



# Long-term follow up of clinical trials: is it worth it?

(or what can long-term follow up of old studies tell us?)

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## Background

- With an increasing number of new trials, interest in past studies often diminishes
- Relatively few clinical trials have long-term follow up data collected and reported
- The resources to do this compete with new studies; staff at recruiting centres often find it difficult (impossible) to work on both old closed studies as well as ongoing ones.

## **Collecting data several years after the first trial results have been reported**

- How this could be done
- Problems encountered
- What scientific value does the information have?

## Cancer Research UK & UCL Cancer Trials Centre

- Has been conducting large phase III cancer treatment trials since 1980
- Most protocols specify follow up until death
- Of particular interest were trials in which most patients were considered 'cured' after initial treatment:
  - Breast
  - Head and neck
  - Anal cancer

## Approach

- Few data sent in by centres regularly. But trials were flagged with the national death registry.
- Dedicated trials centre staff to work on the breast cancer studies (because there were several); otherwise co-ordinators considered long-term follow up as part of the trial
- Keen clinical investigators at recruiting centres who wanted to see long-term results
- Motivated research nurses/data managers at centres who kindly found time to obtain the data
- Not having the standard case report forms (ie 1 form per patient), but rather a **simple data sheet** for each centre with clear instructions
- **Request only a few key variables**

## Specially developed data forms

Patients who had died but with no recurrence reported

ID	Name	Birthdate	Date of recurrence	Local or distant	Date of cardiovascular event
001					
002					

Patients who had not died according to last data held in trials centre

ID	Name	Birthdate	Date of recurrence	Local or distant	Date of new tumour	Date of cardiovascular event	Date of death	Cause of death	Date last seen alive (if not died)
003									
004			ignore	ignore					

## Costs

- Co-ordinator in the trials centre; full-time for ~3 years & some data management support. Funded on the core grant (Cancer Research UK)
- Recently, a payment has been offered to centres with many patients, which depends on the number of patients:
  - £200 for ~50 patients
  - £500 for ~200 patients
- This would go to the hospital or directly to the research nurse as personal extra work
- Costs incurred by each centre; probably 0.5 to 5 days, depending on number of patients and number of variables

## Some problems encountered

- Old closed trials almost always take second place to ongoing studies
- Records moved from one hospital to another, so difficult to find
- Only one chance at data collection; should not ask for additional variables after the initial request
- Target larger centres, but potential problem is that these are the ones that don't have enough resources for this



## Three examples of trials

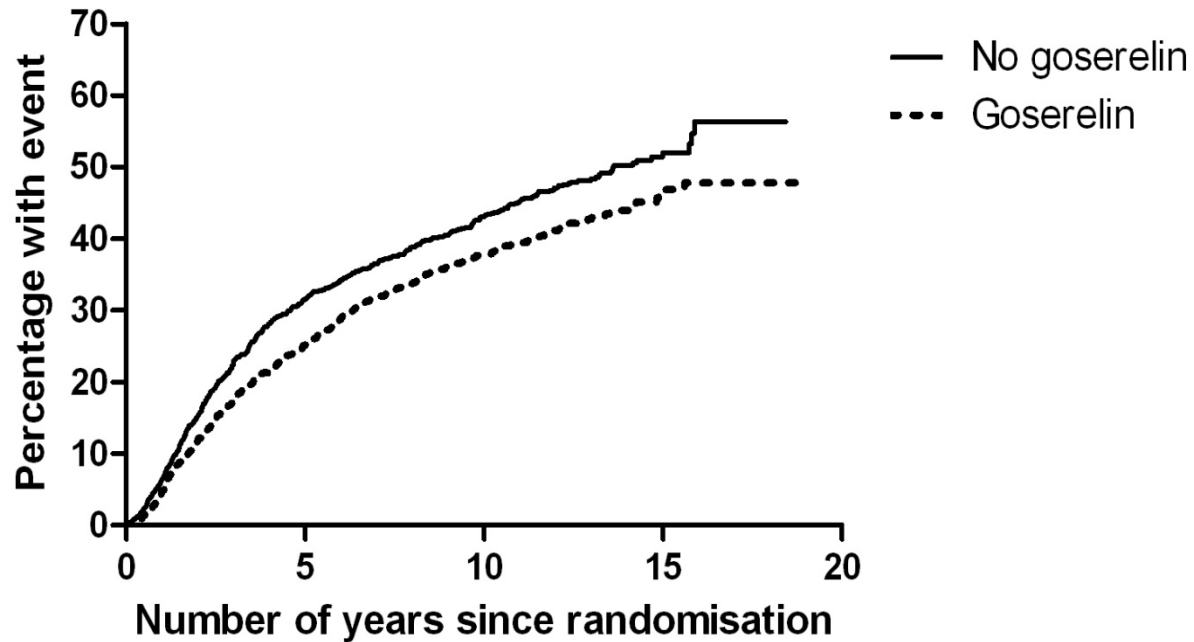
<b>Trial</b>	<b>Interventions</b>	<b>Data chase (year)</b>	<b>% of all pts who were last known to be alive but without any data in previous 3 years</b>	<b>Long-term results reported in</b>	<b>Median follow up (total person years)</b>
ZIPP Breast cancer (n=2706)	Zoladex & tamoxifen	2007	13%	JNCI 2009	12 years (26,545)
UKHAN Head & neck cancer (n=966)	Non-platinum chemo-radiation	2008	9%	Lancet Oncology 2010	10 years (4397)
ACT I Anal cancer (n=577)	Chemo-radiation	2007	22%	BJC 2010	13 years (3685)

