Experience in using Real World Data in metastatic colorectal cancer (mCRC)

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Disclaimers 2013-2016

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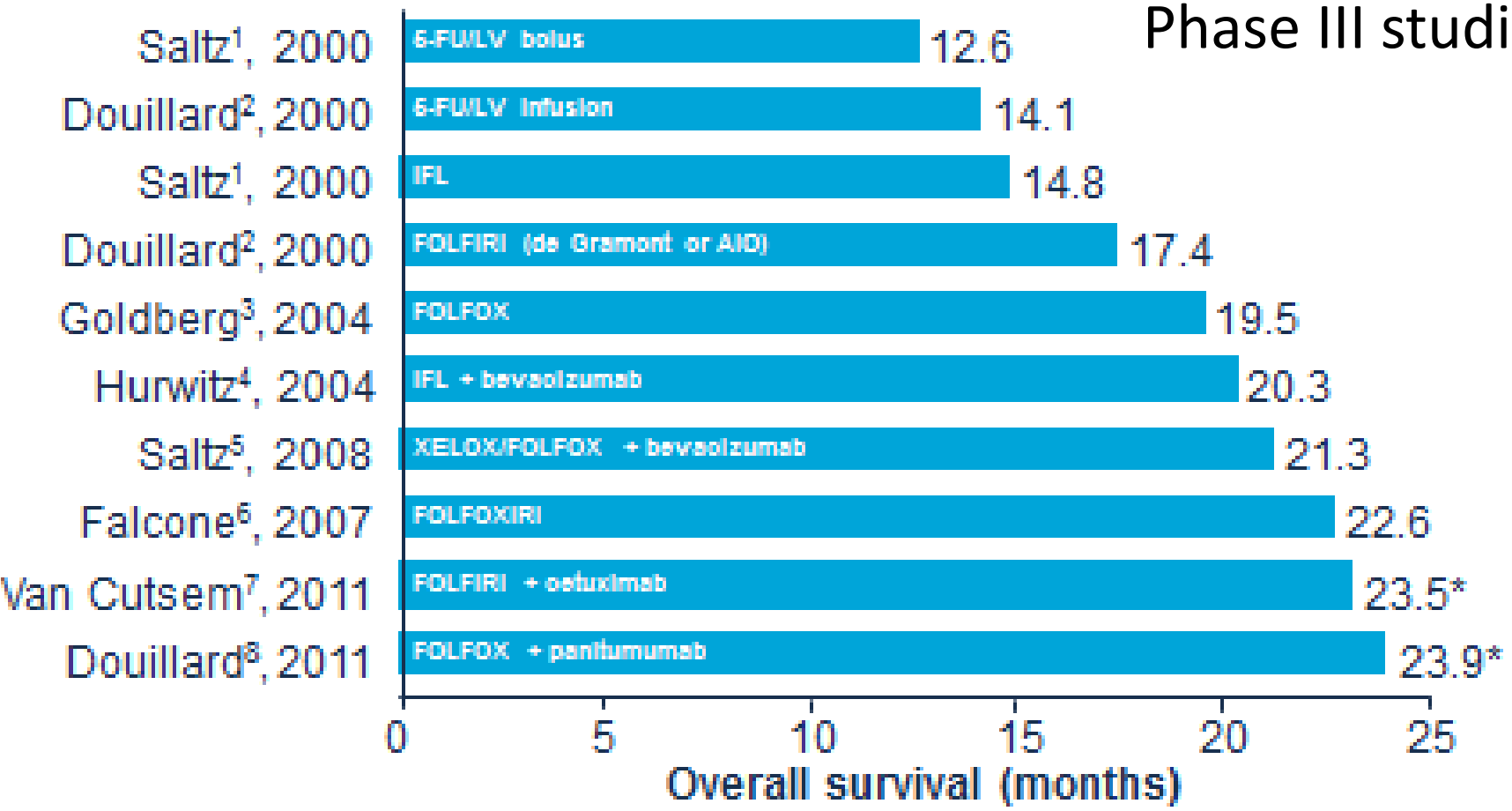
Overall survival from mCRC has improved incrementally over the past decade



CALGB/SWOG 80405

FOLFOX/FOLFIRI + cetuximab or bevacizumab: 30 months

How representative are phase III studies?

- Only 2-4% of adult cancer patients included into trials.
- Generalizability is reduced if a large number of patients seen in daily practice are ineligible, or if many eligible patients do not enter the study.

- A critical issue is whether patients enrolled in studies are representative for the general cancer population.

How representative are phase III studies?

