Bedeutung von **PRO's** und **QoL** für Therapieentscheidungen in der kurativen onkologischen Therapie

PRO = **P**atient **R**eported **O**utcomes

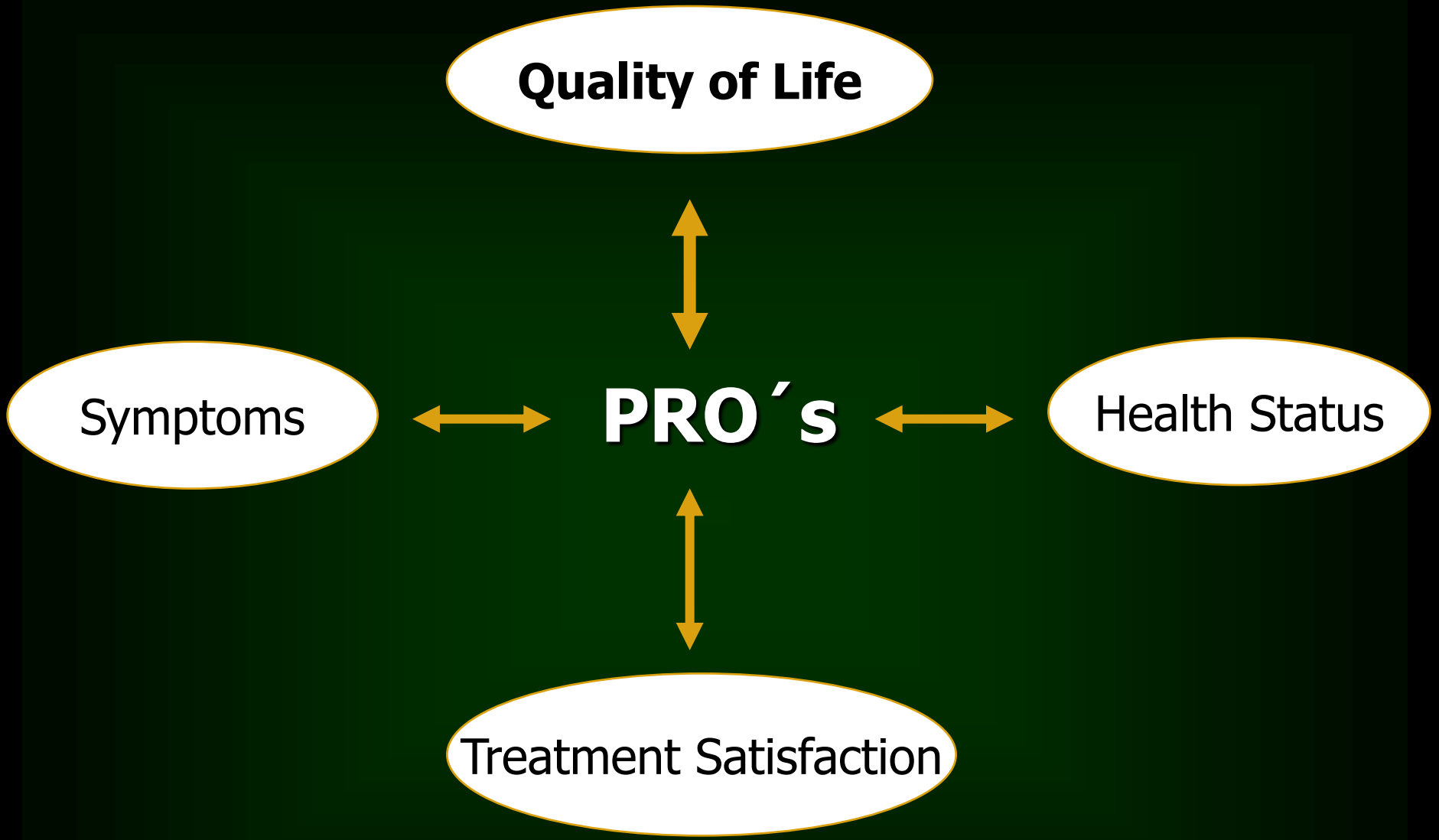
QoL = **Q**uality **o**f **L**ife

Patient Reported Outcomes (PRO`s)