## ZIPP – breast cancer

Factorial trial of 2 yrs goserelin (LHRH agonist) and 2 yrs tamoxifen

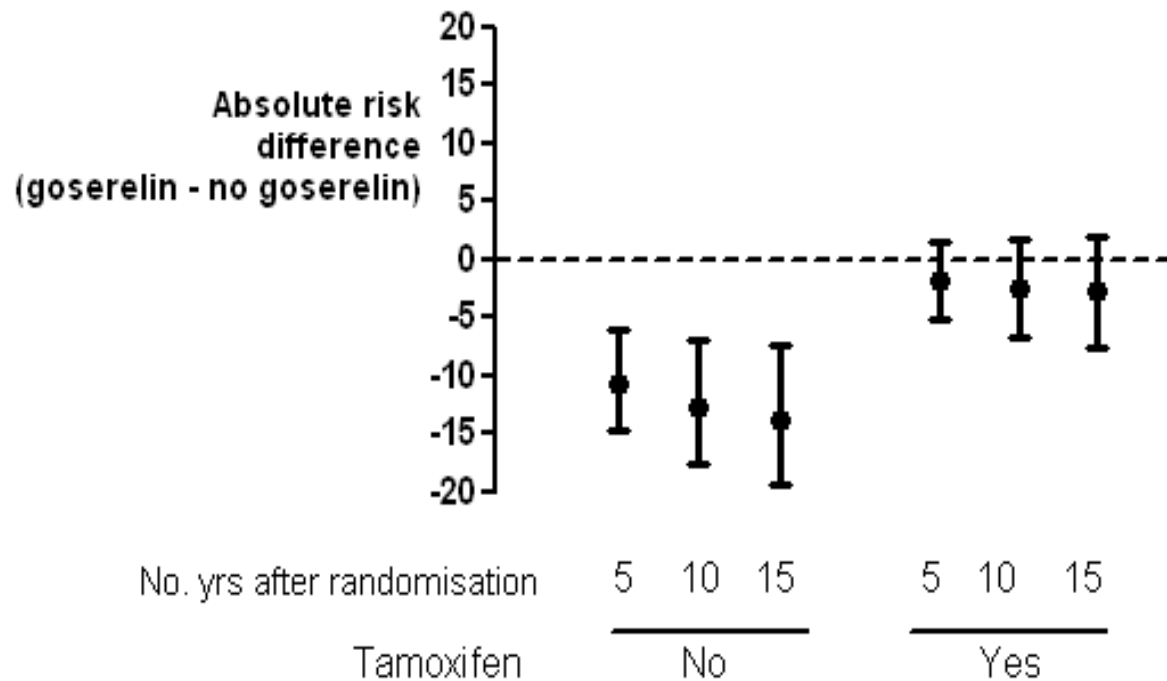
<b>Endpoint</b>	<b>First report (5.5 yrs follow up)</b>	<b>Second report (13 yrs follow up)</b>	
Recurrence, new tumour or death (whichever occurred first)	800	1148	44% more
Death from breast cancer	328	630	92% more
All deaths	414	690	67% more

## Event-free survival: clear long term benefit of goserelin



No. at risk				
no goserelin	1355	895	544	85
goserelin	1351	975	613	88

### Risk of an event (recurrence, new tumour, death)



Clear long-term benefits (statistically significant) on event-free survival but only in women who did not have tamoxifen.

Small effect of goserelin in those who did have tamoxifen.

