Quality of Life as an Endpoint in Clinical Trials and as a Movable Target Thereafter

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  - Roche
  - Pfizer
  - GSK
  - Novartis
  - Astellas/Aveo
Quality of Life as an Endpoint in Clinical Trials and as a Movable Target Thereafter
QoL as an endpoint in clinical trials

Topics

- QoL definition, QoL in oncology, criteria to evaluate outcomes in cancer treatment and factors influencing QoL
- Why have QoL endpoints evolved as part of clinical trials over the past 2 decades?
- Why measure QoL in oncology?
- Main challenges in incorporating these QoL or symptom measurement data into clinical trials
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QoL Definition WHO 1948

Absence of disease

Mental wellbeing

Social wellbeing

Absence of infirmity
QoL in Oncology

Four factors contribute the most to the overall impact of the disease and its treatment on a patient’s QoL.

- **Physical and occupational function** (strength, energy, ability to carry on expected normal activities)
- **Psychological state** (depression, anxiety, fear, wellbeing)
- **Social interaction** (with family members, with friends)
- **Somatic sensation** (symptoms due to the disease or treatment toxicity)
HRQoL in Oncology

- HRQoL is a concept referring to the effect of an illness and its therapy upon a patient’s
  - physical
  - psychological
  - and social wellbeing
  as perceived by the patient himself

- Clinicians when focusing on HRQoL should consider that, for extremely sick patients, almost any aspect of life can be regarded as health related
QoL is influenced by many other factors not related to health

- Physical and occupational function
- Job satisfaction
- Economic situation
- Somatic sensation
- Psychological state
- Security
- Freedom
- Social interaction
- Etc......
Cancer treatments may influence some but not all aspects related to QoL...
Criteria to evaluate outcomes of cancer treatments

- Treatment should be concerned with 2 types of effects:
  - 1) indices of activity (cancer outcomes such as response...etc)
  - 2) indices of efficacy (patient outcomes, essentially survival and QoL)

- An active drug is not necessarily an effective drug
  - A new treatment shown to improve OS should be considered the most effective therapy
  - unfortunately, the main purpose of cancer treatment is not cure but rather to control symptoms and/or delay disease progression
  - in these cases, the improvement of patients QoL is the primary goal of treatment
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Why have QoL endpoints evolved as part of clinical trials over the last decade?

1. Advances in the medical field, two or three different options with relatively equivalent outcomes

   - *e.g. in localized prostate cancer, radical prostatectomy or radiation have equivalent survival, but each of these interventions may have different toxicity profile, e.g. prostatectomy may result in sexual dysfunction while radiation may lead to bowel dysfunction:*

   - *in this context, QoL is important to allow patients to choose between two different treatments with similar survival results*

2. The field as a whole has moved toward a more patient centered view: while survival and morbidity are important endpoints for treatment trials: how is the patient affected as a whole?
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Why measure QoL in oncology (1)

- Standard end points do not measure the effects of cancer or its treatment on the emotional, spiritual and social dimensions of patients‘ lives
- The description of how two compared treatments influence QoL and OS is important to select the best strategy
  - A treatment may be preferred if it improves the QoL even if survival is not superior to that conferred by comparable treatment
  - A treatment may be unsatisfactory and should not be used in clinical practice when QoL remains similar to that under the comparable treatment without advantages in terms of survival
However, there are two situations in which the outcome is difficult to interpret...

1. If the treatment induces a lower chance of survival but improves QoL
2. If QoL is worse but chances of survival are improved by the treatment (depends on length of survival improvement)

- In these 2 situations, one can make a choice
  - by either describing the patient the positive and negative effects on QoL and OS or
  - by resorting to measure the combine quality with quantity of life such as QUALY (quality-adjusted life years) and Q-TWIST (quality adjusted time without symptoms and toxicity)
Why measure QoL in oncology (2)

- Evaluating QoL can be important for the cost-utility analysis of new drugs
- The choice among different treatment options has also to consider their costs, important to control health expenditure
Why measure QoL in oncology (3)

- QoL are not simple extensions of toxicity scales...these scales measure only the maximum toxicity observed in a patient but do not take into account the duration of toxicity, while QoL instruments do take this point into account.

