SUPPLEMENTARY MATERIAL

Clinicopathological features and outcomes comparing patients with invasive ductal and lobular breast cancer

Oesterreich S, et al.

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This retrospective cohort study included female adults (aged > 18 years) who were diagnosed with breast cancer from 1990 to 2017 treated at any of the three academic medical centers: UPMC (Magee Women's Hospital and Hillman Cancer Center), Cleveland Clinic, and Ohio State University Comprehensive Cancer Center. Institutional review boards at each institution approved this study and waived informed consent because all of the data used were deidentified. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Clinical data included in the study were obtained from each institution's Cancer Registry; these data were retrospectively abstracted manually according to the data standards of the North American Association of Central Cancer Registries.

In order to test whether the Great Lakes Breast Cancer (GLBC) cohort was representative of the larger IDC/ILC populations, we extracted demographics data from National Program of Cancer Registries (NPCR) within the Surveillance, Epidemiology and End Results (SEER) data set [30].

Oncotype Dx Breast Recurrence Score® result (hereafter denoted as Recurrence Score® [RS]) data were received from Exact Sciences (Redwood City, CA) for a subset of patients and matched into the data based on the deidentified patient ID.

Study Population, Outcomes, and Variable Definitions

In the raw datasets, there were 44,278 records from 42,740 patients in total (UPMC: 17,933 records from 16,932 patients; CCF: 16,336 records from 15,811 patients; OSUCCC: 10,009 records from 9,997 patients). Due to the goal of this study, we filtered the dataset according to the following criteria: 1) excluding 518 records (483 patients) with size Tis or Stage 0; 2) excluding 5,645 records (5,295 patients) with ICD histology codes not consistent with either IDC or ILC; 3) excluding 4,453 records (3,300 patients) with multiple records (**Figure 1**).

Briefly, diagnosis of ILC is similar at all three institutions, in that sections from diagnostic biopsies were analyzed histopathologically using information on growth pattern and cytologic features. Briefly, ILC is diagnosed based on identification of small cells that lack cohesion and are individually dispersed throughout the tissue, arranged in single-file linear cords. The use of E-cadherin staining differs between the sites, with CCF using it for more challenging cases, including lobular variants, and UPMC and OSUCCC using not only E-cadherin but frequently dual E-cadherin and p120 staining in the majority of ILC cases. This however is not consistent since the cohort spans almost 30 years and approaches changed over the time.

Two outcomes, overall survival (OS) and disease-free survival (DFS), are used in this study. If not directly provided, overall survival was defined as the difference between the date of death and date of first diagnosis. If the date of death was not available, it was replaced by the date of last contact with survival status being censored. DFS is defined as the difference between the date of first breast cancer recurrence and date of diagnosis and it a summation of the locoregional and distant recurrences. If the date of first recurrence was not available, it was replaced by the date of death or date of last

contact with DFS status being censored. DFS does not include second primary cancers or new contralateral breast cancers. More details can be found in the Data Manual, which is available upon request.

Five deidentified patient unique variables (record ID, patient ID, duplicated indicator, record time, and hospital), four demographic related variables (age, race, BMI, menopausal status), ten basic clinical variables (laterality, stage (using AJCC 6^{th} and 7^{th} edition), grade, size, ER, progesterone receptor (PR), HER2, RS, Oncotype Dx® and TAILORx RS category (low/intermediate or high risk stratified at a RS of 25), and histology), and four treatment variables (radiation therapy, hormonal therapy, chemotherapy, and surgery). Some data were missing, mostly due to lack of collection of specific variables in earlier years as summarized in **Supplementary Figure 1**. There was no significant association between the missing data and histology. Briefly, we evaluated the missing pattern of each variable in the ER+ group separately by fitting the logistic regression of missing patterns against histological type and the variable of interest. After adjusting for the other clinical variables (Age, BMI, PR, HER2, Stage, Grade, OS, DFS), the results show that there is no significant relationship between missing patterns and the histological subtype (**Supplementary Figure 1B**) and thus can be considered at random.

Information on 16 metastasis site indicators (bone, liver, lung, central nervous system, orbit, distant lymph node, peritoneal carcinomatosis, gastrointestinal tract, pericardium or pericardial fluid, skin, genitourinary tract, gynecological sites, connective soft tissue, bone marrow, thyroid, and chest wall) were extracted from the raw dataset obtained from the cancer registry of individual institutions. Manual chart review was performed

when needed to clarify recurrence sites that were designated as “other". The details of variable definition are included in the Data Manual.

Statistical Analysis

All continuous data are expressed as median (IQR), and categorial/ordinal variables are expressed as count (frequencies (%)). Mann–Whitney U test was used for the continuous variables (age and BMI), Pearson's chi-squared test with no continuity correction was used for categorical variables (laterality, race, ER, PR, HER2, and treatments), and Cochran-Armitage test was used for ordinal variables (stage, grade, lymph node status, size, and RS result) in the comparative analyses.

Kaplan-Meier curves are used for visualizing survival, and the corresponding p-values are calculated by log-rank test to test for difference between the groups. Cox proportional hazard regression models are fitted when co-variates adjustment was needed, and the estimated hazard ratios (HR) are reported with the 95% confidence interval. We use the R package *survival* [31] to perform the analysis.

To determine whether treatments (lumpectomy, mastectomy, radiation therapy, chemotherapy, and hormone therapy) were more beneficial for either IDC or ILC, we selected comparable cohorts using propensity score matching (PSM) approaches. We used nearest neighbor matching strategy in R package *MatchIt* [32] to match over age, stage, grade, nodal status, and institution, and the treatment information was adjusted in the subsequent survival analysis. For example, for those who received adjuvant hormone therapy, the matching procedure was as follows: starting from all patients with

ER+ tumors who received hormone therapy, patients with IDC and ILC were matched over age, stage, grade, institution, and lymph nodal status. After propensity score matching, using Cox proportional hazards regression modeling, we then test whether the histology was associated with survival in the matched cohort after adjusting for the other treatments (surgery, radiation therapy, and chemotherapy). All samples with missing data were excluded from inclusion in the propensity score matching. Results are presented as standardized mean differences (SMD) before and after PSM. All PSM analysis was performed for all patients with ER+ IDC and ER+ ILC.

To study changes over time, we calculated the mean tumor size, the proportion of different surgery types and the use of hormonal therapy, chemotherapy and radiation both IDC and ILC for each year over the study period (1990-2017). Loess regressions (stat::loess() function in R) with 95% confidence interval were fitted to show trends of tumors size and treatments over time.

A p-value < 0.05 is considered statistically significant, and 95% confidence intervals are reported. When adequate, we corrected for multiple comparisons using conservative Bonferroni correction, and present both raw p-values and corrected p-values. Since we have large sample size, effect size is also considered in the interpretation in addition to p-values. All the statistical analyses are conducted in R 4.0.

Supplementary Table 1: Comparison of our GLBC cohort to other published datasets.

Characteristic	GLBC, N = 33,662	Metabric, N = 1,642	ScanB, N = 2,988	TCGA, N = 1,117	Arpino_ILC, N = 49,309	Chen_SEER, N = 796,335
Histology						
IDC	30,045 (89.3%)	1,500 (91.4%)	2,602 (87.1%)	901 (80.7%)	45,169 (91.6%)	711,287 (89.3%)
ILC	3,617 (10.7%)	142 (8.6%)	386 (12.9%)	216 (19.3%)	4,140 (8.4%)	85,048 (10.7%)
Age						
<= 50	10,525 (31.3%)	372 (22.7%)	636 (21.3%)	351 (31.4%)	11,364 (26.8%)	
> 50	23,136 (68.7%)	1,270 (77.3%)	2,352 (78.7%)	766 (68.6%)	31,088 (73.2%)	
Unknown	1	0	0	0	6,857	
Stage						
1 ~ 2	24,406 (88.5%)	1,081 (90.8%)	2,501 (96.9%)	832 (75.8%)		660,664 (83.0%)
3 ~ 4	3,175 (11.5%)	110 (9.2%)	79 (3.1%)	266 (24.2%)		135,671 (17.0%)
Unknown	6,081	451	408	19		0
Grade						
1	4,679 (16.9%)	122 (7.7%)				153,608 (19.6%)
2	12,640 (45.5%)	610 (38.5%)				344,373 (43.9%)
3	10,441 (37.6%)	852 (53.8%)				286,920 (36.6%)
Unknown	5,902	58				11,434
ER						
Positive	19,788 (78.7%)	1,220 (74.3%)	2,605 (92.4%)	543 (76.8%)	40,515 (82.2%)	625,471 (78.8%)
Negative	5,370 (21.3%)	422 (25.7%)	215 (7.6%)	164 (23.2%)	8,794 (17.8%)	168,560 (21.2%)
Unknown	8,504	0	168	410	0	2,304
PR						
Positive	17,074 (68.2%)	829 (50.5%)	2,346 (86.9%)	473 (67.2%)	29,419 (60.8%)	533,738 (67.5%)
Negative	7,945 (31.8%)	813 (49.5%)	354 (13.1%)	231 (32.8%)	18,962 (39.2%)	257,023 (32.5%)
Unknown	8,643	0	288	413	927	5,574

Supplementary Table 2: Comparison of our cohort to National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology, and End Results (SEER) databases.

	NPCR US (2001-2017)	NPCR PA (2001-2017)	NPCR OH (2001-2017)	SEER-9 (1990-2017)
Total N	2,872,831	138,766	122,025	437,381
Histology (Chen et al 2005)				
ILC (ICDO-3=8520)	319,750 (11.1%)	16,023 (11.5%)	13,227 (10.8%)	48,428 (11.1%)
IDC (ICDO-3=8500)	2,553,081 (88.9%)	122,743 (88.5%)	108,798 (89.2%)	388,953 (88.9%)
Age				
20-49	598,685 (20.8%)	26,321 (19.0%)	23,374 (19.2%)	97,613 (22.3%)
50+	2,274,146 (79.2%)	112,445 (81.0%)	98,651 (80.8%)	339,768 (77.7%)
Stage				
Localized	1,817,911 (64.5%)	88,759 (64.8%)	77,230 (64.4%)	216,752 (65.5%)
Regional	861,438 (30.6%)	39,998 (29.2%)	36,475 (30.4%)	98,883 (29.9%)
Distant	140,213 (5.0%)	8,169 (6.0%)	6,305 (5.3%)	15,167 (4.6%)
unknown	53,269	1,840	2,015	106,579
Grade				
1	543,361 (20.4%)	24,847 (19.3%)	24,370 (22.0%)	80,041 (20.5%)
2	1,173,129 (44.1%)	59,293 (46.0%)	48,068 (43.4%)	170,700 (43.8%)
3	943,407 (35.5%)	44,741 (34.7%)	38,367 (34.6%)	138,938 (35.7%)
unknown	212,934	9,885	11,220	47,702
ER Status (2004+)				
Positive	1,828,653 (80.6%)	94,135 (82.0%)	80,306 (80.3%)	319,801 (80.0%)
Negative	440,142 (19.4%)	20,668 (18.0%)	19,733 (19.7%)	80,020 (20.0%)
unknown	604,036	23,963	21,986	37,560
PR Status (2004+)				
Positive	1,567,929 (70.0%)	82,012 (71.9%)	69,381 (69.6%)	273,847 (69.3%)
Negative	672,267 (30.0%)	32,058 (28.1%)	30,359 (30.4%)	121,571 (30.7%)
unknown	632,635	24,696	22,285	41,963
Race				
White	2,420,064 (84.6%)	124,099 (89.8%)	107,376 (88.3%)	355,302 (81.5%)
Black	323,288 (11.3%)	11,873 (8.6%)	12,498 (10.3%)	41,493 (9.5%)
Other	117,819 (4.1%)	2,240 (1.6%)	1,668 (1.4%)	39,174 (9.0%)
unknown	11,660	554	483	1,412

Supplementary Table 3: Patient characteristics broken down by institution.

Characteristic	UPMC, N = 14,033[a]	CCF, N = 12,194[a]	OSU, N = 7,435[a]	p-value[b]
Histology				<0.001
IDC	12,691 (90%)	10,687 (88%)	6,667 (90%)	
ILC	1,342 (9.6%)	1,507 (12%)	768 (10%)	
Age (Year)	57 (48, 67)	58 (48, 68)	57 (48, 66)	<0.001
Unknown	0	1	0	
BMI	27 (23, 31)	27 (24, 32)	29 (25, 33)	<0.001
Unknown	1,391	6,471	1,999	
Laterality				0.50
Left	7,118 (51%)	0 (NA%)	3,806 (51%)	
Right	6,889 (49%)	0 (NA%)	3,610 (49%)	
Unknown	26	12,194	19	
Race				<0.001
Black	780 (5.6%)	1,581 (13%)	661 (8.9%)	
White	13,067 (93%)	10,290 (85%)	6,551 (89%)	
Other	186 (1.3%)	243 (2.0%)	223 (3.0%)	
Unknown	0	80	0	
Stage				<0.001
I	6,696 (56%)	4,990 (54%)	3,097 (49%)	
II	4,155 (35%)	3,041 (33%)	2,427 (38%)	
III	1,010 (8.4%)	839 (9.1%)	621 (9.8%)	
IV	171 (1.4%)	365 (4.0%)	169 (2.7%)	
Unknown	2,001	2,959	1,121	
Grade				<0.001
1	2,025 (16%)	1,525 (18%)	1,129 (16%)	
2	6,012 (48%)	3,436 (41%)	3,192 (46%)	
3	4,391 (35%)	3,487 (41%)	2,563 (37%)	
Unknown	1,605	3,746	551	

Characteristic	UPMC, N = 14,033[a]	CCF, N = 12,194[a]	OSU, N = 7,435[a]	p-value[b]
ER				<0.001
Positive	10,834 (80%)	5,505 (77%)	3,449 (77%)	
Negative	2,712 (20%)	1,612 (23%)	1,046 (23%)	
Unknown	487	5,077	2,940	
PR				<0.001
Positive	9,610 (71%)	4,536 (64%)	2,928 (65%)	
Negative	3,842 (29%)	2,541 (36%)	1,562 (35%)	
Unknown	581	5,117	2,945	
HER2				<0.001
Positive	816 (15%)	915 (19%)	582 (17%)	
Negative	4,473 (82%)	3,811 (81%)	2,735 (81%)	
Equivocal	199 (3.6%)	1 (<0.1%)	69 (2.0%)	
Unknown	8,545	7,467	4,049	
Lymph Nodes				<0.001
N0	8,786 (64%)	6,197 (62%)	4,283 (60%)	
N1	3,143 (23%)	2,256 (22%)	1,822 (26%)	
N2	562 (4.1%)	402 (4.0%)	321 (4.5%)	
N3	240 (1.7%)	153 (1.5%)	174 (2.4%)	
NX	1,081 (7.8%)	1,068 (11%)	539 (7.6%)	
Unknown	221	2,118	296	
Size				<0.001
T0	460 (3.3%)	214 (2.4%)	266 (3.7%)	
T1	9,074 (65%)	5,485 (61%)	4,073 (57%)	
T2	3,163 (23%)	2,126 (23%)	1,940 (27%)	
T3	514 (3.7%)	276 (3.0%)	293 (4.1%)	
T4	155 (1.1%)	105 (1.2%)	89 (1.2%)	
TX	531 (3.8%)	848 (9.4%)	482 (6.7%)	
Unknown	136	3,140	292	

Characteristic	UPMC, N = 14,033[a]	CCF, N = 12,194[a]	OSU, N = 7,435[a]	p-value[b]
OncotypeDX Recurrence Score				0.57
Low Risk	1,318 (59%)	715 (58%)	400 (58%)	
Intermediate Risk	699 (32%)	393 (32%)	217 (32%)	
High Risk	202 (9.1%)	126 (10%)	68 (9.9%)	
Unknown	11,814	10,960	6,750	
Hormone Therapy				<0.001
No	3,773 (28%)	5,938 (49%)	2,647 (36%)	
Yes	9,784 (72%)	6,245 (51%)	4,788 (64%)	
Unknown	476	11	0	
Chemotherapy				<0.001
No	7,242 (53%)	6,167 (57%)	3,537 (48%)	
Yes	6,537 (47%)	4,597 (43%)	3,898 (52%)	
Unknown	254	1,430	0	
Surgery				<0.001
Lumpectomy	7,664 (55%)	2,076 (17%)	3,582 (52%)	
Mastectomy	5,832 (42%)	7,861 (65%)	3,322 (48%)	
None	513 (3.7%)	2,158 (18%)	42 (0.6%)	
Unknown	24	99	489	

a Median (IQR); n (%)
b Kruskal-Wallis rank sum test; Pearson's Chi-squared test (all tests were 2-sided).

