

# Patient-Reported Outcomes Assessment in International Cancer Clinical Trials: The EORTC Experience

EGAM EORTC QL Group Meeting

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Neil Aaronson

Chairman

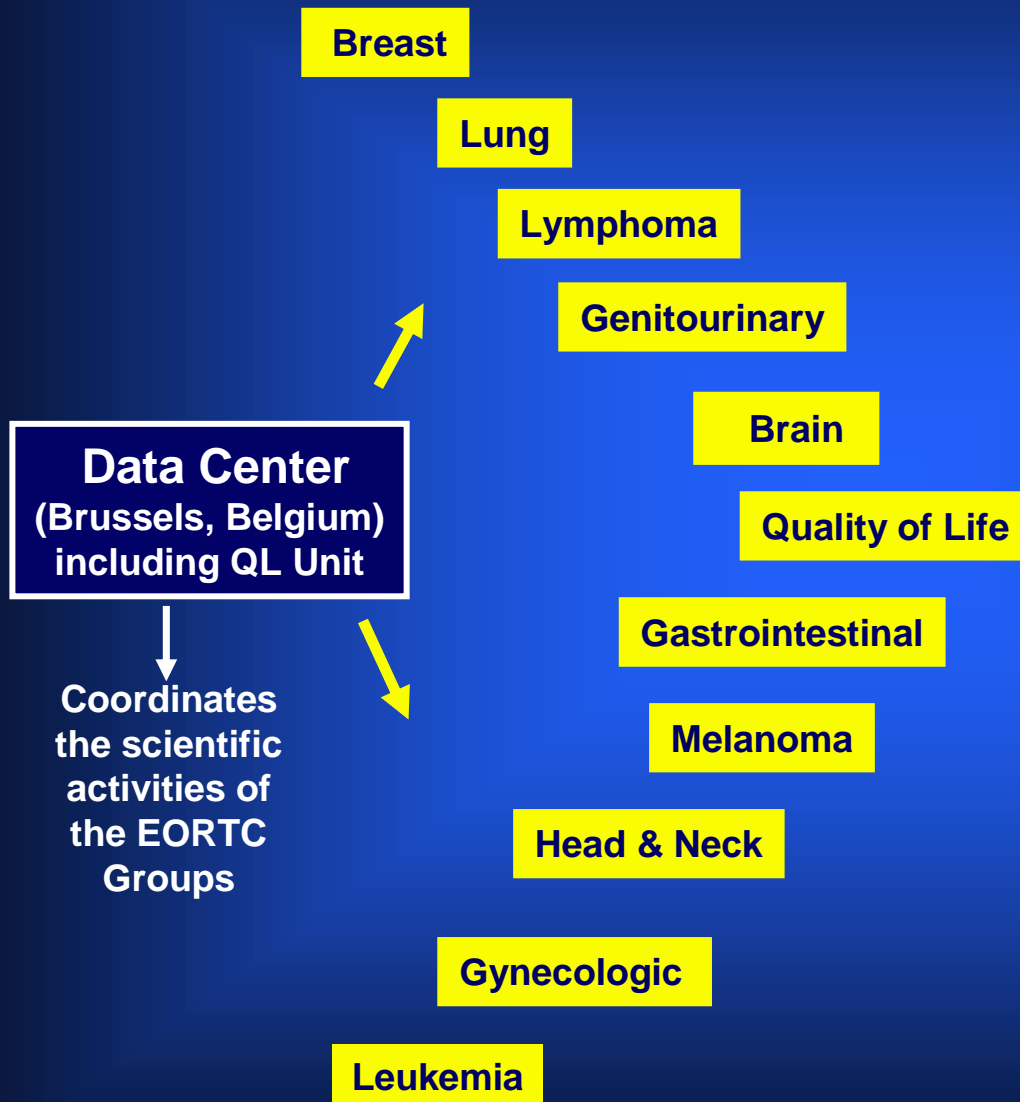
EORTC Quality of Life Group

Andrew Bottomley

Head

EORTC Quality of Life Unit

# EORTC Structure



**2000-2005**

**34,102 patients enrolled into clinical trials**

**90% Europe**

**10% Rest of the world**

**2000 clinicians in 33 countries**

**Since 1980 some 130 HRQL studies activated (mostly past decade)**

# Quality of Life Group

Established in 1981

- Multidisciplinary
- Multicultural
- Volunteers with day jobs
- Core business:
  - develop and validate HRQL instruments for use in cancer clinical trials
  - collaborate with Data Center and clinical groups in implementing HRQL endpoints in clinical trials
  - during 1st decade +, liaison function between clinical groups and Data Center

# Quality of Life Unit

- Established in 1993
- Staff members of EORTC Data Center
- Core business:
  - conducting EORTC and intergroup trial-based HRQL studies
  - coordinate translations
  - disseminate questionnaires and support materials
  - provide training in HRQL assessment
  - conduct research on quality of HRQL studies; prognostic value of HRQL data

