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Survival analysis and stage at diagnosis:
population based studies using Cancer Registry data

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What we do at ECRIC….

- We are part of the UKACR as one of eight regional cancer registries
- Collect and collate information from over 20 data sources – mainly electronic data feeds
- Register all cancers and selected other neoplasms diagnosed in our region
- We follow the patient from diagnosis, through the patient pathway, and for their lifetime
- Serve 5.7 million population in the East of England
- We are the national specialist registry for Brain and Central Nervous System tumours

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When I arrived at ECRIC in 2005, basically all data collection was manual – we were just starting to receive direct electronic data (Pathology reports and death notifications).

We completed the transition to fully electronic data (direct electronic data feeds or online access to hospital systems) around two years ago-

But every registration is evaluated by a human being… we need this to maintain precision, consistency and quality.

What we do at ECRIC (contd.)….

- We are the developers of the ENCORE (English National Cancer Online Registration Environment) system
  - A single secure online database used by all eight regional cancer registries
  - Patient treatment pathways can be followed throughout the country
  - Site-specific cancer registries can instantly access data on all cases in England.
  - Initial data on most cancer registrations can be collected within three months of diagnosis
- A monthly snapshot of the database is generated for information analysis

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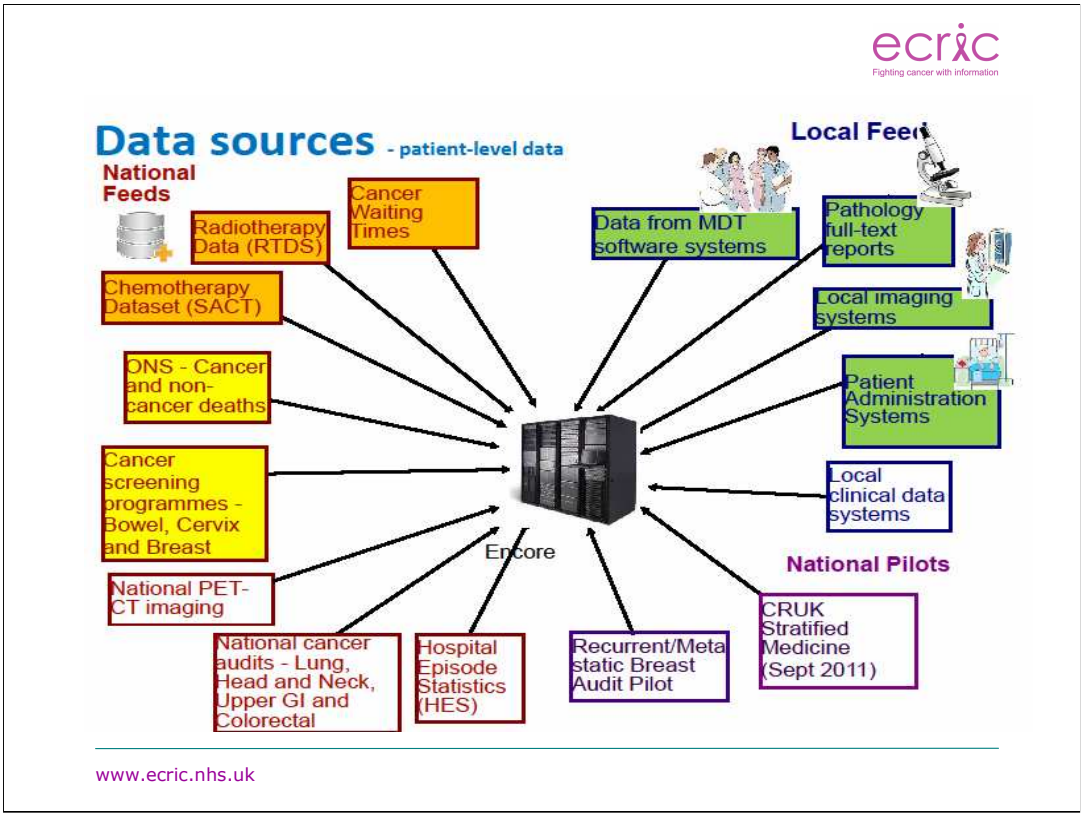
There used to be 8 independent regional registries, which is fine if you only want to do cross-sectional incidence studies

But not so good if you want to follow patients for their lifetime as they don't stay in one place and they don't always go to hospitals in their "designated" area…

So we are now moving close to having the whole of England on a single system – 4 of the 8 regional registries are already on ENCORE and two more will go on during the Spring bank holiday at the end of May.



