

# The use of patient's self-reported quality of life outcomes as prognostic factors for survival: *challenges and recent findings*

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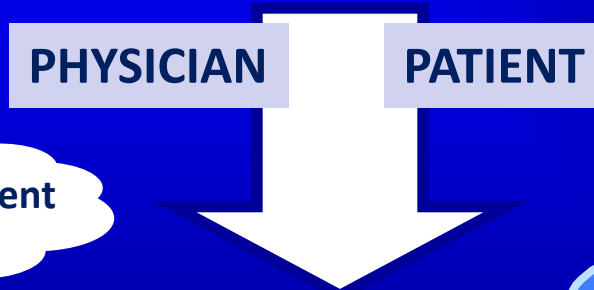
**Italian Group for Adult Hematologic Diseases (GIMEMA)**

GIMEMA Data Center

Rome, Italy

# Do patient's self-reported Quality of Life (QoL) parameters provide prognostic information for clinical outcomes ?

**"...Prognosis has been part of the practice of medicine much longer than diagnosis."**  
*(Mackillop WJ, 2001)*



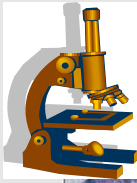
How long this patient will survive?



# Traditional Areas of Prognostic Factor Research in Oncology

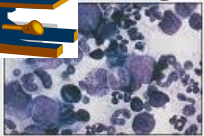
## Patient-related

(age, gender, comorbidity...)



## Tumor-related

(stage of disease, histology, laboratory data)



## Clinician-reported data

(performance status, Toxicity)



Intervention  
(type of treatment)

Intervention  
(type of treatment)

Outcome of interest



### Examples...

- Disease-free survival
- Clinical response
- Progression-free survival
- Overall survival

Were we missing something?



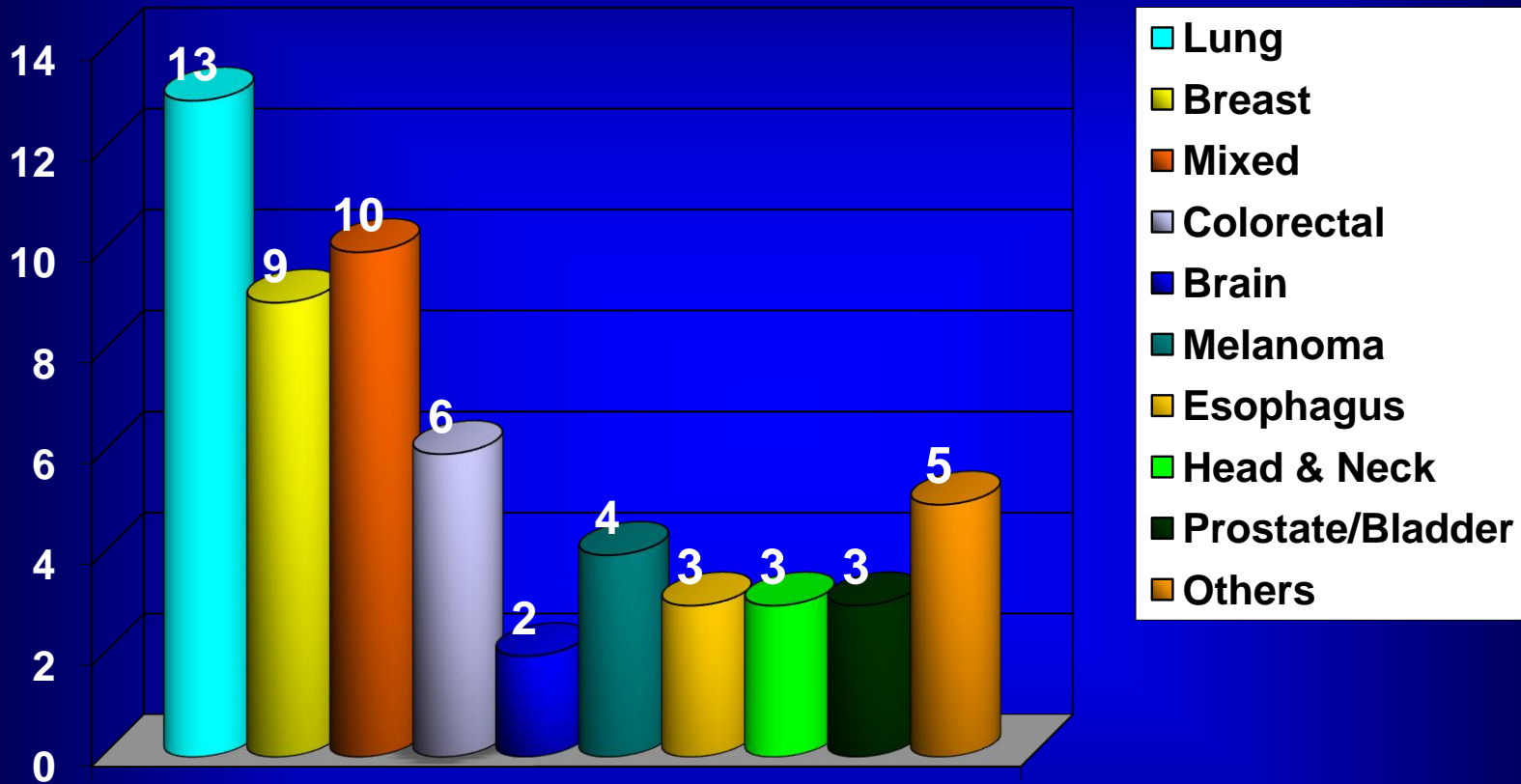
## Patient's self-reported health status

(QoL and Symptoms)



# Systematic review of QoL prognostic factor studies in oncology

Adapted from: Gotay C, Kawamoto C, Bottomley A, Efficace F. *Journal of Clinical Oncology*, 26:1355-1363, 2008



**QoL linked with survival  
(Multivariate analyses)**

YES= 55

NO= 3



**AUTHOR/JOURNAL:**

Efficace et al, *J Clin Oncol*, 2004  
 Goodwin et al, *J Clin Oncol*, 2004  
 Coates et al, *J Clin Oncol*, 2000