# Quality of Life Group

## Modular Approach to HRQL Assessment

CORE questionnaire

+

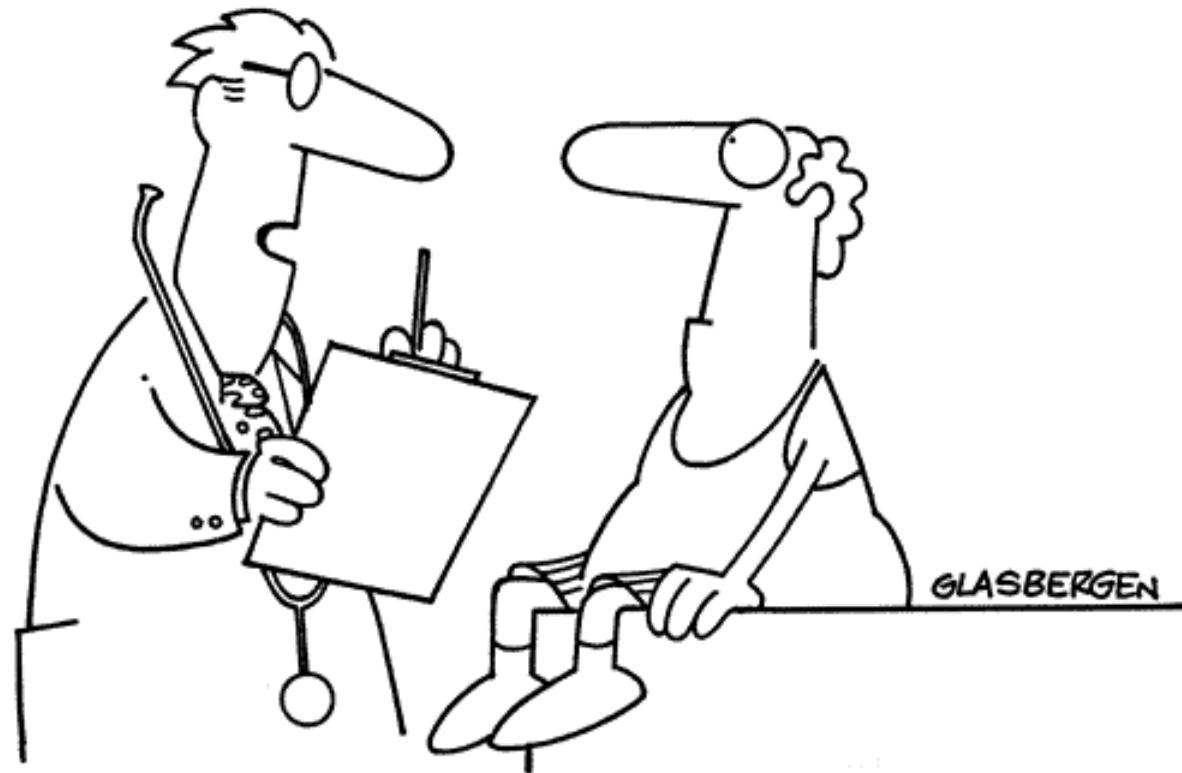
condition-specific or treatment-specific  
modules

# Core questionnaire

## The QLQ-C30 (version 3.0)

- common physical symptoms of cancer and its treatment (e.g., fatigue, pain, nausea and vomiting)
- physical, role, emotional, cognitive, and social functioning
- global health and quality of life
- organized into 9 multi-item scales + single items
- yields multidimensional profile; no summary scores available (at the moment)

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**“We can’t find anything wrong with you, so we’re going to treat you for Symptom Deficit Disorder.”**

# Supplementary modules

- specific disease symptoms
- specific treatment side-effects
- additional HRQL and related PRO domains (e.g. spirituality; treatment satisfaction; patient information needs)

# Lung cancer module

- dyspnea
- cough
- pain
- additional drug toxicities

# Prostate cancer module

- urinary and bowel symptoms and function
- pain
- intimacy/sexuality
- additional drug toxicities

- **UNIFORMITY** for cross-study comparisons
- **FLEXIBILITY** for adaptation to specific study needs

# Procedures for questionnaire development and testing

- 4 phases of development and testing according to standard (“blue book”) procedures
- multicultural professional and patient input
- documentation required at each step
- internal review and approval process
- external peer review
- not accomplished in a day (or a week or a month)

# Translations

- standardized, iterative, forward-backward procedures (“blue book”)
- full documentation and review of all steps required
- QLQ-C30 available in 65 languages from Arabic to Zulu (with gender sensitivity)
- Need to demonstrate comparability of measurement properties across all translations?
  - In the long term, yes
  - In the short term???