This is a schema of the incoming data feeds

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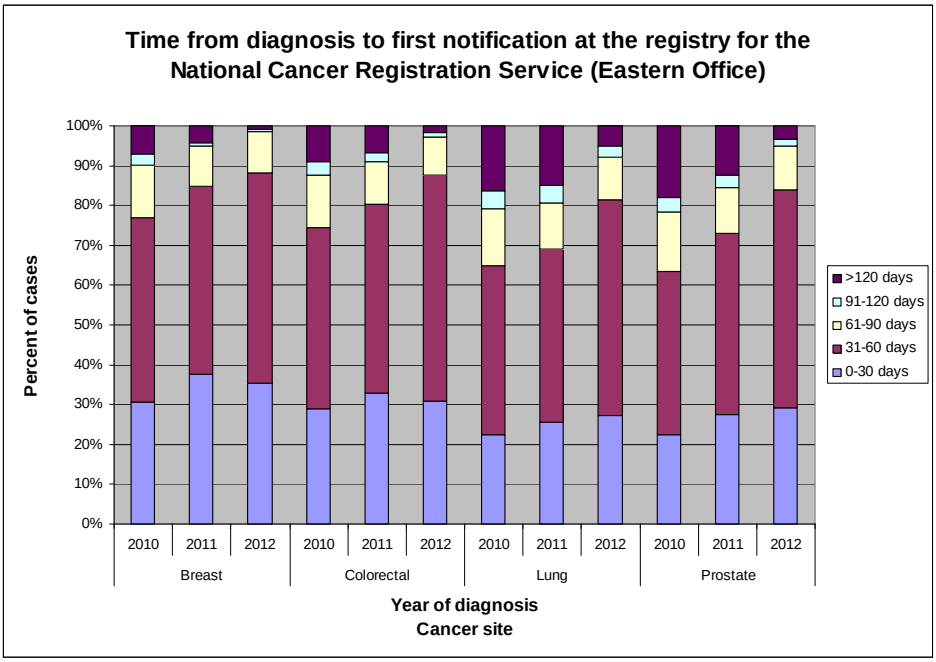

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And, as we have gone electronic we have got quicker – this is now probably as close as we can get to real-time when using monthly data feeds….

Information currently held includes…

- Patient demographics
- Neoplasm Site, Behaviour, Morphology, Grade and Stage…
  - and, increasingly, data on tumour markers, such as PSA in Prostate; ER, PgR, & HER2 status in Breast; CA125 in Ovarian…
- Treatment
- Hospitals where treated
- Causes of death (both cancer and non-cancer deaths)

Some of the data we hold ….

Examples of data use….

- Research on treatment of Mixed Mullerian uterine tumours established that use of adjuvant radiotherapy improved patient outcomes
  - Expected to save 3 lives per year in the East of England
- UK study on risk of transmission of *Glioblastoma multiforme* by organ transplant – with UK Transplant and Cambridge University Medical School
  - Found no transmission of any brain tumour in transplants from nearly 200 donors to over 400 recipients
  - Addenbrooke's now accepts organs for transplant from donors with GBM
- **PREDICT –** an online mathematical model for patients and doctors to help them decide on the ideal course of treatment following breast cancer surgery. It is the first model of this type to include tumour HER2 and KI67 status. http://www.predict.nhs.uk/predict.shtml

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These are a few examples of how we have analysed ECRIC data in collaborative projects which are leading to significant improvement in outcomes for patients.

Methods

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- Clinical outcome trials tend to use Randomised Control Trial designs, with subjects and controls matched for age and other relevant demographic characteristics; this is not possible with registry data

- Registries generally use a relative survival methodology, based on the probability of survival of a person with cancer as compared with people of the same age and sex in the reference population (generally the whole population of England)

Methods (2)

- The ideal measure of survival is net survival, i.e. the survival of cancer patients in the hypothetical situation in which cancer is the only possible cause of death.

- The method used here* to estimate net survival used here is a development of relative survival.
(**Pohar Perme et al. Biometrics 2011*)

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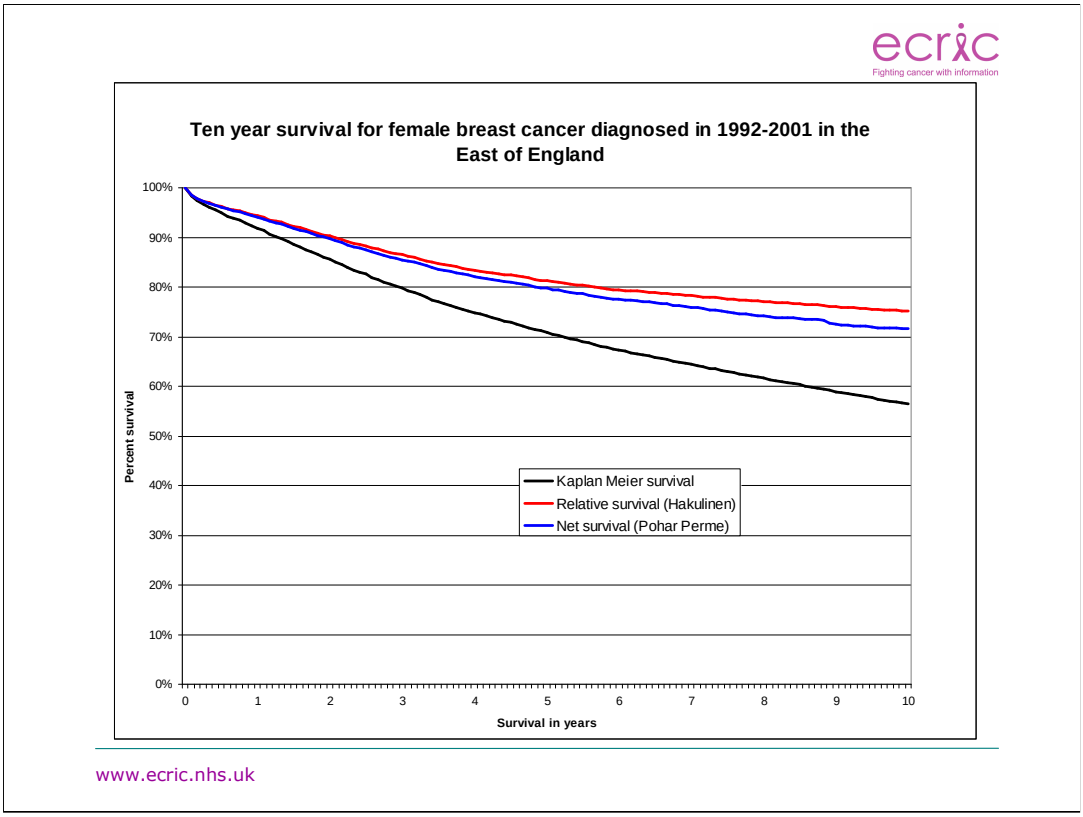
- The 'Big 4' cancers, Breast, Prostate, Colorectal and Lung make up more than half of cancers diagnosed in the UK