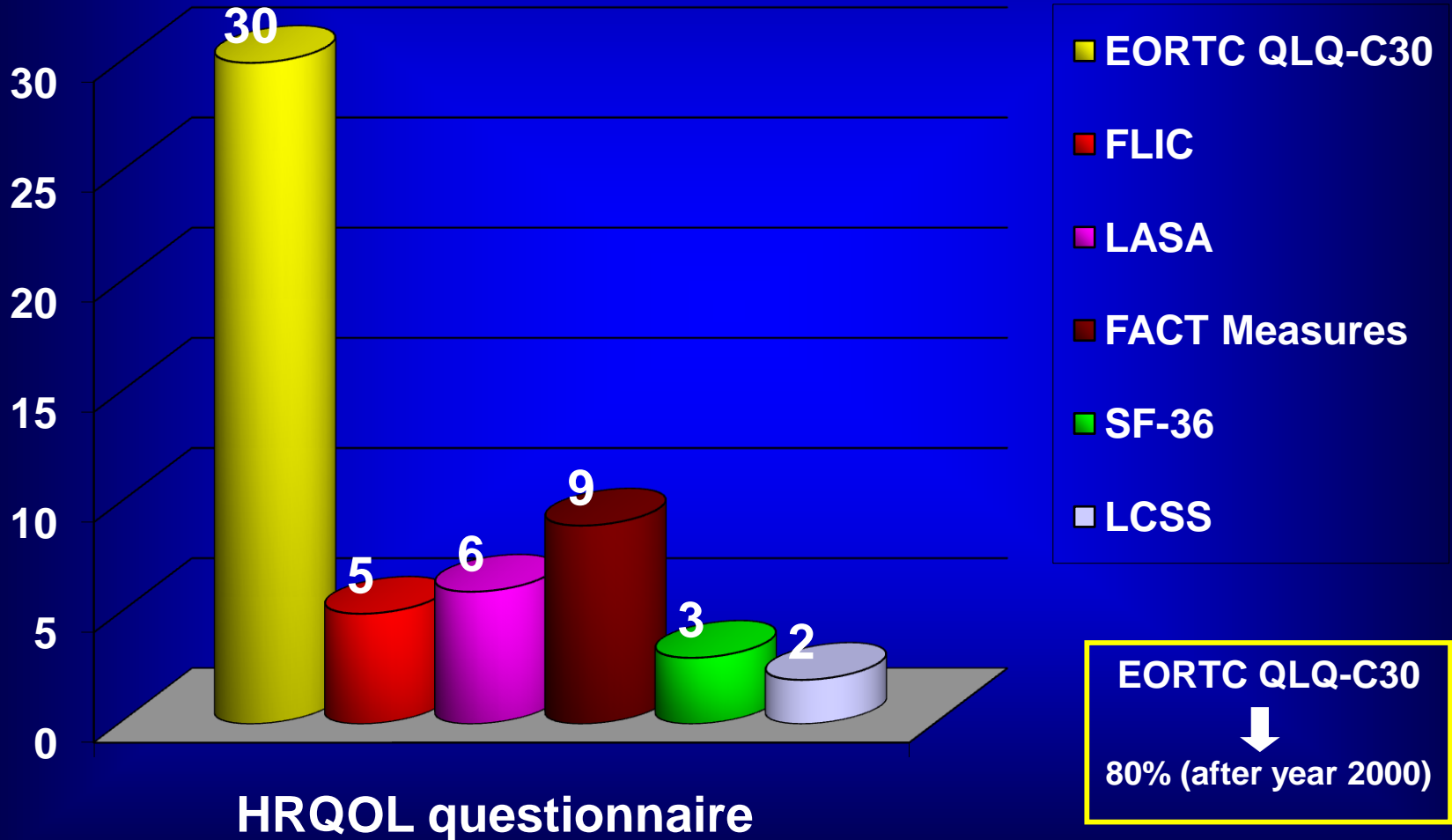
**POPULATION:**

(Early Breast Cancer)  
 (Early Breast Cancer)  
 (Early Breast Cancer)

