THE ORDER OF RADIOTHERAPY AND CHEMOTHERAPY IN EARLY BREAST CANCER AND ITS EFFECT ON OUTCOME

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Background

- Early breast cancer patients with unfavourable prognostic factors are often treated with both chemotherapy (CT) and radiotherapy (RT).
- Delay in the start of RT or CT may result in increased risk of locoregional and/or distant recurrence.
- The optimal sequence of RT and CT is subject for debate.

Background

- Concurrent administration of RT and CT might improve locoregional control
- Concurrent CT and RT is not advised in the Netherlands because of the excess risk of treatment-related side effects
- Studies until now are often preformed with selected (small) populations
- Sequencing in the Netherlands was arbitrary and not according to national guidelines

Aim of the study

Determine the effect of RT and CT sequence on overall survival (OS) and recurrence-free survival (RFS) using a large dataset from a population-based cancer registry.

Materials & methods

- Cases selected from the Netherlands Cancer Registry
- All primary breast cancers diagnosed 1999-2008

- Cox and competing risk regression was used to compare OS and RFS in two treatment groups
  - RT first
  - CT first
- adjustment for important prognostic variables

Selection of cases

- 131,122 primary breast cancers in 1999-2008
  - Exclusion: Tis, TX, T4, M1, second breast cancers, no surgery, neo-adjuvant treatment
- 93,399 T1-3M0 treated with surgery
  - Exclusion: no combination of RT and CT
- 22,045 primary breast cancer patients received both CT and RT (after surgery)
  - 9,977 (45%) received RT first
  - 2,068 (55%) received CT first.
  - during a total of 112,872 patient years of follow-up (median 57 months), 3,075 patients died.

Distributions of the treatment options

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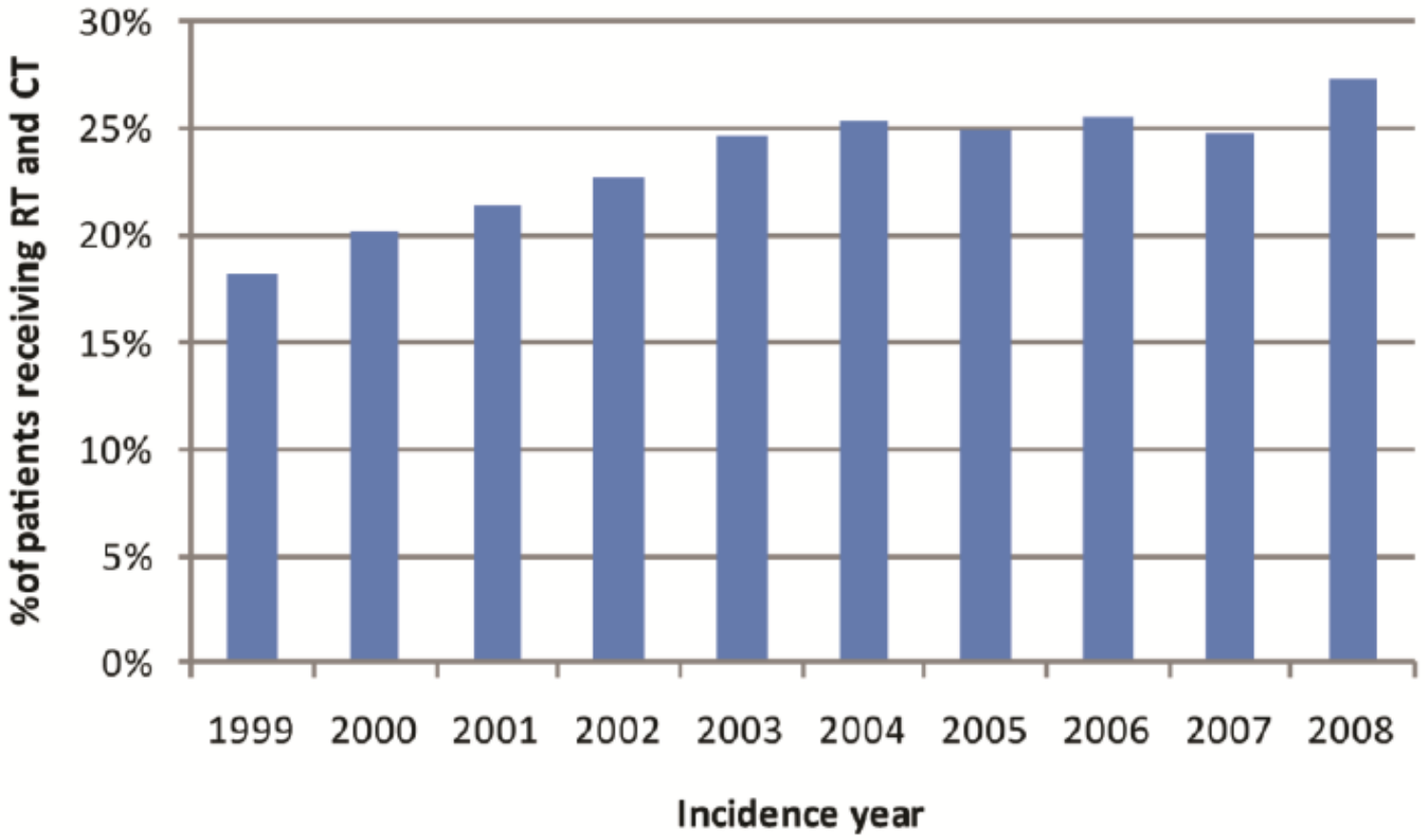
A



