Supplemental Online Content

Leon-Ferre RA, Jonas SF, Salgado R, et al. Tumor-infiltrating lymphocytes in triple-negative breast cancer. *JAMA*. doi:10.1001/jama.2024.3056

This supplemental material has been provided by the authors to give readers additional information about their work.

1. Study population

We received data on 2211 patients from 13 institutions:

- 22 patients without TILs value were excluded,
- 41 patients with ER levels above 1% (when the information was available) were excluded,
- 18 patients with PR levels above 1% (when the information was available) were excluded,
- 133 patients treated with neodjuvant chemotherapy were excluded,
- 21 patients without follow-up information were excluded,
- 1 patient with two cancers at diagnostic was excluded,
- 1 patient with preinvasive cancer was excluded,
- 8 patients without surgery were excluded.

After exclusions, a total of 1966 patients were included in the analysis.

eTable 1-A. Details on Patients Included/Excluded From Each Cohort

Study	Initial number	Missing TILs	ER >1%	PR >1%	Chemo-treated	Missing follow-up	Two cancers at diagnosis	No surgery	Preinvasive cancer	Final number
Genova, Italy	16	0	0	0	0	0	0	0	0	16
Padova, Italy	40	0	1	1	0	0	0	0	0	38
Gothenburg, Sweden	65	5	3	0	0	0	0	4	0	53
Lyon, France*	59	0	NA	NA	0	0	1	0	0	58
Gustave Roussy, Paris, France*	98	3	NA	NA	0	0	0	0	0	95
Tokyo, Japan	125	0	13	3	0	0	0	0	0	109
UUCM Seoul, Korea*	117	0	NA	NA	1	0	0	0	0	116
Curie, Paris, France	150	2	0	0	0	0	0	0	0	148
Milan, Italy	190	11	0	0	0	20	0	0	0	159
Mayo, MN, USA	182	1	0	0	0	0	0	0	0	181
Erasmus, Rotterdam, Netherlands	243	0	0	0	0	1	0	0	1	241
UBC, Vancouver, Canada	445	0	0	0	132	0	0	4	0	309
NKI, Amsterdam, Netherlands	481	0	24	14	0	0	0	0	0	443
Total	2211	22	41	18	133	21	1	8	1	1966

* ER/PR threshold used in this cohort was 10%, specific % value was not available

Information on the level of TIL and on the time elapsed between surgery (or the date of diagnosis) and the events considered (see details in section 3.1) or the date of the last follow-up were a pre-requisite to include the patient in the analysis.

In addition, all 13 centers provided data on requested covariates: tumor size, number of positive lymph nodes, age, histological grade, radiotherapy, type of surgery. Sporadic missing data were possible on these covariates (see details in the table S.2).

Additional covariates on histologic subtypes and menopausal status were also available for most studies, these covariates being used for descriptive purposes only.

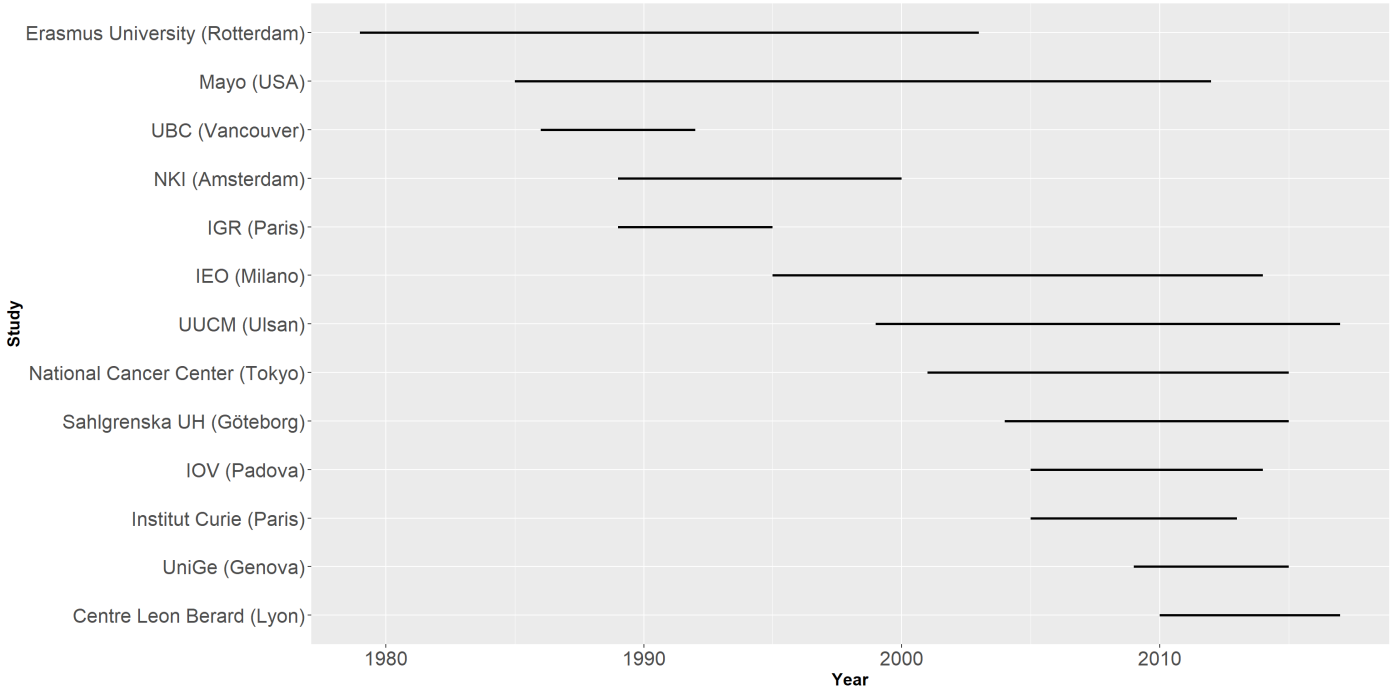
eTable 1-B. Criteria Used by Each Cohort To Define ER, PR, and HER2–Negative Status

Study	ER neg	PR neg	HER2 neg
Mayo (USA)	1% threshold	1% threshold	IHC 0, 1+, or 2+ w/ FISH neg
NKI (Amsterdam)	1% threshold (24 patients excluded)	1% threshold (15 patients excluded including 1 with ER>0)	IHC 0, 1+, or 2+ w/ SISH neg/equivocal
UUCM (Ulsan)	10% threshold	10% threshold	IHC 0, 1+, or 2+ w/ FISH neg
IGR (Paris)	10% threshold	No IHC data	IHC 0
UBC (Vancouver)	1% threshold	1% threshold	IHC 0, 1+, or 2+ w/ FISH neg
IEO (Milano)	1% threshold	1% threshold	IHC 0, 1+, or 2+ w/ FISH neg
Curie (Paris)	1% threshold	1% threshold	IHC 0, 1+, or 2+ w/ FISH neg
Centre Leon Berard (Lyon)	10% threshold	10% threshold	IHC 0, 1+, or 2+ w/ FISH neg
IOV (Padova)	1% threshold (1 patient excluded)	1% threshold (1 patient excluded)	IHC 0, 1+, or 2+ ISH not amplified
UniGe (Genova)	1% threshold	1% threshold	IHC 0, 1+, or 2+ w/ FISH neg
SahIgrenska UH (Göteborg)	1% threshold (3 patients excluded)	1% threshold	IHC 0, 1+, or 2+ w/ FISH neg
National Cancer Center (Tokyo)	1% threshold (13 patients excluded)	1% threshold (10 patients excluded including 7 with ER>0)	IHC 0, 1+, or 2+ w/ FISH neg
Erasmus University (Rotterdam)	1% threshold	1% threshold	IHC 0, 1+, or 2+ ISH not amplified

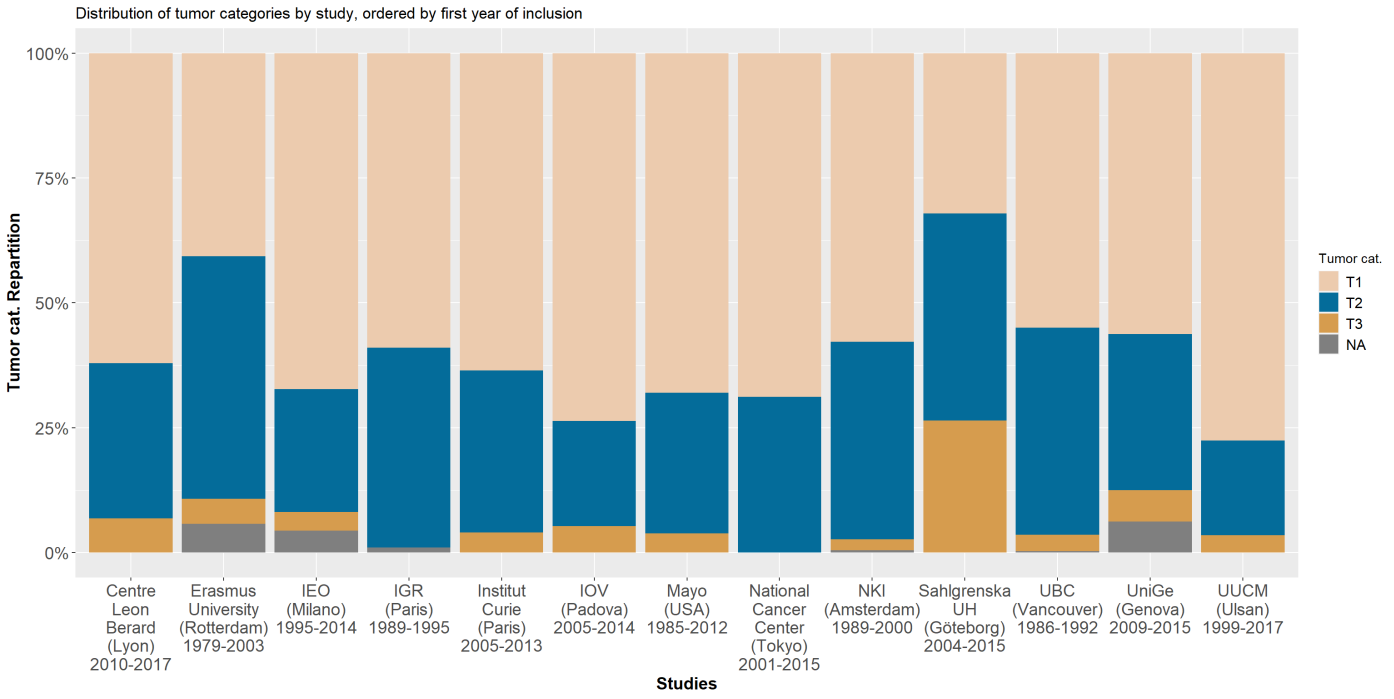
The following cohorts (which included patients treated prior to routine clinical testing of HER2 status) Evaluated HER2 status directly from tumor tissue, using the criteria noted in table S1A: Mayo Clinic (USA), UBC (Vancouver), NKI (Amsterdam), IEO (Milano), IGR (Paris), Sahlgrenska UH (Göteborg), Erasmus (Rotterdam).

The following cohorts abstracted HER2 status from the medical record without tissue retesting: IOV (Padova), National Cancer Center (Tokyo). Please note that period of enrollment for these cohorts was more recent, after HER2 testing became standard in the clinic.

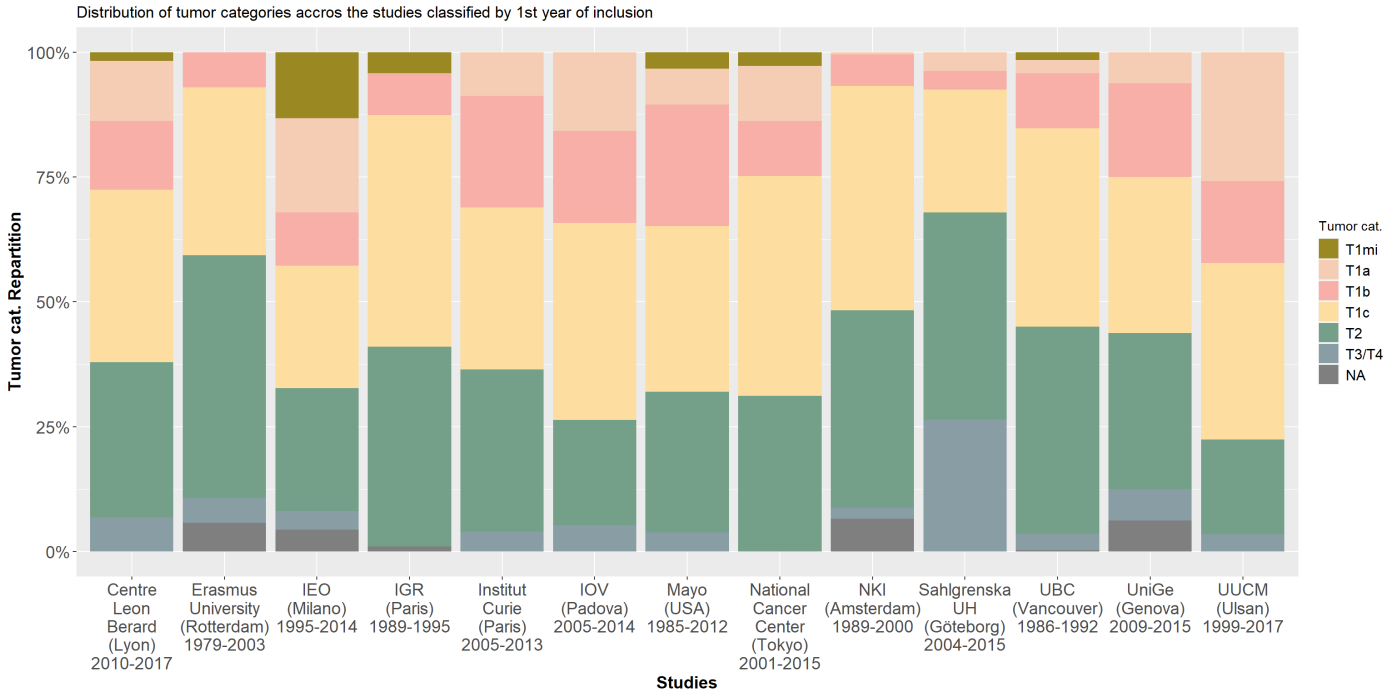
eFigure 1-A. Inclusion Period According to Each Cohort



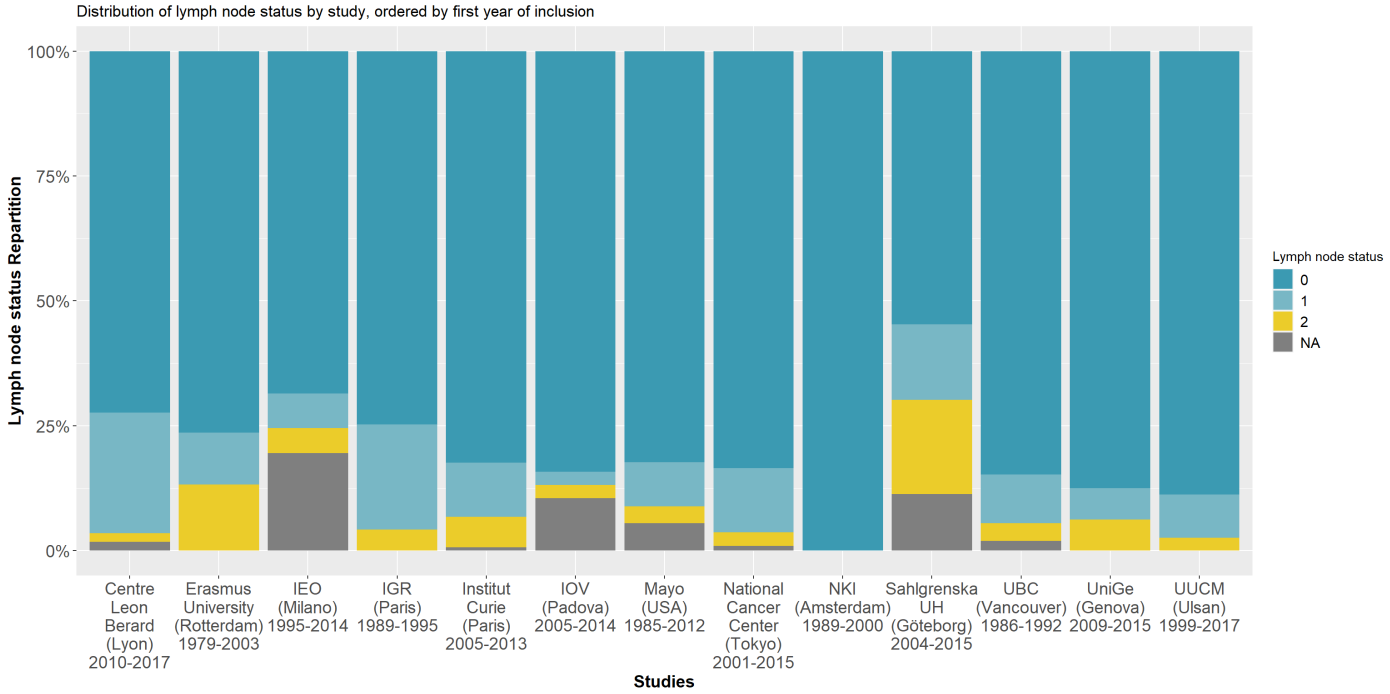
eFigure 1-B. Tumor Size Distribution per Cohort, Ordered According to First Year of Inclusion



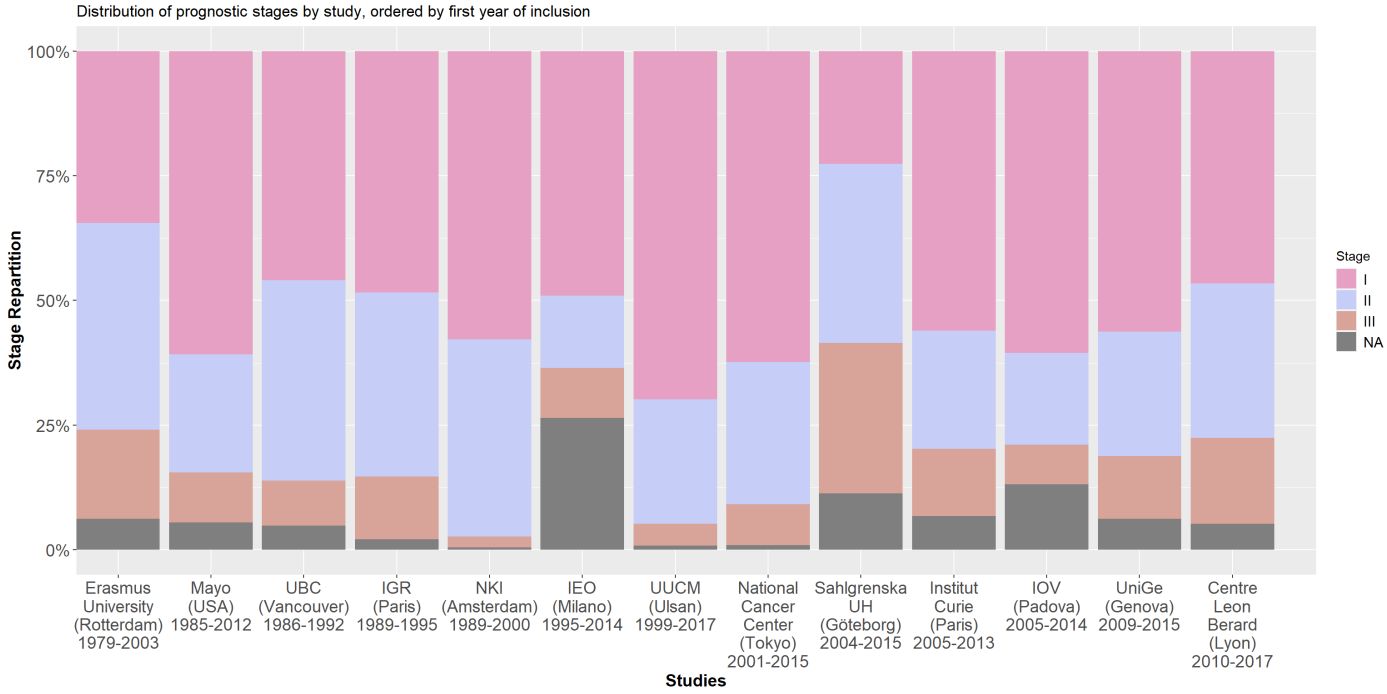
eFigure 1-C. T1 Substage Distribution per Cohort, Ordered According to First Year of Inclusion



eFigure 1-D. Nodal Stage Distribution per Cohort, Ordered According to First Year of Inclusion



eFigure 1-E. Overall Stage Distribution per Cohort, According to First Year of Inclusion



eTable 1-C. Characteristics of the Population Included in the Study

	UBC (Vancouver)	*Curie (Paris)*	*Erasmus (Rotterdam)*	*UniGe (Genova)*	*IGR (Paris)*	*National Cancer Center (Tokyo)*	*UUCM (Ulsan)*	*Leon Berard (Lyon)*	*Mayo (USA)*	*IEO (Milano)*	*NKI (Amsterdam)*	*IOV (Padova)*	*Sahlgrenska (Göteborg)*	*Overall*
	n= 309	*n= 148*	*n= 241*	*n= 16*	*n= 95*	*n= 109*	*n= 116*	*n= 58*	*n= 181*	*n= 159*	*n= 443*	*n= 38*	*n= 53*	***n= 1966***
Date of surgery (or diagnosis)														
Min-Max	1986 - 1992	2005- 2013	1979 - 2003	2009 - 2015	1989-1995	2001 - 2015	1999-2017	2010- 2017	1985-2012	1995 - 2014	1989 - 2000	2005 - 2014	2004 - 2015	**1979 -2017**
Age														
Mean	57.7	72.4	55.4	75.1	50.5	65.1	58.6	72.1	62.6	66.0	34.6	68.2	77.7	**55.9**
SD	12.9	12.8	13.6	12.8	10.0	13.3	14.3	12.8	14.8	14.2	3.6	13.2	9.7	**17.5**
Median	59.0	76.0	56.0	80.5	50.5	69.0	59.5	75.5	63.8	67.0	35.0	70.5	78.0	**56.0**
Q1-Q3	49.0 - 68.0	62.8 - 82.0	45.0 - 66.0	64.8 - 82.0	43.4 - 57.8	56.0 - 74.0	48.0 - 70.0	62.8 - 81.0	52.0 - 73.8	55.0 - 76.5	32.0 - 38.0	58.5 - 77.0	73.0 - 84.0	**38.9 - 71.0**
Min-Max	27.0 - 89.0	37.0 - 94.0	28.0 - 88.0	45.0 - 90.0	29.1 - 69.5	32.0 - 99.0	24.0 - 88.0	28.0 - 89.0	30.0 - 93.7	27.0 - 96.0	22.0 - 39.0	31.0 - 88.0	43.0 - 95.0	**22.0 - 99.0**
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Age (category)														
[18-49y], *n* (%)	90 (29.1)	7 (4.7)	91 (37.8)	1 (6.2)	45 (47.4)	17 (15.6)	36 (31)	2 (3.4)	40 (22.1)	23 (14.5)	443 (100)	3 (7.9)	2 (3.8)	**800 (40.7)**
[50+y], *n* (%)	219 (70.9)	141 (95.3)	150 (62.2)	15 (93.8)	50 (52.6)	92 (84.4)	80 (69)	56 (96.6)	141 (77.9)	136 (85.5)	0 (0)	35 (92.1)	51 (96.2)	**1166 (59.3)**
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Menopausal status														
Premenopausal, *n* (%)	81 (27.1)	8 (5.6)	95 (39.6)	1 (6.2)	46 (48.4)	0 (0)	0 (NaN)	5 (8.6)	47 (26)	19 (11.9)	0 (NaN)	6 (15.8)	0 (NaN)	**308 (23.4)**
Postmenopausal, *n* (%)	217 (72.6)	134 (94.4)	145 (60.4)	15 (93.8)	49 (51.6)	87 (100)	0 (NaN)	53 (91.4)	134 (74)	140 (88.1)	0 (NaN)	32 (84.2)	0 (NaN)	**1006 (76.5)**
Pregnant, *n* (%)	1 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (NaN)	0 (0)	0 (0)	0 (0)	0 (NaN)	0 (0)	0 (NaN)	**1 (0.1)**
Missing	10	6	1	0	0	22	116	0	0	0	443	0	53	**651**
TILs value (cont)														
Mean	22.0	26.9	24.8	11.9	18.6	17.1	25.3	22.5	26.0	13.0	37.6	15.4	22.2	**25.4**
SD	19.8	24.0	26.7	20.1	18.5	18.5	30.1	25.1	21.0	18.9	33.3	20.5	25.0	**26.5**
Median	15.0	20.0	15.0	4.0	10.0	10.0	10.0	12.5	20.0	4.0	20.0	7.0	10.0	**15.0**
Q1-Q3	5.0 - 35.0	5.0 - 40.0	5.0 - 35.0	1.0 - 15.0	5.0 - 25.0	0.0 - 30.0	1.8 - 40.0	5.0 - 28.8	10.0 - 40.0	2.0 - 15.0	5.0 - 70.0	3.0 - 19.3	5.0 - 30.0	**5.0 - 40.0**
Min-Max	1.0 - 90.0	0.0 - 90.0	1.0 - 95.0	1.0 - 80.0	0.0 - 80.0	0.0 - 70.0	1.0 - 90.0	1.0 - 80.0	0.0 - 80.0	0.0 - 80.0	1.0 - 95.0	1.0 - 80.0	1.0 - 95.0	**0.0 - 95.0**
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
TILs value (cat)														
[0-29], *n* (%)	217 (70.2)	86 (58.1)	165 (68.5)	14 (87.5)	74 (77.9)	77 (70.6)	74 (63.8)	43 (74.1)	115 (63.5)	134 (84.3)	231 (52.1)	32 (84.2)	38 (71.7)	**1300 (66.1)**
[30-49], *n* (%)	59 (19.1)	31 (20.9)	33 (13.7)	1 (6.2)	10 (10.5)	20 (18.3)	14 (12.1)	3 (5.2)	30 (16.6)	10 (6.3)	30 (6.8)	2 (5.3)	6 (11.3)	**249 (12.7)**
[50-74], *n* (%)	28 (9.1)	25 (16.9)	15 (6.2)	0 (0)	9 (9.5)	12 (11)	14 (12.1)	8 (13.8)	30 (16.6)	13 (8.2)	87 (19.6)	3 (7.9)	5 (9.4)	**249 (12.7)**
[75-100], *n* (%)	5 (1.6)	6 (4.1)	28 (11.6)	1 (6.2)	2 (2.1)	0 (0)	14 (12.1)	4 (6.9)	6 (3.3)	2 (1.3)	95 (21.4)	1 (2.6)	4 (7.5)	**168 (8.5)**
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Histological subtype														
Ductal, *n* (%)	234 (84.5)	92 (62.2)	197 (82.1)	12 (75)	0 (NaN)	69 (63.3)	99 (85.3)	33 (56.9)	115 (63.5)	119 (74.8)	372 (84)	24 (63.2)	34 (64.2)	**1427 (76.3)**
Lobular, *n* (%)	5 (1.6)	12 (8.1)	5 (2.1)	0 (0)	0 (NaN)	3 (2.8)	0 (0)	7 (12.1)	0 (0)	3 (1.9)	2 (0.5)	1 (2.6)	3 (5.7)	**41 (2.2)**
Medullary, *n* (%)	31 (10)	3 (2)	17 (7.1)	0 (0)	0 (NaN)	0 (0)	0 (0)	0 (0)	31 (17.1)	3 (1.9)	34 (7.7)	1 (2.6)	0 (0)	**120 (6.4)**
Tubular, *n* (%)	1 (0.3)	2 (1.4)	0 (0)	0 (0)	0 (NaN)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	**3 (0.2)**
Mucinous, *n* (%)	4 (1.3)	2 (1.4)	2 (0.8)	0 (0)	0 (NaN)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)	0 (0)	0 (0)	**9 (0.5)**
Other, *n* (%)	5 (1.6)	32 (21.6)	10 (4.2)	4 (25)	0 (NaN)	37 (33.9)	9 (7.8)	13 (22.4)	35 (19.3)	31 (19.5)	35 (7.9)	8 (21.1)	13 (24.5)	**232 (12.4)**
Metaplastic, *n* (%)	2 (0.6)	5 (3.4)	9 (3.8)	0 (0)	0 (NaN)	0 (0)	8 (6.9)	5 (8.6)	0 (0)	24 (1.3)	0 (0)	4 (10.5)	3 (5.7)	**38 (2)**
Missing	0	0	1	0	95	0	0	0	0	0	0	0	0	**96**

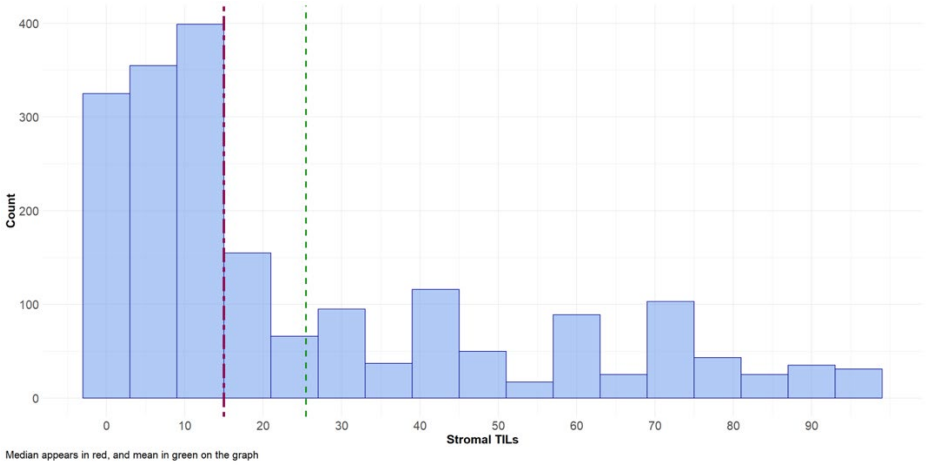
	UBC (Vancouver)	*Curie (Paris)*	*Erasmus (Rotterdam)*	*UniGe (Genova)*	*IGR (Paris)*	*National Cancer Center (Tokyo)*	*UUCM (Ulsan)*	*Leon Berard (Lyon)*	*Mayo (USA)*	*IEO (Milano)*	*NKI (Amsterdam)*	*IOV (Padova)*	*Sahlgrenska (Göteborg)*	*Overall*
	n= 309	*n= 148*	*n= 241*	*n= 16*	*n= 95*	*n= 109*	*n= 116*	*n= 58*	*n= 181*	*n= 159*	*n= 443*	*n= 38*	*n= 53*	***n= 1966***
Tumor size (cm)														
Mean	2.3	2.0	2.6	2.0	2.1	1.7	1.6	2.2	2.0	1.6	2.2	1.9	3.8	**2.1**
SD	1.3	1.5	1.4	1.3	0.9	1.0	1.4	1.8	1.8	1.6	1.2	1.8	2.9	**1.5**
Median	2.0	1.7	2.3	2.0	2.0	1.7	1.3	1.9	1.5	1.2	2.0	1.6	2.7	**2.0**
Q1-Q3	1.5 - 2.8	0.9 - 3.0	1.7 - 3.0	1.0 - 2.5	1.6 - 2.5	1.1 - 2.5	0.5 - 2.0	0.8 - 2.5	1.0 - 2.5	0.3 - 2.3	1.5 - 2.5	0.8 - 2.2	1.9 - 5.2	**1.2 - 2.6**
Min-Max	0.1 - 9.9	0.3 - 8.0	0.6 - 9.0	0.4 - 5.5	0.0 - 5.0	0.1 - 4.6	0.2 - 10.0	0.1 - 8.0	0.1 - 15.0	0.0 - 10.7	0.5 - 14.0	0.2 - 10.0	0.3 - 13.4	**0.0 - 15.0**
Missing	1	0	14	1	1	0	0	0	0	7	50	0	0	**74**
Tumor category														
T1, *n* (%)	170 (55.2)	94 (63.5)	98 (43.2)	9 (60)	56 (59.6)	75 (68.8)	90 (77.6)	36 (62.1)	123 (68)	107 (70.4)	256 (58)	28 (73.7)	17 (32.1)	**1159 (59.7)**
T2, *n* (%)	128 (41.6)	48 (32.4)	117 (51.5)	5 (33.3)	38 (40.4)	34 (31.2)	22 (19)	18 (31)	51 (28.2)	39 (25.7)	175 (39.7)	8 (21.1)	22 (41.5)	**705 (36.3)**
T3/T4, *n* (%)	10 (3.2)	6 (4.1)	12 (5.3)	1 (6.7)	0 (0)	0 (0)	4 (3.4)	4 (6.9)	7 (3.9)	6 (3.9)	10 (2.3)	2 (5.3)	14 (26.4)	**76 (3.9)**
Missing	1	0	14	1	1	0	0	0	0	7	2	0	0	**26**
T1 subsets														
T1mi, *n* (%)	5 (1.6)	0 (0)	0 (0)	0 (0)	4 (4.3)	3 (2.8)	0 (0)	1 (1.7)	6 (3.3)	21 (13.8)	0 (0)	0 (0)	0 (0)	**40 (2.1)**
T1a, *n* (%)	8 (2.6)	13 (8.8)	0 (0)	1 (6.7)	0 (0)	12 (11)	30 (25.9)	7 (12.1)	13 (7.2)	30 (19.7)	2 (0.5)	6 (15.8)	2 (3.8)	**124 (6.5)**
T1b, *n* (%)	34 (11)	33 (22.3)	17 (7.5)	3 (20)	8 (8.5)	12 (11)	19 (16.4)	8 (13.8)	44 (24.3)	17 (11.2)	28 (6.8)	7 (18.4)	2 (3.8)	**232 (12.1)**
T1c, *n* (%)	123 (39.9)	48 (32.4)	81 (35.7)	5 (33.3)	44 (46.8)	48 (44)	41 (35.3)	20 (34.5)	60 (33.1)	39 (25.7)	199 (48.1)	15 (39.5)	13 (24.5)	**736 (38.5)**
T2, *n* (%)	128 (41.6)	48 (32.4)	117 (51.5)	5 (33.3)	38 (40.4)	34 (31.2)	22 (19)	18 (31)	51 (28.2)	39 (25.7)	175 (42.3)	8 (21.1)	22 (41.5)	**705 (36.9)**
T3/T4, *n* (%)	10 (3.2)	6 (4.1)	12 (5.3)	1 (6.7)	0 (0)	0 (0)	4 (3.4)	4 (6.9)	7 (3.9)	6 (3.9)	10 (2.4)	2 (5.3)	14 (26.4)	**76 (4)**
Positive lymph nodes														
Mean	0.4	0.6	1.2	0.7	0.9	0.6	0.3	0.4	0.4	1.0	0.0	0.2	2.3	**0.5**
SD	1.6	2.2	3.0	2.3	2.7	2.6	1.2	1.0	1.6	4.1	0.0	1.0	5.0	**2.2**
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	**0.0**
Q1-Q3	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.5	0.0 - 0.0	0.0 - 0.0	0.0 - 1.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 0.0	0.0 - 1.5	**0.0 - 0.0**
Min-Max	0.0 - 14.0	0.0 - 20.0	0.0 - 17.0	0.0 - 9.0	0.0 - 21.0	0.0 - 22.0	0.0 - 9.0	0.0 - 7.0	0.0 - 12.0	0.0 - 38.0	0.0 - 0.0	0.0 - 6.0	0.0 - 21.0	**0.0 - 38.0**
Missing	6	1	0	0	0	1	0	1	10	31	0	4	6	**60**
Positive lymph nodes (cat.)														
N0 (0), *n* (%)	262 (86.5)	122 (83)	184 (76.3)	14 (87.5)	71 (74.7)	91 (84.3)	103 (88.8)	42 (73.7)	149 (87.1)	109 (85.2)	443 (100)	32 (94.1)	29 (61.7)	**1651 (86.6)**
N1 (1-3), *n* (%)	30 (9.9)	16 (10.9)	25 (10.4)	1 (6.2)	20 (21.1)	14 (13)	10 (8.6)	14 (24.6)	16 (9.4)	11 (8.6)	0 (0)	1 (2.9)	8 (17)	**166 (8.7)**
N2 (4-9), *n* (%)	9 (3)	8 (5.4)	23 (9.5)	1 (6.2)	2 (2.1)	1 (0.9)	3 (2.6)	1 (1.8)	4 (2.3)	3 (2.3)	0 (0)	1 (2.9)	6 (12.8)	**62 (3.3)**
N3 (10+), *n* (%)	2 (0.7)	1 (0.7)	9 (3.7)	0 (0)	2 (2.1)	2 (1.9)	0 (0)	0 (0)	2 (1.2)	5 (3.9)	0 (0)	0 (0)	4 (8.5)	**27 (1.4)**
Missing	6	1	0	0	0	1	0	1	10	31	0	4	6	**60**
Histological grade														
1, *n* (%)	8 (2.7)	29 (20.9)	5 (2.1)	3 (18.8)	2 (2.1)	7 (6.4)	4 (3.5)	2 (3.6)	4 (2.2)	22 (14.4)	3 (0.7)	2 (5.4)	4 (7.5)	**95 (4.9)**
2, *n* (%)	64 (21.3)	50 (36)	44 (18.3)	6 (37.5)	44 (46.8)	38 (34.9)	45 (39.1)	20 (35.7)	26 (14.4)	54 (35.3)	59 (13.3)	11 (29.7)	12 (22.6)	**473 (24.4)**
3, *n* (%)	229 (76.1)	60 (43.2)	191 (79.6)	7 (43.8)	48 (51.1)	64 (58.7)	66 (57.4)	34 (60.7)	151 (83.4)	77 (50.3)	381 (86)	24 (64.9)	37 (69.8)	**1369 (70.7)**
Missing	8	9	1	0	1	0	1	2	0	6	0	1	0	**29**

	UBC (Vancouver)	*Curie (Paris)*	*Erasmus (Rotterdam)*	*UniGe (Genova)*	*IGR (Paris)*	*National Cancer Center (Tokyo)*	*UUCM (Ulsan)*	*Leon Berard (Lyon)*	*Mayo (USA)*	*IEO (Milano)*	*NKI (Amsterdam)*	*IOV (Padova)*	*Sahlgrenska (Göteborg)*	*Overall*
	n= 309	*n= 148*	*n= 241*	*n= 16*	*n= 95*	*n= 109*	*n= 116*	*n= 58*	*n= 181*	*n= 159*	*n= 443*	*n= 38*	*n= 53*	***n= 1966***
AJCC Prognostic Stages														
I, *n* (%)	142 (48.3)	83 (60.1)	83 (36.7)	9 (60)	46 (49.5)	68 (63)	81 (70.4)	27 (49.1)	110 (64.3)	78 (66.7)	256 (58)	23 (69.7)	12 (25.5)	**1018 (54.9)**
II, *n* (%)	124 (42.2)	35 (25.4)	100 (44.2)	4 (26.7)	35 (37.6)	31 (28.7)	29 (25.2)	18 (32.7)	43 (25.1)	23 (19.7)	175 (39.7)	7 (21.2)	19 (40.4)	**643 (34.7)**
III, *n* (%)	28 (9.5)	20 (14.5)	43 (19)	2 (13.3)	12 (12.9)	9 (8.3)	5 (4.3)	10 (18.2)	18 (10.5)	16 (13.7)	10 (2.3)	3 (9.1)	16 (34)	**192 (10.4)**
Missing	15	10	15	1	2	1	1	3	10	42	2	5	6	**113**
AJCC Anatomic Stages														
I, *n* (%)	147 (48.7)	88 (59.9)	83 (36.6)	9 (60)	46 (48.9)	68 (63)	82 (70.7)	29 (50.9)	110 (64.3)	80 (66.1)	256 (58)	24 (70.6)	12 (25.5)	**1034 (55)**
II, *n* (%)	141 (46.7)	48 (32.7)	111 (48.9)	5 (33.3)	44 (46.8)	37 (34.3)	31 (26.7)	25 (43.9)	52 (30.4)	33 (27.3)	185 (42)	9 (26.5)	22 (46.8)	**743 (39.5)**
III, *n* (%)	14 (4.6)	11 (7.5)	33 (14.5)	1 (6.7)	4 (4.3)	3 (2.8)	3 (2.6)	3 (5.3)	9 (5.3)	8 (6.6)	0 (0)	1 (2.9)	13 (27.7)	**103 (5.5)**
Missing	7	1	14	1	1	1	0	1	10	38	2	4	6	**86**
	UBC (Vancouver)	***Curie (Paris)***	***Erasmus (Rotterdam)***	***UniGe (Genova)***	***IGR (Paris)***	***National Cancer Center (Tokyo)***	***UUCM (Ulsan)***	***Leon Berard (Lyon)***	***Mayo (USA)***	***IEO (Milano)***	***NKI (Amsterdam)***	***IOV (Padova)***	***Sahlgrenska (Göteborg)***	***Overall***
	n= 309	*n= 148*	*n= 241*	*n= 16*	*n= 95*	*n= 109*	*n= 116*	*n= 58*	*n= 181*	*n= 159*	*n= 443*	*n= 38*	*n= 53*	***n= 1966***
Radiotherapy														
No, *n* (%)	138 (44.7)	40 (27)	64 (27.6)	5 (31.2)	15 (15.8)	66 (60.6)	75 (64.7)	23 (39.7)	105 (58.7)	48 (30.2)	125 (28.2)	13 (34.2)	26 (50)	**743 (38)**
	UBC (Vancouver)	***Institut Curie (Paris)***	***Erasmus University (Rotterdam)***	***UniGe (Genova)***	***IGR (Paris)***	***National Cancer Center (Tokyo)***	***UUCM (Ulsan)***	***Centre Leon Berard (Lyon)***	***Mayo (USA)***	***IEO (Milano)***	***NKI (Amsterdam)***	***IOV (Padova)***	***Sahlgrenska UH (Göteborg)***	***Overall***
	n= 309	*n= 148*	*n= 241*	*n= 16*	*n= 95*	*n= 109*	*n= 116*	*n= 58*	*n= 181*	*n= 159*	*n= 443*	*n= 38*	*n= 53*	***n= 1966***
Yes, *n* (%)	171 (55.3)	108 (73)	168 (72.4)	11 (68.8)	80 (84.2)	43 (39.4)	41 (35.3)	35 (60.3)	74 (41.3)	111 (69.8)	318 (71.8)	25 (65.8)	26 (50)	**1211 (62)**
Missing	0	0	9	0	0	0	0	0	2	0	0	0	1	**12**
Type of surgery														
Partial mastectomy, *n* (%)	163 (52.8)	97 (65.5)	141 (58.5)	10 (62.5)	70 (73.7)	51 (46.8)	81 (69.8)	23 (39.7)	87 (48.1)	132 (83)	298 (68.3)	30 (78.9)	18 (34)	**1201 (61.3)**
Complete mastectomy, *n*	146 (47.2)	51 (34.5)	100 (41.5)	6 (37.5)	25 (26.3)	58 (53.2)	35 (30.2)	35 (60.3)	94 (51.9)	27 (17)	138 (31.7)	8 (21.1)	35 (66)	**758 (38.7)**
Missing	0	0	0	0	0	0	0	0	0	0	7	0	0	**7**
Overall survival														
Alive, *n* (%)	85 (27.5)	125 (84.5)	128 (53.1)	10 (62.5)	59 (62.1)	94 (86.2)	89 (76.7)	51 (87.9)	84 (46.4)	123 (77.4)	275 (62.1)	22 (57.9)	18 (34)	**1163 (59.2)**
Dead, *n* (%)	224 (72.5)	23 (15.5)	113 (46.9)	6 (37.5)	36 (37.9)	15 (13.8)	27 (23.3)	7 (12.1)	97 (53.6)	36 (22.6)	168 (37.9)	16 (42.1)	35 (66)	**803 (40.8)**
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Follow-up (years) ¤*														
Median*	32.5	5.7	11.2	6.2	22.1	8.0	9.6	1.7	15.0	9.9	24.0	7.2	8.4	**18.0**
Confidence interval 95%	32.0 - 33.5	4.6 - 6.3	10.3 - 13.7	6.0 - NA	21.6 - 23.2	6.7 - 9.2	9.0 - 10.1	0.5 - 3.0	12.7 - 19.3	8.9 - 10.9	24.0 - 25.0	6.6 - 10.0	8.2 - NA	**15.3 - 20.0**
Min-Max	0.1 - 35.2	0.0 - 14.1	0.3 - 27.0	2.8 - 10.4	0.9 - 25.8	0.0 - 17.8	0.3 - 21.8	0.1 - 10.2	0.0 - 28.8	0.0 - 21.7	0.0 - 29.0	0.4 - 13.7	0.5 - 11.6	**0.0 - 35.2**

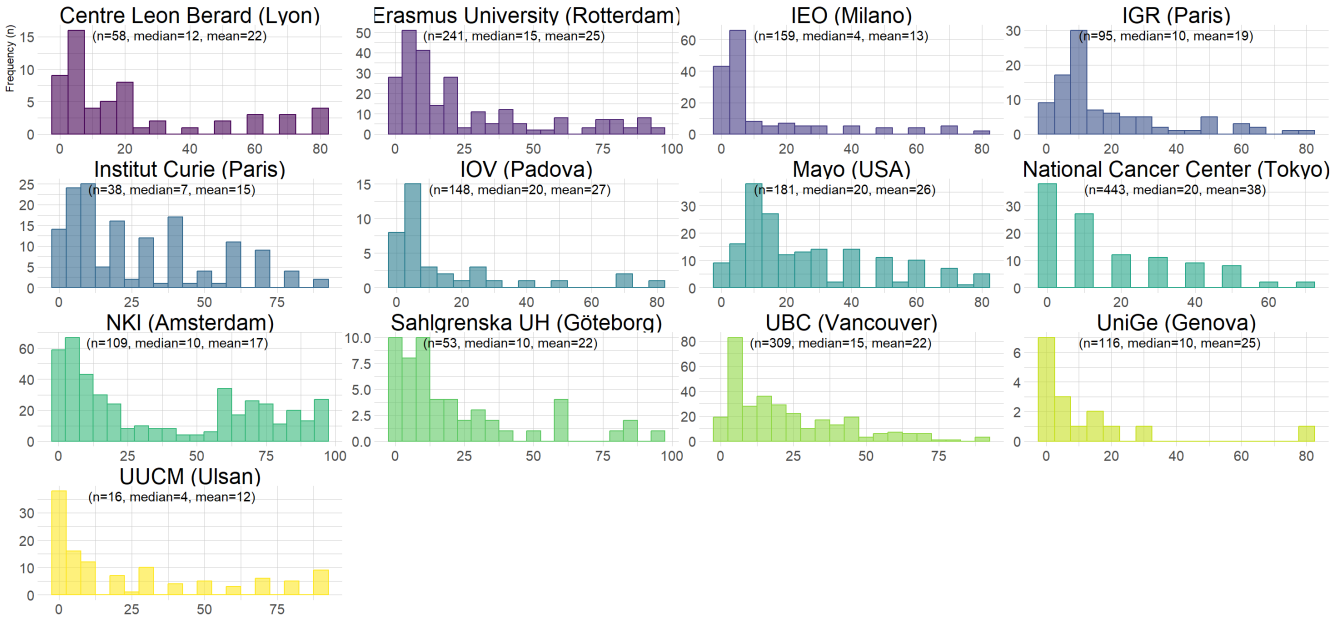
*Calculated with reverse Kaplan-Meier method.