Supplementary Table 4: Comparison of BMI across cohorts within the GLBC data.

Cohort	IDC; median (SD)	ILC; median (SD)	P-value
Entire Cohort	27 (6)	27 (6)	0.15
ER+ Only	27 (6)	27 (6)	0.27
ER+/HER2-	28 (6)	27 (6)	0.09
ER+ Pre-menopausal women	26 (6)	25 (6)	0.32
ER+ Post-menopausal women	28 (6)	28 (6)	0.88

Supplementary Table 5: Patient characteristics for those who had ER+/HER2- tumors.

	Entire Cohort				Cohort with ER+/HER2-			
Characteristic	**ILC, N = 3,617[a]**	**IDC, N = 30,045[a]**	**p-value[b]**	**q-value[c]**	**ILC, N = 1,558[a]**	**IDC, N = 7,650[a]**	**p-value[b]**	**q-value[c]**
Age (Year)	61 (52, 70)	57 (48, 67)	<0.001	<0.001	62 (53, 70)	60 (51, 69)	<0.001	<0.001
Unknown	0	1						
BMI	27 (24, 32)	27 (24, 32)	0.15	>0.9	27 (24, 33)	28 (24, 33)	0.095	>0.9
Unknown	1,102	8,759			209	973		
Laterality			0.6	>0.9			0.4	>0.9
Left	1,083 (52%)	9,841 (51%)			500 (52%)	2,590 (51%)		
Right	1,017 (48%)	9,482 (49%)			455 (48%)	2,514 (49%)		
Unknown	1,517	10,722			603	2,546		
Race			0.004	0.046			0.4	>0.9
Black	276 (7.6%)	2,746 (9.2%)			137 (8.8%)	615 (8.1%)		
White	3,275 (91%)	26,633 (89%)			1,388 (89%)	6,849 (90%)		
Other	60 (1.7%)	592 (2.0%)			29 (1.9%)	175 (2.3%)		
Unknown	6	74			4	11		
Stage			<0.001	<0.001			<0.001	<0.001
I	1,406 (46%)	13,377 (54%)			619 (45%)	4,298 (62%)		
II	1,008 (33%)	8,615 (35%)			476 (34%)	1,994 (29%)		
III	502 (17%)	1,968 (8.0%)			246 (18%)	535 (7.7%)		
IV	112 (3.7%)	593 (2.4%)			42 (3.0%)	114 (1.6%)		
Unknown	589	5,492			175	709		
Grade			<0.001	<0.001			<0.001	<0.001
1	631 (24%)	4,048 (16%)			377 (26%)	1,792 (25%)		
2	1,656 (64%)	10,984 (44%)			946 (66%)	3,750 (52%)		
3	294 (11%)	10,147 (40%)			111 (7.7%)	1,658 (23%)		
Unknown	1,036	4,866			124	450		
ER			<0.001	<0.001				
Positive	2,564 (96%)	17,224 (77%)						
Negative	104 (3.9%)	5,266 (23%)						
Unknown	949	7,555						
PR			<0.001	<0.001			<0.001	0.002
Positive	2,144 (81%)	14,930 (67%)			1,306 (84%)	6,693 (88%)		
Negative	508 (19%)	7,437 (33%)			247 (16%)	947 (12%)		
Unknown	965	7,678			5	10		
HER2			<0.001	<0.001				
Positive	169 (9.4%)	2,144 (18%)						
Negative	1,607 (90%)	9,412 (80%)						
Equivocal	19 (1.1%)	250 (2.1%)						
Unknown	1,822	18,239						
LymphNodes			<0.001	<0.001			<0.001	<0.001
N0	1,892 (57%)	17,374 (63%)			870 (59%)	4,985 (68%)		
N1	805 (24%)	6,416 (23%)			319 (22%)	1,447 (20%)		
N2	173 (5.3%)	1,112 (4.0%)			100 (6.7%)	358 (4.9%)		
N3	150 (4.6%)	417 (1.5%)			88 (5.9%)	133 (1.8%)		
NX	273 (8.3%)	2,415 (8.7%)			106 (7.1%)	365 (5.0%)		
Unknown	324	2,311			75	362		
Size			<0.001	<0.001			<0.001	<0.001
T0	13 (0.6%)	927 (3.3%)			1 (<0.1%)	99 (1.3%)		
T1	1,107 (49%)	17,525 (63%)			506 (49%)	5,175 (70%)		
T2	695 (31%)	6,534 (23%)			327 (32%)	1,647 (22%)		
T3	307 (14%)	776 (2.8%)			172 (17%)	172 (2.3%)		
T4	15 (0.7%)	334 (1.2%)			3 (0.3%)	54 (0.7%)		
TX	100 (4.5%)	1,761 (6.3%)			28 (2.7%)	225 (3.1%)		
Unknown	1,380	2,188			521	278		
Oncotype			<0.001	<0.001			<0.001	0.003
Low Risk	407 (65%)	2,026 (58%)			328 (66%)	1,684 (60%)		
Intermediate Risk	204 (33%)	1,105 (31%)			160 (32%)	858 (31%)		
High Risk	12 (1.9%)	383 (11%)			7 (1.4%)	261 (9.3%)		
Unknown	2,994	26,531			1,063	4,847		

[a]Median (IQR); n (%)

[b]Wilcoxon rank sum test; Pearson's Chi-squared test; Kruskal-Wallis rank sum test

[c]Bonferroni correction for multiple testing

[d]Other includes Hispanic, Asian, and American Indian.

Supplementary Table 6: Standardized mean differences (SMD) after propensity score matching to show that cohorts were well-matched.

	SMD before PSM	SMD after PSM
Patients under lumpectomy matching group		
Age	0.308	0.008
Stage	0.213	0.067
Grade	0.487	0.107
Site	0.508	0.036
Lymph Node Status	0.190	0.050
Patients under mastectomy matching group		
Age	0.180	0.021
Stage	0.616	0.110
Grade	0.524	0.049
Site	0.777	0.070
Lymph Node Status	0.375	0.097
Patients under radiation therapy matching group		
Age	0.170	0.001
Stage	0.476	0.072
Grade	0.509	0.093
Site	0.493	0.043
Lymph Node Status	0.366	0.052
Patients under chemotherapy matching group		
Age	0.380	0.012
Stage	0.546	0.057
Grade	0.700	0.088
Site	0.283	0.091
Lymph Node Status	0.456	0.115
Patients under hormone therapy matching group		
Age	0.207	0.020
Stage	0.442	0.045
Grade	0.487	0.070
Site	0.551	0.044
Lymph Node Status	0.305	0.054

Supplementary Table 7: Use of different cutoffs for OncotypeDX Recurrence Score.

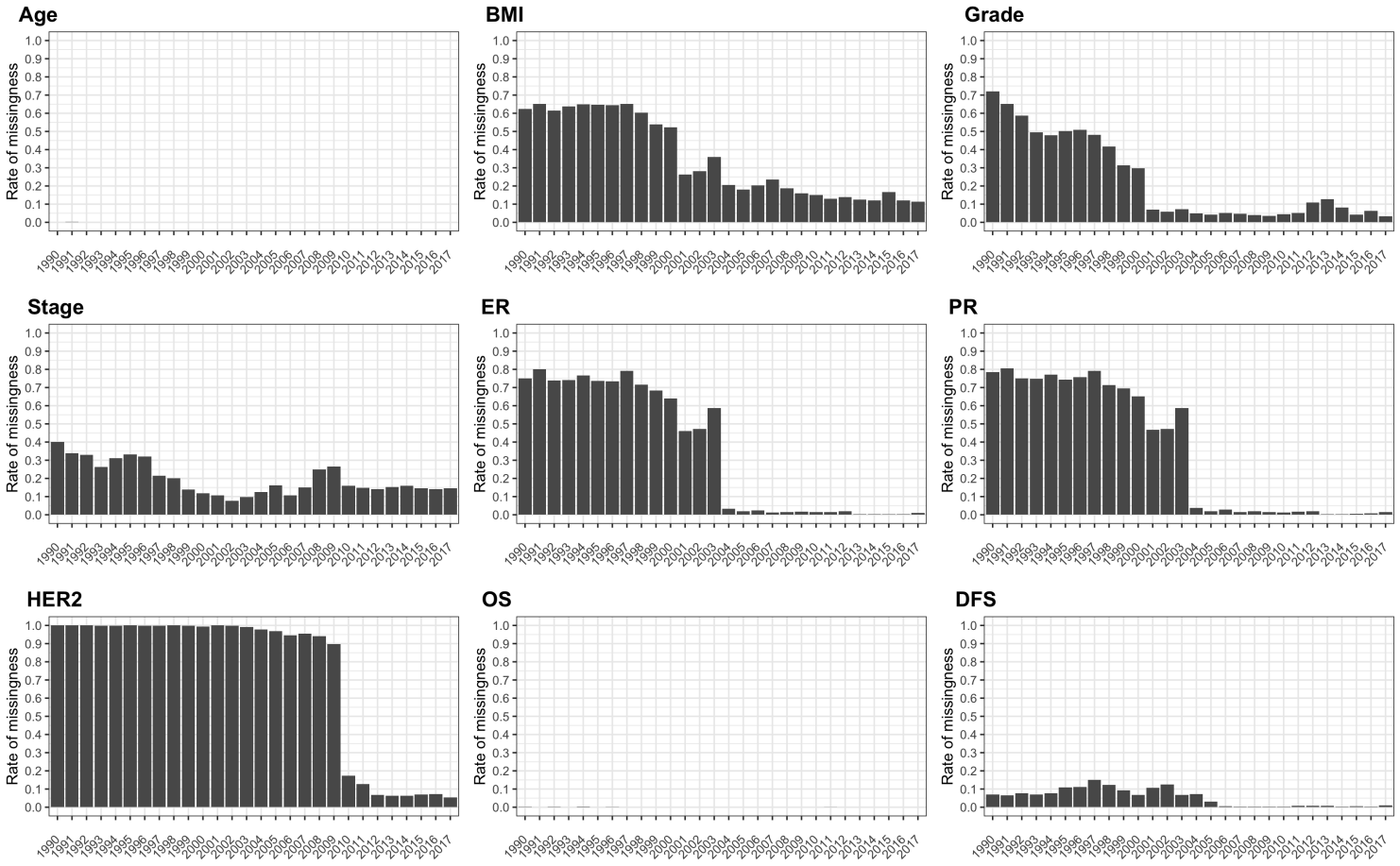
	Continuous	**TAILORX**	**Oncotype DX**
Overall Survival [HR (p-value)]			
Overall	1.02 (0.0236)	2.08 (0.000345)	1.39 (0.09); 2.14 (0.00197)
IDC	1.02 (0.0078)	2.36 (9.83e-0.5)	1.56 (0.03958); 2.52 (0.00034)
ILC	0.99 (0.804)	1.13 (0.866)	0.89 (0.797); 0 (0.997)
# Records	3096	3712	4066
Disease-Free Survival [HR (p-value)]			
Overall	1.03 (3.83e-05)	2.78 (1.83e-06)	2.23 (0.000239); 3.60 (1.32e-06)
IDC	1.03 (0.000189)	2.93 (1.2e-06)	2.17 (0.000867); 3.47 (4.27e-06)
ILC	1.05 (0.367)	0 (0.998)	2.821 (0.108); 0 (0.998)

Regardless of the cutoff, the results remain consistent with the TAILORx, continuous and OncotypeDx scores all providing significance RS in IDC but no significance in ILC. We do however note the challenge in such studies of the low number of patients with ILC.

Supplementary Table 8: Time to recurrence (DFS) of different metastatic sites.