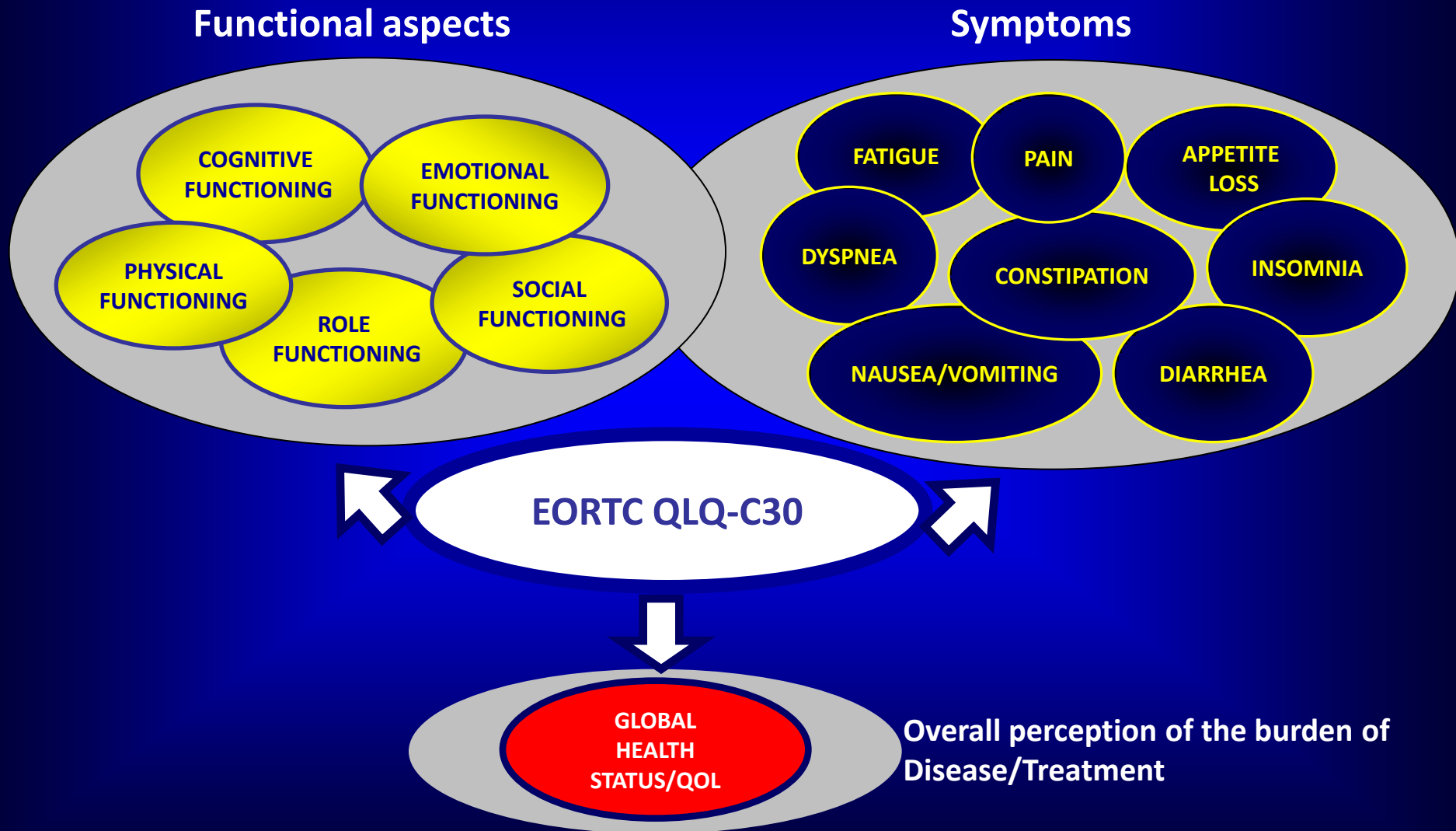
**ENDPOINT:**

OS and DFS  
 OS and DFS  
 DFS

# Most common measures used to test the prognostic value of patient's self-reported QoL parameters

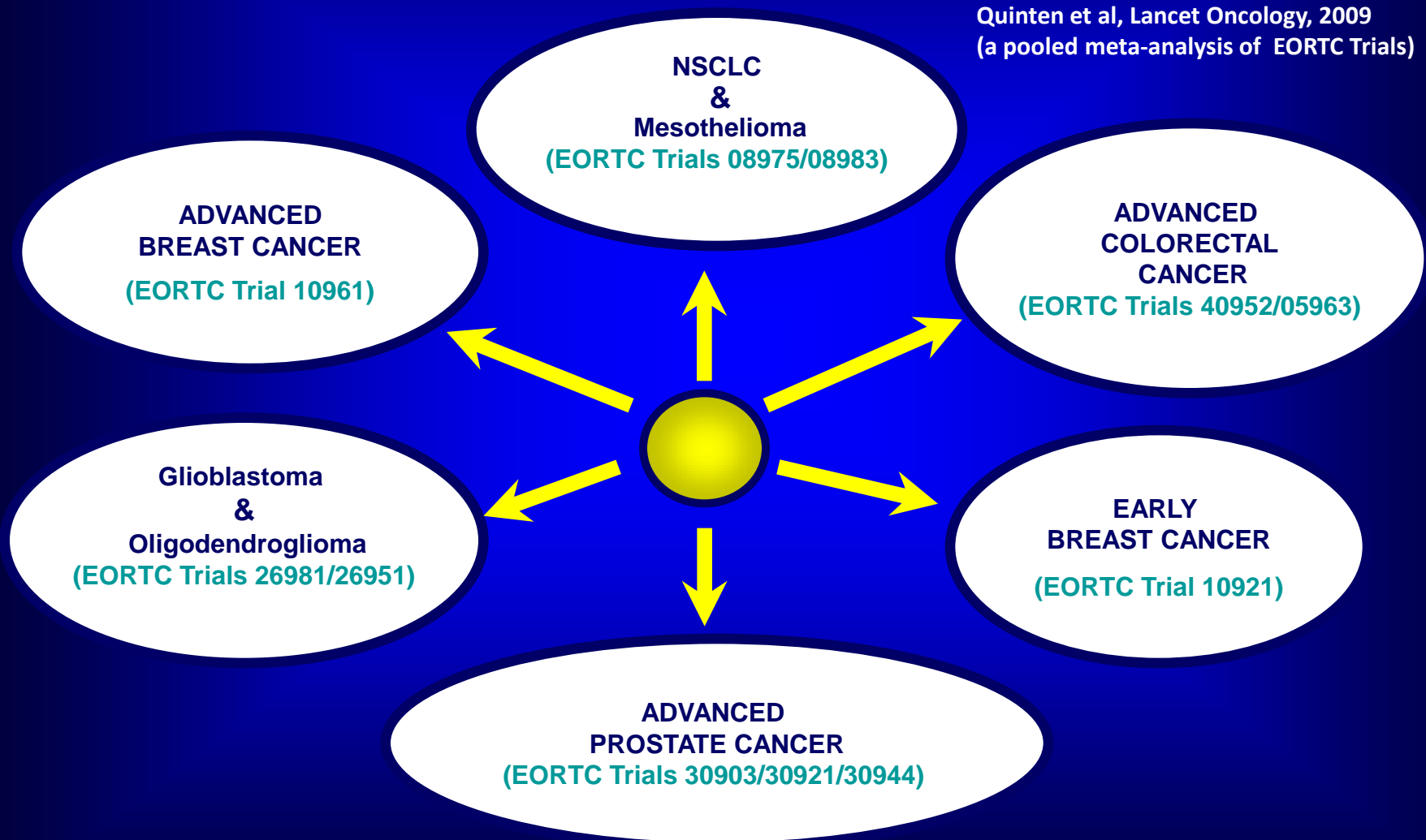


# Quality of Life Parameters measured by the **EORTC QLQ-C30**



# The prognostic value of pre-treatment patient's self-reported health status in EORTC clinical trials

Quinten et al, Lancet Oncology, 2009  
(a pooled meta-analysis of EORTC Trials)



# MULTIVARIATE ANALYSES

|   | No. Patients   | Independent QOL prognostic factor ? |           |
|---|----------------|-------------------------------------|-----------|
| <b>Early Breast</b><br>(Efficace et al. J Clin Oncol, 2004)   | <b>359</b>     | Yes                                 | <b>No</b> |
| <b>Advanced Lung</b><br>(Efficace et al., Ann Oncol, 2006)  | <b>391</b>     | <b>Yes</b>                          | No        |
| <b>Advanced Colorectal</b><br>(Efficace et al. <u>Eur J Cancer</u> , 2006;<br>and <u>J Clin Oncol</u> , 2008)         | <b>299/443</b> | <b>Yes</b>                          | No        |
| <b>Advanced Breast</b><br>(Efficace et al. Eur J Cancer, 2004)  | <b>219</b>     | <b>Yes</b>                          | No        |
| <b>Mesothelioma</b><br>(Bottomley et al. J Clin Oncol, 2008)  | <b>229</b>     | <b>Yes</b>                          | No        |
| <b>Advanced Prostate</b><br>(Collette et al. J Clin Oncol, 2004)  | <b>391</b>     | <b>Yes</b>                          | No        |
| <b>Oligodendrogliomas/Glioblastoma</b><br>(Mauer et al, <u>Br J Cancer</u> , 2007;<br>and <u>J Clin Oncol</u> , 2007) | <b>247/490</b> | <b>Yes</b>                          | No        |

# ADVANCED BREAST CANCER PATIENTS

Efficace et al. Eur J Cancer, 2004

## PATIENTS AND METHODS

- 219 patients included
- 14 QOL parameters evaluated by EORTC QLQ-C30 and QLQ-BR23