# Psychometric evidence

- QLQ-C30
  - extensive documentation of reliability, validity, responsiveness in multicultural research settings
  - abbreviated version (15 items) for palliative care setting
- Modules
  - 8 fully validated
  - 16 in various stages of development and testing

# On-going and planned measurement projects

- Use of modern (item-response) test theory to:
  - identify differences in item “performance” across cultures, languages, demographic and clinical groups (DIF)
  - generate abbreviated versions of the QLQ-C30 (e.g., palliative care)
  - develop computer-adaptive version(s) for use in clinical research and practice
- Generate higher order component or summary scores
- Define clinically meaningful (change) scores (reference values; empirically derived benchmarks)

## Early experiences with clinical trial-based QL outcome assessment

“In theory there is no difference between theory and practice. In practice there is.”

Yogi Bera

- Large number of ‘false starts’ and aborted efforts due to significant levels of investigator/institutional non-compliance with HRQL data collection schedules
- “Youthful” enthusiasm outpaced logistical capabilities at both central and local institutional level

## **A (relative) success story from early QL investigations: EORTC study 10801**

- RCT comparing radical mastectomy (RM) with breast-conserving surgery (BCT) in stage I and II breast cancer patients (N = 900+ patients)
- Primary endpoint: survival
- Secondary endpoints: local recurrence rate and HRQL
- No significant differences in survival or local recurrences
- HRQL research hypothesis: BCT would preserve body image but heighten fear of disease recurrence
- HRQL questionnaire: 10 items assessing body-image, fear of recurrence, and overall satisfaction with treatment

- HRQL questionnaire data were available from 278 patients (127 in the mastectomy arm and 151 in the breast-conserving arm) approximately 2 years post-treatment
- BCT group reported significantly better body image than RM group
- No significant group differences observed in fear of recurrence
- The HRQL results supported hypothesis of better body-image with BCT; indicated that this does not come at the expense of heightened fear of recurrence

# Lessons learned from early trials

- Invest in clinical groups with a clear HRQL-related research agenda and committed investigators
- Centralize and professionalize HRQL input to clinical groups (i.e., fulltime staff)
- Identify a local coordinator for HRQL component of trial
- Make HRQL assessment a mandatory part of trial  
Include baseline HRQL as eligibility criterion
- Monitor compliance and provide regular feedback to local centers
- Have clear stopping rules for HRQL component of trial

**“The future ain’t what it used to be.”**

**Yogi Berra**

**(mentee of Casey Stengel)**

# **EORTC HRQOL Program**

## **The last Decade 1997 - 2007**

- Resources invested into specialized Unit at the Data Center
- Closer collaboration between Unit and QLG
- Closer collaboration between Unit and Clinical groups
- New internal policies and procedures developed
- Better management of process in later trials (approx 70)
  - Protocol review (more systematic)
  - SOP for data management
  - SOP for analysis
  - Dedicated and trained full time central statistical expert allocated to HRQL component of trials
- Guidelines and procedure manuals from the QLG and QLU

# EORTC Clinical trials with HRQOL outcomes

## Total QOL in clinical studies

	Accumulated totals by 1998 (Kiebert <i>et al.</i> 1998)	Accumulated Total by 2007	Change in 9 years
Phase II	6	9	+ 3
Feasibility	1	1	0
Phase II/III	2	11	+ 9
Phase III	32	101	+ 69
Measurement field study	3	8	+ 5

On average 8 new Phase III trials per year with a HRQOL study

**EORTC**

# Standardization

- HRQL assessment mandatory in all participating centers for trials with an HRQOL endpoint (with a few exceptions)
- Guidelines and templates for key HRQOL paragraphs (design, measures, analysis plan) of clinical trial protocols
- Standard procedures for monitoring compliance with HRQOL assessment
- Minimal level of compliance now set before reviewing closure of study
- Basic, standardized analysis strategy for examining missing data patterns and for group comparisons over time
- More recently, guidelines have been developed for writing up the HRQOL components of clinical trials for publication

**Three recent examples of clinical trials in the EORTC with HRQOL**

# EORTC study 26981 \*

- RCT comparing radiotherapy (RT) in glioblastoma patients to RT plus **temozolomide**
- Primary endpoint: survival
- Secondary endpoints: HRQOL
- Significant survival differences in favor of RT plus **temozolomide**
- HRQOL research hypothesis: HRQOL may deteriorate more severely during intense treatment (RT + TMZ) compared to standard (RT), but improved later
- HRQOL questionnaire: EORTC QLQ-C30 and BN 20

## EORTC study 26981 continued

- HRQOL questionnaire data were available from standard 286 (RT only) and 287 in the experimental arm (RT/TMZ). 80% compliance and over 76% compliance at 2 years
- No negative impact of concomitant/adjuvant TMZ on HRQOL during treatment
- Slight improvement in HRQOL during first year following treatment in the RT plus temozolomide arm
- The HRQOL results support that some argue the survival benefit is not huge we can say **quality of survival is important**. Now RT plus temozolomide is the standard of care