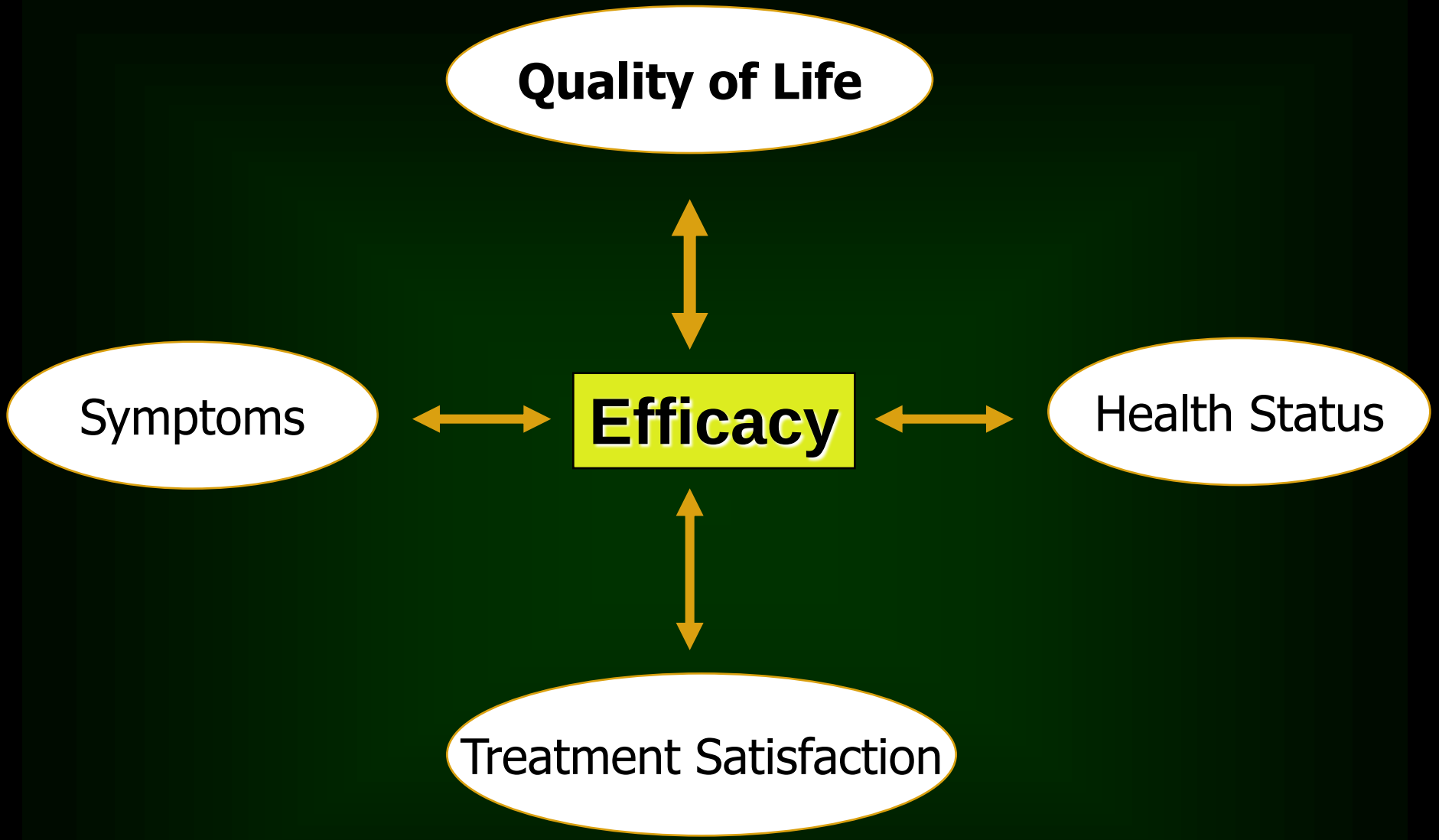
PRO`s Definition

*„a measurement of **any** aspect of a patient‘s health status that comes directly from patient (**without interpretation of the patient‘s responses by a physician or anyone else**)“*

US Department of Health and Human Services,
FDA: Patient-reported outcome measures
Draft guidance February 2006



PRO‘s sind: schwierig zu messen bzw. zu objektivieren und damit zu quantifizieren bzw. zu vergleichen !



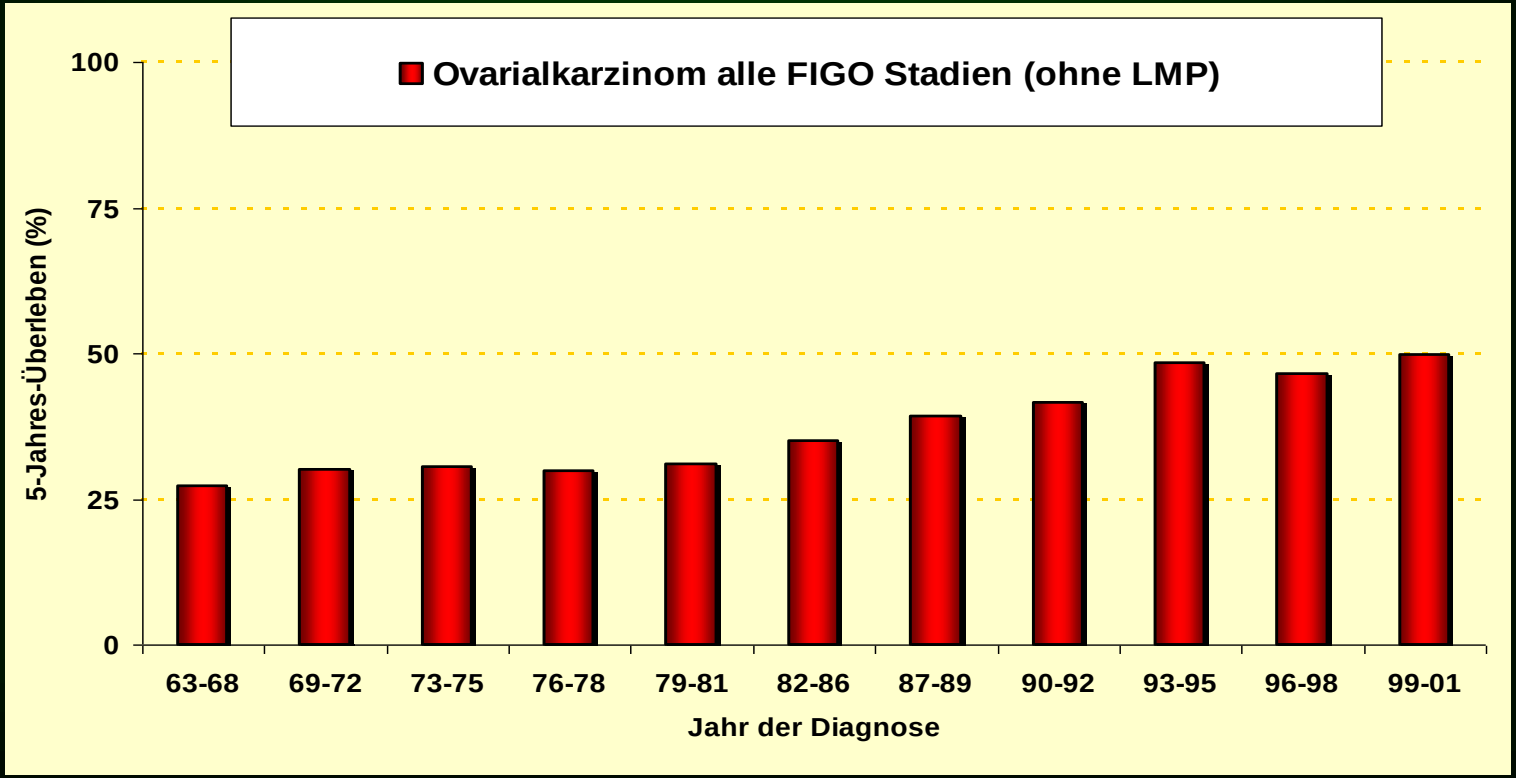
Warum nicht Efficacy (OR, PFS, OS) als Surrogat nehmen ?
-> quantitativ messbar, standardisiert, objektiv, akzeptiert