## 15 years after randomisation Goserelin vs no goserelin

	Women who did not take tamoxifen	
	Risk difference	NNT
Any event	-13.9%	7
Breast cancer recurrence	-12.8%	8
Death from breast cancer	-8.5%	12

\* Negative value means the risk was lower with goserelin than no goserelin

## Main results 15 years after randomisation Goserelin vs no goserelin

	Women who did not take tamoxifen		Women who took tamoxifen	
	Risk difference	NNT	Risk difference	NNT
Any event	-13.9%	7	-2.8%	36
Breast cancer recurrence	-12.8%	8	-2.8%	36
Death from breast cancer	-8.5%	12	-2.6%	38

\* Negative value means the risk was lower with goserelin than no goserelin

## Implications for practice

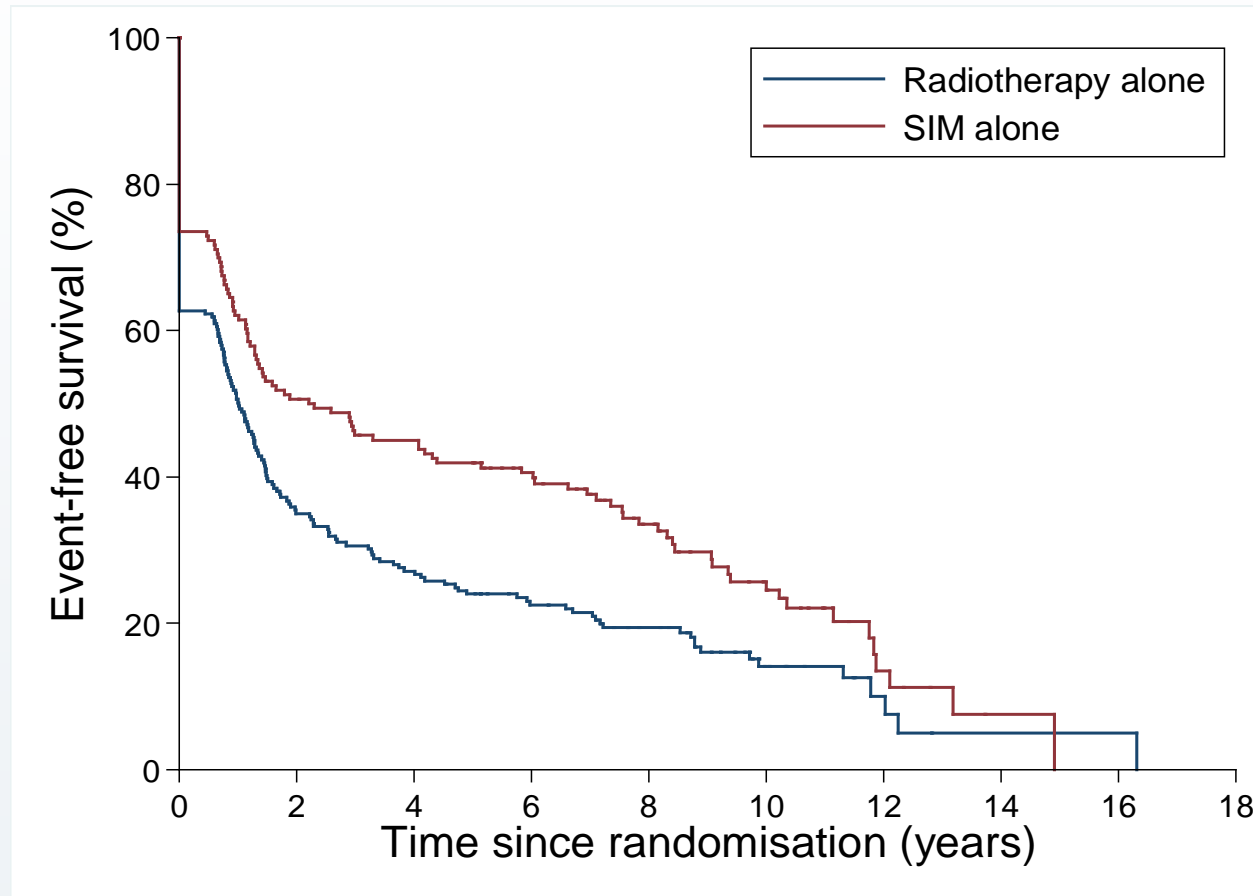
- Women can be assured of clinical benefits up to 15 years later
- 2 years of goserelin was as effective as 2 years of tamoxifen
- Even though tamoxifen is currently recommended for 5 years, many women do not complete treatment (80% by 2 years, ~50% by 5 years).
- Therefore, 2 years of goserelin (monthly injections) might be a preferable treatment for these women