Ratio RT/CT first over the years

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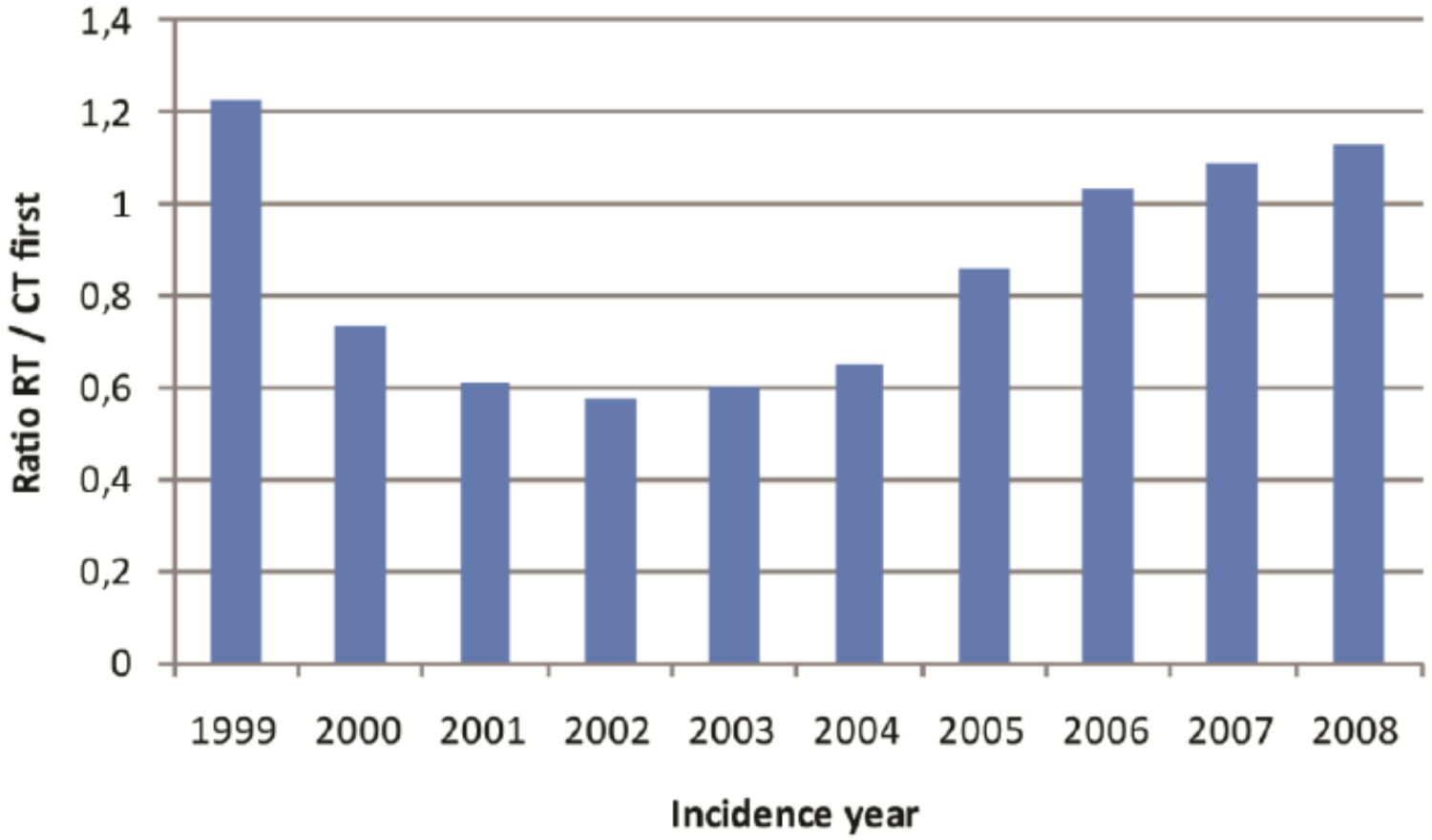
B