When registering cancers these can be grouped into over 100 sites (ie which part of the body is involved) – I will concentrate on the most frequent ones here…



As I mentioned earlier in the methods we need to try to estimate cancer survival particularly as cancer is mainly a disease of older people, who are clearly likely to die from a range of other causes. Here you can see how much the curve for crude survival diverges from those for net and relative survival. The mean age at diagnosis of breast cancers was ~63 years, so 10 years later they would have been well within 10 years of overall life expectancy…

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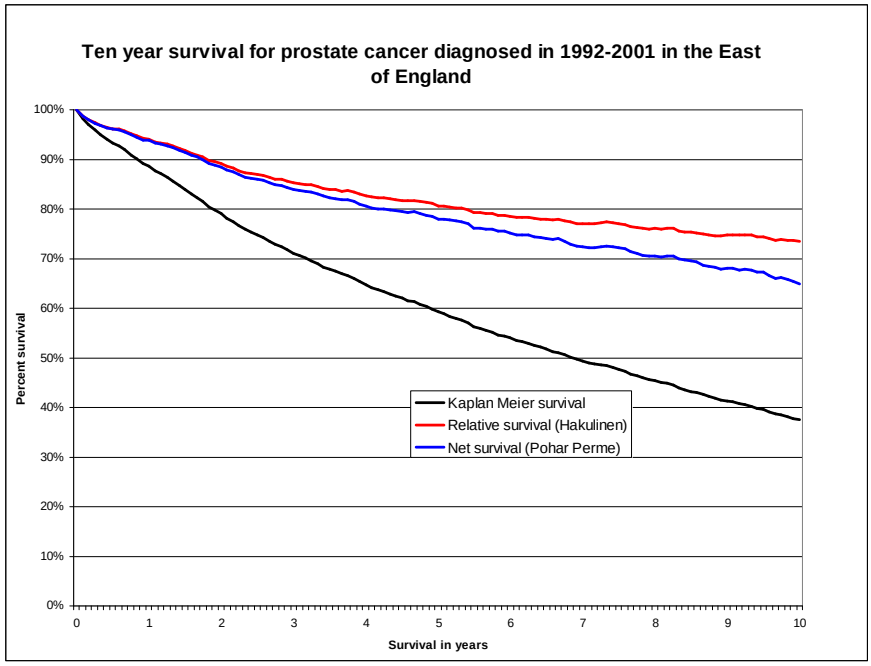

