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

NCI Conference: Patient-Reported Outcomes Assessment in Cancer Trials

Bethesda

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3800 miles
Brussels
Bethesda

Belgium is famous for 3 things:

Chocolates

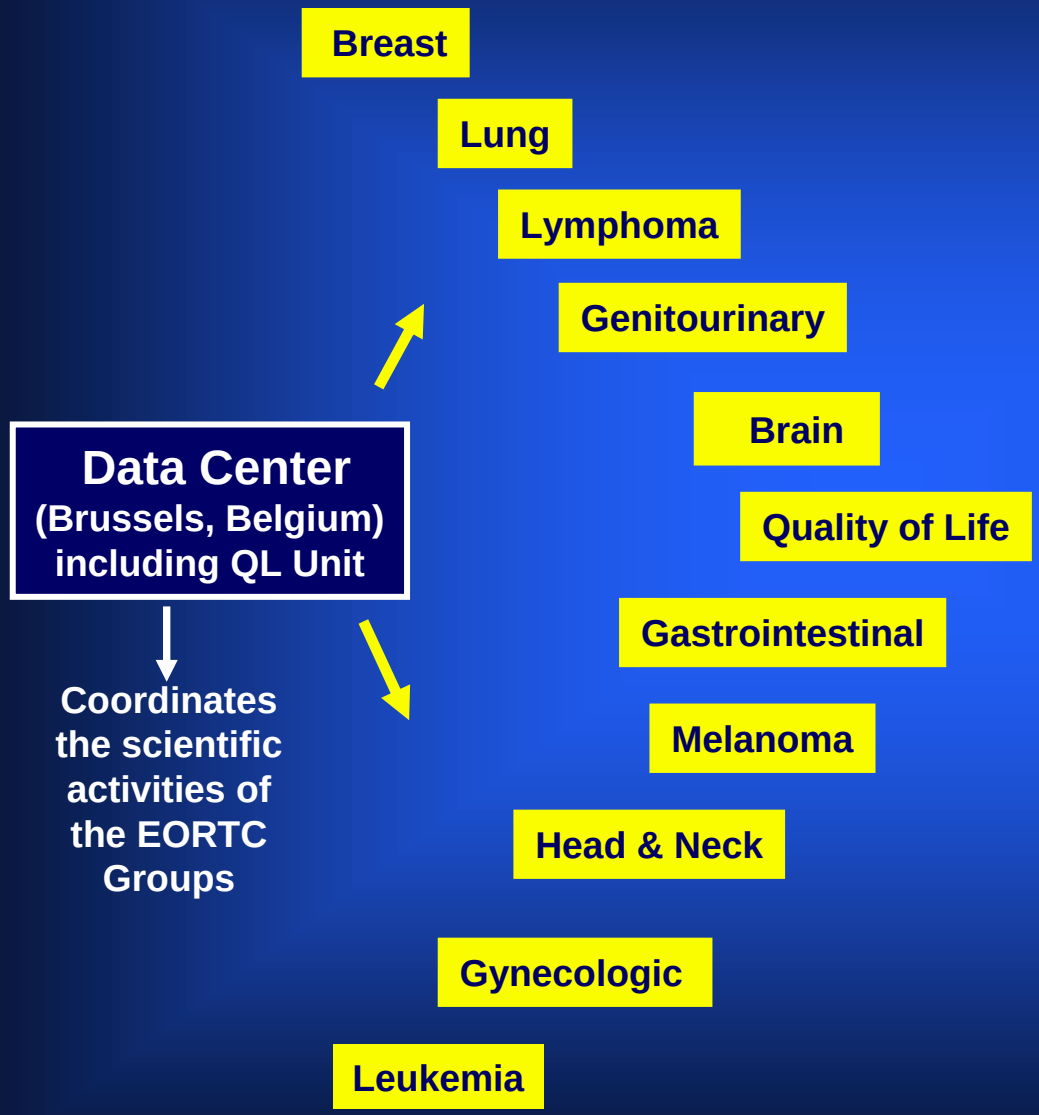
Beer

Europe

European Organization for Research and Treatment of Cancer (EORTC)

- Private non-profit organization created in 1962
- Core activity: conduct clinical trials
  - International
  - Multidisciplinary
  - Develop new treatments/define new standards of care
  - Large trials, primarily in academic centers/hospitals