- Furthermore, there is less effect on QoL from acute than from chronic and late toxicity.
  - *e.g. patients with debilitating neuropathy often have poor QoL despite good control of their cancer*
Why measure QoL in oncology (4)

- The physician is often quite intuitive when determining what can be done for a patient in order to maximize the patient’s QoL.

- Sometimes however counter-intuitive results are observed:
  - *e.g. an aggressive therapy may result in an improved QoL: comparison of continuous versus intermittent chemotherapy in patients with MBC: unexpectedly, patients on continuous CHT had a better QoL and also survived longer*¹

¹ Coates A et al., New Engl J Med 1987
Why measure QoL in oncology (5)

- QoL instruments may provide **prognostic information independent of other factors** including performance status.

- e.g. Sloan et al demonstrated that QoL does appear to be prognostic for survival\(^1\): a single item was prognostic for OS while controlling for other variables.

- This has been confirmed in patients with breast, lung, GI cancer and melanoma\(^2\)–\(^5\).

- **Initial QoL may therefore be measured in all patients and used as a stratification factor in randomized trials**.

Several standardized QoL questionnaires have been used over the past 2 decades

- Some commonly used measures include the
  - *Functional Assessment of Cancer Therapy (FACT)*\(^1\)
  - *MD Anderson Symptom Inventory (MDASI)*\(^2\)
  - *European Organization for Research and Treatment of Cancer (EORTC QLQ)*\(^3\)

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Main challenges in incorporating these QoL or symptom measurement data into clinical trials

- Identifying the appropriate time points for assessing QoL so that both treatment arms are evaluated fairly
- Minimizing missing data
- Collecting data at clinically meaningful times: it is important to ask clinicians WHEN they would expect that at least one of these treatment would be having some effect on patient QoL, in order to assess at that time point
- To have just baseline QoL assessment and one at the end is a mistake seen in past trials: missing the rich data in between those two time endpoints, where one wants to describe how the treatment or intervention is impacting the patient
- There is a need for accurate assessment throughout the trial but yet not overburdening the patient
Challenges in incorporating these QoL or symptom measurement data into clinical trials (2)

- Requirement of an upfront decision on what QoL endpoints to you want to include in your trial?
- There is a whole menu of QoL questionnaires and researchers need guidance on how to collect the most valid and reliable measure of important QoL factors in the clinical trial
- **Some investigators make the mistake of just grabbing any QoL out there and throwing it into the trial and they have no idea how their endpoints are impacted or what to expect as a result of the trial**
Quality of Life as an Endpoint in Clinical Trials and as a Movable Target Thereafter
Whenever the topic of QoL is raised in clinical practice, additional factors need to be considered:

1. Whether a treatment is active and effective for the outcome may not only depend on the potential of the treatment itself but also on different views in multidisciplinary teams.

2. Are QoL reports of clinical trials reliable enough and to which extent does pharmaceutical advertisement material influence our treatment decision?

3. Do we influence our patients when communicating the QoL issue?

4. Patients with similar prognostic features may have their own views on the topic of QoL related to survival.
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Patient MG

- Female patient, 74 years
- Fully active, no major morbidities
  - hypothyroidism (T4 replacement),
  - obesity (BMI 30)
- History of total endoprosthesis (femoral head necrosis)
- December 2010: pain left hip followed by inability to walk
Diagnosis: Hip Dislocation

Surgery planned
Pre-Surgical Investigations and Findings

- Investigations
  - ECG: sinusrhythm, HR 61/min, normal ST-segment and T-waves
  - BP: normal
  - Chest-x-ray: no abnormalities
  - Lab: electrolytes normal, creatinine 1.29, normal liver function, mild anemia, thrombocytosis
An Echocardiography is Performed...
6 cm Tumor Thrombus Right Atrium
Consequence