## CLINICAL VARIABLES INCLUDED

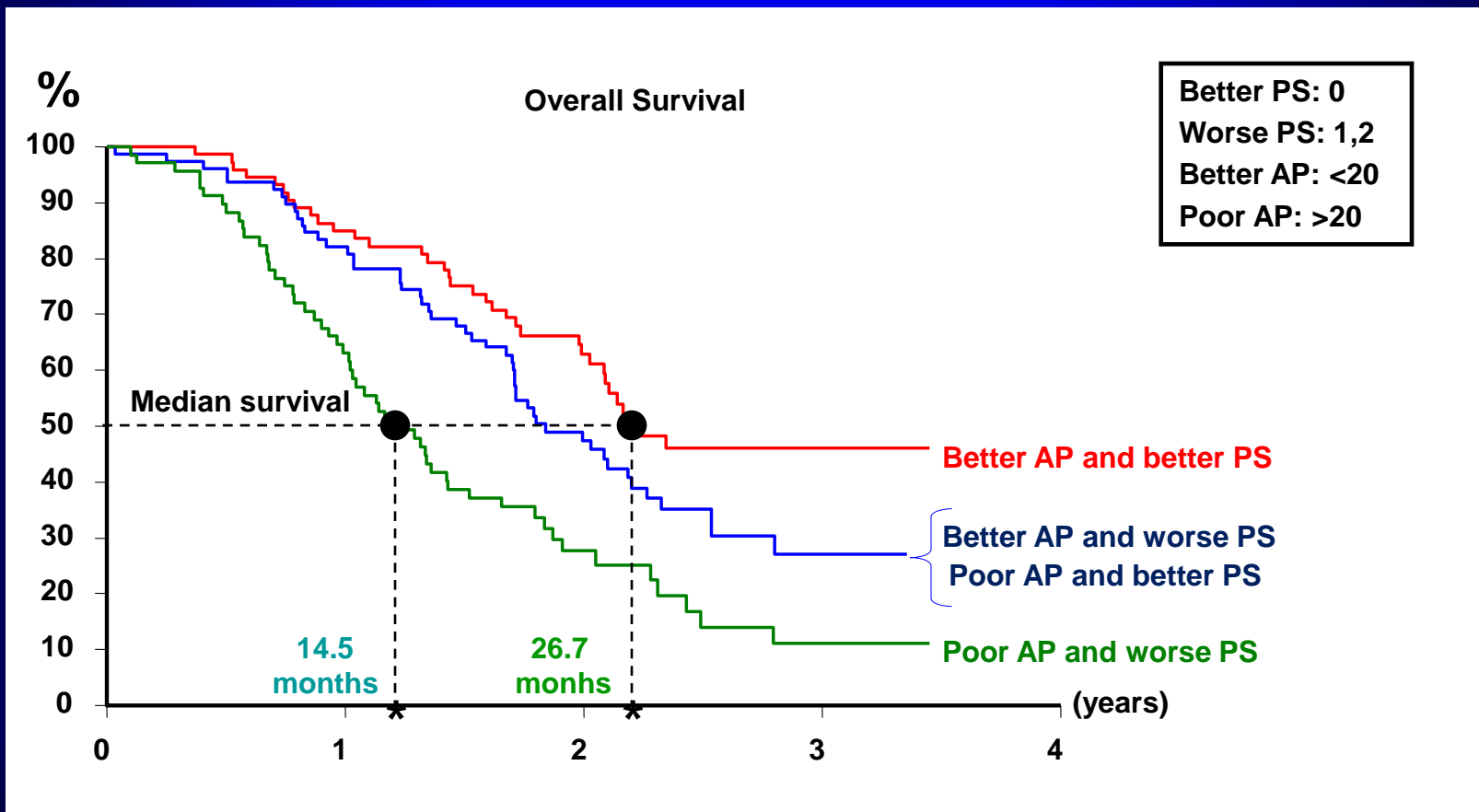
Age, Performance status, Bone metastases, Dominant site of disease, Number of sites involved, Disease free-interval, Estrogen and Progesterone receptor status

## STATISTICS

Cox proportional hazards regression model for Overall survival

# Multivariate model predicting survival

| Variables                           | Hazard Ratio | 95% CI               | P value          |
|-------------------------------------|--------------|----------------------|------------------|
| <b>Appetite loss (AP) 10 points</b> | <b>1.08</b>  | <b>1.020 – 1.138</b> | <b>0.005</b>     |
| <b>Performance status (PS)</b>      | <b>1.77</b>  | <b>1.340 – 2.359</b> | <b>&lt;0.001</b> |



# Correlation matrix between QOL variables and “Appetite loss”

| QOL variables                 | Appetite loss |
|-------------------------------|---------------|
| Global health status          | - 0.46099     |
| Fatigue                       | 0.53928 *     |
| Nausea / Vomiting             | 0.45220       |
| Pain                          | 0.33373       |
| Dyspnoea                      | 0.31978       |
| Insomnia                      | 0.35241       |
| Role Functioning              | - 0.55337 *   |
| Physical Functioning          | - 0.51810 *   |
| Social Functioning            | - 0.35337     |
| Emotional Functioning         | - 0.19366     |
| Cognitive Functioning         | - 0.21826     |
| Systemic therapy side effects | 0.35093       |
| Future perspective            | - 0.14217     |

# ADVANCED COLORECTAL CANCER PATIENTS

Efficace et al. Eur J Cancer, 2006

## PATIENTS AND METHODS

- 299 Patients have valid baseline QOL data
- 10 QOL parameters evaluated by the EORTC QLQ-C30

## CLINICAL VARIABLES INCLUDED

Performance status, WBC count, alkaline phosphatase, number of metastatic sites involved, presence of liver metastases, previous adjuvant chemotherapy and primary site of disease

## STATISTICS

- Cox proportional hazards regression model for Overall survival
- Internal validation - Bootstrap Validation technique (1000 simulation datasets)

## Clinical characteristics (N=299 Advanced colorectal cancer patients)

| Variables                           | N (%)      |
|-------------------------------------|------------|
| <b>Age</b>                          |            |
| Median                              | 61.7       |
| Range                               | 29.4-76.1  |
| <b>Sex</b>                          |            |
| Male                                | 180 (60.2) |
| Female                              | 118 (39.5) |
| <b>Performance status</b>           |            |
| WHO 0                               | 157 (52.5) |
| WHO 1                               | 121 (40.5) |
| WHO 2                               | 19 (6.4)   |
| <b>Adjuvant chemotherapy</b>        |            |
| Yes                                 | 40 (13.4)  |
| No                                  | 258 (86.3) |
| <b>Liver metastases</b>             |            |
| Yes                                 | 246 (82.3) |
| No                                  | 53 (17.7)  |
| <b>Site of Primary Tumor</b>        |            |
| Colon                               | 148 (49.5) |
| Rectum                              | 150 (50.2) |
| <b>Number of sites involved</b>     |            |
| 1                                   | 80 (26.8)  |
| >1                                  | 219 (73.2) |
| <b>White Blood Cell (WBC) count</b> |            |
| $\leq 10 \times 10^9 / l$           | 231 (77.3) |
| $> 10 \times 10^9 / l$              | 68 (22.7)  |
| <b>Alkaline Phosphatase</b>         |            |
| $\leq 300$ U/l                      | 210 (70.2) |
| $>300$ U/l                          | 89 (29.8)  |

# BOOTSTRAP VALIDATION PROCEDURE



**ORIGINAL DATASET**  
N patients



**IDEA:**

Original dataset is a 'random' sample of patients from the general population.

Generate a number (B) of datasets each of which have the same sample size as the original one:

- Copy the full data from N randomly chosen patients with replacement (ie. an already selected patient may be selected again)
- Repeat B times



**Simulation dataset**

1



**Model 1**



**Simulation dataset**

2



**Model 2**

....



**Simulation dataset**

B



**Model B**

(B sets of N patients)

