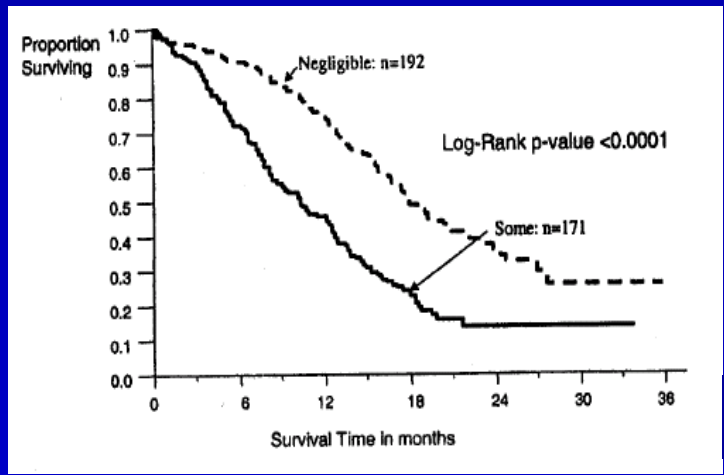
EORTC-C30 is an independent predictor of survival



Physical



Role Function



Anorexia

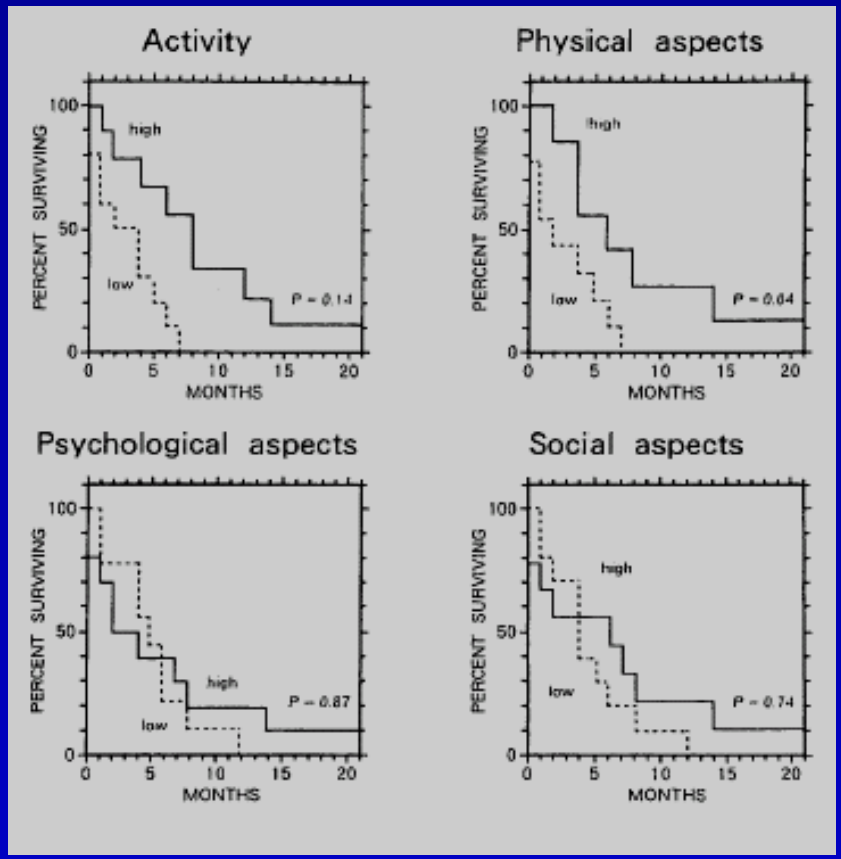
D. Roychowdhury et al.
J Clin Oncol 2003, 21:673