Median DFS (Month)	Bone	Liver	Lung	CNS	Distant LN	Peritoneum
Overall	43.00	41.00	48.00	40.00	50.00	52.00
IDC	42.00	40.00	47.00	41.00	50.00	44.00
ILC	55.00	42.49	62.69	34.50	56.00	59.50
P-value*	0.07332	0.4947	0.4853	0.5679	0.1596	0.05917

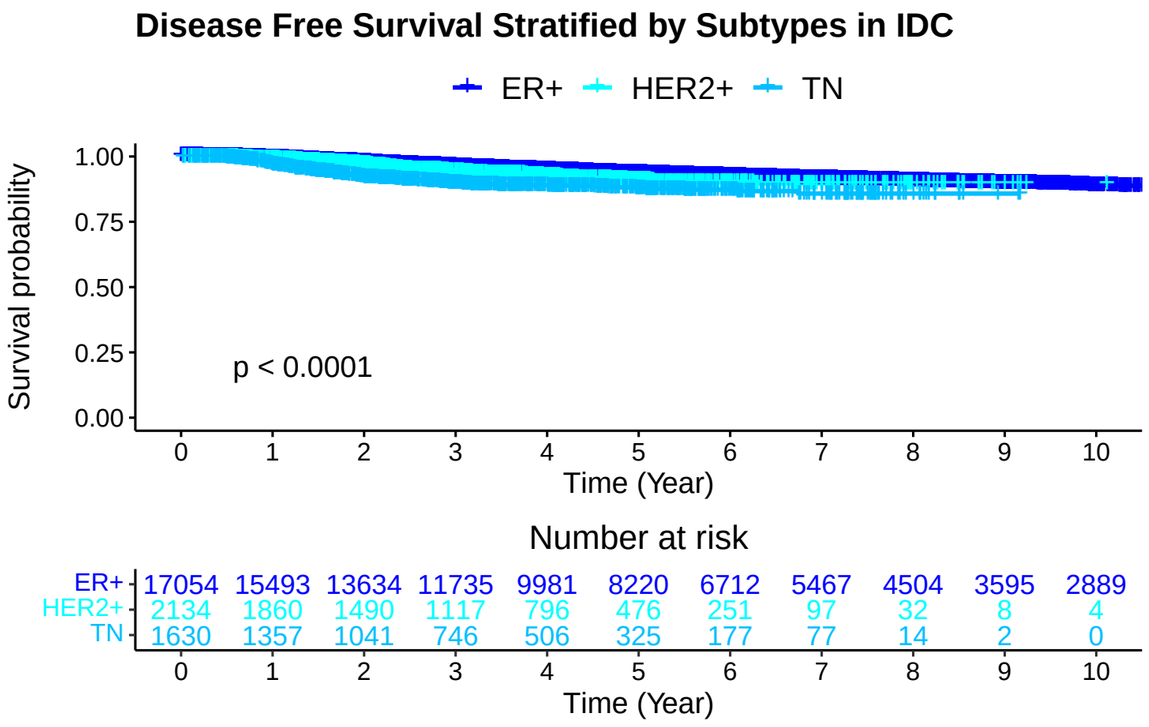
Supplementary Figure 1: Missingness of data by year of diagnosis.
We consider the data is missing completely at random. The main reason of missingness is the record time. We first showcase the missing patterns across years. The missing rate of ER, PR, and HER2 drops dramatically in 2004, 2004, and 2010 respectively. The missing rate of BMI and Grade starts to decrease in 2000 and 2001, and the missing rate of stage is relatively stable. There is nearly no missingness for age, OS and DFS. We next evaluate the missing pattern of each variable in ER+ group separately by fitting the logistic regression of missing pattern against histology type, the variable of interest, after adjusting for the other clinical variables
(Age, BMI, PR, HER2, Stage, Grade, OS, DFS), and the results show that there is no significant relation between missing patterns and the histology type. (p-values are listed in the table).

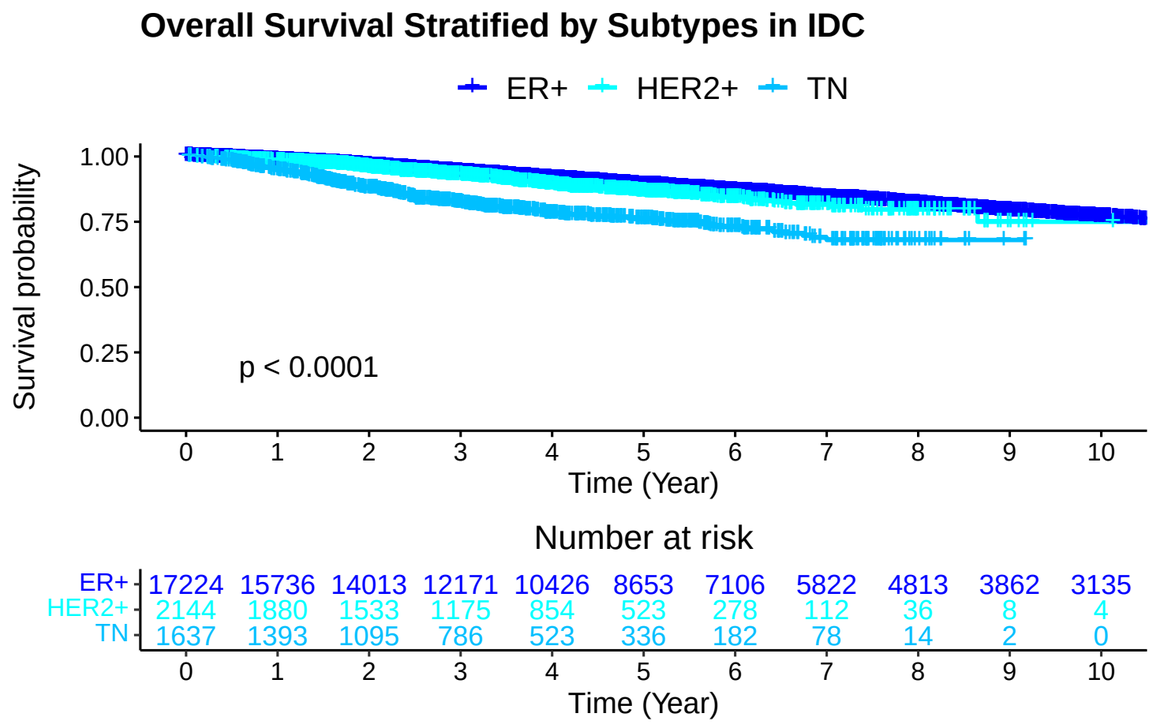


Variable	Start from	P-value
BMI	1990	0.9406
Grade	1990	0.8641
Stage	1990	0.4819
PR	1990	0.8212
HER2	2010	0.7065
DFS	1990	0.3118

Supplementary Figure 2

A





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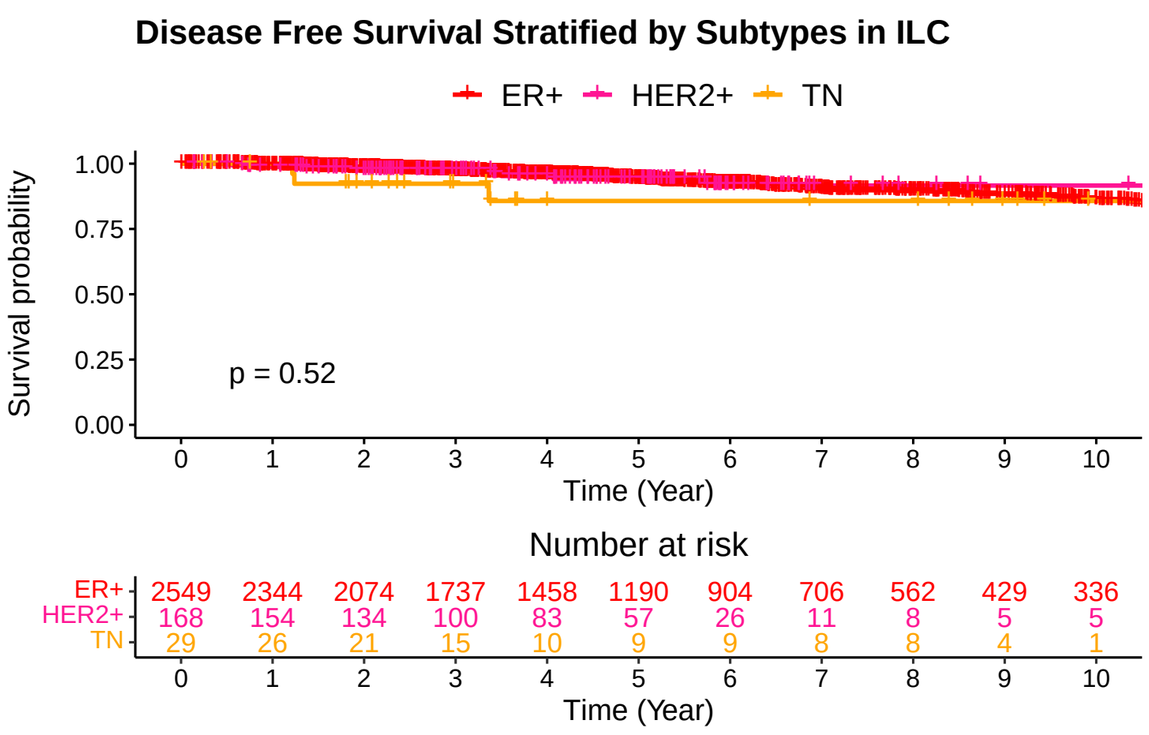

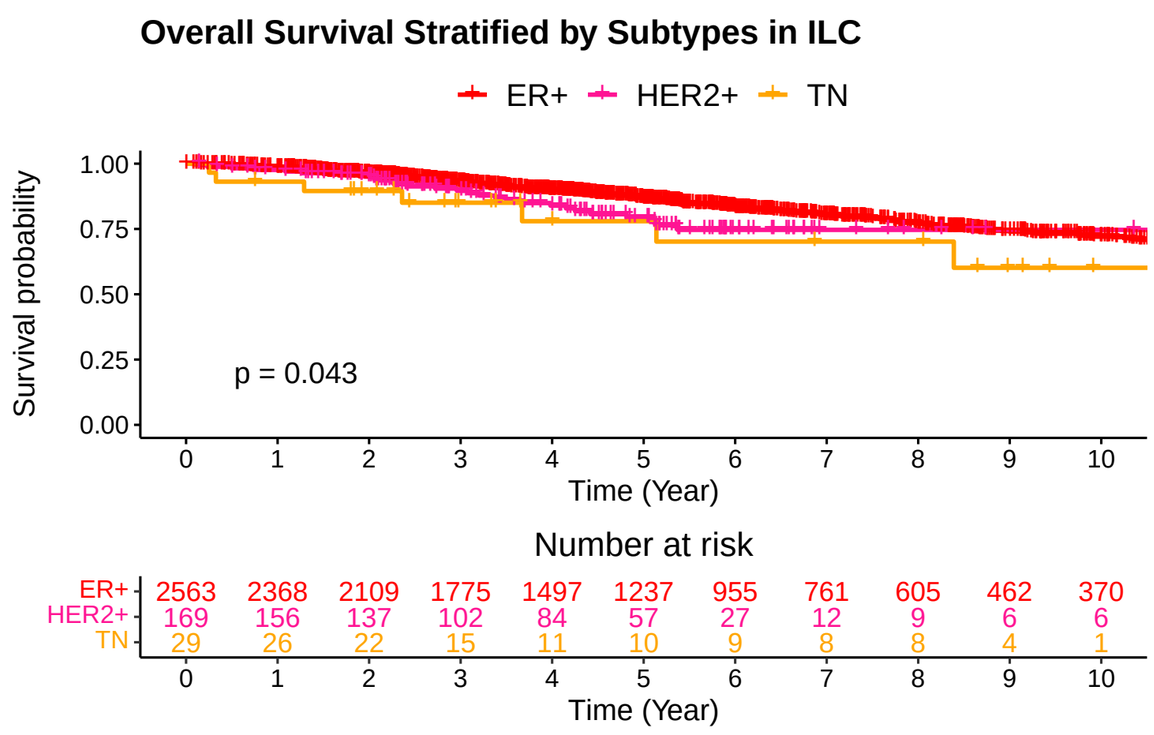

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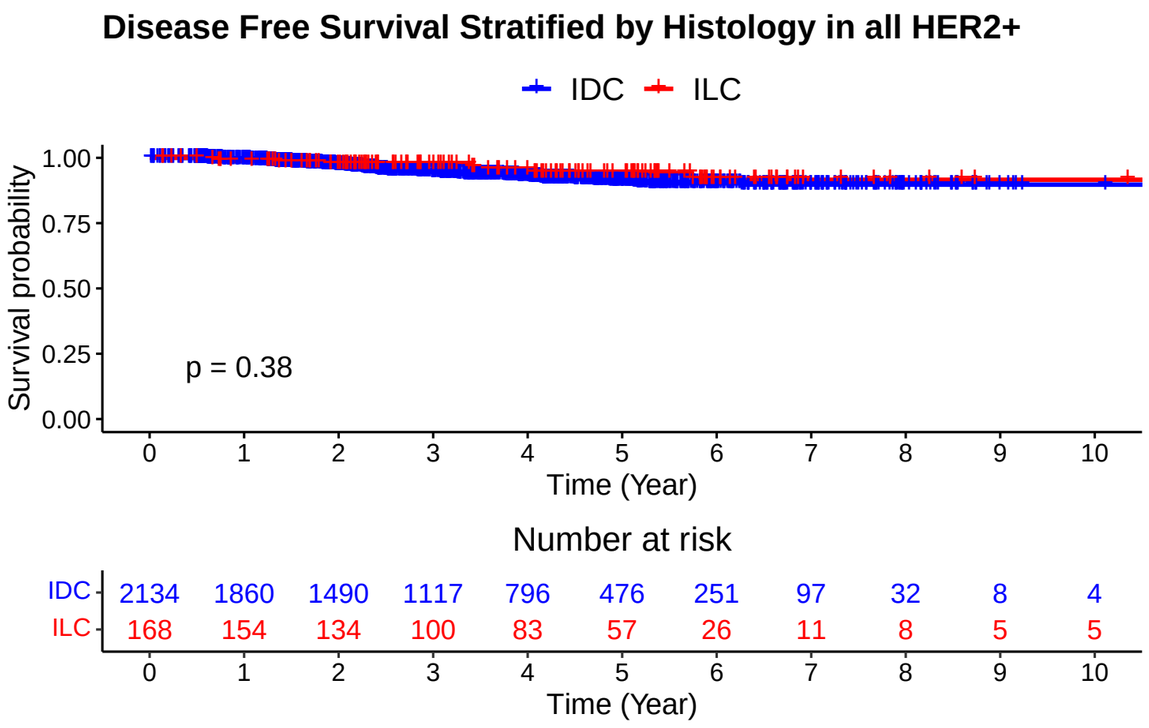