- Groups underrepresented in cancer trials.
  - elderly
  - patients with poor performance status
  - patients with co-morbidities
  - individuals of low socioeconomic status
  - racial and ethnic minorities

- Are phase III results of treatment transferable to cancer patients in the general population?
- Will they achieve the same benefit of the treatment?

- Study: To examine if metastatic colorectal cancer patients enrolled in trials are representative of a general cancer population concerning patient characteristics and survival.

- Prospectively collected population-based cohort of non-resectable mCRC patients from 3 Scandinavian regions (Uppsala, Bergen, Odense).
- Includes all patients in the uptake area diagnosed with unresectable mCRC 2003-2006

- 798 patients:
  - 39% PS 2-4 (31% PS 0) (trials usually <5% PS2)
  - 37% > 75 years of age
  - 57% received palliative chemotherapy
  - 25% included into studies

Sorbye et al Cancer 2009;115:4679-87.

- Trial patients in our cohort were a selected sub-population with much better prognostic factors.
- mCRC
  - younger (median age 61 vs 72)
  - better performance status (PS 0: 70% vs 30%)
  - less co-morbidity
  - better baseline prognostic factors

Real world survival ?

- Survival in a prospective unselected mCRC population
  - 21.3 months when given chemotherapy in a trial
  - 18 months with combination chemotherapy
  - 15.8 months receiving chemotherapy
  - 10.7 months considering all patients.

  short survival in patients aged >75 years of age and in patients not given chemotherapy (2.8 m)

  Rejected by JCO, editor: biased population…..

Phase III data relevant for all mCRC patients ?

Age	CT	Comb CT vs Single	BSC	mOS CT
< 65 y	86 %	92 vs. 8 %	11 %	18.0 mo
66-70 y	74 %	93 vs. 7 %	20 %	15.1 mo
71-75 y	63 %	71 vs. 29 %	32 %	18.0 mo
76-80 y	40 %	13 vs. 87 %	50 %	10.2 mo
> 80 y	13 %	0 vs. 100 %	72 %	8.7 mo

- Median survival for synchronous mCRC during 2006-2008 in cancer registry in Norway, Sweden and Denmark: 10-11 months.

- So why is the marked improvement in median survival in mCRC trials not better reflected in samples selected from the general mCRC population?

- Could the progress in mCRC trial results only be relevant for small subgroups of patients?

Better outcome for mCRC?

- Survival data from patients with synchronous mCRC were collected from cancer registries.
  - National Norwegian Cancer Registry (1980-2008)
  - Swedish (1996-2008) Uppsala/orobro
  - National Danish (2001-09)

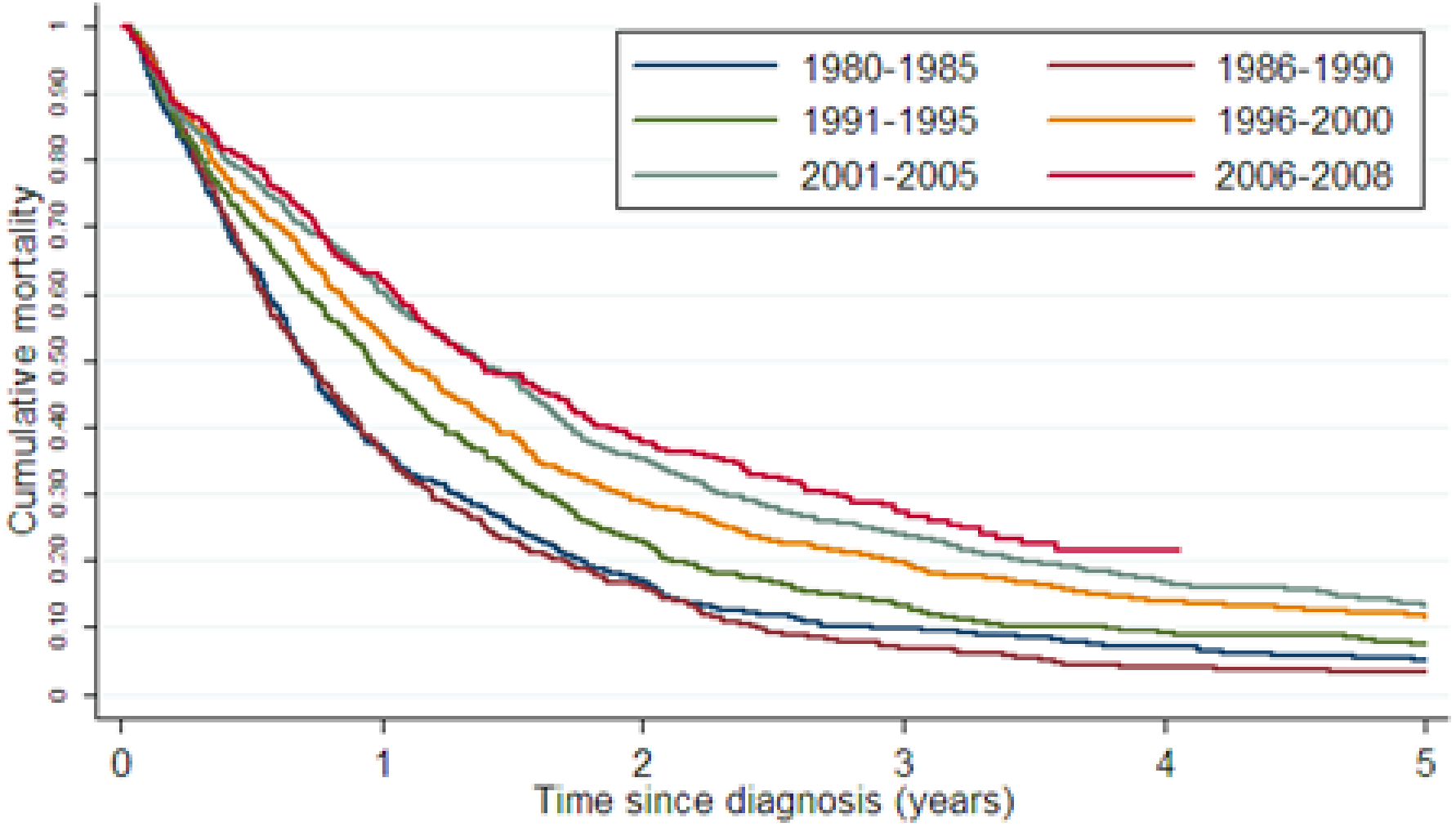
- A total of 29 628 patients were identified.