2. TIL distribution

eFigure 2-A. Distribution of the Stromal TILs in the Overall Study



eFigure 2-B. Distribution of the Stromal TILs per Cohort



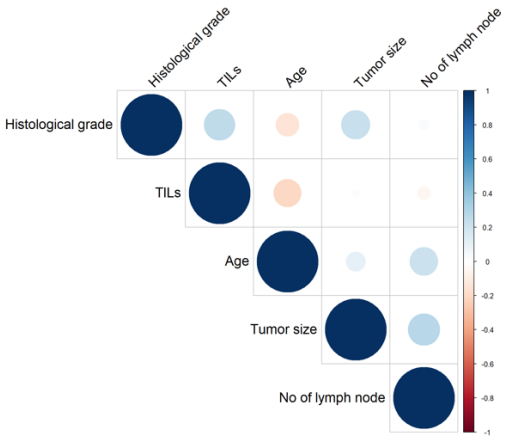
eTable 2-A. Summary of TILs Values by Cohort

Study	Min	Quantile 25%	Median	Mean	Std	Quantile 75%	Max	n
Centre Leon Berard (Lyon)	1	5.0	12.5	22.5	25.1	28.8	80	58
Erasmus University (Rotterdam)	1	5.0	15.0	24.8	26.7	35.0	95	241
IEO (Milano)	0	2.0	4.0	13.0	18.9	15.0	80	159
IGR (Paris)	0	5.0	10.0	18.6	18.5	25.0	80	95
Institut Curie (Paris)	0	5.0	20.0	26.9	24.0	40.0	90	148
IOV (Padova)	1	3.0	7.0	15.4	20.5	19.2	80	38
Mayo (USA)	0	10.0	20.0	26.0	21.0	40.0	80	181
National Cancer Center (Tokyo)	0	0.0	10.0	17.1	18.5	30.0	70	109
NKI (Amsterdam)	1	5.0	20.0	37.6	33.3	70.0	95	443
Sahlgrenska UH (Göteborg)	1	5.0	10.0	22.2	25.0	30.0	95	53
UBC (Vancouver)	1	5.0	15.0	22.0	19.8	35.0	90	309
UniGe (Genova)	1	1.0	4.0	11.9	20.1	15.0	80	16
UUCM (Ulsan)	1	1.8	10.0	25.3	30.1	40.0	90	116

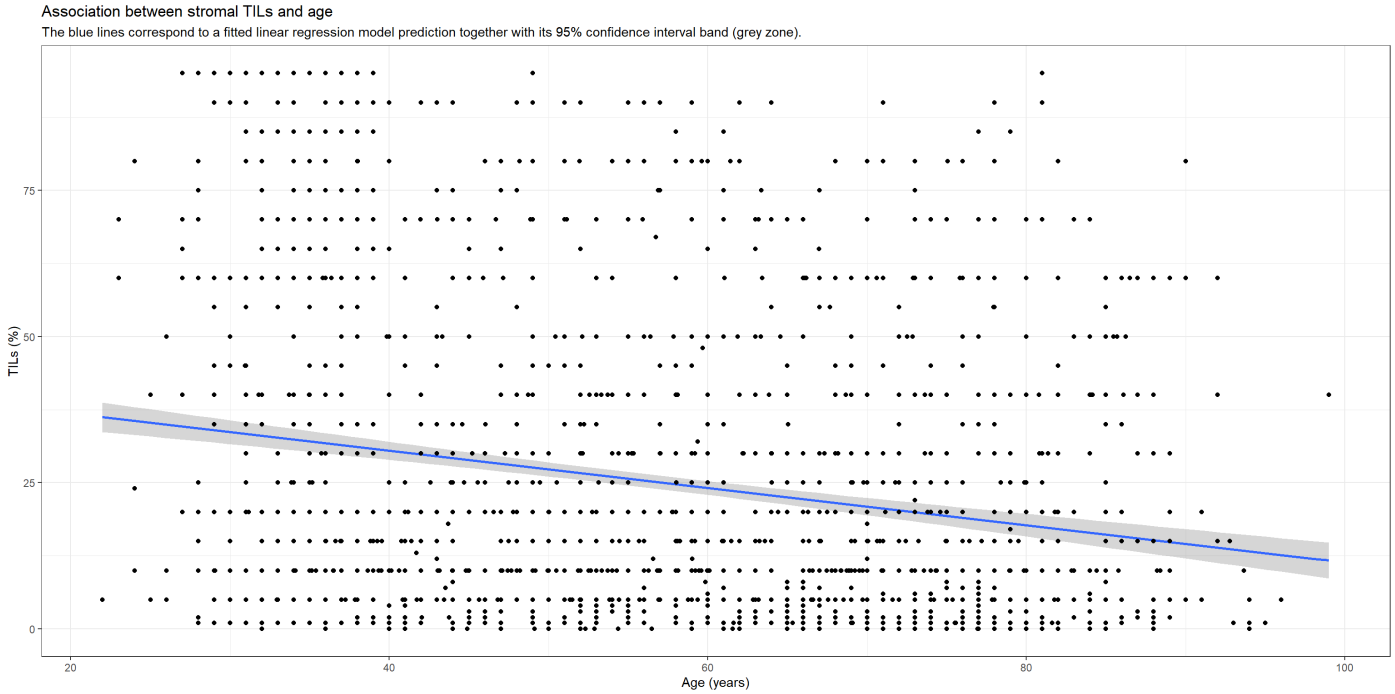
eTable 2-B. Correlation Matrix Between Clinicopathological Characteristics and TILs				
	Tumor size	**Histological grade**	**Number of lymph nodes**	**Stromal TILs**
Age	0.0 [0.0; 0.1] p =0.12	-0.2 [-0.2; -0.1] p $\leq 10^{-5}$	0.3 [0.3; 0.3] p $\leq 10^{-6}$	-0.2 [-0.2; -0.1] p $\leq 10^{-6}$
Tumor size	---	0.3 [0.2; 0.3] p $\leq 10^{-6}$	0.2 [0.2; 0.3] p $\leq 10^{-6}$	0.0 [0.0; 0.1] p =0.22
Histological grade	---		0.0 [0.0; 0.1] p =0.45	0.3 [0.3; 0.3] p $\leq 10^{-6}$
Number of lymph nodes	---			0.0 [-0.1; 0.0] p =0.18

Pairwise correlation between the clinicopathological characteristics using Spearman's correlation (when both or at least one of the two variables compared were numerical). Otherwise, we used the Kendall's tau when the two variables compared were categorical. The correlation was assessed, for each pair, on complete observations (pairwise complete observations technique for the handling of missing data). Correlation coefficients values and confidence intervals obtained with bootstrap are given in Table 2.

eFigure 2-B. Graphical Display of the Correlation Matrix Between Clinicopathological Characteristics and TILs



eFigure 2-C. Scatterplot of Age vs TILs



While the association between age and TILs was significant, the Spearman correlation value was relatively weak (-0.2). We graphed age according to TILs level to evaluate if both variables are linearly linked. No pattern is easily visible which suggests the absence of a linear relationship between age and the level of TILs.

3. Statistical Methods

Survival endpoints

Composite events were defined according to the guidelines of the Updated Standardized Definitions for Efficacy End Points (STEEP) in Adjuvant Breast Cancer Clinical Trials, second edition[1]. Survival times were calculated from the date of surgery in all studies when it was available and from date of diagnosis when it was not available. This later was the case for: UBC (Vancouver) and NKI (Amsterdam). Then survival delays were calculated from this start point to the date of occurrence of the event. Patients who did not experience the event are censored at the date of last follow-up. Considered events were: death, local and regional recurrence, distant recurrence, contralateral invasive breast cancer and second primary malignancy (other than breast cancer) for the following composite events:

eTable 3-A. Breast Cancer Clinical Trial End Points per STEEP 2.0

	Death (any cause)	Distant recurrence	Local regional invasive recurrence	Invasive ipsilateral breast tumor recurrence	Second primary invasive cancer (non-breast)	Invasive contralateral breast cancer
OS	X					
DDFS	X	X			X	
DRFS	X	X				
RFS	X	X	X	X		
IBCFS	X	X	X	X		X
IDFS	X	X	X	X	X	X

In older cohorts, invasive contra-lateral breast cancer may not be differentiated from second cancer. This is the case in the IGR cohort (Paris) where the two events are confounded on a single variable. Consequently, the DDFS and IBCFS criteria will be slightly overestimated by 7% and 5% respectively.

In addition, some cohorts do not differentiate the ipsilateral invasive event from locoregional relapse; the former being counted as locoregional relapse without detail. No information on second primary invasive cancer (non breast) was available for the UBC (Vancouver) study.

Number of events

eTable 3-B. Number and Percentage of Composite Events, by Study and in Total

	OS	DDFS	DRFS	RFS	IBCFS	IDFS
UBC (Vancouver) (n=309)	224 (72.5%)	225 (72.8%)	225(72.8%)	229 (74.1%)	239 (77.3%)	239 (77.3%)
Institut Curie (Paris) (n=148)	23 (15.5%)	33 (22.3%)	27 (18.2%)	33 (22.3%)	34 (23%)	39 (26.4%)
Erasmus University (Rotterdam) (n=241)	113 (46.9%)	128 (53.1%)	116 (48.1%)	122 (50.6%)	134 (55.6%)	143 (59.3%)
UniGe (Genova) (n=16)	6 (37.5%)	7 (43.8%)	6 (37.5%)	6 (37.5%)	6 (37.5%)	7 (43.8%)
IGR (Paris) (n=95)	36 (37.9%)	50 (52.6%)	39 (41.1%)	46 (48.4%)	56 (58.9%)	56 (58.9%)
National Cancer Center (Tokyo) (n=109)	15 (13.8%)	23 (21.1%)	21 (19.3%)	27 (24.8%)	28 (25.7%)	30 (27.5%)
UUCM (Ulsan) (n=116)	27 (23.3%)	31 (26.7%)	29 (25%)	38 (32.8%)	40 (34.5%)	41 (35.3%)
Centre Leon Berard (Lyon) (n=58)	7 (12.1%)	8 (13.8%)	7 (12.1%)	10 (17.2%)	11 (19%)	12 (20.7%)
Mayo (USA) (n=181)	97 (53.6%)	104 (57.5%)	100 (55.2%)	103 (56.9%)	114 (63%)	118 (65.2%)
IEO (Milano) (n=159)	36 (22.6%)	39 (24.5%)	37 (23.3%)	52 (32.7%)	58 (36.5%)	60 (37.7%)
NKI (Amsterdam) (n=443)	168 (37.9%)	191 (43.1%)	174 (39.3%)	221 (49.9%)	263 (59.4%)	273 (61.6%)
IOV (Padova) (n=38)	16 (42.1%)	18 (47.4%)	16 (42.1%)	17 (44.7%)	17 (44.7%)	19 (50%)
SahIgrenska UH (Göteborg) (n=53)	35 (66%)	37 (69.8%)	35 (66%)	36 (67.9%)	36 (67.9%)	37 (69.8%)
TOTAL (n=1966)	**803 (40.8%)**	**894 (45.5%)**	**832 (42.3%)**	**940 (47.8%)**	**1036 (52.7%)**	**1074 (54.6%)**

eTable 3-C. provides the number and percentage of each **first** event occurring for each patient. In case of simultaneous events, the order was as follows: Invasive ipsilateral breast tumor recurrence, Local regional invasive recurrence, Invasive contralateral breast cancer, Second primary invasive cancer, Distant recurrence and Death.

eTable 3-C. Number and Percentage of First Events, by Study and in Total

	UniGe (Genova)	IOV (Padova)	Sahlgrenska UH (Göteborg)	Centre Leon Berard (Lyon)	IGR (Paris)	National Cancer Center (Tokyo)	UUCM (Ulsan)	Institut Curie (Paris)	IEO (Milano)	Mayo (USA)	Erasmus University (Rotterdam)	UBC (Vancouver)	NKI (Amsterdam)	TOTAL
Death (any cause)	4 (25%)	10 (26%)	13 (25%)	6 (10%)	5 (5%)	4 (4%)	14 (12%)	7 (5%)	12 (8%)	44 (24%)	4 (2%)	120 (39%)	45 (10%)	288
Distant recurrence	1 (6%)	2 (5%)	14 (26%)	3 (5%)	25 (26%)	8 (7%)	6 (5%)	15 (10%)	14 (9%)	35 (19%)	58 (24%)	44 (14%)	59 (13%)	284
Local regional invasive recurrence	0 (0%)	4 (11%)	2 (4%)	1 (2%)	13 (14%)	6 (6%)	16 (14%)	3 (2%)	20 (13%)	4 (2%)	36 (15%)	25 (8%)	12 (3%)	142
Invasive ipsilateral breast tumor recurrence	0 (0%)	0 (0%)	3 (6%)	0 (0%)	0 (0%)	4 (4%)	0 (0%)	5 (3%)	0 (0%)	5 (3%)	5 (2%)	29 (9%)	59 (13%)	110
Invasive contralateral breast cancer	1 (6%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)	3 (3%)	1 (1%)	6 (4%)	14 (8%)	22 (9%)	21 (7%)	70 (16%)	140
Second primary invasive cancer	1 (6%)	3 (8%)	5 (9%)	1 (2%)	13 (14%)	7 (6%)	2 (2%)	8 (5%)	8 (5%)	16 (9%)	18 (7%)	Missing	28 (6%)	110
Alive	9 (56%)	19 (50%)	16 (30%)	46 (79%)	39 (41%)	79 (72%)	75 (65%)	109 (74%)	99 (62%)	63 (35%)	98 (41%)	70 (23%)	170 (38%)	892
TOTAL	**16**	**38**	**53**	**58**	**95**	**109**	**116**	**148**	**159**	**181**	**241**	**309**	**443**	**1966**

Statistical models

The Cox regression models will be used to test the independent prognostic value of the TILs to the standard clinicopathological variables through the use of likelihood ratio tests. Our standard clinicopathological variables include tumor size (continuous), tumor grade (well differentiated, moderately differentiated and poorly differentiated), age (continuous), numbers of positive lymph nodes (continuous), and radiotherapy treatment (RT) (yes/no). We will test the log-linearity assumption of the continuous variables of the model using fitting with linear tail-restricted cubic splines. The models are stratified on study. The following models will be fitted:

- Model 1: TILs (univariable)
- Model 2: age + tumor size + tumor grade + positive lymph nodes + RT
- Model 3: age + tumor size + tumor grade + positive lymph nodes + RT + TILs

For each model, the followings will be calculated: adjusted hazard ratios (HR), associated 95% confidence interval and p-value for each variable. The prognostic value of the TILs will be tested by comparing likelihood values between model 1 and the null model with a likelihood ratio test. The independent prognostic additional value of stromal TILs will be tested by comparing likelihood values between models 2 and 3 with a likelihood ratio test.

We will test the prognostic value of the TILs on each of the endpoints detailed above: IDFS, OS, DDFS, RFS and IBCFS

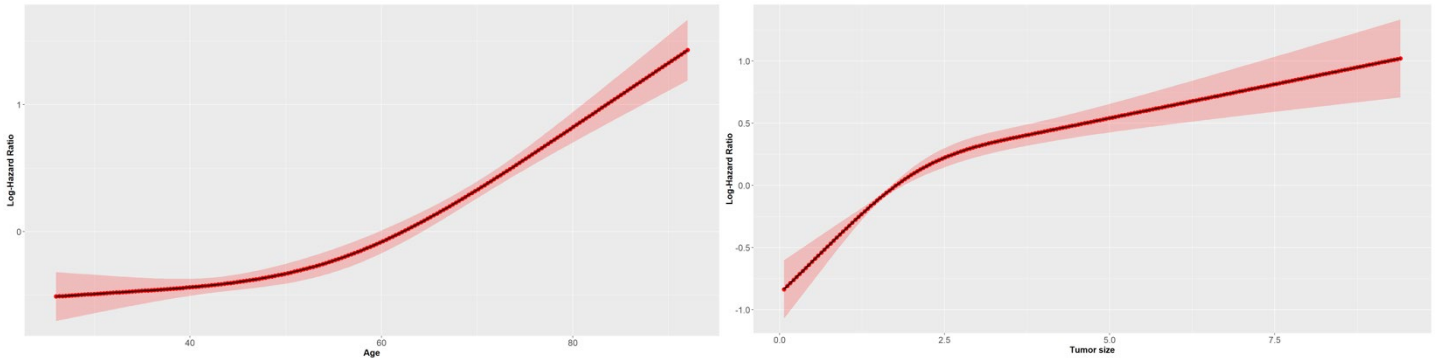
Before the statistical analysis, all the continuous variables included in the model will be tested for their linear effect. In case of non-linear effect, a fitted cubic spline version of the variable will be considered.

Pre-tests on log-linearity

All the continuous variables included in the model (Age, Tumor size) are evaluated for their linear effect.

Univariable graphic

Each continuous variable with its version fitted by cubic splines with **3 knots** (in red) is plotted with its confidence interval. Knots are located at the 0.1, 0.5 and 0.9th quantile. OS is the event of interest. The `Positive nodes' variable was not tested for its linear effect; its distribution is incompatible with the identification of 3 knots.



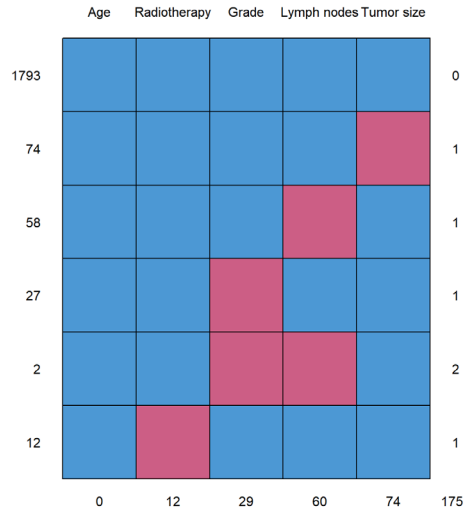
Handling of missing values

In this section, we look at the missing values in the adjustment variables which are: age, number of positive lymph nodes, tumor size, histological grade and radiotherapy.

eTable 3-D. Details on Missing Values

	Tumor size	Lymph nodes	Grade	Radiotherapy
Missing (n)	74	60	29	12
% of total values	4	3	1	1

173 (8.8%) patients have at least one missing value. Among whom, 2 (0.1%) patients have two missing values.



eFigure 3-A. Pattern of Missing Values

eTable 3-E. Percentages and Contribution of Missing Values in Each Study on the 5 Adjustment Variables

	% of missing values	Contribution on missing values
UBC (Vancouver)	4.90%	8.70%
Institut Curie (Paris)	6.80%	5.80%
Erasmus University (Rotterdam)	10%	13.90%
UniGe (Genova)	6.20%	0.60%
IGR (Paris)	2.10%	1.20%
National Cancer Center (Tokyo)	0.90%	0.60%
UUCM (Ulsan)	0.90%	0.60%
Centre Leon Berard (Lyon)	5.20%	1.70%
Mayo (USA)	6.60%	6.90%

IEO (Milano)	26.40%	24.30%
NKI (Amsterdam)	11.30%	28.90%
IOV (Padova)	13.20%	2.90%
SahIgrenska UH (Göteborg)	13.20%	4%

eTable 3-F. Comparison of the Characteristics of the Population With and Without Missing Values

	Patients with at least one missing value *n= 173*	***Patients without missing value*** *n= 1793*	***Overall*** ***n= 1966***
Date of surgery (or diagnosis) Min-Max	1979-2017	1979-2017	1979-2017
Age			
Mean	57.7	55.7	**55.9**
SD	20.3	17.2	**17.5**
Median	59.0	56.0	**56.0**
Q1-Q3	37.0 - 75.0	39.0 - 70.0	**38.9 - 71.0**
Min-Max	23.0 - 99.0	22.0 - 96.0	**22.0 - 99.0**
n	173	1793	**1966**
Missing	0	0	**0**
Menopausal status			
Premenopausal, *n* (%)	18 (15.7)	290 (24.2)	**308 (23.4)**
Postmenopausal, *n* (%)	97 (84.3)	909 (75.8)	**1006 (76.5)**
Pregnant, *n* (%)	0 (0)	1 (0.1)	**1 (0.1)**
Missing	58	593	**651**
TILs value			
Mean	23.4	25.6	**25.4**
SD	27.1	26.4	**26.5**
Median	10.0	15.0	**15.0**
Q1-Q3	3.0 - 40.0	5.0 - 40.0	**5.0 - 40.0**
Min-Max	0.0 - 95.0	0.0 - 95.0	**0.0 - 95.0**
n	173	1793	**1966**
Missing	0	0	**0**
Histological subtype			
Ductal, *n* (%)	123 (72.4)	1304 (76.7)	**1427 (76.3)**
Lobular, *n* (%)	3 (1.8)	38 (2.2)	**41 (2.2)**
Medullary, *n* (%)	10 (5.9)	110 (6.5)	**120 (6.4)**
Tubular, *n* (%)	0 (0)	3 (0.2)	**3 (0.2)**
Mucinous, *n* (%)	2 (1.2)	7 (0.4)	**9 (0.5)**
Other, *n* (%)	28 (16.5)	204 (12)	**232 (12.4)**
Metaplastic, *n* (%)	9 (5.3)	53 (3.2)	**38 (2)**
Missing	3	93	**96**
Tumor size (cm)			
Mean	2.0	2.2	**2.1**
SD	1.8	1.5	**1.5**
Median	1.8	2.0	**2.0**
Q1-Q3	0.9 - 2.8	1.2 - 2.6	**1.2 - 2.6**
Min-Max	0.0 - 9.4	0.0 - 15.0	**0.0 - 15.0**
n	99	1793	**1892**
Missing	74	0	**74**
Details on T1			
T1mi, *n* (%)	34 (1.9)	6 (5)	**40 (2.1)**
T1a, *n* (%)	114 (6.4)	10 (8.3)	**124 (6.5)**
T1b, *n* (%)	218 (12.2)	14 (11.7)	**232 (12.1)**
T1c, *n* (%)	707 (39.4)	29 (24.2)	**736 (38.5)**
T2, *n* (%)	651 (36.3)	54 (45)	**705 (36.9)**
T3/T4, *n* (%)	69 (3.8)	7 (5.8)	**76 (4)**
Missing	0	53	**53**
Tumor category			
T1, *n* (%)	86 (58.5)	1073 (59.8)	**1159 (59.7)**
T2, *n* (%)	54 (36.7)	651 (36.3)	**705 (36.3)**
T3/T4, *n* (%)	7 (7.1)	69 (3.8)	**76 (3.9)**
Missing	26	0	**26**

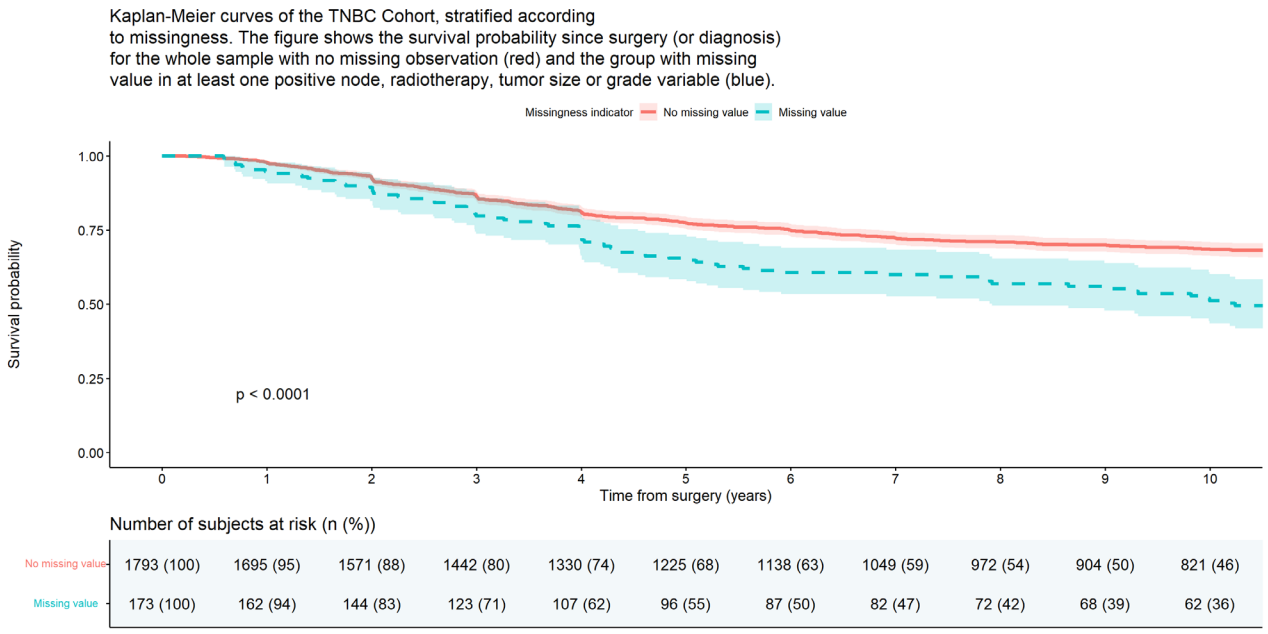
	Patients with at least one missing value *n= 173*	***Patients without missing value*** *n= 1793*	***Overall*** ***n= 1966***
Positive lymph nodes			
Mean	0.8	0.5	**0.5**
SD	2.5	2.2	**2.2**

Median	0.0	0.0	**0.0**
Q1-Q3	0.0 - 0.0	0.0 - 0.0	**0.0 - 0.0**
Min-Max	0.0 - 12.0	0.0 - 38.0	**0.0 - 38.0**
n	113	1793	**1906**
Missing	60	0	**60**
Positive lymph nodes (cat.)			
N0 (0), *n* (%)	98 (86.7)	1553 (86.6)	**1651 (86.6)**
N1 (1-3), *n* (%)	5 (4.4)	161 (9)	**166 (8.7)**
N2 (4-9), n (%)	6 (5.3)	56 (3.1)	**62 (3.3)**
N3 (10+), *n* (%)	4 (3.5)	23 (1.3)	**27 (1.4)**
Missing	60	0	**60**
Histological grade			
1, *n* (%)	9 (6.2)	86 (4.8)	**95 (4.9)**
2, *n* (%)	37 (25.7)	436 (24.3)	**473 (24.4)**
3, *n* (%)	98 (68.1)	1271 (70.9)	**1369 (70.7)**
Missing	29	0	**29**
Radiotherapy			
No, *n* (%)	68 (42.2)	675 (37.6)	**743 (38)**
Yes, *n* (%)	93 (57.8)	1118 (62.4)	**1211 (62)**
Missing	12	0	**12**
Type of surgery			
Partial mastectomy, *n* (%)	113 (65.7)	1088 (60.9)	**1201 (61.3)**
Complete mastectomy, *n* (%)	59 (34.3)	699 (39.1)	**758 (38.7)**
Missing	1	6	**7**
Overall survival			
Alive, *n* (%)	83 (48)	1080 (60.2)	**1163 (59.2)**
Dead, *n* (%)	90 (52)	713 (39.8)	**803 (40.8)**
Missing	0	0	**0**
Follow-up (years)			
Median¤*	17.6	18.0	**18.0**
Confidence interval 95%*	12.7 - 25.0	15.3 - 20.0	**15.3 - 20.0**
Min-Max	0.1 - 35.0	0.0 - 35.2	**0.0 - 35.2**

*Calculated with reverse Kaplan-Meier method.

The missingness is strongly related to survival as shown on the figure below, which displays the Kaplan-Meier survival curves for those with (n = 173) and without (n = 1793) data on all variables included in the Cox model. Missing values are highly study dependent, with some studies having more than 25% missing values while others have almost none. For this reason, multiple imputation must consider the hierarchical structure of the data.

eFigure 3-B. Survival Among Patients With Missing Data vs Not



Imputation of missing values

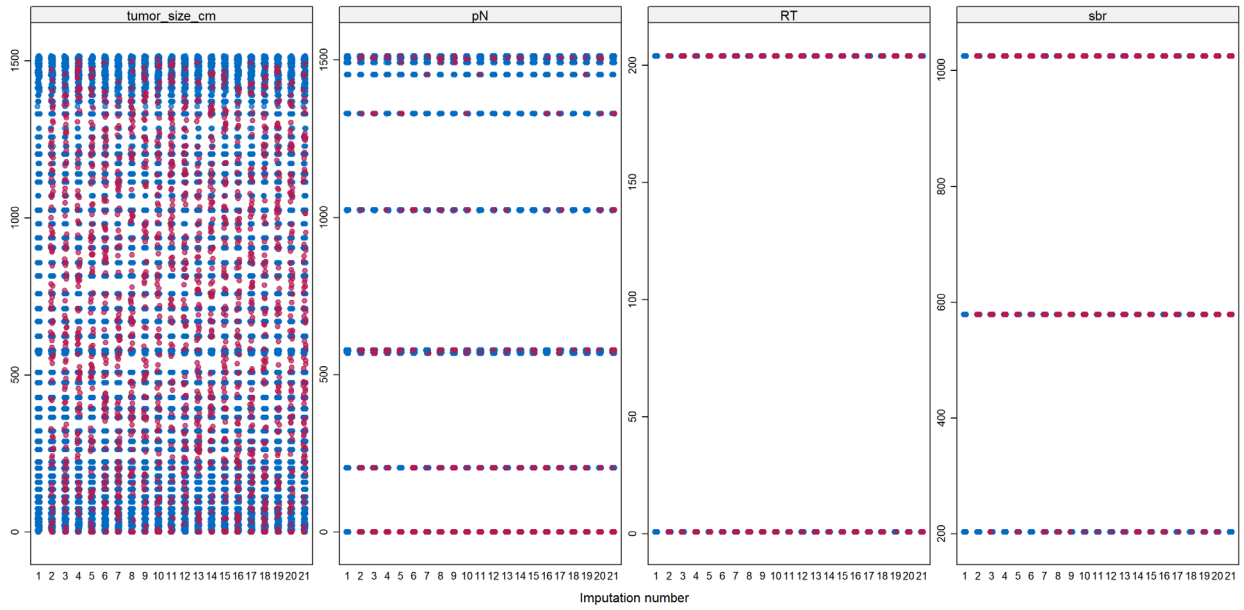
We used multi-level multiple imputation[4] recommended in meta-analyses of individual patient data (see also Chapter 7 in van Buuren's book[5]). As we have seen before, the missingness is related to the study and we cannot ignore this characteristic. We use the *MICE* package and its add-on *miceadds* for multiple imputation.

In practice, to do multiple imputation, it is recommended in Section 5 in White et al.(2011)[6] to use covariates and the result of the analysis models, as well as predictors of the incomplete variable. Also, White and Royston (2009)[7] recommend using the Nelson-Aalen estimate of cumulative hazard (instead of time to event) and event indicator. We will therefore keep the death status as well as the Nelson-Aalen of time to death and all the covariates including tils.

Regarding the method used for multiple imputation: for continuous variable (tumor size), we chose the Gibbs sampler from Kasim and Raudenbush (1998)[8] which fits the situation where the within-group variance is heterogeneous, which was the case in our data. For the binary covariate (radiotherapy), we chose a multilevel imputation method for binary data based on the generalized linear mixed model presented in Jolani et al. (2015)[9] which is adapted to meta-analysis data. For the categorical covariate (histological grade) and the integer (number of positive lymph nodes), we chose a generic function based on a two-level predictive mean matching based on a normal linear mixed effects model[10].

Additionally, we have tumor category information for almost all patients in the NKI cohort. We use this information to impute missing tumor sizes in this study by performing constrained imputation.

eFigure 3-C. Imputed Missing Values in the 20 Imputed Datasets (in Red): First Number Corresponds to Initial Dataset



Regarding the pooling of results from the 20 imputed datasets, we will use Rubin's rules adapted to the statistic under consideration and, if necessary, the estimates will be transformed according to the current guidelines, see references for more details: Marschall & al. (2009)[11] and Van Buuren (2018)[12].

4. Cox Models

We evaluated the effect of TILs on each of the selected endpoints described earlier (OS, DDFS, DRFS, IDFS, IBCFS and RFS). A correction for multiplicity of tests will not be applied to the results of the log-likelihood tests, since the various endpoints are similar.

TIL values are divided by 10. The hazard ratios associated with the tils can be understood as the effect of a 10% increase in the TIL value.

For each model, we test the proportional hazards assumption for a Cox regression model fit[13]. The test is designated "PH" in the table. A value of less than 5% indicates a non-proportionality of the covariates in the model. Significant PH tests will be investigated in the appendix.

eTable 4-A. Cox Models of Clinicopathological Variables and TILs vs Overall Survival

	Model 1 *n= 1966* *e= 803* *PH <10^{-2}*	**Model 2** *n= 1966* *e= 803* *PH <10^{-6}*	**Model 3** *n= 1966* *e= 803* *PH <10^{-6}*
Age at surgery	---	1.01 [0.99 ; 1.03] p = 0.19	1.01 [0.99 ; 1.03] p = 0.18
Age at surgery'	---	1.03 [1.01 ; 1.05] p <10^{-2}	1.03 [1.01 ; 1.05] p = 0.01
Number of positive lymph nodes	---	1.13 [1.10 ; 1.16] p <10^{-6}	1.13 [1.11 ; 1.16] p <10^{-6}
Tumor size	---	1.47 [1.22 ; 1.76] p <10^{-4}	1.49 [1.24 ; 1.79] p <10^{-4}
Tumor size'	---	0.77 [0.66 ; 0.91] p <10^{-2}	0.76 [0.64 ; 0.89] p <10^{-3}
Histological grade 3	---	1	1
Histological grade 1	---	0.66 [0.41 ; 1.08] p = 0.10	0.52 [0.32 ; 0.85] p <10^{-2}
Histological grade 2	---	0.98 [0.82 ; 1.18] p = 0.85	0.83 [0.70 ; 1.00] p = 0.05
Radiotherapy: no	---	1	1
Radiotherapy: yes	1	0.93 [0.80 ; 1.09] p = 0.37	0.93 [0.80 ; 1.09] p = 0.38
Tils	0.88 [0.86 ; 0.91] p <10^{-6}	---	0.88 [0.85 ; 0.91] p <10^{-6}
	χ^2=70.16 p-value <10^{-6} (df=1)	*Likelihood ratio* χ^2=67.71 p-value <10^{-6} (df=1)	
Considered end-point: OS			

eTable 4-B. Cox Models of Clinicopathological Variables and TILs vs RFS

	Model 1 *n= 1966* *e= 940* *PH <10^{-3}*	**Model 2** *n= 1966* *e= 940* *PH <10^{-6}*	**Model 3** *n= 1966* *e= 940* *PH <10^{-6}*
Age at surgery	---	1.00 [0.98 ; 1.01] p = 0.82	1.00 [0.98 ; 1.01] p = 0.83
Age at surgery'	---	1.03 [1.02 ; 1.05] p <10^{-3}	1.03 [1.01 ; 1.05] p <10^{-3}
Number of positive lymph nodes	---	1.11 [1.09 ; 1.13] p <10^{-6}	1.11 [1.09 ; 1.14] p <10^{-6}
Tumor size	---	1.31 [1.11 ; 1.55] p <10^{-2}	1.32 [1.12 ; 1.56] p <10^{-2}
Tumor size'	---	0.86 [0.74 ; 1.00] p = 0.05	0.85 [0.73 ; 0.99] p = 0.03
Histological grade 3	---	1	1
Histological grade 1	---	0.68 [0.44 ; 1.05] p = 0.08	0.55 [0.35 ; 0.85] p <10^{-2}
Histological grade 2	---	0.98 [0.83 ; 1.16] p = 0.82	0.85 [0.72 ; 1.00] p = 0.05
Radiotherapy: no	---	1	1
Radiotherapy: yes	1	0.96 [0.83 ; 1.11] p = 0.59	0.96 [0.83 ; 1.11] p = 0.62
Tils	0.90 [0.88 ; 0.93] p <10^{-6}	---	0.90 [0.87 ; 0.92] p <10^{-6}
		Likelihood ratio	
	χ^2=61.08 p-value <10^{-6} (df=1)	χ^2=61.51 p-value <10^{-6} (df=1)	
Considered end-point: RFS			

eTable 4-C. Cox Models of Clinicopathological Variables and TILs vs DDFS

	Model 1 *n= 1966* *e= 894* *PH <10^{-2}*	**Model 2** *n= 1966* *e= 894* *PH <10^{-6}*	**Model 3** *n= 1966* *e= 894* *PH <10^{-6}*
Age at surgery	---	1.02 [1.00 ; 1.03] p = 0.03	1.02 [1.00 ; 1.03] p = 0.03
Age at surgery'	---	1.01 [1.00 ; 1.03] p = 0.14	1.01 [0.99 ; 1.03] p = 0.27
Number of positive lymph nodes	---	1.11 [1.08 ; 1.13] p <10^{-6}	1.11 [1.09 ; 1.14] p <10^{-6}
Tumor size	---	1.36 [1.15 ; 1.62] p <10^{-3}	1.38 [1.16 ; 1.64] p <10^{-3}
Tumor size'	---	0.84 [0.72 ; 0.98] p = 0.03	0.83 [0.71 ; 0.97] p = 0.02
Histological grade 3	---	1	1
Histological grade 1	---	0.74 [0.48 ; 1.13] p = 0.17	0.57 [0.37 ; 0.88] p = 0.01
Histological grade 2	---	0.98 [0.82 ; 1.16] p = 0.78	0.82 [0.69 ; 0.97] p = 0.02
Radiotherapy: no	---	1	1
Radiotherapy: yes	1	0.92 [0.79 ; 1.06] p = 0.25	0.92 [0.79 ; 1.07] p = 0.27
Tils	0.88 [0.85 ; 0.91] p <10^{-6}	---	0.87 [0.85 ; 0.90] p <10^{-6}
		Likelihood ratio	
	χ^2=82.36 p-value <10^{-6} (df=1)	χ^2=83.31 p-value <10^{-6} (df=1)	

Considered end-point: DDFS

eTable 4-D. Cox Models of Clinicopathological Variables and TILs vs DRFS

	Model 1 *n= 1966* *e= 832* *PH <10^{-2}*	**Model 2** *n= 1966* *e= 832* *PH <10^{-6}*	**Model 3** *n= 1966* *e= 832* *PH <10^{-6}*
Age at surgery	---	1.01 [1.00 ; 1.03] p = 0.16	1.01 [1.00 ; 1.03] p = 0.15
Age at surgery'	---	1.02 [1.00 ; 1.04] p = 0.02	1.02 [1.00 ; 1.04] p = 0.05
Number of positive lymph nodes	---	1.12 [1.09 ; 1.14] p <10^{-6}	1.12 [1.10 ; 1.15] p <10^{-6}
Tumor size	---	1.45 [1.21 ; 1.74] p <10^{-4}	1.47 [1.22 ; 1.76] p <10^{-4}
Tumor size'	---	0.80 [0.68 ; 0.94] p <10^{-2}	0.79 [0.67 ; 0.93] p <10^{-2}
Histological grade 3	---	1	1
Histological grade 1	---	0.64 [0.39 ; 1.03] p = 0.07	0.49 [0.30 ; 0.80] p <10^{-2}
Histological grade 2	---	0.98 [0.83 ; 1.17] p = 0.86	0.83 [0.69 ; 0.99] p = 0.04
Radiotherapy: no	---	1	1
Radiotherapy: yes	1	0.93 [0.80 ; 1.08] p = 0.36	0.93 [0.80 ; 1.09] p = 0.37
Tils	0.88 [0.85 ; 0.90] p <10^{-6}	---	0.87 [0.84 ; 0.90] p <10^{-6}
		Likelihood ratio	
	χ^2=80.64 p-value <10^{-6} (df=1)	χ^2=80.82 p-value <10^{-6} (df=1)	

Considered end-point: DRFS

eTable 4-E. Cox Models Including Clinicopathological Variables and TILs on IBCFS

	Model 1	**Model 2**	**Model 3**
	n= 1966	*n= 1966*	*n= 1966*
	e= 1036	*e= 1036*	*e= 1036*
	PH <10^{-3}	*PH <10^{-6}*	*PH <10^{-6}*
Age at surgery	---	0.99 [0.97 ; 1.00] p = 0.03	0.99 [0.97 ; 1.00] p = 0.04
Age at surgery'	---	1.04 [1.03 ; 1.06] p <10^{-6}	1.04 [1.02 ; 1.06] p <10^{-5}
Number of positive lymph nodes	---	1.11 [1.09 ; 1.13] p <10^{-6}	1.11 [1.09 ; 1.13] p <10^{-6}
Tumor size	---	1.22 [1.05 ; 1.43] p = 0.01	1.22 [1.05 ; 1.43] p = 0.01
Tumor size'	---	0.91 [0.79 ; 1.05] p = 0.19	0.91 [0.79 ; 1.05] p = 0.18
Histological grade 3	---	1	1
Histological grade 1	---	0.62 [0.40 ; 0.95] p = 0.03	0.52 [0.33 ; 0.80] p <10^{-2}
Histological grade 2	---	1.01 [0.86 ; 1.18] p = 0.92	0.90 [0.76 ; 1.05] p = 0.18
Radiotherapy: no	---	1	1
Radiotherapy: yes	1	0.96 [0.83 ; 1.10] p = 0.54	0.96 [0.83 ; 1.10] p = 0.54
Tils	0.92 [0.90 ; 0.94] p <10^{-6}	---	0.92 [0.89 ; 0.94] p <10^{-6}
		Likelihood ratio	
	χ^2=43.77 p-value <10^{-6} (df=1)	χ^2=42.78 p-value <10^{-6} (df=1)	

Considered end-point: IBCFS

eTable 4-F. Cox Models of Clinicopathological Variables and TILs vs IDFS

	Model 1	**Model 2**	**Model 3**
	n= 1966	*n= 1966*	*n= 1966*
	e= 1074	*e= 1074*	*e= 1074*
	PH <10^{-3}	*PH <10^{-6}*	*PH <10^{-6}*
Age at surgery	---	0.99 [0.98 ; 1.00] p = 0.17	0.99 [0.98 ; 1.00] p = 0.20
Age at surgery'	---	1.04 [1.02 ; 1.05] p <10^{-4}	1.03 [1.02 ; 1.05] p <10^{-4}
Number of positive lymph nodes	---	1.10 [1.08 ; 1.12] p <10^{-6}	1.10 [1.08 ; 1.13] p <10^{-6}
Tumor size	---	1.19 [1.02 ; 1.39] p = 0.02	1.19 [1.02 ; 1.39] p = 0.02
Tumor size'	---	0.93 [0.82 ; 1.07] p = 0.33	0.93 [0.81 ; 1.07] p = 0.32
Histological grade 3	---	1	1
Histological grade 1	---	0.68 [0.46 ; 1.03] p = 0.07	0.57 [0.38 ; 0.86] p <10^{-2}
Histological grade 2	---	1.00 [0.86 ; 1.17] p = 0.99	0.89 [0.76 ; 1.04] p = 0.14
Radiotherapy: no	---	1	1
Radiotherapy: yes	1	0.96 [0.84 ; 1.10] p = 0.60	0.97 [0.85 ; 1.11] p = 0.64
Tils	0.92 [0.90 ; 0.94] p <10^{-6}	---	0.92 [0.89 ; 0.94] p <10^{-6}
		Likelihood ratio	
	χ^2=45.74 p-value <10^{-6} (df=1)	χ^2=45.16 p-value <10^{-6} (df=1)	

Considered end-point: IDFS

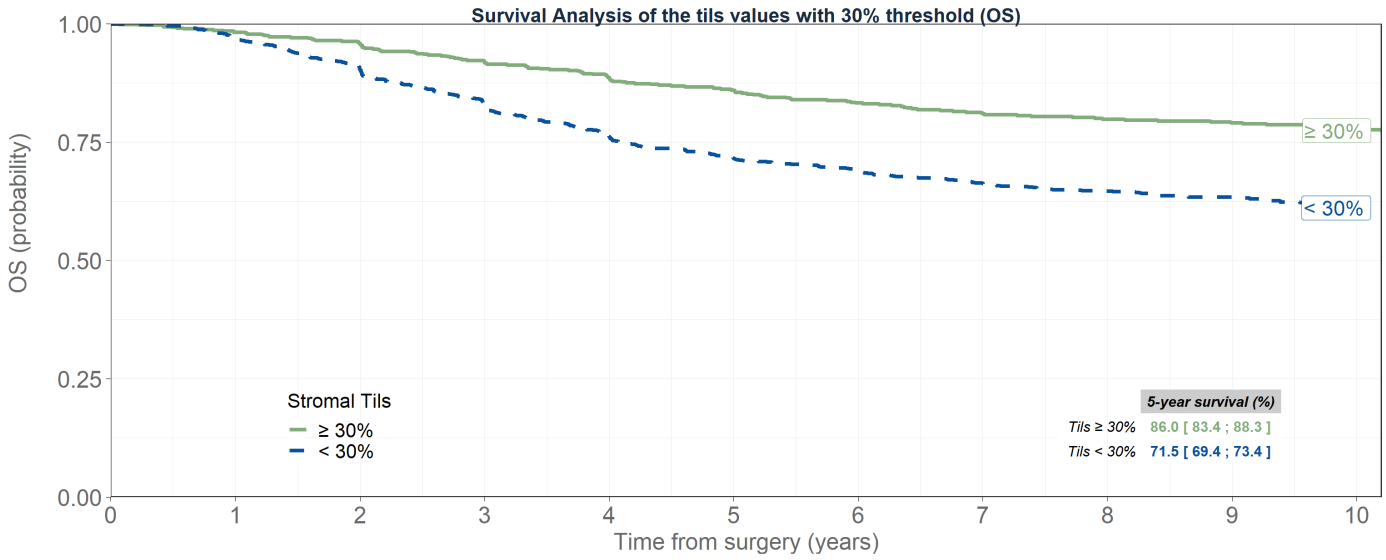
5. Detailed Clinical Outcomes According to Various TIL Thresholds and According to Stage

eTable 5-A. Clinical Outcomes According to TIL Thresholds in the Overall Study Population, According to Age and Stage

			Estimated survival with 95% bootstrapped confidence interval									
			IDFS		**RFS**		**DDFS**		**DRFS**		**OS**	
	TILs	**N (%)**	**5-year**	**10-year**	**5-year**	**10-year**	**5-year**	**10-year**	**5-year**	**10-year**	**5-year**	**10-year**
All patients (N=1966)	0-100	1966 (100%)	65% [63-67]	54% [52-56]	69% [67-71]	60% [58-62]	71% [70-73]	62% [60-64]	73% [71-75]	65% [63-67]	76% [75-78]	67% [65-69]
	<30	1300 (66%)	60% [58-63]	49% [47-52]	63% [61-66]	54% [52-57]	66% [64-68]	55% [53-58]	68% [66-70]	59% [57-61]	72% [69-74]	62% [59-64]
	≥30	666 (34%)	74% [71-77]	63% [60-66]	79% [77-82]	71% [68-74]	81% [79-84]	75% [72-78]	84% [81-86]	77% [74-80]	86% [84-88]	78% [75-80]
	≥50	417 (21%)	78% [74-81]	67% [62-71]	83% [80-86]	75% [71-78]	86% [83-89]	81% [77-84]	88% [85-90]	82% [79-85]	90% [88-93]	82% [79-86]
	≥75	168 (9%)	84% [79-89]	73% [67-79]	90% [86-93]	81% [76-86]	92% [88-95]	89% [85-93]	94% [91-97]	90% [86-94]	96% [93-98]	90% [86-94]
Age <50 (n=800)	0-100	800 (100%)	65% [63-68]	57% [54-60]	70% [67-73]	65% [62-68]	74% [71-76]	69% [66-71]	75% [73-77]	71% [69-74]	79% [77-82]	74% [71-76]
	<30	467 (58%)	58% [54-62]	51% [47-55]	62% [58-66]	57% [53-61]	65% [61-68]	58% [54-62]	67% [63-70]	62% [58-66]	72% [68-76]	66% [62-69]
	≥30	333 (42%)	76% [72-80]	66% [62-70]	82% [79-86]	77% [73-81]	86% [83-89]	83% [80-86]	87% [84-90]	84% [81-88]	89% [86-92]	84% [81-88]
	≥50	249 (31%)	79% [75-83]	68% [63-73]	86% [82-89]	79% [75-83]	89% [86-92]	87% [83-90]	91% [88-94]	88% [84-91]	93% [90-96]	88% [84-91]
	≥75	119 (15%)	86% [80-91]	72% [65-79]	91% [87-95]	82% [76-88]	95% [92-98]	93% [90-97]	96% [92-98]	94% [91-97]	97% [94-100]	94% [90-97]
Age ≥50 (n=1166)	0-100	1166 (100%)	64% [62-67]	51% [48-53]	68% [65-70]	55% [53-58]	69% [67-72]	56% [53-59]	72% [69-74]	60% [57-62]	74% [72-77]	61% [59-64]
	<30	833 (71%)	62% [58-65]	48% [44-51]	64% [62-67]	52% [49-56]	66% [64-69]	53% [50-56]	69% [66-71]	57% [53-60]	71% [69-74]	58% [55-61]
	≥30	333 (29%)	72% [68-77]	59% [54-64]	76% [72-80]	64% [59-69]	77% [72-81]	64% [59-69]	80% [76-84]	67% [62-72]	83% [79-86]	69% [64-74]
	≥50	168 (14%)	75% [69-81]	63% [57-71]	79% [73-84]	66% [59-73]	80% [75-86]	68% [61-75]	83% [78-88]	71% [64-77]	86% [81-90]	72% [65-78]
	≥75	49 (4%)	81% [71-89]	78% [67-89]	87% [79-94]	80% [69-89]	83% [74-91]	77% [65-87]	89% [82-96]	78% [67-89]	91% [84-98]	78% [66-88]
pN0 (n=1711)[1]	0-100	1711 (100%)	69% [67-71]	58% [56-60]	73% [71-75]	64% [62-66]	76% [74-77]	67% [65-69]	78% [76-79]	70% [68-72]	81% [79-83]	72% [70-74]
	<30	1123 (66%)	65% [62-67]	53% [51-56]	68% [66-71]	59% [56-61]	71% [69-73]	61% [58-63]	73% [70-75]	64% [62-67]	77% [75-79]	67% [64-69]
	≥30	588 (34%)	77% [74-80]	66% [63-69]	82% [80-85]	75% [72-78]	84% [82-87]	78% [76-81]	87% [84-89]	81% [78-84]	89% [87-91]	82% [79-85]
	≥50	377 (22%)	80% [77-84]	70% [66-74]	86% [83-89]	78% [74-82]	89% [86-91]	84% [80-87]	91% [88-93]	85% [82-88]	93% [91-95]	86% [82-89]
	≥75	161 (9%)	85% [81-90]	74% [68-80]	91% [87-95]	83% [78-88]	93% [90-96]	91% [87-94]	96% [92-98]	92% [88-95]	97% [94-99]	92% [88-95]
Stage I (n=1081)[1]	0-100	1081 (100%)	73% [70-75]	61% [59-64]	77% [75-79]	68% [65-70]	79% [77-81]	71% [69-73]	82% [80-83]	74% [72-76]	85% [83-87]	76% [74-79]
	<30	727 (67%)	69% [66-72]	58% [55-61]	73% [70-76]	64% [61-67]	76% [73-78]	66% [63-69]	78% [75-80]	70% [67-73]	82% [79-84]	72% [69-75]
	≥30	354 (33%)	80% [76-83]	68% [63-72]	85% [82-88]	76% [72-80]	87% [84-90]	81% [77-84]	90% [87-92]	83% [80-87]	91% [88-94]	84% [81-88]
	≥50	227 (21%)	84% [80-88]	70% [64-75]	89% [86-93]	78% [73-83]	91% [88-94]	86% [82-90]	94% [91-96]	88% [84-91]	95% [92-97]	89% [85-92]
	≥75	109 (10%)	86% [80-92]	73% [65-80]	91% [87-95]	80% [74-87]	92% [88-96]	90% [85-95]	95% [92-98]	92% [88-96]	96% [93-99]	92% [88-96]
pT1mi N0 (n= 38)[1]	0-100	38 (100%)	86% [76-95]	76% [64-88]	92% [84-97]	85% [74-95]	92% [84-97]	88% [78-97]	95% [89-100]	91% [81-97]	97% [92-100]	90% [80-100]
	<30	24 (63%)	83% [69-96]	72% [54-87]	92% [79-100]	86% [73-96]	88% [75-96]	82% [67-96]	92% [83-100]	86% [72-96]	96% [88-100]	85% [71-100]
	≥30	14 (37%)	92% [77-100]	83% [63-100]	92% [78-100]	83% [63-100]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]
	≥50	9 (24%)	88% [67-100]	70% [40-100]	88% [67-100]	70% [40-100]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]
	≥75	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
pT1a N0 (n= 118)[1]	0-100	119 (100%)	85% [79-91]	68% [58-77]	92% [87-96]	79% [71-87]	90% [85-95]	79% [70-87]	95% [92-98]	86% [79-92]	98% [96-100]	89% [83-95]
	<30	73 (61%)	84% [75-91]	69% [57-80]	92% [85-97]	77% [67-88]	89% [81-95]	80% [69-89]	94% [88-98]	86% [77-94]	98% [95-100]	88% [81-96]
	≥30	46 (39%)	87% [79-95]	67% [52-82]	92% [84-98]	84% [71-94]	92% [85-98]	76% [61-89]	97% [92-100]	86% [76-97]	97% [92-100]	91% [81-98]
	≥50	30 (25%)	87% [76-96]	74% [56-91]	92% [83-100]	85% [67-96]	91% [81-100]	80% [60-96]	96% [88-100]	89% [73-100]	96% [88-100]	96% [88-100]
	≥75	12 (10%)	91% [73-100]	NA[2]	100% [100-100]	NA[2]	91% [75-100]	NA[2]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]