Efficacy als Therapieentscheidungskriterium: Probleme am Beispiel des Ovarialkarzinoms

- neue Therapien meist nur marginal „besser“
- substantieller Anteil nicht geheilter Patientinnen
- keine Prädiktoren für Therapieeffektivität etabliert
- neue Therapien haben neue Therapiefolgen und Risiken
- keine trade-off Modelle etabliert
- Interaktionen mit Folgetherapien wenig geklärt

5-Jahres Überlebensrate beim Ovarialkarzinom ca. 50% -> „AGO-OVAR Doppelstrategie“

- Verbesserung der Überlebenschancen durch Evaluation neuer Therapien
- Verbesserung der Lebensqualität – insbesondere wenn Heilung nicht möglich ist



S Pecorelli et al., 26th annual report on the results of the treatment in gynaecological cancer 2006

AGO OVAR-3 Studie

n=798 Pat. FIGO IIB-IV

OPERATION → RANDOMIZED

- Experimenteller Arm (N=407): Carboplatin+Paclitaxel
- Standard Arm (N=391): Cisplatin+Paclitaxel

Primärer Outcome:
Gesamtüberlebenszeit
Progressionsfreie Überlebenszeit

Sekundärer Outcome:
Toxizität, Tumor response
Lebensqualität

A Randomized Clinical Trial of Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel as First-Line Treatment of Ovarian Cancer

Andreas du Bois, Hans-Joachim Lück, Werner Meier, Hans-Peter Adams, Volker Möbus, Serban Costa, Thomas Bauknecht, Barbara Richter, Matthias Warm, Willibald Schröder, Sigrid Olbricht, Ulrike Nitz, Christian Jackisch, Günther Emons, Uwe Wagner, Walther Kuhn, Jacobus Pfisterer

For the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer Study Group

[J Natl Cancer Inst 2003;95:1320–30]

Walpole-Preis
Dt Krebsgesellschaft 2006

VOLUME 24 · NUMBER 4 · FEBRUARY 1 2006

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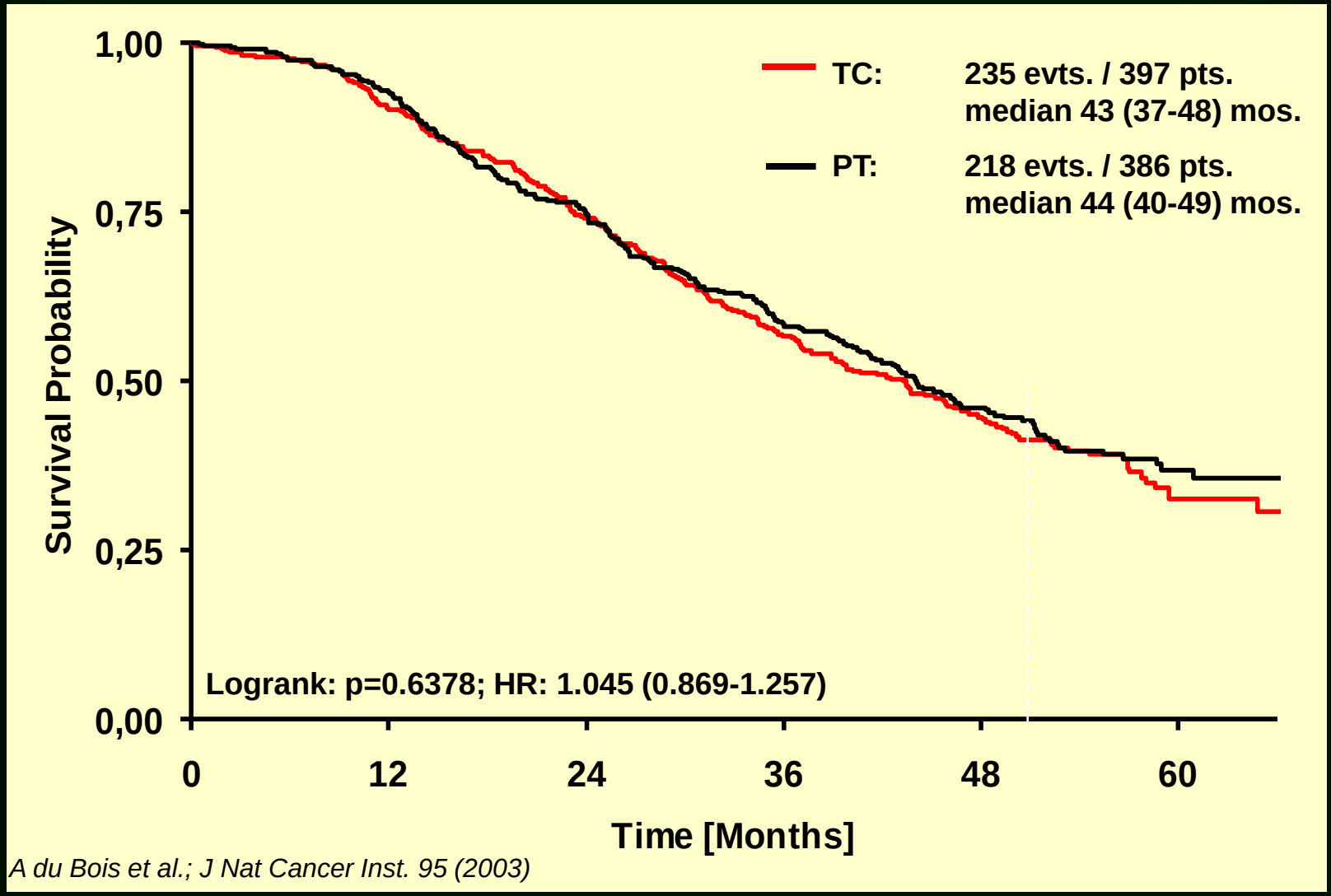
ORIGINAL REPORT

Randomized Study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group Comparing Quality of Life in Patients With Ovarian Cancer Treated With Cisplatin/Paclitaxel Versus Carboplatin/Paclitaxel