Sorbye: Ann Oncol 2013 24: 2349-2353

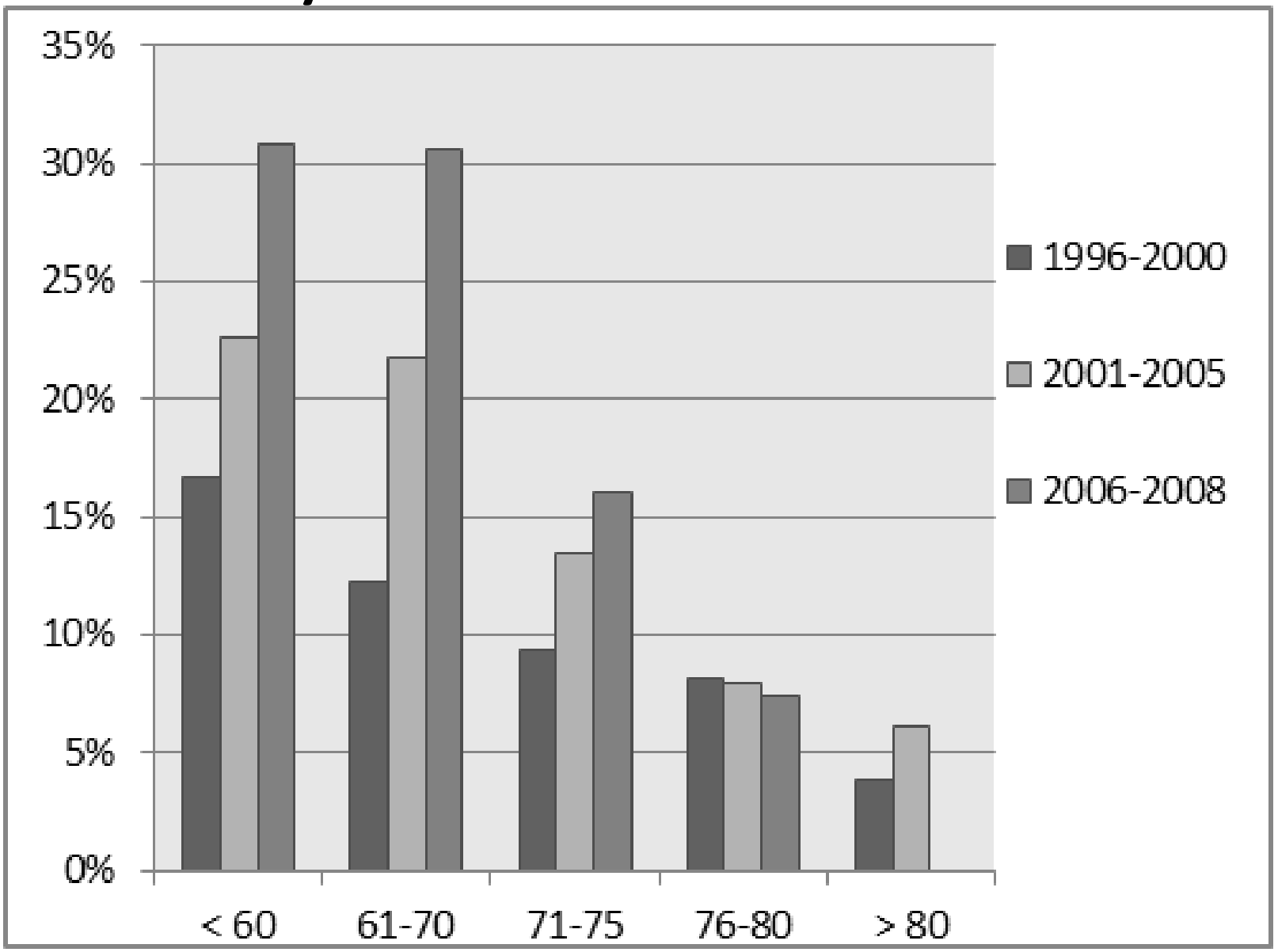
Survival synchronous CRC Norwegian Cancer Registry