			IDFS		RFS		DDFS		DRFS		OS	
	TILs	**N (%)**	**5-year**	**10-year**	**5-year**	**10-year**	**5-year**	**10-year**	**5-year**	**10-year**	**5-year**	**10-year**
pT1b N0 (n= 222)[1]	0-100	222 (100%)	74% [69-79]	59% [53-65]	80% [75-84]	68% [62-74]	84% [80-88]	72% [67-78]	86% [82-90]	77% [72-83]	90% [87-94]	79% [74-84]
	<30	154 (69%)	71% [65-77]	54% [46-61]	76% [70-82]	64% [57-71]	81% [75-86]	66% [58-73]	83% [77-88]	72% [66-79]	88% [83-93]	75% [68-81]
	≥30	68 (31%)	81% [72-89]	70% [59-80]	89% [81-95]	78% [67-87]	92% [85-97]	87% [78-94]	93% [88-98]	89% [81-95]	95% [90-99]	88% [81-95]
	≥50	37 (17%)	82% [71-92]	68% [53-82]	94% [88-100]	76% [62-89]	94% [86-100]	87% [76-97]	97% [91-100]	90% [80-100]	97% [91-100]	90% [80-97]
	≥75	18 (8%)	76% [59-94]	71% [50-88]	88% [75-100]	76% [59-93]	88% [75-100]	88% [75-100]	94% [82-100]	94% [83-100]	94% [83-100]	94% [83-100]
pT1c N0 (n= 702)[1]	0-100	702 (100%)	69% [67-72]	60% [56-63]	73% [70-76]	65% [62-68]	76% [73-78]	68% [65-71]	77% [75-80]	70% [67-73]	80% [78-83]	73% [70-76]
	<30	476 (68%)	66% [62-69]	57% [53-61]	69% [65-72]	61% [57-65]	72% [68-75]	64% [60-68]	73% [70-76]	66% [62-69]	77% [73-80]	69% [65-72]
	≥30	226 (32%)	77% [72-82]	66% [61-71]	82% [78-86]	73% [68-78]	84% [80-88]	78% [73-82]	87% [83-90]	80% [75-84]	88% [85-92]	81% [77-86]
	≥50	151 (22%)	83% [78-88]	70% [64-76]	88% [84-92]	78% [72-83]	90% [86-94]	85% [80-90]	92% [89-96]	87% [82-91]	94% [90-97]	87% [82-91]
	≥75	79 (11%)	87% [81-94]	71% [62-79]	91% [86-96]	79% [71-87]	94% [88-97]	91% [86-96]	95% [91-99]	91% [86-96]	96% [92-99]	91% [85-96]
Stage II (n=779)[1]	0-100	779 (100%)	62% [59-64]	50% [47-53]	65% [62-68]	56% [53-60]	67% [64-70]	57% [54-60]	69% [66-72]	60% [57-63]	73% [70-76]	62% [59-65]
	<30	*499 (64%)*	55% [51-59]	43% [39-47]	58% [54-61]	48% [44-52]	61% [57-64]	47% [44-51]	62% [59-66]	52% [48-55]	66% [63-70]	54% [50-58]
	≥30	*280 (36%)*	73% [68-77]	62% [57-68]	78% [73-82]	71% [67-76]	79% [75-84]	73% [69-78]	81% [77-85]	75% [70-79]	84% [81-88]	75% [71-80]
	≥50	*172 (22%)*	74% [68-80]	67% [61-73]	79% [74-84]	76% [71-81]	84% [79-88]	79% [74-84]	85% [81-90]	80% [75-85]	89% [85-93]	80% [74-85]
	≥75	*55 (7%)*	86% [78-93]	79% [70-87]	91% [83-96]	89% [82-96]	95% [89-100]	92% [86-98]	96% [92-100]	92% [86-98]	98% [95-100]	92% [85-98]

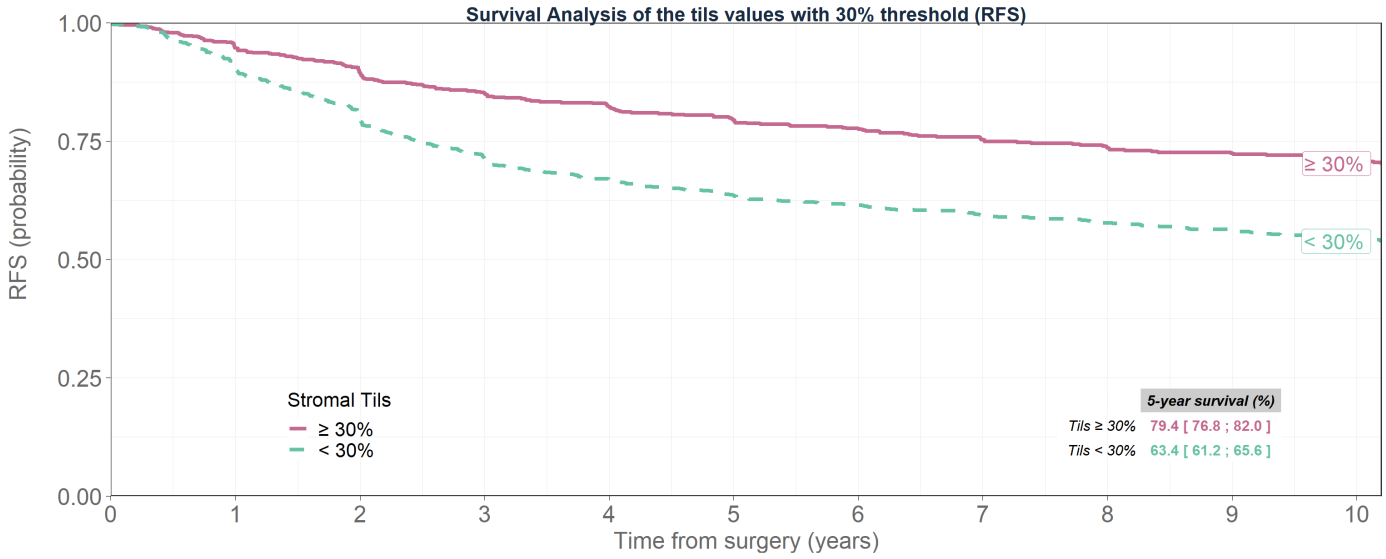
eFigure 5-A. Overall Survival According to TILs <30% vs ≥30%



Number of subjects at risk (n (%))

≥ 30%	666 (100)	632 (95)	599 (90)	565 (85)	541 (81)	505 (76)	477 (72)	444 (67)	422 (63)	404 (61)	378 (57
< 30%	1300 (100)	1225 (94)	1116 (86)	1000 (77)	896 (69)	816 (63)	748 (58)	687 (53)	622 (48)	568 (44)	505 (39

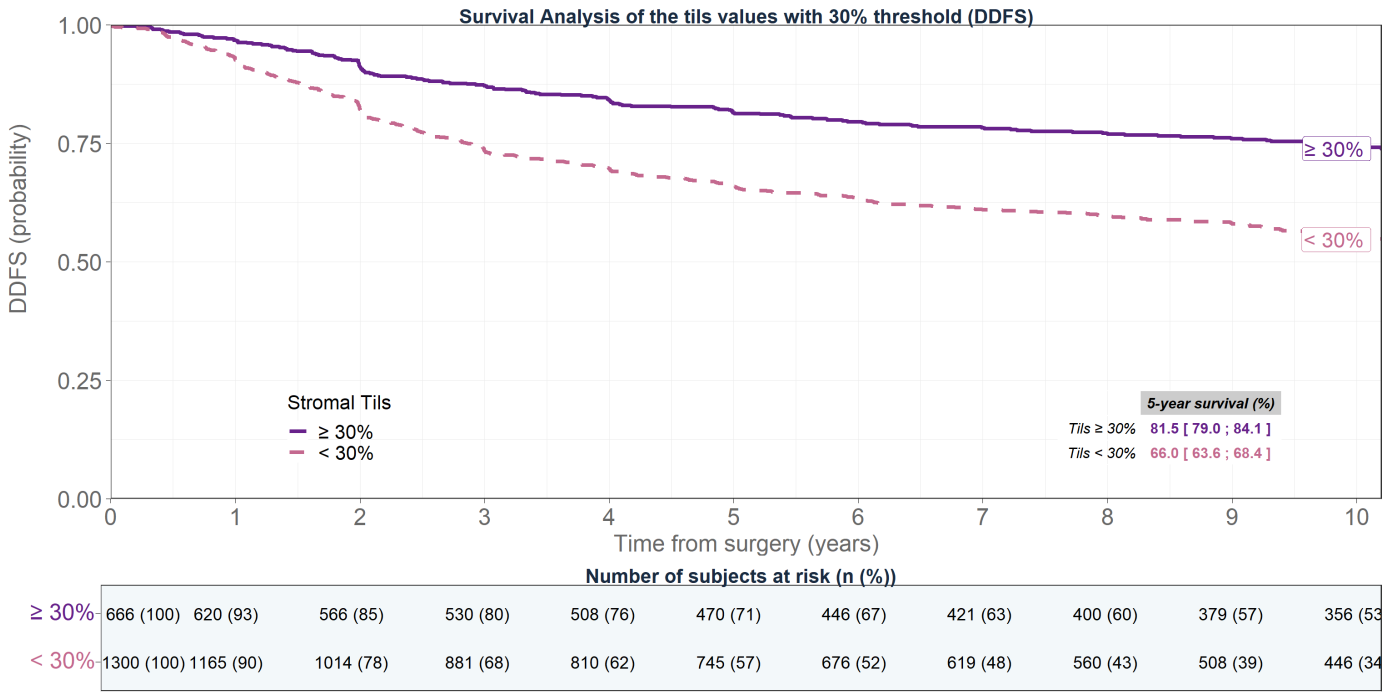
eFigure 5-B. RFS According to TILs <30% vs ≥30%



Number of subjects at risk (n (%))

≥ 30%	666 (100)	607 (91)	554 (83)	516 (77)	495 (74)	458 (69)	435 (65)	402 (60)	379 (57)	360 (54)	337 (51
< 30%	1300 (100)	1142 (88)	988 (76)	859 (66)	783 (60)	721 (55)	661 (51)	606 (47)	547 (42)	498 (38)	444 (34

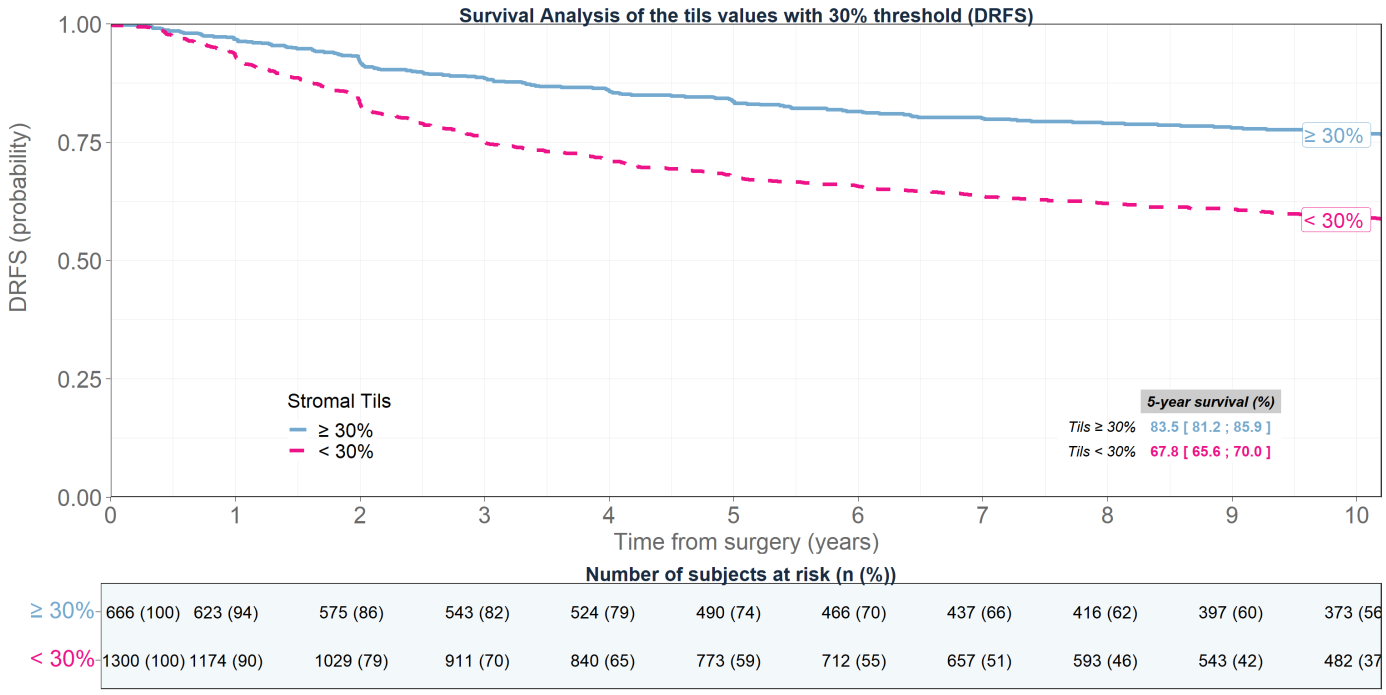
eFigure 5-C. DDFS According to TILs <30% vs ≥30%



Number of subjects at risk (n (%))

≥ 30%	666 (100)	620 (93)	566 (85)	530 (80)	508 (76)	470 (71)	446 (67)	421 (63)	400 (60)	379 (57)	356 (53
< 30%	1300 (100)	1165 (90)	1014 (78)	881 (68)	810 (62)	745 (57)	676 (52)	619 (48)	560 (43)	508 (39)	446 (34

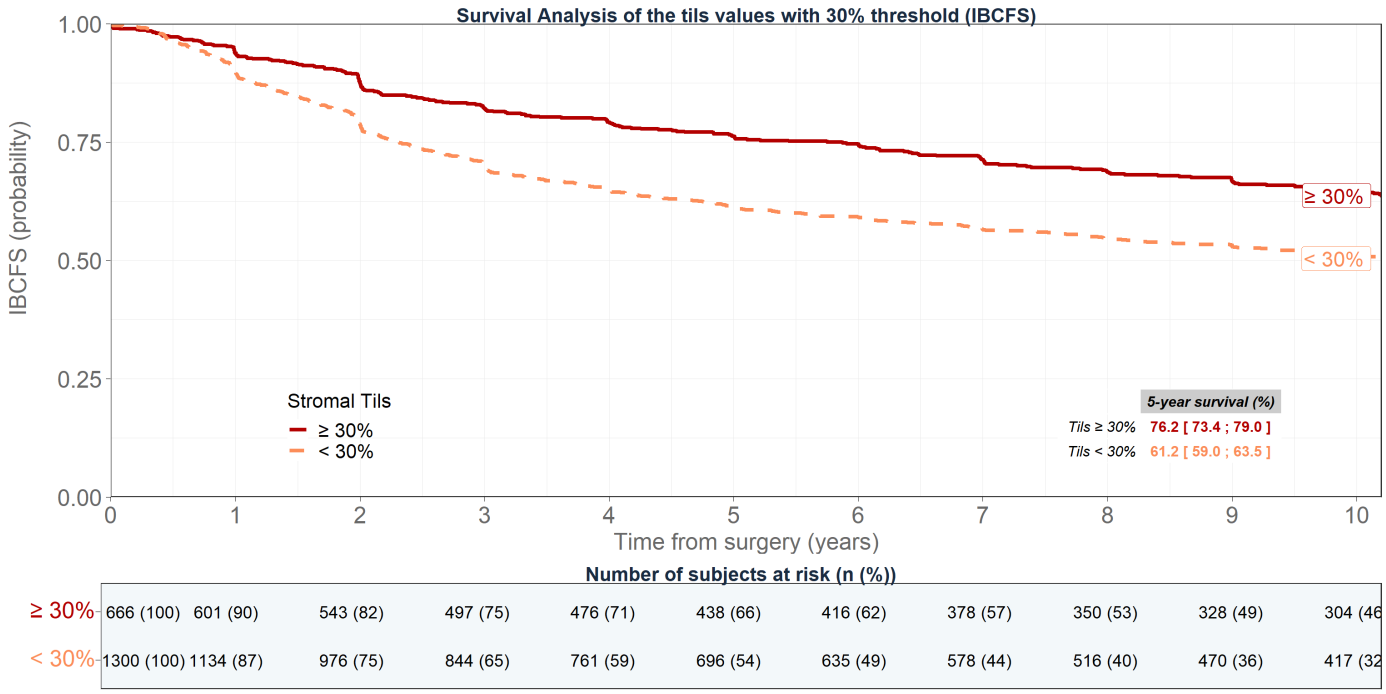
eFigure 5-D. DRFS According to TILs <30% vs ≥30%



Number of subjects at risk (n (%))

≥ 30%	666 (100)	623 (94)	575 (86)	543 (82)	524 (79)	490 (74)	466 (70)	437 (66)	416 (62)	397 (60)	373 (56
< 30%	1300 (100)	1174 (90)	1029 (79)	911 (70)	840 (65)	773 (59)	712 (55)	657 (51)	593 (46)	543 (42)	482 (37

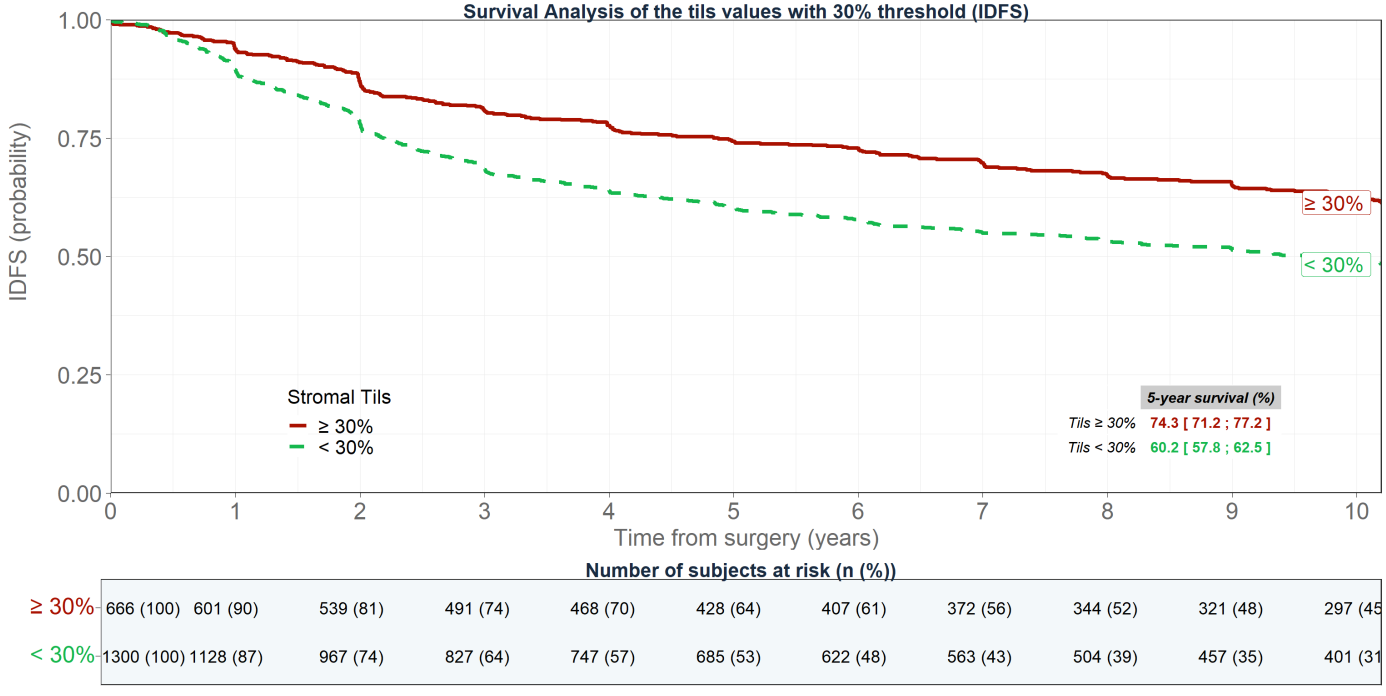
eFigure 5-E. IBCFS According to TILs <30% vs ≥30%



Number of subjects at risk (n (%))

≥ 30%	666 (100)	601 (90)	543 (82)	497 (75)	476 (71)	438 (66)	416 (62)	378 (57)	350 (53)	328 (49)	304 (46
< 30%	1300 (100)	1134 (87)	976 (75)	844 (65)	761 (59)	696 (54)	635 (49)	578 (44)	516 (40)	470 (36)	417 (32

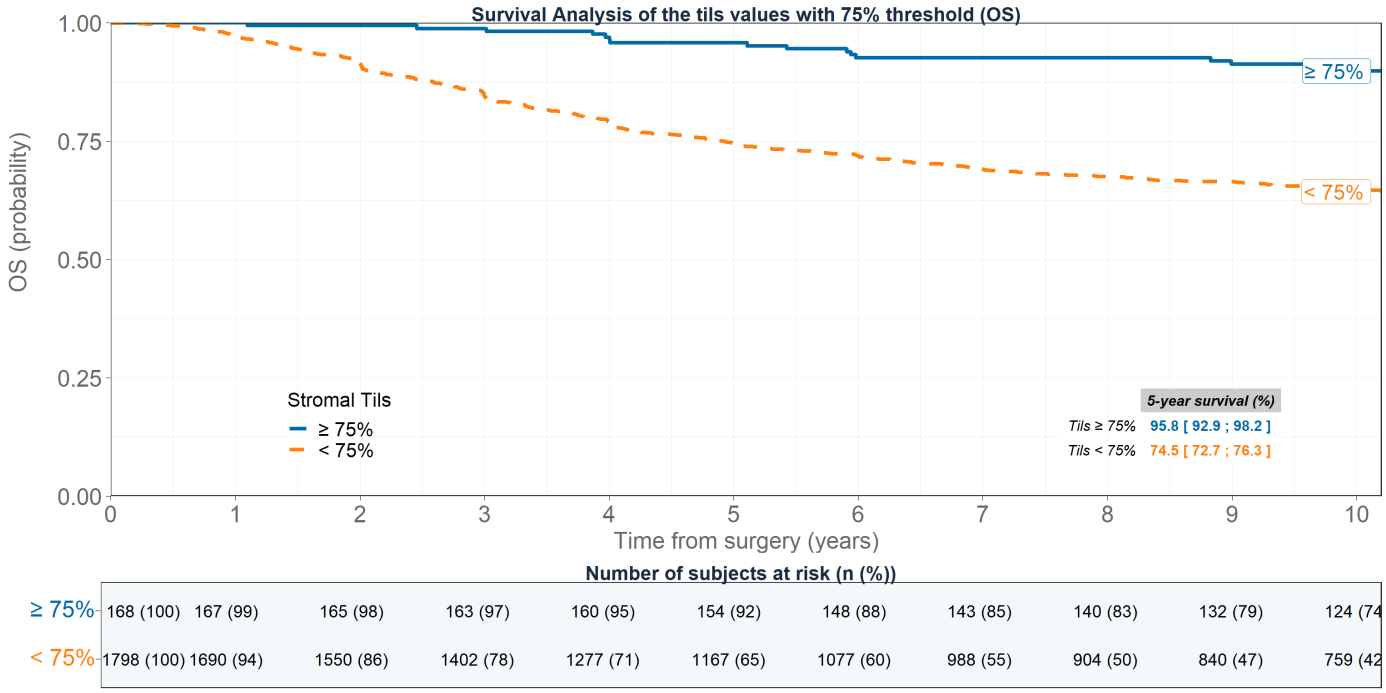
eFigure 5-F. IDFS According to TILs <30% vs ≥30%



Number of subjects at risk (n (%))

≥ 30%	666 (100)	601 (90)	539 (81)	491 (74)	468 (70)	428 (64)	407 (61)	372 (56)	344 (52)	321 (48)	297 (45
< 30%	1300 (100)	1128 (87)	967 (74)	827 (64)	747 (57)	685 (53)	622 (48)	563 (43)	504 (39)	457 (35)	401 (31

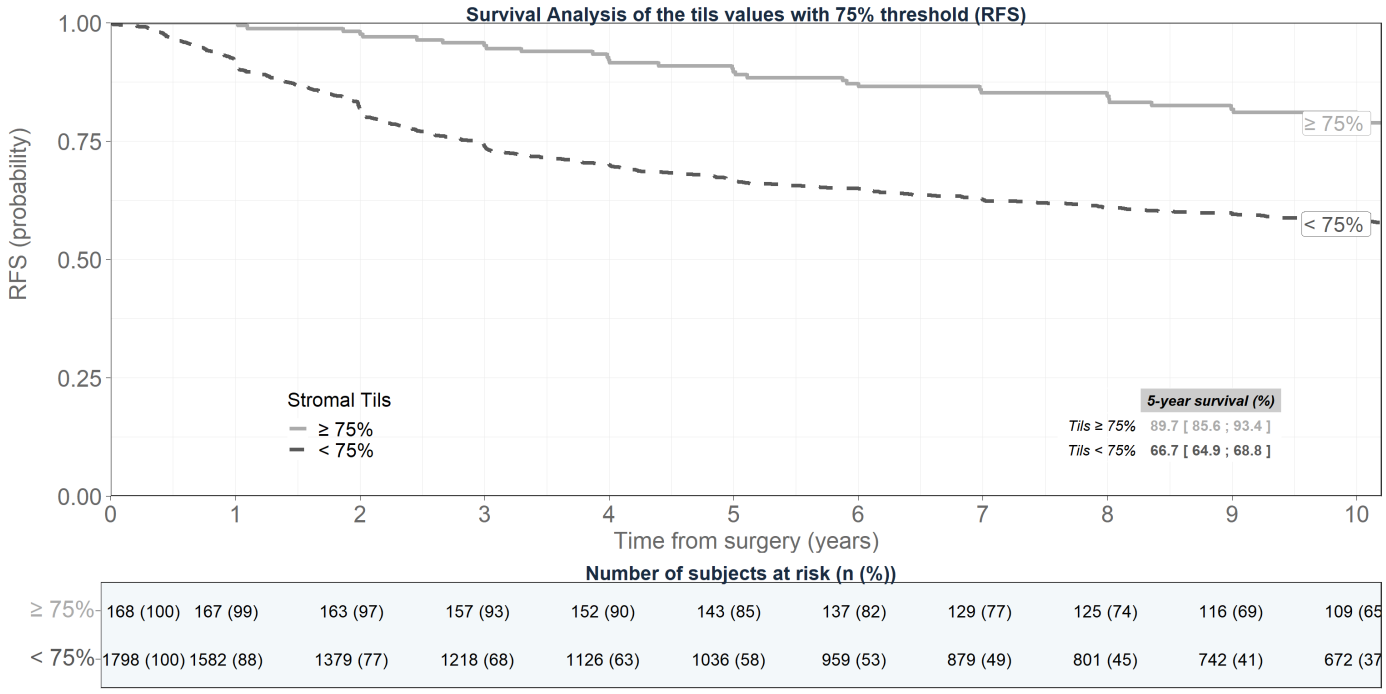
eFigure 5-G. Overall Survival According to TILs <75% vs ≥75%



Number of subjects at risk (n (%))

≥ 75%	168 (100)	167 (99)	165 (98)	163 (97)	160 (95)	154 (92)	148 (88)	143 (85)	140 (83)	132 (79)	124 (74
< 75%	1798 (100)	1690 (94)	1550 (86)	1402 (78)	1277 (71)	1167 (65)	1077 (60)	988 (55)	904 (50)	840 (47)	759 (42

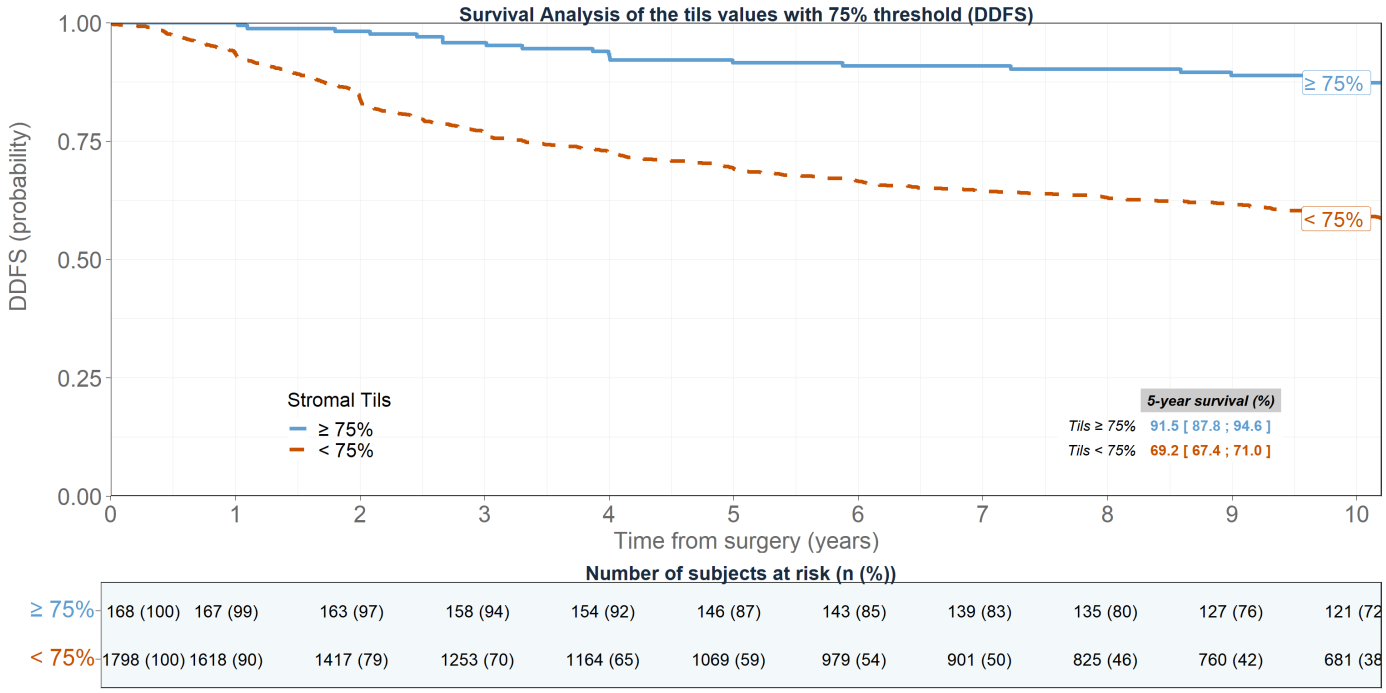
eFigure 5-H. RFS According to TILs <75% vs ≥75%



Number of subjects at risk (n (%))

≥ 75%	168 (100)	167 (99)	163 (97)	157 (93)	152 (90)	143 (85)	137 (82)	129 (77)	125 (74)	116 (69)	109 (65
< 75%	1798 (100)	1582 (88)	1379 (77)	1218 (68)	1126 (63)	1036 (58)	959 (53)	879 (49)	801 (45)	742 (41)	672 (37

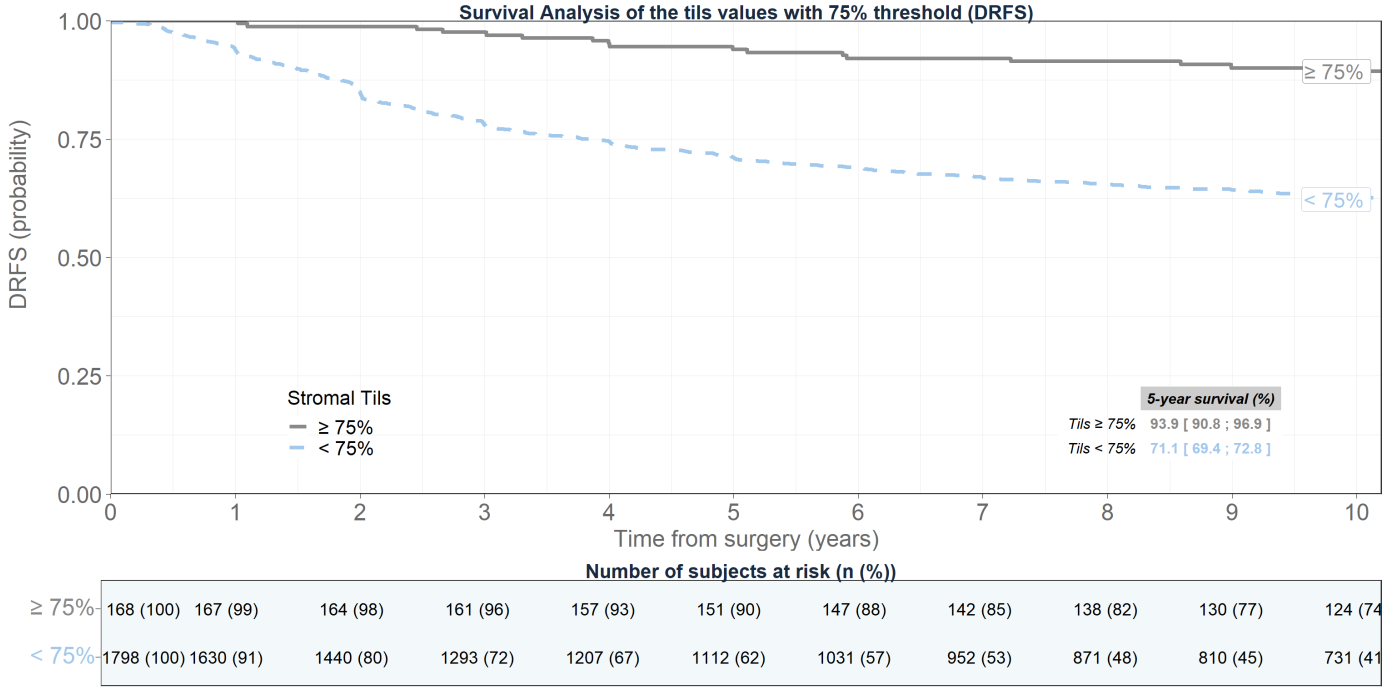
eFigure 5-I. DDFS According to TILs <75% vs ≥75%



Number of subjects at risk (n (%))

≥ 75%	168 (100)	167 (99)	163 (97)	158 (94)	154 (92)	146 (87)	143 (85)	139 (83)	135 (80)	127 (76)	121 (72
< 75%	1798 (100)	1618 (90)	1417 (79)	1253 (70)	1164 (65)	1069 (59)	979 (54)	901 (50)	825 (46)	760 (42)	681 (38

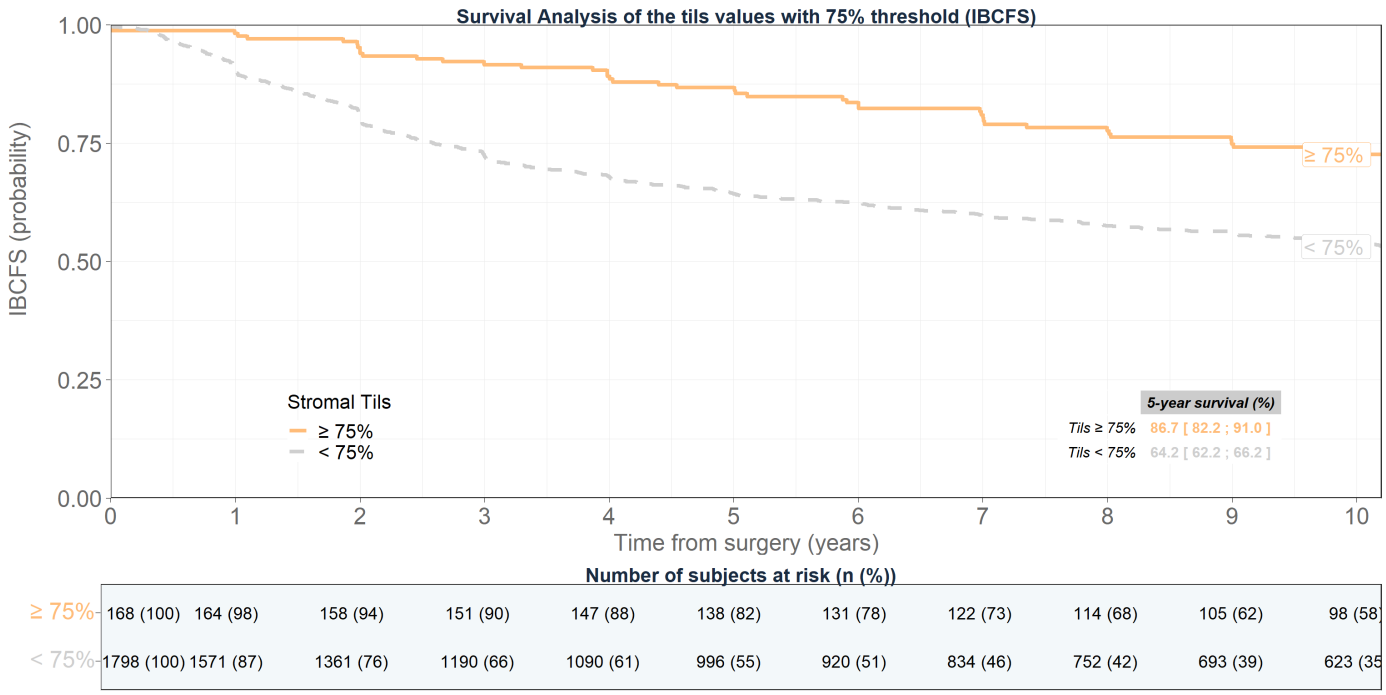
eFigure 5-J. DRFS According to TILs <75% vs ≥75%



Number of subjects at risk (n (%))

≥ 75%	168 (100)	167 (99)	164 (98)	161 (96)	157 (93)	151 (90)	147 (88)	142 (85)	138 (82)	130 (77)	124 (74
< 75%	1798 (100)	1630 (91)	1440 (80)	1293 (72)	1207 (67)	1112 (62)	1031 (57)	952 (53)	871 (48)	810 (45)	731 (41

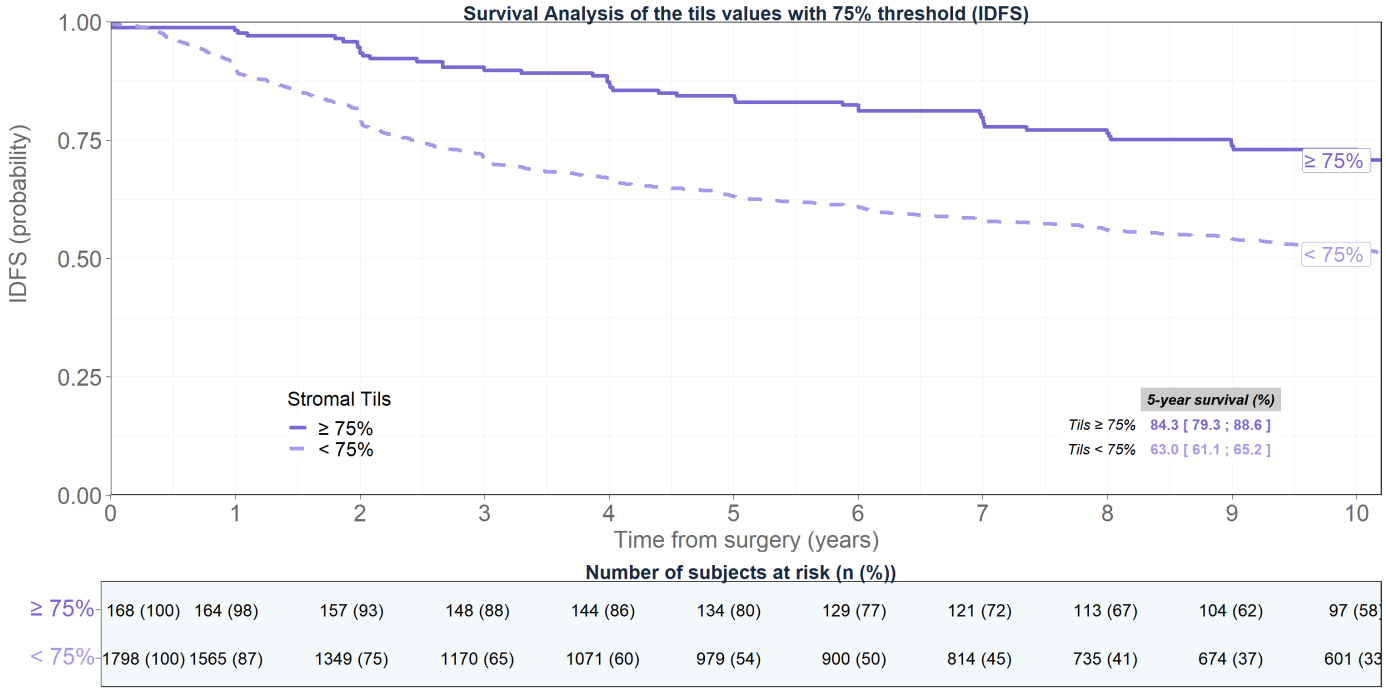
eFigure 5-K. IBCFS According to TILs <75% vs ≥75%



Number of subjects at risk (n (%))

≥ 75%	168 (100)	164 (98)	158 (94)	151 (90)	147 (88)	138 (82)	131 (78)	122 (73)	114 (68)	105 (62)	98 (58)
< 75%	1798 (100)	1571 (87)	1361 (76)	1190 (66)	1090 (61)	996 (55)	920 (51)	834 (46)	752 (42)	693 (39)	623 (35)

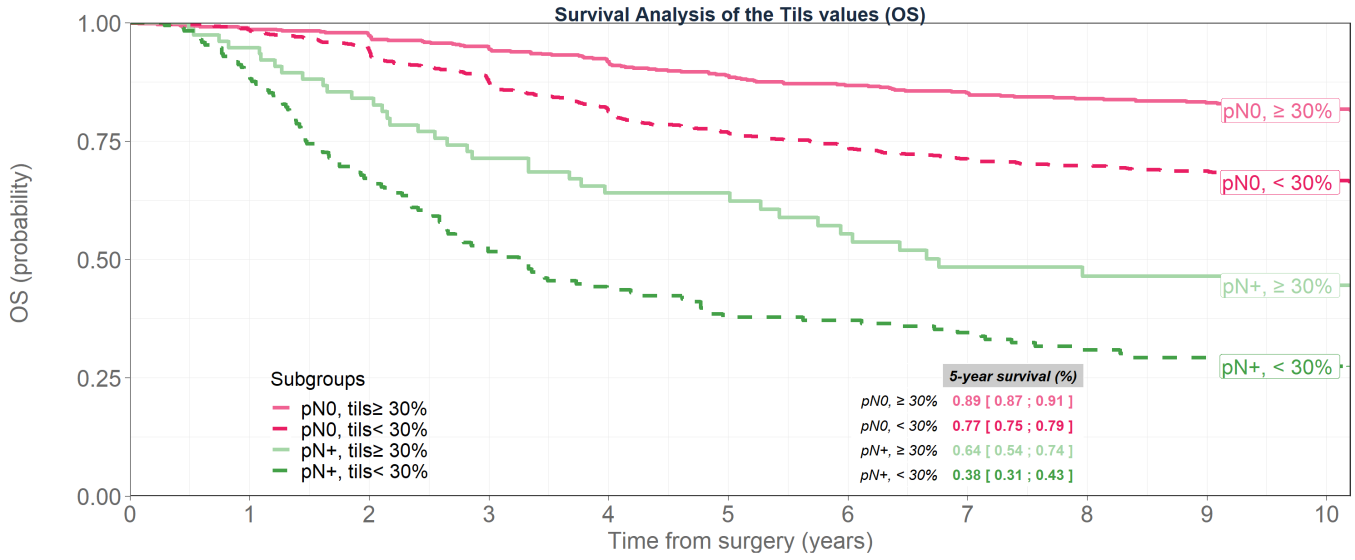
eFigure 5-L. IDFS According to TILs <75% vs ≥75%



Number of subjects at risk (n (%))

≥ 75%	168 (100)	164 (98)	157 (93)	148 (88)	144 (86)	134 (80)	129 (77)	121 (72)	113 (67)	104 (62)	97 (58)
< 75%	1798 (100)	1565 (87)	1349 (75)	1170 (65)	1071 (60)	979 (54)	900 (50)	814 (45)	735 (41)	674 (37)	601 (33)

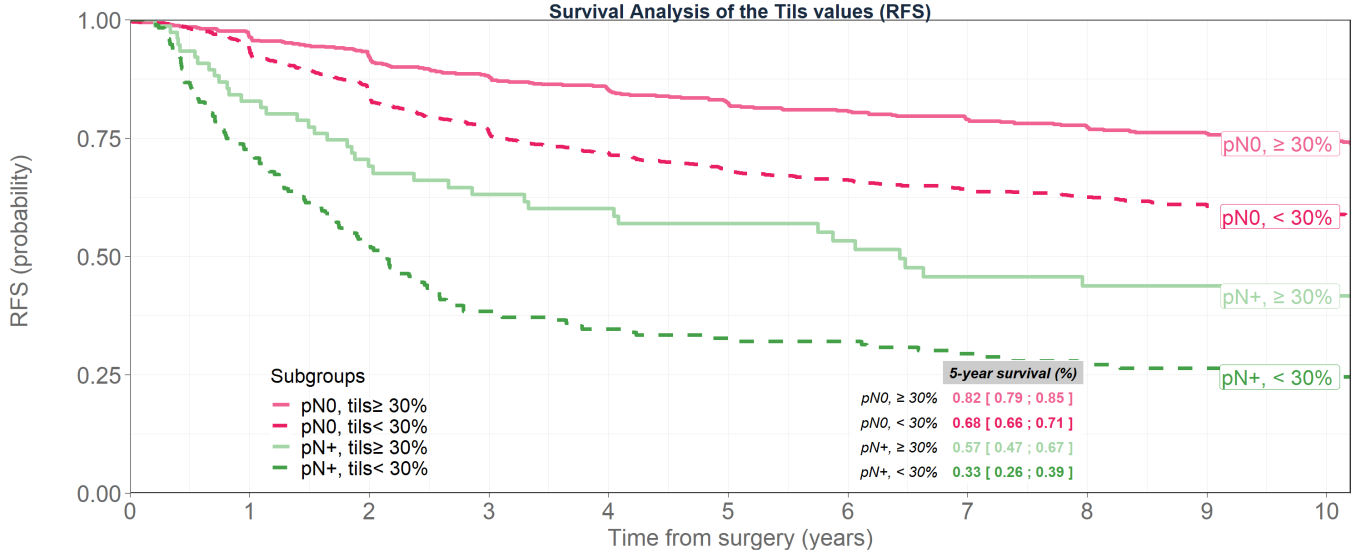
eFigure 5-M. Overall Survival According to Nodal Status and TILs <30 vs ≥30%