Results

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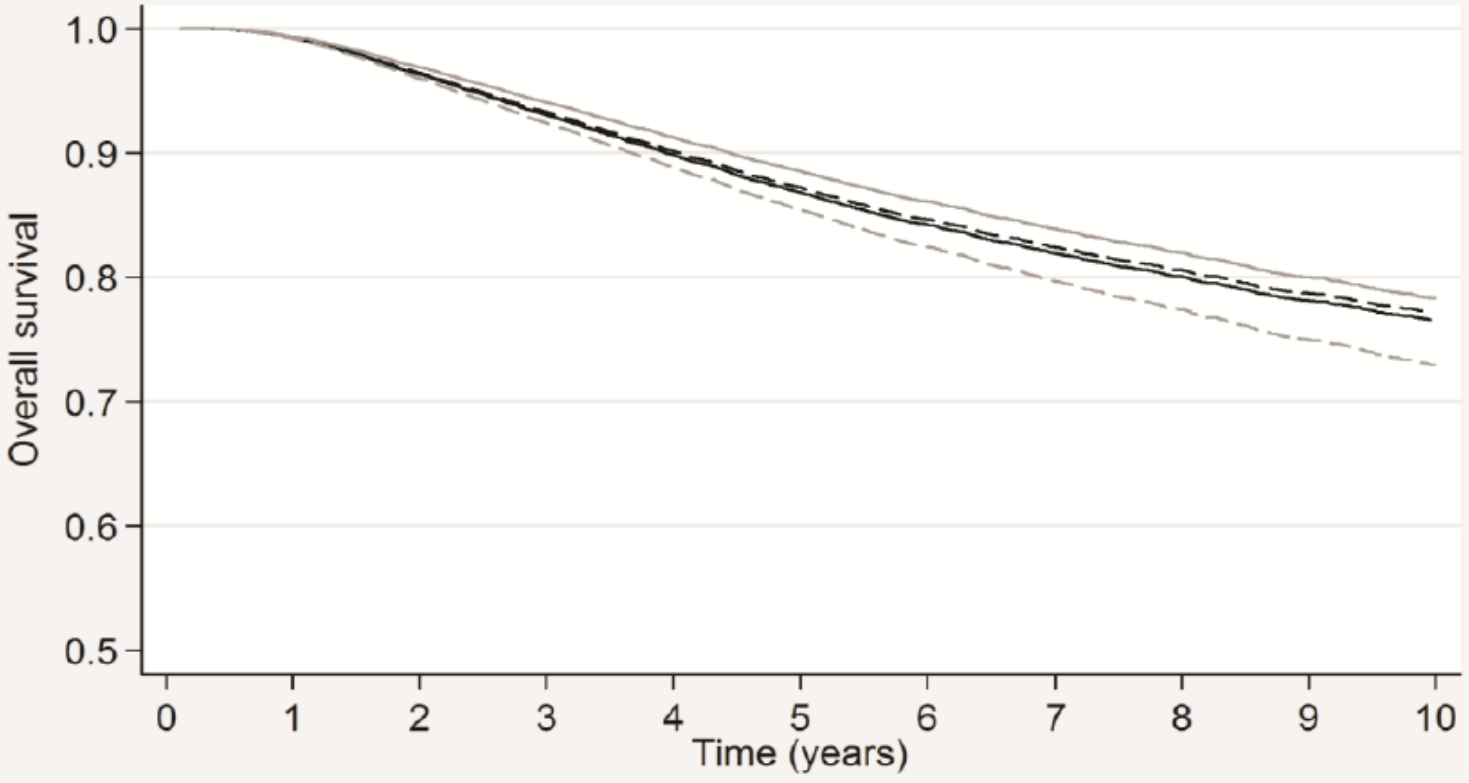
Overall survival (OS)