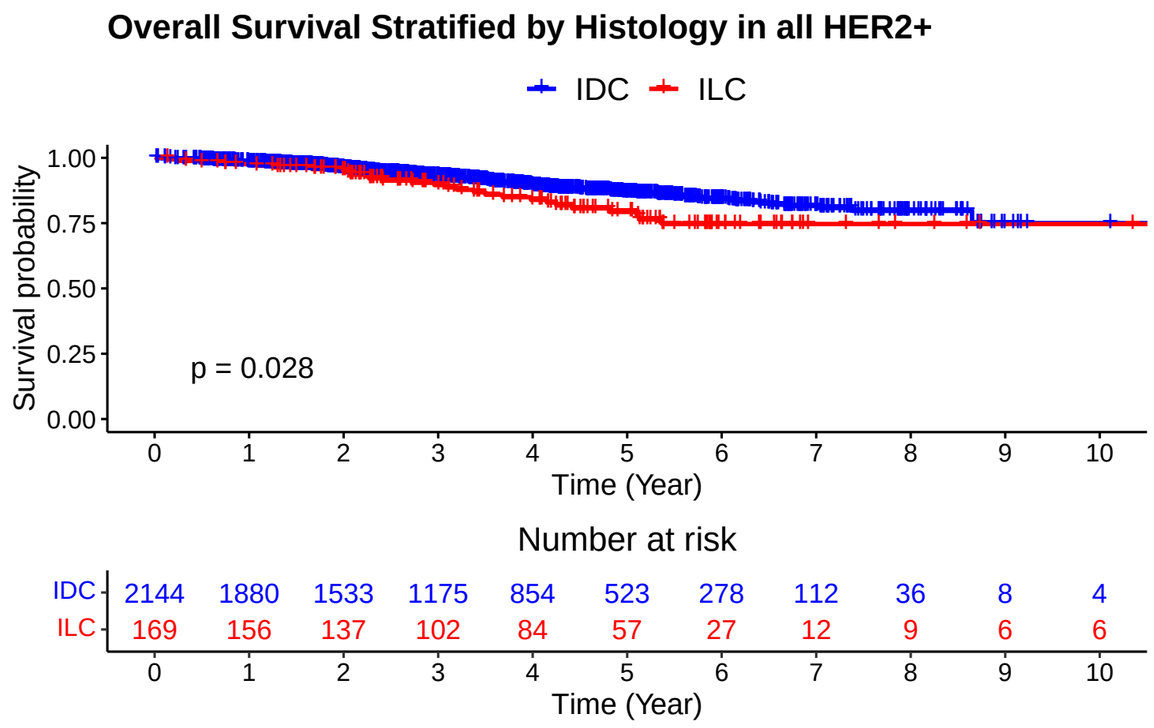

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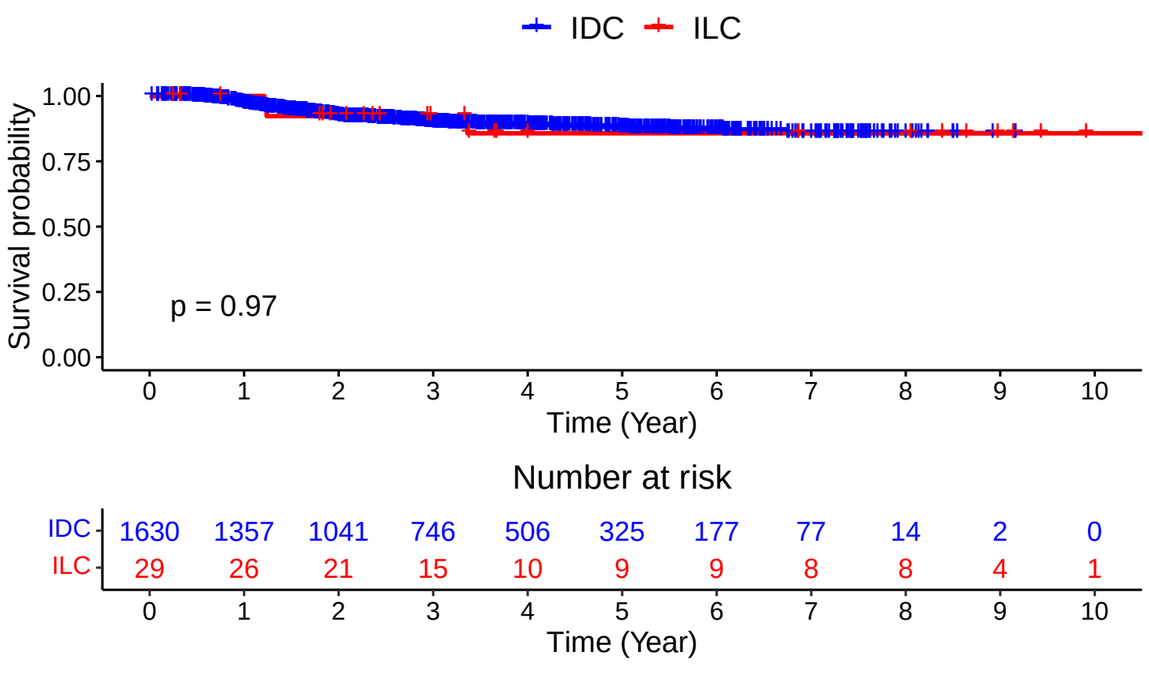
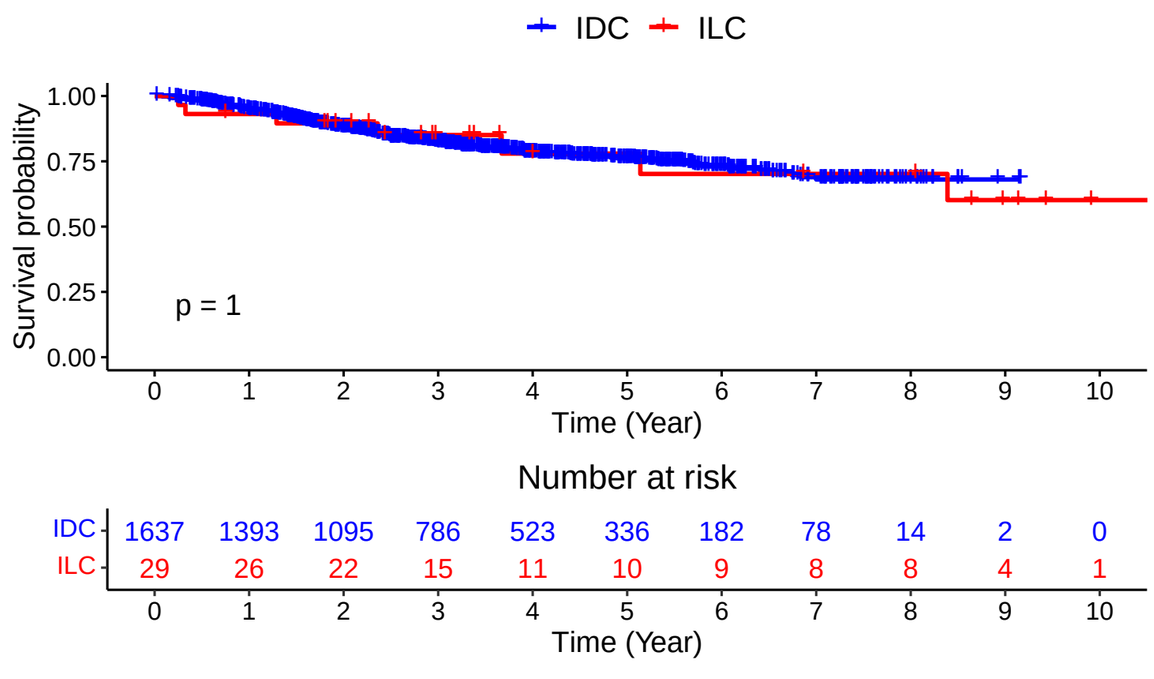
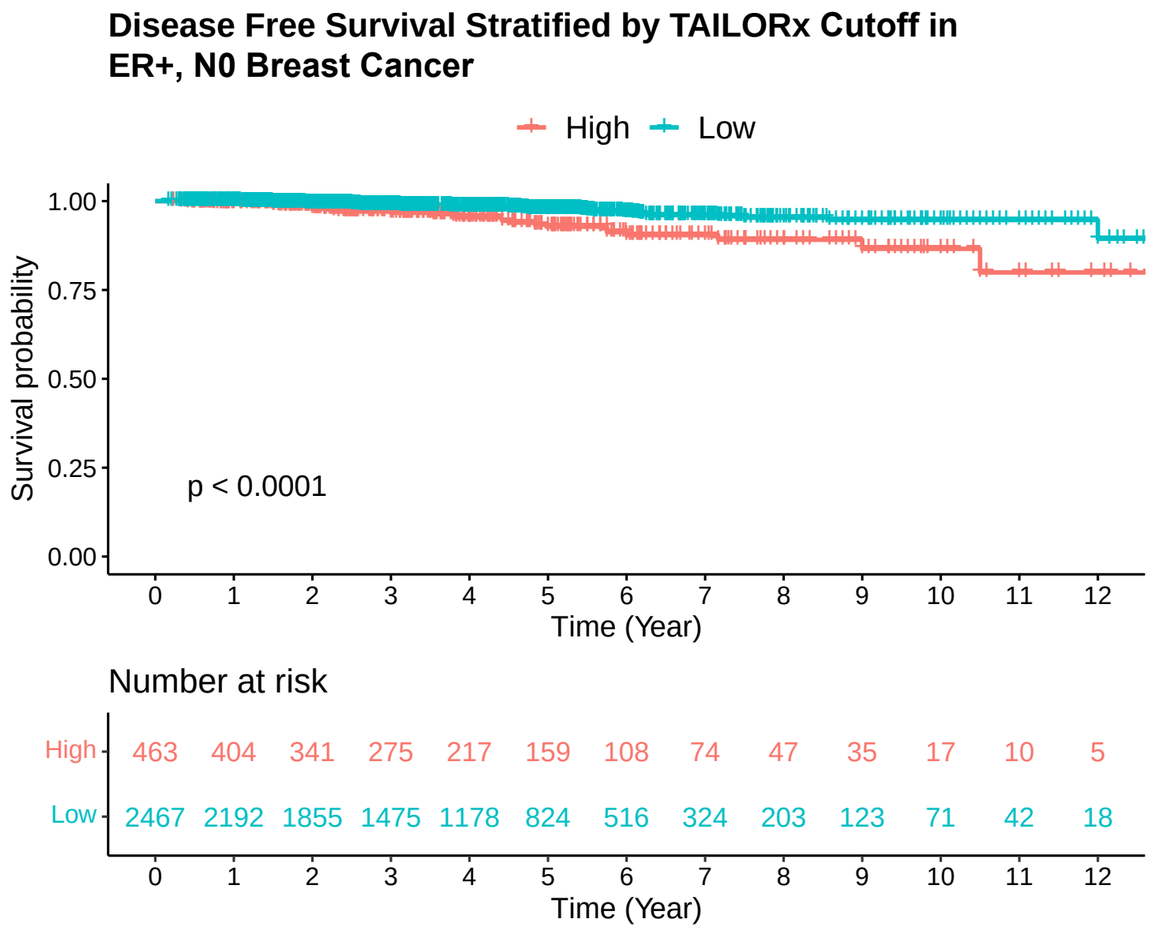
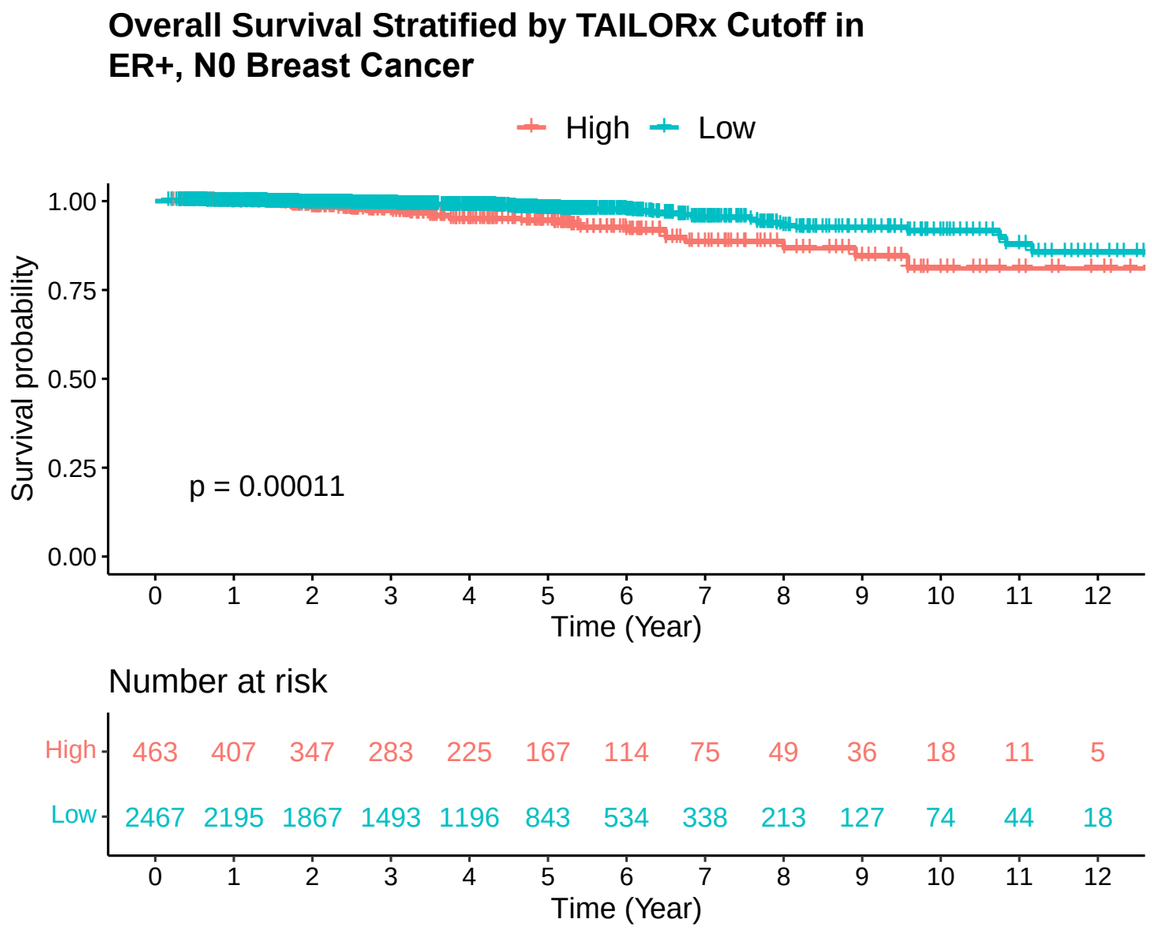