## UKHAN – head and neck cancer

- Radiotherapy (RT) alone
- Chemotherapy given simultaneously with RT (SIM)
- Chemo given after RT (SUB)
- Chemo given at both times (SIM+SUB)
  
- Non-platinum chemotherapy used:
  - VBMF (vincristine, bleomycin, methotrexate, fluorouracil) or
  - Methotrexate

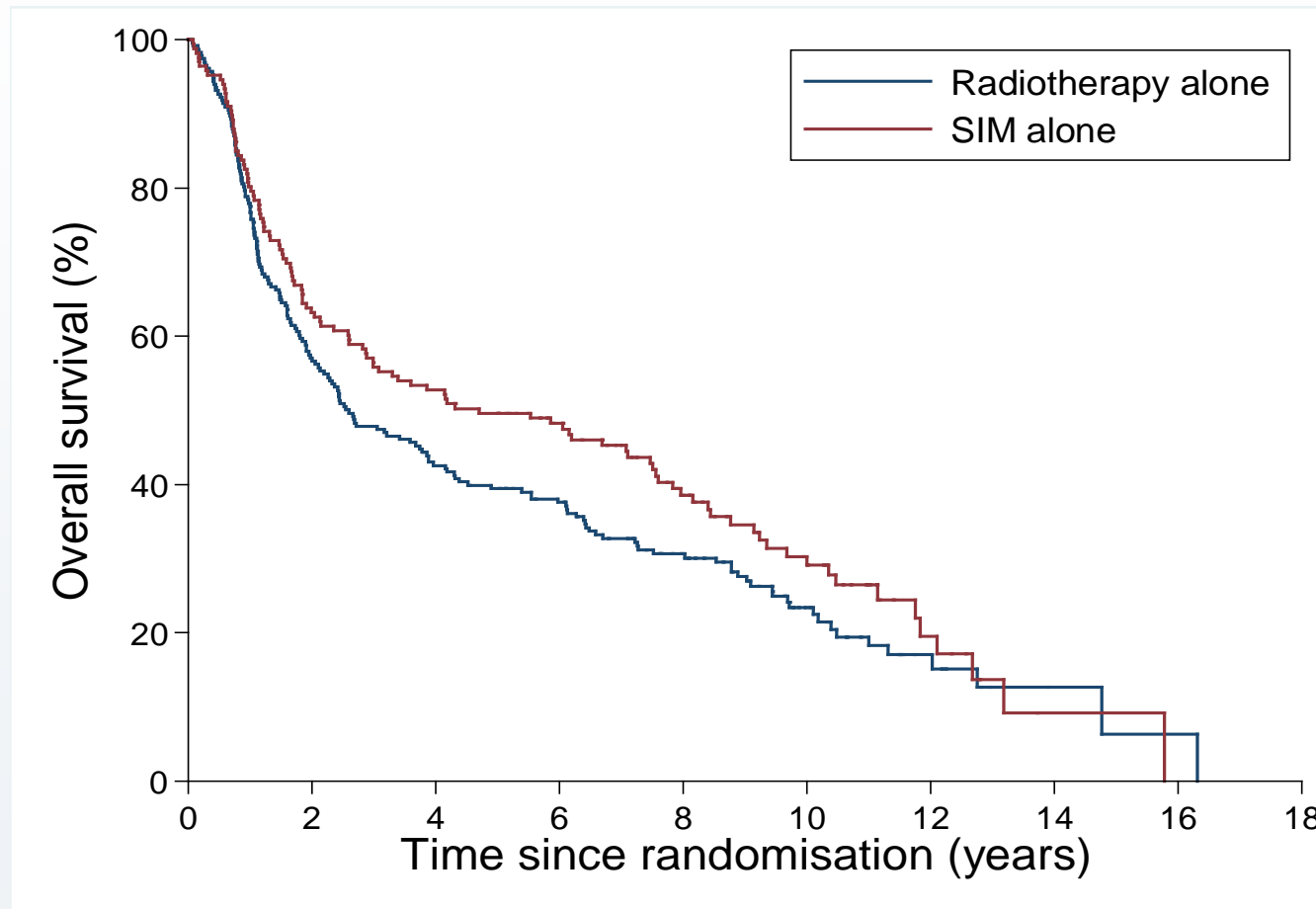


## No previous surgery – Event-free survival



P=0.002

## No previous surgery – Overall survival



P=0.09

## Main conclusions

- Median survival:
- Concurrent chemotherapy with RT (SIM) vs RT alone  
4.7 years vs 2.6 years
- High compliance to SIM (92%)
- Long-term serious side effects (>6 months): 6% (SIM) vs 6% (RT)
- 10 years after concurrent chemoradiotherapy (compared to RT alone), there are an estimated:
  - 11% fewer events (recurrences, new tumour, deaths)
  - 7% fewer deaths