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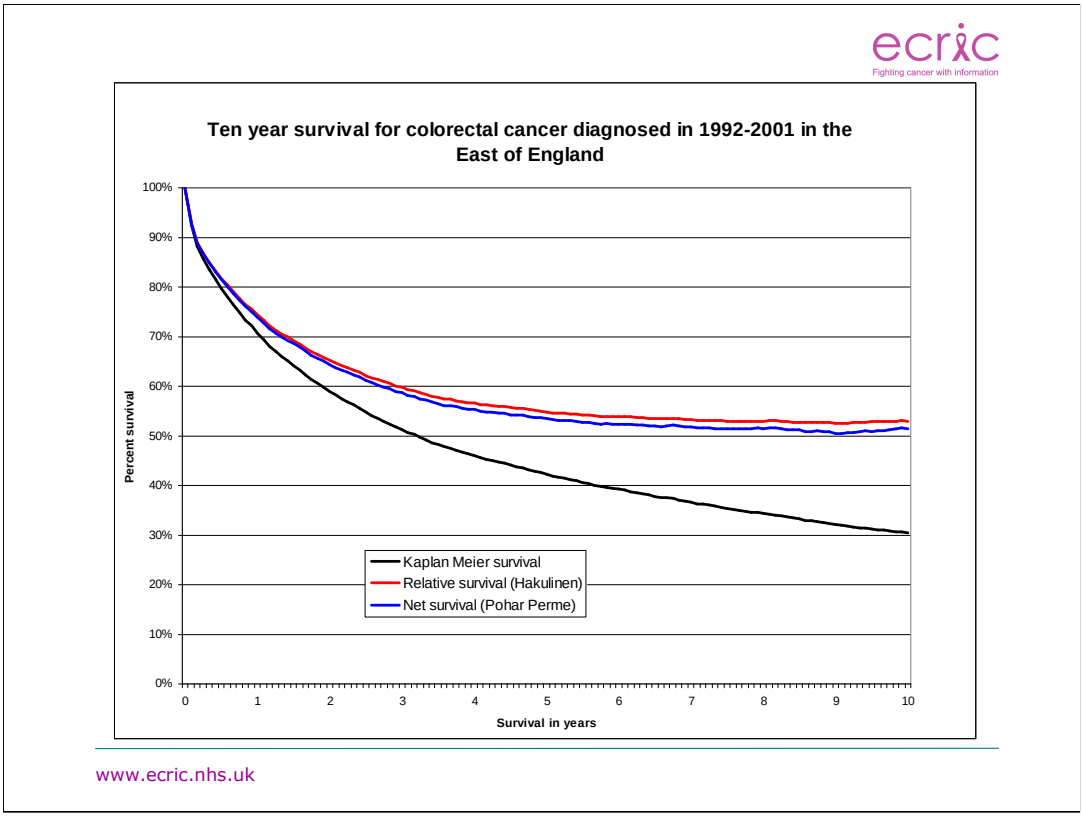
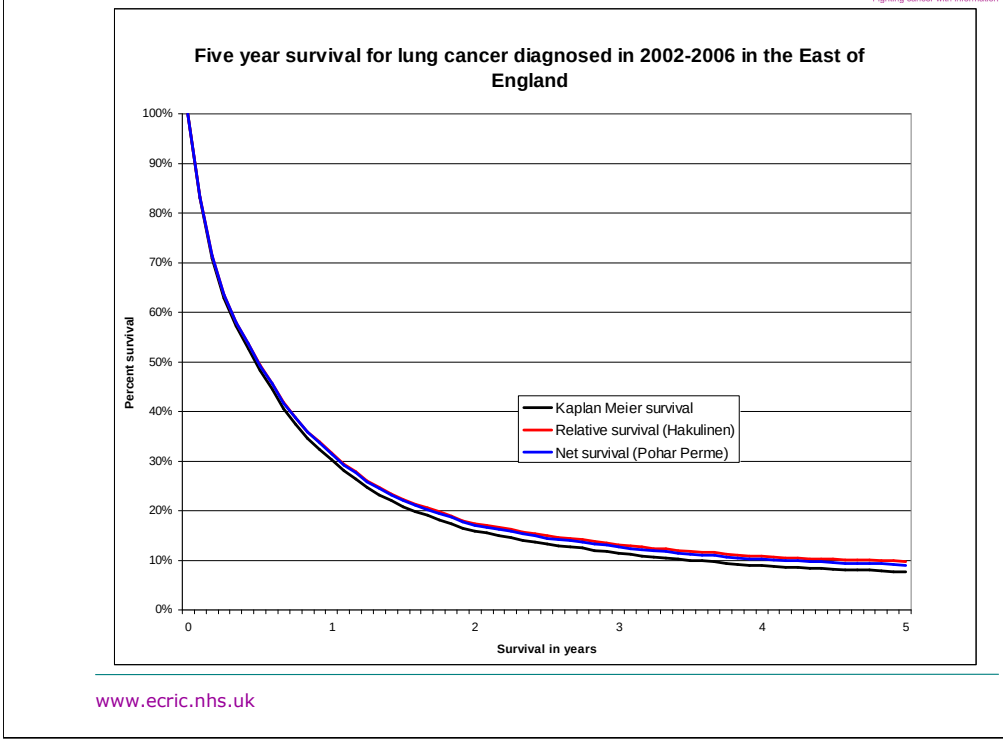
In prostate cancer where the mean age at diagnosis as ~74 years, the curves diverge even more..



With colorectal cancer, where the mean age at diagnosis was ~72 years, divergence is similar to prostate, but the curves have a different shape as patients with colorectal cancer who survive for more then ~3-5 year or so are generally cured of the disease, though overall net survival is worse than breast or prostate cancer.



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Lung cancer has a similar mean age at diagnosis (~72 years) but lung cancer survival is so poor that the graphs hardly diverge…

Survival comparisons

- Whatever method of survival analysis is used, breast and prostate are, on average, long-survival cancers, colorectal is medium-survival and lung is poor survival
  - but, even in the poorer survival cancers, some people do survive for many years

- How do we identify the potentially better survivors?

Stage at diagnosis

To make meaningful comparisons of cancer survival between demographic, diagnostic or treatment populations, cancers should be at a comparable stage.

- Most cancers can be staged by the TNM classification system, where
  - T describes the size of the tumour and whether it has invaded nearby tissue,
  - N describes regional lymph nodes that are involved,
  - M describes distant metastasis (spread of cancer from one body part to another).
- T,N and M are combined into an integrated stage from 1 (early) to 4 (late)

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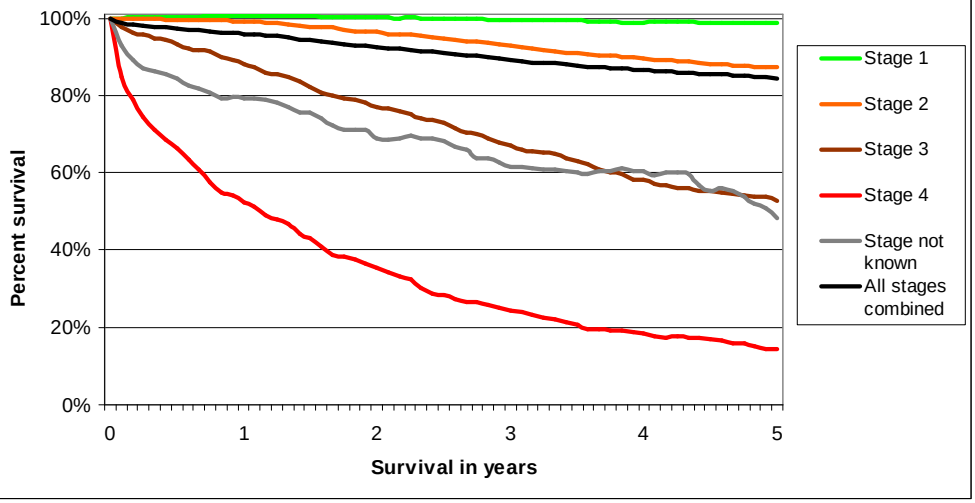
Net Survival* by TNM stage for Female Breast cancer diagnosed 2002-2006 in the Anglia Cancer Network
Pohar Perme et al. Biometrics2011