Number of subjects at risk (n (%))

pN0, tils≥ 30%	588 (100)	561 (95)	539 (92)	515 (88)	498 (85)	467 (79)	445 (76)	417 (71)	397 (68)	380 (65)	361 (61
pN0, tils< 30%	1122 (100)	1075 (96)	1009 (90)	917 (82)	827 (74)	758 (68)	691 (62)	636 (57)	583 (52)	532 (47)	476 (42
pN+, tils≥ 30%	78 (100)	71 (91)	60 (77)	50 (64)	43 (55)	38 (49)	32 (41)	27 (35)	25 (32)	24 (31)	17 (22
pN+, tils< 30%	178 (100)	150 (84)	107 (60)	83 (47)	69 (39)	58 (33)	57 (32)	51 (29)	39 (22)	36 (20)	29 (16

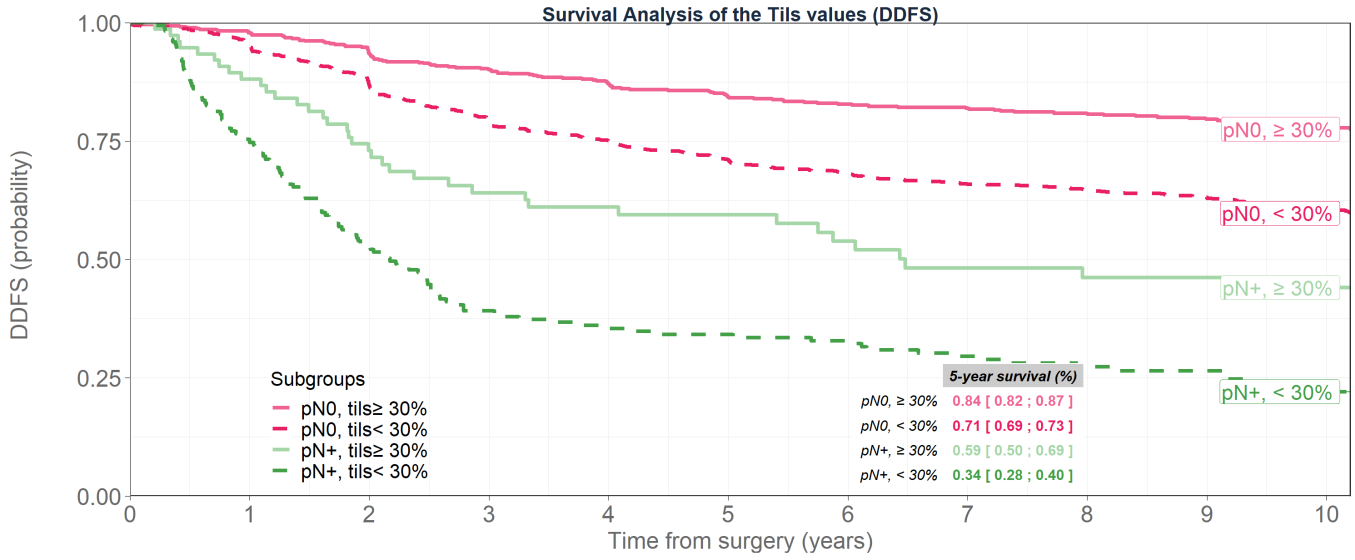
eFigure 5-N. RFS According to Nodal Status and TILs <30 vs ≥30%



Number of subjects at risk (n (%))

pN0, tils≥ 30%	588 (100)	546 (93)	507 (86)	474 (81)	457 (78)	426 (72)	406 (69)	378 (64)	357 (61)	339 (58)	322 (55
pN0, tils< 30%	1122 (100)	1020 (91)	902 (80)	797 (71)	728 (65)	671 (60)	612 (55)	563 (50)	513 (46)	466 (42)	417 (37
pN+, tils≥ 30%	78 (100)	61 (78)	47 (60)	42 (54)	38 (49)	32 (41)	29 (37)	24 (31)	22 (28)	21 (27)	15 (19
pN+, tils< 30%	178 (100)	122 (69)	86 (48)	62 (35)	55 (31)	50 (28)	49 (28)	43 (24)	34 (19)	32 (18)	27 (15

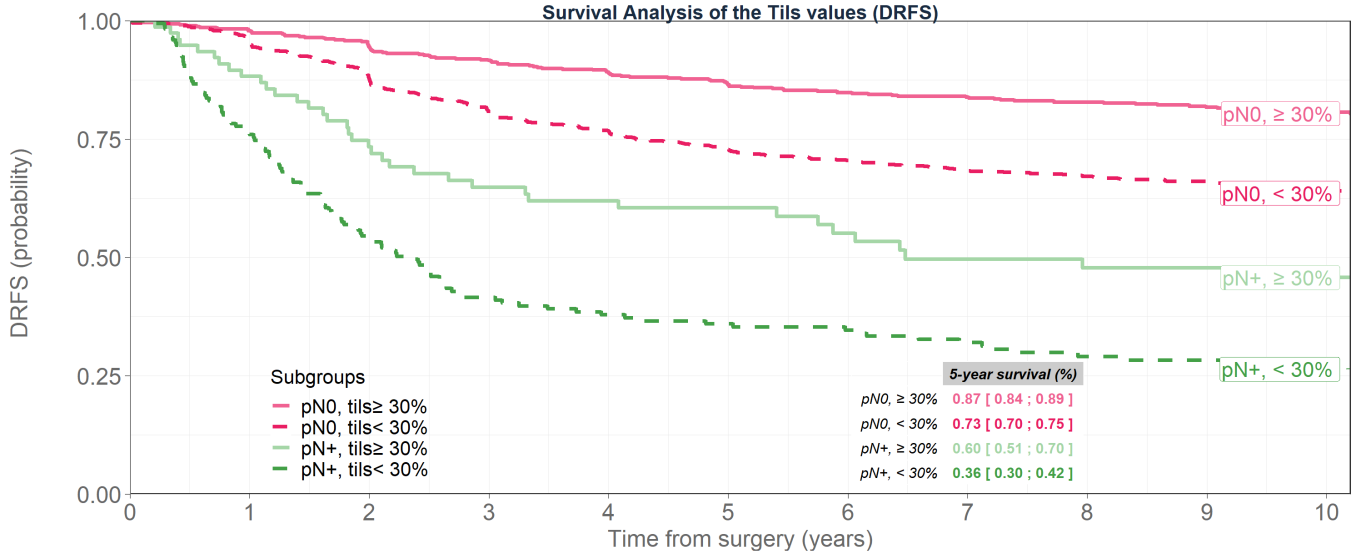
eFigure 5-O. DDFS According to Nodal Status and TILs <30 vs ≥30%



Number of subjects at risk (n (%))

pN0, tils≥ 30%	588 (100)	555 (94)	516 (88)	488 (83)	470 (80)	437 (74)	417 (71)	396 (67)	377 (64)	357 (61)	340 (58
pN0, tils< 30%	1122 (100)	1039 (93)	928 (83)	818 (73)	754 (67)	693 (62)	627 (56)	576 (51)	526 (47)	476 (42)	421 (38
pN+, tils≥ 30%	78 (100)	65 (83)	50 (64)	42 (54)	38 (49)	33 (42)	29 (37)	25 (32)	23 (29)	22 (28)	16 (21
pN+, tils< 30%	178 (100)	126 (71)	86 (48)	63 (35)	56 (31)	52 (29)	49 (28)	43 (24)	34 (19)	32 (18)	25 (14

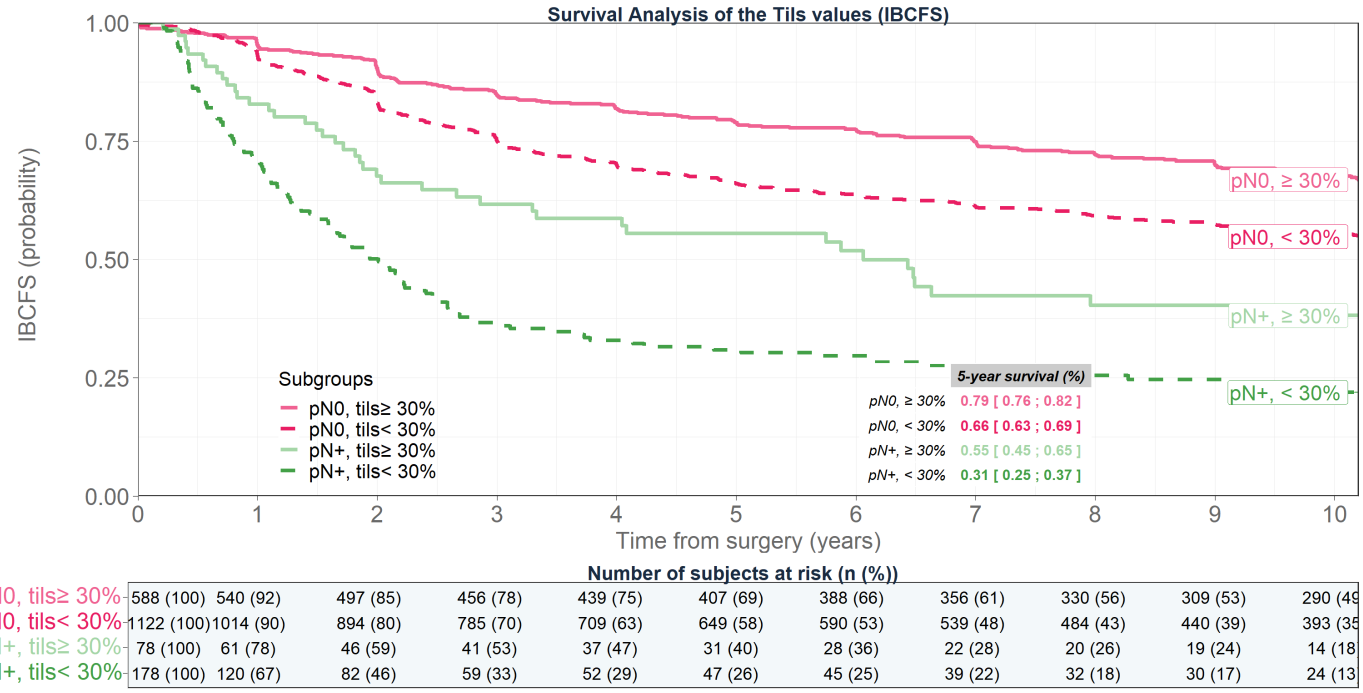
eFigure 5-P. DRFS According to Nodal Status and TILs <30 vs ≥30%



Number of subjects at risk (n (%))

pN0, tils≥ 30%	588 (100)	557 (95)	523 (89)	498 (85)	483 (82)	455 (77)	435 (74)	410 (70)	391 (66)	373 (63)	356 (61
pN0, tils< 30%	1122 (100)	1046 (93)	940 (84)	844 (75)	780 (70)	718 (64)	659 (59)	610 (54)	557 (50)	509 (45)	454 (40
pN+, tils≥ 30%	78 (100)	66 (85)	52 (67)	45 (58)	41 (53)	35 (45)	31 (40)	27 (35)	25 (32)	24 (31)	17 (22
pN+, tils< 30%	178 (100)	128 (72)	89 (50)	67 (38)	60 (34)	55 (31)	53 (30)	47 (26)	36 (20)	34 (19)	28 (16

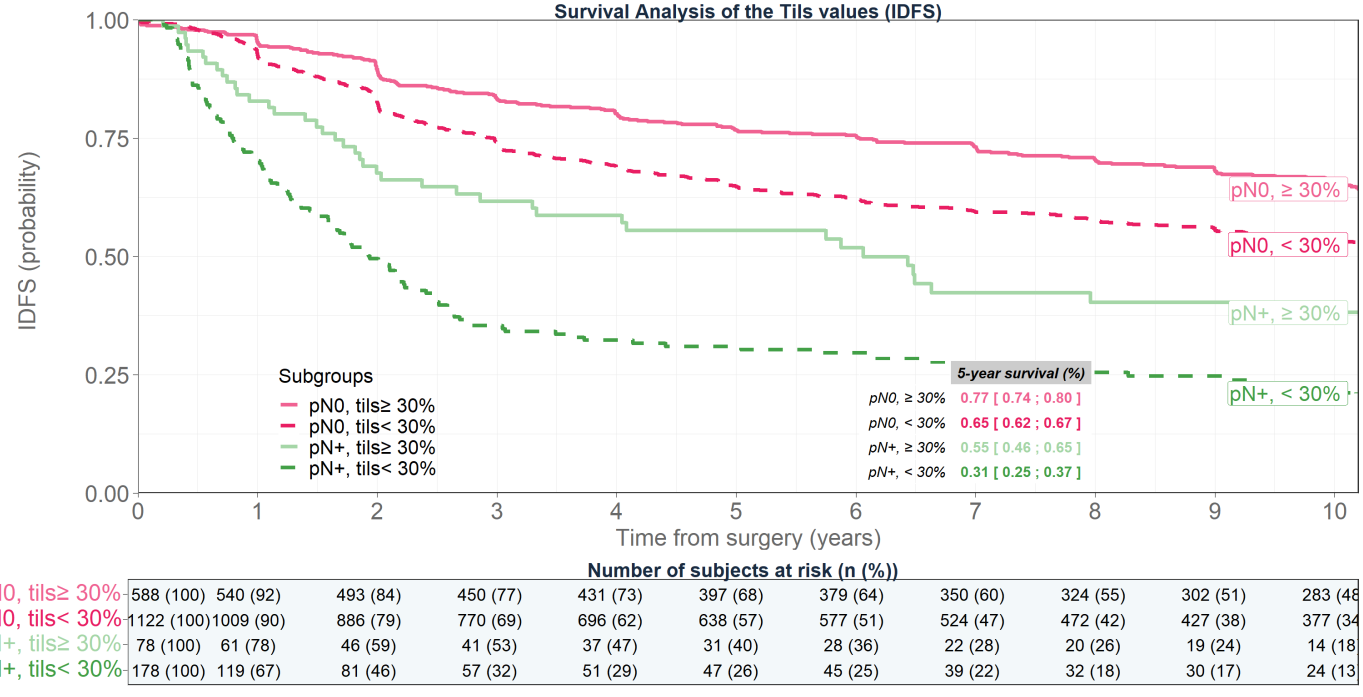
eFigure 5-Q. IBCFS According to Nodal Status and TILs <30 vs ≥30%



Number of subjects at risk (n (%))

pN0, tils≥ 30%	588 (100)	540 (92)	497 (85)	456 (78)	439 (75)	407 (69)	388 (66)	356 (61)	330 (56)	309 (53)	290 (49
pN0, tils< 30%	1122 (100)	1014 (90)	894 (80)	785 (70)	709 (63)	649 (58)	590 (53)	539 (48)	484 (43)	440 (39)	393 (35
pN+, tils≥ 30%	78 (100)	61 (78)	46 (59)	41 (53)	37 (47)	31 (40)	28 (36)	22 (28)	20 (26)	19 (24)	14 (18
pN+, tils< 30%	178 (100)	120 (67)	82 (46)	59 (33)	52 (29)	47 (26)	45 (25)	39 (22)	32 (18)	30 (17)	24 (13

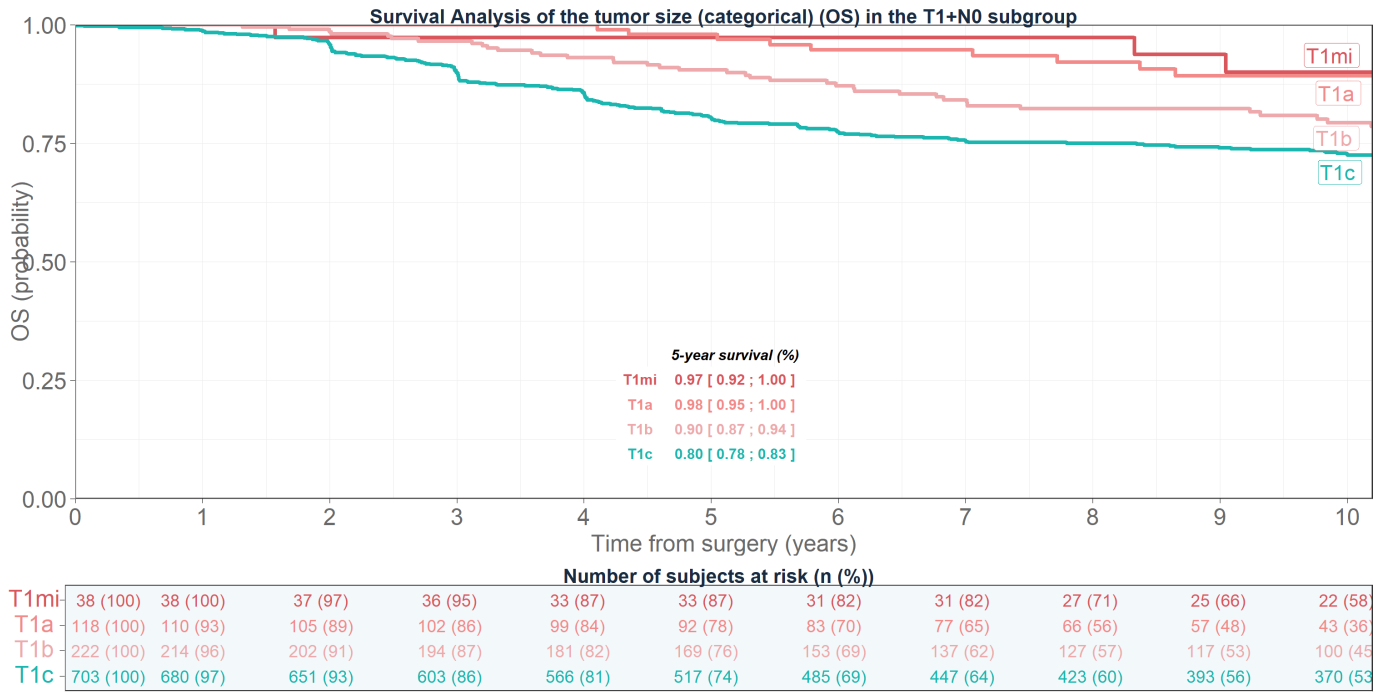
eFigure 5-R. IDFS According to Nodal Status and TILs <30 vs ≥30%



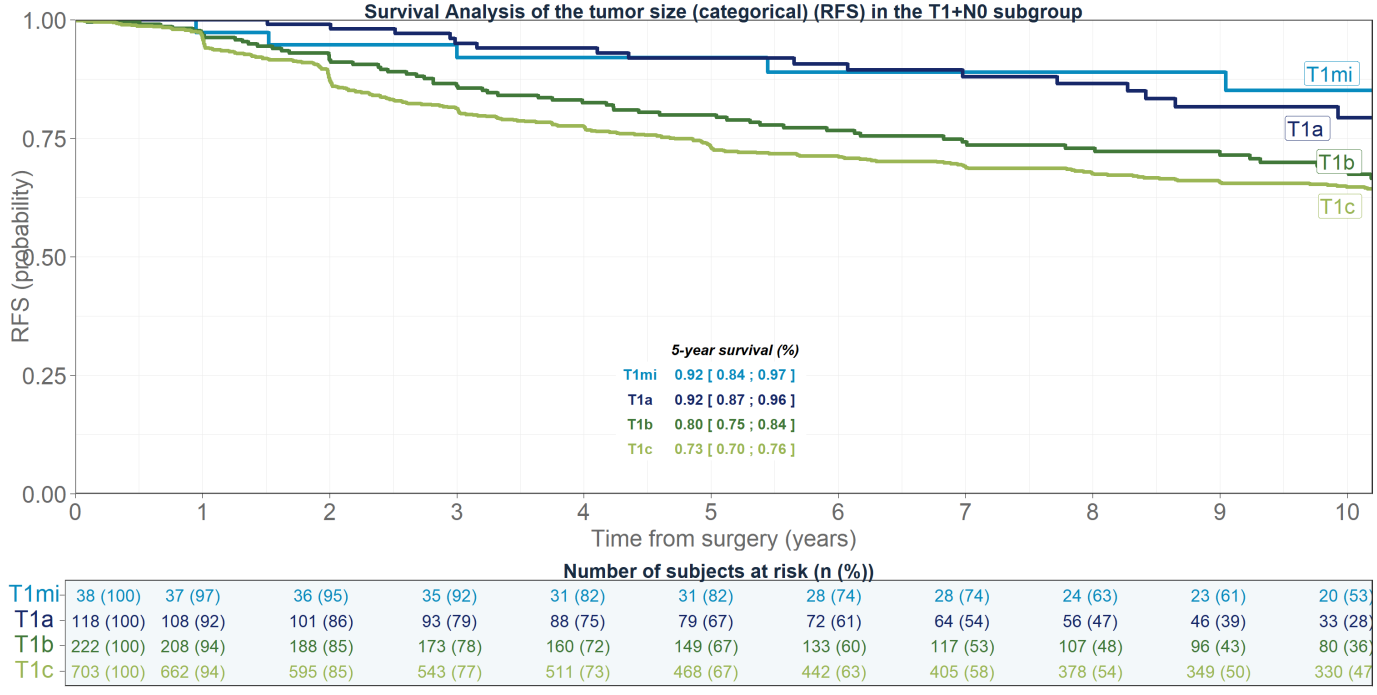
Number of subjects at risk (n (%))

pN0, tils≥ 30%	588 (100)	540 (92)	493 (84)	450 (77)	431 (73)	397 (68)	379 (64)	350 (60)	324 (55)	302 (51)	283 (48
pN0, tils< 30%	1122 (100)	1009 (90)	886 (79)	770 (69)	696 (62)	638 (57)	577 (51)	524 (47)	472 (42)	427 (38)	377 (34
pN+, tils≥ 30%	78 (100)	61 (78)	46 (59)	41 (53)	37 (47)	31 (40)	28 (36)	22 (28)	20 (26)	19 (24)	14 (18
pN+, tils< 30%	178 (100)	119 (67)	81 (46)	57 (32)	51 (29)	47 (26)	45 (25)	39 (22)	32 (18)	30 (17)	24 (13

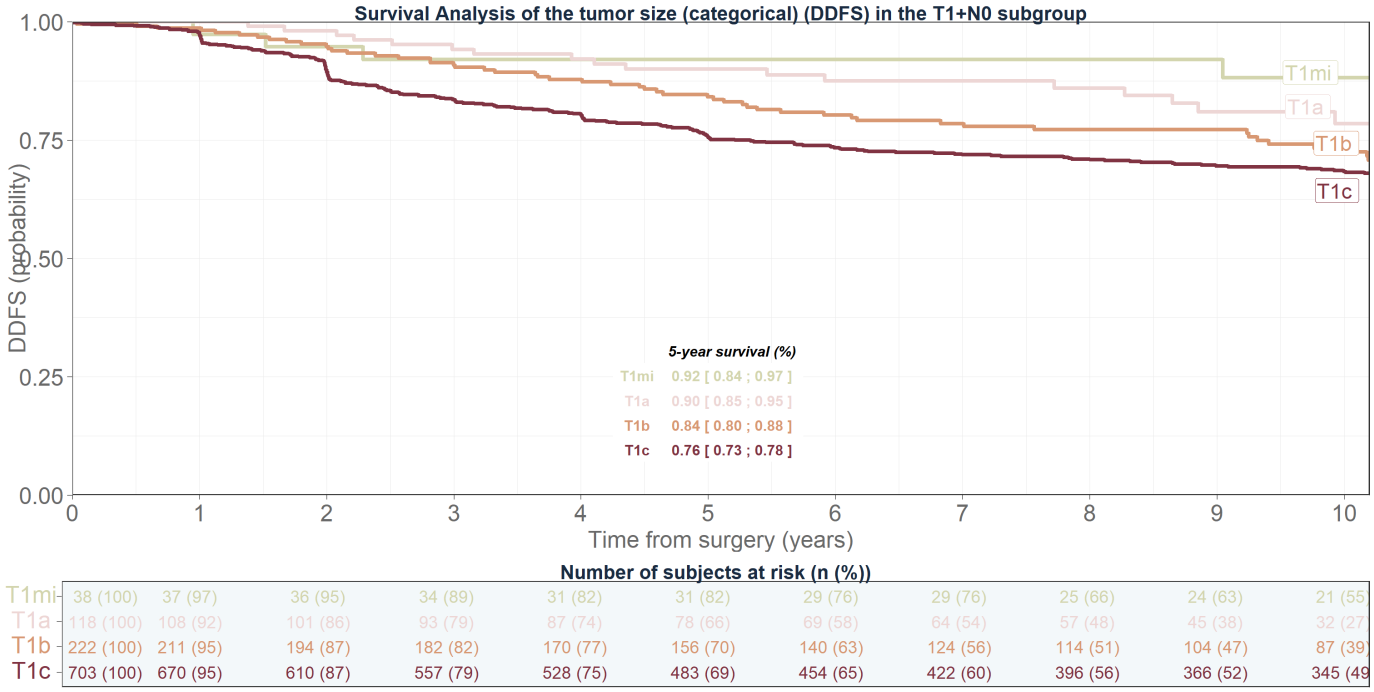
eFigure 5-S. Overall Survival According to T1 Substage Among Patients With Stage I TNBC (Regardless of TILs)



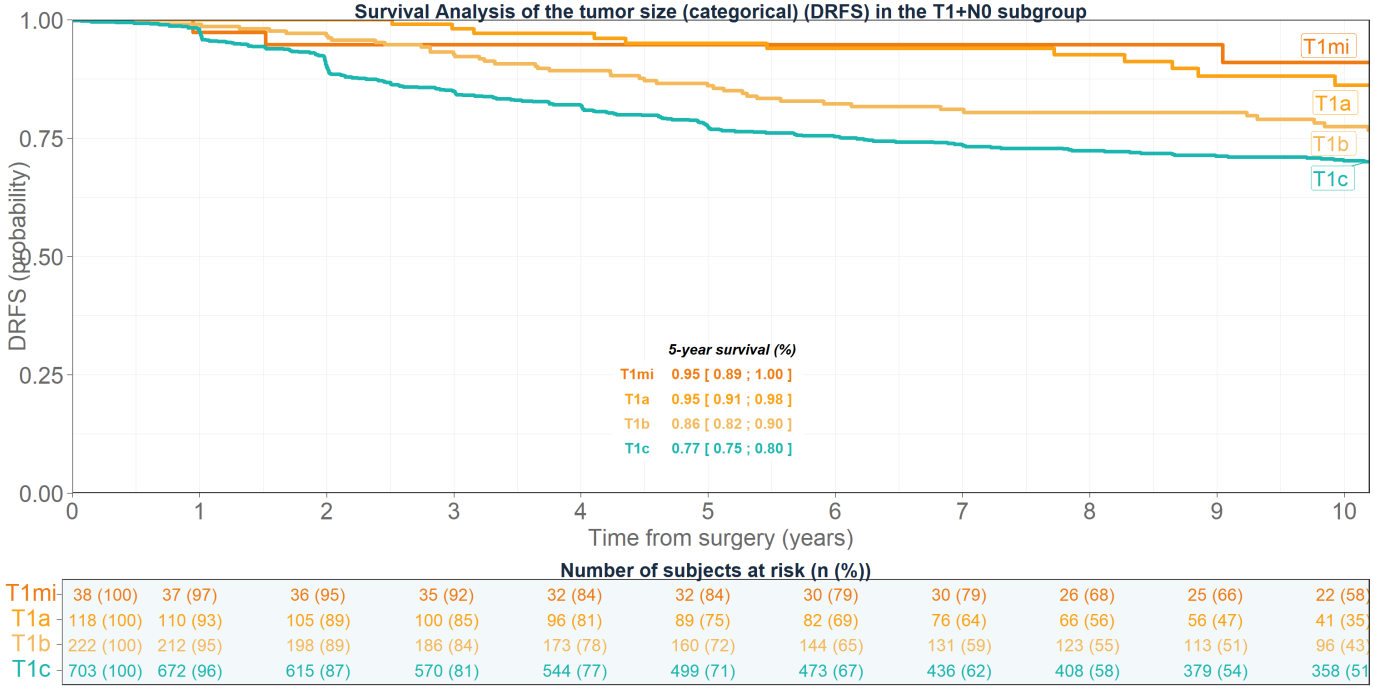
eFigure 5-T. RFS According to T1 Substage Among Patients With Stage I TNBC (Regardless of TILs)



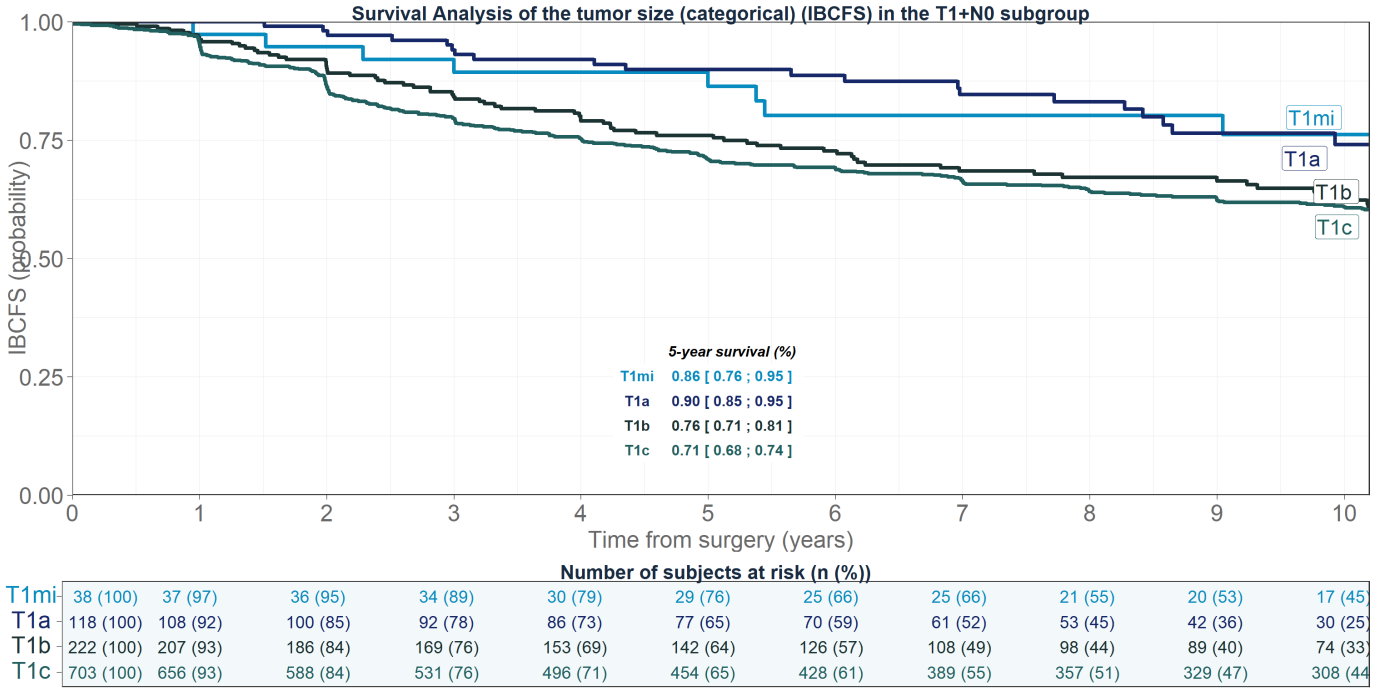
eFigure 5-U. DDFS According to T1 Substage Among Patients With Stage I TNBC (Regardless of TILs)



eFigure 5-V. DRFS According to T1 Substage Among Patients With Stage I TNBC (Regardless of TILs)



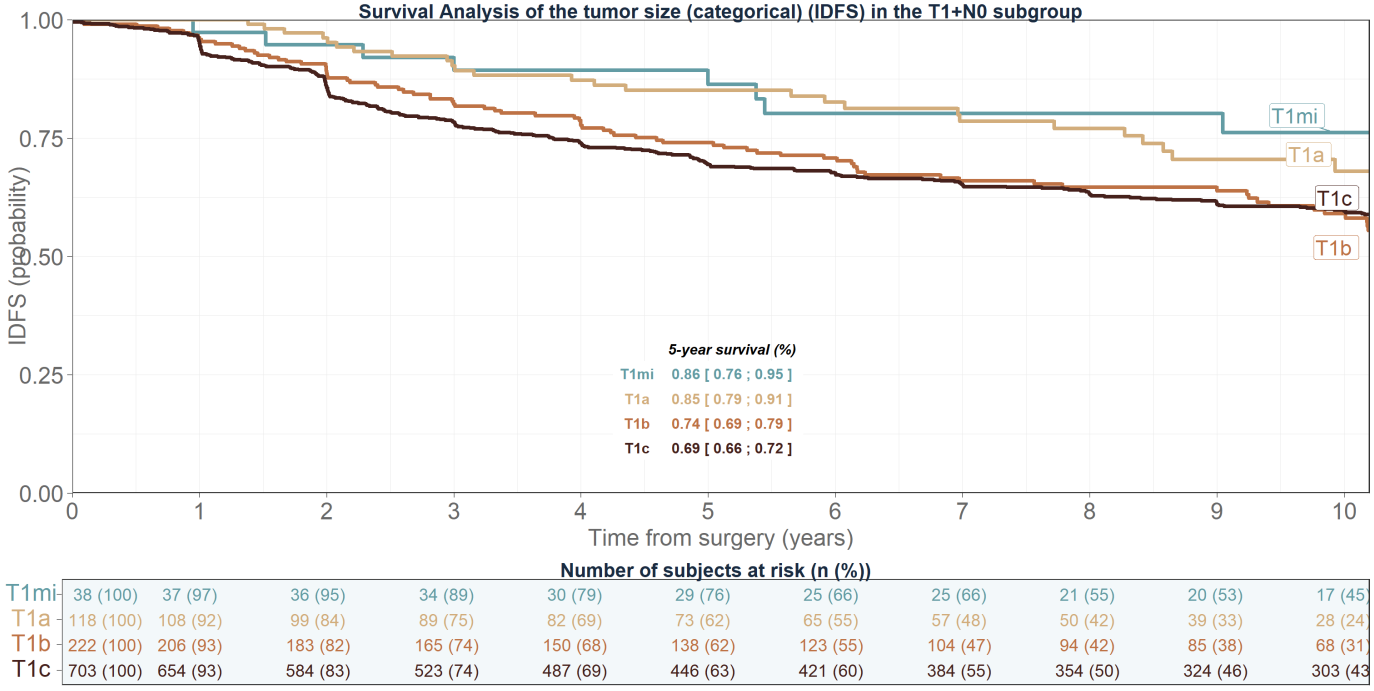
eFigure 5-W. IBCFS According to T1 Substage Among Patients With Stage I TNBC (Regardless of TILs)



Number of subjects at risk (n (%))

T1mi	38 (100)	37 (97)	36 (95)	34 (89)	30 (79)	29 (76)	25 (66)	25 (66)	21 (55)	20 (53)	17 (45)
T1a	118 (100)	108 (92)	100 (85)	92 (78)	86 (73)	77 (65)	70 (59)	61 (52)	53 (45)	42 (36)	30 (25)
T1b	222 (100)	207 (93)	186 (84)	169 (76)	153 (69)	142 (64)	126 (57)	108 (49)	98 (44)	89 (40)	74 (33)
T1c	703 (100)	656 (93)	588 (84)	531 (76)	496 (71)	454 (65)	428 (61)	389 (55)	357 (51)	329 (47)	308 (44)

eFigure 5-X. IDFS According to T1 Substage Among Patients With Stage I TNBC (Regardless of TILs)



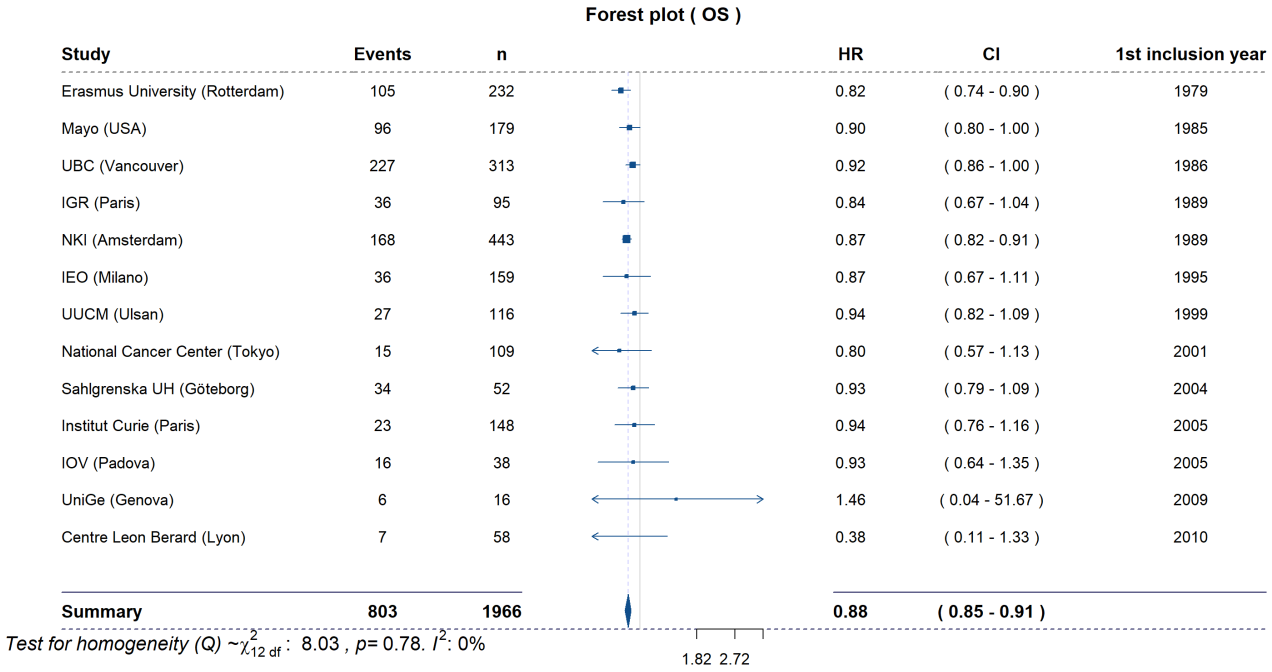
Number of subjects at risk (n (%))

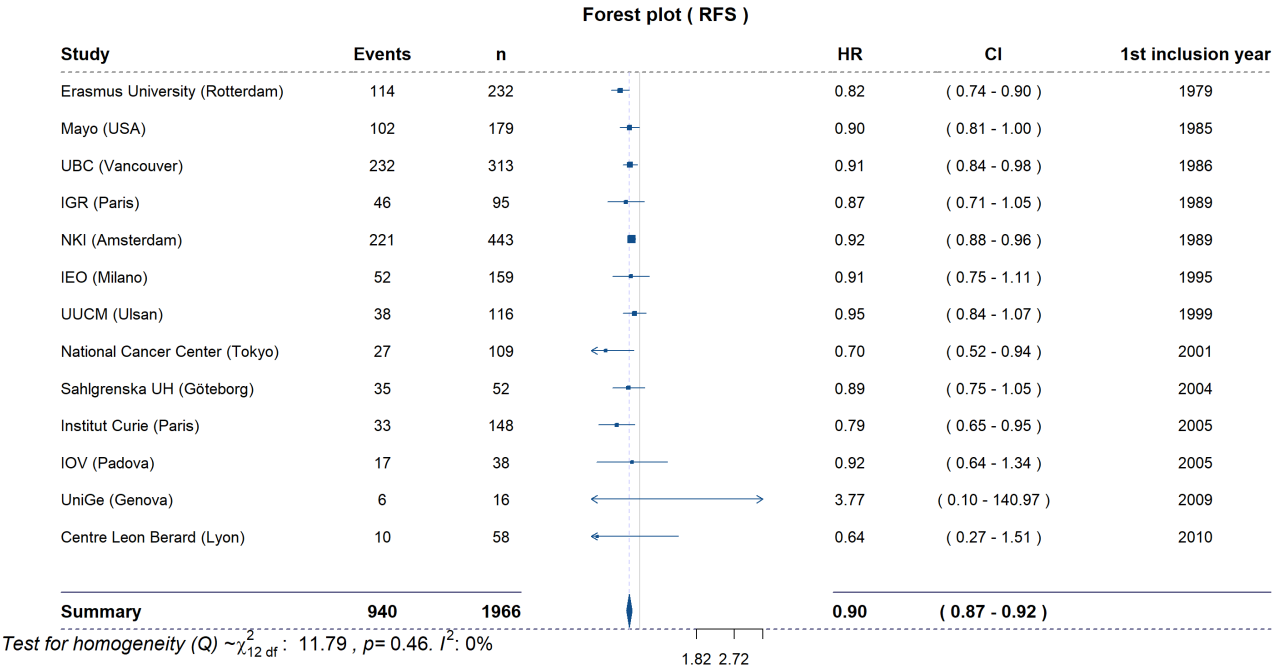
T1mi	38 (100)	37 (97)	36 (95)	34 (89)	30 (79)	29 (76)	25 (66)	25 (66)	21 (55)	20 (53)	17 (45)
T1a	118 (100)	108 (92)	99 (84)	89 (75)	82 (69)	73 (62)	65 (55)	57 (48)	50 (42)	39 (33)	28 (24)
T1b	222 (100)	206 (93)	183 (82)	165 (74)	150 (68)	138 (62)	123 (55)	104 (47)	94 (42)	85 (38)	68 (31)
T1c	703 (100)	654 (93)	584 (83)	523 (74)	487 (69)	446 (63)	421 (60)	384 (55)	354 (50)	324 (46)	303 (43)

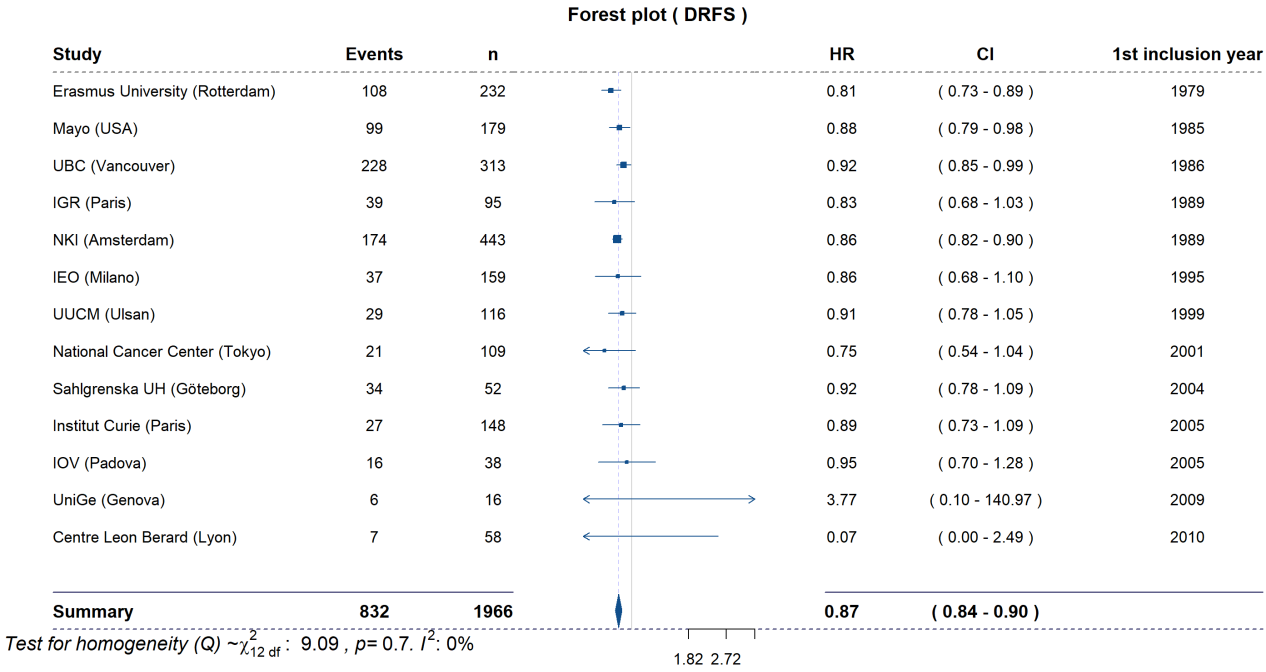
6. Forest Plots

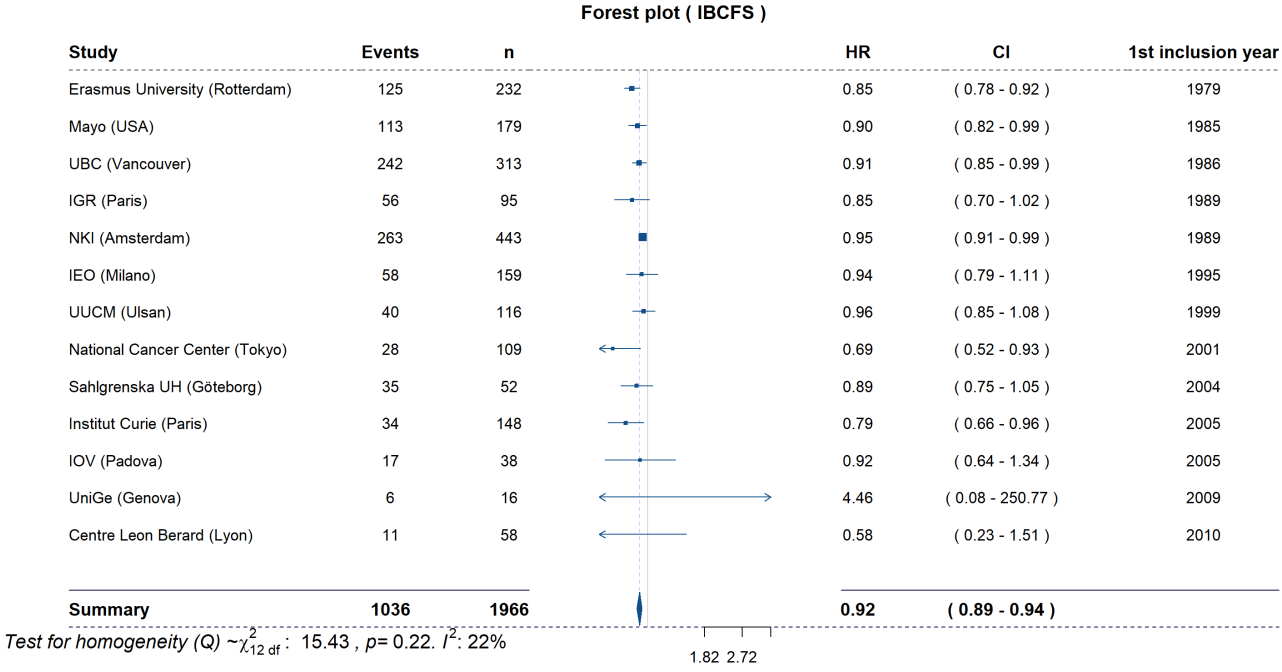
Below are the **adjusted forest plots** according to the different endpoints. The Cox models used to construct the forest plots are adjusted on the clinicopathologic variables. On each graph, we report the Cochran's Q test to assess the heterogeneity of effect-size estimates from the individual studies, as well as the heterogeneity index I^2. A non-significant Q test indicates that the TILs effect is the same across studies and variations across studies are simply caused by chance. I^2 provides an estimate of the percentage of variability in results across studies that is due to real differences and not due to chance. An I^2 of less than 25% is considered as low heterogeneity. Missing data are imputed in each study separately by multiple imputations with 20 imputed data sets.