*Direct adjustment for T Stage (T1,2 or 3), N Stage (N0,1,2 or 3), B&R Grade (1,2 or 3), Hormonal therapy use (yes/no), tertiles of Age and Number of positive lymph nodes.

Overall survival (OS)

- adjustments for age, stage, number of positive lymph nodes, histological grade and administration of hormone therapy:
  - no survival difference for CT first compared to RT first (hazard ratio (HR) 0.97; 95%CI 0.90-1.05; P=0.46).
- Additional adjustment for hormone receptor status, HER2 status and tumor diameter available for a subgroup of 9,951 patients:
  - confirmation of these results (HR 0.96; 95%CI 0.79-1.16; P=0.66).

OS according to type of surgery

	valid n	HR (95% CI); p
Lumpectomy (complete case)	14590	
RT First	7551	reference
CT First	7039	0,94 (0,85-1,05); 0,27
Lumpectomy (imputed)	16028	
RT First	8217	reference
CT First	7811	0,91 (0,82-1,00); 0,06
Mastectomy (complete case)	5286	
RT First	1555	reference
CT First	3731	1,01 (0,89-1,15); 0,87
Mastectomy (imputed)	6017	
RT First	1760	reference
CT First	4257	1,02 (0,91-1,15); 0,72

OS according to nr of positive lymph nodes

	valid n	HR (95% CI); P
LN= 0 (complete case)	6310	
RT first	3810	reference
CT first	2500	0,92 (0,76-1,11); 0,36
LN=0 (imputed)	6763	
RT first	4072	reference
CT first	2691	0,90 (0,75-1,08); 0,25
LN=1-3 (complete case)	7418	
RT first	3754	reference
CT first	3664	0,99 (0,85-1,15); 0,89
LN=1-3 (imputed)	8200	
RT first	4129	reference
CT first	4071	0,97 (0,85-1,11); 0,68
LN≥4 (complete case)	6117	
RT first	1521	reference
CT first	4596	0,99 (0,88-1,10); 0,83
LN≥4 (imputed)	6883	
RT first	1700	reference
CT first	5183	0,99 (0,89-1,10); 0,80

Disease-free survival (DFS)

- In 6,582 patients data on recurrent disease were specifically documented (period 2003-2006)
- 30,762 patient years of follow-up (median 61 months)
- 1,259 patients experienced one or more recurrences

Recurrence type documented in the recurrence cohort

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	RT first (n=2479 (38%))		CT first (n=4103 (62%))	
	number	*%*	*number*	*%*
Recurrent disease event				
No event	2079	84%	3244	79%
Any event	400	16%	859	21%
Multiple events	32	1%	60	1%
Event type				
Local	49	12%	119	14%
Regional	51	13%	75	9%
Distant metastasis	334	84%	728	85%

Disease-free survival (DFS)

- No significant recurrence-free survival benefit was seen for either treatment sequence (HR 0.97; 95%CI 0.86-1.10; P=0.64).