Elfriede R. Greimel, Vesna Bjelic-Radisic, Jacobus Pfisterer, Felix Hilpert, Fedor Daghofer, and Andreas du Bois

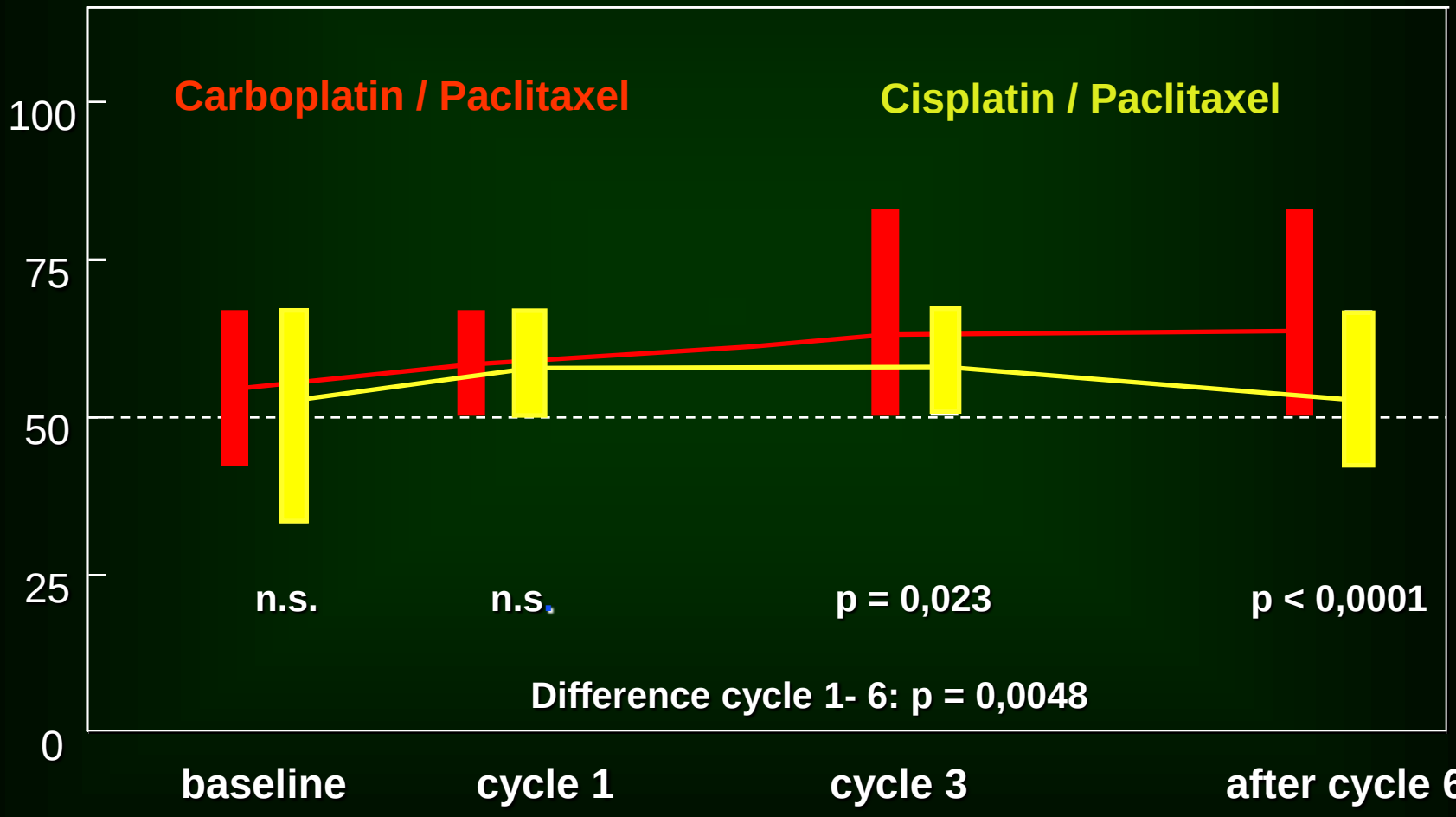
Lilly Qualiy of Life Preis 2006

ÜBERLEBEN AGO-OVAR 3



A du Bois et al.; J Nat Cancer Inst. 95 (2003)