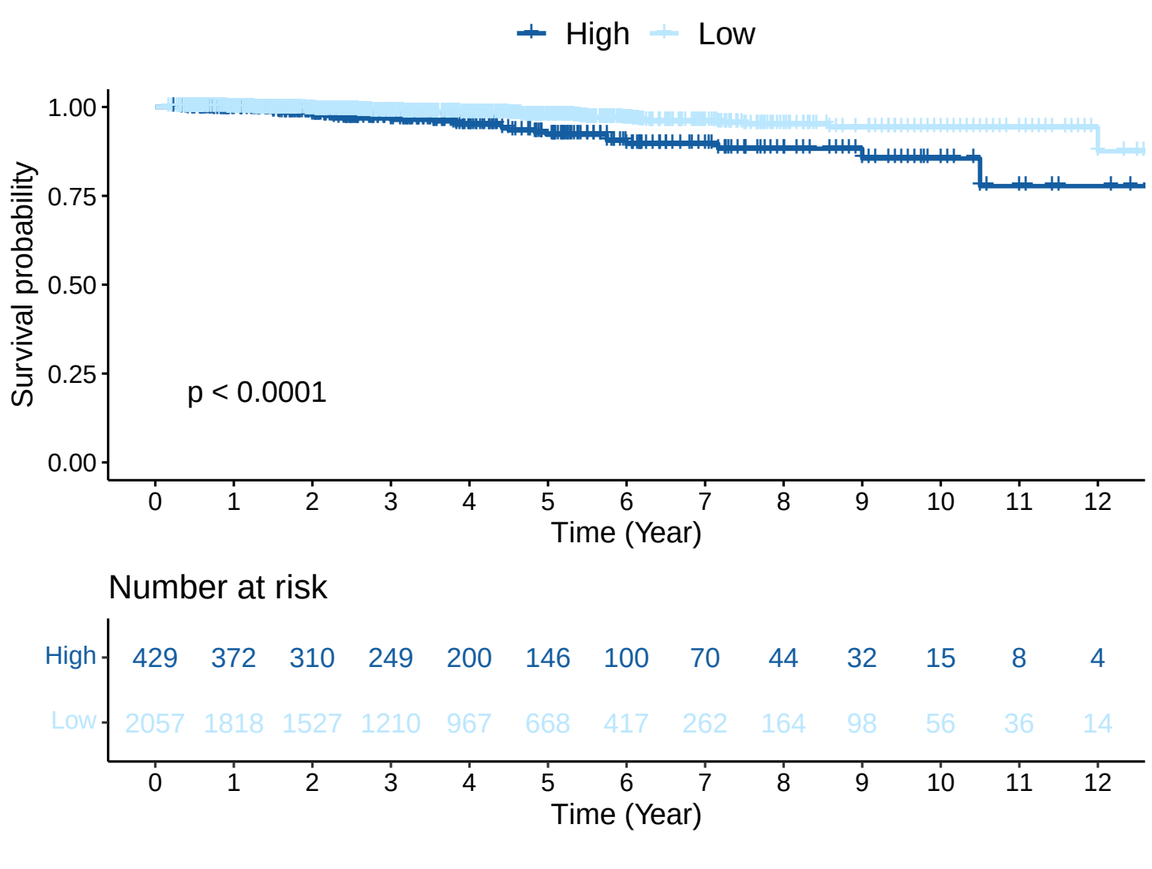
Supplementary Figure 3A:
Survival curves stratified by OncotypeDX TAILORx Cutoff in patients with node negative disease

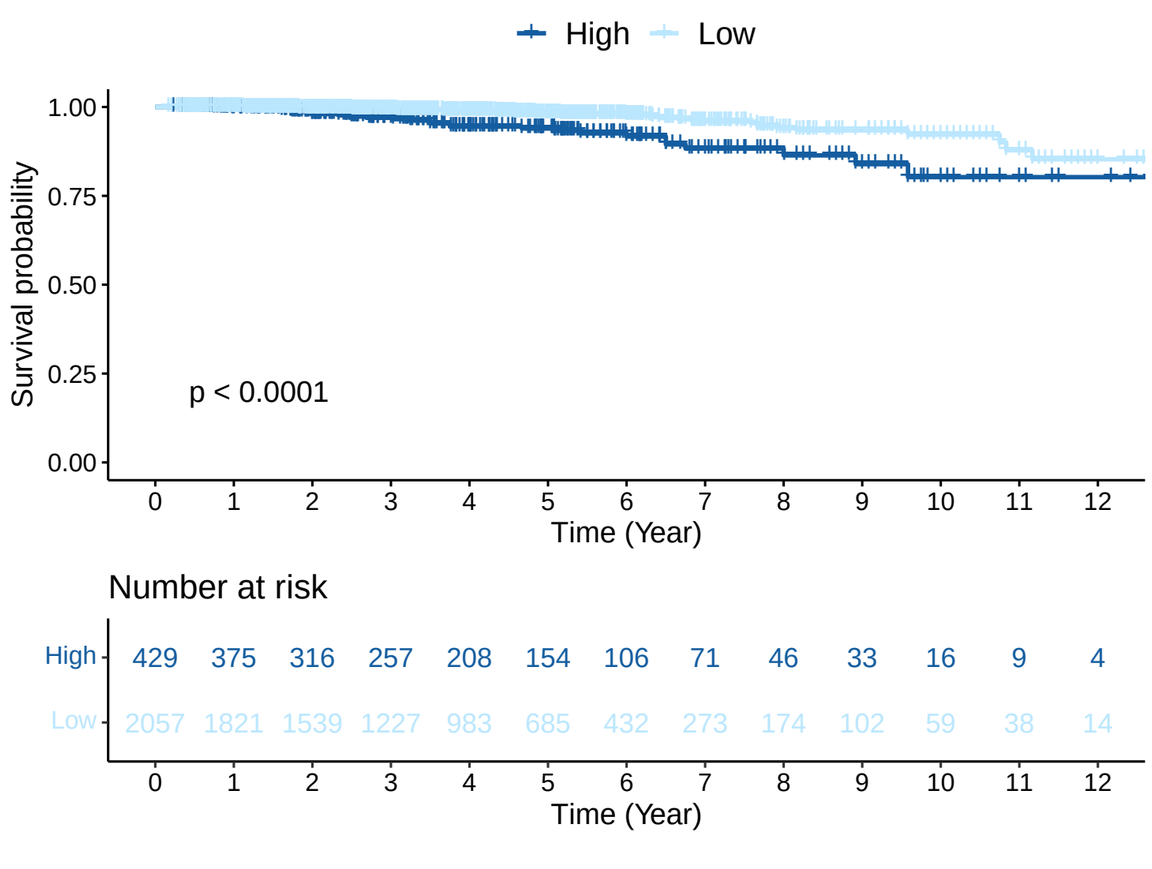
A





B





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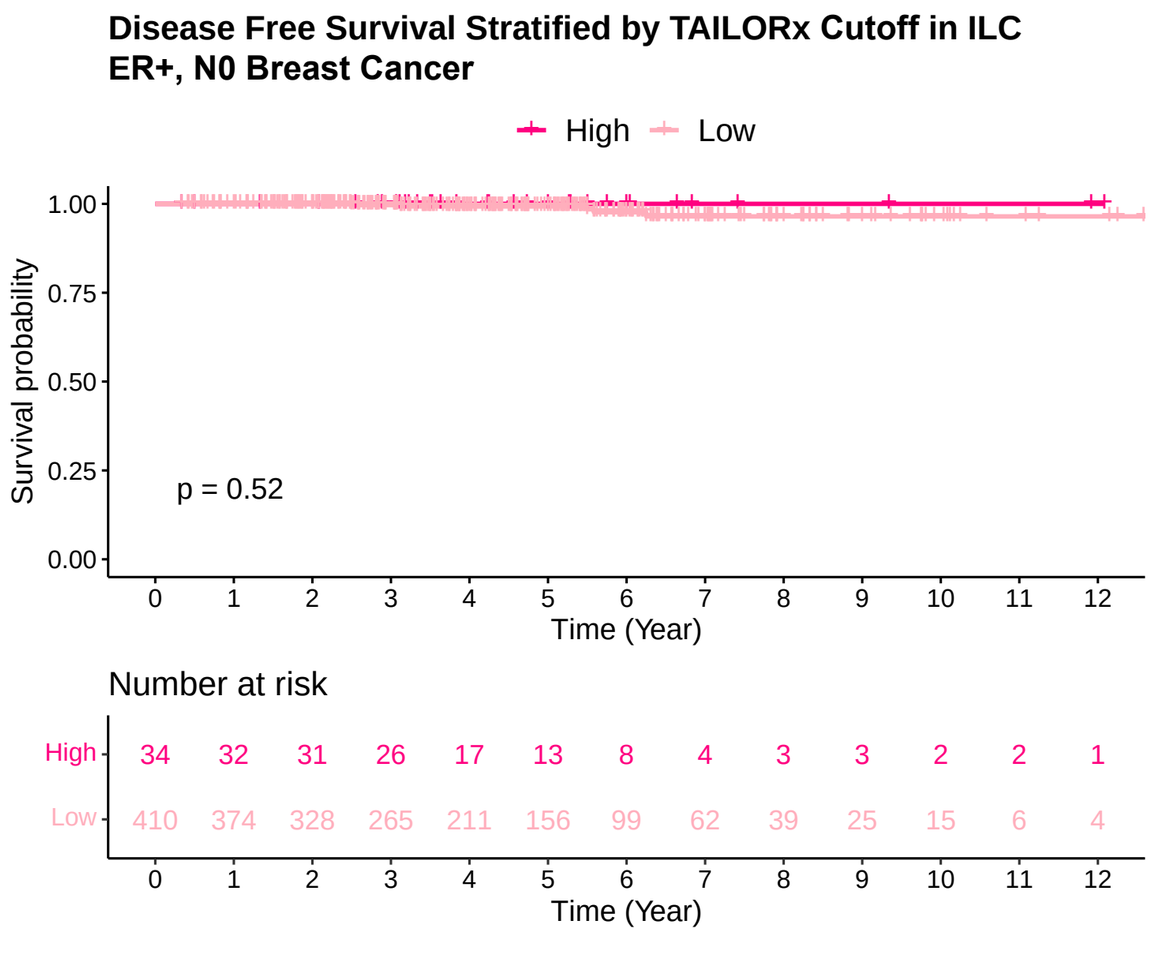
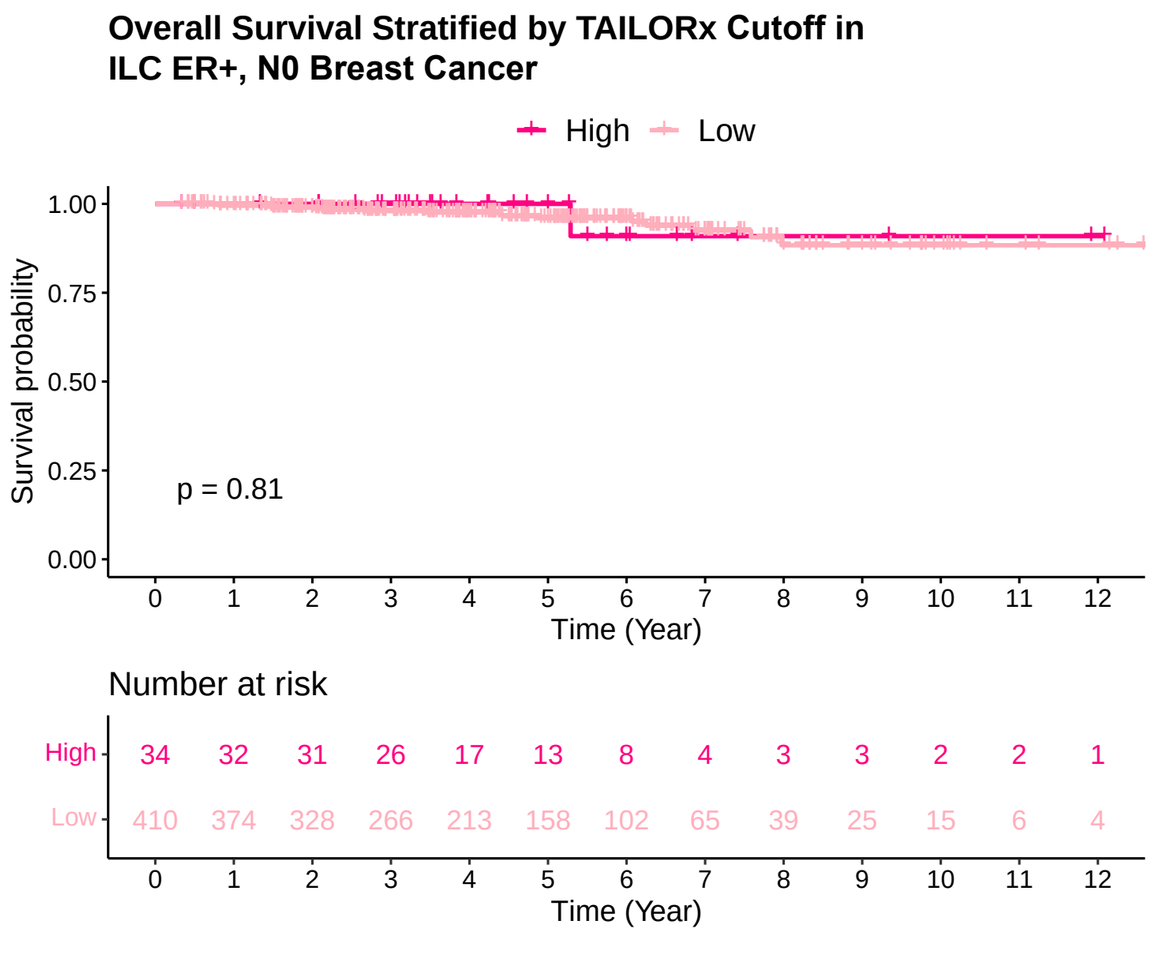
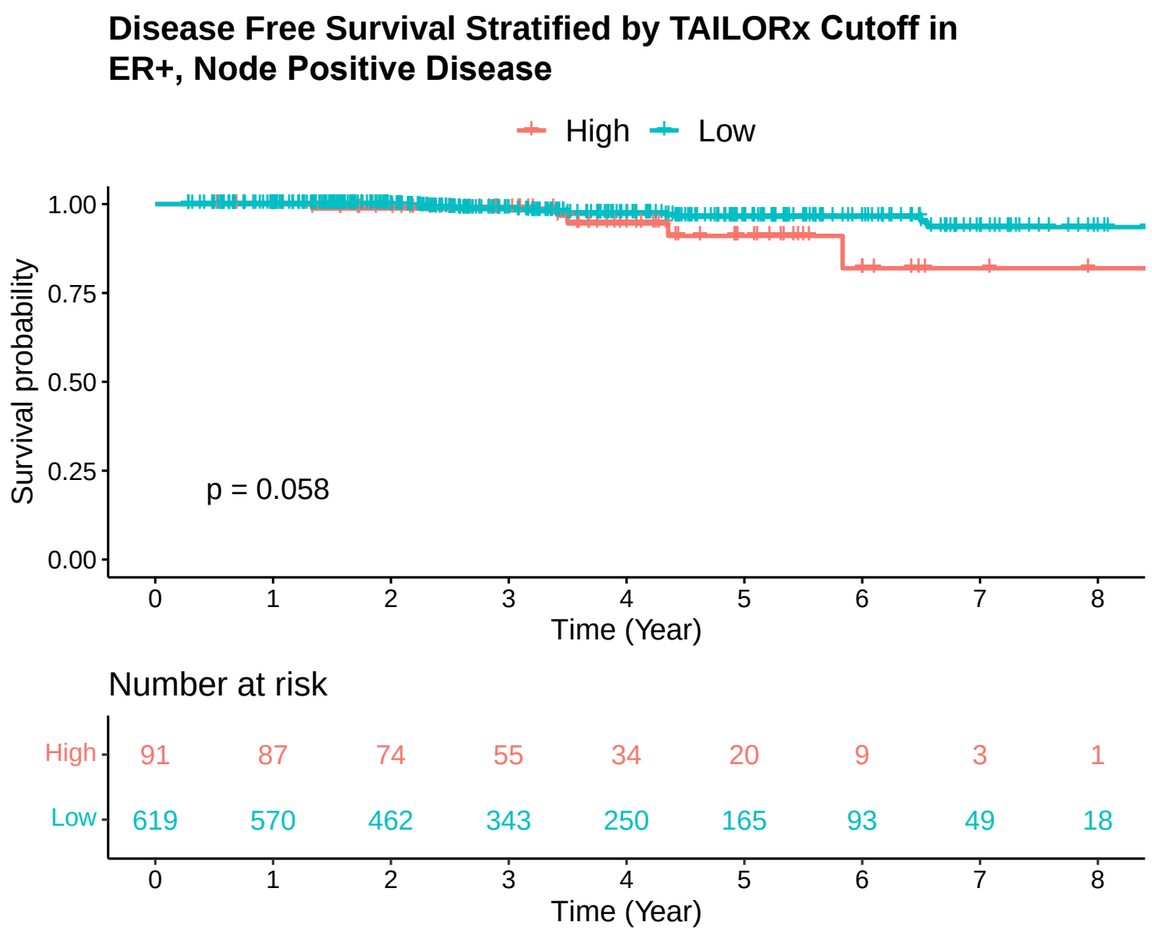
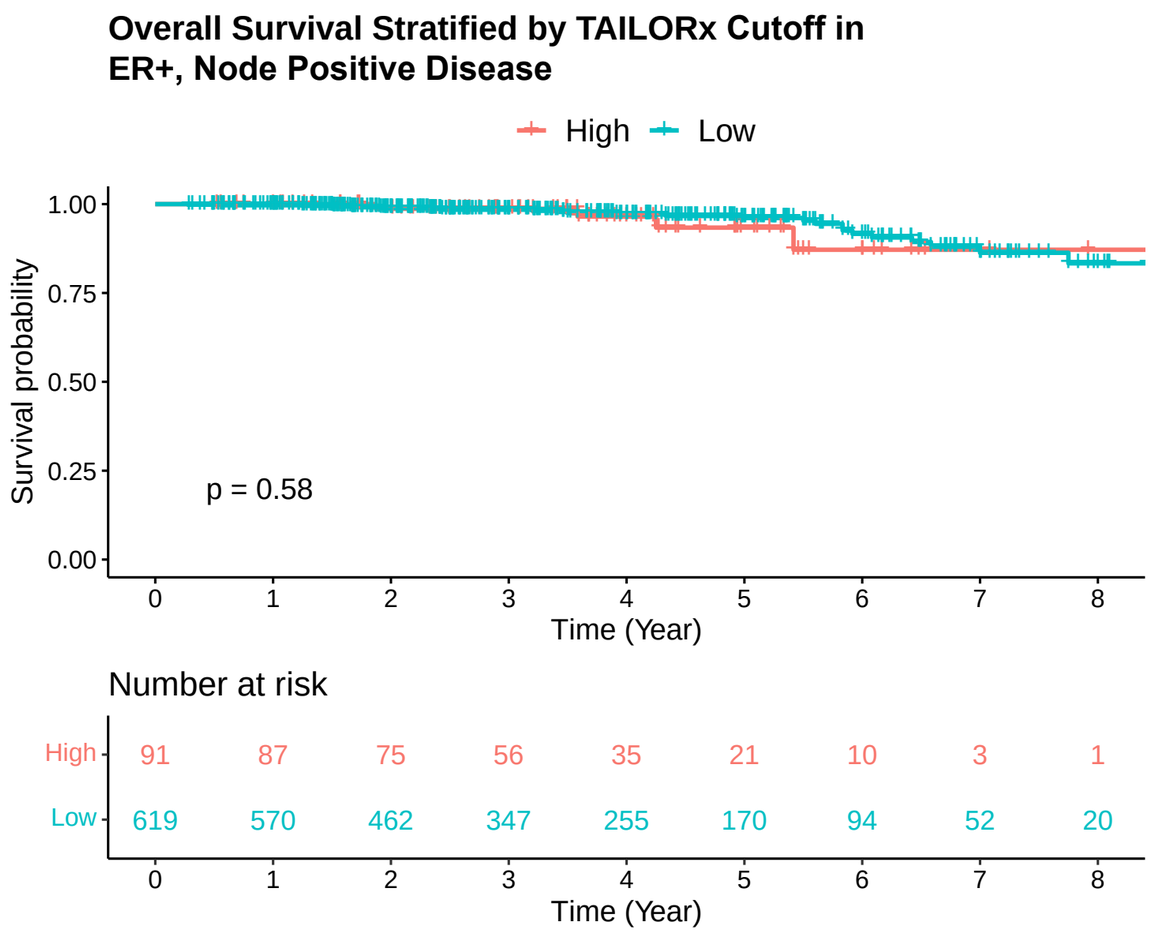