RFS according to type of surgery

	valid n	RFS HR (95%CI);P	LRFS HR (95%CI);P	RRFS HR (95%CI);P	DRFS HR (95%CI);P
Lumpectomy (complete case)	4317	0,97 (0,82-1,15); 0,71	1,33 (0,86-2,06); 0,20	0,87 (0,55-1,38) 0,56	0,90 (0,75-1,08); 0,25
Lumpectomy (imputed)	4622	0,95 (0,81-1,12); 0,53	1,29 (0,85-1,96); 0,24	0,82 (0,53-1,28), 0,38	0,89 (0,74-1,06); 0,20
Mastectomy (complete case)	1733	1,02 (0,82-1,26); 0,89	1,69 (0,78-3,64); 0,18	0,95 (0,48-1,87); 0,88	0,97 (0,77-1,22); 0,79
Mastectomy (imputed)	1960	1,02 (0,83-1,26); 0,82	1,43 (0,74-2,76); 0,29	0,78 (0,42-1,45); 0,43	0,99 (0,80-1,24); 0,96

RFS according to nr of positive lymph nodes

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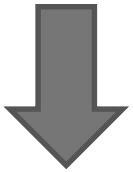
		valid n	RFS HR (95%CI); P	LRFS HR (95%CI); P	RRFS HR (95%CI); P	DRFS HR (95%CI); P
0 LN+	Complete case	1866	0,95 (0,72-1,25); 0,70	1,90 (0,95-3,79); 0,07	0,52 (0,26-1,06); 0,07	0,88 (0,64-1,21); 0,42
	Imputed	1954	0,92 (0,70-1,21); 0,57	1,90 (0,97-3,71); 0,06	0,47 (0,23-0,95); 0,04	0,88 (0,64-1,21); 0,44
1-3 LN+	Complete case	2116	0,91 (0,71-1,16); 0,44	1,26 (0,69-2,29); 0,45	0,74 (0,37-1,49); 0,40	0,87 (0,66-1,13); 0,30
	Imputed	2305	0,89 (0,71-1,12); 0,32	1,21 (0,68-2,15); 0,52	0,67 (0,37-1,49); 0,23	0,87 (0,68-1,11); 0,30
>3LN+	Complete case	2052	1,04 (0,86-1,27); 0,66	1,35 (0,72-2,55); 0,35	2,72 (0,98-7,58); 0,06	0,97 (0,79-1,19); 0,76
	Imputed	2274	1,04 (0,87-1,25); 0,66	1,22 (0,69-2,17); 0,49	2,29 (0,91-5,81); 0,08	0,97 (0,80-1,18); 0,75

Conclusion

A large analysis of prospectively collected cancer registry data of primary breast cancer patients after a median follow-up of approximately 5 years



The sequence of radio- and chemotherapy as practiced in routine clinical care did not affect overall-survival or recurrence-free survival