PSagnier 05/04

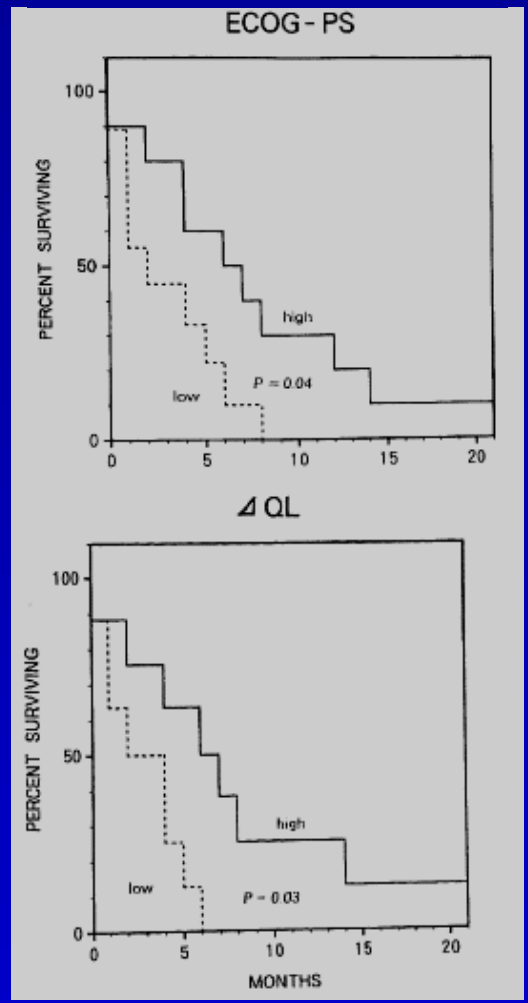
Advanced breast cancer

HRQoL (QOL-ACD) independently predicts survival

Baseline scores



Change scores



N= 47
Japanese
patients

K. Shimozuma et al.
Surg Today 2000, 30: 255

Advanced colo-rectal cancer

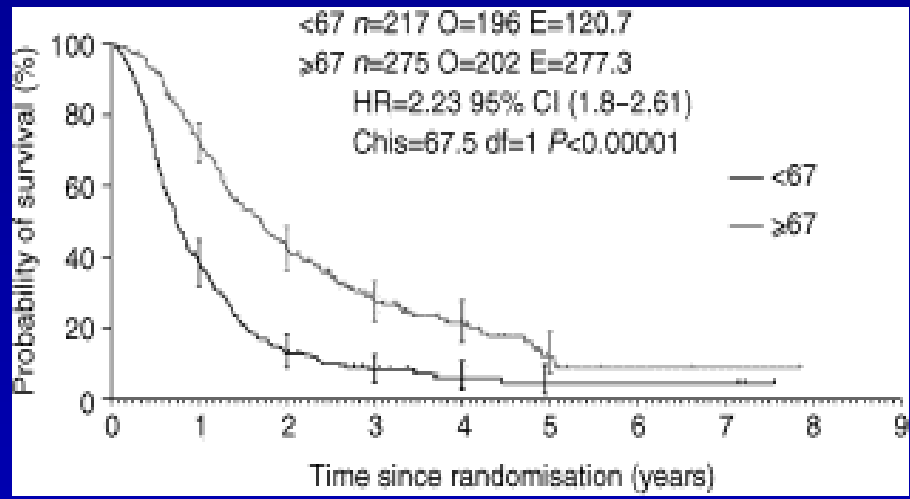
HRQoL (QLQ-C30) predicts survival

Table 3
Baseline multivariate model

Clinical variable	*P* value	Hazard ratio (95% CI)
Significant factor		
PS (0–1 versus 2)	<0.0001	1.71 (1.33–2.19)
Tumour location (left versus right)	0.033	0.79 (0.63–0.98)
Metastases (yes versus no)	0.04	1.38 (1.02–1.87)
Haemoglobin (⩽ or > 110 g/l)	0.006	1.44 (1.11–1.87)
Weight loss (yes versus no)	0.003	1.39 (1.11–1.72)
CEA (⩾ versus < median value)	<0.0001	1.89 (1.47–2.42)
Albumin (⩽ versus >40 g/l)	<0.0001	0.62 (0.50–0.77)
Non-significant factors		
WCC (⩾ or $<9.0\times10^9$ cells/l)	0.47	–
Sex	0.77	–
Age	0.87	–

CI, confidence intervals; PS, performance status; CEA, carcino-embryonic antigen; WCC, white cell count.

