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

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“Value Added” and BS Bingo

| synergy          | strategic fit    | core competencies | best practice  | bottom line
|------------------|------------------|-------------------|----------------|-------------
| revisit          | take that off-line | 24 / 7            | out of the loop | benchmark   |
| value-added      | proactive        | win-win           | think outside the box | fast track |
| result-driven    | empower          | knowledge base    | solution       | touch base  |
| mindset          | client focus     | paradigm           | game plan      | leverage    |
Value-added defined

• If it walks like a duck and quacks like a duck, it's a duck at $1.50/lb.

• But if it's a really big duck, we can call it a goose. And goose goes for $2.75/lb.

• And then there’s Foi Gras, going for $50/lb.

• “Of or relating to the estimated value that is added to a product or material at each stage of its manufacture or distribution.”
Use of HRQOL outcomes in clinical trials
An informal, simple-minded literature search

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

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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)

Adapted from Moinpour CM et al. J Natl Cancer Inst 1989; 81:485-495
Clinical trials where HRQOL outcomes are likely to result in value-added

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- survival is expected to be equivalent but HRQOL to differ as a function of treatment
- survival is expected to be marginally (but significantly) better in one arm, and HRQOL to be better in the other

HRQOL measurement 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.”
…and 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
Amputation vs limb-sparing procedure in soft-tissue sarcoma cont..

- 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).

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

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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

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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

573 newly diagnosed GBM

Concomitant TMZ RT

Adjuvant TMZ

N=287

N=286

RT Alone

Temozolomide 75 mg/m² po qd for 6 weeks, then 150-200 mg/m² po qd every 28 days for 6 cycles
Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

*For prophylaxis was required for patients receiving TMZ during the concomitant phase.
Clinical findings

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
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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 – trend for reduced all-cause mortality (18% versus 15%; p = 0.31)

- Prostatectomy - decrease in prostate-specific death rates (9% versus 5%; RR 0.50, 0.27 to 0.91, p = 0.02)
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  

- 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

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
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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…