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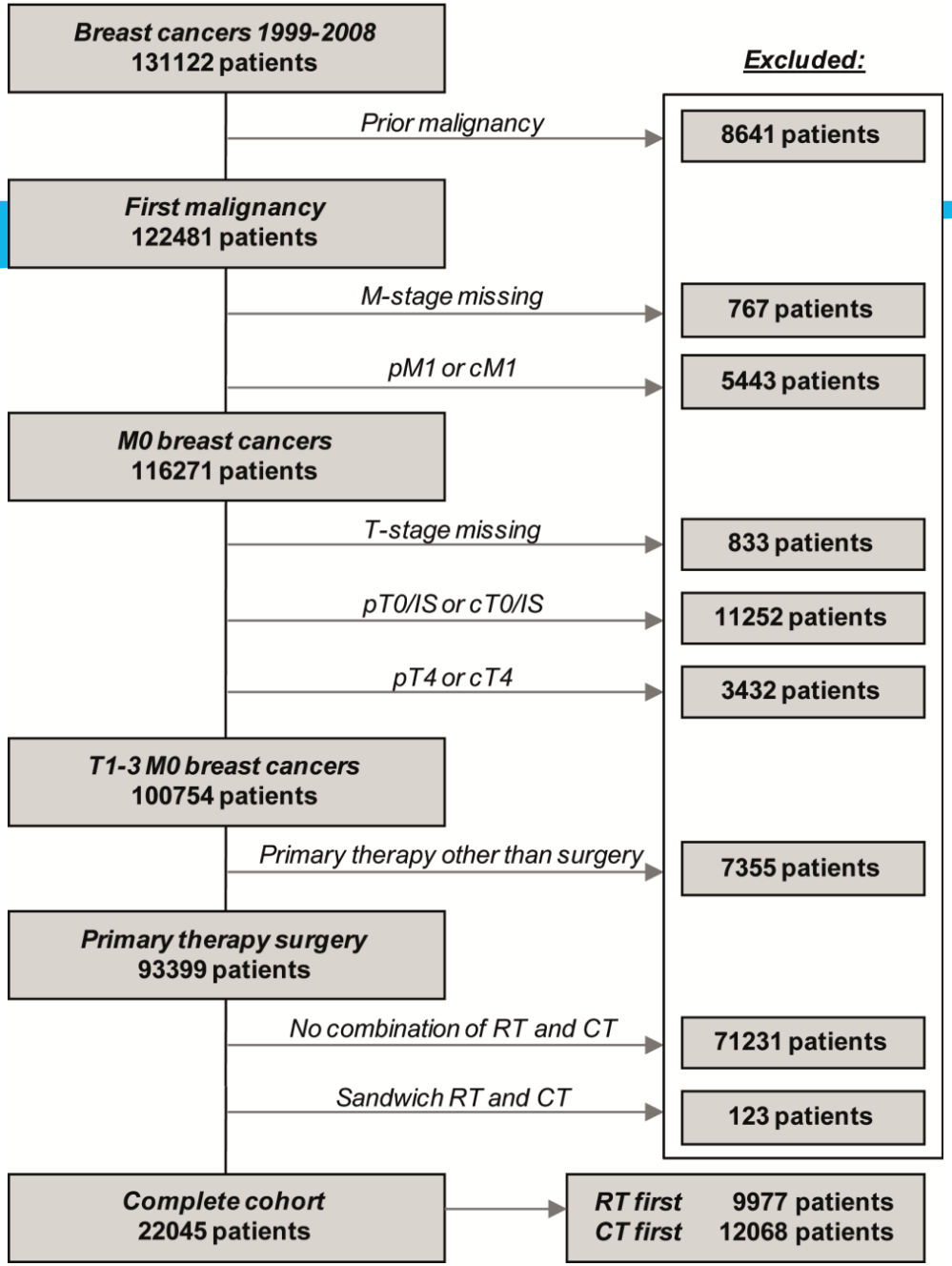

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CT-RT sequence in relation to OS in the full cohort and 2005 cohort

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	valid n	Model 1 HR (95% CI); P	Model 2 HR (95% CI); P
Full cohort (complete case)	19876		
RT first	9106	reference	
CT first	10770	0,99 (0,91-1,07); 0,73	-
Full cohort (imputed)	22045		
RT first	9977	reference	
CT first	12068	0,97 (0,90-1,05); 0,46	-
2005 cohort (complete case)	8839		
RT first	4585	reference	
CT first	4254	1,13 (0,92-1,38); 0,26	1,03 (0,84-1,27); 0,78
2005 cohort (imputed)	9951		
RT first	5042	reference	
CT first	4909	1,03 (0,85-1,25); 0,79	0,96 (0,79-1,16); 0,66