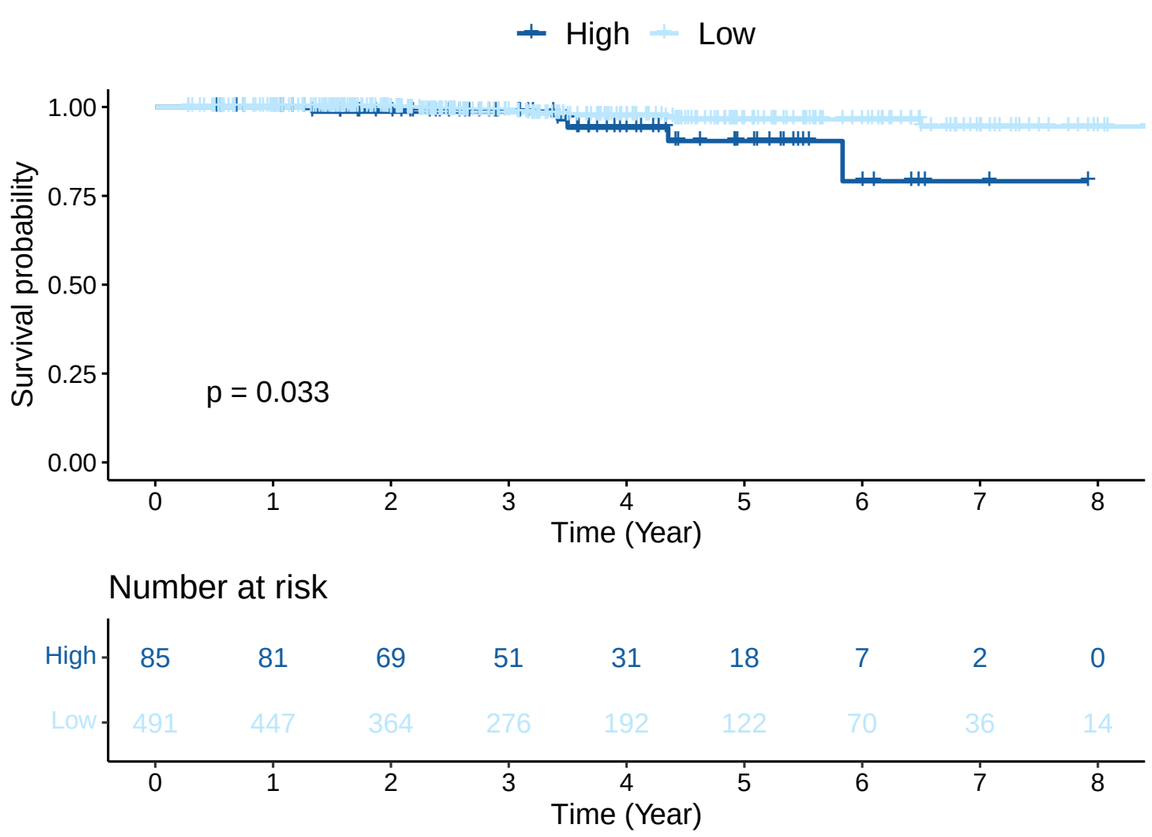
Supplementary Figure 3B:
Survival curves stratified by OncotypeDX TAILORx Cutoff in patients with node positive disease