Maisey et al.
Eur J Cancer 2002, 38:1351



Multivariate HR: 2.17 [1.75-2.69]
p<.0001

"QOl appears to be a stronger predictor of overall survival than ECOOG-PS, a clinician-based measure"

QOL added value in predicting outcome

The breast cancer example

Regression analysis of QOL scores

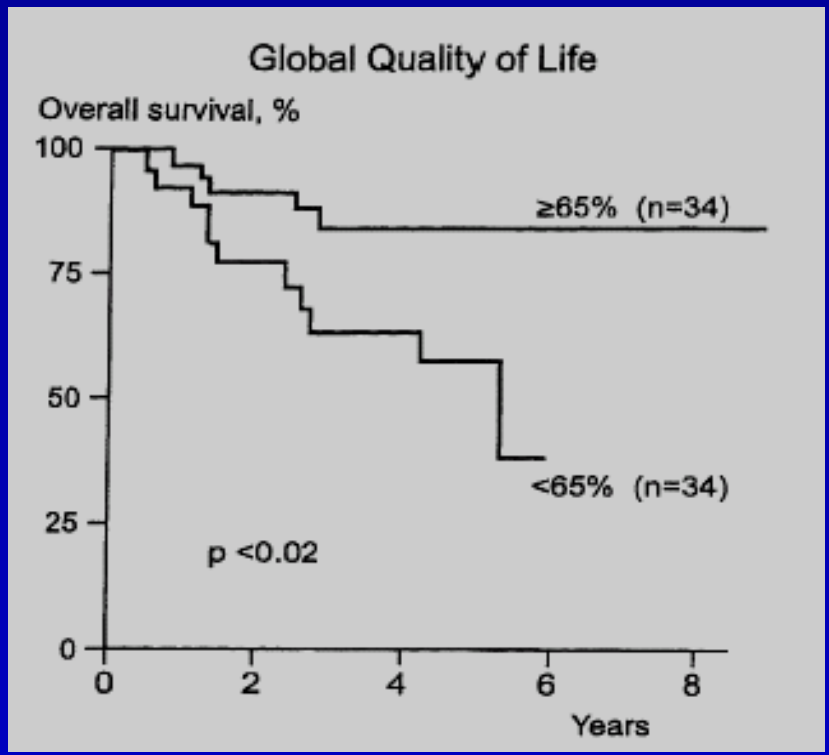
		At Start of Adjuvant Therapy on DFS				At 6 Months After Relapse on Overall Survival			
Trial	QL Scale	No. of Patients	No. of Relapses	Hazards Ratio*	*p*	No. of Patients	No. of Deaths	Hazards Ratio*	*p*
VI	PWB	1,212	580	0.97	.09	206	137	0.91	.03
	Mood	1,209	575	1.00	.93	205	136	0.93	.11
	Appetite	1,214	581	0.98	.26	206	137	0.92	.03
	PACIS	1,218	582	0.98	.28	206	137	0.96	.36
	PWB	963	460	0.99	.58	154	110	0.85	<.0001
VII	Mood	960	458	1.01	.70	154	110	0.88	.002
	Appetite	962	459	1.01	.44	153	110	0.86	.0001
	PACIS	969	458	1.03	.12	156	113	0.85	.0001
		*Hazards Ratio represents the effect of a change of one unit of QL in the square root scale. A hazards ratio less than 1 indicates better QL associated with reduced risk of death.							

QOL predicts survival in metastatic forms

but not in early stages

A. Coates et al. J Clin Oncol 2000, 18:3768

Aggressive Lymphoma: global QOL (EORTC-QLQ-C30) was most potent predictor of long-term survival