Lebensqualität im Therapieverlauf



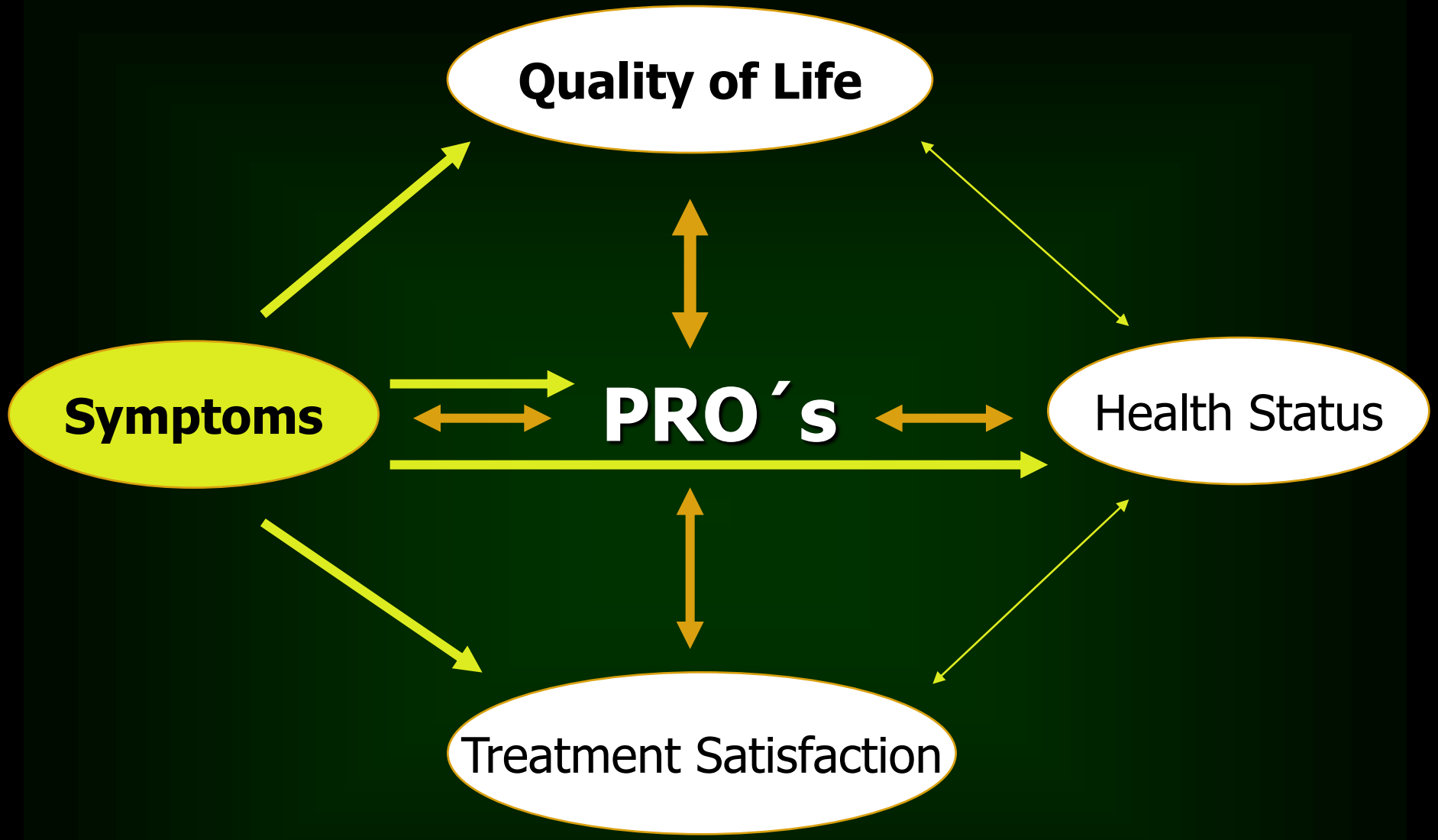
Klinische Bedeutung der AGO-OVAR 3 Studie

Carboplatin/Paclitaxel ist International anerkannter Standard für die Primärtherapie des fortgeschrittenen Ovarialkarzinoms

....basierend „**nur**" auf

- besserer Lebensqualität bei unterschiedlichem Tox-profil
- besserer Praktikabilität

War es das Tox-Profil, das den Unterschied erklärt,….oder



Warum nicht Symptome als Surrogat nehmen (NCI-CTC) ?

-> messbar, standardisiert, „objektiv“, semi-quantitativ

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Patient-Reported Outcomes and the Evolution of Adverse Event Reporting in Oncology

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From the Division of Radiation Oncology, H. Lee Moffitt Cancer Center at University of South Florida, Tampa, FL; Division of Oncology, Stanford University, Stanford, CA; Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD; and Health Outcomes Research Group, Memorial Sloan-Kettering Cancer Center, New York, NY.

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0732-183X/07/2532-5121/$20.00

DOI: 10.1200/JCO.2007.12.4784

ABSTRACT

Adverse event (AE) reporting in oncology has evolved from informal descriptions to a highly systematized process. The Common Terminology Criteria for Adverse Events (CTCAE) is the predominant system for describing the severity of AEs commonly encountered in oncology clinical trials. CTCAE clinical descriptors have been developed empirically during more than 30 years of use. The method of data collection is clinician based. Limitations of the CTC system include potential for incomplete reporting and limited guidance on data analysis and presentation methods. The Medical Dictionary for Regulatory Activities (MedDRA) is a comprehensive medical terminology system used for regulatory reporting and drug labeling. MedDRA does not provide for severity ranking of AEs. CTC-based data presentations are the primary method of AE data reporting used in scientific journals and oncology meetings. Patient-reported outcome instruments (PROs) cover the subjective domain of AEs. Exploratory work suggests PROs can be used with a high degree of patient engagement and compliance. Additional studies are needed to determine how PROs can be used to complement current AE reporting systems. Potential models for integrating PROs into AE reporting are described in this review. AE reporting methods will continue to evolve in response to changing therapies and growing interest in measuring the impact of cancer treatment on health status. Although integration of PROs into AE reporting may ultimately improve the comprehensiveness and quality of collected data, it may also increase the administrative burden and cost of conducting trials. Therefore, care must be used when developing health outcomes and safety data collection plans.

J Clin Oncol 25:5121-5127. © 2007 by American Society of Clinical Oncology

INTRODUCTION

severity ranking was rare.[1] The routine pursuit of clinical trials in the 1980s provided the opportunity