## Other considerations

- No material difference in the treatment effect between using platinum and non-platinum agents (meta-analysis, Pignon et al 2009)
- Although platinum drugs are commonly used, there are no long-term data on efficacy or safety.
- Long-term follow up of UKHAN provides reassuring evidence for non-platinum drugs
- Indirect comparisons suggest lower acute toxicity rates during treatment (28%, UKHAN) compared to trials of cisplatin (77% RTOG, 41% EORTC)

## Implications for practice

- Non-platinum therapy is an effective alternative to platinum therapy, especially those judged unfit for cisplatin:
  - Simple to administer
  - Cheaper
  - Low toxicity (during treatment and long-term)
  - High compliance (better chance of cure)
  - Known long-term benefit

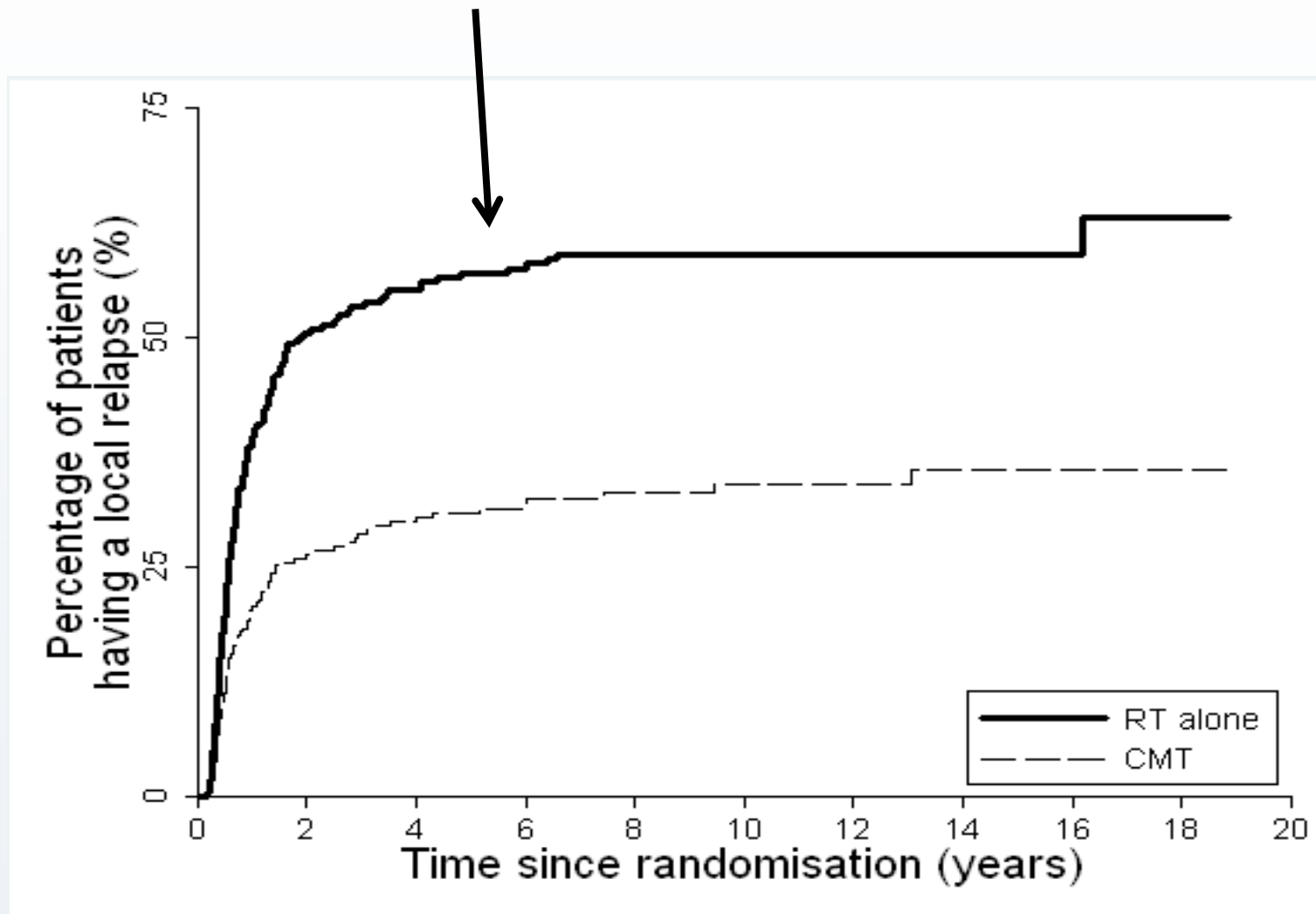
# ACT I – Anal cancer

Combined Modality Treatment (CMT) with chemoradiotherapy vs radiotherapy alone (RT)

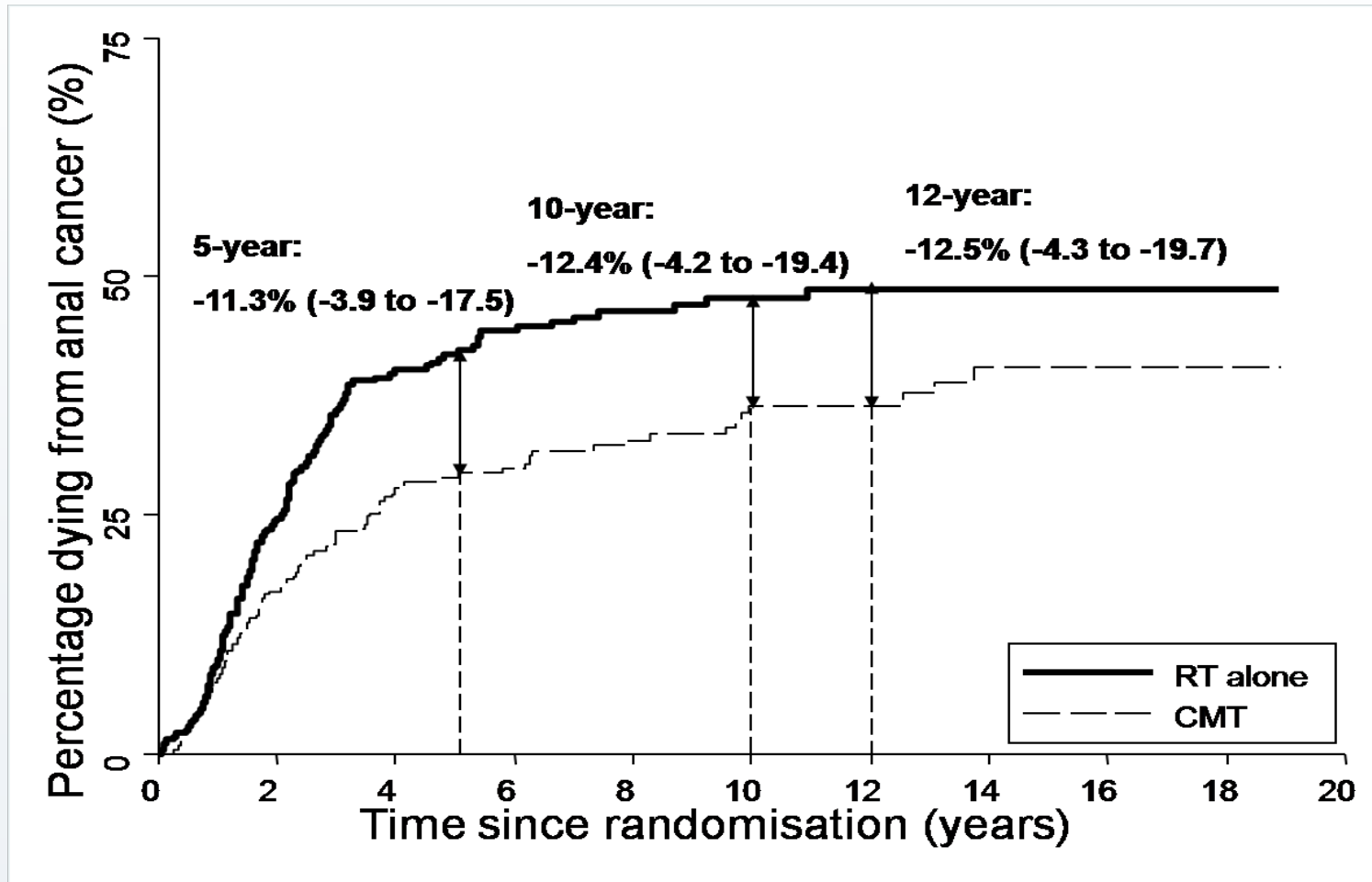
Similar point estimates of the treatment effect, but with some greater precision