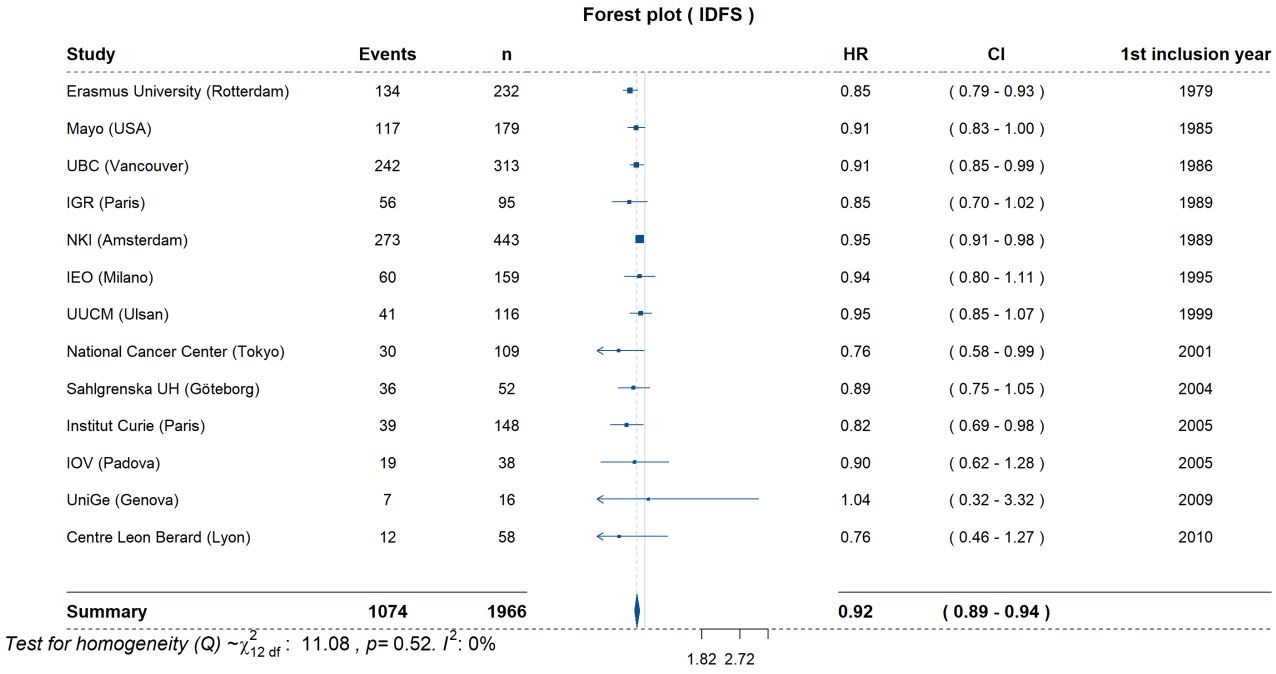
The forest plots are ordered according to the first year of inclusion of the study. The effect of TILs across studies over time are similar, with no clear visual trend suggesting an association between the first year of inclusion on the HR.











7. Survival rates in Subgroups

eTable 7-A. Survival Rates at 3 Years for Stage I TNBC

			IDFS	RFS	DDFS	DRFS	OS
			3-year survival	3-year survival	3-year survival	3-year survival	3-year survival
T1N0	General	*1081*	81% [79-83]	84% [82-86]	86% [85-88]	88% [87-90]	93% [91-94]
	[0-29]	*728 (67%)*	78% [76-81]	81% [79-84]	83% [81-86]	85% [83-88]	91% [89-92]
	[30-100]	*353 (33%)*	86% [83-89]	91% [88-93]	93% [90-95]	94% [92-96]	97% [95-98]
	[0-49]	*855 (79%)*	79% [76-81]	81% [79-84]	84% [82-86]	86% [84-88]	91% [89-93]
	[50-100]	*226 (21%)*	90% [87-93]	95% [92-97]	96% [93-98]	97% [95-99]	99% [97-100]
	[0-74]	*973 (90%)*	80% [77-82]	83% [81-85]	85% [83-87]	87% [85-89]	92% [90-93]
	[75-100]	*108 (10%)*	92% [87-95]	97% [94-100]	96% [93-99]	98% [95-100]	99% [97-100]
T1mi N0	General	*38*	92% [84-100]	95% [87-100]	92% [84-97]	95% [89-100]	97% [92-100]
	[0-29]	*24 (63%)*	88% [75-96]	92% [83-100]	88% [75-100]	92% [83-100]	96% [88-100]
	[30-100]	*14 (37%)*	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]
	[0-49]	*29 (76%)*	90% [79-97]	93% [86-100]	90% [79-100]	93% [86-100]	97% [90-100]
	[50-100]	*9 (24%)*	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]	100% [100-100]
	[0-74]	*38 (100%)*	92% [84-100]	95% [89-100]	92% [84-100]	95% [89-100]	97% [92-100]
T1a N0	General	*118*	90% [85-95]	95% [91-98]	94% [90-98]	98% [96-100]	100% [100-100]
	[0-29]	*72 (61%)*	90% [84-96]	95% [90-100]	94% [88-98]	97% [93-100]	100% [100-100]
	[30-100]	*46 (39%)*	90% [81-98]	95% [89-100]	95% [89-100]	100% [100-100]	100% [100-100]
	[0-49]	*88 (75%)*	90% [83-95]	95% [90-99]	94% [89-98]	97% [95-100]	100% [100-100]
	[50-100]	*30 (25%)*	92% [82-100]	96% [88-100]	96% [88-100]	100% [100-100]	100% [100-100]
	[0-74]	*106 (90%)*	90% [85-95]	94% [90-98]	95% [90-98]	98% [95-100]	100% [100-100]
	[75-100]	*12 (10%)*	91% [75-100]	100% [100-100]	91% [75-100]	100% [100-100]	100% [100-100]
T1mi and T1a N0	General	*156*	91% [86-94]	95% [92-98]	94% [90-97]	97% [95-99]	99% [98-100]
	[0-29]	*96 (62%)*	90% [84-94]	94% [90-98]	92% [87-97]	96% [92-99]	99% [97-100]
	[30-100]	*60 (38%)*	92% [86-98]	96% [92-100]	96% [92-100]	100% [100-100]	100% [100-100]
	[0-49]	*117 (75%)*	90% [85-94]	94% [91-98]	93% [89-96]	96% [93-99]	99% [97-100]
	[50-100]	*39 (25%)*	94% [86-100]	97% [91-100]	97% [91-100]	100% [100-100]	100% [100-100]
	[0-74]	*144 (92%)*	91% [87-95]	95% [91-98]	94% [90-97]	97% [95-99]	99% [98-100]
	[75-100]	*12 (8%)*	91% [75-100]	100% [100-100]	91% [73-100]	100% [100-100]	100% [100-100]
T1b N0	General	*222*	82% [78-86]	86% [82-90]	91% [88-94]	93% [90-96]	97% [94-99]
	[0-29]	*154 (69%)*	80% [75-85]	83% [78-88]	88% [84-92]	91% [87-95]	96% [94-99]
	[30-100]	*68 (31%)*	87% [80-94]	92% [87-97]	97% [92-100]	97% [93-100]	97% [92-100]
	[0-49]	*185 (83%)*	81% [76-86]	84% [79-89]	90% [85-93]	92% [88-95]	96% [94-98]
	[50-100]	*37 (17%)*	88% [79-97]	97% [91-100]	97% [91-100]	97% [91-100]	97% [91-100]
	[0-74]	*204 (92%)*	82% [77-86]	85% [81-90]	91% [87-94]	93% [89-96]	97% [95-99]
	[75-100]	*18 (8%)*	88% [75-100]	94% [82-100]	94% [82-100]	94% [83-100]	94% [83-100]
T1c N0	General	*703*	78% [76-81]	81% [79-84]	84% [81-86]	85% [83-87]	90% [88-92]
	[0-29]	*478 (68%)*	76% [72-79]	78% [75-81]	80% [77-83]	82% [79-85]	87% [84-90]
	[30-100]	*225 (32%)*	85% [80-89]	89% [85-92]	91% [87-94]	92% [89-95]	96% [94-98]
	[0-49]	*553 (79%)*	75% [72-78]	78% [75-81]	80% [78-83]	82% [79-85]	88% [85-90]
	[50-100]	*150 (21%)*	90% [86-94]	94% [90-97]	95% [92-98]	96% [93-99]	99% [97-100]
	[0-74]	*625 (89%)*	77% [74-79]	79% [76-82]	82% [79-84]	83% [81-86]	89% [87-91]
	[75-100]	*78 (11%)*	92% [87-97]	97% [95-100]	97% [95-100]	99% [96-100]	100% [100-100]

eTable 7-B. Survival Rates at 3, 5, and 10 Years According to Age and TIL Levels

Sample	Tils levels	*n(%)*	Estimated survival with 95% bootstrapped interval confidence															
			IDFS			RFS			DDFS			DRFS			OS			
			3-year	5-year	10-year	3-year	5-year	10-year	3-year	5-year	10-year	3-year	5-year	10-year	3-year	5-year	10-year	
T1N0	General	*1081*	81% [79-83]	73% [70-75]	61% [58-64]	84% [82-86]	77% [75-79]	68% [65-70]	86% [85-88]	79% [77-81]	71% [69-73]	88% [87-90]	82% [79-84]	74% [72-77]	93% [91-94]	85% [83-87]	76% [74-79]	
	[0-29]	*728 (67%)*	78% [76-81]	69% [66-72]	58% [55-61]	81% [79-84]	73% [70-76]	64% [61-67]	83% [81-86]	76% [73-78]	66% [63-69]	85% [83-88]	78% [75-80]	70% [67-73]	91% [89-92]	82% [79-84]	72% [69-75]	
	[30-100]	*353 (33%)*	86% [83-89]	80% [76-83]	68% [63-72]	91% [88-93]	85% [82-88]	76% [71-80]	93% [90-95]	87% [84-90]	81% [77-84]	94% [92-96]	90% [87-92]	83% [80-87]	97% [95-98]	91% [88-94]	84% [81-88]	
	[50-100]	*226 (21%)*	90% [87-93]	84% [80-88]	70% [64-75]	95% [92-97]	89% [86-93]	78% [73-83]	96% [93-98]	91% [88-94]	86% [81-90]	97% [95-99]	94% [91-96]	88% [84-91]	99% [97-100]	95% [92-97]	89% [85-92]	
	[60-100]	*189 (17%)*	90% [86-93]	85% [81-89]	70% [64-76]	95% [92-98]	90% [87-94]	78% [72-83]	96% [94-98]	92% [89-95]	87% [82-91]	97% [95-99]	94% [92-97]	89% [85-93]	99% [97-100]	96% [93-98]	90% [86-94]	
	[75-100]	*108 (10%)*	92% [87-96]	86% [80-91]	73% [65-80]	97% [94-99]	91% [87-95]	80% [73-87]	96% [93-99]	92% [88-96]	90% [86-95]	98% [95-100]	95% [92-98]	92% [88-96]	99% [97-100]	96% [93-99]	92% [88-96]	
T1N0 40+y	General	*749*	85% [82-87]	75% [72-78]	62% [59-66]	87% [85-89]	79% [76-82]	69% [65-72]	88% [86-90]	81% [78-84]	70% [67-73]	91% [89-92]	84% [81-86]	74% [71-77]	94% [92-95]	87% [85-89]	77% [74-80]	
	[0-29]	*540 (72%)*	83% [80-85]	73% [69-76]	59% [55-63]	85% [83-88]	76% [73-79]	65% [61-69]	87% [85-89]	78% [75-82]	67% [63-71]	89% [87-92]	81% [78-84]	71% [67-74]	93% [91-95]	84% [82-87]	74% [70-77]	
	[30-100]	*209 (28%)*	89% [86-93]	82% [77-87]	72% [66-78]	91% [88-95]	87% [83-91]	79% [74-84]	92% [89-95]	87% [83-91]	79% [74-84]	94% [91-97]	91% [87-94]	83% [77-88]	96% [94-98]	92% [89-95]	85% [80-89]	
	[50-100]	*112 (15%)*	94% [90-98]	89% [83-94]	78% [71-86]	96% [92-99]	93% [88-97]	82% [75-89]	95% [91-98]	93% [88-97]	85% [77-91]	97% [94-99]	96% [93-99]	87% [81-93]	98% [95-100]	97% [94-99]	90% [84-95]	
	[60-100]	*85 (11%)*	94% [88-97]	92% [87-97]	83% [74-91]	96% [92-100]	96% [92-99]	85% [77-93]	95% [90-99]	95% [90-99]	88% [81-95]	97% [94-100]	97% [94-100]	90% [82-96]	99% [96-100]	99% [96-100]	93% [87-98]	
	[75-100]	*41 (5%)*	92% [85-98]	90% [82-97]	87% [77-95]	97% [93-100]	97% [92-100]	92% [83-100]	92% [85-100]	92% [85-98]	92% [84-98]	97% [92-100]	97% [92-100]	95% [89-100]	97% [92-100]	97% [92-100]	95% [89-100]	
T1N0 18-40 y	General	*332*	73% [69-77]	66% [62-71]	57% [53-62]	78% [75-82]	72% [68-76]	65% [61-70]	82% [79-86]	76% [72-80]	72% [67-75]	83% [80-86]	77% [73-81]	73% [69-77]	90% [87-93]	81% [77-84]	75% [71-78]	
	[0-29]	*188 (57%)*	66% [60-72]	59% [53-65]	53% [47-60]	69% [63-75]	64% [58-70]	59% [53-65]	74% [68-79]	68% [62-73]	63% [57-69]	75% [69-80]	68% [62-73]	64% [59-70]	85% [80-89]	74% [69-80]	67% [62-73]	
	[30-100]	*144 (43%)*	83% [78-88]	76% [70-82]	63% [56-69]	90% [85-93]	82% [77-87]	72% [66-78]	94% [90-97]	87% [82-92]	82% [77-88]	94% [90-97]	88% [84-92]	84% [79-89]	97% [95-99]	89% [85-94]	84% [79-89]	
	[50-100]	*114 (34%)*	87% [81-92]	80% [73-86]	63% [56-71]	94% [89-97]	87% [81-92]	74% [67-81]	96% [94-99]	90% [86-95]	86% [80-91]	96% [94-99]	92% [88-96]	88% [82-93]	99% [97-100]	93% [89-96]	88% [82-93]	
	[60-100]	*104 (31%)*	86% [81-92]	80% [73-86]	62% [54-69]	94% [90-98]	86% [81-91]	73% [66-79]	97% [94-100]	90% [85-95]	85% [80-91]	97% [94-100]	92% [87-96]	87% [82-92]	99% [97-100]	93% [88-97]	87% [81-92]	
	[75-100]	*67 (20%)*	91% [85-97]	84% [76-91]	65% [56-76]	97% [93-100]	88% [82-94]	74% [66-83]	99% [96-100]	93% [87-97]	89% [83-95]	99% [96-100]	94% [90-99]	91% [85-97]	100% [100-100]	96% [91-99]	91% [85-97]	

8. Competing Risk Analysis

We aim to see the effect of TILs on the occurrence of a second cancer and distant relapse or death. To do this, we will estimate cumulative incidence functions from the competing risks data, as well as estimates and 95% confidence intervals for survival rates.

In this analysis, TILs are classified into two categories. First, TILs levels above and below 30%, and then above and below 50%.

Data on second cancers was not available in the UBC cohort (309 patients) and as such was excluded from this additional analysis.

eTable 8-A. Competing Events

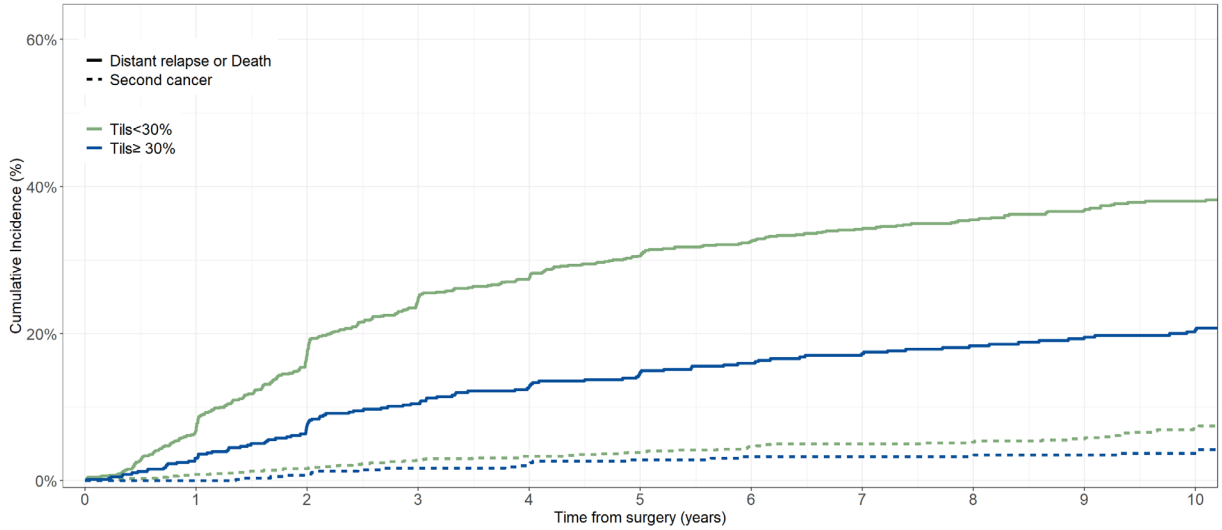
Censored	Distant relapse or Death	Second cancer	Sum
988	541	128	**1657**

We plot below Aalen-Johansen curves for competing events. The confidence intervals for cumulative incidence estimates are calculated in the following way[14]: $x^{exp(\pm z*se/(x*log(x)))}$, where x is the cumulative incidence estimate, se is the standard error estimate, and z is the z-score associated with the confidence level of the interval, e.g. $z=1.96$ for a 95% CI.

eTable 8-B. Competing Events According to TILs Level (30% Threshold)

	Censored	Distant relapse or Death	Second cancer	Sum
TILs <30%	591	404	88	**1083**
TILs ≥ 30%	397	137	40	**574**
Sum	**988**	**541**	**128**	**1657**

eFigure 8-A. Influence of TILs <30% vs ≥30% on Distant Relapse, Death, or Second Cancers

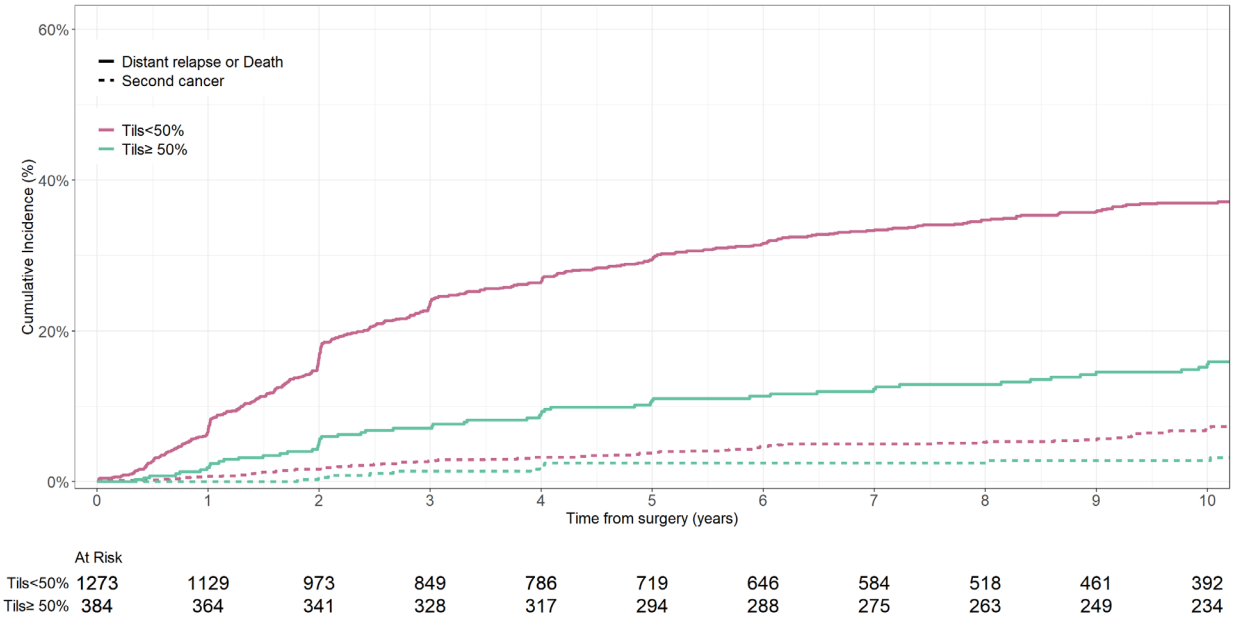


Characteristic	N	3-year cum inc	5-year cum inc	10-year cum inc
Distant relapse or Death				
Total	1,657			
Tils<30%	1,083	25% (22%, 28%)	31% (28%, 34%)	38% (35%, 41%)
Tils≥ 30%	574	10% (8.1%, 13%)	15% (12%, 18%)	21% (17%, 24%)
Second cancer				
Total	1,657			
Tils<30%	1,083	2.8% (1.9%, 4.0%)	3.9% (2.8%, 5.2%)	7.3% (5.6%, 9.2%)
Tils≥ 30%	574	1.7% (0.83%, 3.1%)	2.8% (1.7%, 4.5%)	3.7% (2.3%, 5.6%)

eTable 8-C. Competing Events According to TILs Level (50% Threshold)

	Censored	Distant relapse or Death	Second cancer	Sum
Tils<50%	708	465	100	**1273**
Tils≥ 50%	280	76	28	**384**
Sum	**988**	**541**	**128**	**1657**

eFigure 8-B. Influence of TILs <50% vs ≥50% on Distant Relapse, Death, or Second Cancers



At Risk

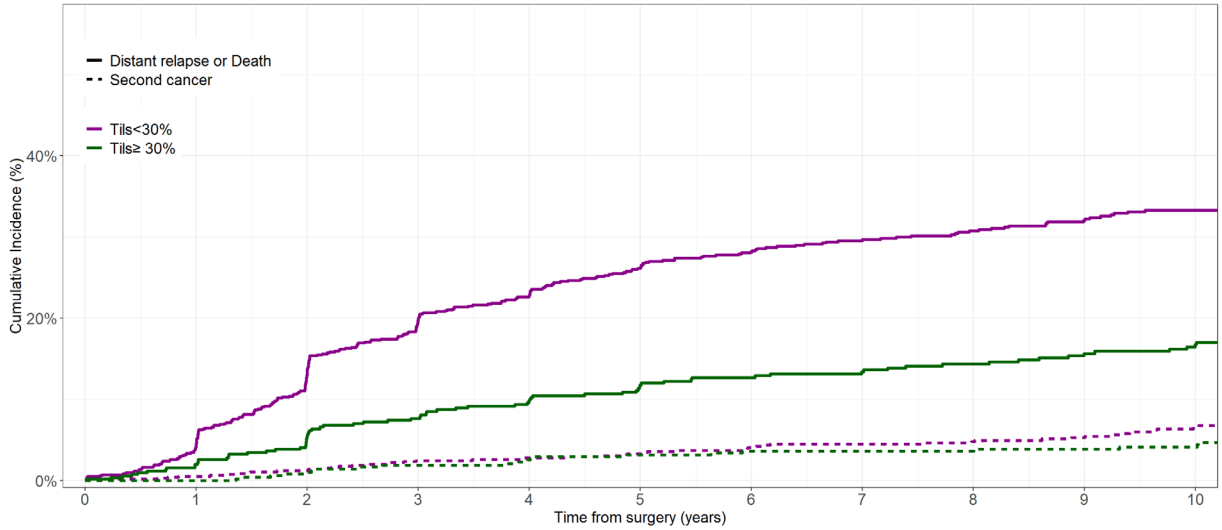
Tils<50%	1273	1129	973	849	786	719	646	584	518	461	392
Tils≥ 50%	384	364	341	328	317	294	288	275	263	249	234

Characteristic	N	3-year cum inc	5-year cum inc	10-year cum inc
Distant relapse or Death				
Total	1,657			
Tils<50%	1,273	24% (21%, 26%)	30% (27%, 32%)	37% (34%, 40%)
Tils≥ 50%	384	7.1% (4.8%, 10%)	11% (7.8%, 14%)	16% (12%, 20%)
Second cancer				
Total	1,657			
Tils<50%	1,273	2.7% (1.9%, 3.8%)	3.8% (2.8%, 5.0%)	7.0% (5.6%, 8.8%)
Tils≥ 50%	384	1.4% (0.53%, 3.0%)	2.5% (1.2%, 4.5%)	2.8% (1.5%, 5.0%)

eTable 8-D. Competing Events According to TILs Level (30% Threshold) in the pN0 Population

	Censored	Distant relapse or Death	Second cancer	Sum
Tils<30%	551	309	74	**934**
Tils≥ 30%	363	106	40	**509**
Sum	**914**	**415**	**114**	**1443**

eFigure 8-C. Influence of TILs <30% vs ≥30% on Distant Relapse, Death, or Second Cancers in Node-Negative TNBC



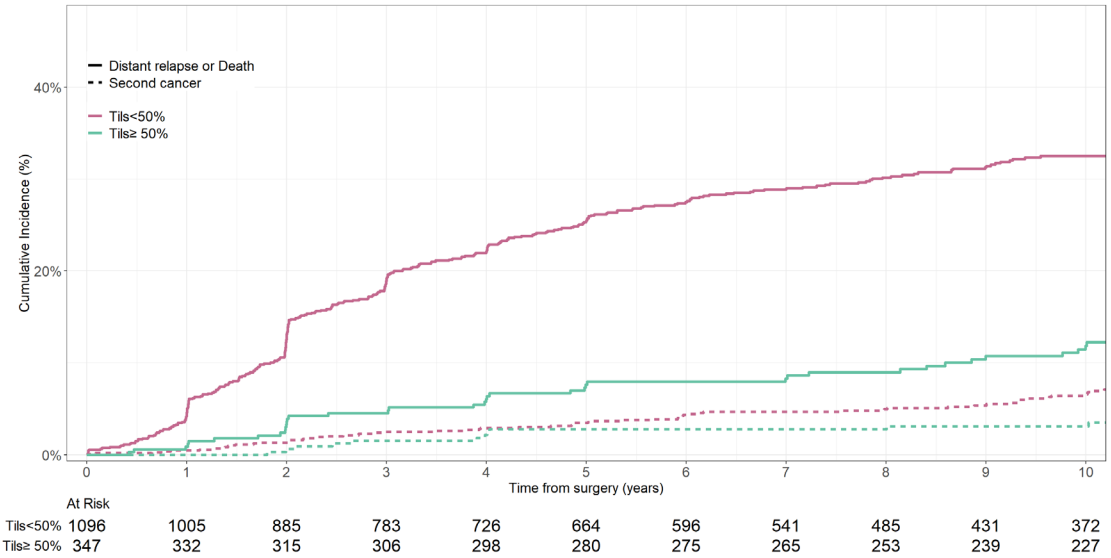
At Risk											
Tils<30%	934	857	755	667	616	563	507	463	413	364	310
Tils≥ 30%	509	480	445	422	408	381	364	343	325	306	289

Characteristic	N	3-year cum inc	5-year cum inc	10-year cum inc
Distant relapse or Death				
Total	1,443			
Tils<30%	934	20% (17%, 23%)	26% (23%, 29%)	33% (30%, 37%)
Tils≥ 30%	509	7.7% (5.5%, 10%)	12% (9.1%, 15%)	17% (13%, 20%)
Second cancer				
Total	1,443			
Tils<30%	934	2.5% (1.6%, 3.7%)	3.3% (2.3%, 4.7%)	6.6% (4.9%, 8.5%)
Tils≥ 30%	509	1.9% (0.94%, 3.4%)	3.2% (1.9%, 5.1%)	4.2% (2.6%, 6.3%)

eTable 8-E. Competing Events According to TILs Level (50% Threshold) in the pN0 Population

	Censored	Distant relapse or Death	Second cancer	Sum
Tils <50%	654	356	86	**1096**
Tils ≥50%	260	59	28	**347**
Sum	**914**	**415**	**114**	**1443**

eFigure 8-D. Influence of TILs <30% vs ≥30% on Distant Relapse, Death, or Second Cancers in Node-Negative TNBC



Characteristic	N	3-year cum inc	5-year cum inc	10-year cum inc
Distant relapse or Death				
Total	1,443			
Tils<50%	1,096	19% (17%, 22%)	26% (23%, 28%)	33% (30%, 36%)
Tils≥ 50%	347	4.5% (2.6%, 7.2%)	7.6% (5.1%, 11%)	12% (8.5%, 16%)
Second cancer				
Total	1,443			
Tils<50%	1,096	2.5% (1.6%, 3.6%)	3.4% (2.4%, 4.7%)	6.6% (5.1%, 8.4%)
Tils≥ 50%	347	1.5% (0.58%, 3.4%)	2.8% (1.4%, 5.0%)	4.2% (1.6%, 5.5%)

9. Time-Dependent ROC curves and AUC

We evaluate the discriminating ability of TILs by measuring the area under the time-dependent ROC curve (**AUC**) estimation at 5 and 10 years.

We use time-dependent ROC curves from censored survival data using Inverse Probability of Censoring Weighting (IPCW) estimates of Cumulative/Dynamic time-dependent ROC curve.[15]. For each element (tils, clinicopathological factors, tils + clinicopathological factors), at each unique marker value, proportions of true and false positives are calculated considering the time threshold of 5 years.

We also show pointwise confidence intervals. They are computed using an estimate of the variance and the quantiles of the standard normal distribution.

eTable 9-A. AUC (IPCW) at 5 Years and Confidence Interval (CI)

	AUC	95% CI	
OS			
Tils	0.61	0.58	0.64
Clinico-pathological factors (CP)	0.67	0.63	0.70
CP + tils	0.71	0.68	0.74
RFS			
Tils	0.60	0.57	0.62
Clinico-pathological factors (CP)	0.65	0.62	0.68
CP + tils	0.69	0.66	0.72
DDFS			
Tils	0.60	0.57	0.63
Clinico-pathological factors (CP)	0.64	0.61	0.67
CP + tils	0.69	0.66	0.71
DRFS			
Tils	0.61	0.58	0.63
Clinico-pathological factors (CP)	0.66	0.63	0.69
CP + tils	0.71	0.68	0.73
IBCFS			
Tils	0.58	0.55	0.61
Clinico-pathological factors (CP)	0.65	0.62	0.68
CP + tils	0.68	0.66	0.71
IDFS			
Tils	0.58	0.55	0.61
Clinico-pathological factors (CP)	0.63	0.60	0.66
CP + tils	0.66	0.64	0.69

eTable 9-B. AUC (IPCW) at 10 Years and Confidence Interval (CI)			
	AUC	95% CI	
OS			
Tils	0.62	0.59	0.65
Clinico-pathological factors (CP)	0.71	0.68	0.74
CP + tils	0.75	0.72	0.78
RFS			
Tils	0.62	0.59	0.65
Clinico-pathological factors (CP)	0.68	0.65	0.71
CP + tils	0.72	0.69	0.74
DDFS			
Tils	0.63	0.60	0.66
Clinico-pathological factors (CP)	0.70	0.67	0.73
CP + tils	0.74	0.71	0.77
DRFS			
Tils	0.63	0.60	0.66
Clinico-pathological factors (CP)	0.71	0.68	0.74
CP + tils	0.75	0.72	0.78
IBCFS			
Tils	0.60	0.57	0.63
Clinico-pathological factors (CP)	0.65	0.62	0.68
CP + tils	0.68	0.66	0.71
IDFS			
Tils	0.60	0.57	0.63
Clinico-pathological factors (CP)	0.64	0.62	0.67
CP + tils	0.68	0.65	0.71

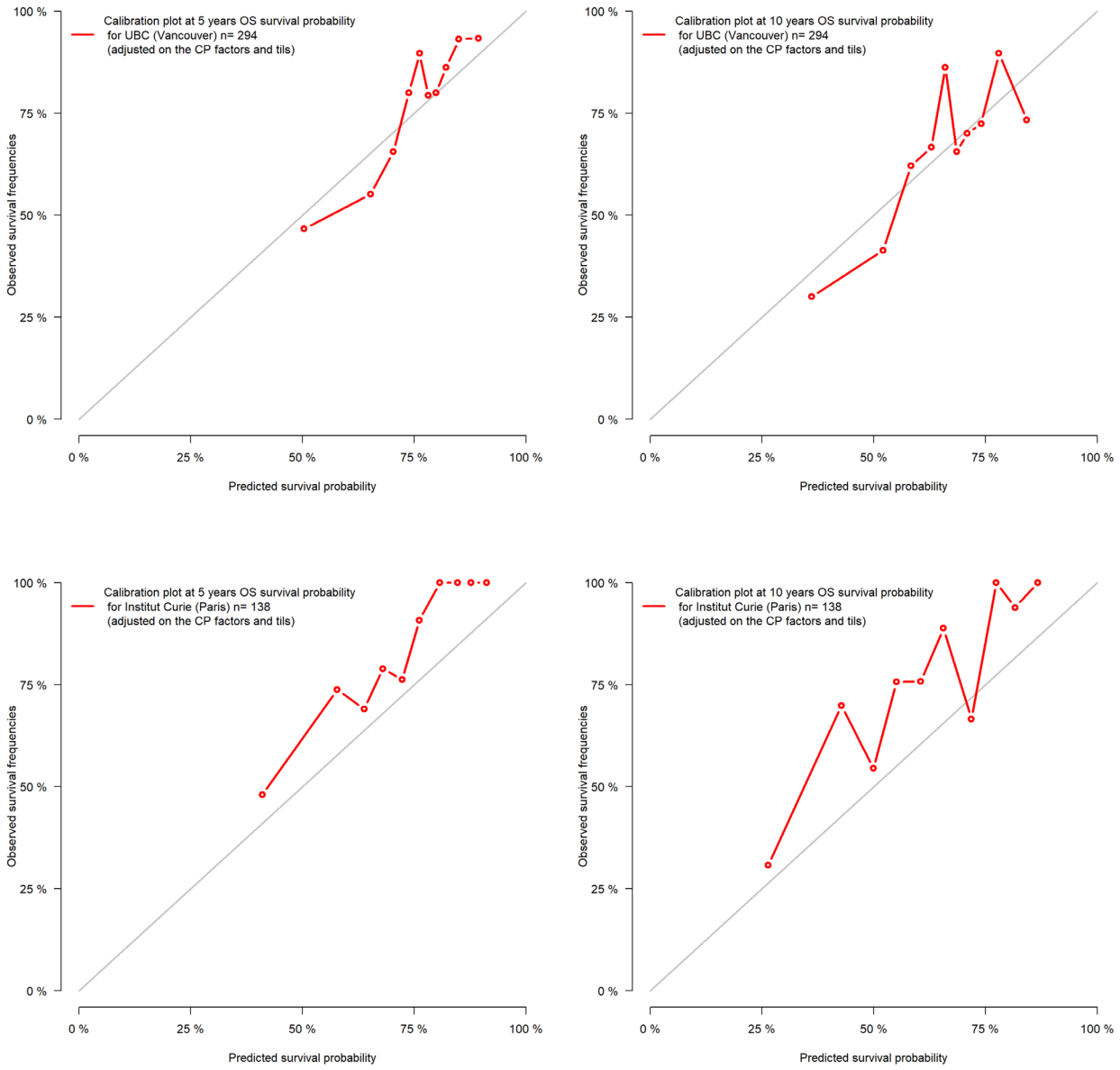
10. Cross-Validation Study

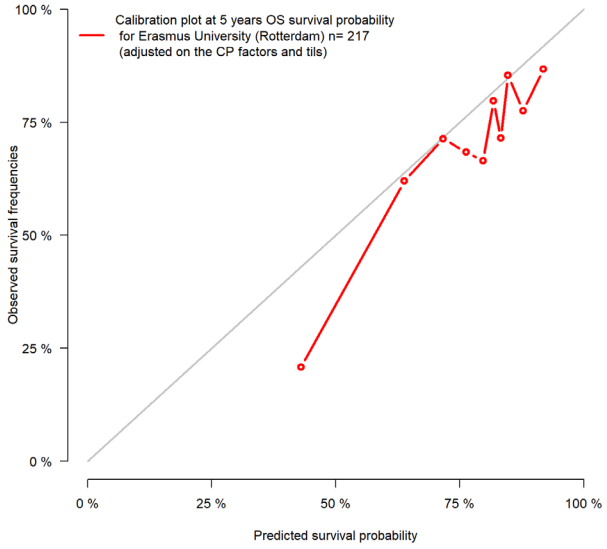
We make a cross-validation analysis to assess how the results of our statistical analysis will generalize to an independent data set. In practice, it is a resampling method. One by one, each study is isolated, while the remaining studies are used to estimate the baseline risk. We then look at the concordance between the 5 year-survival predicted by the model and the actual 5 year-survival of the study. The results are presented in the form of graphs representing the observed results compared to the predicted results. A perfect match would be on the gray line in the center of the graph. This analysis allows to estimate how accurately this predictive model will perform in practice.

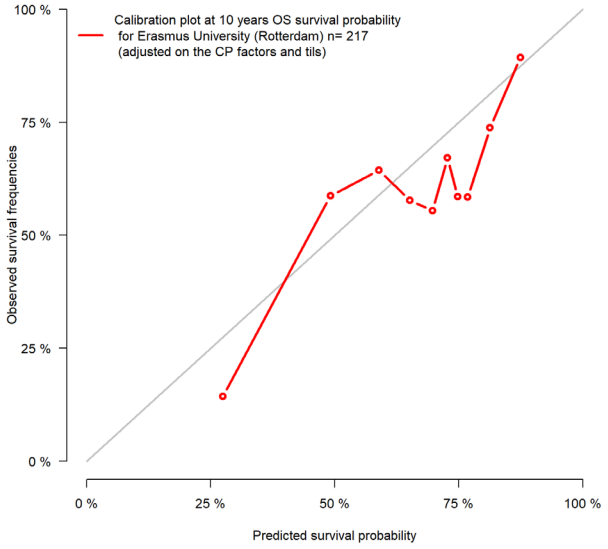
The clinicopathologic factors (age, number of positive lymph nodes, tumor size, histological grade, radiotherapy) and the tils are the adjustment factors.

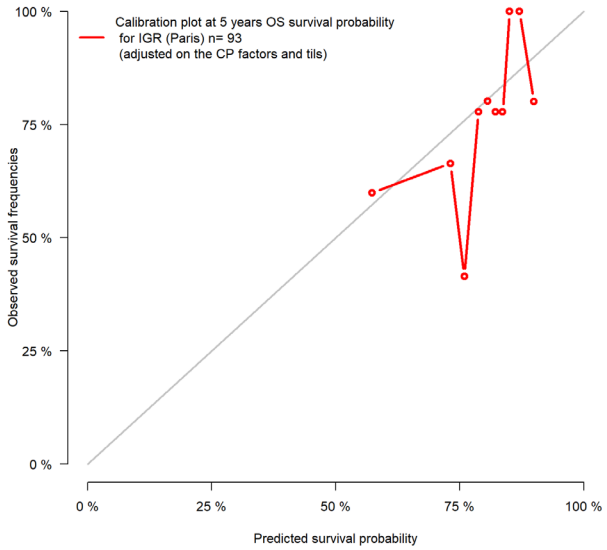
Studies with less than 50 patients have been regrouped (Lyon, Padova, Genova, Göteborg)

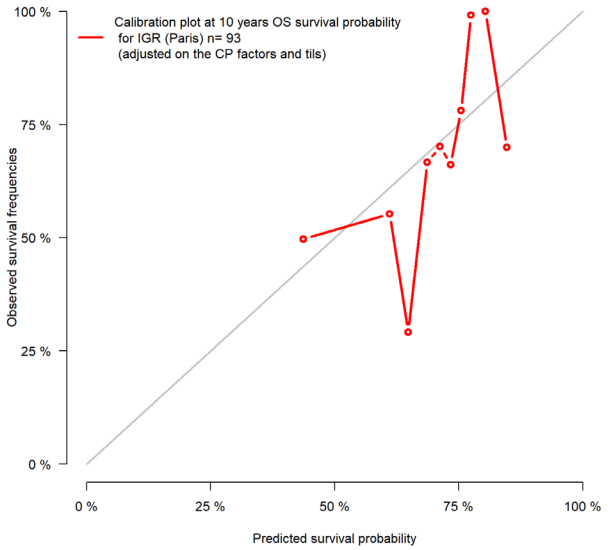
eFigure 10-A. Overall Survival Calibration Plots