- Surgery postponed
- CT scans…
Patient MG

RCC right kidney
Patient MG

VCI-thrombus
Referred to Urologist

- Biopsy: cc-RCC
- NO DISTANT METASTASES
The Beginning of a Troublesome Story

Plan: radical nephrectomy and thrombectomy: CURATIVE APPROACH!
Expected 5 year DFS: 58%\(^1\)
Level of TT is not an independent prognostic factor\(^1\)

Ciancion G et al., J Urol 2010
The Beginning of a Troublesome Story

Difficulties to walk due to hip dislocation
Obesity

Heart surgeon: patient with cancer!!!
ECOG 3 (wheelchair)
„this patient will not benefit from surgery“
Phone Calls and Tumorboards
However: The medical oncologist is a difficult person…

- who unnessecarily prolongs the duration of the tumorboard by reminding the surgeons
- …that this otherwise healthy patient could be cured by surgery
- that in contrast to surgery, chronic medical treatment is unlikely to cure her
- that ECOG 3 in this case is a misinterpretation because the inability to walk is entirely due to an orthopedic problem
- …and that if the patient was really ECOG 3, chronic medical treatment can’t be considered „safer“ than surgery, because these agents have side effects after all …
The former relaxed and optimistic patient is meanwhile scared to death and prefers medical treatment from her medical oncologist.
Treatment

- Begins TKI-treatment January 2010
- Best response: SD
- Side effects:
  - diarrhoea 2, stomatitis 1, hypertension 3
- Tolerability: appears acceptable
- However: patient perceives her QoL as poor
- In a wheelchair-bound patient diarrhoea grade 2 might be a heavy burden
- Patient begins thinking that all of this wouldn‘t be necessary if she had undergone surgery...
Course of the Treatment

- After 9 months of treatment, primary tumor still stable, no distant metastases
- Intermittent TKI-interruption required due to wound healing problems
- Medical oncologist calls surgeons:
  - „Patient still stable, no mets, no internal issues, anticancer treatment needs to be interrupted for unknown period, please perform curative surgery“
- Surgeon: …“what’s the point if she is stable anyway…”
What Does the Patient Want in the First Place?
The medical oncologist wants the very best outcome for the patient....

HIP SURGERY IS PLANNED!!!
At Least One Problem Solved for the Patient?

Orthopedic surgeon

ANESTHESIOLOGIST

TRUST ME, YOU WON'T FEEL A THING.
At Least One Problem Solved for the Patient?

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Treatment Outcome

- Progressing RCC
- Still free of metastases for 30 months = active treatment
- Normal LVF, normal liver and kidney function
- Poor QoL = ineffective treatment
  - due to inability to walk properly
  - due to difficulties to manage otherwise mild side effects because of immobility

The patient may have experienced not only activity of the treatment (stable disease) but also efficacy e.g. in terms of prolonged survival, symptom control etc. if the multidisciplinary team had considered QoL rather than treatment (surgery) associated risks in the first place.
Whenever the topic of QoL is raised in clinical practice, additional factors need to be considered:

1. Whether a treatment is active and effective for the outcome may not only depend on the potential of the treatment itself but also on different views in multidisciplinary teams.

2. Are QoL reports in published clinical trials reliable enough and to which extend does pharmaceutical advertisement influence our treatment decision?

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4. Patients with similar prognostic features may have their own views on the topic of QoL related to survival.
Patient-centered studies may be founded by academia or by pharmaceutical industry

- If founded by pharma, careful interpretation of results is mandatory for clinicians

- Patient reported outcomes (PRO‘s) are frequently included in registration clinical trials for multiple purposes, including
  - Support of product approvals and labeling claims of treatment benefit
  - Support of primary endpoints
  - To provide a basis for publication and communication strategies
  - More importantly, increased competition in a global market requires pharmaceutical companies to seek methods to differentiate their products from those of competitors
Example Renal Cell Carcinoma