Hazard ratio (95% CI); p-value	1996 paper	2010 paper
Locoregional failure	0.54 (0.42 – 0.69); P<0.0001	0.46 (0.35 – 0.60); P<0.001
Overall survival	0.86 (0.67 – 1.11); P=0.25	0.86 (0.70 – 1.04); P=0.12
Anal cancer deaths	0.71 (0.53 – 0.95); p=0.02	0.67 (0.51 – 0.88); P=0.004

After 5 years, there were only 11 known local recurrences; this questions the relevance of having stringent follow up in routine practice



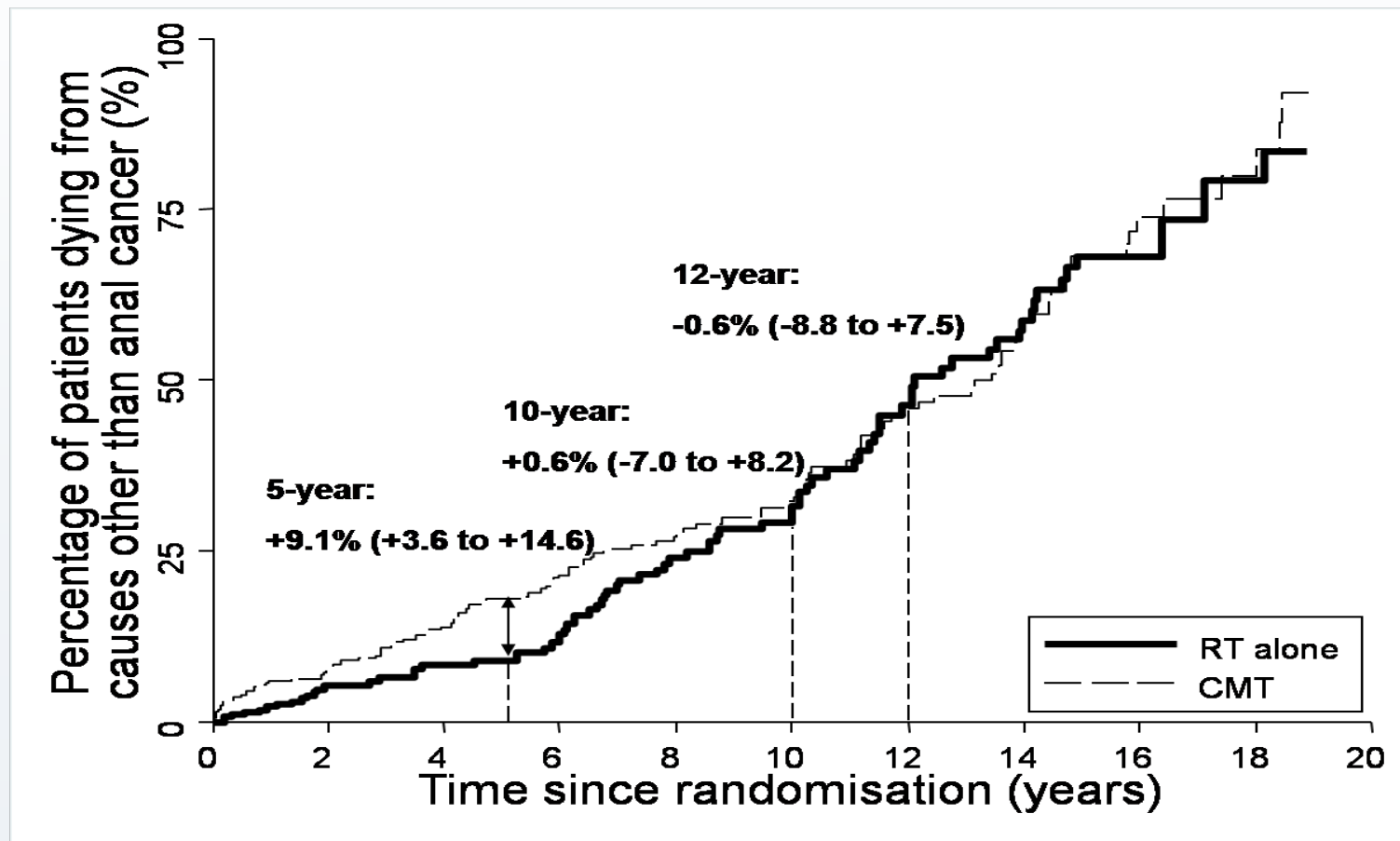
## Clear long-term benefit of chemoradiotherapy (CMT) on anal cancer death