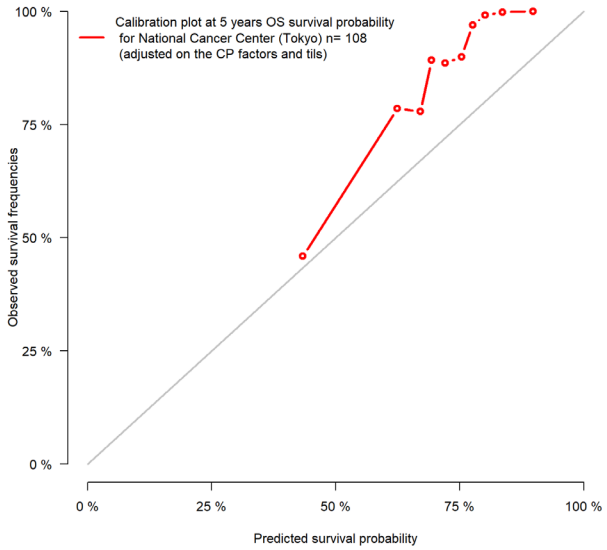


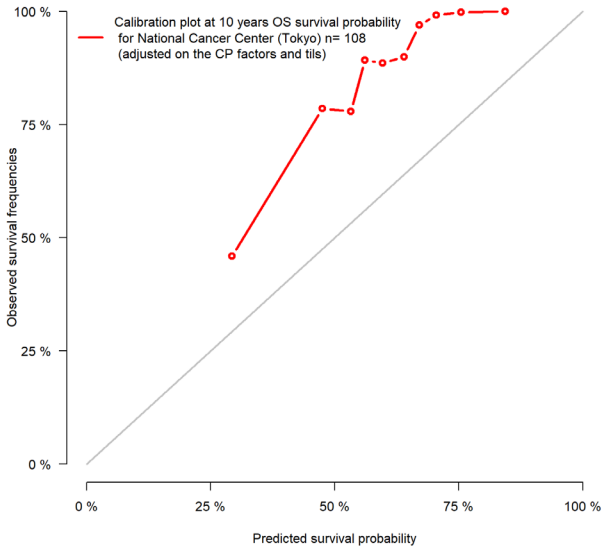


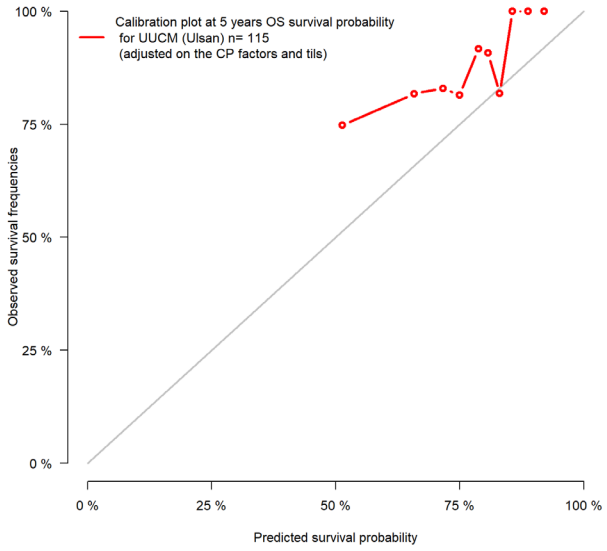


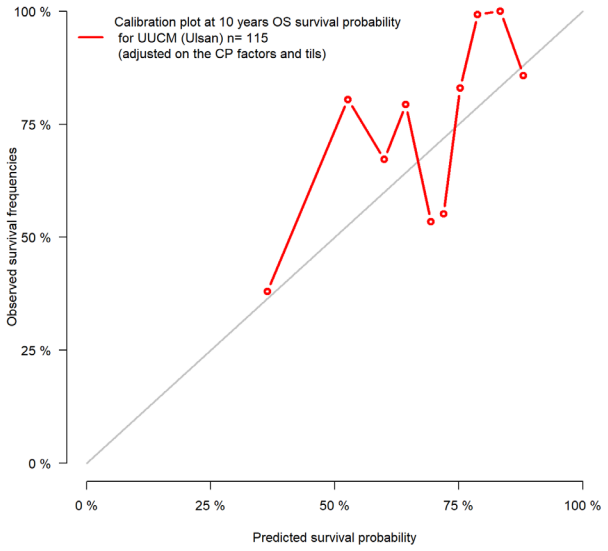


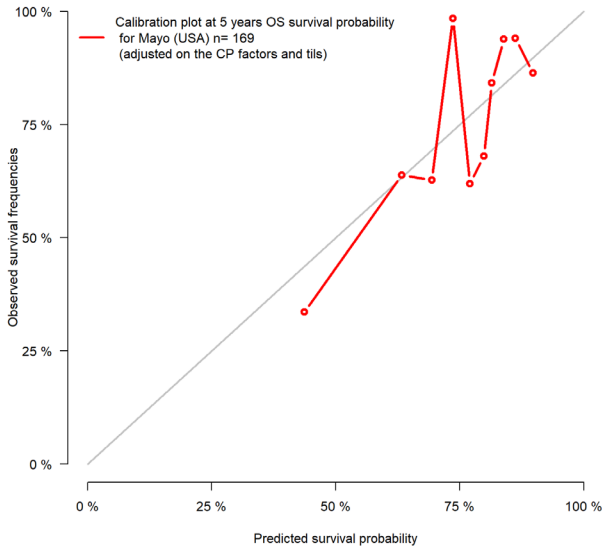


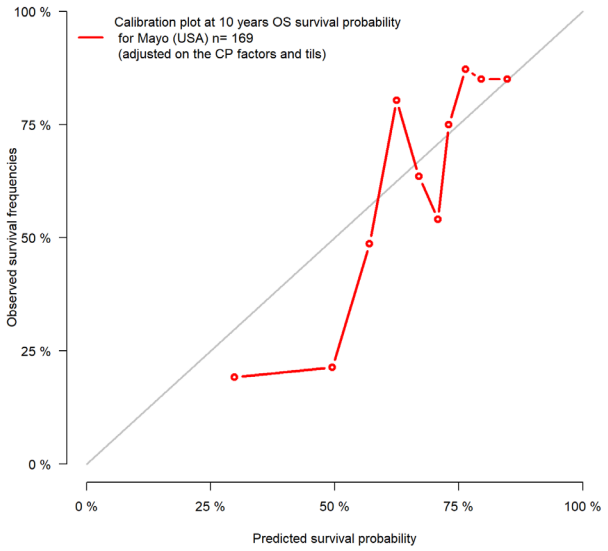


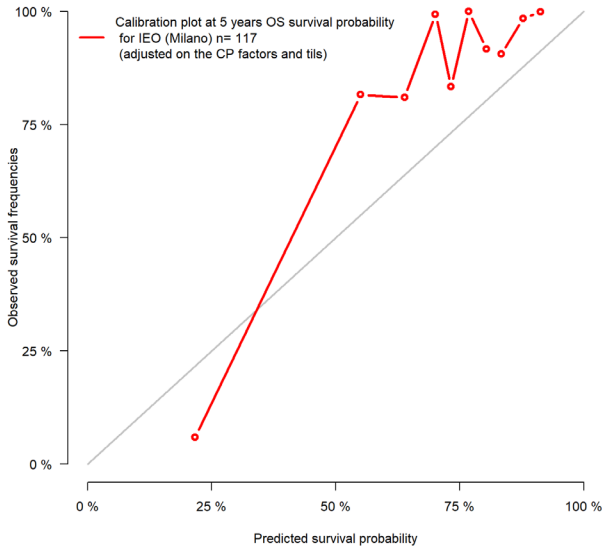


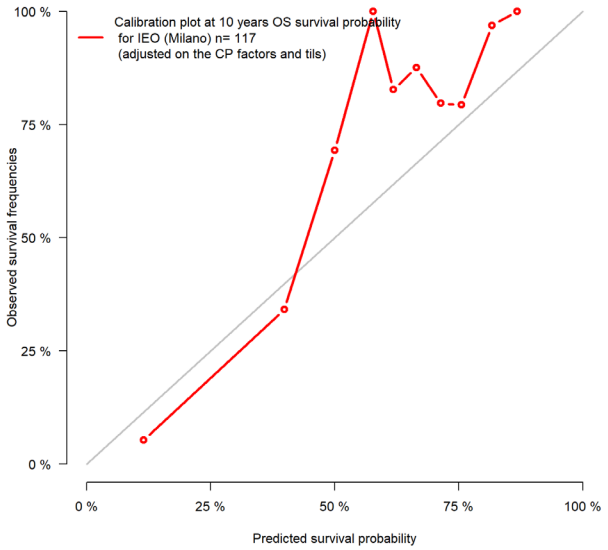


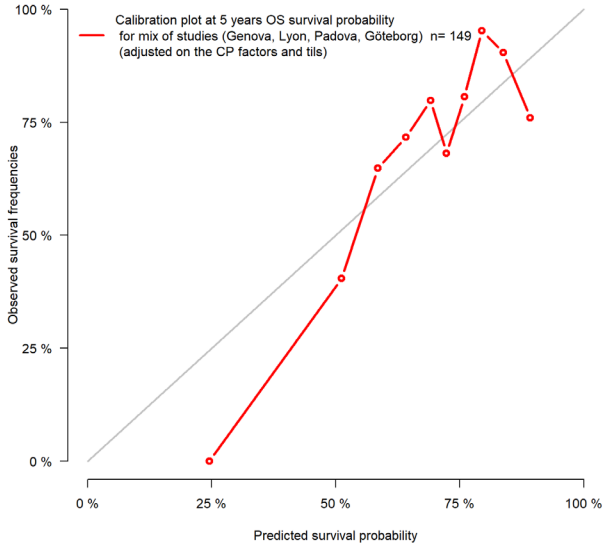


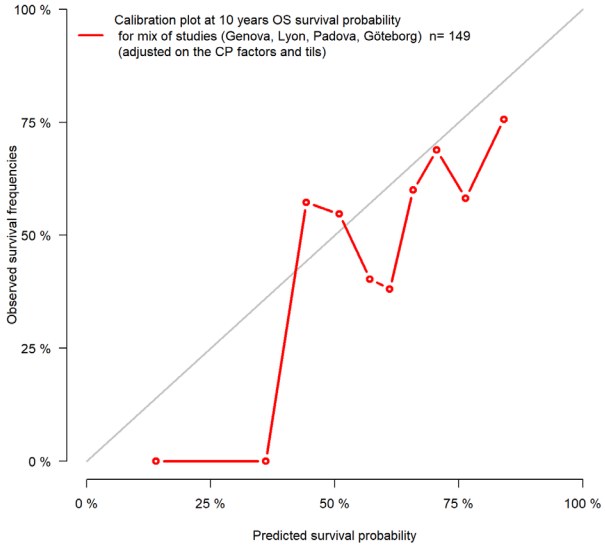


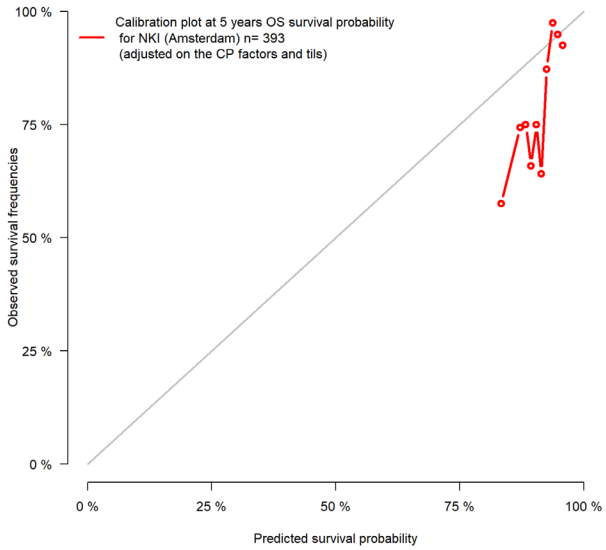


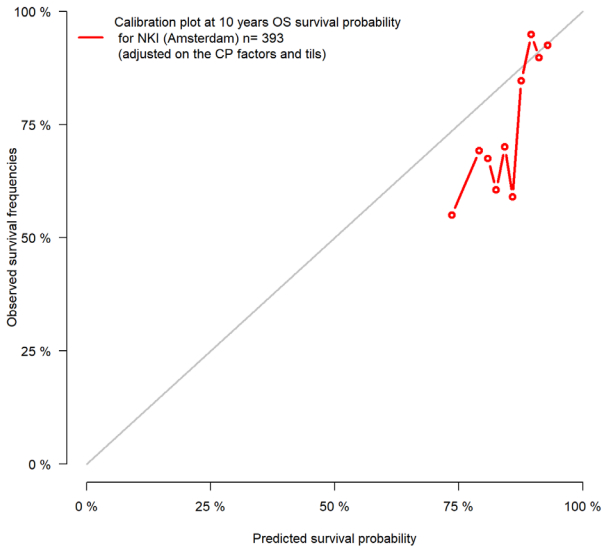




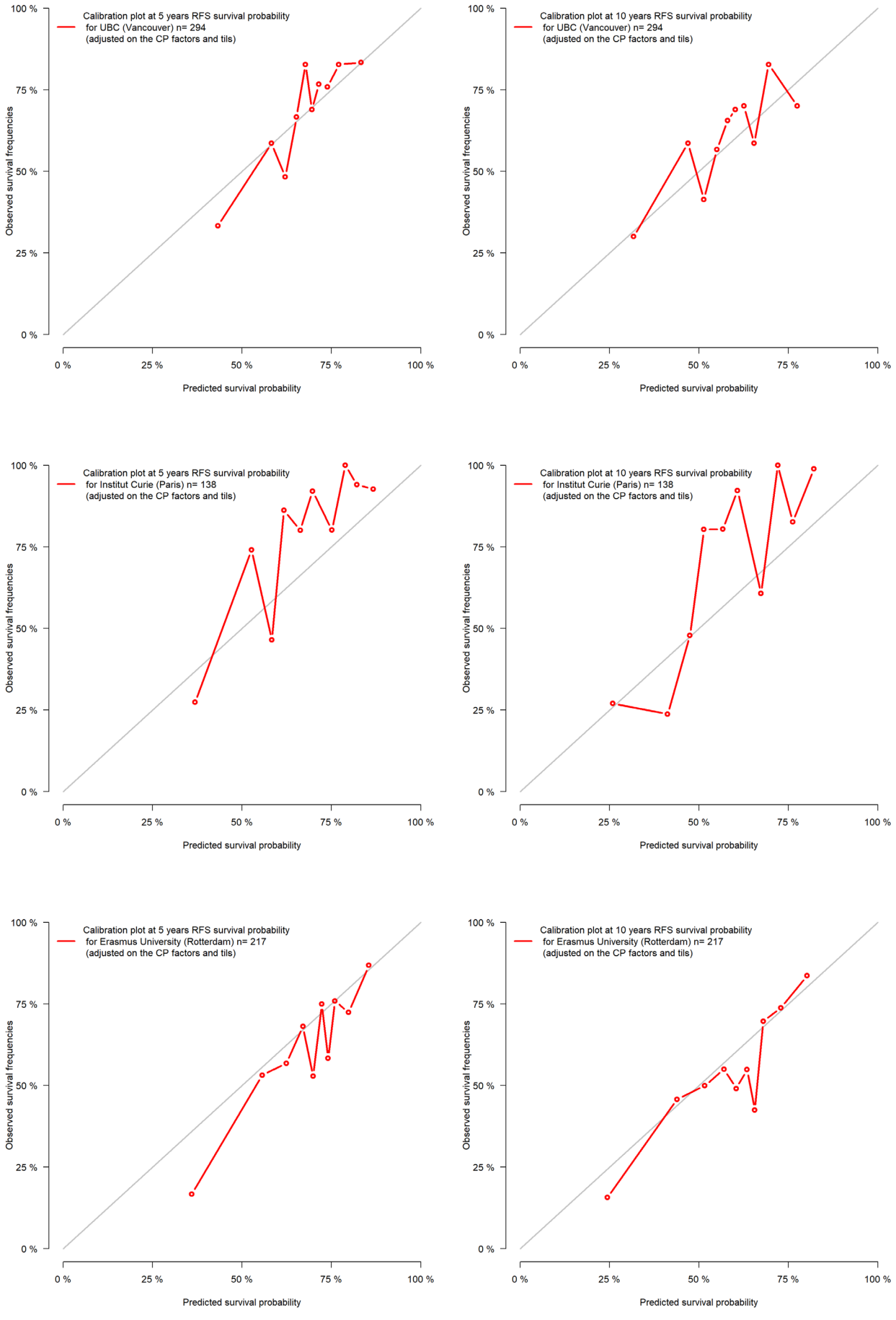


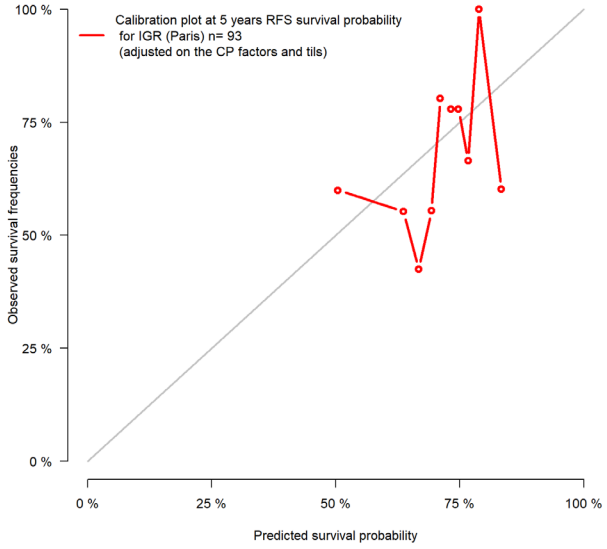


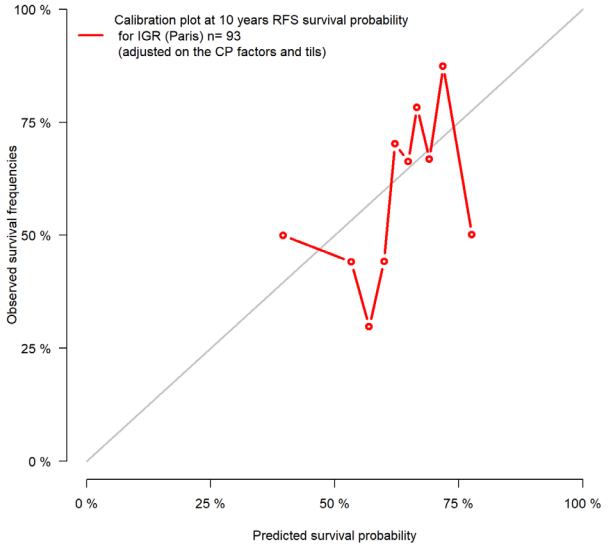


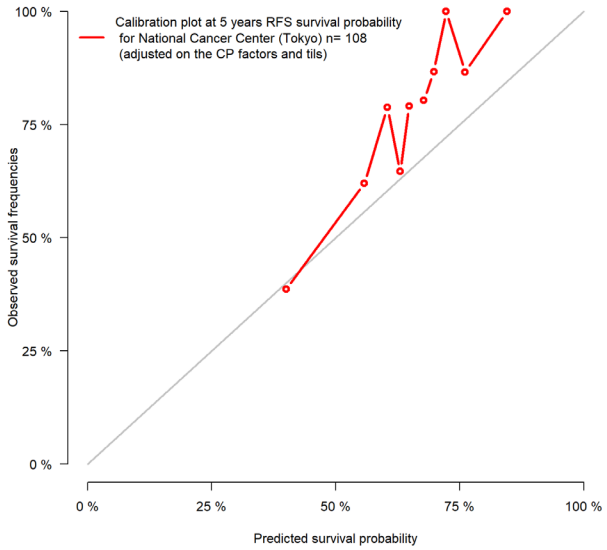


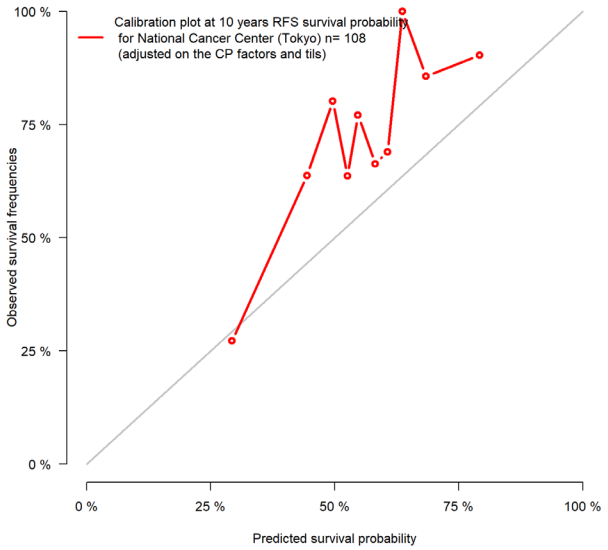
eFigure 10-B. Recurrence-Free Survival Calibration Plots

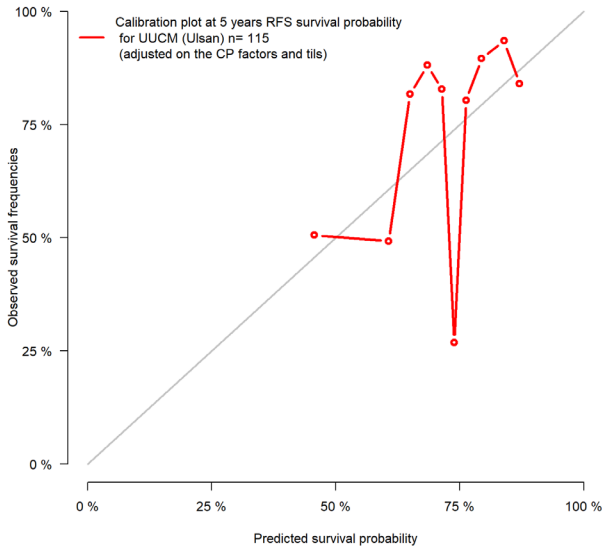


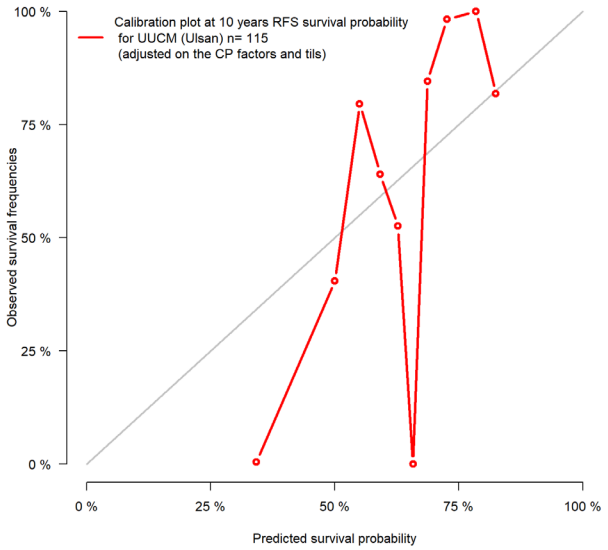


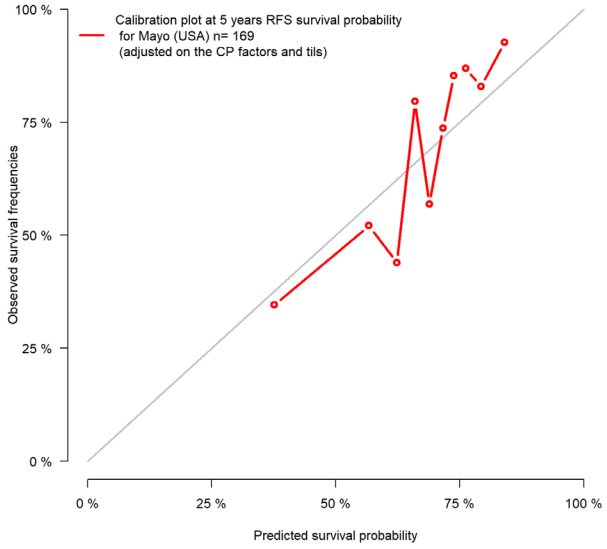


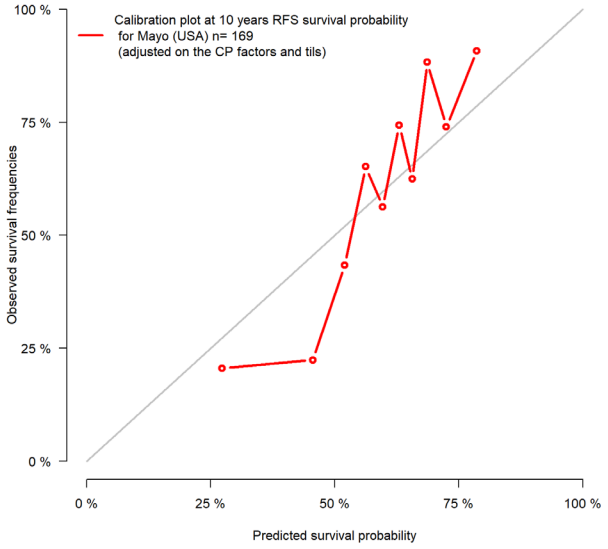


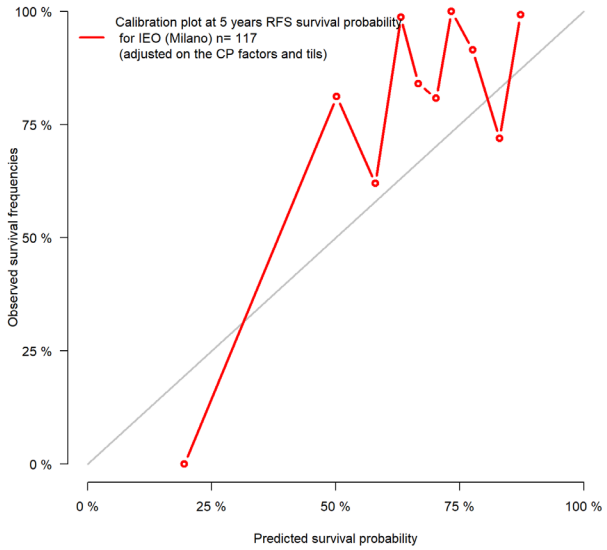


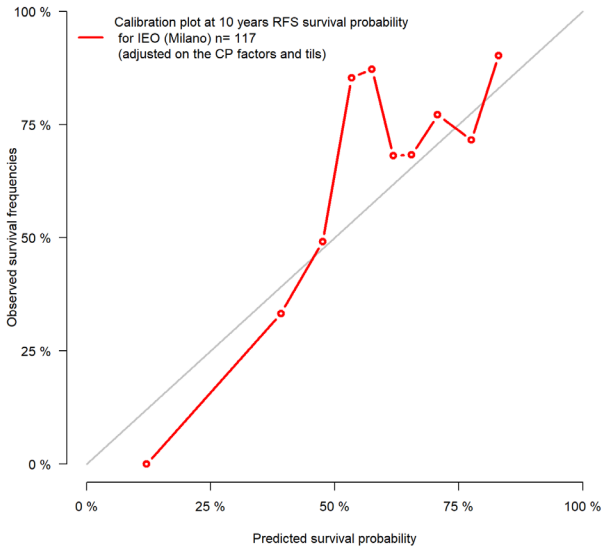


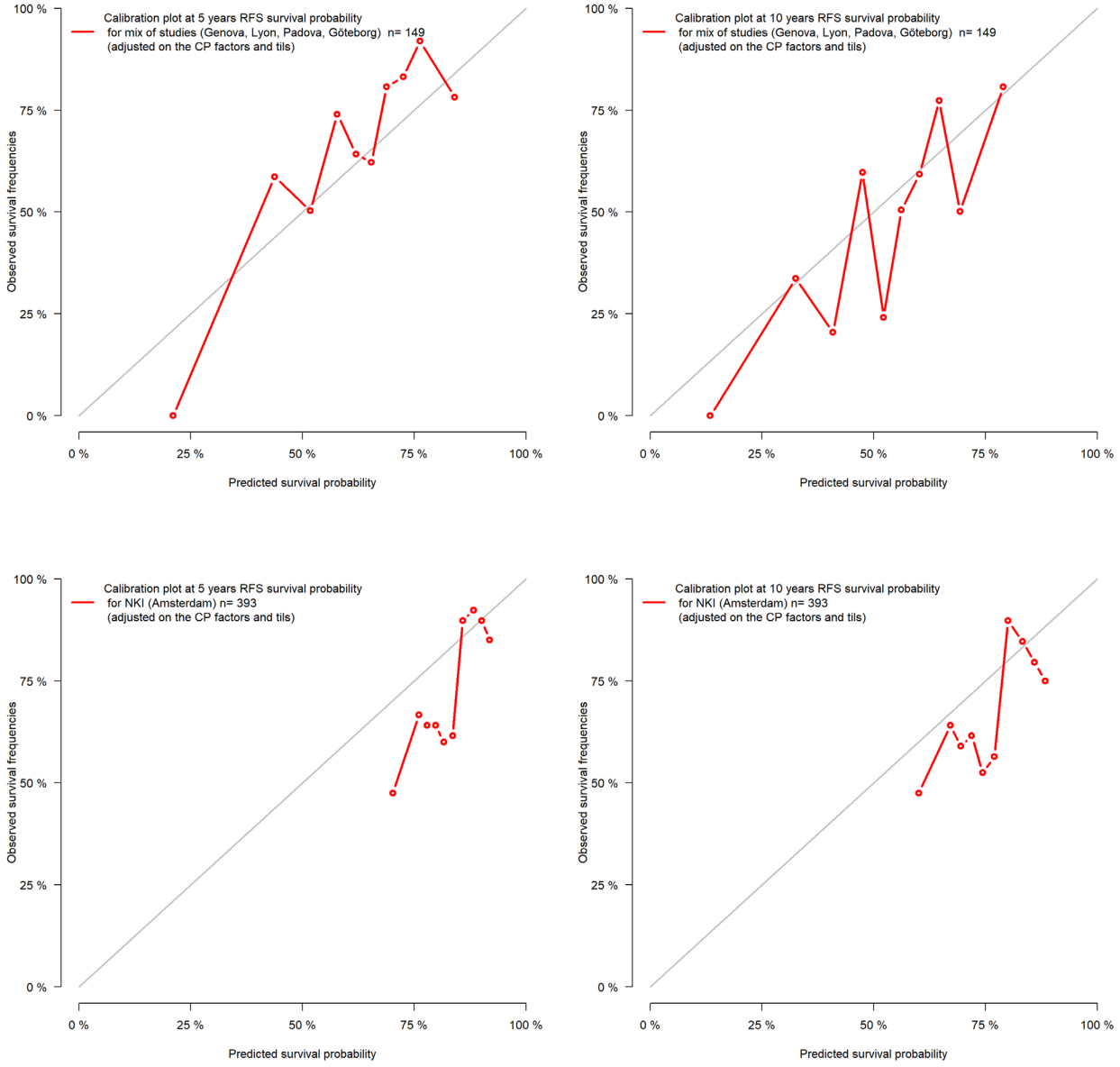




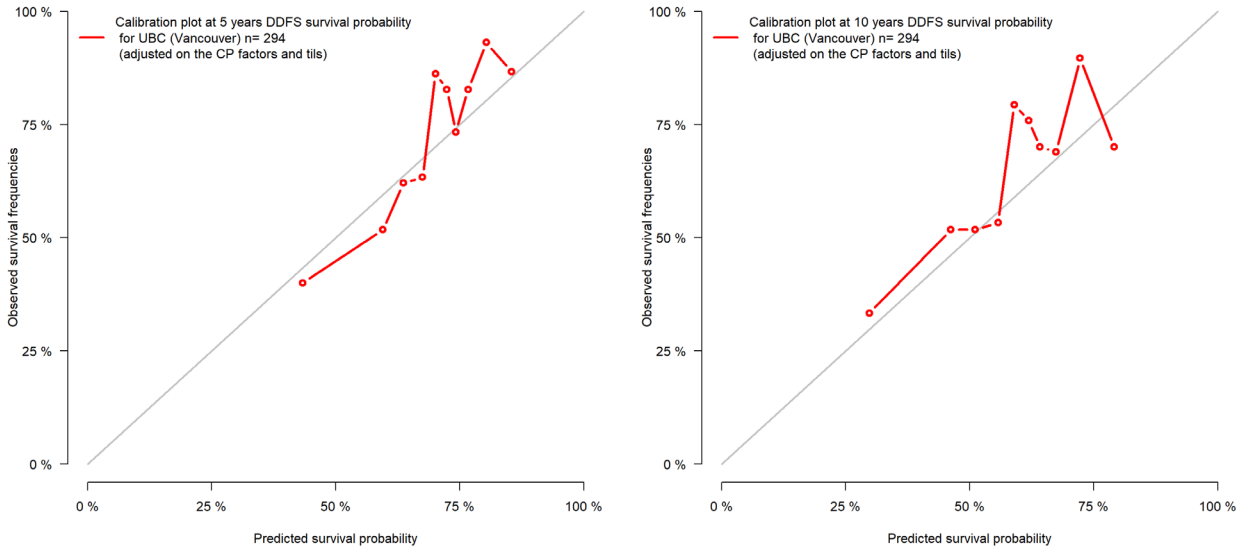


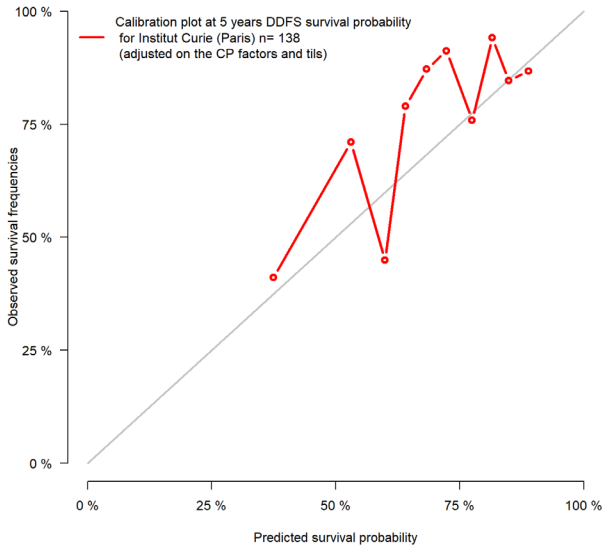


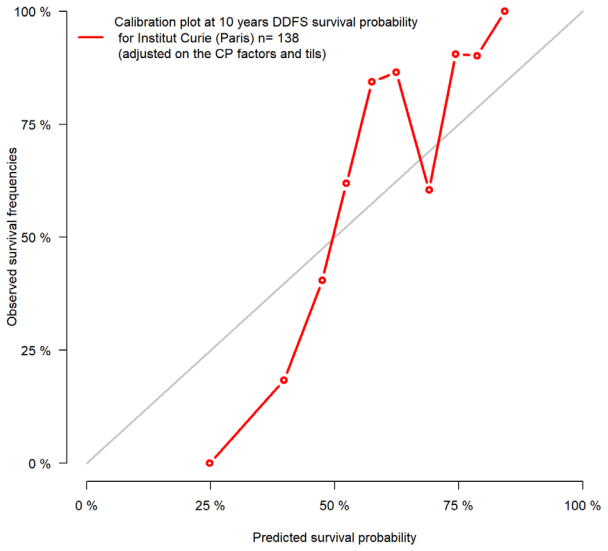


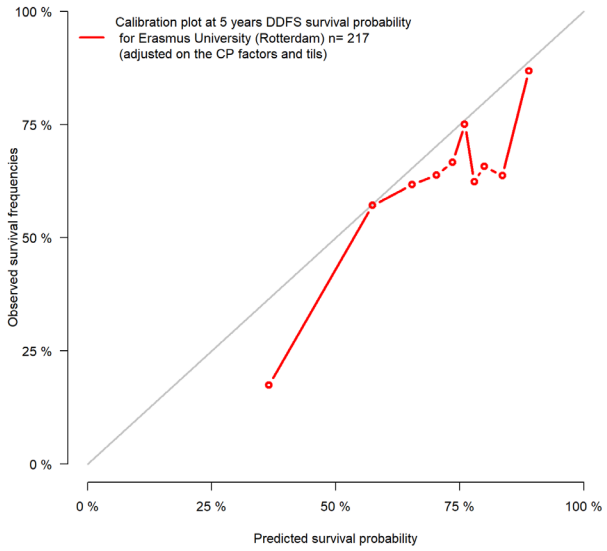


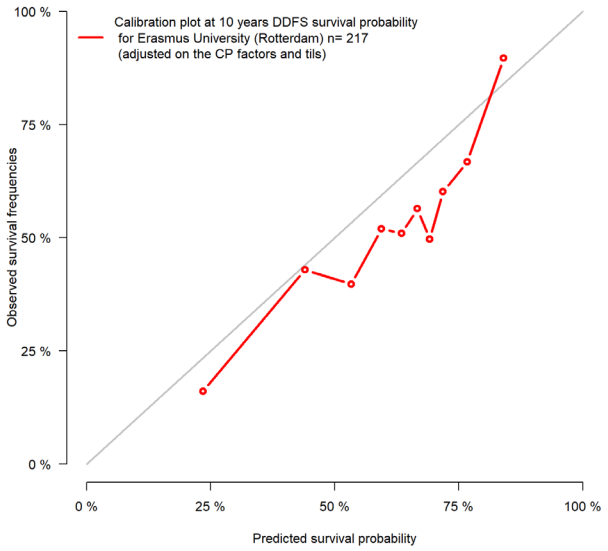
eFigure 10-C. Distant-Disease Free Survival Calibration Plots

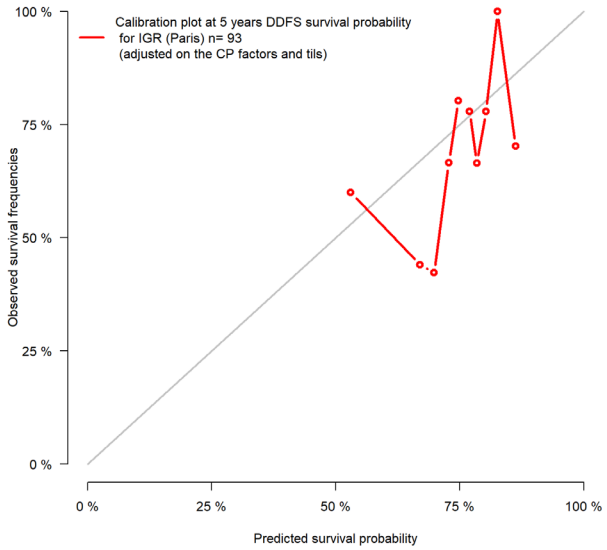


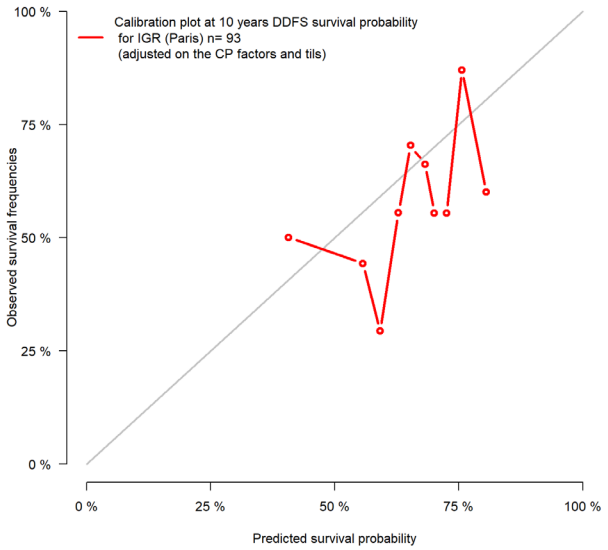


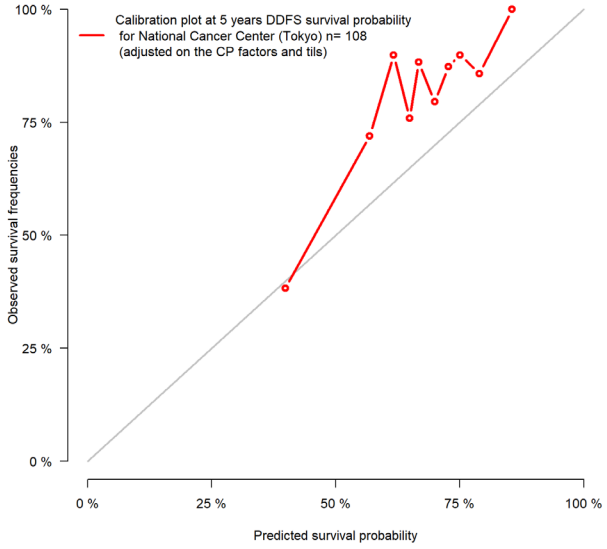


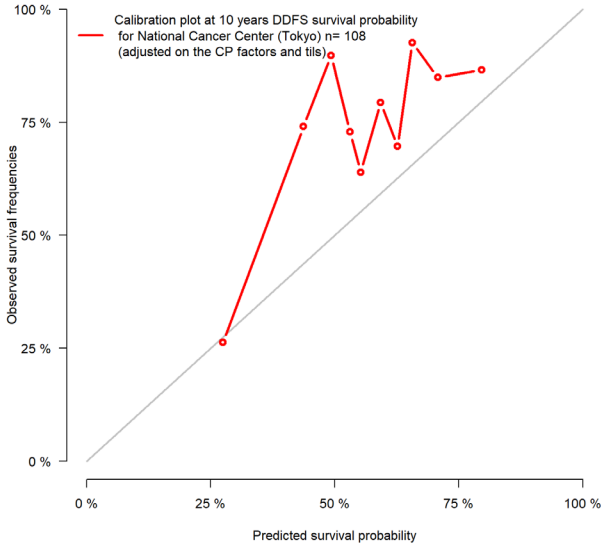


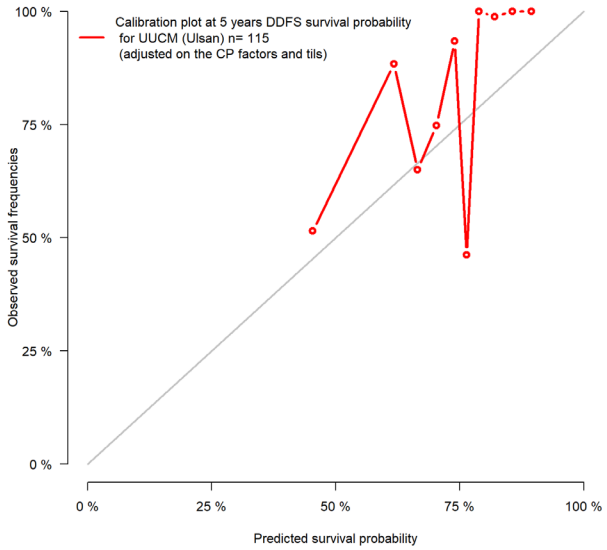


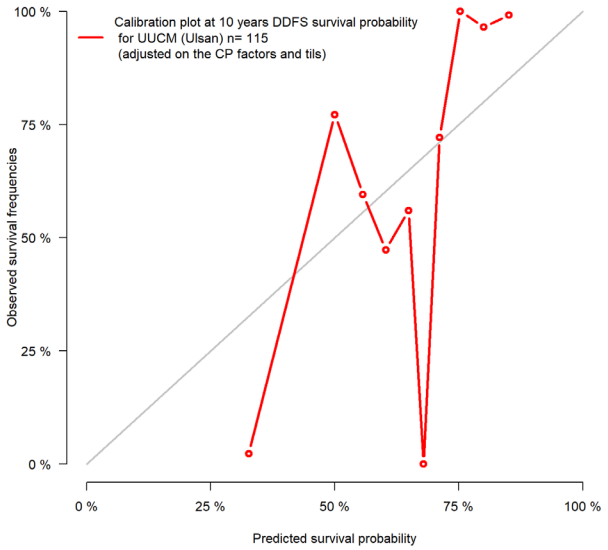


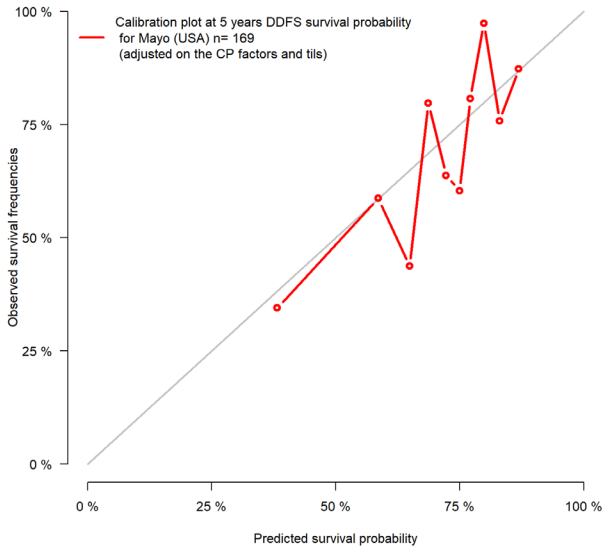


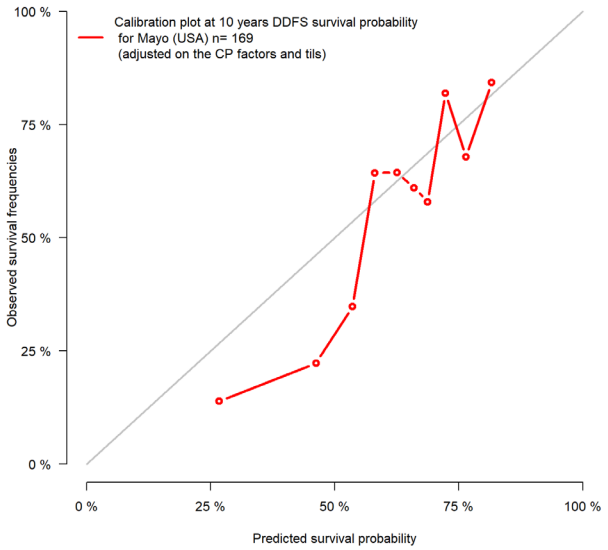


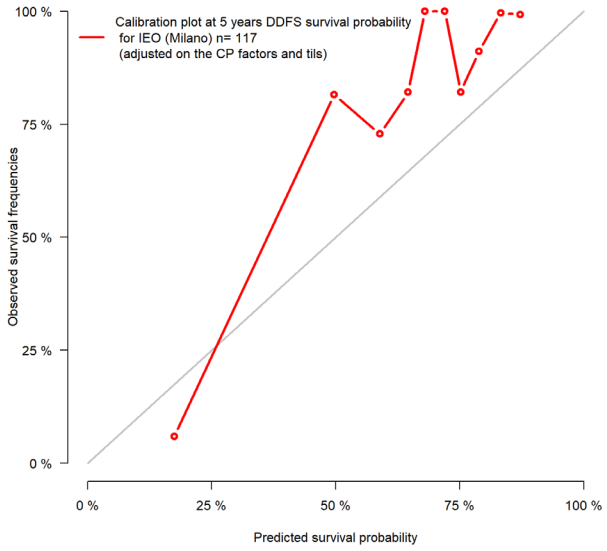


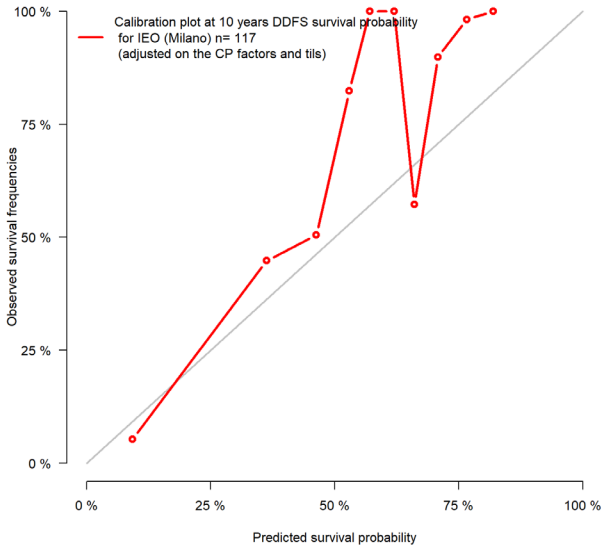


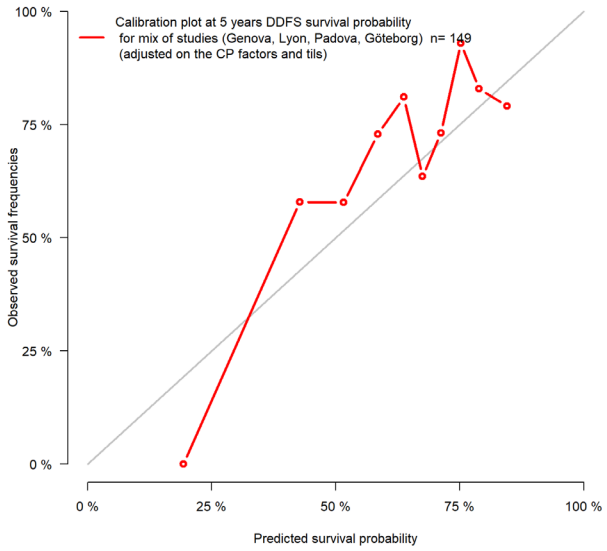


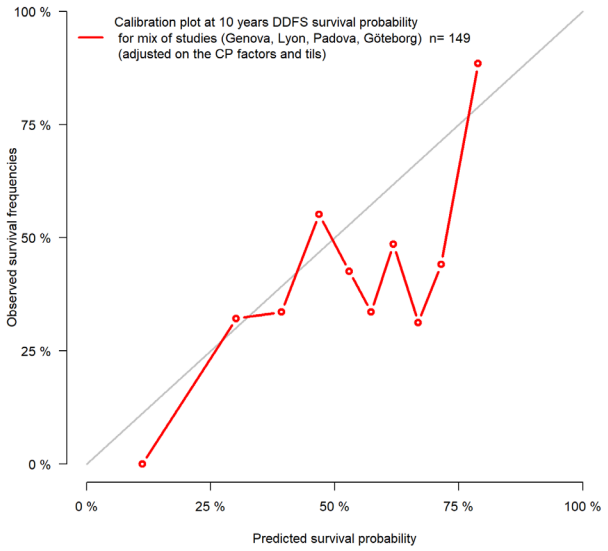


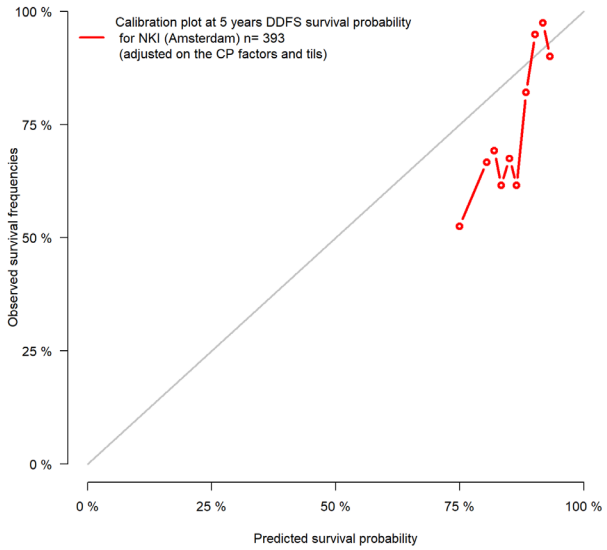


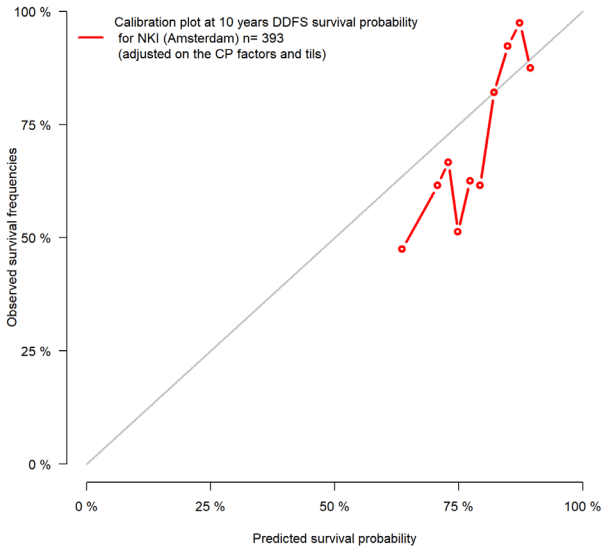




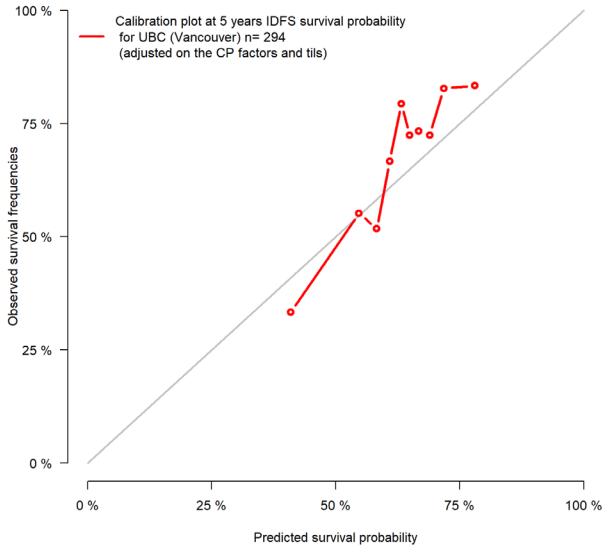


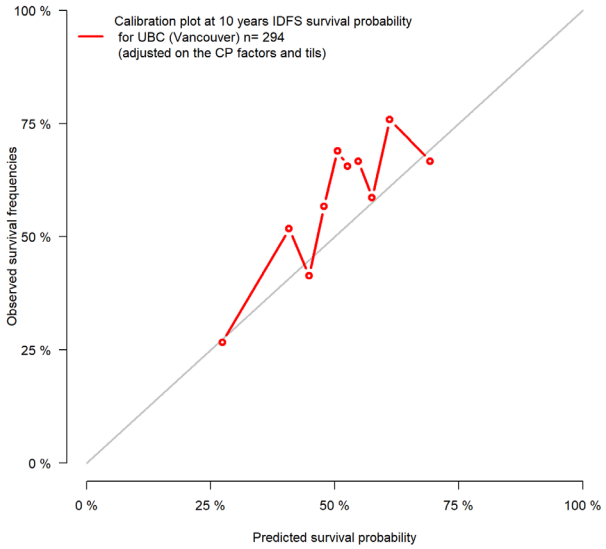


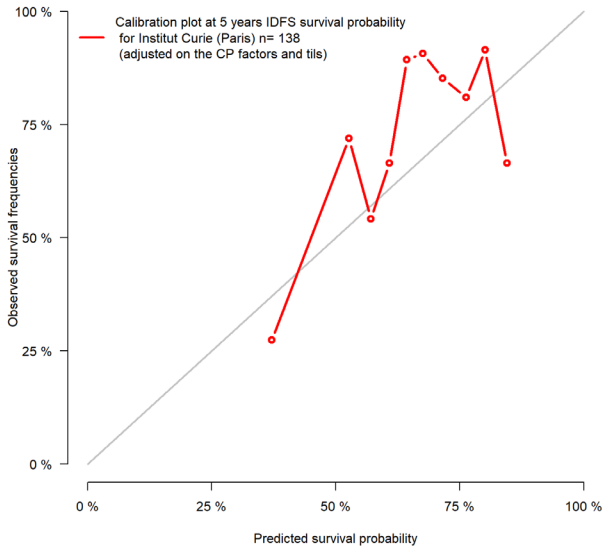


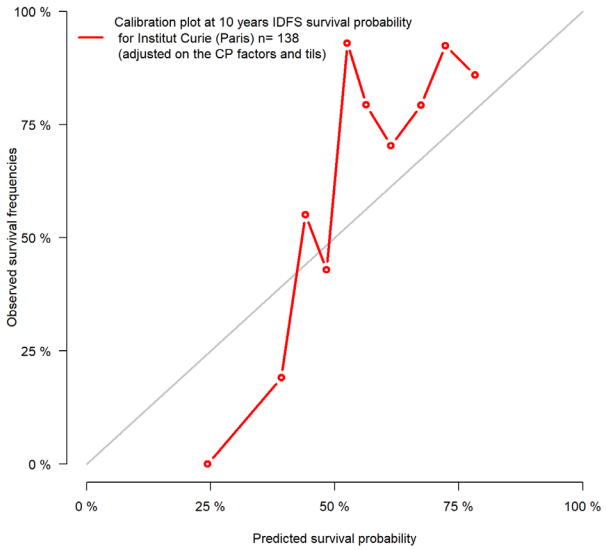


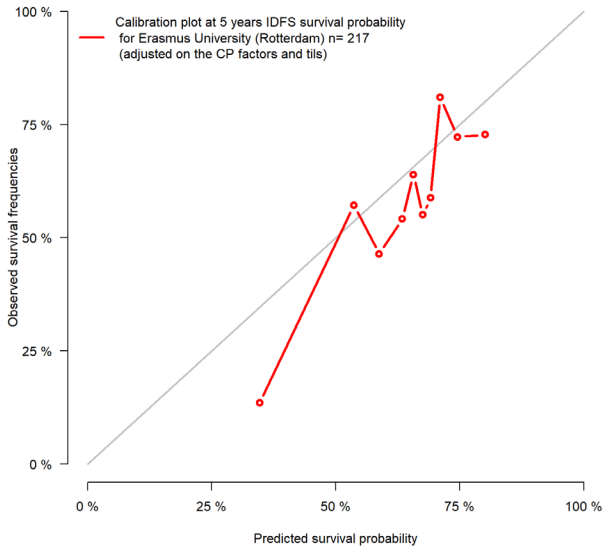
eFigure 10-D. Invasive Disease-Free Survival Calibration Plots