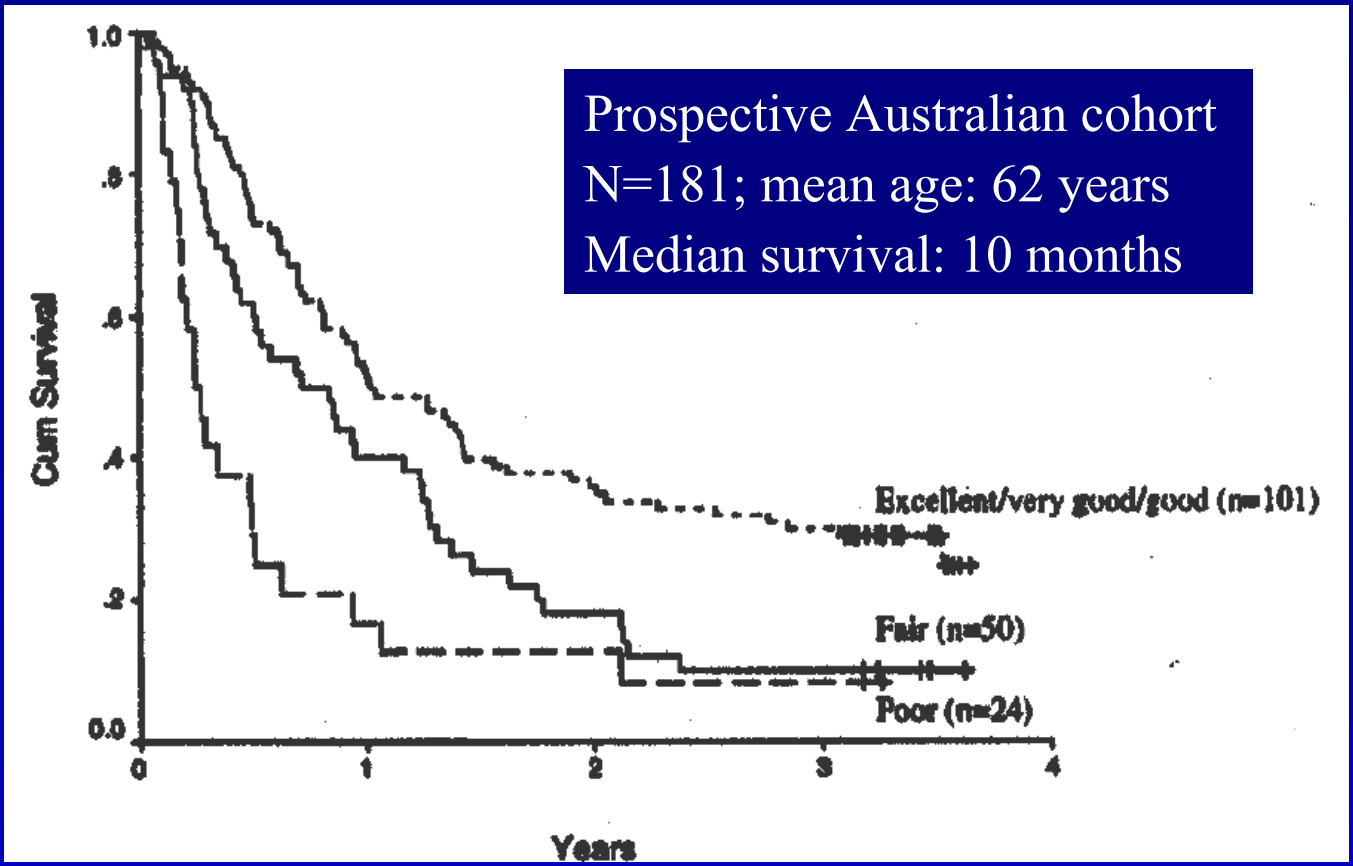
"...In an homogeneous patient population receiving chemotherapy with curative intention, it may be of use in defining risks groups requiring more intensive therapy"

Nordic Lymphoma Group

M. Jerkeman et al. Med Oncol 2001, 18:85

Advanced cancer

Self-reported health at baseline is a strong predictor of survival



Stepwise Cox model: SRH***, ECOG**, Diagnosis**, Treatment*
SF36 (ns) , QLC-C30 (ns)

B. Shadbolt et al. J Clin Oncol 2002, 20:2515

PROs added value in oncology

- Instrument development, analysis, reporting
- Burden of diseases
- Short and long-term evaluation of treatments: “from care to cure”
- Prognostic factor of outcome
- Regulatory views

CPMP/ EWP/ 205/ 95 Rev 2: Anticancer MP in Man AG

4. Phase III Trials

4.1 Objectives and background

4.12. To study the effects of a new agent, appropriate end-points of assessment include: progression- free/ recurrence- free/ relapse- free survival, overall survival, response rate, symptom control/ quality of life

4.5 Evaluation of Efficacy

4.5.4. Symptom control and quality of life: The choice of scales should be justified and the validity of the scale for the specific study population and its reliability should be documented. Cultural aspects should be taken into account, especially in the case of multinational studies.

5. Requirements for authorisation

5.3.2. Quality of Life Studies: QOL studies may be used to support symptom control data provided that established quality of life questionnaires (including for example level of hospitalisation) are used, which are relevant to the study population treated.