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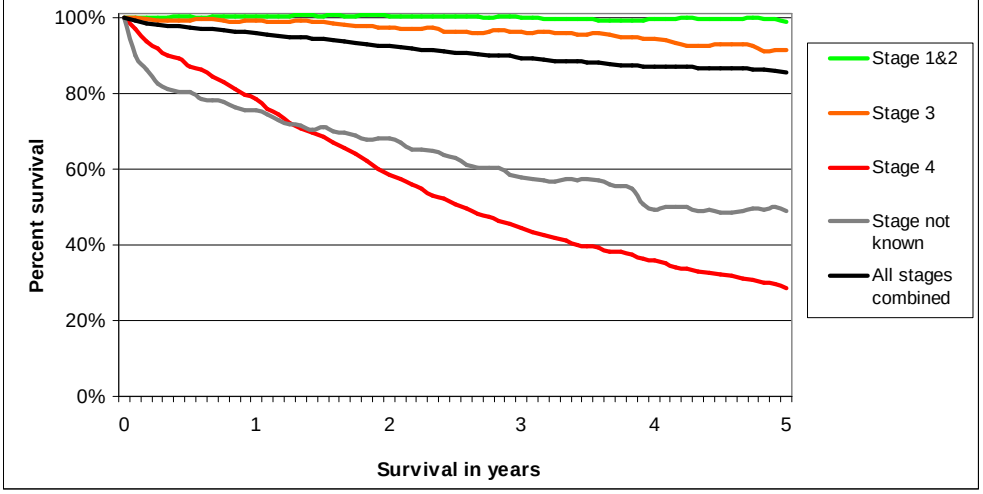
Net Survival* by TNM stage for Prostate cancer diagnosed 2002-2006 in the Anglia Cancer Network
Pohar Perme et al. Biometrics2011



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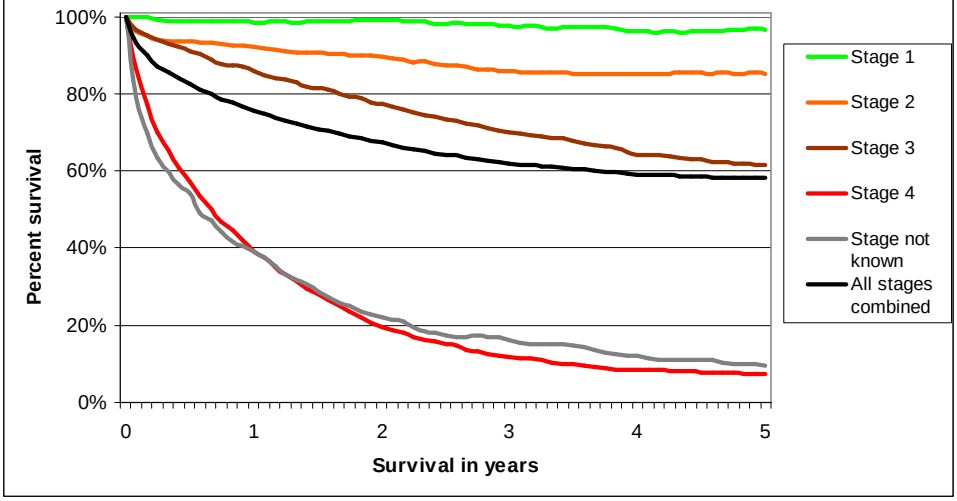
Net Survival* by TNM stage for Colorectal cancer diagnosed 2002-2006 in the Anglia Cancer Network
Pohar Perme et al. Biometrics2011



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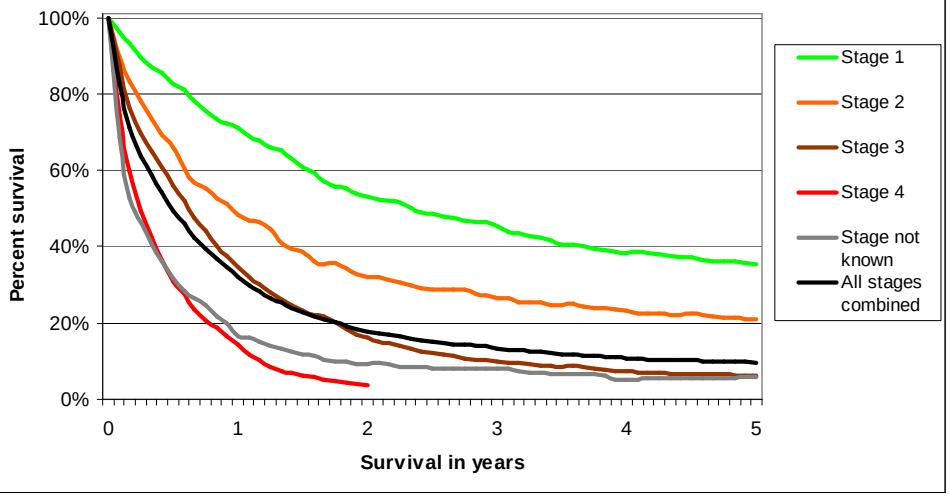
Net Survival* by TNM stage for Lung cancer diagnosed 2003-2006 in the Anglia Cancer Network
Pohar Perme et al. Biometrics2011