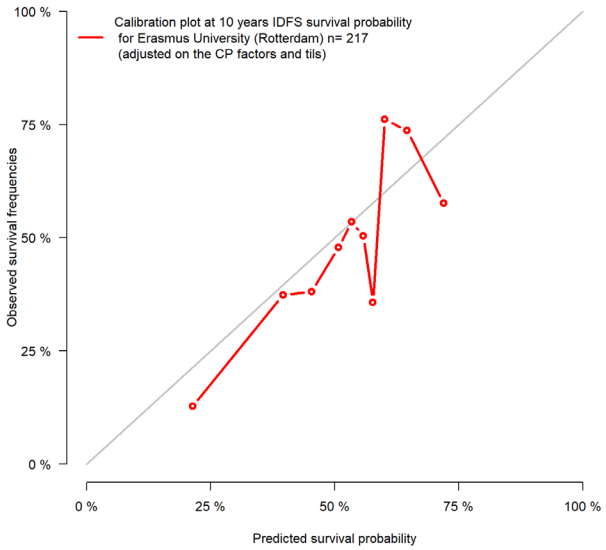


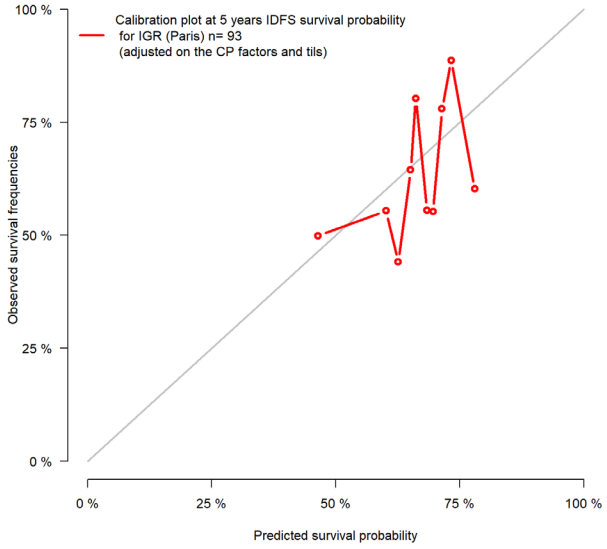


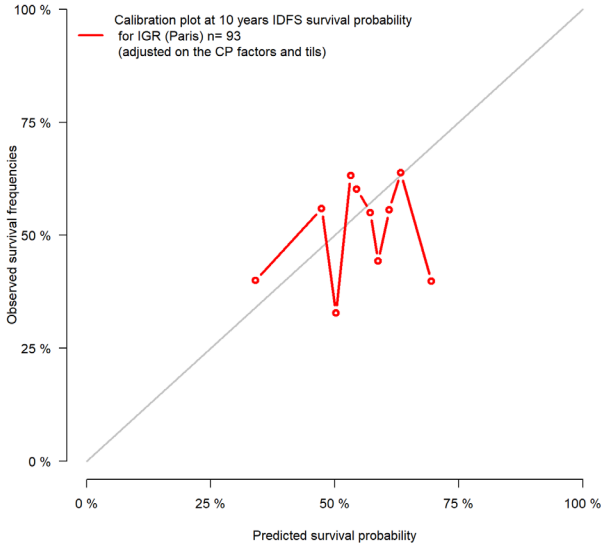


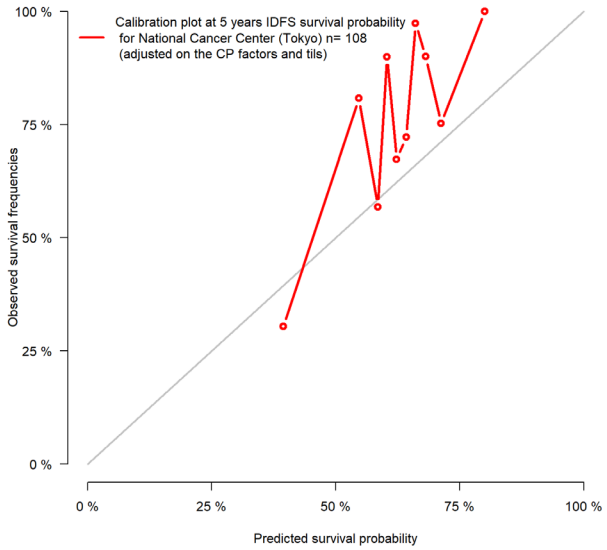


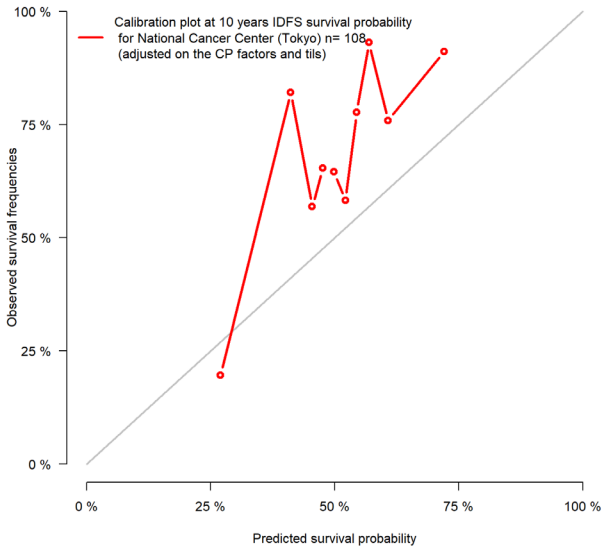


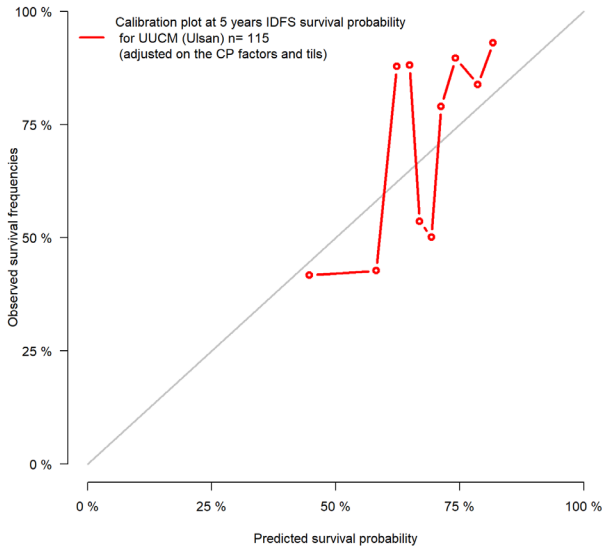


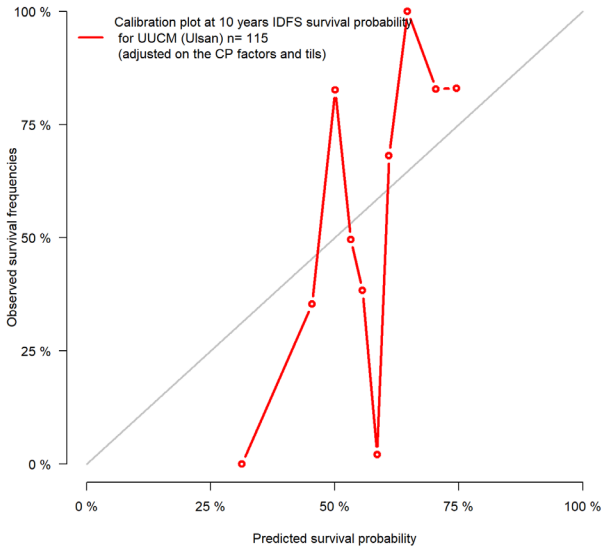


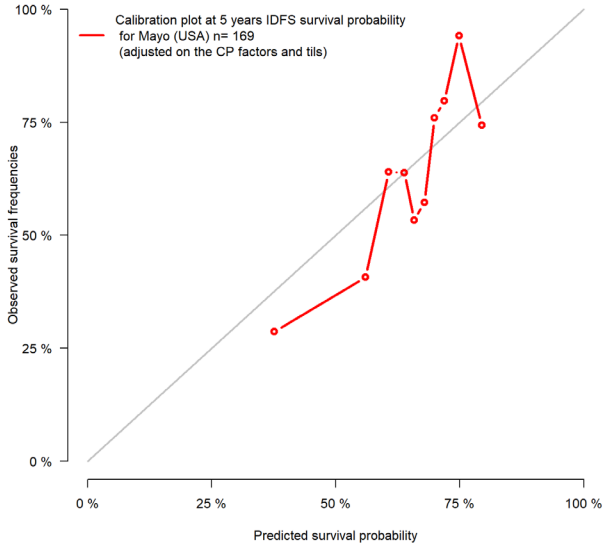


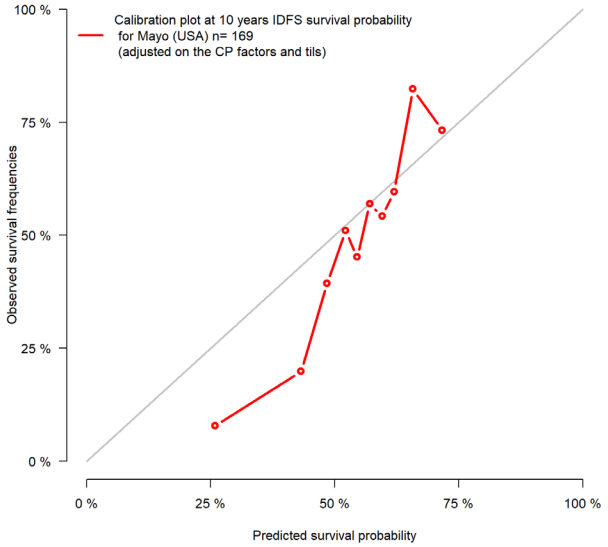


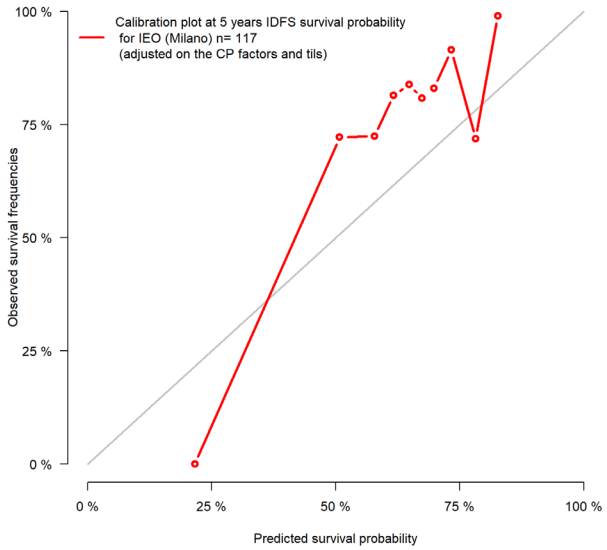


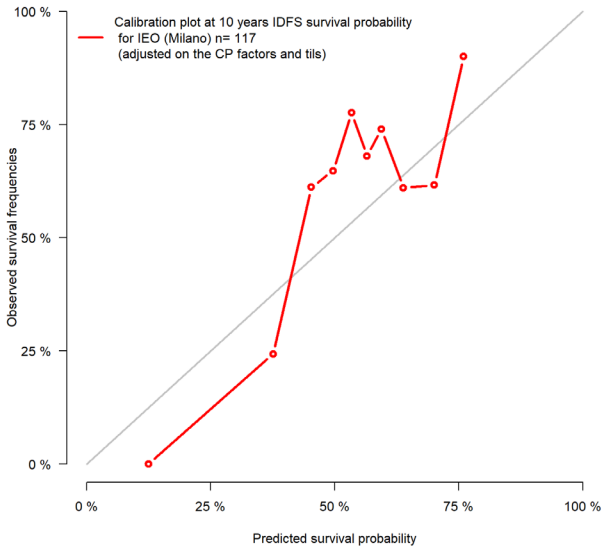


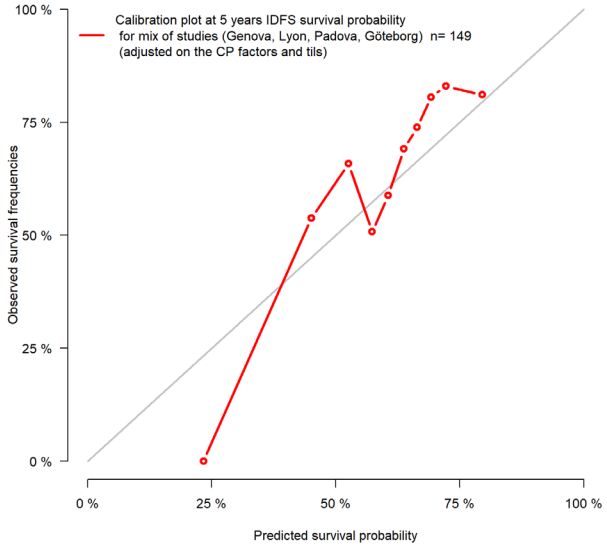


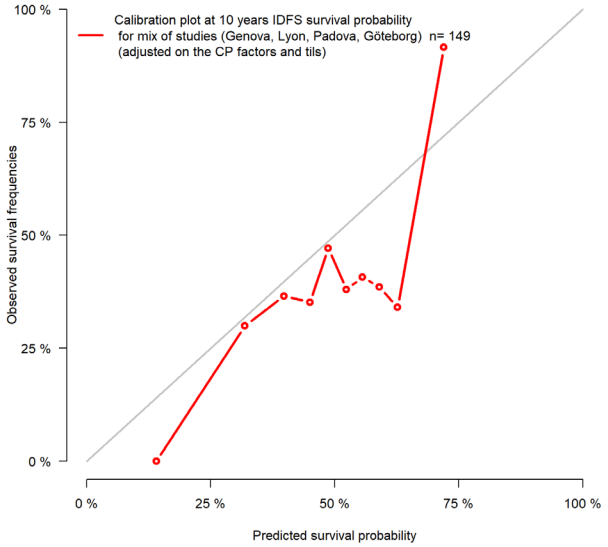


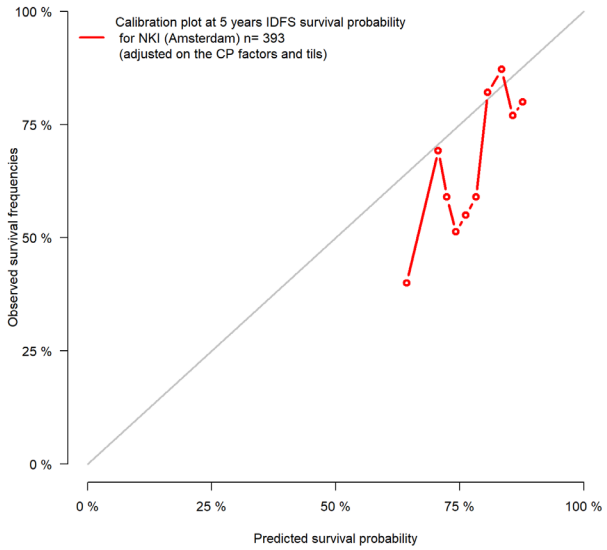


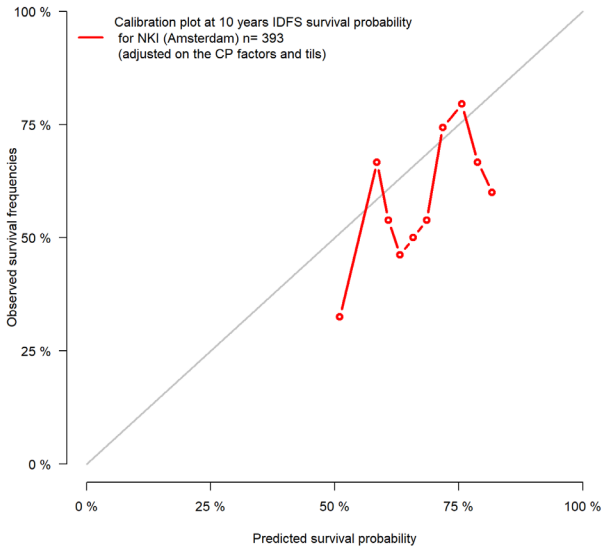




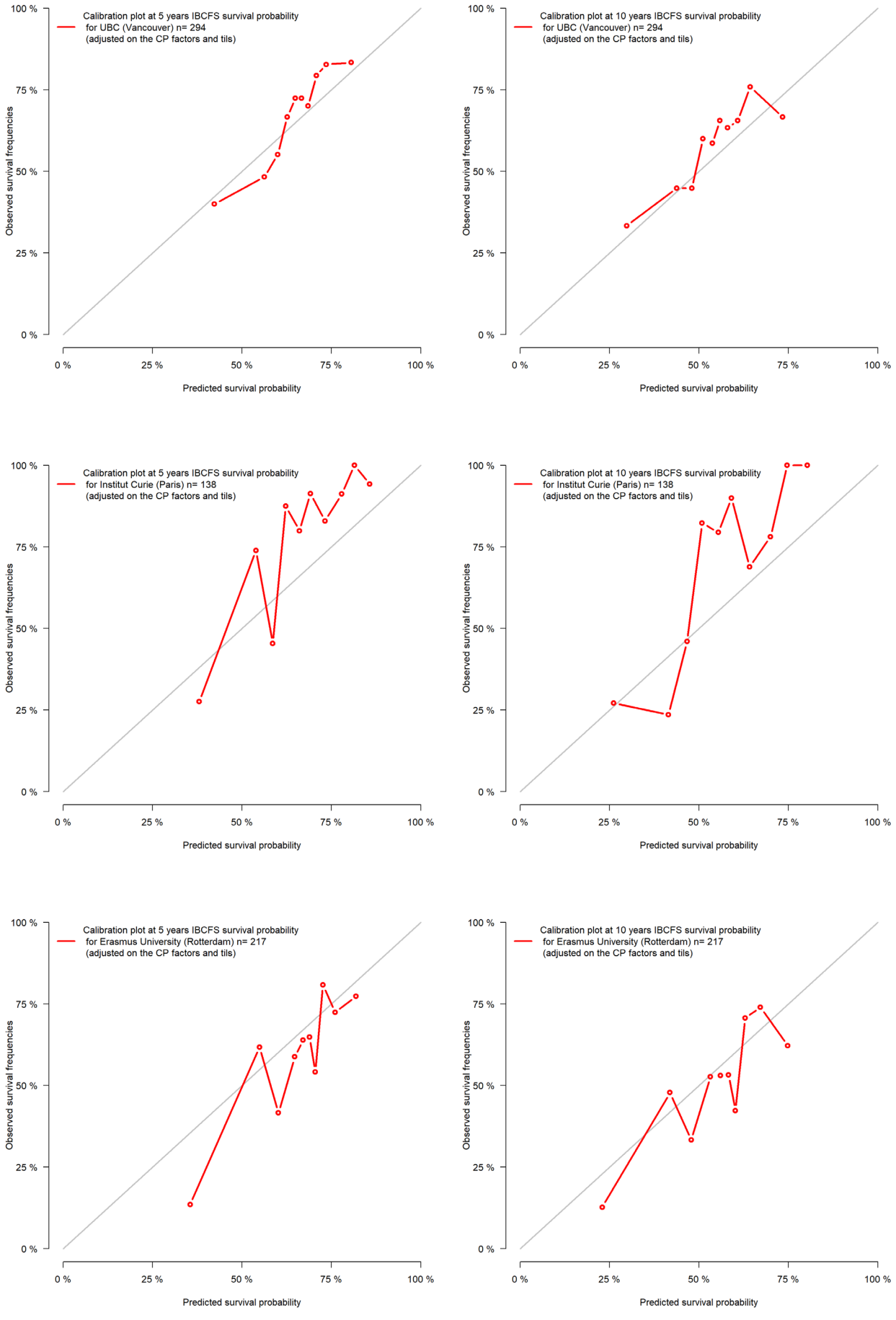


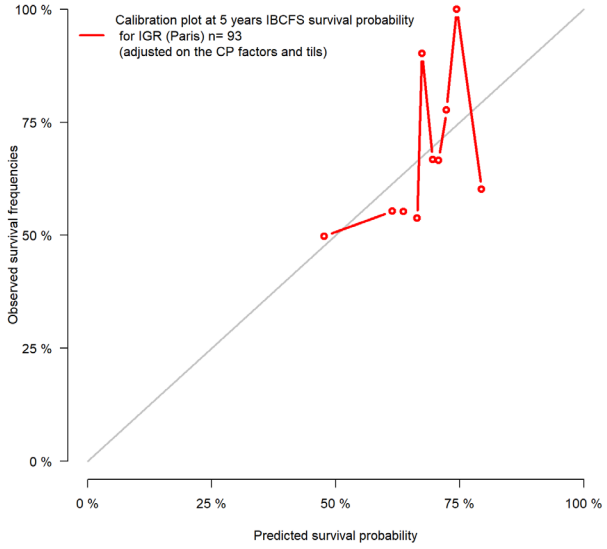


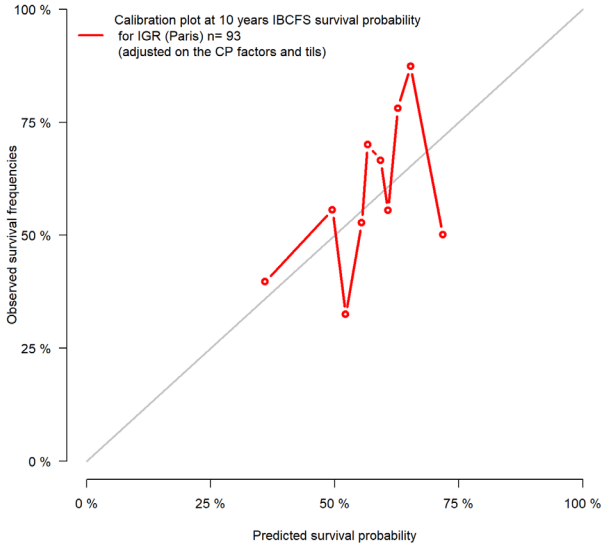


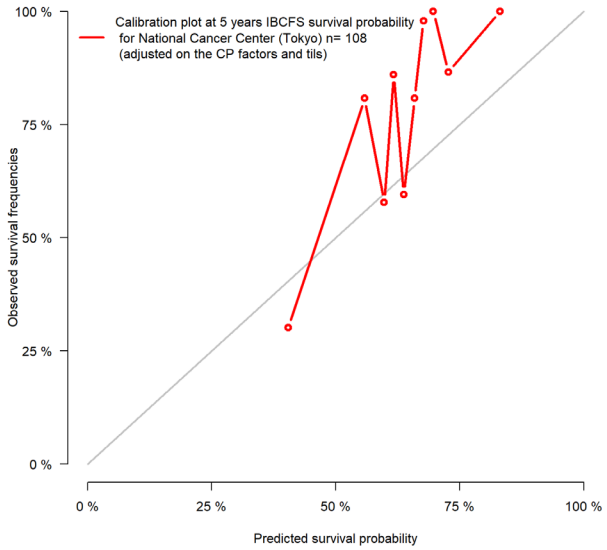


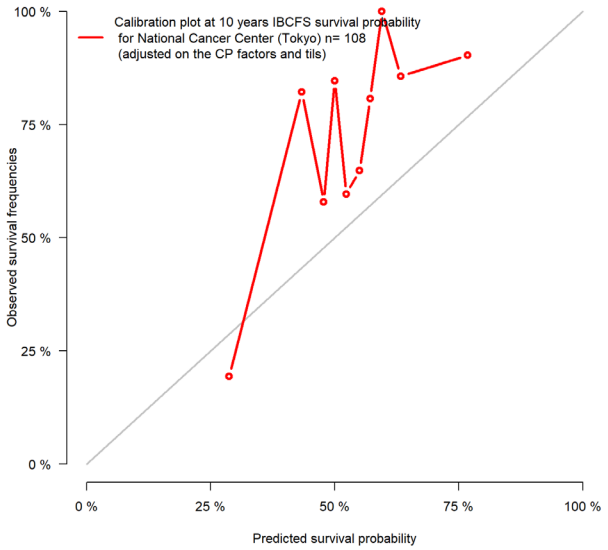
eFigure 10-E. Invasive Breast Cancer–Free Survival Calibration Plots

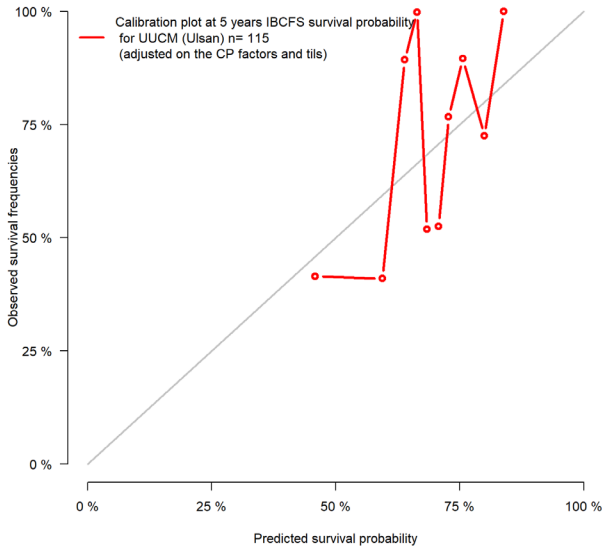


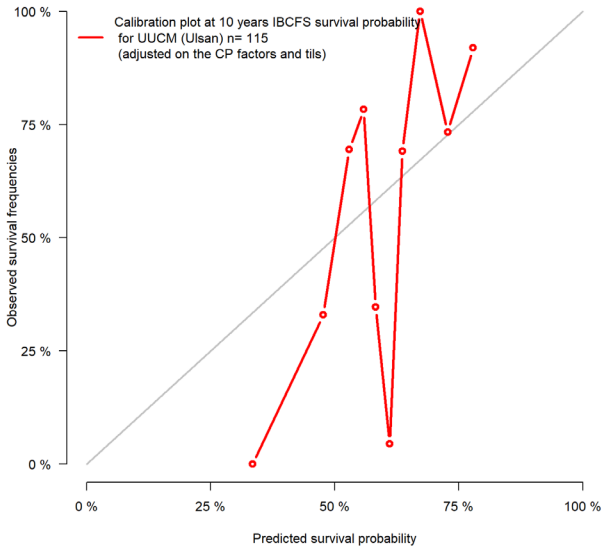


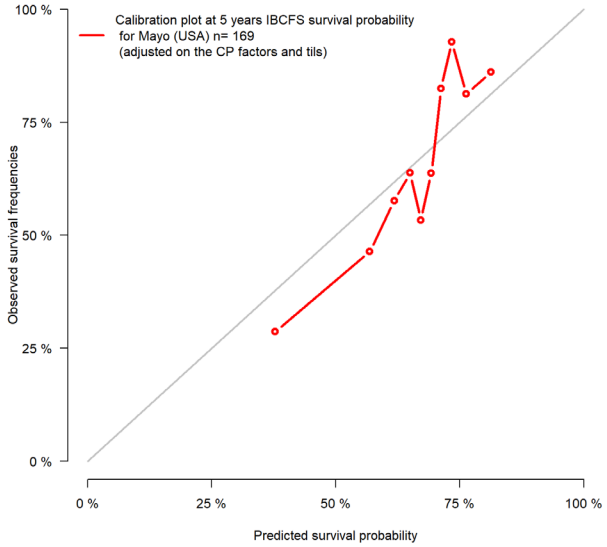


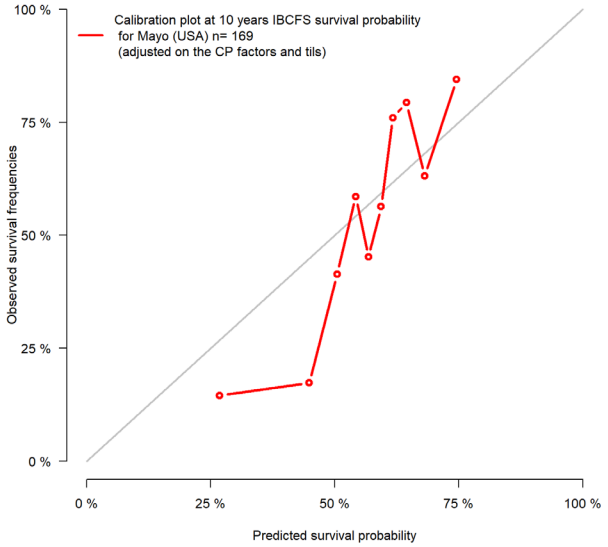


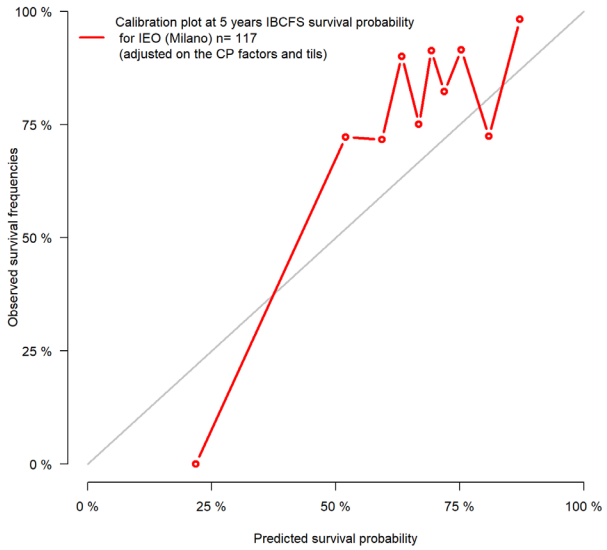


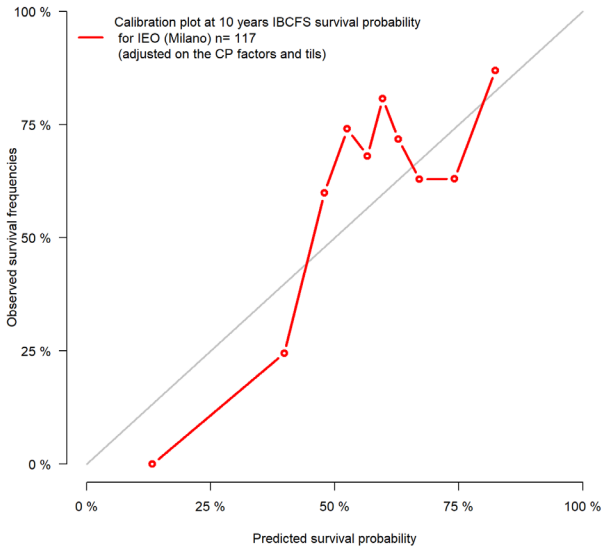


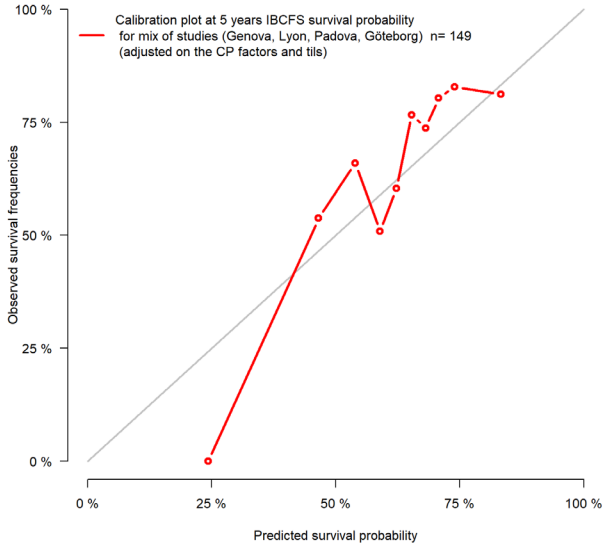


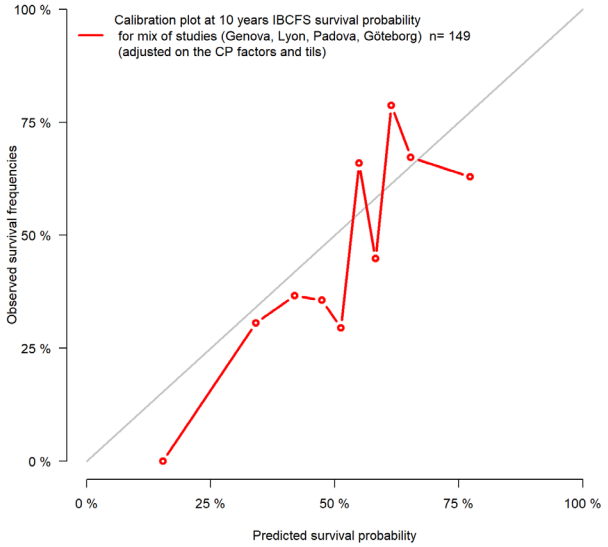


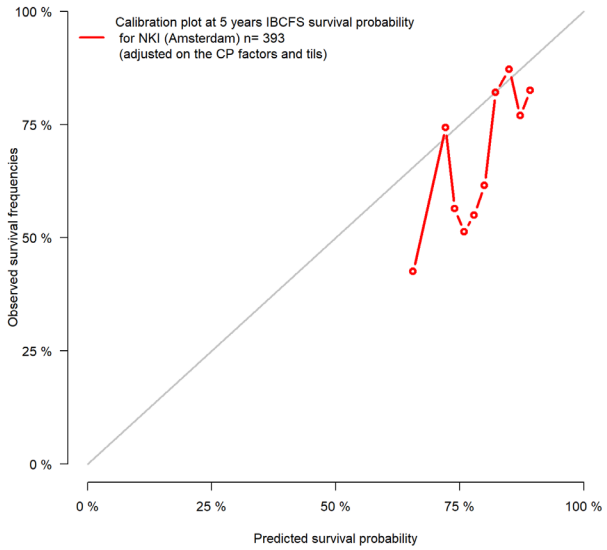


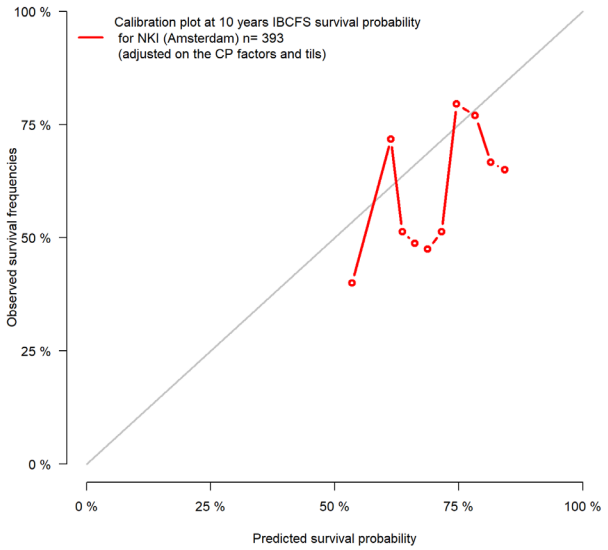










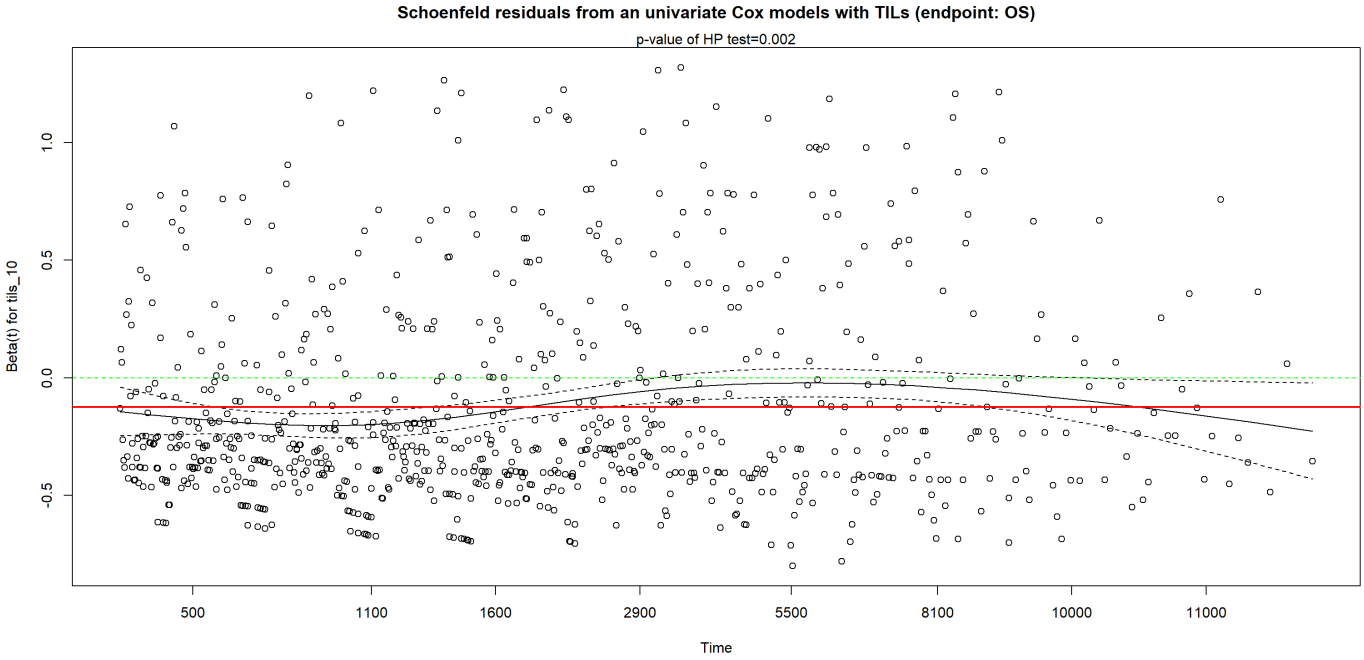


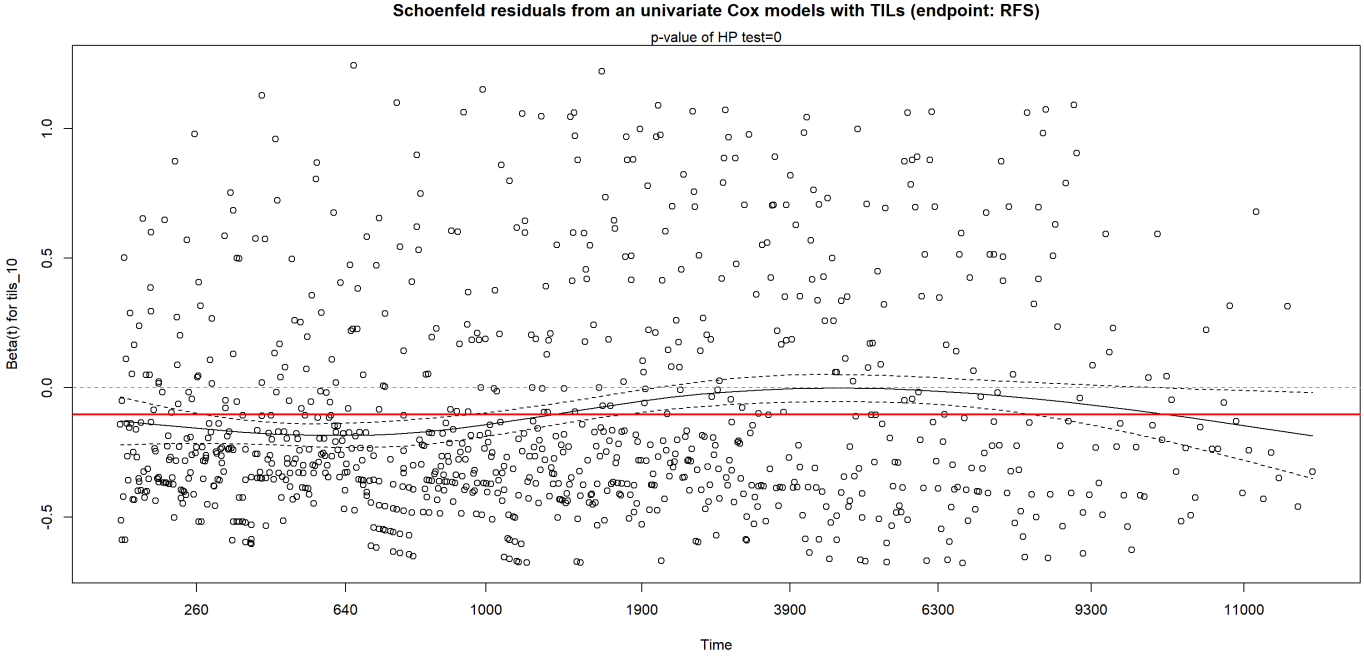
11. Investigation of the Violation of the Proportional Effects Assumption in the Cox Model

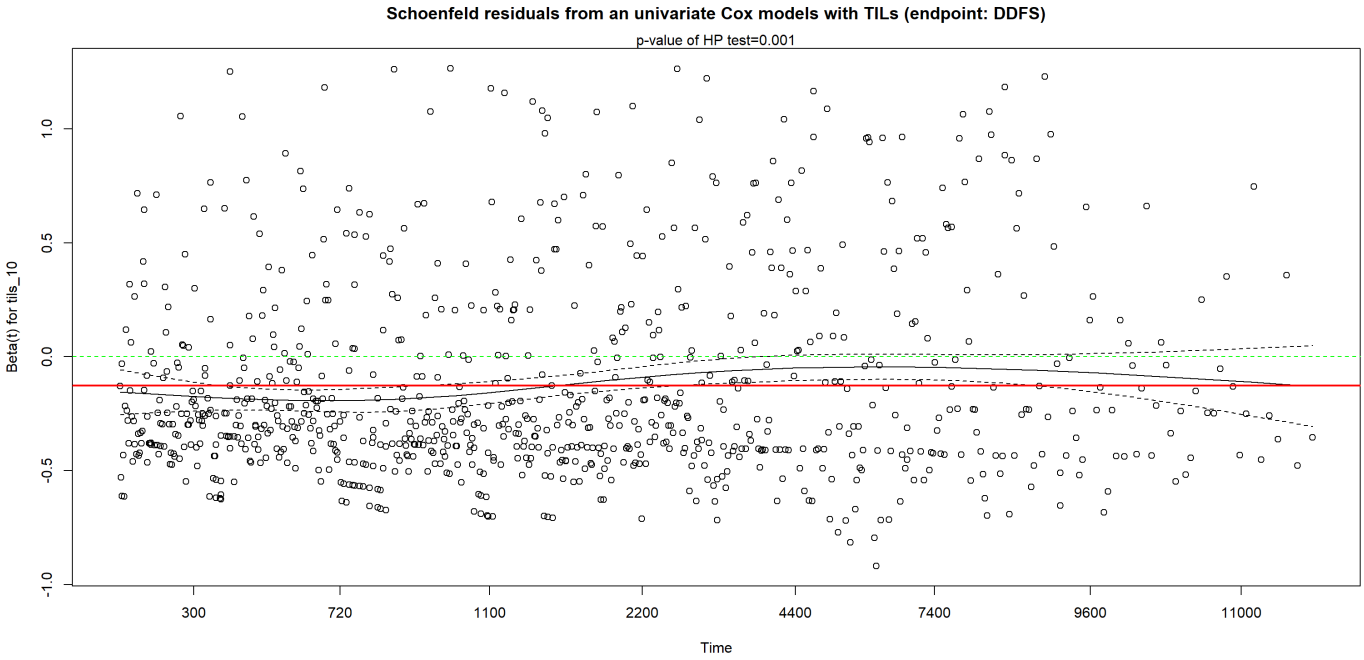
The Cox models presented in the sections above were associated with a significant test for the overall proportional hazards hypothesis[16]. This means that one or more covariates do not have a proportional effect on survival over time. To investigate further, we will first plot the Schoenfeld residuals to have a better idea of the effect of each covariate over time.

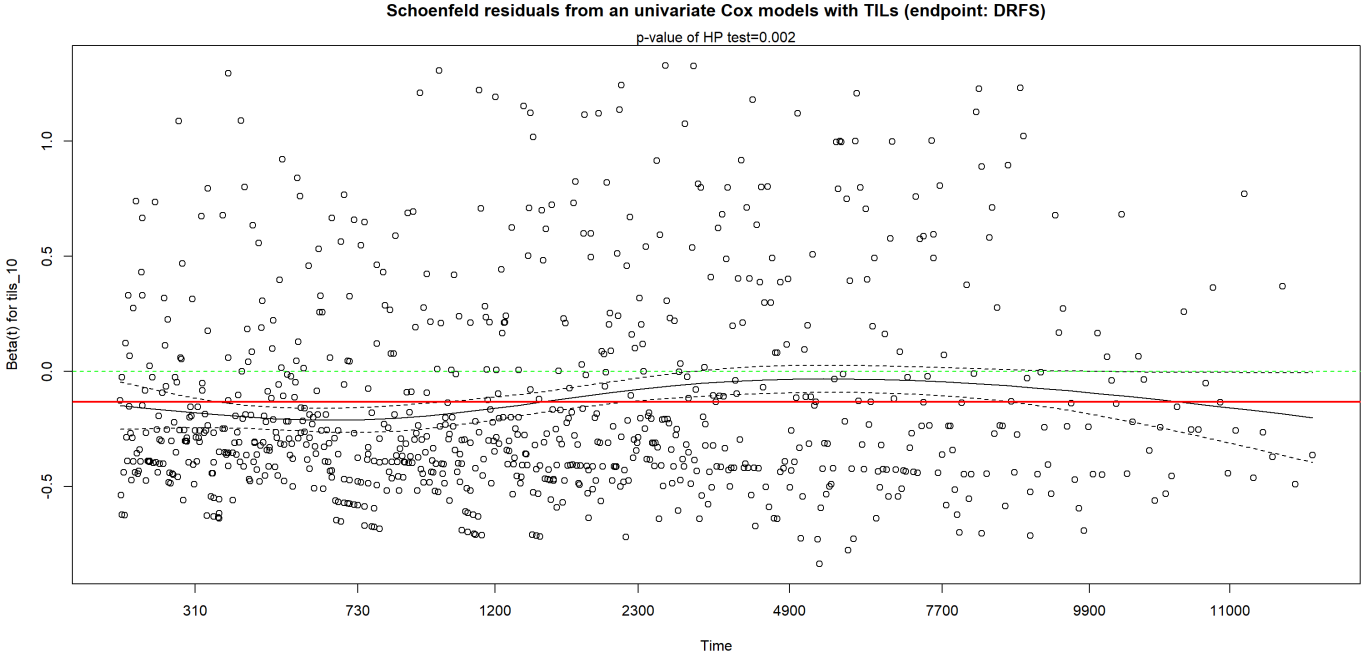
eFigure 11-A. Schoenfeld Residuals of the Univariate Models for Each End Point

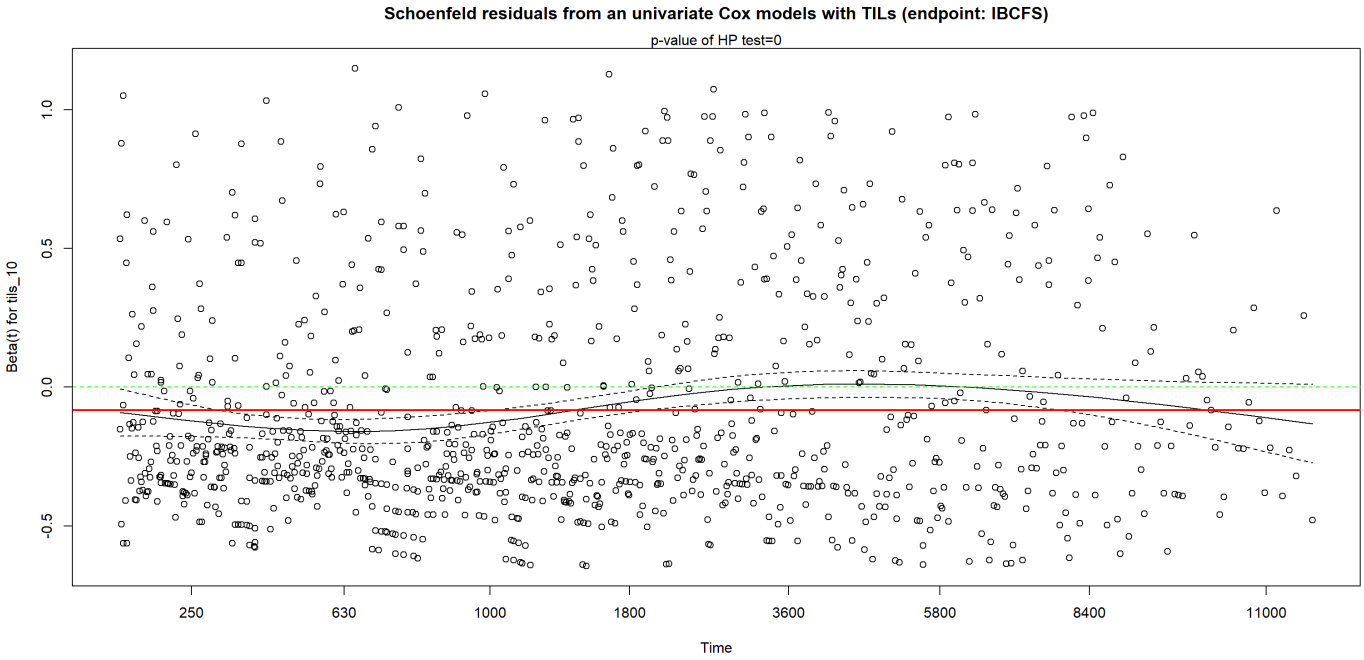
The first graphs represent the Schoenfeld residuals of the univariate models (only the TILs) with in red, the estimated coefficient from the Cox model and in green the null coefficient with the different endpoints.