- 2 anti-VEGFR-TKIs approved in first-line, sunitinib (Pfizer) and Pazopanib (GSK)
- Sunitinib was first...
- When Pazopanib came on the market, GSK initiated a non-inferiority trial
- Endpoint: to demonstrate that PFS of pazopanib is not inferior to sunitinib
- Secondary endpoint: QoL: intention: as pazopanib has a slightly different toxicity profile, differences in QoL in favor of pazopanib may change the market
COMPARZ Study Design

Key Eligibility Criteria
- Advanced/metastatic RCC
- Clear-cell histology
- No prior systemic therapy
- Measurable disease (RECIST 1.0)
- KPS ≥ 70
- Adequate organ function

Stratification Factors
- KPS 70/80 vs 90/100
- Prior nephrectomy
- Baseline LDH >1.5 vs ≤1.5 × ULN

Pazopanib
800 mg qd
continuous dosing
Dose reductions to 600 mg or 400 mg

Sunitinib
50 mg qd
4 wk on/2 wk off
Dose reductions to 37.5 mg or 25 mg
Study Assessments

- Disease assessments weeks 6, 12, 18, 24 and then every 12 weeks
- Other assessments - 6 week cycles
  - Safety
    - Baseline, Day 28 & Day 42 of every cycle through cycle 9, Day 42 of every cycle from cycle 10
  - Patient-reported outcomes
    - Baseline (except for CTSQ), Day 28 every cycle
    - Measures:
      - FACIT-Fatigue
      - FACT Kidney Symptom Index (FKSI-19)
      - Cancer Therapy Satisfaction Questionnaire (CTSQ)
      - Supplementary Quality of Life Questionnaire (SQLQ)
Statistical Analysis Plan

- PFS non-inferiority demonstrated if upper bound of 95% CI for HR < 1.25
  - Cox proportional hazard analysis adjusted for stratification factors
  - By independent review
- 631 PFS events needed for 80% power
- Planned enrollment of 1100 patients
If the hazard Ratio is not above 1.22 or 1.25....

Translation into PFS numbers

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Median months in pazo</th>
<th>Not unacceptable loss in months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25</td>
<td>9.6</td>
<td>2.4</td>
</tr>
<tr>
<td>1.22</td>
<td>9.8</td>
<td>2.2</td>
</tr>
<tr>
<td>1.09</td>
<td>11</td>
<td>1</td>
</tr>
</tbody>
</table>

On advice of EMA, HR upper bound should have been 1.22
COMPARZ: PFS (IRC-assessed)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib</td>
<td>557</td>
<td>8.4 months (8.3–10.9)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553</td>
<td>9.5 months (8.3–11.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td>1.05 (0.90–1.22)</td>
</tr>
</tbody>
</table>

Motzer et al. NEJM 2013
## QoL Results (Secondary Endpoint)

### Quality of Life Results (first 6 months)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Domain Description</th>
<th>Treatment difference: mean change from baseline</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACIT-F</td>
<td>Fatigue/Total score</td>
<td>2.32</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Kidney Symptom Index/Total score</td>
<td>1.41</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>0.78</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>Emotional</td>
<td>0.05</td>
<td>0.409</td>
</tr>
<tr>
<td></td>
<td>Treatment Side Effects</td>
<td>0.31</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>Functional Well Being</td>
<td>0.31</td>
<td>0.098</td>
</tr>
<tr>
<td>FKSII-19</td>
<td>Expectations of Therapy</td>
<td>1.41</td>
<td>0.284</td>
</tr>
<tr>
<td></td>
<td>Feelings about Side Effects</td>
<td>8.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Satisfaction with Therapy</td>
<td>3.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Worst mouth/throat soreness</td>
<td>0.505</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Worst foot soreness</td>
<td>0.204</td>
<td>0.016</td>
</tr>
<tr>
<td></td>
<td>Worst hand soreness</td>
<td>0.267</td>
<td>0.0008</td>
</tr>
<tr>
<td></td>
<td>Limitations due to mouth/throat soreness</td>
<td>0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Limitations due to foot soreness</td>
<td>0.65</td>
<td>0.014</td>
</tr>
</tbody>
</table>

*Pre-specified analysis. HRQoL changes in mean scores over time were analyzed with a repeated measures analysis of covariance (ANCOVA).