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

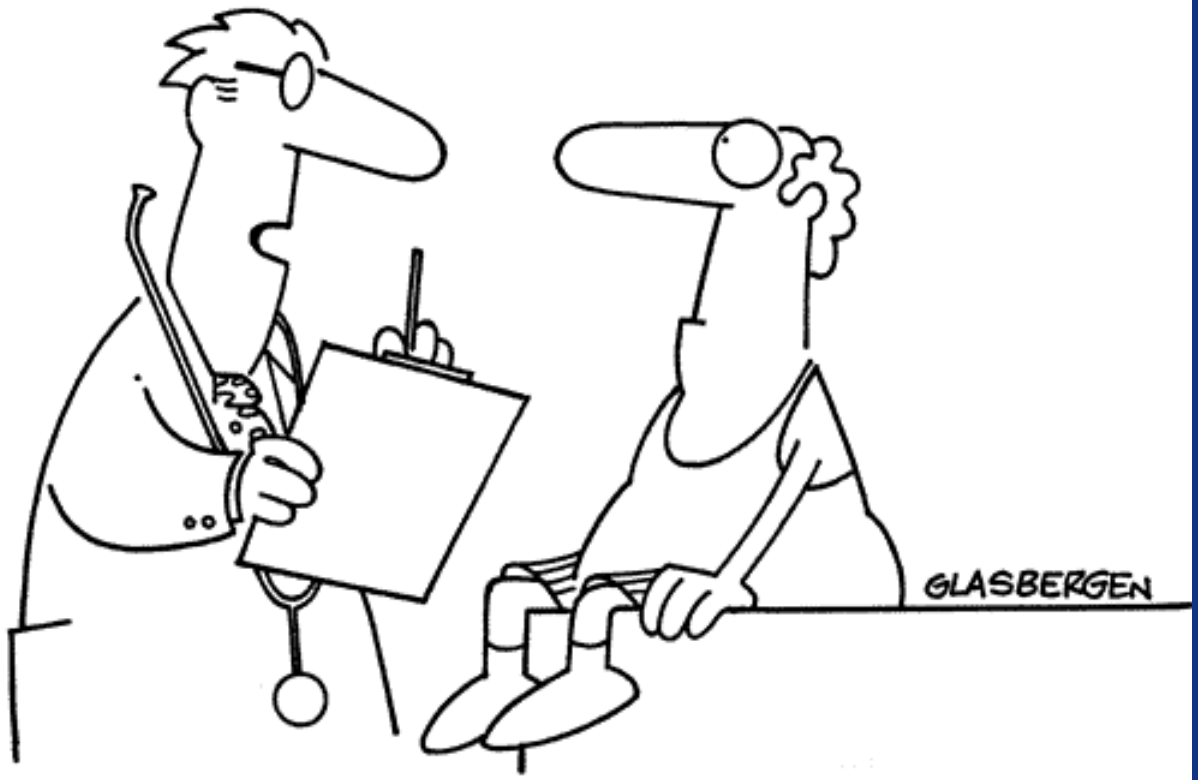
+

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



"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
- Multicultual 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

Curran D, van Dongen JP, Aaronson NK et al. Eur J Cancer 1998 Feb;34(3):307-14

Lessons learned from early trials

- Invest 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 HRQL Program
1997 - 2006

- 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 HRQL outcomes
Total QOL in clinical studies

	Accumulated totals by 1998 (Kiebert *et al.* 1998)	Accumulated Total by 2006	Change in 8 years
Phase II	6	9	+ 3
Feasibility	1	1	0
Phase II/III	2	11	+ 9
Phase III	32	98	+ 66
Measurement field study	3	8	+ 5

Standardization

- HRQL assessment mandatory in all participating centers for trials with an HRQL endpoint (with a few exceptions)
- Guidelines and templates for key HRQL paragraphs (design, measures, analysis plan) of clinical trial protocols
- Standard procedures for monitoring compliance with HRQL assessment (every county has different systems for data collection!)
- 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 HRQL components of clinical trials for publication

A recent example of successful EORTC phase III clinical trial with HRQL endpoints