	All	< 60 y	61-70 y	71-75 y	76-80 y	> 80 y
1980-1985	5 mo	8 mo	6 mo	5 mo	3 mo	2 mo
1986-1990	5 mo	8 mo	6 mo	5 mo	4 mo	3 mo
1991-1995	6 mo	11 mo	8 mo	6 mo	5 mo	3 mo
1996-2000	7 mo	12 mo	9 mo	7 mo	5 mo	3 mo
2001-2005	8 mo	16 mo	11 mo	6 mo	4 mo	3 mo
2006-2008	10 mo	16 mo	13 mo	10 mo	6 mo	3 mo

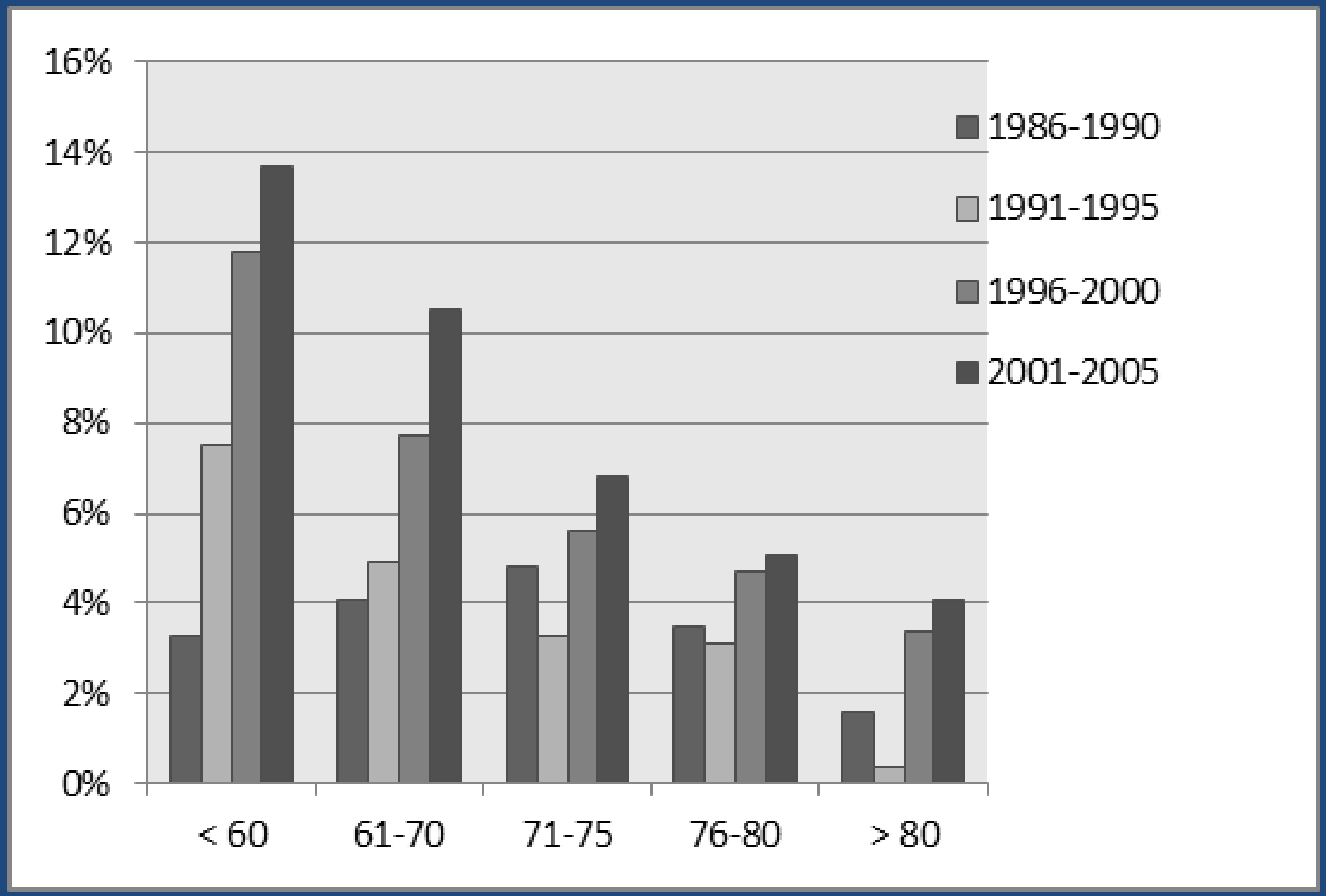
Norway age< 60



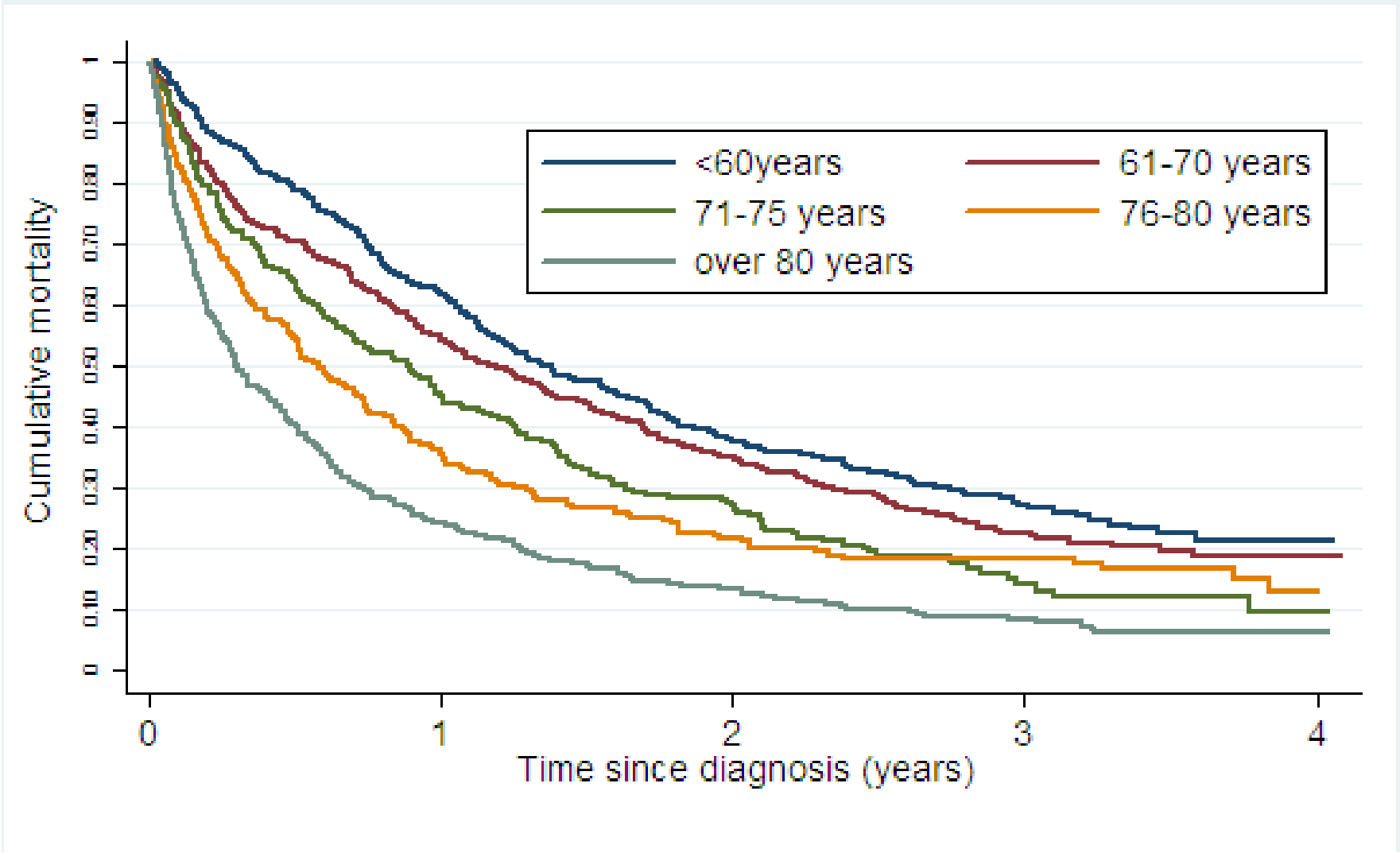
3-year survival Sweden



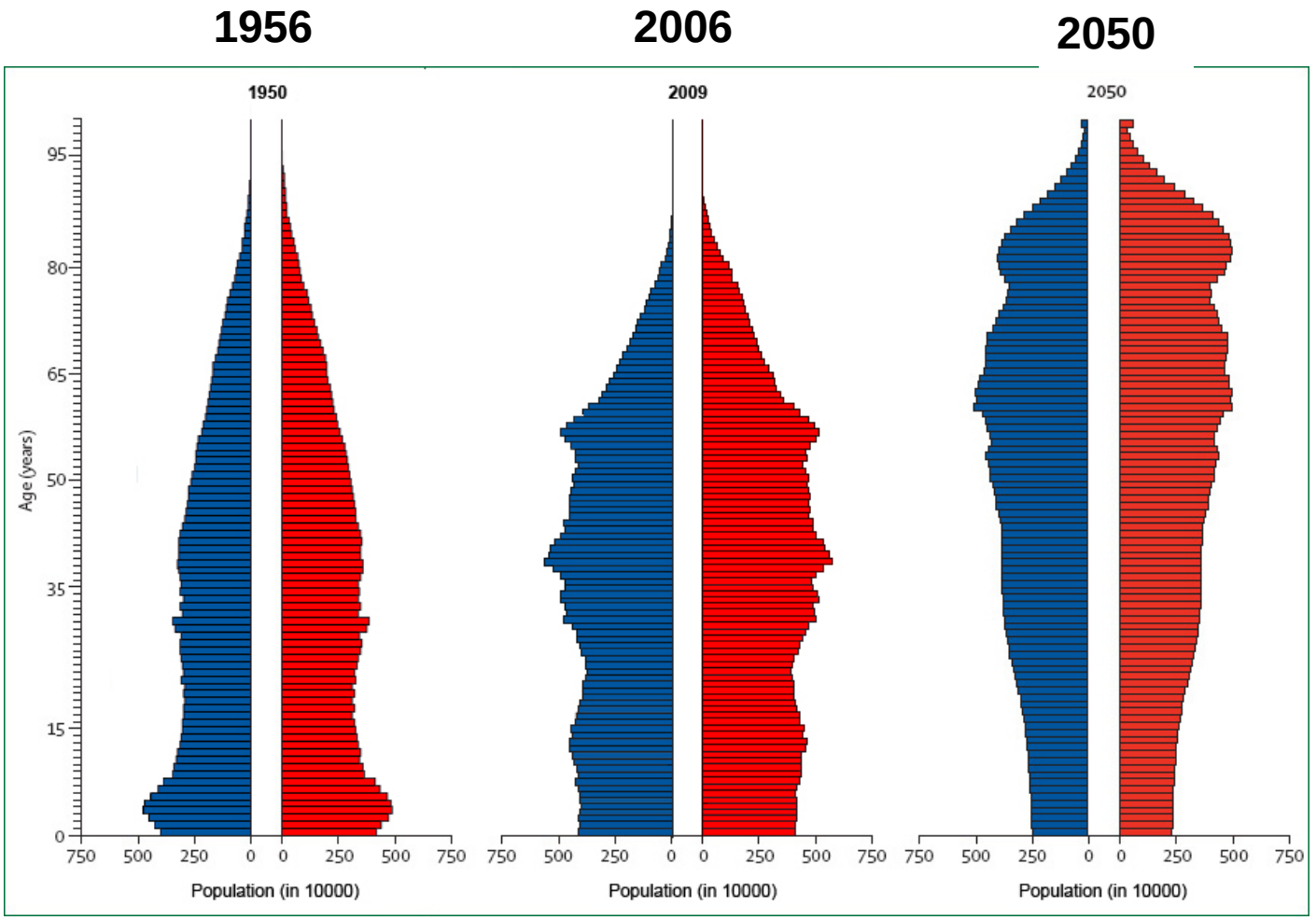
5-year survival Norway



Norway 2006-08



Future challenges



Christensen K et al. Lancet 2009

Elderly mCRC patients

- 40% of CRC patients are 75 years or older.
- Elderly patients are
  - Usually excluded from studies
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We need RWD!