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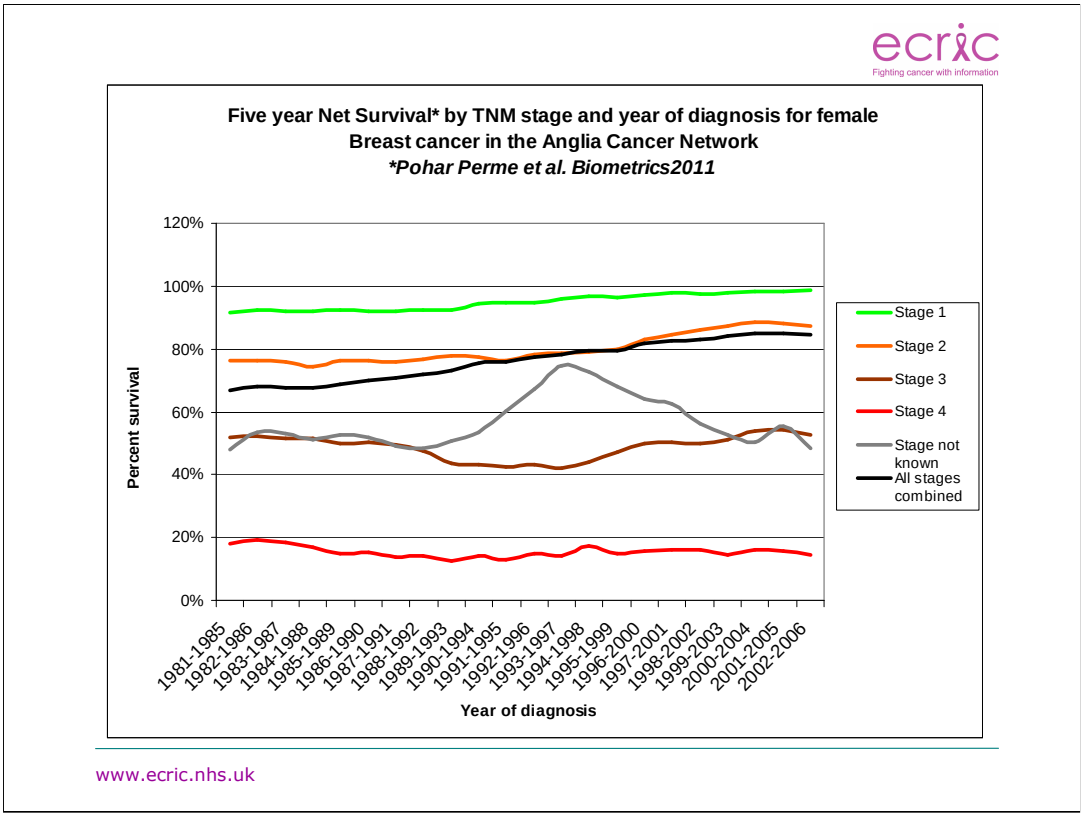
Stage at diagnosis (comments)

- "Failure to pick up cancer at an early stage costs the lives of up to 10,000 a year in England"
  http://news.bbc.co.uk/1/hi/health/8385793.stm
- "..significantly more patients could be diagnosed at an early stage, and thus have better survival, if inequalities by age, gender or deprivation were to be eliminated."
  http://www.cancerresearchuk.org/cancer-info/news/archive/cancernews/2012-11-13-Closing-inequality-gap-could-mean-earlier-diagnosis-for-thousands-of-people

Prof. Sir Mike Richards, National Cancer Director 2009/2012

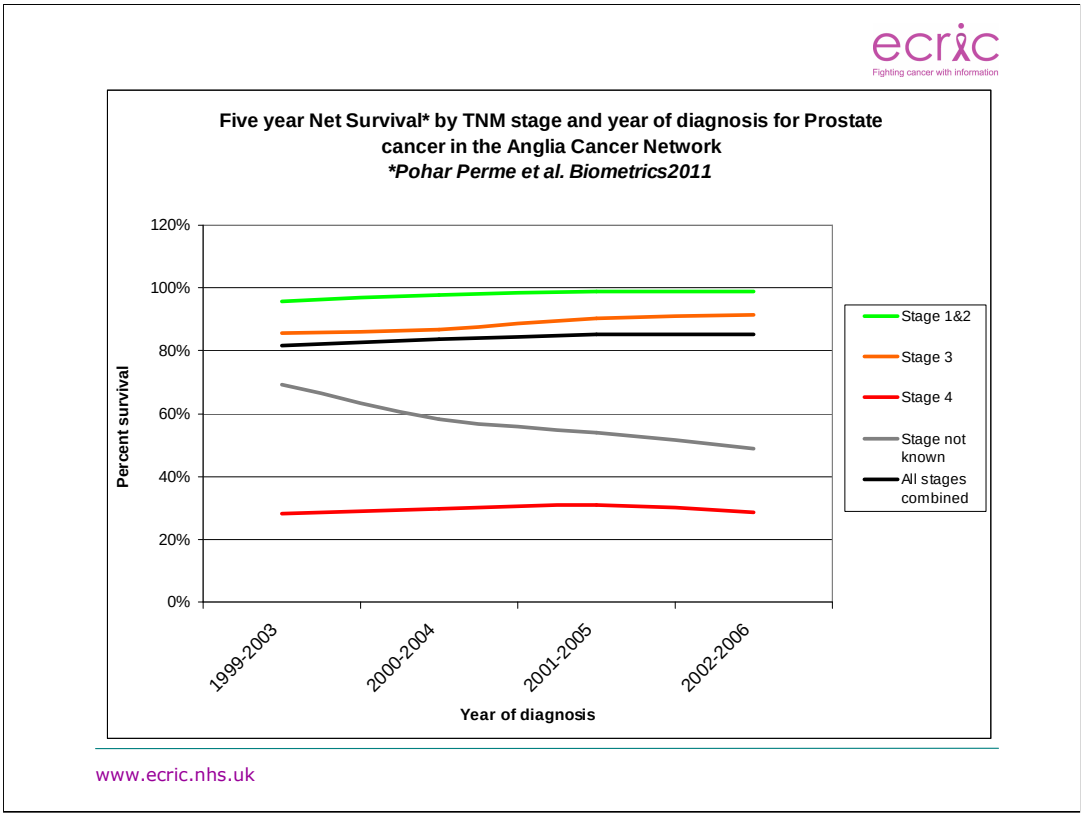
Trends in survival:
- overall and by stage