Patient reported outcomes – Clinican reported outcomes

PRO´s

CRO´s

Objektive und subjektive Daten

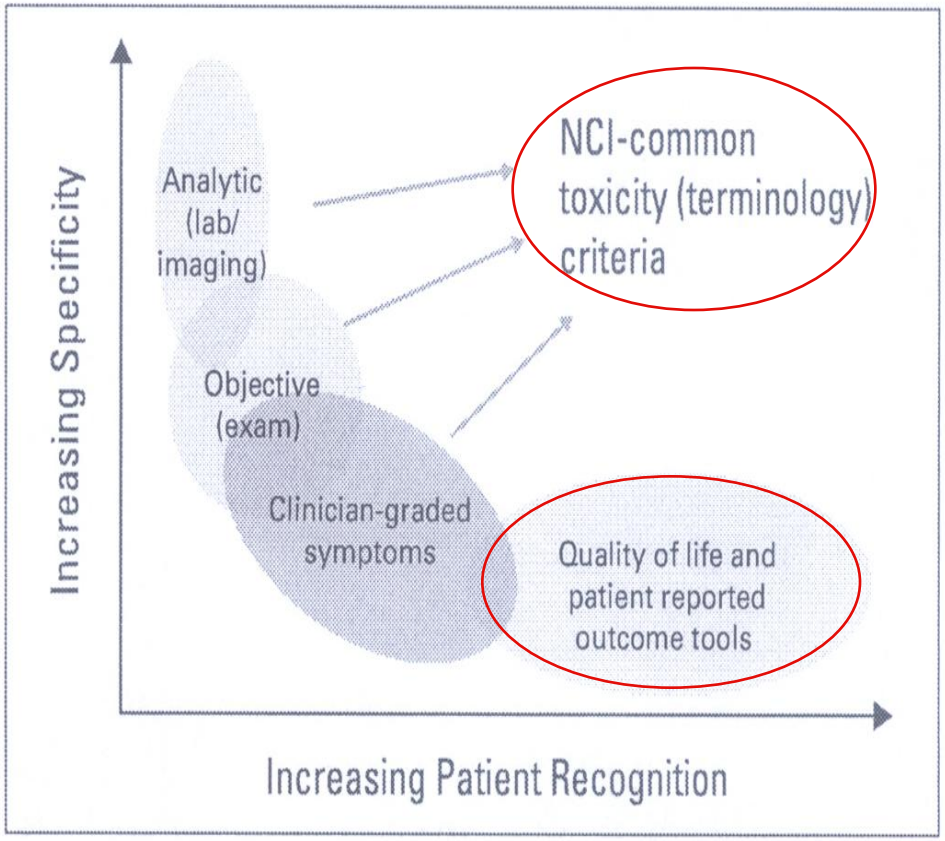

Fig 1. Adverse effects domains. NCI, National Cancer Institute. Adapted with permission.[8]

Erfassung und Dokumentation der Daten

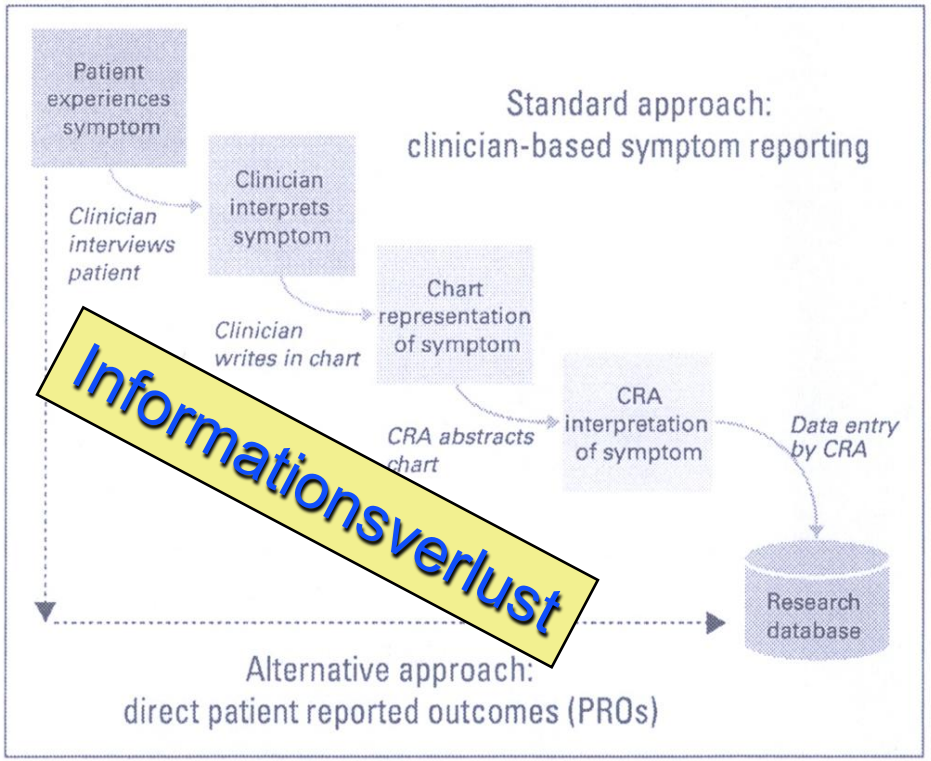

Fig 2. Flow of symptom information in cancer treatment trials. CRA, clinical research assistant. Reprinted with permission.[36]

Trotti et al: J Clin Oncol 2007

Patient versus clinician symptom reporting using the National Cancer Institute Common Terminology Criteria for Adverse Events: results of a questionnaire-based study

Ethan Basch, Alexia Iasonos, Tiffani McDonough, Allison Barz, Ann Culkin, Mark G Kris, Howard I Scher, Deborah Schrag

Summary

Background The Common Terminology Criteria for Adverse Events (CTCAE) are used as standard practice in trials of cancer treatments by clinicians to elicit and report toxic effects. Alternatively, patients could report this information directly as patient-reported outcomes, but the accuracy of these reports compared with clinician reports remains unclear. We aimed to compare the reporting of symptom severity reported by patients and clinicians.

Methods Between March and May, 2005, a questionnaire with 11 common CTCAE symptoms was given to consecutive outpatients and their clinicians (physicians and nurses) in lung and genitourinary cancer clinics in the Memorial Sloan-Kettering Cancer Center, New York, NY, USA. Patients completed a version that used language adapted from the CTCAE for patient self-reporting. The results from the questionnaire were compared with clinician reporting of the same symptoms.

Findings Of 435 patients and their clinicians asked to take part in the study, 400 paired surveys were completed. For most symptoms, agreement between patient and clinician was high, and most discrepancies were within a grade difference of one point. Agreement was higher for symptoms that could be observable directly, such as vomiting and diarrhoea, than for more subjective symptoms, such as fatigue and dyspnoea. Differences in symptom reporting rarely would have changed treatment decisions or dosing, and patients assigned greater severity to symptoms more than did clinicians. No significant differences were recorded between the results when the questionnaire was completed by the patient before or after the clinician.

Interpretation Patient reporting of symptoms could add to the current approach to symptom monitoring in cancer treatment trials. Future research should assess the effect of self reporting on clinical outcomes and efficiency, and the use of real-time collection of patient-reported outcomes for early detection of potentially serious adverse events.