# EORTC study 08983\*

- RCT comparing Tomudex with cisplatin versus cisplatin alone in malignant pleural mesothelioma (MPM )
- Primary endpoint: survival
- Secondary endpoints: HRQOL
- A significant ( $p=.048$ ) difference in survival favoring Tomudex with cisplatin HRQOL
- Research hypothesis: HRQOL will be the same in both arms
- HRQOL questionnaire: EORTC QLQ-C30 and LC13

\* Bottomley, Rabab Gaafa, Christian Manegold, Sjaak Burgers, Corneel Coens, Catherine Legrand, Mark Vincent, Giuseppe Giaccone, Jan Van Meerbeeck, JCO Mar 20 2006: 1435-1442.

# EORTC study 08983 continued

- HRQOL questionnaire data were available for the standard arm (Cisplatin only) of 126 patients and in the experimental arm (Cisplatin plus Tomudex) for 124 patients 124. 91% compliance at baseline and 80 % at one year
- No negative impact of adding Tomudex on any HRQOL scales
- Evidence in the **combination arm** of significant (and clinically meaningful) reduction in dyspnoea over the treatment when compared to **Cisplatin alone** (Key symptom in MPM patients)
- The HRQOL results combined with the survival results support the new combination treatment as the treatment of choice in selected MPM patients

# EORTC study 26951\*

- RCT comparing adjuvant chemotherapy (procarbazine, CCNU, vincristine; PCV) following radiotherapy (RT) compared to RT alone in the anaplastic oligodendrogliomas patients
- Primary endpoint: survival
- Secondary endpoints: HRQOL
- No significant difference in overall survival, but the progression-free survival in the adjuvant PCV treatment arm was significantly longer than in the standard treatment arm (23.0 versus 13.2 months, respectively;  $p = .0018$ )
- HRQOL research hypothesis: Adjuvant PCV would have a temporarily negative impact on HRQOL (pre-selected scales) during and shortly following PCV
- HRQL questionnaire: EORTC QLQ-C30 and BN 20

## **EORTC study 26951 continued**

- HRQOL questionnaire data were available for 183 patients in the RT alone and 185 patients in the RT plus chemotherapy. Baseline compliance was 79%, approx 72% up to 2.5 years post treatment
- The major impact of the adjuvant PCV chemotherapy on HRQOL is on nausea/vomiting with a much higher percentage of patients in the RT/PCV arm who experienced a worsening from baseline compared to the RT alone arm.
- There are no long-term effects of the adjuvant PCV chemotherapy. Longer term results show both groups to have comparable HRQOL

# Key lessons learned...

- Focus on clinical trials with the largest potential HRQOL payoff
- Preselect the most clinically important endpoints
- Educate the collaborators, providing guidelines and training opportunities; hold HRQOL planning meetings
- Monitor HRQOL compliance continuously, and provide timely feedback
- Follow a predetermined analysis plan, including detailed evaluation of patterns of missing data

# Key lessons learned...

- Provide guidelines for interpreting the clinical significance of results (e.g., 10 point change)
- Require that groups with poor performance in assessing HRQOL outcomes evaluate source of problems and justify logic of any further investment in HRQL investigations
- Always budget costs of HRQOL component of trials
- Centralize HRQOL activities (planning, data collection monitoring, analysis) to enhance efficiency and quality of work done. Ongoing resources are needed for this

# Given the challenges and benefits will we continue to have HRQOL in EORTC trials?

**Without a doubt ! Possible new phase III trials coming in 2007**

- **26051; To assess the clinical benefits of DepoCyt in comparison to no Intra Thecal (IT) therapy in adult patients with leptomeningeal metastasis from solid tumors**
- **62064-22064: Pre-versus postoperative external beam radiotherapy in the treatment of localized soft tissue sarcoma of the extremities: a randomized phase III trial**
- **Phase III randomized study comparing sunitinib to imatinib in non pre-treated patients with advanced gastro-intestinal stromal tumor without KIT exon 11 mutations**
- **18071: Adjuvant immunotherapy with anti-CTLA-4 monoclonal antibody (ipilimumab) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group**

# Future challenges for international clinical trials HRQOL research and directions

- To maximize HRQOL compliance in trials by means of realistic data collection schedules, closer monitoring and sufficient funding
- To have adequate resources to support high quality HRQOL within EORTC trials
- To liaise with and provide training opportunities for EMEA/FDA regarding the intent, methodology, value added and limitations of trial-based HRQOL investigations
- To use modern test theory (IRT and CAT methods) to develop more efficient and robust HRQOL measures for use in both clinical trials and clinical practice