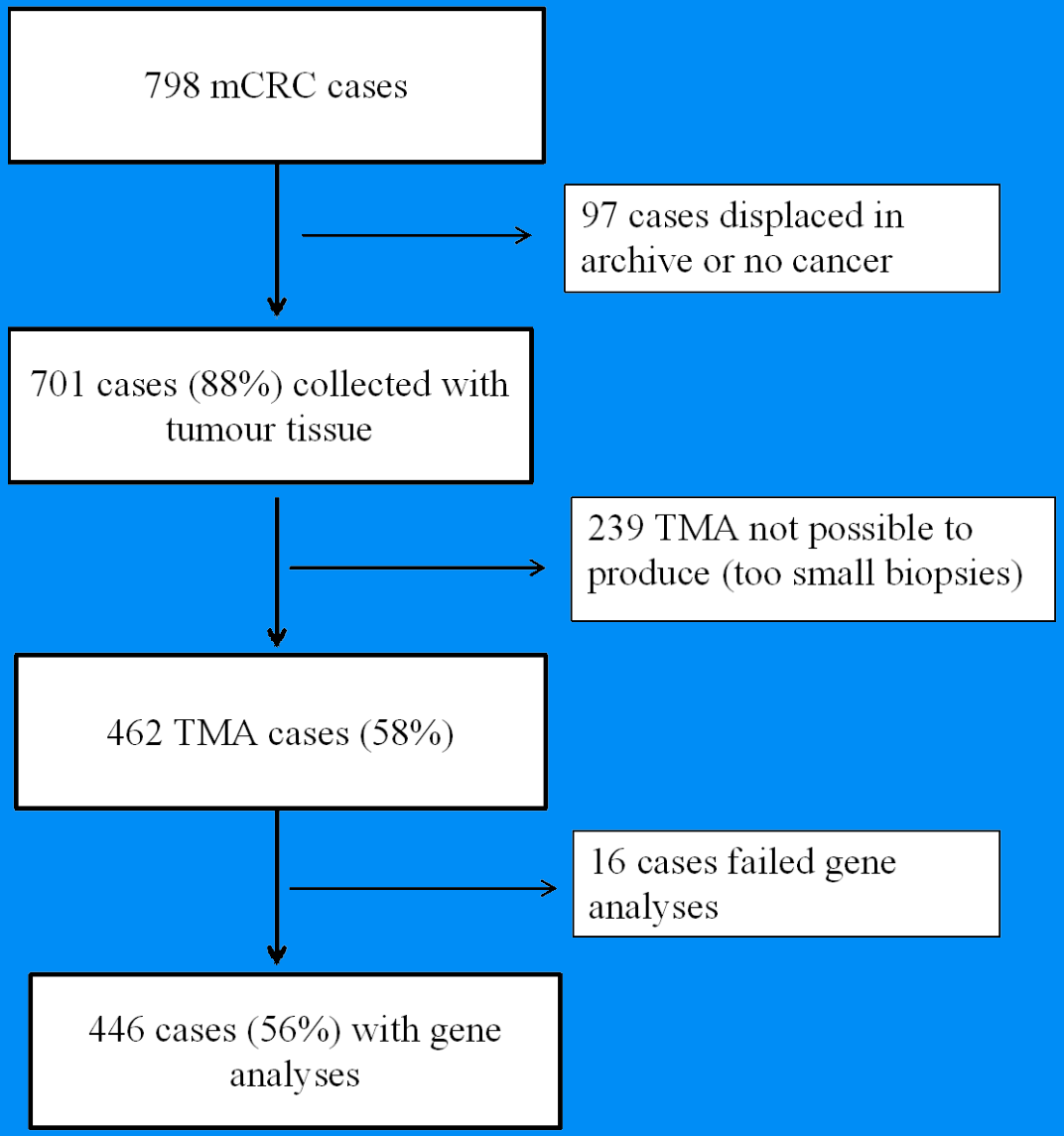
Generalizability of translational studies?

- How representative are trial patients with tumor blocks for translational studies (tissue micro array - TMA) compared to the general population with mCRC?

- Patients with tumor tissue blocks are a selected group; larger biopsies, surgical specimens etc.
  Retrieval rate 50% in patient cohorts.

- Lack of available tissue is an important underexposed issue which may introduce sample bias in translational studies. Venderbosch S et al. Clin Cancer Res 2014;20; 5322-30.