- Improvements in overall survival over time could be due to:
  - a higher proportion of cases diagnosed at an earlier stage
  - improved outcomes for each stage due to advances in treatment

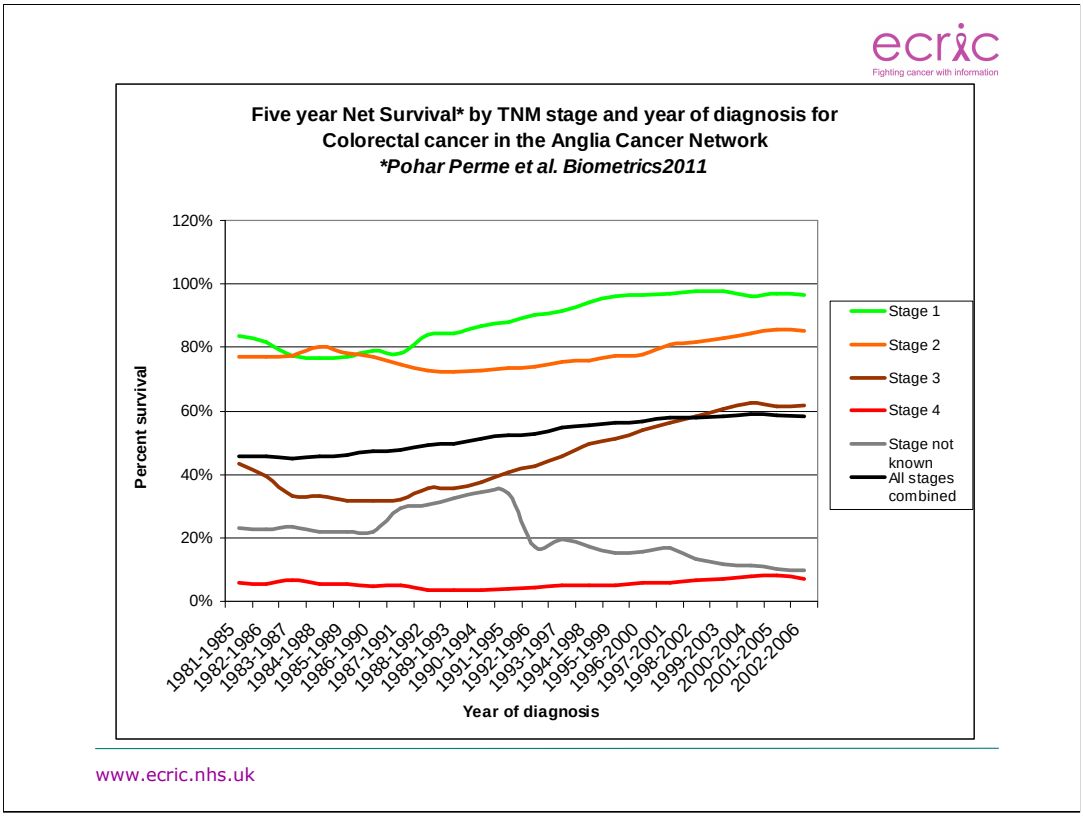


Survival has improved for all stages combined and for Stages 1& 2 – so, in that the all stage slope is a bit steeper than that for Stages 1& 2, there has a trend towards earlier stage diagnosis and some improvement in outcomes for stage 1&2 (?improvements due to treatment?)