Lancet Oncol 2006; 7: 903–09
Published Online October 18, 2006
DOI:10.1016/S1470-2045(06)70910-X

See Reflection and Reaction page 883

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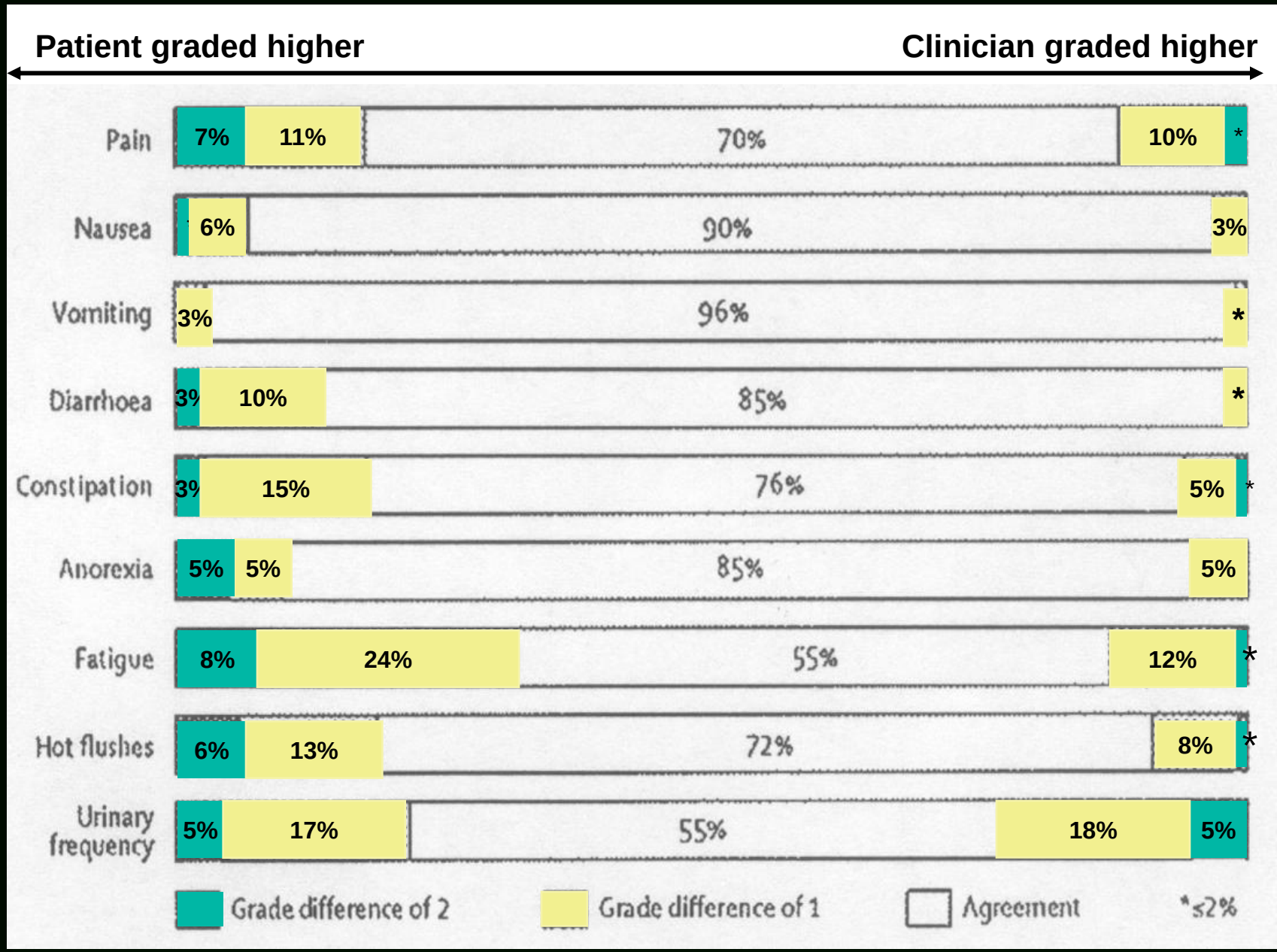
Lancet Oncol 2006;7:903-909



Basch et al: Lancet Oncol 2006;7:903-909

Fragestellung QoL Projekt AGO-OVAR 3-7

1. Wie beurteilen Experten und Expertinnen die Auswirkung der Toxizität auf die LQ?

2. Inwieweit stimmen die Tox. Beurteilungen mit der LQ der Patientinnen überein?

3. Inwieweit zeigen sich adverse events in den LQ-Beurteilungen der Patientinnen?

Expertenbeurteilungen (N=18)

Qualitative Zuordnung der Tox. Parameter unabhängig vom Schweregrad zu den LQ Fragen

Bitte beurteilen Sie, welche Tox. Parameter sich auf welche Bereiche der LQ auswirken

0=mit hoher Wahrscheinlichkeit keine Auswirkung auf LQ
1=wahrscheinlich nur geringe Auswirkung auf LQ
2=wahrscheinlich mäßige/mittelgradige Auswirkung auf LQ
3=mit hoher Wahrscheinlichkeit maßgebliche Auswirkung auf LQ