Clinical and outcomes research in oncology

The need for integration

- The gloomy side
  - Only in exceptional circumstances so far, has the EMEA granted expedited approval for cancer drugs
  - “PROs perceived as complex and costly, plagued by several unresolved methodological problems”
  - Persisting reluctance to accept PRO measures, despite the fact that surrogate tumor-based and clinical benefit measures may even be considered a “worse option”
- The brighter view
  - 25% of European Public Assessment Reports include an HRQoL claim, most (25%) in oncology products
  - The revised EMEA NFG in oncology accepts HR-QoL to support tumor shrinking and/or toxicity and symptoms endpoints, justified case by case

G. Apolone Health & Quality Outcomes 2003, 1: 3

The FDA perspective on PROs to support cancer drug approval

End points supporting regular approval of oncology drug marketing applications, 01/01/1990 to 01/11/2002		
Total		57
Survival		18
Response rate (RR) and/or TTP alone		18
	(predominantly hormone treatment of breast cancer or hematologic malignancies)	
Tumor-related signs & symptoms		**13**
	RR + tumor-related signs and symptoms	**(9)**
	Tumor-related signs and symptoms al	**(4)**
Disease-free survival (adjuvant setting)		**2**
Recurrence of malignant pleural effusion		2
Decreased incidence of new breast cancer		2
Decreased impairment creatinine clearance		1
Decreased xerostomia		1

G. Williams, R. Pazdur, B. Temple.
J Biopharm Stat 2004, 1:5-21

- RecommendtTumor-related symptoms & signs, time to symptomatic progression, and composite endpoints that include PRO/HCU
- S&S scores representing "obvious benefits" + clear clinical benefit facilitate early approval (before survival data)
- Face validity: multidimensional HRQoL scales "may not discriminate between symptoms and toxicity"
- Missing data "probably most significant problem" in evaluating morbidity
- Appropriate population "critical" for documenting patient benefit: ITT
- For all PROs (incl. HRQoL), importance of EP2 meetings, and encouragements to sollicit written feed-back via SPAs

“ It seems self-evident that cancer patients will in most cases be the best source for determining effects on patient symptoms and that use of formal PRO scales is likely to be more common in the future”

G. Williams, R. Pazdur, B. Temple
2004

Aza C

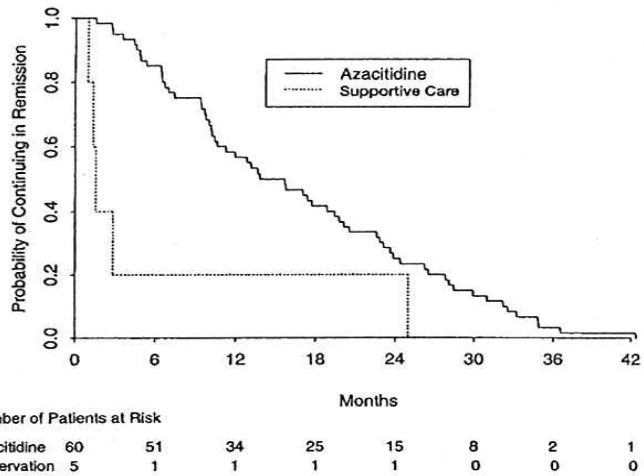


Fig 2. Duration of response. Measured from time of initial response to relapse in patients with CR, PR, or improvement and estimated according to the method of Kaplan-Meier.

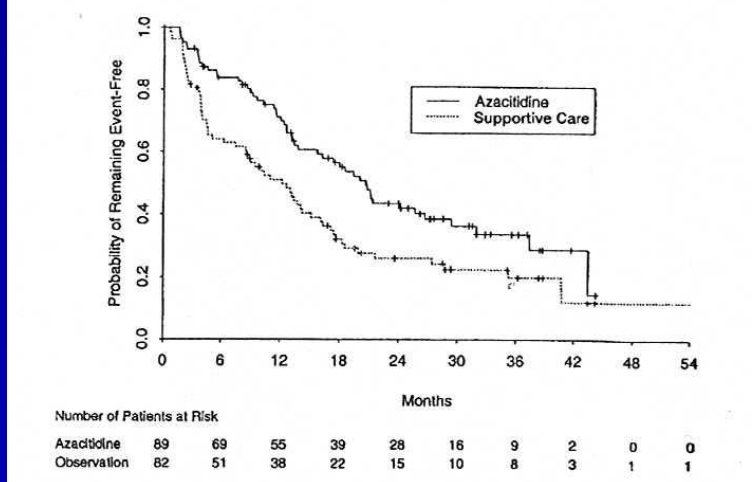


Fig 3. Time to AML transformation or death. Measured from entry on study to the time of first event, either transformation to AML or death, and estimated according to the Kaplan-Meier method.