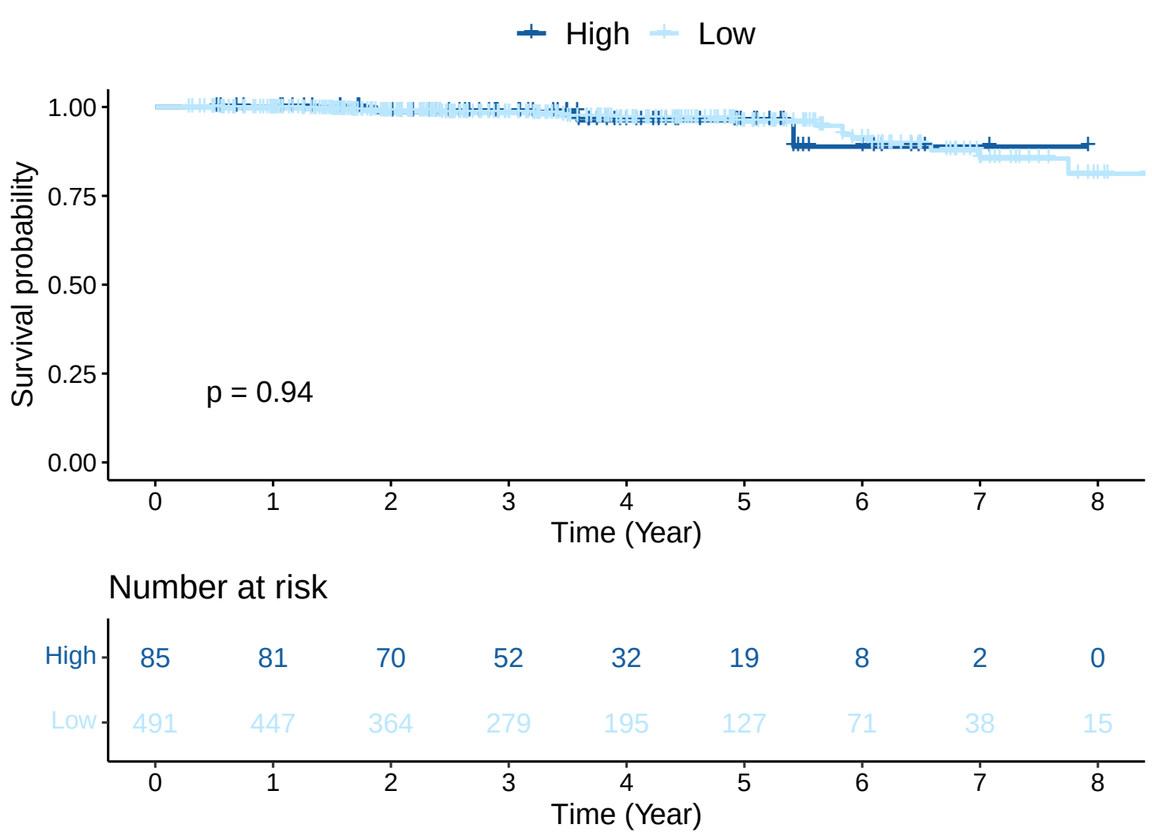
A





B





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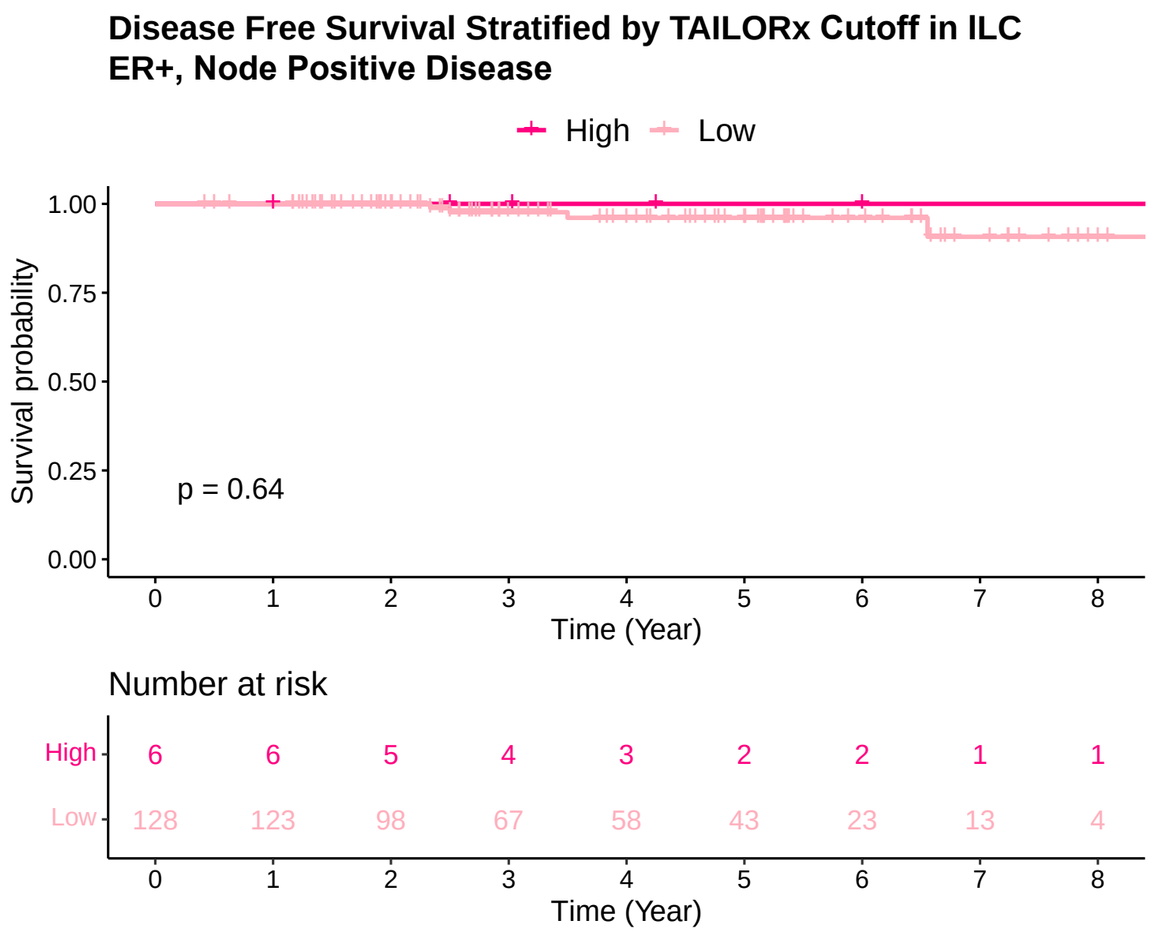
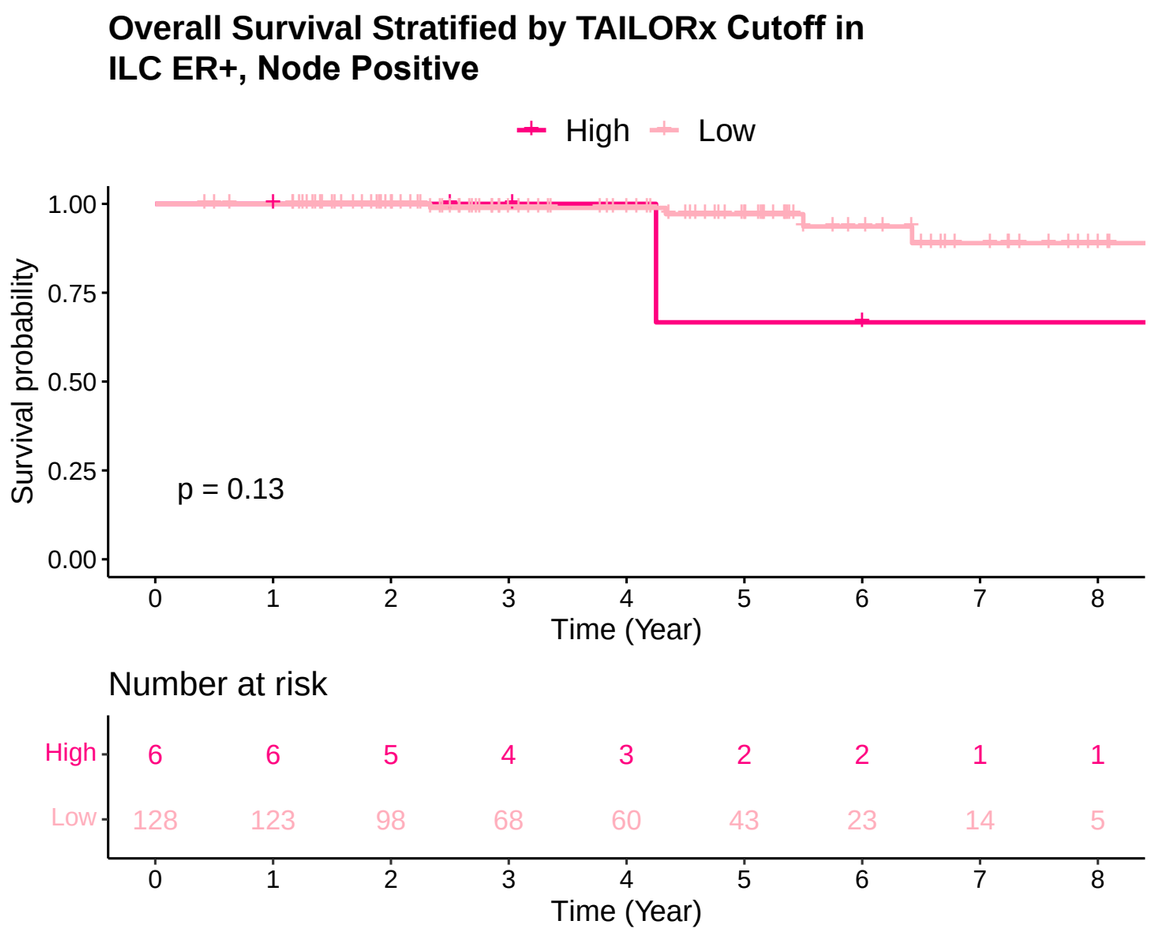
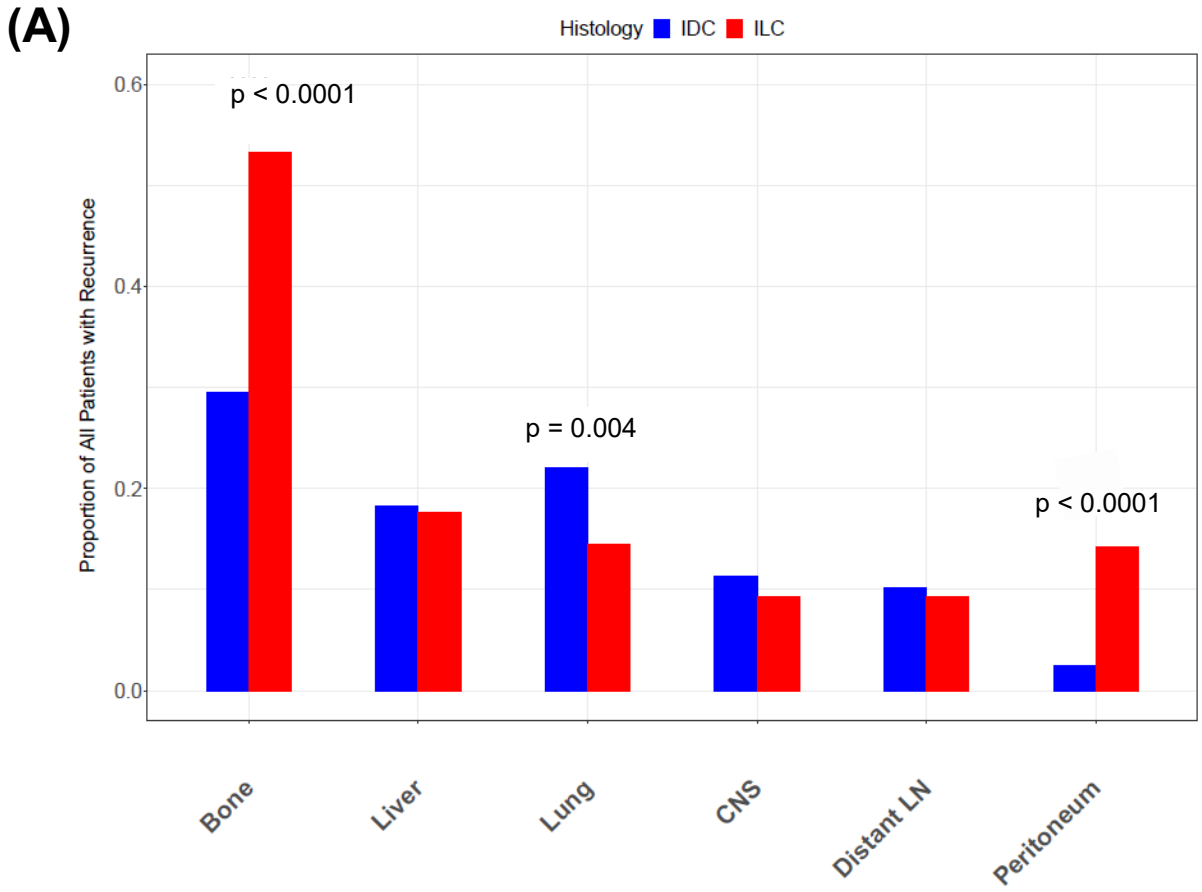
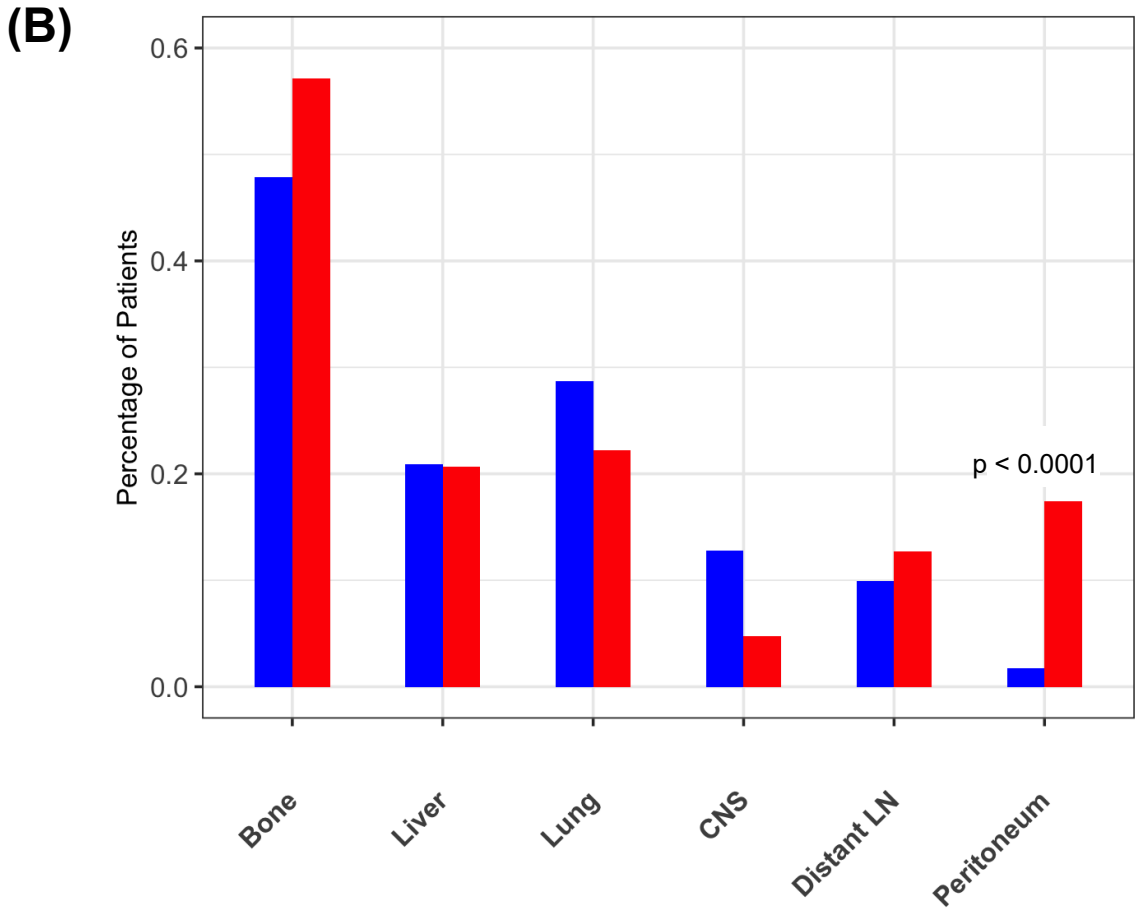




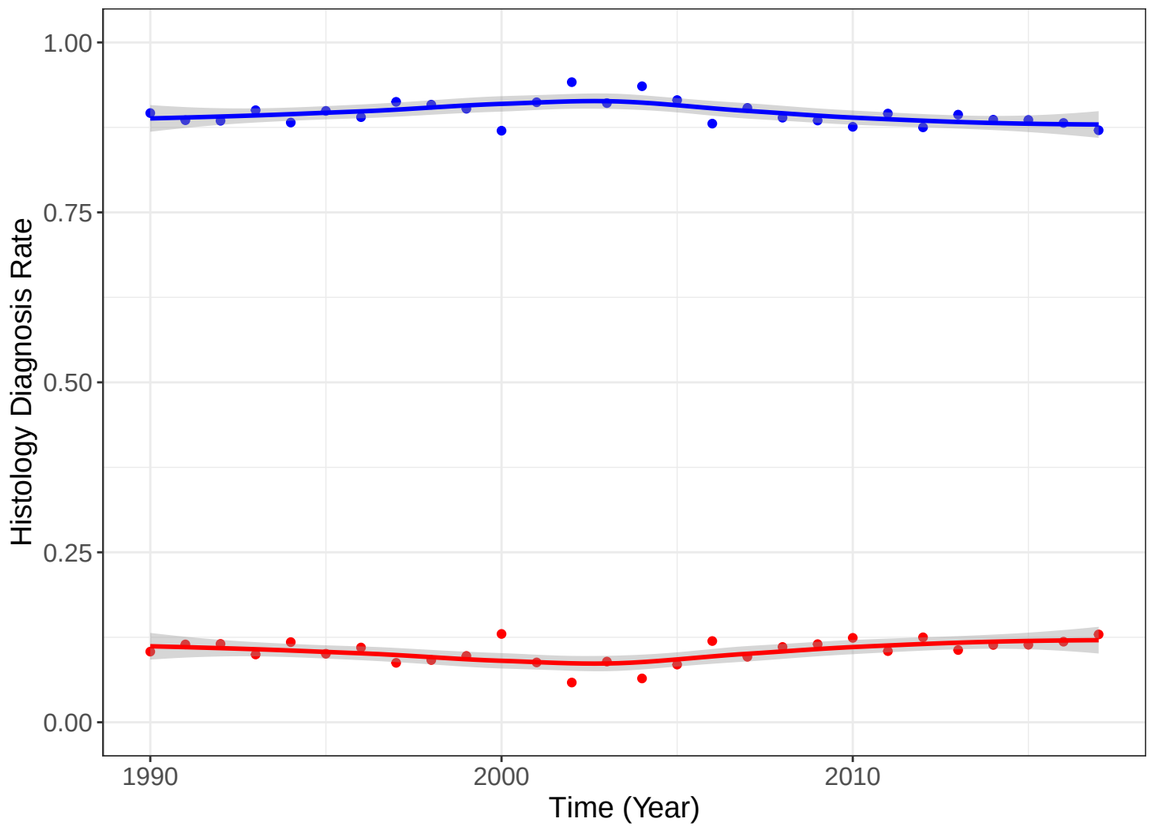
Supplementary Figure 4: (A) Site of recurrence of patients from the entire cohort; **(B)** If limiting the cohort to only those diagnosed between 1990 and 2000 to allow for a longer follow up, the site of recurrence is very similar to the result seen in (A).