Beispiel: Experte XY

EORTC QLQ-C30	Hemoglobin	Leukocytes	Neutrophils	Platelets	Creatinine	Audioty/Hearing	Allergic Reaction	Alopecia	Cardiovascualr Arrhythmia	Edema	Cardiovascular General	Nausea	Emesis/Vomiting	Diarrhea	Constipation	Mucositis	Febrile Neuropenia	Infections	Neupathy cranial	Neuropathy sensory	Myalgia	Pain	Dyspnea
1. Bereitet es Ihnen Schwierigkeiten sich körperlich anzustrengen?	3	0	0	0	1	0	3	0	3	3	3	3	3	3	3	3	3	3	2	3	3	3	3
2. Bereitet es Ihnen Schwierigkeiten, einen längeren Spaziergang zu machen?	3	0	0	0	0	0	1	0	3	3	3	3	3	3	2	2	2	2	2	3	3	3	3
3. Bereitet es Ihnen Schwierigkeiten, eine kurze Strecke ausser Haus zu gehen?	3	0	0	0	0	0	1	0	3	3	3	3	3	3	2	2	3	3	2	3	3	3	3
4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	0	0	0	0	0	2	0	3	3	3	3	3	3	2	3	3	3	2	3	3	3	3
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	0	0	0	0	0	2	0	2	2	2	1	1	2	2	2	2	2	1	3	3	3	3
6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	2	1	1	0	0	3	2	1	3	3	3	3	3	3	2	3	3	3	2	2	3	3	3
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	2	0	0	0	0	3	2	2	3	3	3	3	3	3	2	3	3	3	2	3	3	3	3
8. Waren Sie kurzatmig?	2	0	0	0	0	0	3	0	3	3	3	2	1	2	1	2	2	2	1	1	1	3	3
9. Hatten Sie Schmerzen?	0	0	0	0	0	0	2	0	0	1	1	3	2	2	1	3	2	2	2	3	3	3	2
10. Mussten Sie sich ausruhen?	3	0	0	0	1	0	2	0	3	3	3	3	3	3	2	3	2	2	2	3	3	3	3
11. Hatten Sie Schlafstörungen?	0	0	0	0	0	0	0	1	3	3	3	3	3	3	2	3	2	2	2	2	2	3	3
12. Fühlten Sie sich schwach?	2	0	0	0	0	0	1	0	3	3	3	3	3	3	2	3	3	3	2	2	3	3	3
13. Hatten Sie Appetitmangel?	1	0	0	0	0	0	0	0	2	1	1	3	3	3	2	3	3	3	1	0	1	2	2
14. War Ihnen übel?	0	0	0	0	0	0	0	0	0	0	0	3	3	3	2	2	2	2	1	0	0	2	1
15. Haben Sie erbrochen?	0	0	0	0	0	0	0	0	0	0	0	2	3	3	2	1	1	1	0	0	0	1	1

Übereinstimmung der Experten/innen

	Total ICC
Hemoglobin	**0.95**
Leukocytes	**0.82**
Neutrophils	**0.83**
Platelets	**0.75**
Creatinine	0.57
Audioty/Hearing	**0.89**
Allergic Reaction	0.64
Alopecia	**0.95**
Cardiovascular Arrhythmia	**0.86**
Edema	**0.86**
Cardiovascular General	**0.88**
Nausea	**0.89**
Emesis/Vomiting	**0.91**
Diarrhea	**0.83**
Constipation	**0.79**
Mucositis	**0.84**
Febrile Neuropenia	**0.91**
Infections	**0.87**
Neupathy cranial	**0.82**
Neuropathy sensory	**0.85**
Myalgia	**0.90**
Pain	**0.91**
Dyspnea	**0.94**

*ICC: intra class correlation coefficient (≥.70 = gute Übereinstimmung)

Erwartete Auswirkung der Tox auf LQ (Functioning Scales)

	Physical	Role	Emot	Cogn	Social	QoL
Hemoglobin	X	X				X
Leukocytes						
Neutrophils						
Platelets						
Febrile Neuropenia	X	X	X		X	X
Auditory/Hearing					X	
Allergic Reaction						
Alopecia					X	X
Cardiac Toxicity	X	X				
Edema						
Mucositis/Stomatitis					X	X
Infections	X	X			X	X
Central Neuropathy		X		X	X	X
Peripheral Neuropathy	X	X				X
Nephrotoxicity						
Pain/Myalgia/Arthralgia	X	X	X	X	X	X
Nausea	X	X			X	X
Emesis/Vomiting	X	X			X	X
Constipation						
Diarrhea	X	X			X	X
Dyspnea	X	X	X	X	X	X

X mäßige bis maßgebliche Auswirkung auf QoL (Expertenbeurteilung ≥ 2)

Analyse LQ- und Toxdaten aus klinischen Studien

Zeigen sich die von den Expertinnen und Experten erwarteten Auswirkungen der Toxizität auf die Lebensqualität im Pat. Kollektiv?

Positive predictive value: adverse event - poor QoL

Functioning Scales

	Physical	Role	Emot	Cogn	Social	Global QoL
Hemato. Tox						
Leukocytes						
Neutrophils						
Non-hemato. Tox						
Alopecia					X19%	X29%
Peripheral Neuropathy	X14%	X27%				
Pain/Myalgia/Arthralgia	X14%	X17%	X11%	X 5%	X17%	X18%
Nausea	X12%	X23%			X16%	X23%
Emesis/Vomiting	X 9%	X15%			X 9%	X17%
Constipation						
Dyspnea	X 9%	X20%	X11%	X11%	X12%	X15%

Zusammenfassung

- Bei geringeren Tox. Graden gute Übereinstimmung mit LQ
- Bei höheren Tox. Graden geringe Übereinstimmung mit LQ
- Tox und LQ Beurteilungen basieren auf unterschiedlichen Klassifikationssystemen
- Für die Bewertung von onkologischen Therapien sind **beide** Systeme von Bedeutung

Integratives Outcome-Konstrukt zur Bewertung therapeutischer Verfahren: 3 obligate Elemente (4 Dimensionen zu erfassen)

Efficacy
+
Toxicity

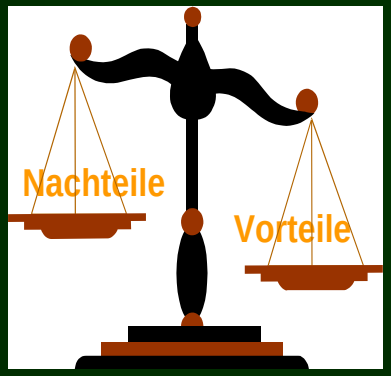
PRO's
+
QoL

Troidl H, Wechsler AS, McKneally MF. How to choose a relevant endpoint.
In: Troidl H, McKneally MF, Mulder DS, Wechsler AS, McPeek B, Spitzer WO, editors.
Surgical research. Basic principles and clinical practice. New York: Springer; 1998. p. 303-19.

Bedeutung von PRO's und QoL Daten

Therapieentscheidungen

- Entscheidungshilfe bei vergleichbaren Therapien
- Entscheidungshilfe bei der Abwägung zwischen Effektivitäts-gewinn und Belastung (z.B. für trade-off Modelle u.a.)



Klinische Bewertung von Therapien

- Erfassung von Effektivität, Nebenwirkungen, aber auch Lebensqualität und PRO's

… und wer bezahlt die Evaluation von PRO's und QoL ?