**Prognostic factor analysis on each simulation dataset**

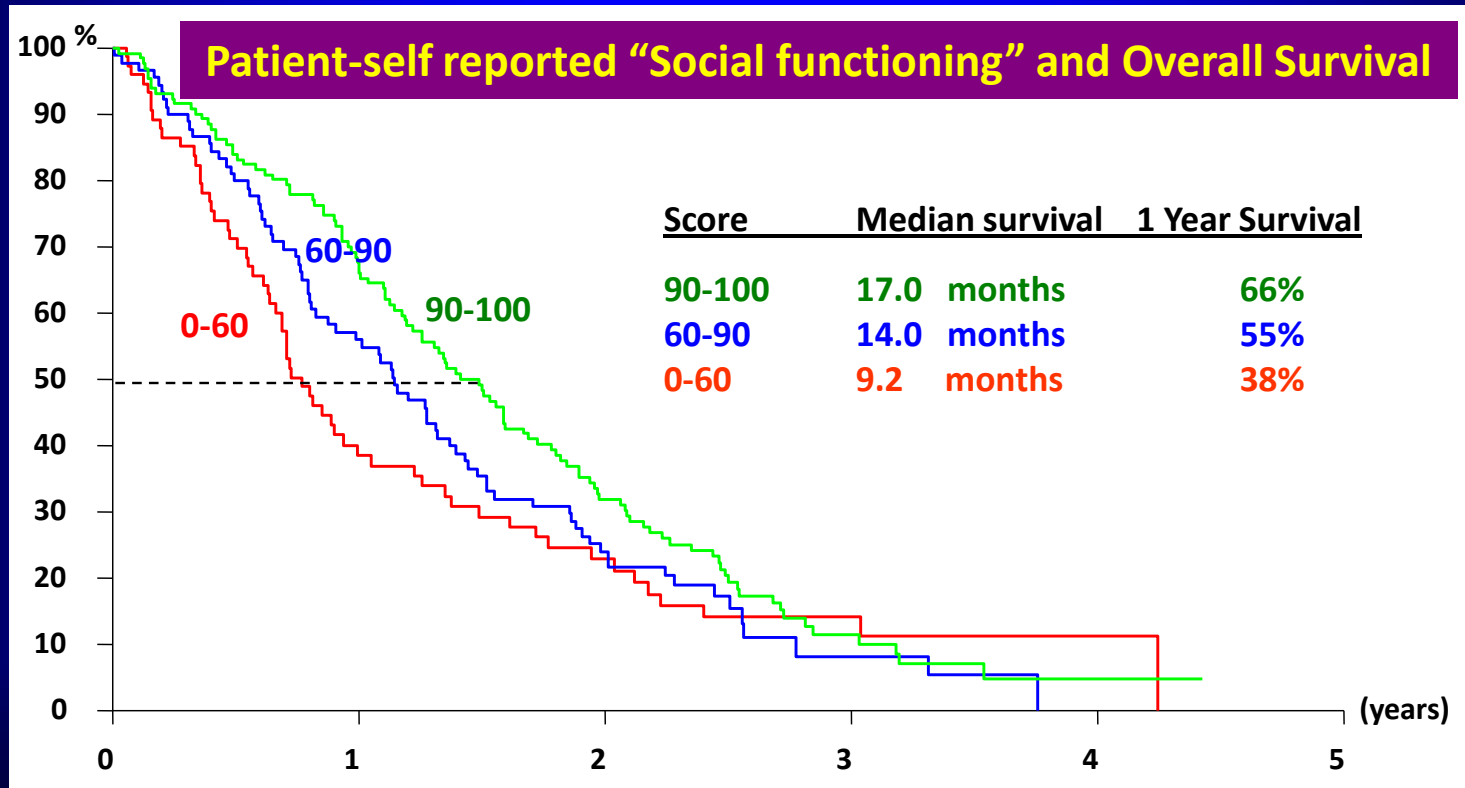
(B = bootstrap size)

# Cox analysis and Bootstrap Validation (1000 Bootstrap samples)

|                                    | Cox Univariate Analysis<br>HR (P-value) | Final Cox Multivariate Model<br>HR (P-value) | Inclusion variable (%) |
|------------------------------------|---|--|------------------------|
| <b>CLINICAL PARAMETERS</b>         |   |  |                        |
| Performance status                 | 1.528 (<.01)                            | -  | 43                     |
| → Number of sites involved         | 1.119 (.003)                            | 1.10 (.010)                                  | 74                     |
| → WBC count                        | 2.064 (<.01)                            | 1.96 (<.01)                                  | 94                     |
| → Alkaline phosphatase             | 1.762 (<.01)                            | 1.50 (.005)                                  | 63                     |
| Liver metastases                   | 1.282 (.143)                            | -  | Not included           |
| Adjuvant chemotherapy              | 0.909 (.609)                            | -  | Not included           |
| Site of primary tumour             | 0.862 (.243)                            | -  | Not included           |
| <b>Patient's reported QOL data</b> |   |  |                        |
| Global health status / QoL         | 0.990 (.001)                            | -  | 21                     |
| Physical Functioning               | 0.991 (.001)                            | -  | 15                     |
| Emotional Functioning              | 0.995 (.064)                            | -  | 7                      |
| → Social Functioning               | 0.993 (.001)                            | 0.91 (<.01)                                  | 73                     |
| Fatigue                            | 1.008 (<.01)                            | -  | Not included           |
| Nausea / Vomiting                  | 1.010 (.009)                            | -  | 23                     |
| Pain                               | 1.003 (.117)                            | -  | Not included           |
| Appetite loss                      | 1.006 (.006)                            | -  | 11                     |
| Constipation                       | 1.004 (.101)                            | -  | Not included           |
| Diarrhoea                          | 1.005 (.054)                            | -  | 31                     |

# Multivariate model predicting survival

| Variables                | Hazard ratio (HR) | 95% confidence interval (CI) | P value |
|--------------------------|-------------------|------------------------------|---------|
| WBC count                | 1.96              | 1.439 - 2.672                | <.001   |
| Alkaline phosphatase     | 1.50              | 1.126 - 2.022                | .005    |
| Number of sites involved | 1.10              | 1.024 - 1.198                | .010    |
| Social Functioning       | 0.91              | 0.987 - 0.996                | <.001   |

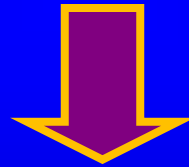


# Independent Validation Study

(Advanced colorectal cancer patients)

## OBJECTIVE

To validate the above reported prognostic multivariate model (EORTC 40952) on an independent dataset of patients and to confirm the independent prognostic value of patients' self-reported Social Functioning.