*Yellow Font*: favors pazopanib; *Blue Font*: favors sunitinib. P-value <0.05 is statistically significant.
PISCES Study

Pazopanib versus sunitinib patient preference study in treatment naïve advanced or metastatic renal cell carcinoma

(A randomised, double-blind, cross-over patient preference study of pazopanib versus sunitinib in treatment-naïve locally advanced or metastatic renal cell carcinoma)
Study design

1:1 randomisation

Both drugs were over-encapsulated

Patients on sunitinib received placebo during 2-week ‘off-period’

ClinicalTrials.gov. NCT01064310.
Primary endpoint: Patient preference for study treatments (Primary analysis population) \(^1\)

- Preferred pazopanib: 70% (n=80)
- Preferred sunitinib: 22% (n=25)
- No preference: 8% (n=9)

90% CI (for difference): 37.0-61.5; \(p<0.001\)

Have COMPARZ and PISCES Identified the Better TKI for the treatment of mRCC?
Is Pazopanib non-inferior?....

Methodological issue 1: Patient population
- Enrollment criteria:
  - Locally advanced or mRCC
  - Clear-cell histology
  - No prior systemic therapy
  - Measurable disease (RECIST 1.0)
  - Adequate organ function

Randomized 1:1
N=1110

Pazopanib 800 mg qd
Continuous daily dosing

Sunitinib 50 mg qd
4/2 schedule

Study start: August 2008

KPS, Karnofsky Performance Scale; RECIST, Response Evaluation Criteria in Solid Tumors.
4/2 schedule 4/2: 4 weeks on treatment, 2 weeks off.
www.clinicaltrials.gov (NCT00739441, NCT01114792)

Methodological issue 2: Non-inferiority not achieved in the PP-population

<table>
<thead>
<tr>
<th>PFS (ITT population)</th>
<th>Pazopanib (n=557)</th>
<th>Sunitinib (n=553)</th>
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</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>8.4 (8.3–10.9)</td>
<td>9.5 (8.3–11.1)</td>
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<tr>
<td>HR (95% CI)</td>
<td>1.05 (0.9–1.22)</td>
<td></td>
</tr>
</tbody>
</table>

PFS (PP-Population) Pazopanib (n=501) Sunitinib (n=494)

| Median PFS, months (95% CI) | 8.4 (8.3–10.9) | 10.2 (8.3–11.1) |
| HR (95% CI) | 1.069 (0.910–1.255) |

Non-inferiority met if upper bound of 95% CI for HR <1.25 (EMA requested ≤1.22)

Methodological issue 3: Timing of disease and HRQoL assessments

Mean change from baseline

- Sunitinib
- Pazopanib

Disease assessments:
- Week 6

HRQoL assessments:
- Week 4

PATIENT PREFERENCE TRIAL: PISCES:
Unfavoured sunitinib arm
Preference question asked once:
on day 28 of treatment in
sunitinib arm=worst day during treatment period
„...yes, but QoL was significantly better for pazopanib-patients than for sunitinib patients....“
HRQoL Instruments should be capable of detecting clinically meaningful effects

- Definition of clinically meaningful HRQoL difference in oncology?
  - hard to define as it depends on the disease setting: from the curative setting to the setting of disease delay to the palliative setting
  - it also may be influenced by cultural factors and the definition of the minimal clinically meaningful difference might be „the difference large enough for the patient to notice there is one"

- The minimal important difference (MID) may be defined as the smallest change perceived by the patient as an advantage/disadvantage or that could lead to a change of treatment

- Of note: from the opposite perspective, it is important but historically often difficult to know whether the absence of a difference in HRQoL measures is an indication of equivalence or a result of employing an instrument that was incapable of detecting changes
**COMPARZ: HRQoL assessments**