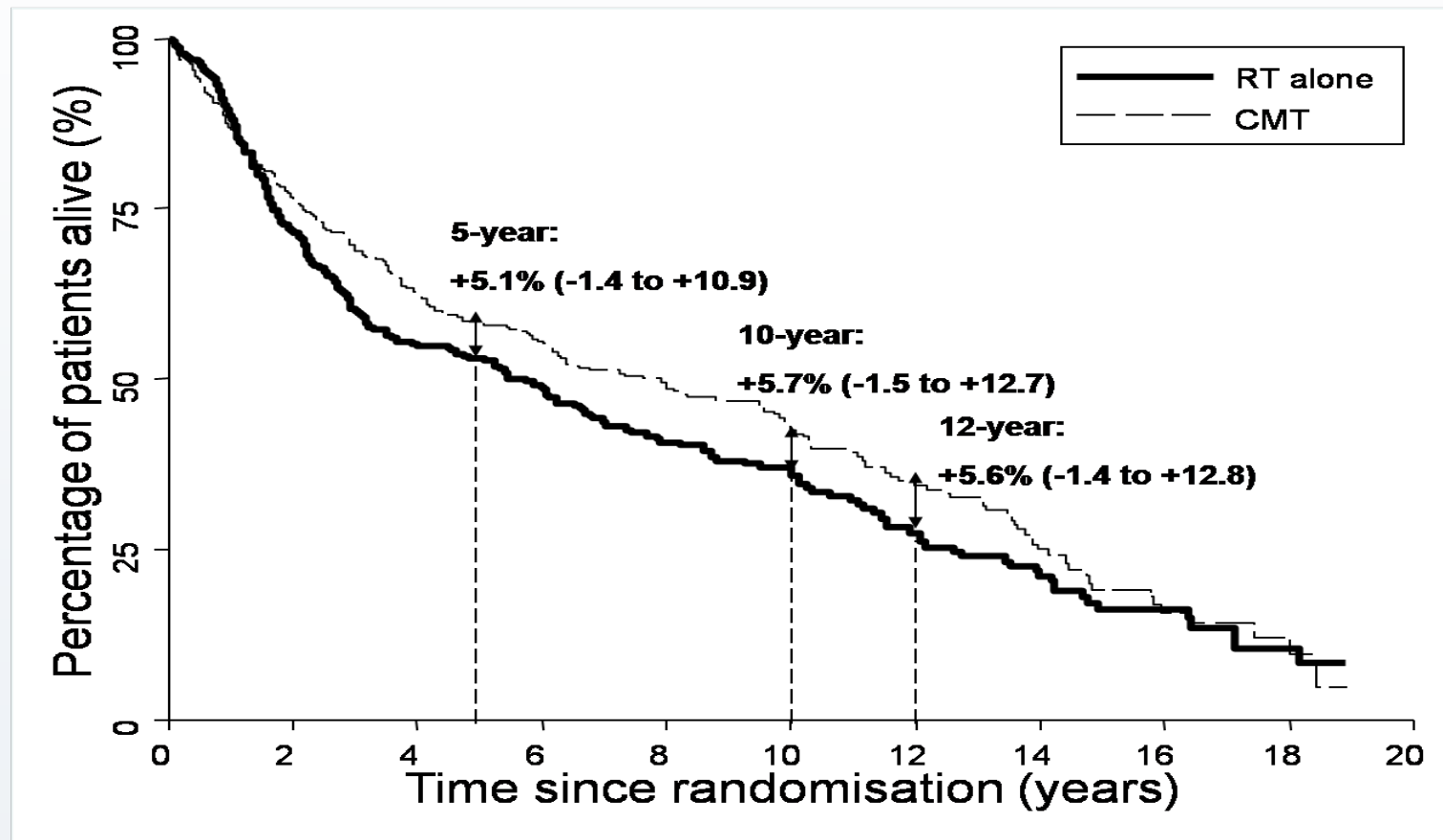


But clear increase in non-anal cancer deaths due to chemoradiotherapy in the first few years.

The excess risk disappeared by 10 years



# Overall benefit on the death rate in favour of chemoradiotherapy (CMT)



## Summary

- Long-term follow up of old trials is not easy (especially without extra resources), but can be done if centres are interested and willing
- The data produced can be very informative
- Ultimately, it gives reassurance to patients that an initial treatment could have benefits lasting for many years