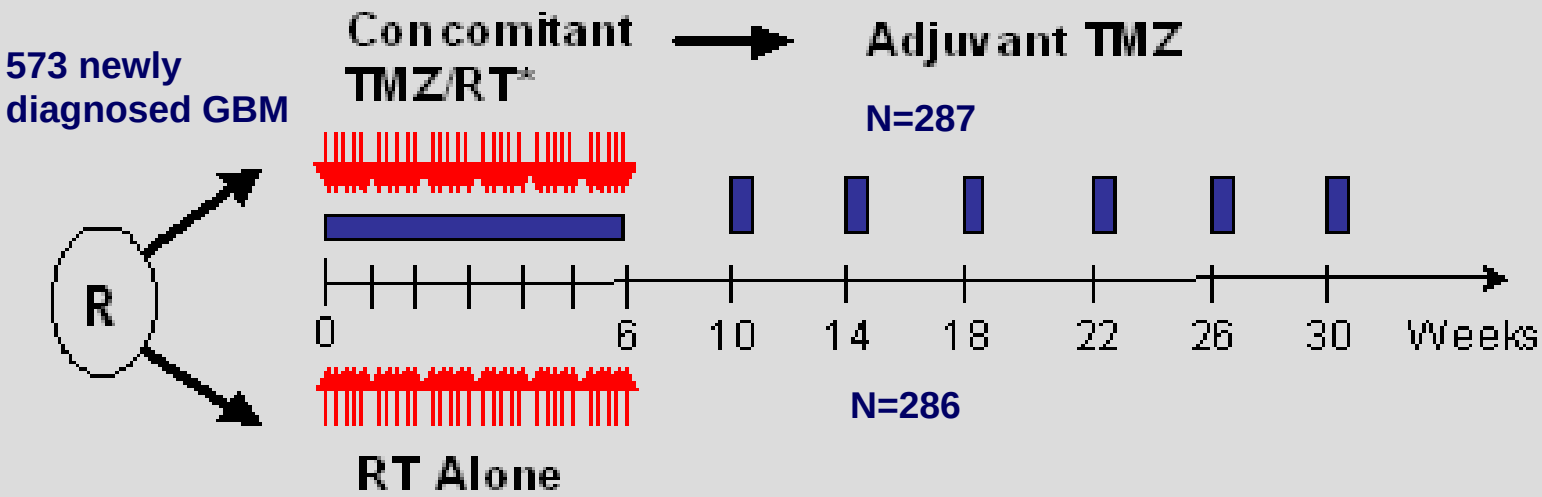
Joint EORTC Brain Tumour Group/Radiotherapy Group and NCIC CTG phase III randomised controlled trial evaluating HRQL in glioblastoma patients*

*** Martin Taphoorn, R Stupp, D Osoba, J Curschmann, R. Kortmann, MJ van den Bent, W Mason, C Coens, E Eisenhauer, A Bottomley. *Lancet Oncol*, December 2005; 6: 937-44**

Glioblastoma multiforme

- Most common primary brain tumor
- Treatment:
  - Adjuvant chemotherapy following RT, has been an issue of debate for years
    - In Europe and Canada, the limited survival benefit of adjuvant chemotherapy was not believed to outweigh treatment-related side effects
  - surgery: biopsy and/or resection
  - focal radiotherapy: 60 Gy in 30 fractions
  - New oral treatment to evaluate: temozolomide
- Prognosis:
  - patients die from recurrent disease in the brain
  - median survival: 9 - 12 months, limited data on HRQL