- FACIT-F and FKSI-19 only validated HRQoL assessments scales reported\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Difference (favouring pazopanib if &gt;0)(^2)</th>
<th>(p)-value</th>
<th>Minimally important difference*</th>
</tr>
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<tbody>
<tr>
<td>FACIT-F</td>
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<td>&lt;0.001</td>
<td>3–4(^3)</td>
</tr>
<tr>
<td>FKSI-19 total</td>
<td>1.41</td>
<td>0.02</td>
<td>2–3(^4)</td>
</tr>
</tbody>
</table>

- Although differences were statistically significant, they were not clinically meaningful\(^2–4\)

COMPARZ: Recent report by French reimbursement agency

- The non-inferiority of pazopanib vs. sunitinib is not conclusive because of a lack of confirmation in the per-protocol analysis

- The upper bound of the 95% CI for HR seen in the per-protocol analysis (1.25) may equate to an unacceptable loss of 2.2 months PFS with pazopanib vs. sunitinib

  - Loss of efficacy with pazopanib is not counterbalanced by improved safety

- The difference in QoL between pazopanib and sunitinib is not clinically meaningful
How were trial results translated in advertisement?
Whenever the topic of QoL is raised in clinical practice, additional factors need to be considered:

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2. Are QoL reports of clinical trials reliable enough and to which extent does pharmaceutical advertisement material influence our treatment decision?

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4. Patients with similar prognostic features may have their own views on the topic of QoL related to survival.
Communication between physician and patient depends on many factors that need to be considered

- The individual, disease-related situation of the patient
  - stage of disease
  - symptomatic versus asymptomatic disease
  - prognosis
  - co-morbidities
Communication between physician and patient depends on many factors that need to be considered:

- The personality of the patient
- Patient’s social background
- Patient’s spiritual background
- Patient’s religious background
Communication between physician and patient depends on many factors that need to be considered

- **The physicians’ background**
  - physicians’ experience with a specific type of cancer
  - physicians’ personality
  - physicians’ spiritual background
  - physicians’ religious background
Communication between physician and patient depends on many factors that need to be considered.

- **Treatment options**
  - various
  - few
  - availability
  - side effects
Flow of the discussion at the first visit

- Although physicians will take the lead, he/she needs to listen carefully
- e.g. it is mandatory to feel which amount of information the patient can tolerate

  Sometimes it‘s important not to answer to questions that haven‘t been asked

- In this context, it might be difficult to mention at the first visit, when treatment decisions are made, that maintenance/improvement of QoL is your main reason for choosing treatment x
Challenges arising from such discussions

- Dilemmas such as better but shorter life are ethical or philosophical in nature, hence with no straightforward answer.
- Similarly, to say that the weight of HRQoL is much more important in the palliative setting as opposed to the curative intent setting brings about the following question: would an improvement in QoL in the palliative setting at the cost of the some small loss in overall survival be acceptable? How could one value the length vs the QoL?
Whenever the topic of QoL is raised in clinical practice, additional factors need to be considered:

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What Weight Should We Give the HRQoL Data in a Benefit: Risk Analysis?

- In life threatening situations accompanied by significant suffering, patients may value improvements in HRQoL more, even at the cost of life-threatening drug effects

- Many cancer patients have little suffering at the begin of course of metastatic disease...efficacy may be their primary treatment goal

- ...to survive long enough to see the availability of novel agents
What is relevant for the patient?

- “And in the end it's not the years in your life that count; it's the life in your years* ”

- Statement of patient EA, 49 years, physician mRCC:
  “that’s so wrong…

- “…it’s my own task to bring life to my years, from my physician, I expect to bring years to my life

*Abraham Lincoln (1809-1865)
Conclusions

- QoL is an important endpoint in clinical trials, reflects efficacy of a treatment and not only activity.
- Incorporation of QoL measurements into clinical trials may prove challenging.
- QoL measurements may help to identify the individually best treatment for a patient.
- In clinical practice, results of published QoL data may not be sufficient to guide treatment strategies...
- Interaction between physicians, communication styles, the patient’s personality, social, spiritual and religious background are important additional factors that need to be considered.