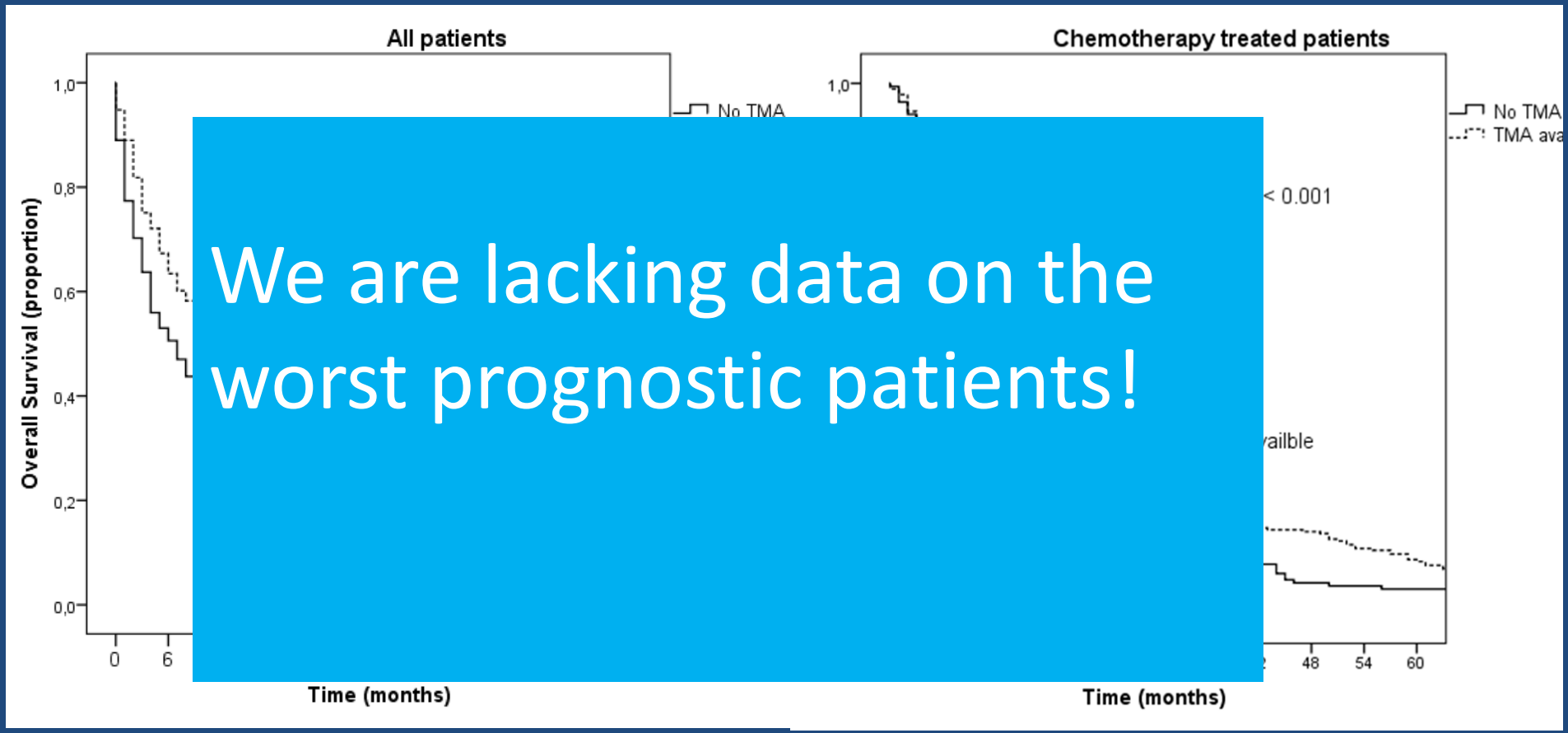
Tumor tissue collection



- Patients without available tumor tissue for analysis had worse prognostic factors and inferior treatment and survival.
  - higher age
  - worse performance status
  - more metastatic sites
  - less often received chemotherapy
  - Inferior survival

Median survival all
(7m vs 11m, p<0.001)

Median survival chemo treated
(12m vs 17m, p<0.001)



We are lacking data on the worst prognostic patients!

BRAF/RAS mutations

- Standard molecular testing on tumor tissue before start of chemotherapy in mCRC.

- RAS wildtype or RAS mutated.
- BRAF mutated: worst prognosis and short survival but fortunately not frequent in trials: 5-10%.

- Our cohort: BRAF mutation was seen in 92 (21%) of 446 patients. (most BRAF mutated never make it to a trial, often poor PS.)

- Continuous selection of BRAF mutated mCRC patients
  - 21% in general population
  - 5-10% in clinical trials
  - 0-2% in liver or lung resections

Translational trials usually select the best sub-populations and do not generate data on the worst prognostic patients !

Sorbye et al :PLoS One. 2015 Jun 29;10(6):e0131046

The Future

- Need more real world data (unselected cancer patients from the general population), especially:
  - elderly patients (37% > 75 years of age)
  - poor prognostic groups as patients with poor performance status (39% PS 2-4).
    Discover molecular explanations why they do so poorly.
  - patients where available tumor tissue is lacking (collecting blood samples for cell free tumor DNA analysis may solve this issue).