Treatment Schema



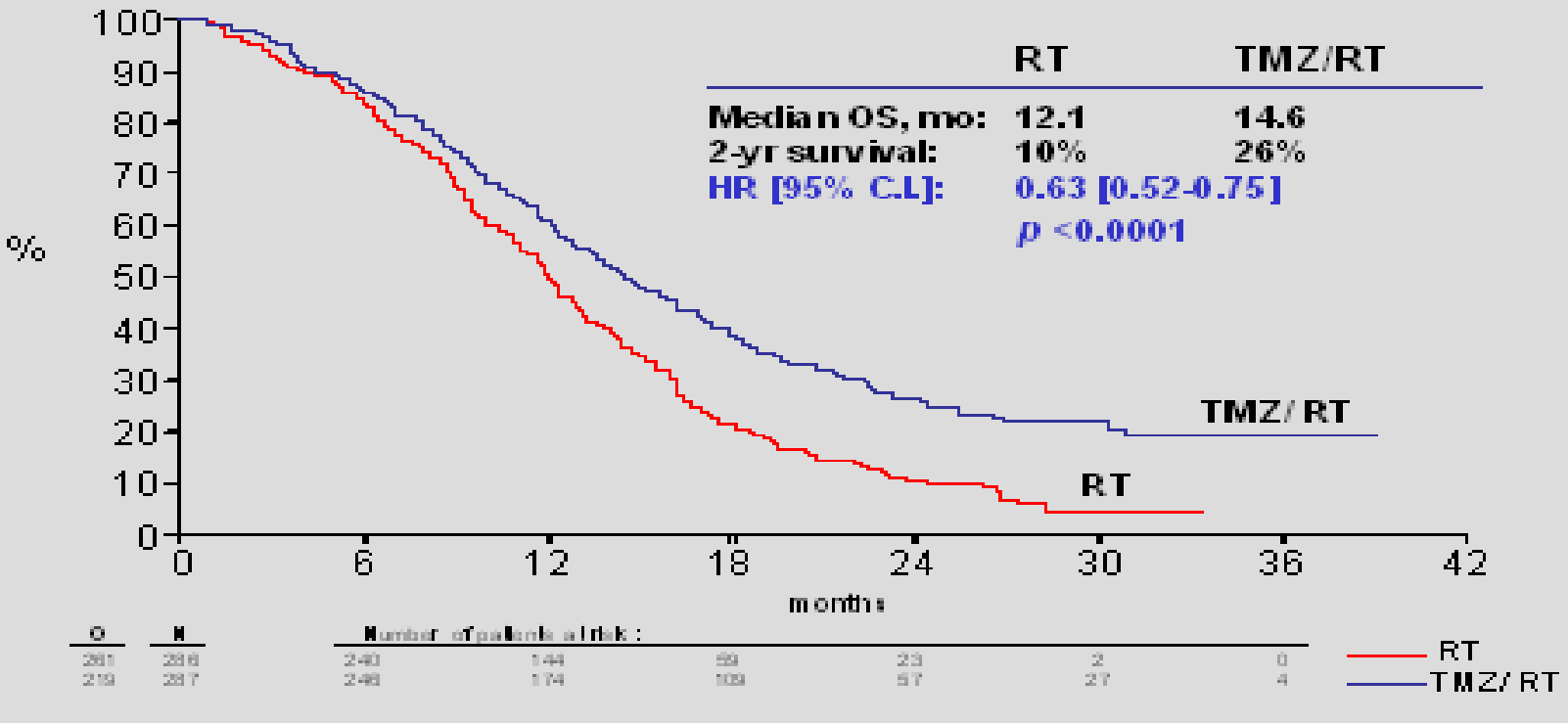
Temozolomide 75 mg/m² po qd for 6 weeks,
then 150–200 mg/m² po qd d1–5 every 28 days for 6 cycles

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



Stupp et al, New Engl. J Med, March 2005

Hypothesis on HRQL

- Using the QLQ-C30 and BN 20 that baseline HRQL will be impaired
- HRQL may deteriorate more severely during intense treatment (RT + TMZ) compared to standard (RT)
- HRQL will improve more slowly following RT + TMZ compared to RT alone
- Following treatment HRQL will not be different between treatment groups

Patients and Methods

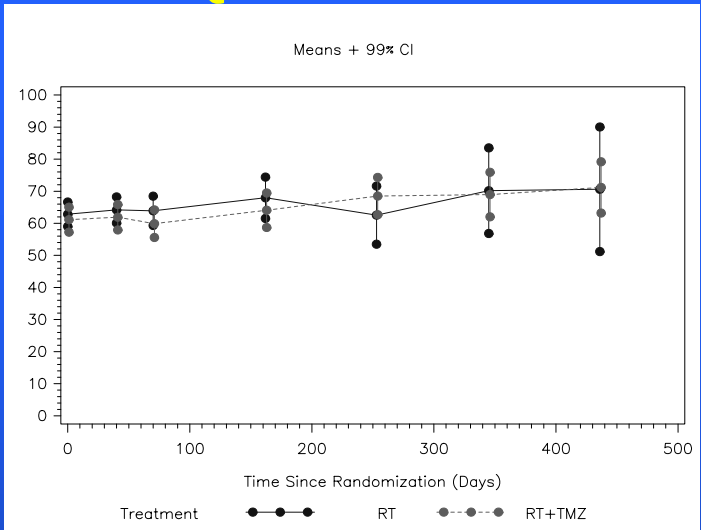
- **573 newly diagnosed GBM patients**, median age 56
  - standard (RT only): 286
  - experimental (RT/TMZ): 287

- **HRQOL assessments**
  - Baseline (over 86%, n = 460)
  - week 4 of radiotherapy (75%)
  - week 4 following radiotherapy (76%)
  - 3 months interval until progression (80%)
- **Pre-selection of 7 scales**
  - **QLQ C-30**: overall QoL, fatigue, insomnia, social and emotional functioning
  - **QLQ BN-20**: communication deficit, future uncertainty