Aza C

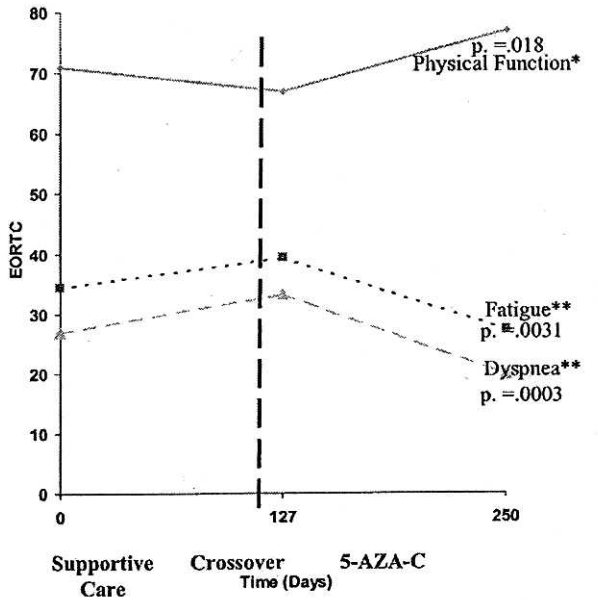


Fig 5. EORTC fatigue, dyspnea, and physical functioning of patients who cross over from supportive care to Aza C (n = 30). *Higher scores indicate better functioning. **Lower scores indicate symptom improvement.

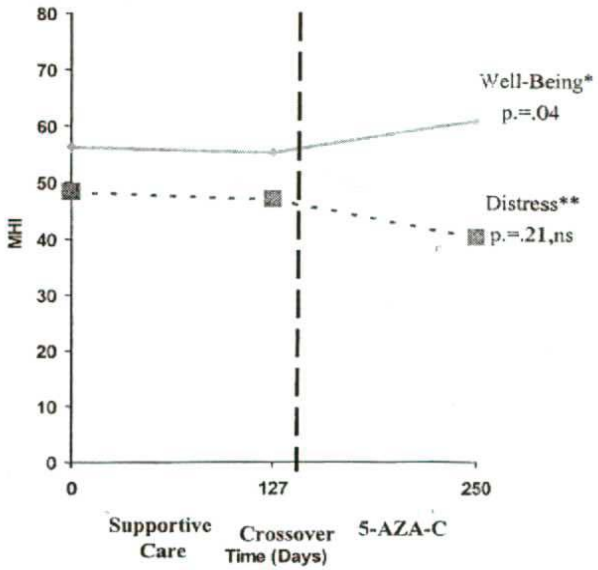


Fig 6. MHI physiological distress and well-being of patients who cross over from supportive care to Aza C (n = 30). *Higher scores indicate better well-being. **Lower scores indicate less distress.

(preliminary) wrap-up...

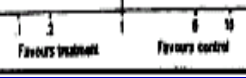
- Extensive ongoing scientific research on PROs in oncology
- Generic oncology HRQoL instruments are validated. Disease-specific modules have been/are being developed for increased clinical sensitivity.
- PRO measures (symptoms, function, etc...) are gaining progressive acceptance should be taken into account as they sometimes are more predictive and/or sensitive. Community is more demanding. Face validity more important that measurement properties. (Mayo Clinic Proceedings)
- We are de afcto in a stepwise process of acceptance of PRO measures in oncology: Need to further define patients population subsets in which PROs are most useful
- The ongoing trends towards more rigorous and powerful designs will lead to enhanced regulatory acceptance.

Figure 1 Psychosocial intervention versus control for all cancers (n = 1062): one-year overall mortality

Comparison: 02 Psychosocial intervention versus control for all cancers
Outcome: 01 4 year overall deaths

Study	Treatment n/N	Control n/N	RR (95%CI Random)	Weight %	RR (95%CI Random)
Cunningham 1998	20 / 30	29 / 36		17.2	0.83[0.61,1.12]
Edelman 1999	48 / 62	47 / 62		22.9	1.02[0.84,1.24]
Fawzy I 1993	0 / 34	7 / 34		0.4	0.07[0.00,1.12]
Goodwin P 2001	128 / 158	59 / 77		25.6	1.06[0.91,1.22]
Ilnyckyj A 1994	29 / 61	11 / 31		8.7	1.34[0.78,2.31]
Spiegel D 1989	38 / 50	36 / 38		25.0	0.76[0.65,0.89]
Total(95%CI)	263 / 395	189 / 278		100.0	0.93[0.77,1.13]

Test for heterogeneity chi-square=16.24 df=5 p=0.0062
Test for overall effect z=-0.71 p=0.5



Myeloma

Discuss PRO approach: Deficiency, Disability, Handicap