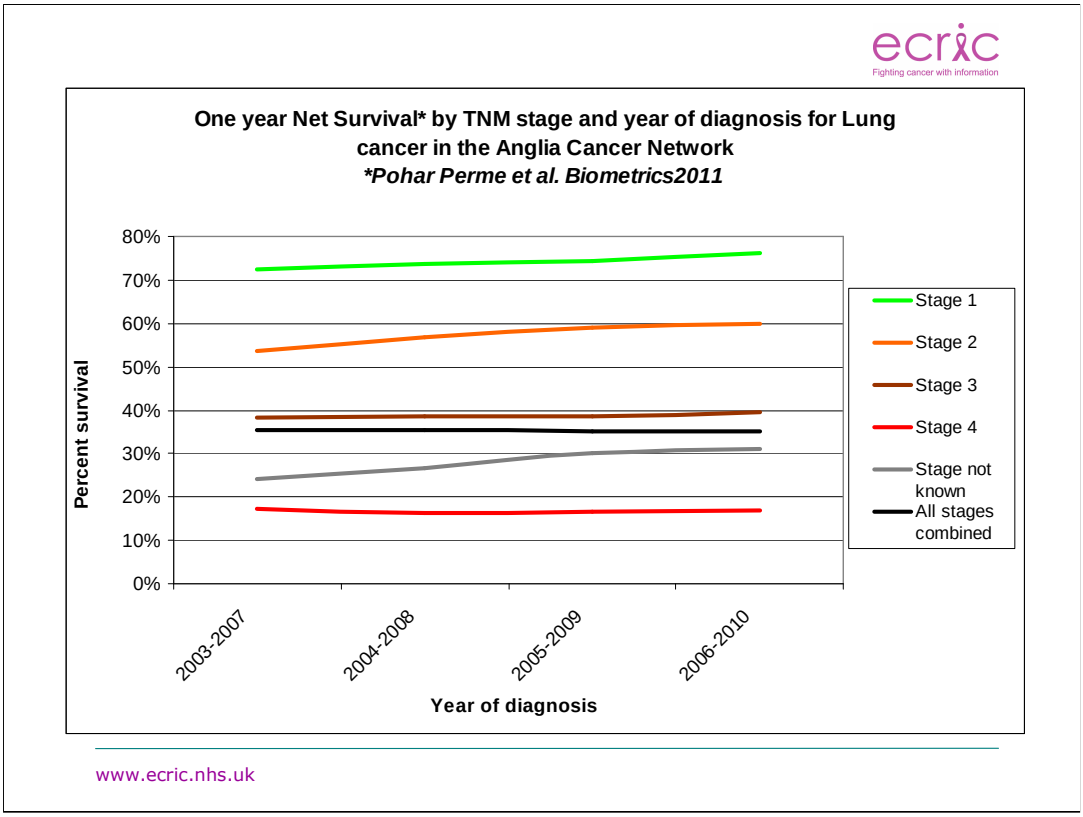
No real change for Stages 3 and 4 (which is where most of the money on drugs has gone…….)



We have only been staging prostate cancer since 1999, but the picture is vaguely similar to breast – improvements in all stages combined and in the earlier stages (Stage 3 prostate has not spread to regional lymph nodes).



Colorectal is rather different in that the most spectacular improvement is in Stage 3 … Treatment is involved here, but, as you will see later, treatment and stage are inter-related….



Lung cancer is again different in that there has been a quite marked inprovement for Stages 1&2, possibly a slight improvement for stage 3, but absolutely no change for all stages combined (or for stage 4)…

So what is going on here?

The Will Rogers phenomenon

- "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states."
  Will Rogers (attrib. 1930's)

- The Will Rogers Phenomenon, named after the comedian, occurs when moving some element from set A to set B increases the mean or median of both A and B.

- Moving the worst prognosis cases in each stage into the next highest stage will improve the prognosis for each stage – but overall prognosis will not improve.

Table 4. Effects of Stage Migration on Six-Month Survival Rates in the 1977 Cohort.* (Lung cancer)

OLD-DATA TNM STAGE *	STAGE MIGRATION	NEW-DATA TNM STAGE *
	six-month survival	
I: 32/42 (76)	→ I: 22/24 (92)	I: 22/24 (92)
	↗ II: 1/1 (100)	
	↘ III: 9/17 (53)	
II: 17/25 (68)	→ II: 12/17 (71)	II: 13/18 (72)
	↘ III: 5/8 (63)	
III: 23/64 (36)	→ III: 23/64 (36)	III: 37/89 (42)
	Total 72/131 (55)	

*TNM denotes tumor, nodes, and metastases.[16] Values are numbers of patients, with percentages in parentheses.

A.R. Feinstein, D.M. Sosin, MD, and C.K. Wells
N Engl J Med 1985; 312:1604-1608; June 20, 1985

Stage migration reasons

- Positron-Electron Tomography/ Computerised Tomography (PET-CT) scanning was adopted nationally for lung cancer, starting in 2007/8
  - this detects 'hidden' metastases and upstages cases to Stage 3 or Stage 4
- 1990s guidelines for colorectal surgery recommended excising and examining at least 12-15 lymph nodes
  - this detects more lymph node metastases and upstages cases from Stage 1/2 to Stage 3

Stage migration (contd.)

- Stage migration can cross-sectional as well as longitudinal comparisons
- A research PET/CT machine was installed at Addenbrooke's in 2005 and also used for "routine" diagnostic staging, while the national PET/CT programme was rolled out from 2007/2008.
- This resulted in lung cancers diagnosed in 2006-2008 in the Addenbrooke's catchment (Cambs, Peterborough & Beds) being upstaged relative to cases diagnosed in the Norfolk & Norwich Hospital catchment (Gt Yarmouth, Norfolk & Suffolk), where PET/CT was installed in 2008.

Conclusion

- Staging cancers and stage stratification or adjustment are fundamental to making meaningful comparisons between groups of cases (ie. by area of residence, by deprivation, by age group, by hospital, by year of diagnosis, etc.)
- but…..
  - care is needed when interpreting results.

Acknowledgments

- The hospitals and pathology laboratories in the East of England
  - notably their Cancer Multi-Disciplinary Teams
- All the staff of the National Cancer Registration Service – Eastern Office