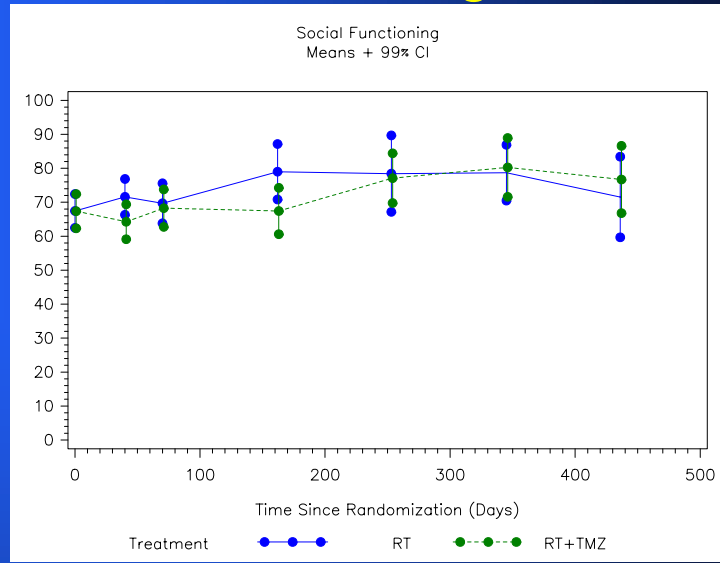
- **Statistics and analysis**
  - Linear mixed effects model, $p < 0.01$, clinical significance
  - Series of sensitivity analyses for missing data