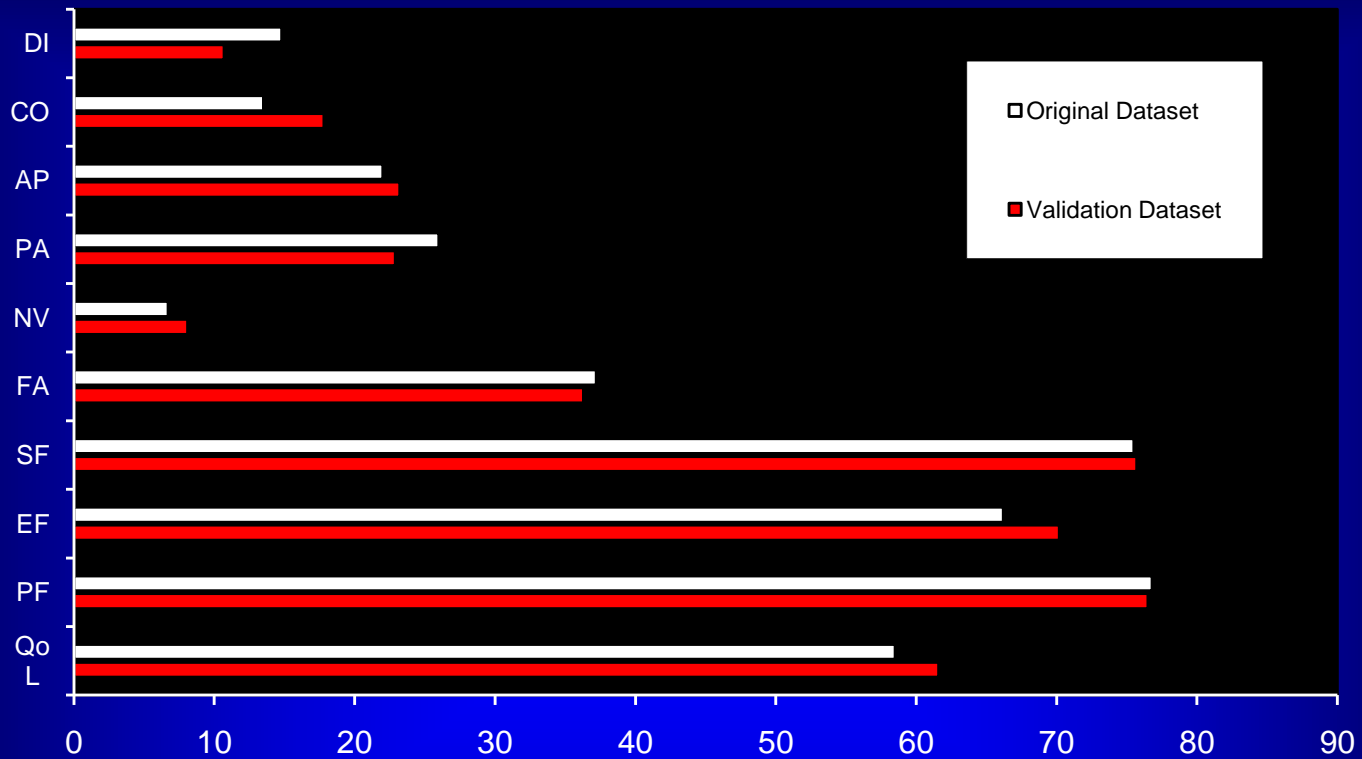


- Validate the prognostic value of patient-self reported Social Functioning
- 443 Advanced colorectal cancer patients
- First line chemotherapy

## Clinical characteristics of patients in the Validation and Original dataset

|                                     | Validation Dataset (N=443) | Original Dataset (N=299) |
|-------------------------------------|----------------------------|--------------------------|
| <b>Age</b>                          |                            |                          |
| Median                              | 62.0                       | 61.7                     |
| Range                               | 22.0 – 75.0                | 29.4-76.1                |
| <b>Sex</b>                          |                            |                          |
| Male                                | 265 (59.8)                 | 180 (60.2)               |
| Female                              | 168 (40.2)                 | 118 (39.5)               |
| <b>Performance status</b>           |                            |                          |
| WHO 0                               | 209 (47.2)                 | 157 (52.5)               |
| WHO 1                               | 188 (42.4)                 | 121 (40.5)               |
| WHO 2                               | 46 (10.4)                  | 19 (6.4)                 |
| <b>Adjuvant chemotherapy</b>        |                            |                          |
| Yes                                 | 79 (17.8)                  | 40 (13.4)                |
| No                                  | 364 (82.2)                 | 258 (86.3)               |
| <b>Liver metastases</b>             |                            |                          |
| Yes                                 | 379 (85.6)                 | 246 (82.3)               |
| No                                  | 63 (14.2)                  | 53 (17.7)                |
| <b>Site of Primary Tumor</b>        |                            |                          |
| Colon                               | 333 (75.2)                 | 148 (49.5)               |
| Rectum                              | 106 (23.9)                 | 150 (50.2)               |
| <b>Number of sites involved</b>     |                            |                          |
| 1                                   | 221 (49.9)                 | 80 (26.8)                |
| >1                                  | 222 (50.1)                 | 219 (73.2)               |
| <b>White Blood Cell (WBC) count</b> |                            |                          |
| ≤10 x 10 <sup>9</sup> /l            | 343 (77.4)                 | 231 (77.3)               |
| > 10 x 10 <sup>9</sup> /l           | 100 (22.6)                 | 68 (22.7)                |
| <b>Alkaline Phosphatase</b>         |                            |                          |
| ≤ 300 U/l                           | 342 (77.2)                 | 210 (70.2)               |
| >300 U/l                            | 101 (22.8)                 | 89 (29.8)                |

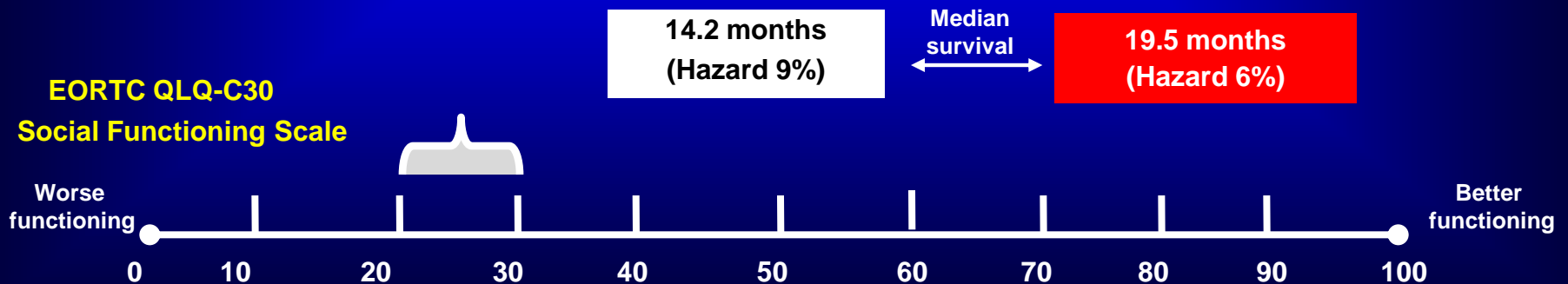
## Mean baseline scores of the EORTC QLQ-C30 by the validation and original datasets



|                    | QoL              | PF               | EF               | SF               | FA               | NV              | PA               | AP               | CO               | DI               |
|--------------------|------------------|------------------|------------------|------------------|------------------|-----------------|------------------|------------------|------------------|------------------|
| Original dataset   | 58.56<br>(22.10) | 76.89<br>(24.23) | 66.25<br>(25.49) | 75.45<br>(29.17) | 37.28<br>(29.16) | 6.77<br>(15.29) | 26.06<br>(30.75) | 21.96<br>(30.84) | 13.49<br>(26.47) | 14.85<br>(27.03) |
| Validation Dataset | 61.65<br>(22.04) | 76.52<br>(26.63) | 70.20<br>(23.28) | 75.72<br>(29.13) | 36.38<br>(27.01) | 8.09<br>(18.23) | 22.91<br>(27.34) | 23.26<br>(31.53) | 17.80<br>(28.26) | 10.78<br>(20.28) |