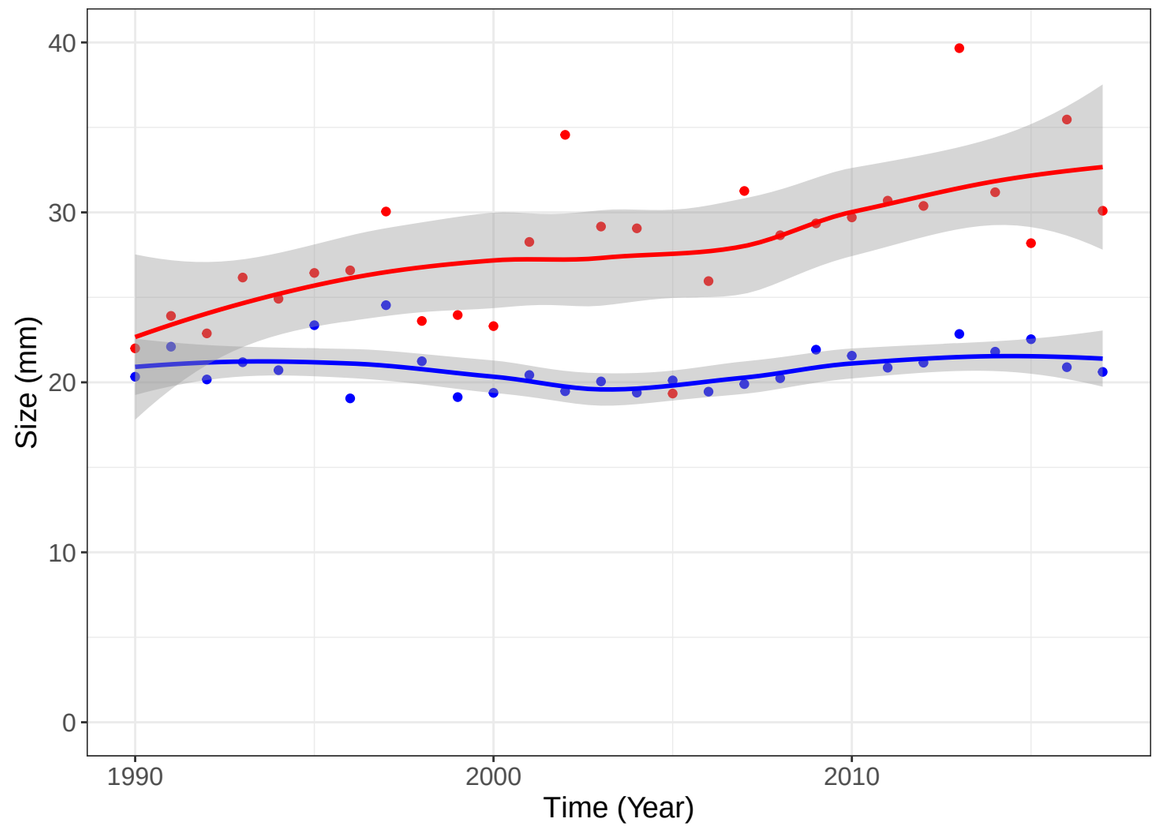


Supplementary Figure 5: Trends in histology type, tumor size and treatment types in entire cohort

A



B



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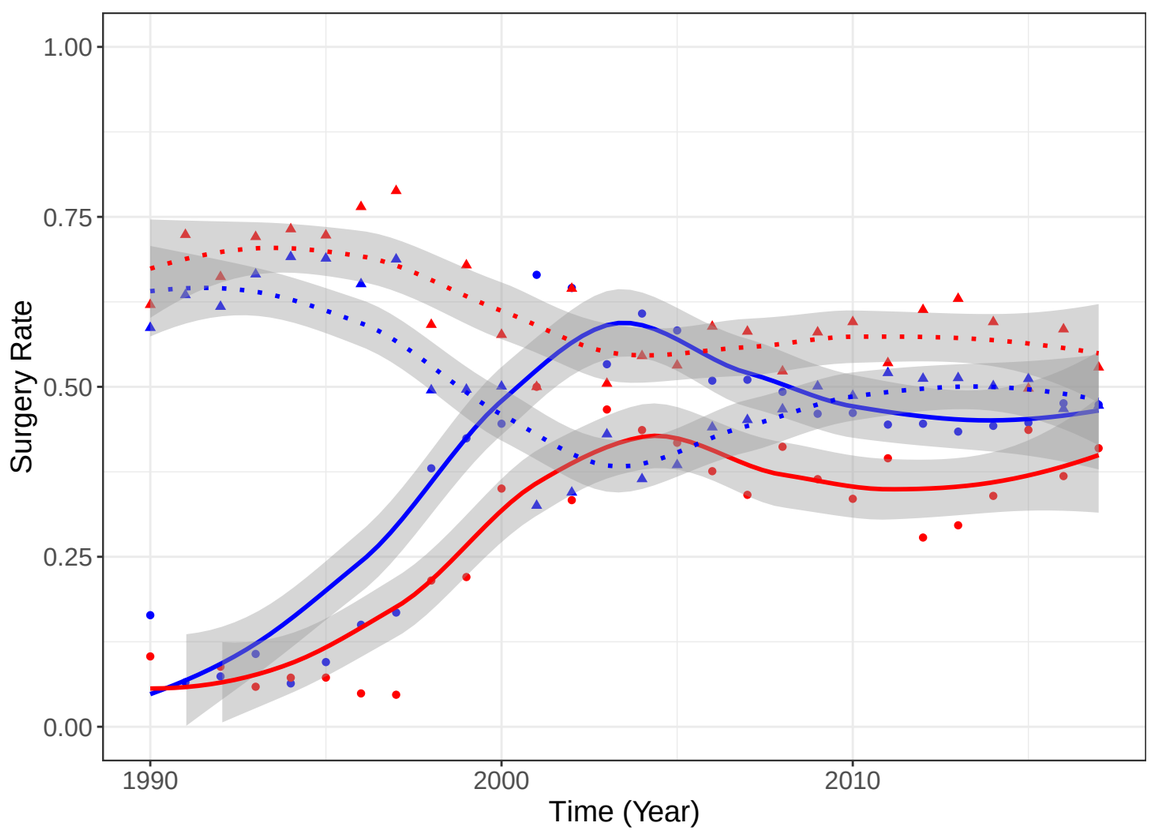

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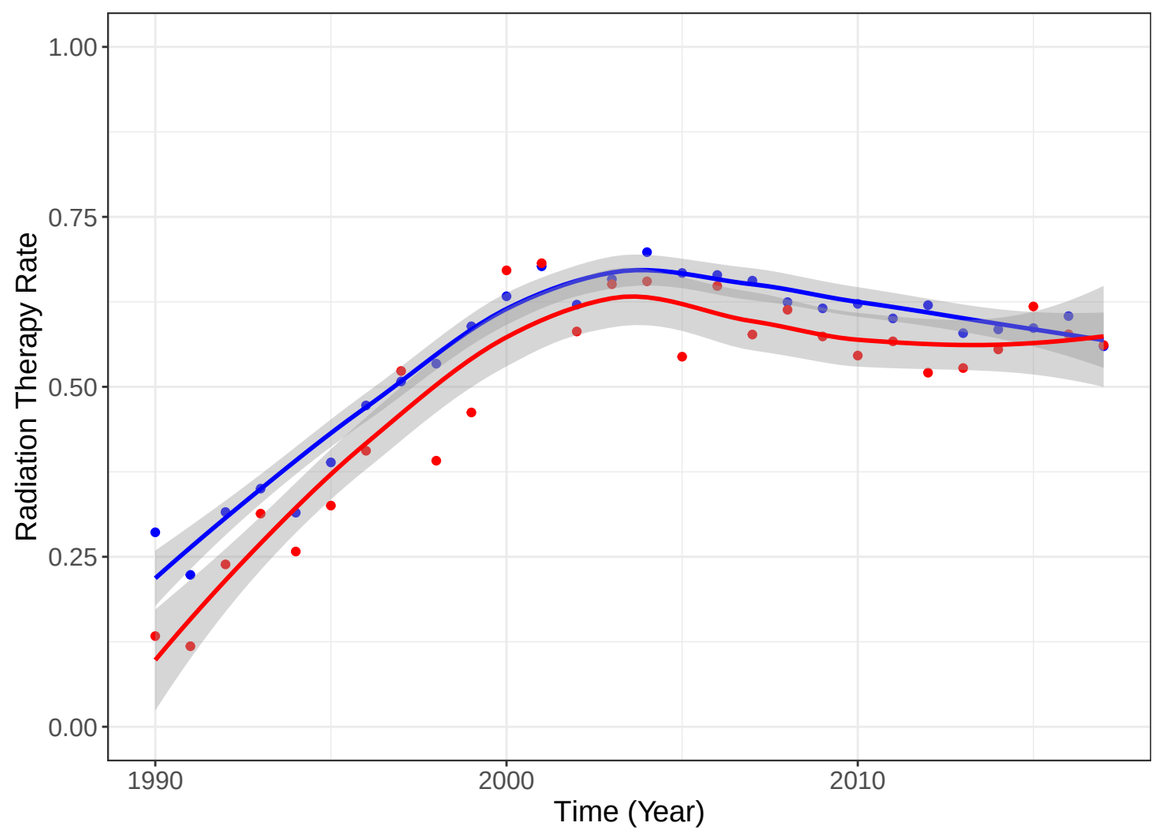

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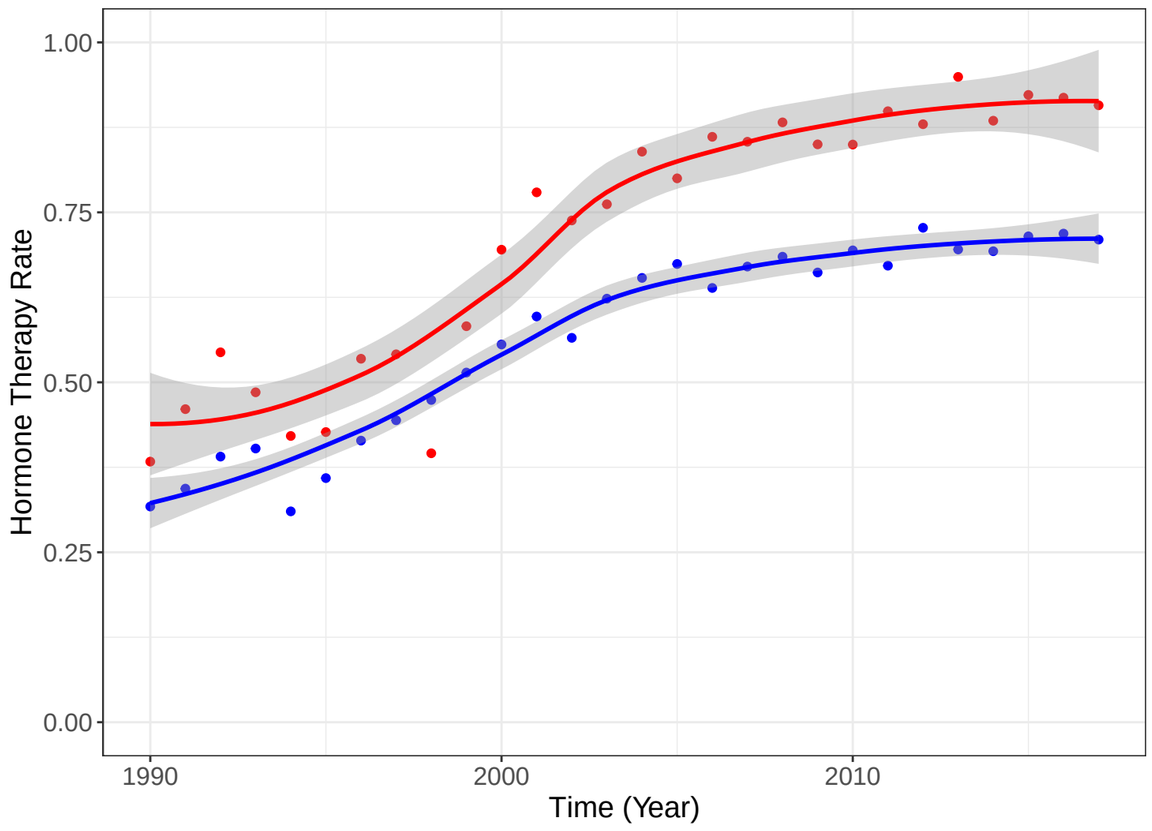

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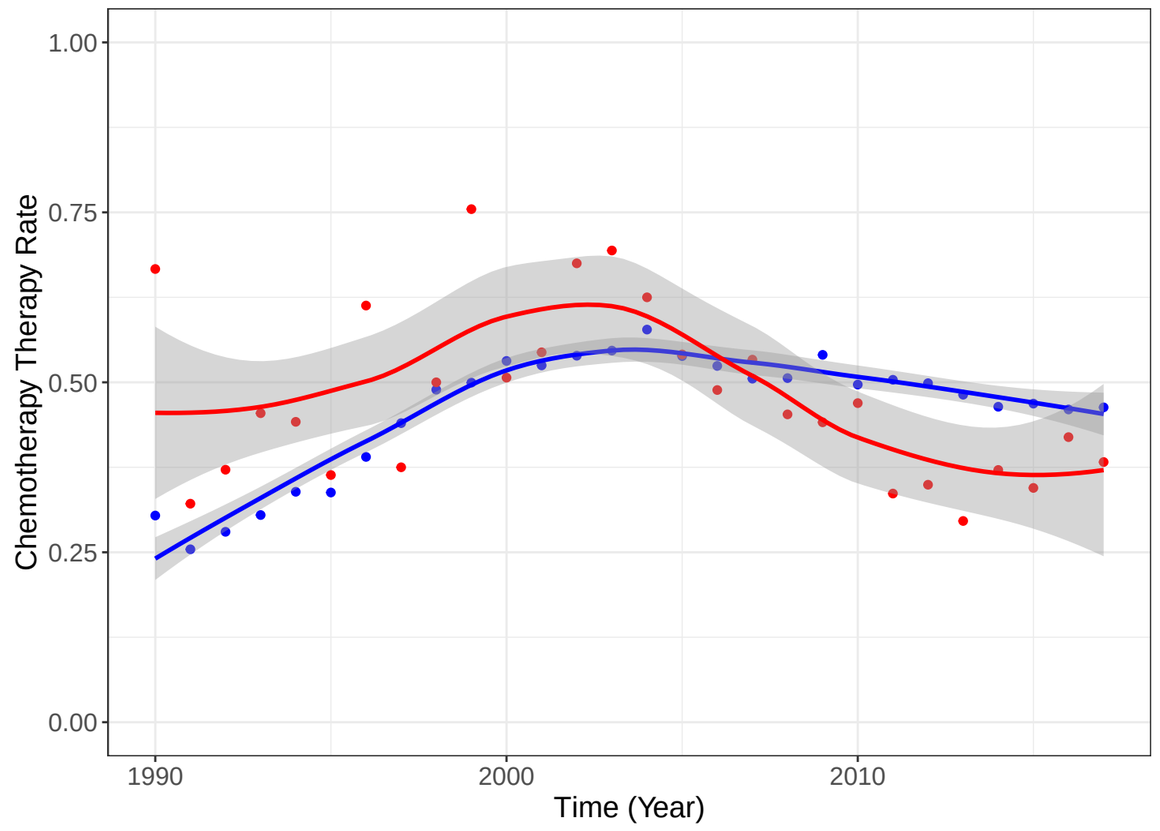

Supplementary Figure 6: Figure summarizing the key findings of the study.