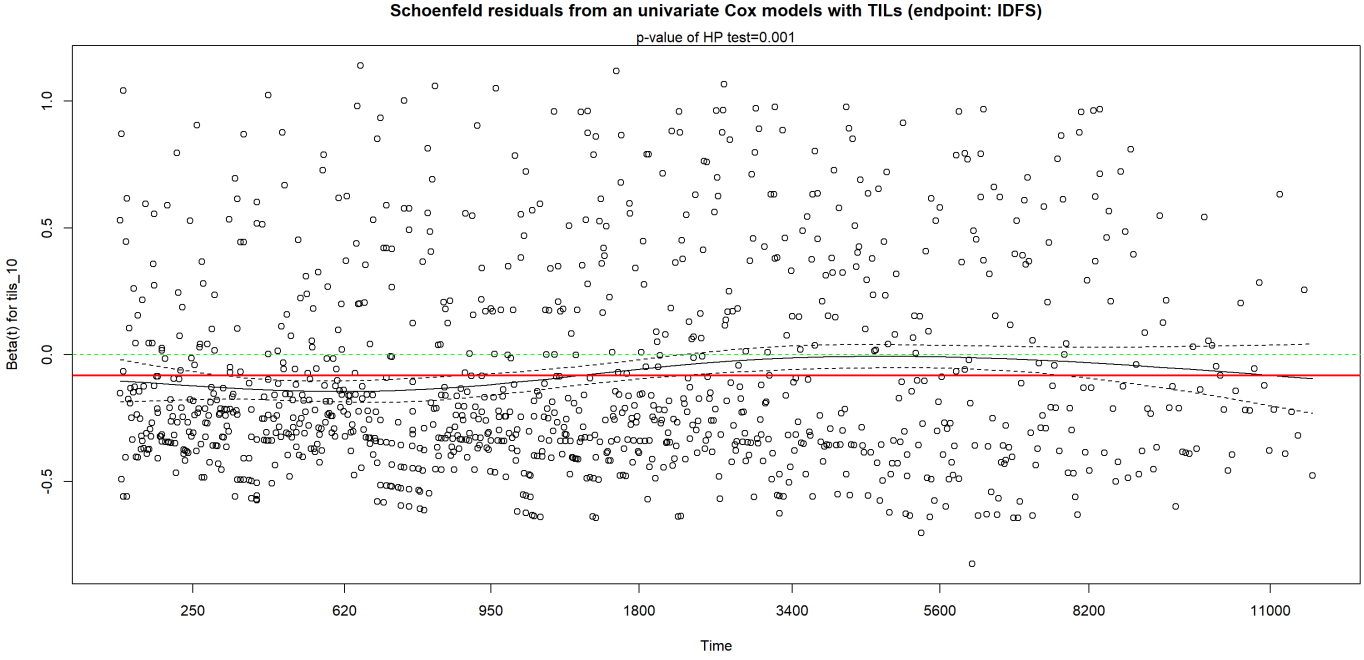






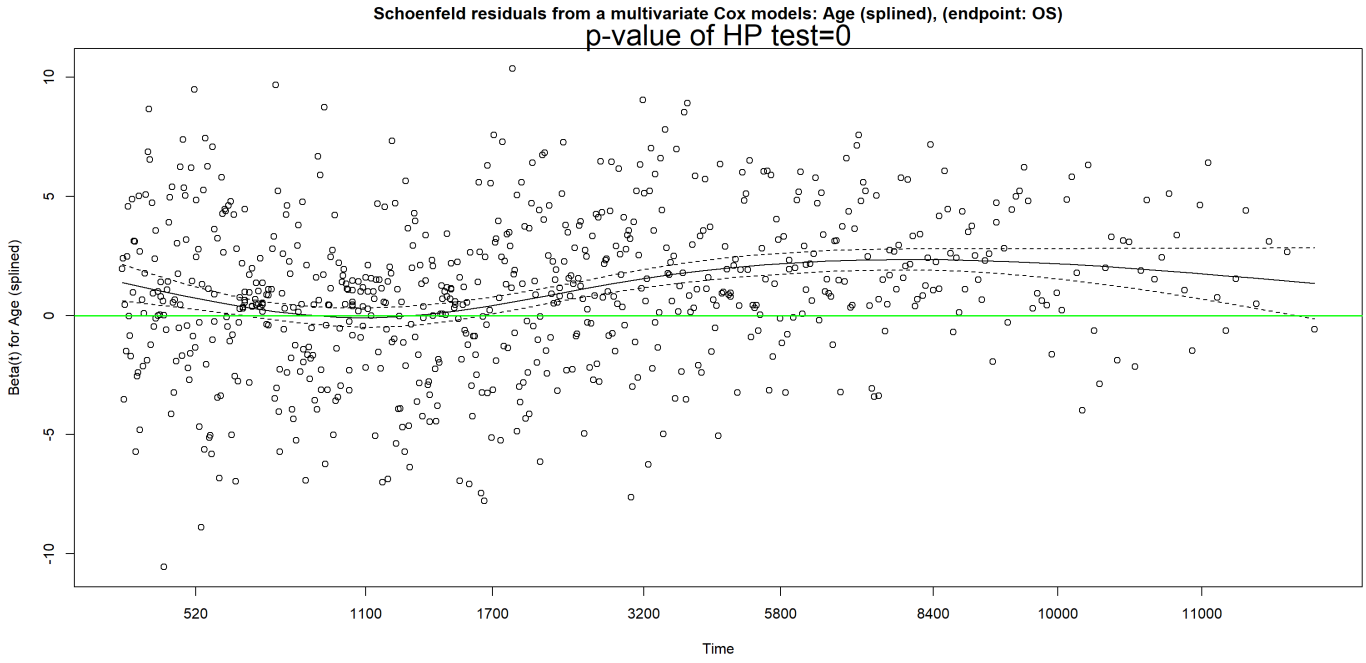


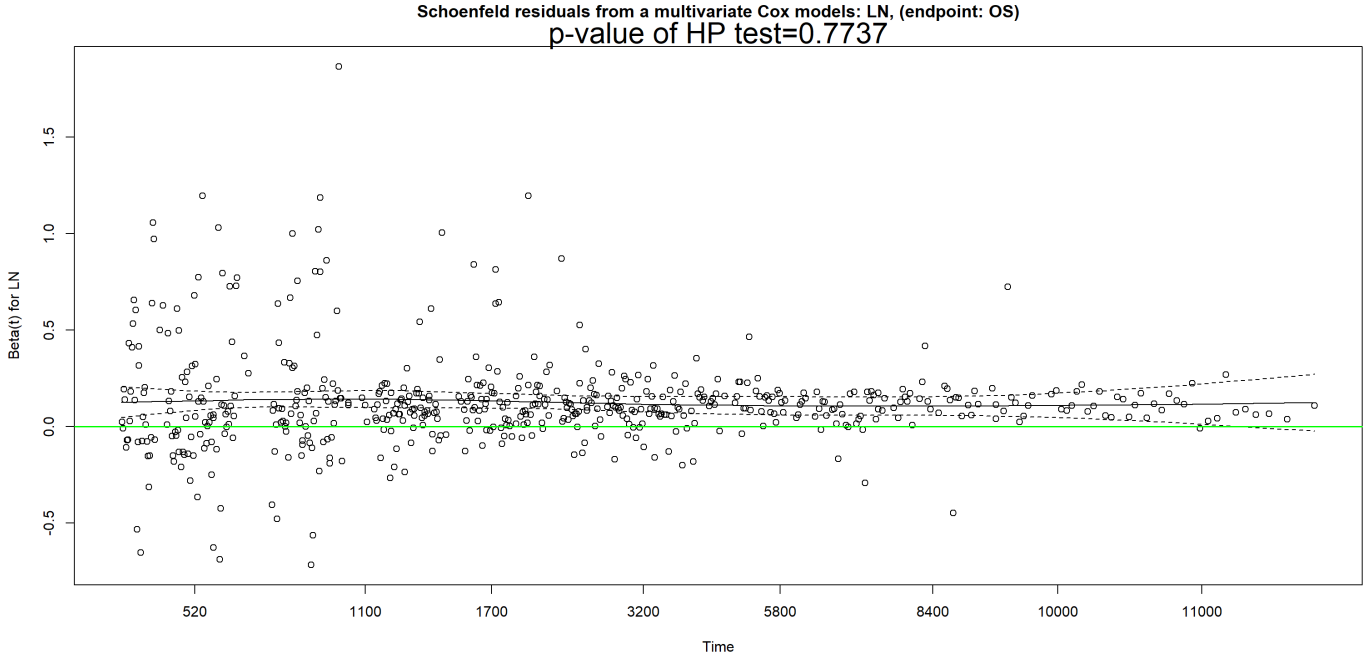


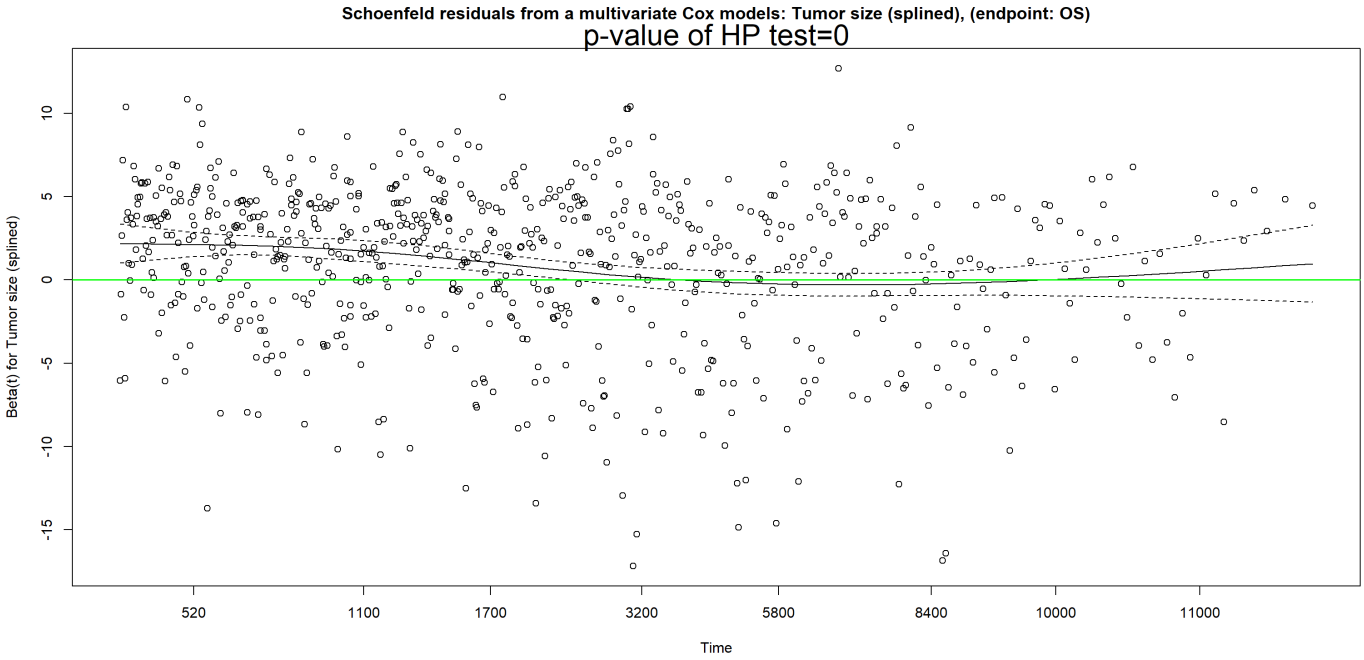


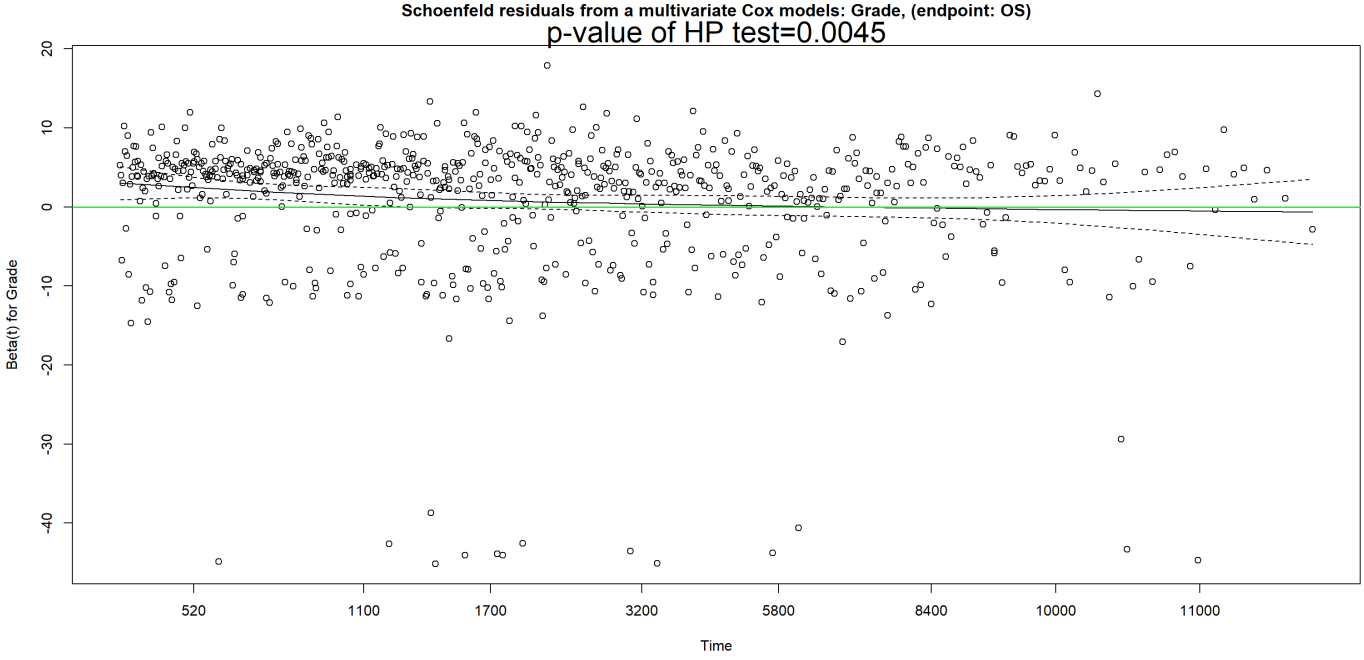
eFigure 11-B. Schoenfeld Residuals of the Multivariable Models for Each End Point

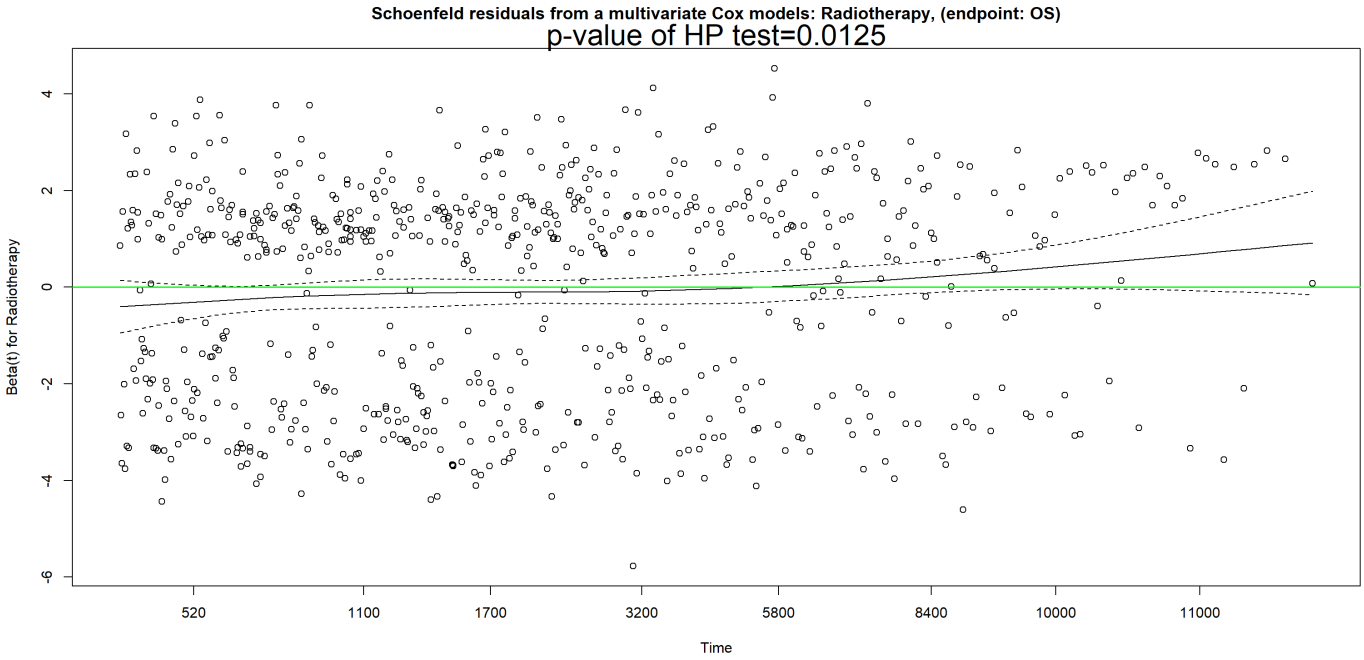
These graphs represent the Schoenfeld residuals of the multivariate model with, in green the null coefficient. OS is the considered endpoint.

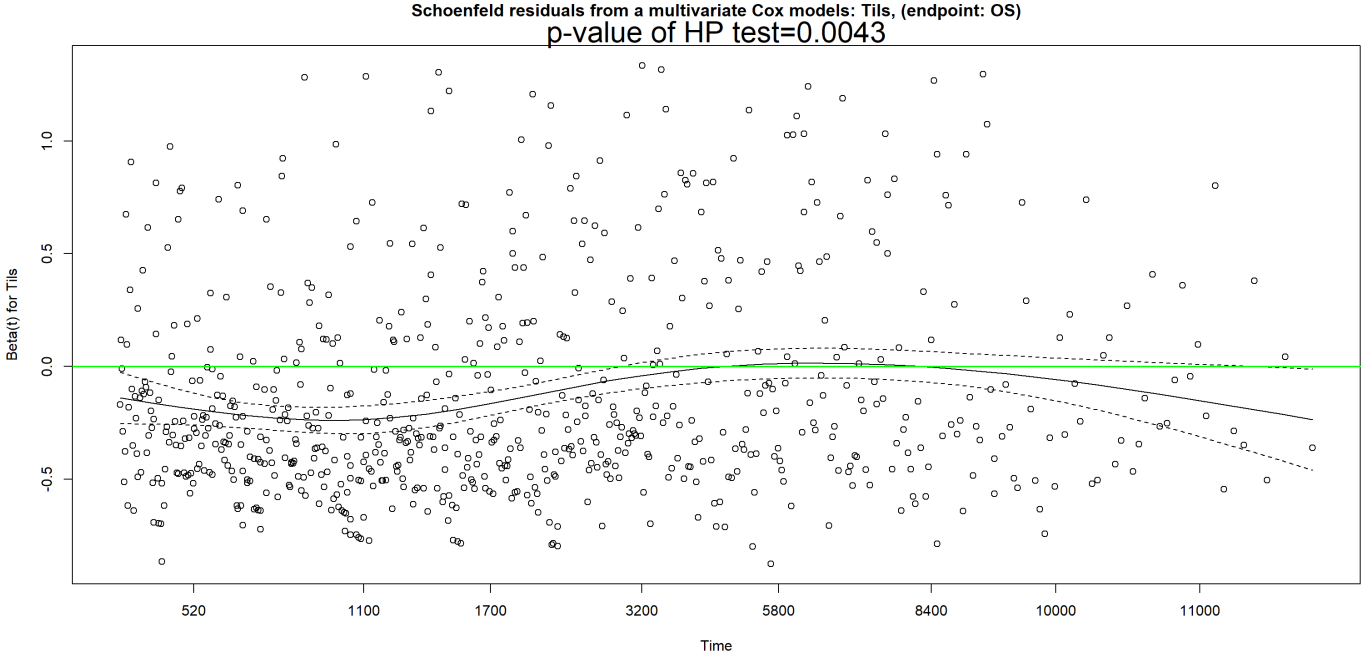












From the plot of the Schoenfeld residuals above, it appears that two variables are particularly affected by the non-proportionality: the size of the tumor and the TILs.

A way to deal with non-proportionality is to divide the time and then stratify the variable that has non-proportional hazard effect over time, on the divided time. From the graph obtained from a univariate model (section above), it appears that the TILs have a strong effect on the risk before 5 years but that the effect is weaker beyond.

Time is divided into several parts: before 5 years, 5-10 years and beyond 10 years. Then, the TILs are stratified on it. After the stratification on the sliced time, we again test the respect of the proportional hazards of the TILs in the multivariate Cox models.

eTable 11. Multivariate Cox Model With End Point: Overall Survival (Just the Coefficients of the TILs are Shown) Stratified on Time

Variable	Beta (SE)	HR (95% CI)	P

eTable 11. Multivariate Cox Model With End Point: Overall Survival (Just the Coefficients of the TILs are Shown) Stratified on Time

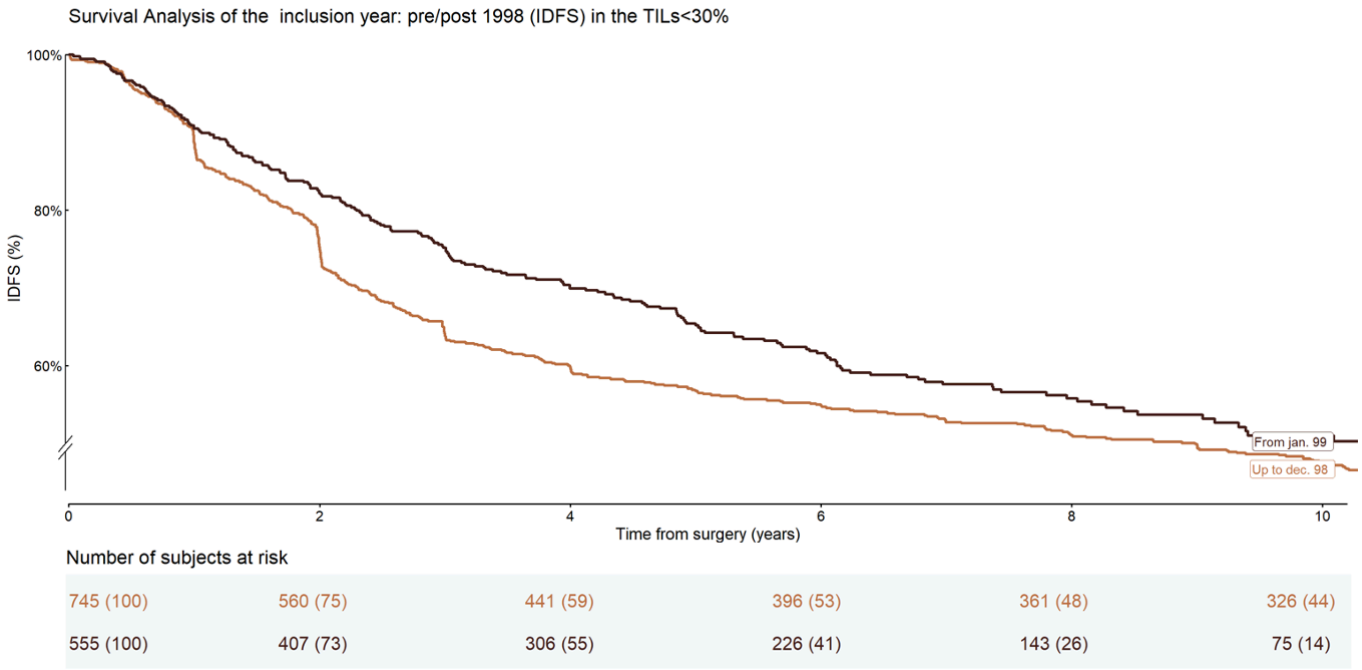
Variable	Beta (SE)	HR (95% CI)	P
TILs before 5 years	-0.13 (0.02)	0.88 (0.85, 0.91)	<0.001
TILs in [5;10] years	-0.05 (0.02)	0.95 (0.91, 1.00)	0.05
TILs after 10 years	-0.04 (0.03)	0.96 (0.91, 1.02)	0.23

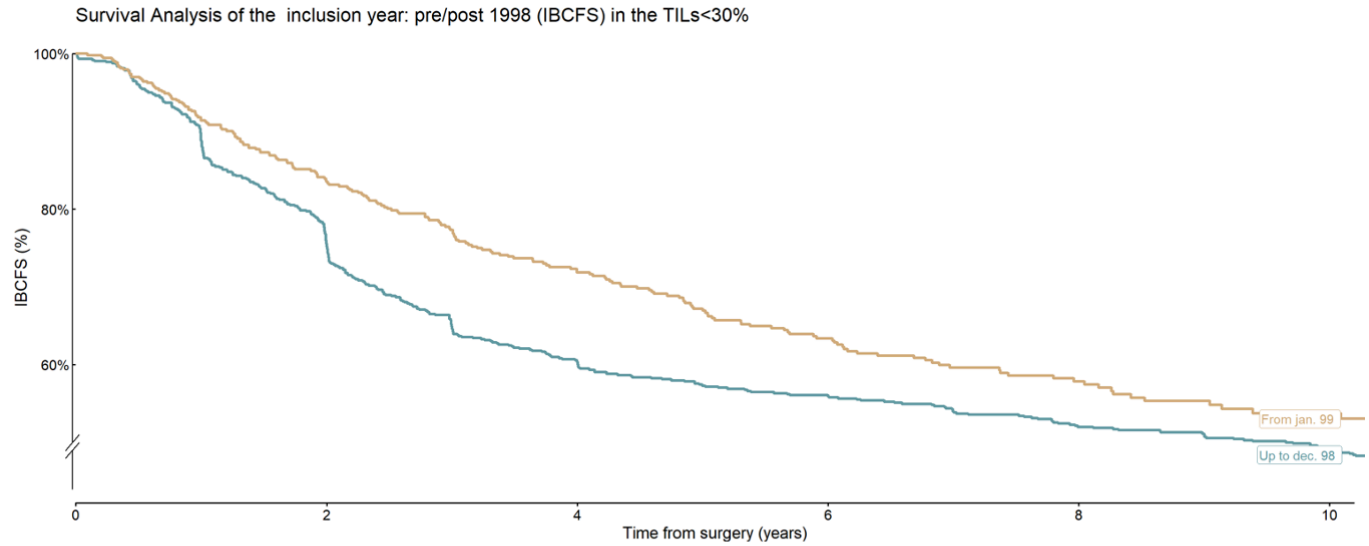
12. Investigation of the Effect of Inclusion Year on Survival End Points According to TILs

eTable 12. Sensitivity Analysis of Survival Outcomes According to TIL Levels Pre- and Post- 1998

Year of surgery	N (%)	TILs	n (%)	5-year IDFS	5-year RFS	5-year DRFS	5-year DDFS	5-year OS
1998 or before	1181 (60%)	**<30**	**745 (63%)**	**57% [54-60]**	**60% [57-63]**	**64% [61-67]**	**62% [59-65]**	**68% [65-71]**
		≥30	436 (37%)	74% [70-77]	79% [76-82]	82% [79-85]	81% [78-84]	85% [82-88]
		≥50	**284 (24%)**	**77% [73-82]**	**84% [81-88]**	**88% [85-91]**	**86% [83-89]**	**91% [88-94]**
		≥75	133 (11%)	86% [80-91]	91% [87-95]	94% [90-97]	92% [89-96]	96% [93-98]
1999 or after	785 (40%)	**<30**	**555 (71%)**	**65% [62-69]**	**69% [65-72]**	**74% [71-77]**	**71% [68-75]**	**77% [74-80]**
		≥30	230 (29%)	75% [71-81]	80% [75-85]	87% [82-90]	83% [79-87]	88% [84-92]
		≥50	**133 (17%)**	**78% [71-84]**	**81% [74-87]**	**88% [82-93]**	**85% [79-91]**	**89% [84-94]**
		≥75	36 (5%)	79% [66-91]	85% [74-94]	94% [87-100]	88% [77-97]	94% [86-100]

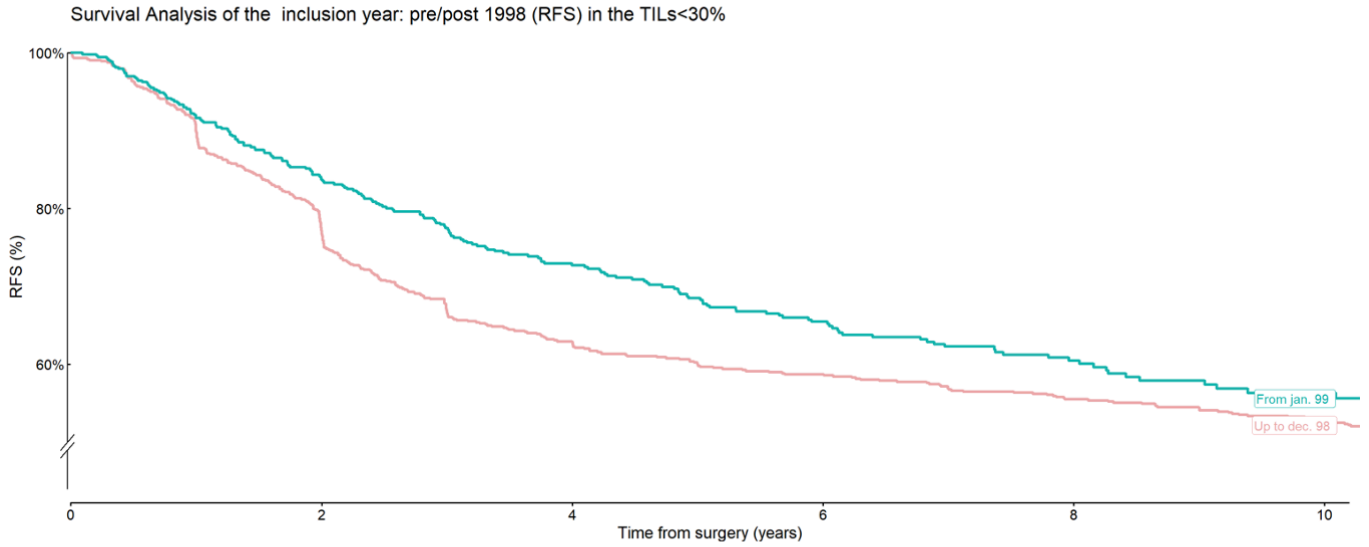
eFigure 12-A. Survival Outcomes in Patients With TNBC and TILs <30% Who Underwent Locoregional Therapy Before vs After 1998





Number of subjects at risk

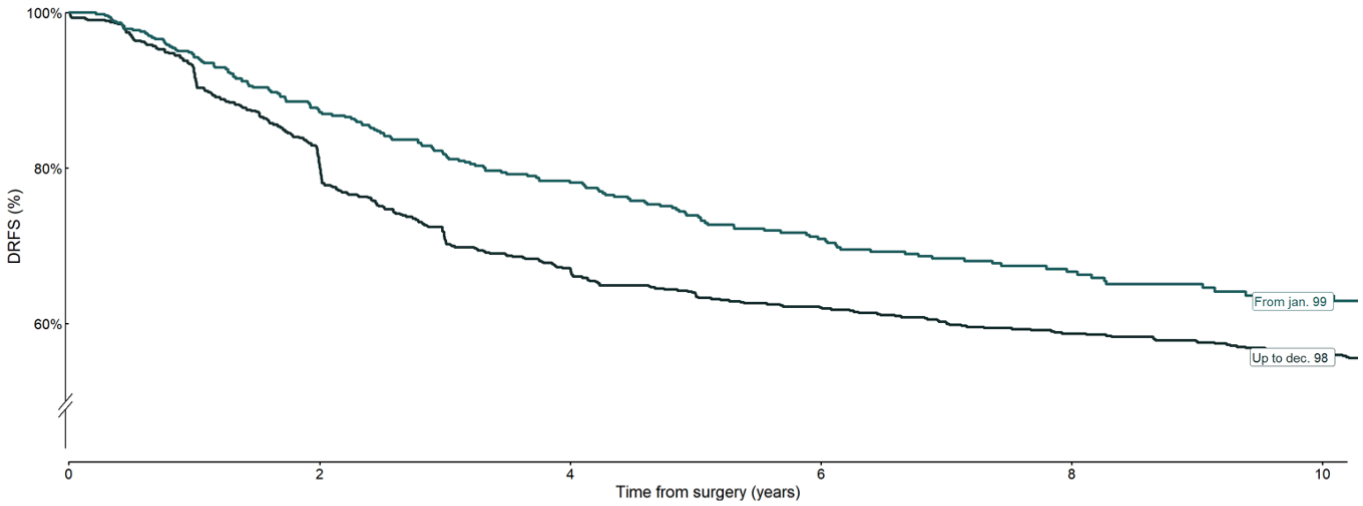
745 (100)	562 (75)	445 (60)	404 (54)	368 (49)	337 (45)
555 (100)	414 (75)	316 (57)	231 (42)	148 (27)	80 (14)



Number of subjects at risk

745 (100)	573 (77)	463 (62)	424 (57)	393 (53)	361 (48)
555 (100)	415 (75)	320 (58)	237 (43)	154 (28)	83 (15)

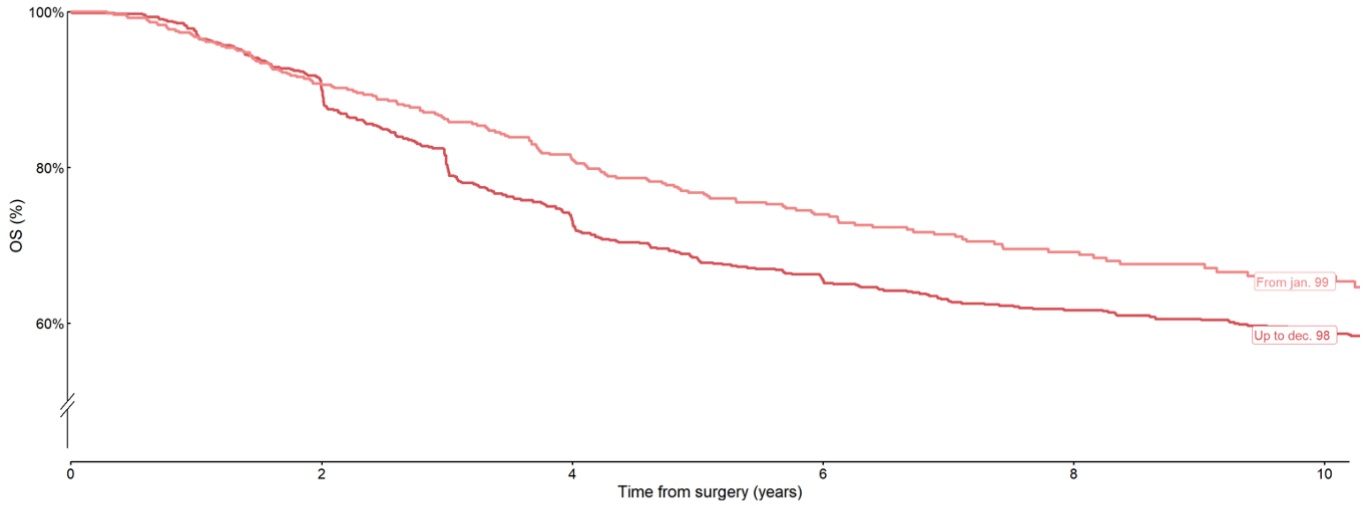
Survival Analysis of the inclusion year: pre/post 1998 (DRFS) in the TILs<30%



Number of subjects at risk

745 (100)	598 (80)	494 (66)	449 (60)	416 (56)	384 (52)
555 (100)	431 (78)	346 (62)	263 (47)	177 (32)	98 (18)

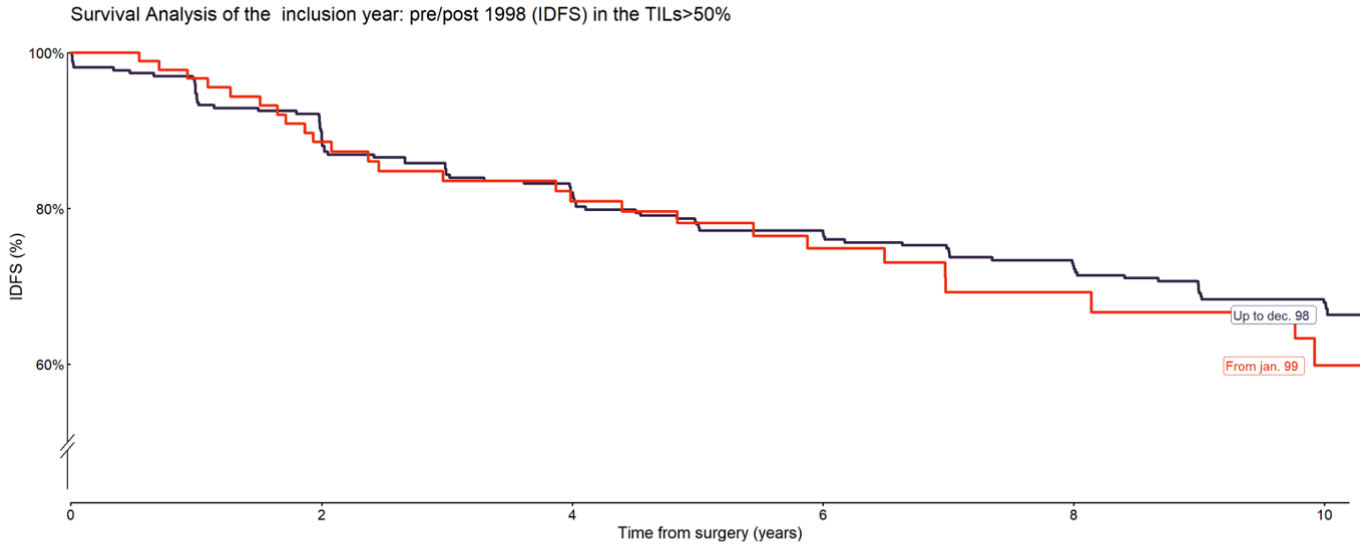
Survival Analysis of the inclusion year: pre/post 1998 (OS) in the TILs<30%



Number of subjects at risk

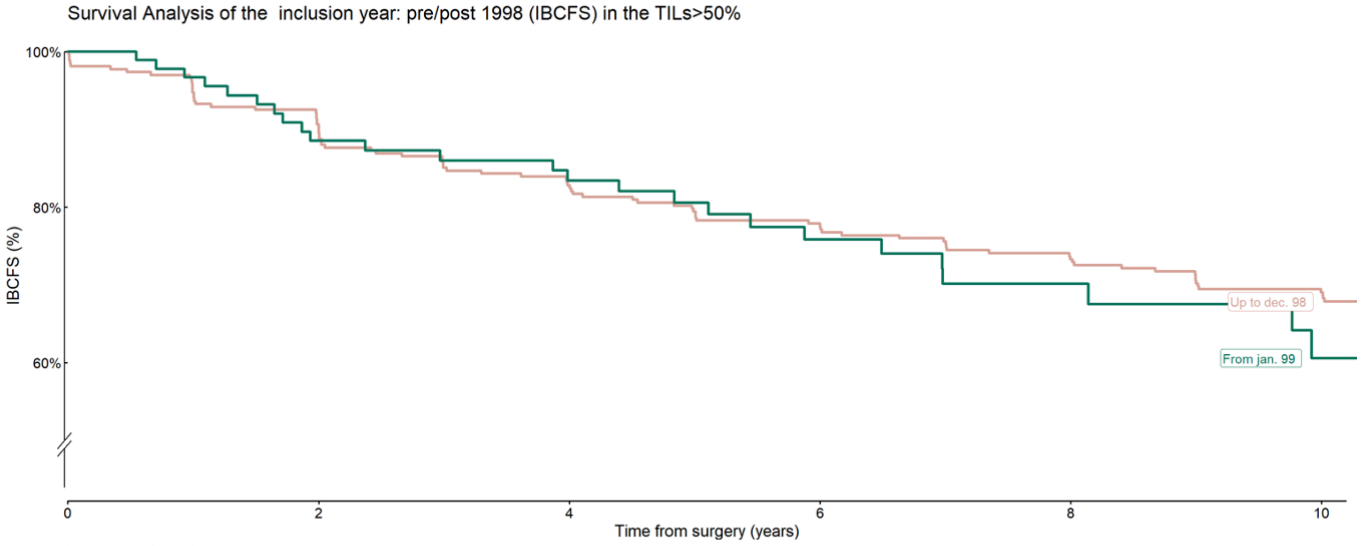
745 (100)	669 (90)	539 (72)	475 (64)	437 (59)	403 (54)
555 (100)	447 (81)	357 (64)	273 (49)	185 (33)	102 (18)

eFigure 12-B. Survival Outcomes in Patients With TNBC and TILs ≥50% Who Underwent Locoregional Therapy Before vs After 1998



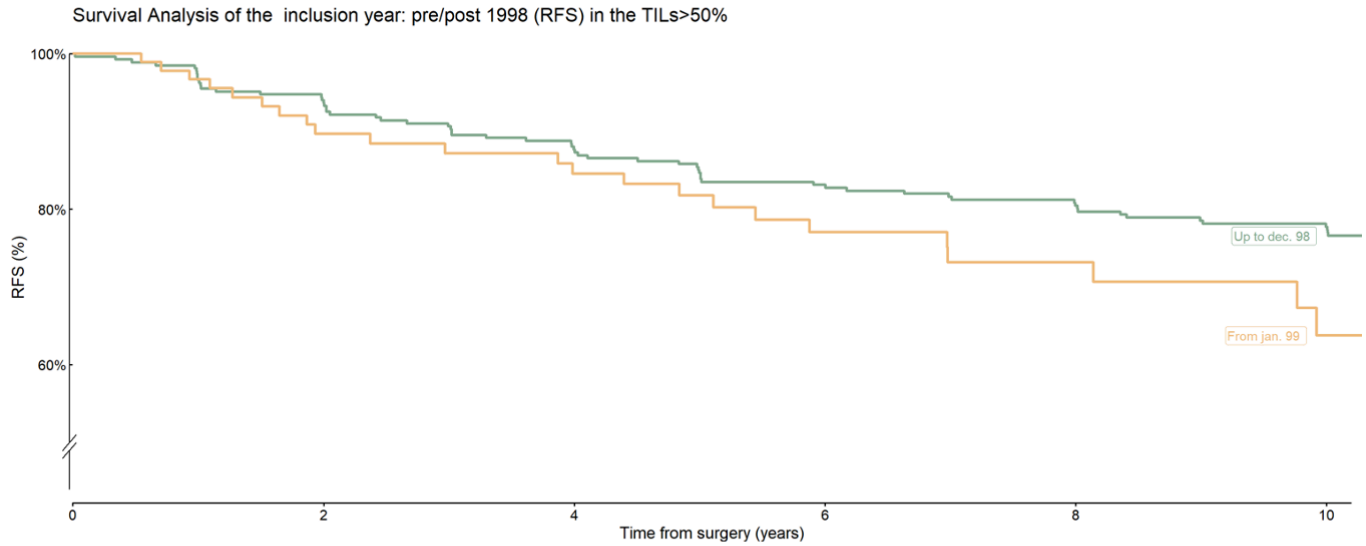
Number of subjects at risk

268 (100)	241 (90)	220 (82)	202 (75)	189 (71)	172 (64)
100 (100)	73 (73)	62 (62)	46 (46)	28 (28)	16 (16)



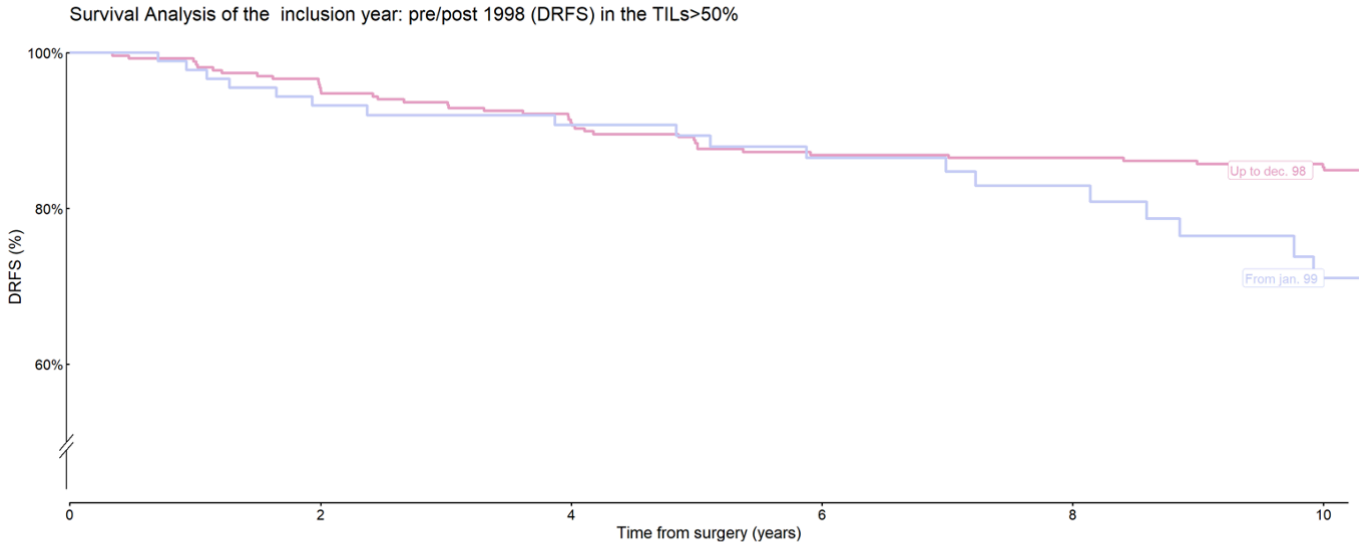
Number of subjects at risk

268 (100)	243 (91)	222 (83)	204 (76)	191 (71)	175 (65)
100 (100)	73 (73)	64 (64)	47 (47)	28 (28)	16 (16)



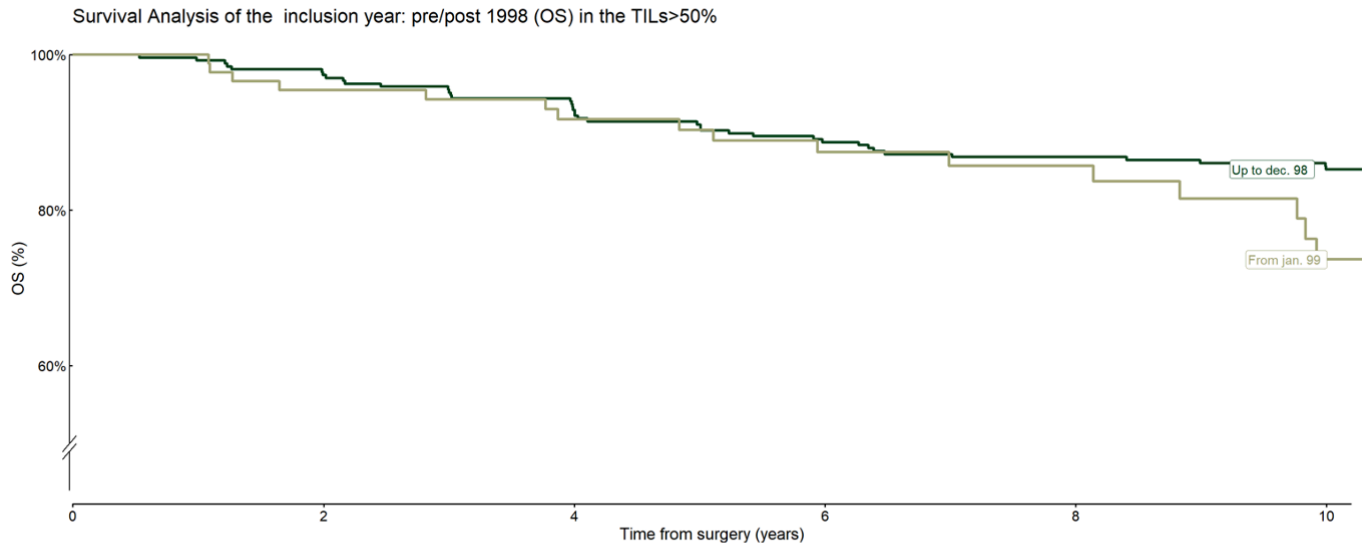
Number of subjects at risk

268 (100)	252 (94)	235 (88)	218 (81)	210 (78)	198 (74)
100 (100)	74 (74)	65 (65)	48 (48)	30 (30)	17 (17)



Number of subjects at risk

268 (100)	256 (96)	244 (91)	228 (85)	226 (84)	217 (81)
100 (100)	78 (78)	72 (72)	59 (59)	40 (40)	25 (25)



Number of subjects at risk

268 (100)	261 (97)	249 (93)	233 (87)	227 (85)	217 (81)
100 (100)	80 (80)	73 (73)	60 (60)	42 (42)	27 (27)

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