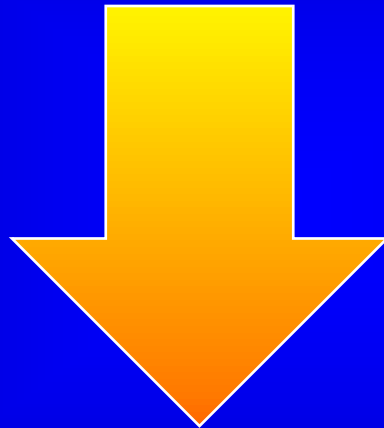
# Final Cox multivariate regression model of survival Original versus Validation dataset

| Variables                                       | Original Dataset (N=299)                                     | Validation Dataset (N=443)                                   |
|---|--|--|
|   | Hazard ratio (HR)<br>95% Confidence Interval (CI)<br>P value | Hazard ratio (HR)<br>95% Confidence Interval (CI)<br>P value |
| WBC count                                       | <b>1.96</b><br>1.439 - 2.672<br>P<.001                       | <b>1.31</b><br>1.018 - 1.693<br>P=0.0360                     |
| Alkaline phosphatase                            | <b>1.50</b><br>1.126 - 2.022<br>P=.005                       | <b>1.51</b><br>1.175 - 1.951<br>P=0.0014                     |
| Number of sites involved                        | <b>1.10</b><br>1.024 - 1.198<br>P=.010                       | <b>1.91</b><br>1.543 - 2.379<br>P <.0001                     |
| Social Functioning<br>(Patient's self-reported) | <b>0.91</b><br>0.876 - 0.958<br>P <.001                      | <b>0.94</b><br>0.906 - 0.977<br>P =0.0014                    |



# The literature on QoL prognostic factor is wider.....

Some examples from the recent literature



Quality of Life (Patient-reported) **VS.** Performance Status (Physician-reported)

**Performance Status (physician assessed)  
versus  
Quality of Life parameters (patient's self-reported)**

**Correlation with Survival in Palliative settings**

| Disease site   | Authors                  | Journal                            | Independent prognostic factor for Survival<br>(Multivariate analysis) |                       |
|--|--------------------------|------------------------------------|---|-----------------------|
|  |                          |                                    | QoL<br>Parameters   | Performance<br>status |
| Bladder  | Roychowdhury DF, et al,  | Journal of Clinical Oncology, 2003 | ✓   | No                    |
| Breast   | Coates a, et al,         | Journal of Clinical Oncology, 1992 | ✓   | No                    |
| Breast   | Efficace F, et al,       | European Journal of Cancer, 2004   | ✓   | ✓                     |
| Colorectal   | Maisey NR, et al,        | European Journal of Cancer, 2002   | ✓   | No                    |
| Colorectal   | Efficace F, et al,       | Journal of Clinical Oncology, 2008 | ✓   | No                    |
| Colorectal   | Efficace F, et al,       | European Journal of Cancer, 2006   | ✓   | No                    |
| Colorectal   | Earlam S, et al,         | Journal of Clinical Oncology, 1996 | ✓   | No                    |
| Esophago-Gastric   | Chau I, et al,           | Journal of Clinical Oncology, 2004 | ✓   | ✓                     |
| Gastric cancers  | Park SH, et al.          | Qual Life Res, 2008                | ✓   | No                    |
| Head and Neck  | Fang FM, et al,          | Cancer, 2004                       | ✓   | No                    |
| Hepatocellular   | Yeo W, et al,            | Annals of Oncology, 2006           | ✓   | No                    |
| Lung   | Maione P, et al,         | Journal of Clinical Oncology, 2005 | ✓   | ✓                     |
| Melanoma   | Chiaron-Sileni V, et al, | European Journal of Cancer, 2003   | ✓   | No                    |
| Mixed cancer population<br>(including leukemia,<br>lymphoma and mveloma) | Shadbolt B, et al,       | Journal of Clinical Oncology, 2002 | ✓   | No                    |
| Myeloma  | Dubois D, et al,         | Journal of Clinical Oncology, 2006 | ✓   | No                    |

# Multiple Myeloma

## Advanced population of relapsed, refractory Multiple Myeloma

(Dubois D et al, J Clin Oncol, 24:976-982, 2006)

### Univariate analysis



Significant baseline variables associated with Overall Survival

- Karnofsky Performance Status
- Albumin
- Platelet Count
- Hemoglobin level
- Total Serum Protein
- % Plasma Cells in Bone Marrow
- Beta2-microglobulin
- C-reactive Protein
- Abnormal cytogenetics
- ISS stage
- Prior use of Thalidomide

### Multivariate analysis

(without including Patient's self-reported QoL parameters)

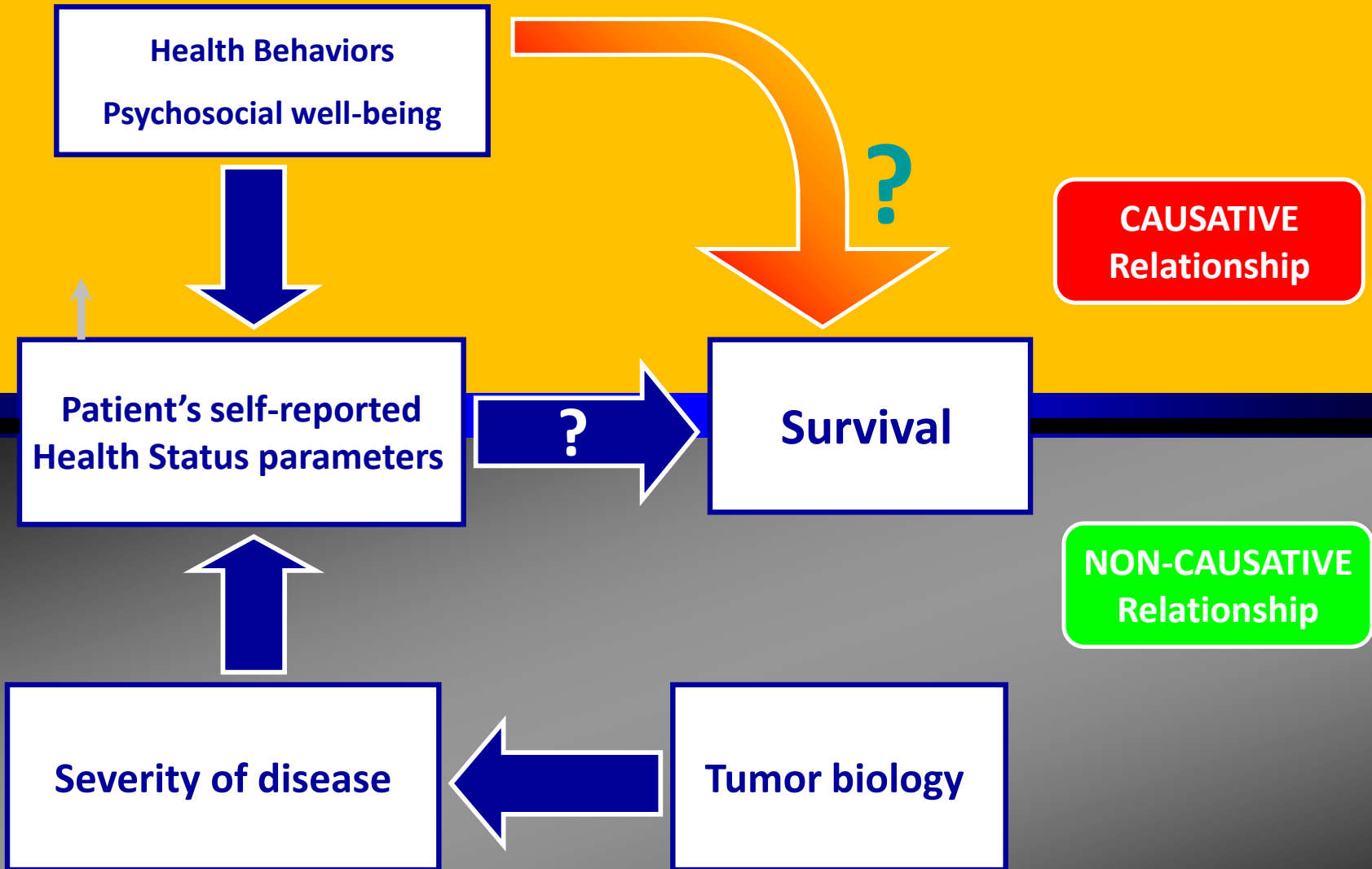
| Variables:                          | P value         | Hazard Ratio |
|-------------------------------------|-----------------|--------------|
| <b>Karnofsky Performance Status</b> | <b>0.01</b>     | <b>0.54</b>  |
| <b>Albumin</b>                      | <b>&lt;0.01</b> | <b>0.43</b>  |
| <b>Platelet Count</b>               | <b>&lt;0.01</b> | <b>0.99</b>  |
| <b>NCI-CTC (neuropathy grade)</b>   | <b>&lt;0.01</b> | <b>0.52</b>  |