QL results

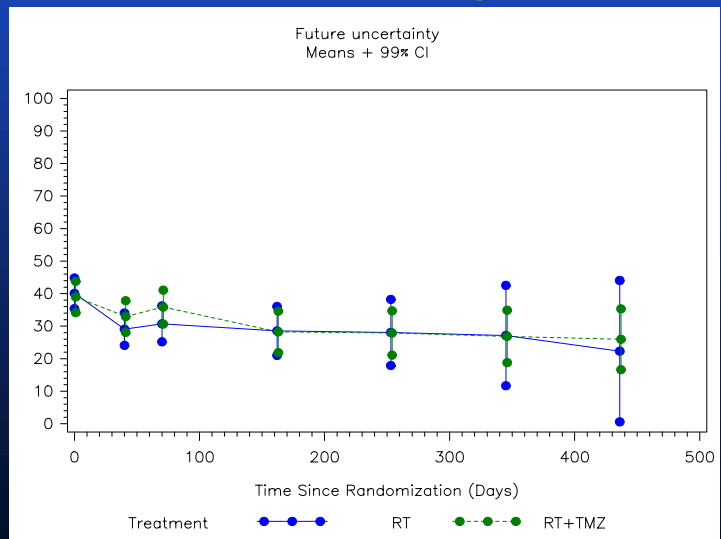
Global QOL scale over time



Social Functioning over time

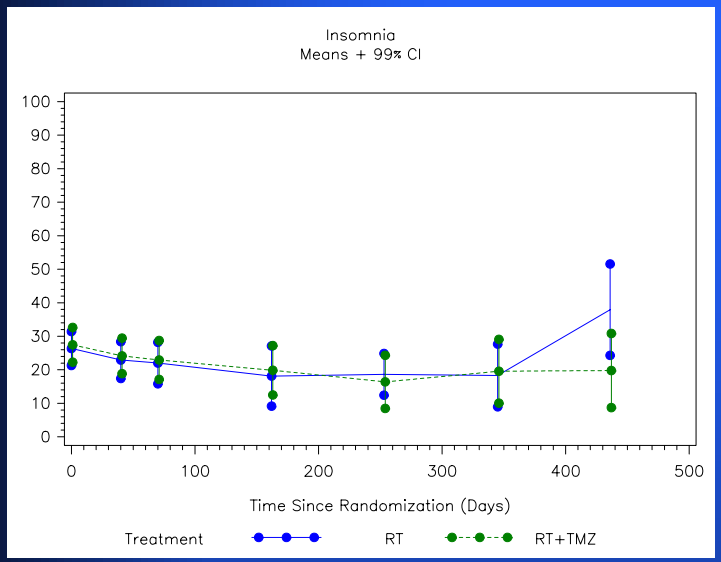


Future Uncertainty over time

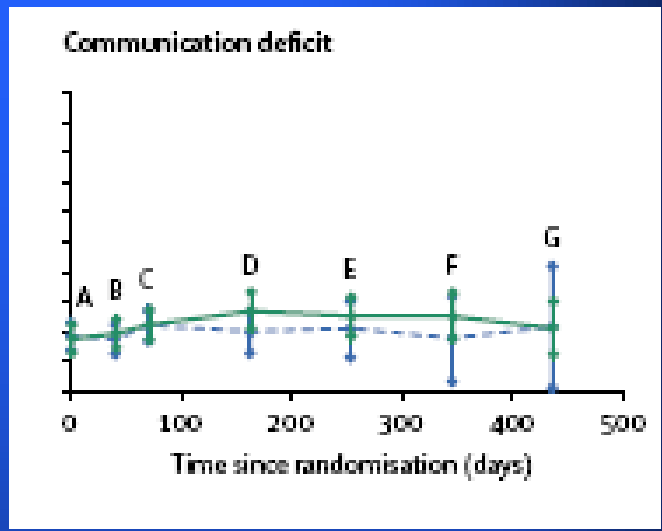


QL results

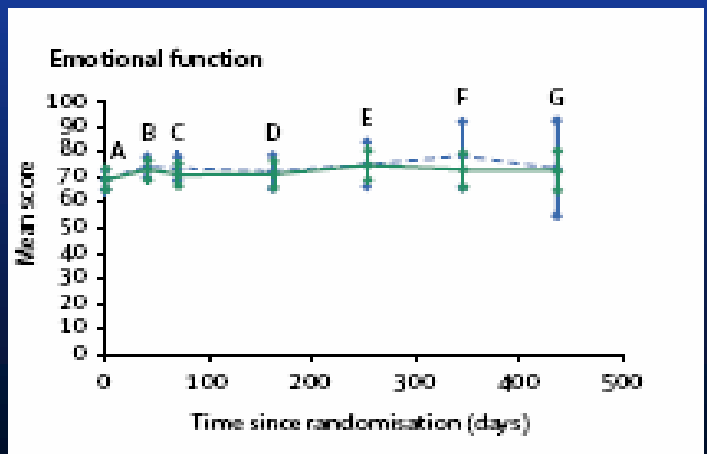
Insomnia



Communication



Emotional functioning



Conclusions

- Baseline HRQL in GBM: Major impairment
- No negative impact of concomitant/adjuvant TMZ on HRQL during treatment
- No decrease/slight improvement in HRQL during first year following treatment
- RT with concomitant and adjuvant TMZ :
  - more effective than standard treatment
  - safe
  - no detrimental effect on HRQL
- While some argue the survival benefit is not huge: we can say quality of survival is important

Key lessons learned...

- Focus on clinical trials with the largest potential HRQL payoff
- Pre-select the most clinically important endpoints
- Educate the collaborators, providing guidelines and training opportunities; hold HRQL planning meetings
- Monitor HRQL 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 HRQL outcomes evaluate source of problems and justify logic of any further investment in HRQL investigations
- Always budget costs of HRQL component of trials
- Centralize HRQL activities (planning, data collection monitoring, analysis) to enhance efficiency and quality of work done

The new EU Clinical Trials Directive

Ideal aims to promote multinational clinical trials in Europe

To harmonize clinical trials procedures and to reinforced patient protection

Costs of trials tripled

Increased legal and insurance cost

Increased complexity/workload

Study activation 4 ➡ 12 month

Some harmonization across EU

Better protection for patients

Less likely that academic trials can be done by large academic centers (and so maybe QL will be excluded as a cost saving factor?) and more industry initiated trials.

This Directive would have made it impossible to undertake the GBM trial due to increased costs/monitoring.

* Therasse et al, EJC 2005; Piccart et al, ASCO 2006

Future challenges for international clinical trials HRQL research and directions

- There are both similar and different challenges facing US and EU researchers. In Europe, efforts must be made to improve the clinical trials setting via lobbying European Commission
- To maximize HRQL compliance in trials by means of realistic data collection schedules, closer monitoring and sufficient funding
- To liaise with and provide training opportunities for EMEA regarding the intent, methodology, value added and limitations of trial-based HRQL investigations
- To use modern test theory (IRT and CAT methods) to develop more efficient and robust HRQL measures for use in both clinical trials and clinical practice