Prognostic studies and the need for guidance

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Outline

1) Biomarker

2) Issues related to biomarker (prognostic) studies

3) Observations from tumor marker prognostic studies

Biomarker

Definition: Biomarkers Definitions Working Group (2001)

[PMID: 11240971]

„A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.“

- Advances in molecular biology and laboratory techniques allowing (large-scale) evaluation of different features in humans
- **Perception:** high relevance for (future) clinical practice in which medical decisions are tailored to individuals
- **Areas of application:**
  screening / differential diagnostics / treatment choice / monitoring / **prognostics** / …

Prognostic biomarker

- Predicting progress of disease

- **Phases in development:** **‚from bench to bedside‘**

  (a) discovery (→ *TG9*)

  ➡ (b) assay development

  ➡ (c) (retrospective) validation

  ➡ (d) prospective assessment (→ *TG6*)

  ➡ (e) clinical implementation

- **Issue:** limited informative value of a single study
  - accumulation of evidence, a prerequisite
  - systematic reviews / meta-analysis

Prognostic biomarker

- **Issue:** only very few biomarkers reach clinical implementation

Malats *et al* (2005) [PMID: 16129368]

- **Background:** p53 (IHC) and bladder cancer
- **Aim:** comprehensive review for use of p53
- **Methods:** systematic review / meta-analysis
- **Conclusions:** evidence not sufficient for any conclusion

> "That a decade of research on P53 and bladder cancer has not placed us in a better position to draw conclusions relevant to the clinical management of patients is **frustrating**."

Prognostic biomarker - Example

Huber *et al* (2014) [PMID: 25422912]

- **Background:** many prognostic biomarkers (IHC) for prostate cancer proposed w/o implemention
- **Aim:** verification of 28 IHC biomarkers
- **Design:** prostate cancer cohort ($N_{patients}$=238, N_{events}=?)
  median follow up 60 months
  outcome: PSA relapse-free survival
- **Results/Conclusion:**

  significant associations seen for 4/28 biomarkers (14%)

  ➡ Many IHC-based studies too over-optimistic

Issues of prognostic biomarker research

- ***‚Hot topic'*** – but not restricted to prognostic biomarker research

  McShane (2005): „What are we missing?“
  [PMID: 16030294]
  Kyzas (2007): „Almost all articles on cancer prognostic markers
  [PMID: 17981458] report statistically significant results“

- **Issues:**
  - Lack in agreed research goal, limited research funding
  - Poor study design
  - Incorrect methods, **NOT** restricted to statistical analysis
  - Faulty interpretation/presentation of results
  - Selective or incomplete reporting (incl. non-publication)

Way out for prognostic biomarker research

Examples:

- Hayes *et al* (1996): tumor marker utility grading system
  [PMID: 8841020]
- McShane *et al* (2005): reporting guideline REMARK
  [PMID: 16106245]
- Riley *et al* (2009): discussion of methodological issues
  [PMID: 19367280]
- Hemingway *et al* (2010): ten steps for improvement
  [PMID: 20042483]
- Andre *et al* (2011): call for biomarker study registry
  [PMID: 21364690]
- **…**

Way out for prognostic biomarker research

- **PROGRESS PARTNERSHIP**
  MRC PROGnosis RESearch Strategy Partnership

  http://progress-partnership.org/

Is that enough?

Observations from tumor marker prognostic studies

- **Situation:**
  - Tumor patients are often closely monitored
  - Routine collection of specimen, clinical data, outcome data
- **Consequence:**
  - Readiness of specimen/data for any retrospective evaluation
- **Temptation:**
  - Design and conduct in a ‚quick and dirty‘ fashion

Observations from tumor marker prognostic studies

Sekula *et al* (2017) [PMID: 28614415]

Evaluation of 106 published studies (2007-2012)

- **Main aim:** to assess whether reporting quality improved

  ➡ **Conclusion:** still poorly reported

- Limited possibility to assess of methodological issues
- Transparent reporting essential

Observations from tumor marker prognostic studies

Study design:

	N (%)
Prospective assessment	17 (16%)
Retrospective assessment based on …	
- prospectively conducted studies (incl. RCT)	33 (31%)
- archived specimen/data (incl. case registry)	56 (53%)

Issue: selection bias – representativeness of sample

- Necessary assumption of representativeness and completeness of collected samples/data
- Even if correct, what about depletion of samples?

Observations from tumor marker prognostic studies

Issue: selection bias – completeness of data

- In presence of missing values, complete case analysis (?)
- Several reports, presentation of data suggests completeness

Example:

„Tumor samples were collected between November 1999 and August 2005,…"

- Retrospective assessment based on archived specimen
- No hint of incomplete data

Table 1 Clinicopathological characteristics of all patients *extract only*

Factors	COX-2		
	Negative $n = 368$	Positive $n = 493$	P
Age at diagnosis (years)			
≤35	35 (9.5)	23 (4.7)	0.005
>35	333 (90.5)	470 (95.3)	
Tumor stage			
T1	143 (38.9)	252 (51.1)	0.002
T2	216 (58.7)	233 (47.3)	
T3–4	9 (2.4)	8 (1.6)	
Node stage			
N0			603
N1			
N2			
N3	24 (6.5)	36 (7.3)	
Histologic grade			
I	41 (11.1)	122 (24.7)	<0.001
II	176 (47.8)	288 (58.4)	
III	151 (41.0)	83 (16.8)	
Estrogen receptor			
Mean ± SD (%)	37.9 ± 39.8	66.8 ± 31.0	<0.001[a]
Negative	171 (46.5)	59 (12.0)	<0.001
Positive	197 (53.5)	434 (88.0)	

Is incompleteness an exclusion criterion?

Observations from tumor marker prognostic studies

Issue: study power – sample size calculation

- Often critizised to be too small
- Studies rarely reported on any power calculation (<5%)
- # Analysed subjects: range 24 - ~4000 (<100: 19%)
- Presumably, study size depended on …
  - Availability of specimens and/or completeness of data
  - Resources (man power and/or funding)
  - Stage of biomarker development / research question
  - …

In summary

Regarding prognostic tumor marker studies:

- Research quality is heavily critizised by many researchers (methodologists) since several years
- First publications providing some guidance available
- Still, not (much) improvement visible

Regarding medical research in general:

- Many (all?) of presented issues exist in other areas as well
- Additional efforts are required

➡ STRATOS INITIATIVE