Adding to the model Patient's self-reported QoL Parameters

| Variables:                             | P value         | Hazard Ratio |
|--|-----------------|--------------|
| <b>Patient's self-reported Fatigue</b> | <b>&lt;0.01</b> | <b>0.95</b>  |
| <b>Albumin</b>                         | <b>0.02</b>     | <b>0.43</b>  |
| <b>Platelet Count</b>                  | <b>&lt;0.01</b> | <b>0.99</b>  |
| <b>NCI-CTC (neuropathy grade)</b>      | <b>&lt;0.01</b> | <b>0.60</b>  |

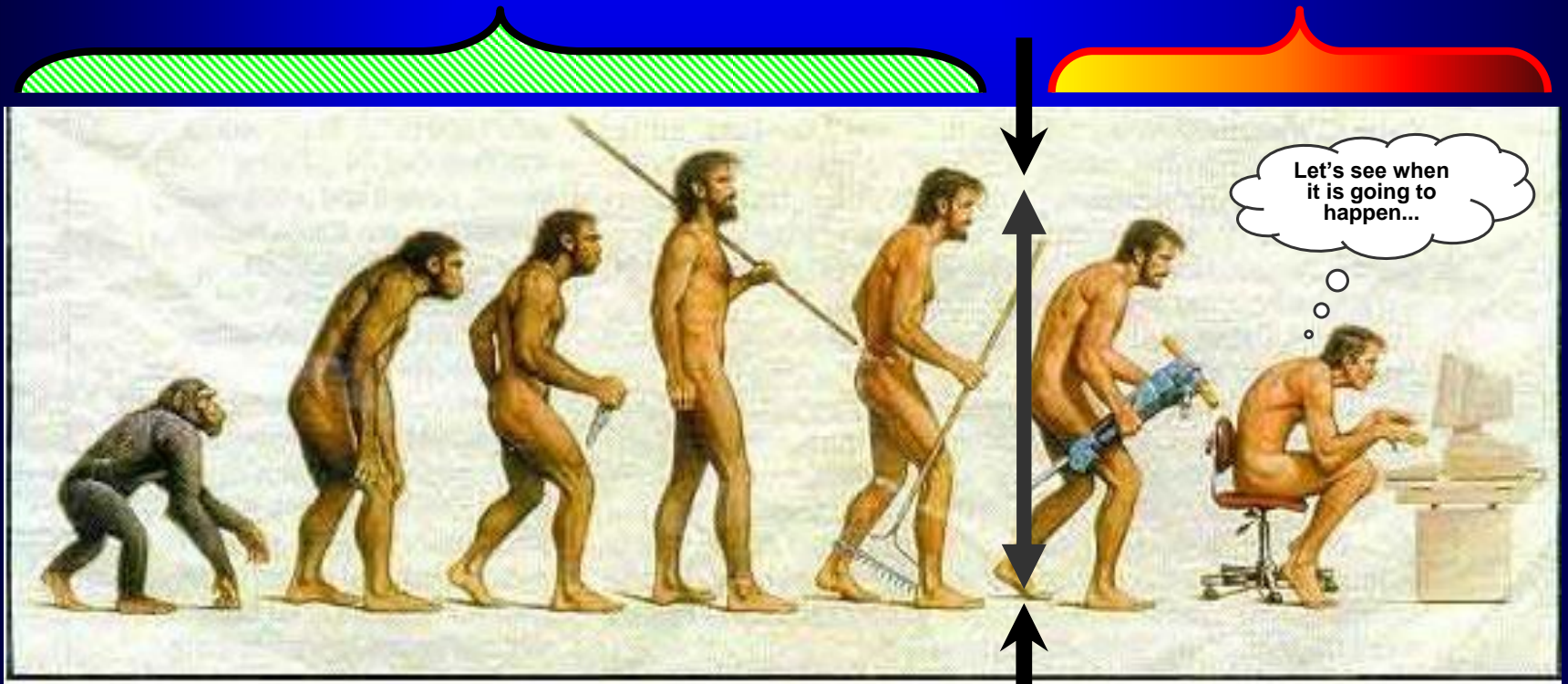
# POSSIBLE MECHANISMS UNDERLYNG THE RELATIONSHIP



# So where are we in the 'science of prognostication' using patient-reported health status outcomes?

- Consistent evidence across cancer disease sites
- Complementary evidence from various QoL measures
- Evidence beyond previously known key prognostic biomedical data

- Identification of specific QOL parameters
- More hypothesis driven prospective studies
- Implementation in routine clinical practice



**BASIC**

**ADVANCED**

# Potential implications

## CLINICAL PRACTICE

➤ **Collection of QOL data in clinical practice:** ↓

To facilitate clinical decision-making

To better monitor disease progression

To improve accuracy of prognosis

Improve physician-patient

**communication** (Velikova et al, J Clin Oncol, 2001 and 2004; Detmar et al, JAMA, 2002)

## CLINICAL RESEARCH

➤ To better stratify patients in cancer clinical trials

➤ To better understand trial results

➤ To identify sensitive scales for a specific population

# Conclusions

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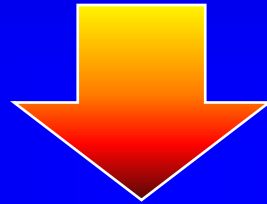
- ➔ Patient's self-reported QOL parameters independently predict survival beyond key biomedical data, in advanced cancer patients.
- ➔ Patient's self-assessment of their own health status provides a better and stronger indicator of their prognosis than a number of traditional biomedical factors.
- ➔ Results provide an evidence-based rationale to further promote a shift towards a more patient-centered approach in clinical decision making.
- ➔ Future research will have to focus on observational studies and in finding way on how to implement this information in routine clinical practice.



Italian Group for Adult Hematologic Diseases (GIMEMA)

Supported by the EORTC Quality of Life Group

**Prognostic significance and longitudinal assessment of patient-reported QoL and symptoms in high-risk Myelodysplastic Syndromes (MDS)**  
*An international prospective observational study*



**Participating Centers:**

➤ **Participating countries:**

**Austria, Italy, Germany, Belgium, India, China, Taiwan, United Kingdom, USA**

➤ **Centers obtained IRB/ethics approval = 48**

**Contact details: Fabio Efficace ([f.efficace@gimema.it](mailto:f.efficace@gimema.it))**