

Appendix A

Table 1. Overall survival by patient's characteristics.

	Overall survival, %				p
	N (events)	12m	60m	120m	
All patients	653 (62)	99.8	91.9	81.2	
Age, years					
<50	159 (17)	100.0	88.2	77.7	0.39
≥50	494 (45)	99.8	93.1	82.4	
cT					
cT1	430 (36)	100.0	93.7	81.6	0.014
cT2	197 (21)	99.5	90.3	82.0	
cT3	26 (5)	100.0	74.3		
cN					
cN0	519 (39)	100.0	94.0	83.1	0.003
cN1	134 (23)	99.3	84.3	74.4	
Stage					
I	372 (26)	100.0	95.5	83.7	<0.05
II	268 (32)	99.6	88.0	79.1	
III	13 (4)	100.0	74.0		
Frozen section before IORT?					
Yes	596 (59)	99.8	92.2	81.4	0.61
No	53 (2)	100.0	95.0		
Was margin extension performed after IORT?					
Yes	151 (17)	100.0	88.7	82.7	0.22
No	495 (45)	99.8	93.0	81.0	
Final paraffin "R" situation					
R0	600 (56)	99.8	92.6	81.8	0.13
R1	52 (6)	100.0	81.5	74.7	
Applicator diameter, cm					

≤3	100 (9)	100.0	91.5	84.7	
≥3.5	509 (45)	99.8	92.1	81.3	0.53
Hormone therapy					
No	105 (14)	100.0	85.5	72.2	
Yes	548 (48)	99.8	93.0	82.6	0.029
Adjuvant chemotherapy					
No	348 (28)	100.0	94.2	85.7	
Yes	305 (34)	99.7	89.1	72.0	0.018
Fractionation					
Hypofractionation (>2Gy/Fx)	159 (3)	100.0	93.6		
Normofractionation (1.8- 2Gy/Fx)	492 (59)	99.8	91.2	80.5	0.058
(y)pT					
(y)pT0	28 (3)	100.0	90.1		
(y)pT1	435 (39)	100.0	92.6	81.0	
(y)pT2	190 (20)	99.5	90.6	82.6	0.56
(y)pN					
(y)pN(-)	501 (36)	100.0	94.6	84.0	
(y)pN(+)	152 (26)	99.3	83.2	72.3	<0.05
Grade					
G1	91 (2)	100.0	100.0	91.7	
G2	331 (30)	99.7	92.5	84.3	
G3	164 (19)	100.0	88.3	77.1	0.036
Estrogen receptors					
Positive	549 (48)	99.8	92.9	82.3	
Negative	100 (14)	100.0	86.0	74.0	0.029
Progesterone receptors					
Positive	499 (43)	99.8	93.2	82.1	
Negative	148 (19)	100.0	87.2	77.7	0.016
HER2					
Positive	105 (13)	100.0	89.8	77.6	
Negative	540 (49)	99.8	92.3	81.7	0.25

Subtype					
Triple negative	68 (9)	100.0	86.7	72.0	
Luminal A	91 (4)	100.0	83.4		
Luminal B	80 (5)	100.0	93.5		
HER2,Luminal/HER2	95 (10)	100.0	91.4	79.0	0.53

Figure 1. Overall survival.

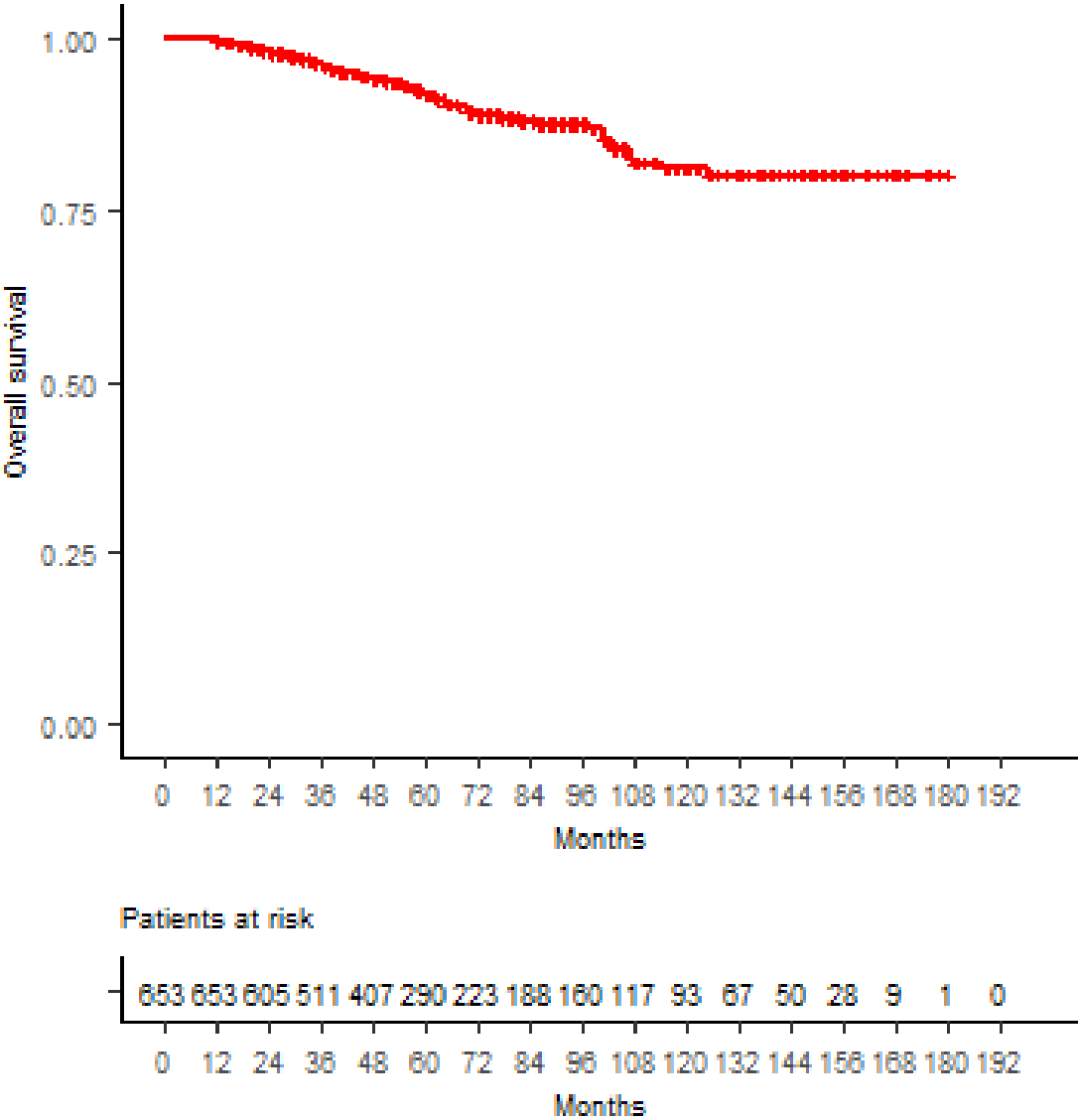


Figure 2. Overall survival according to cT.

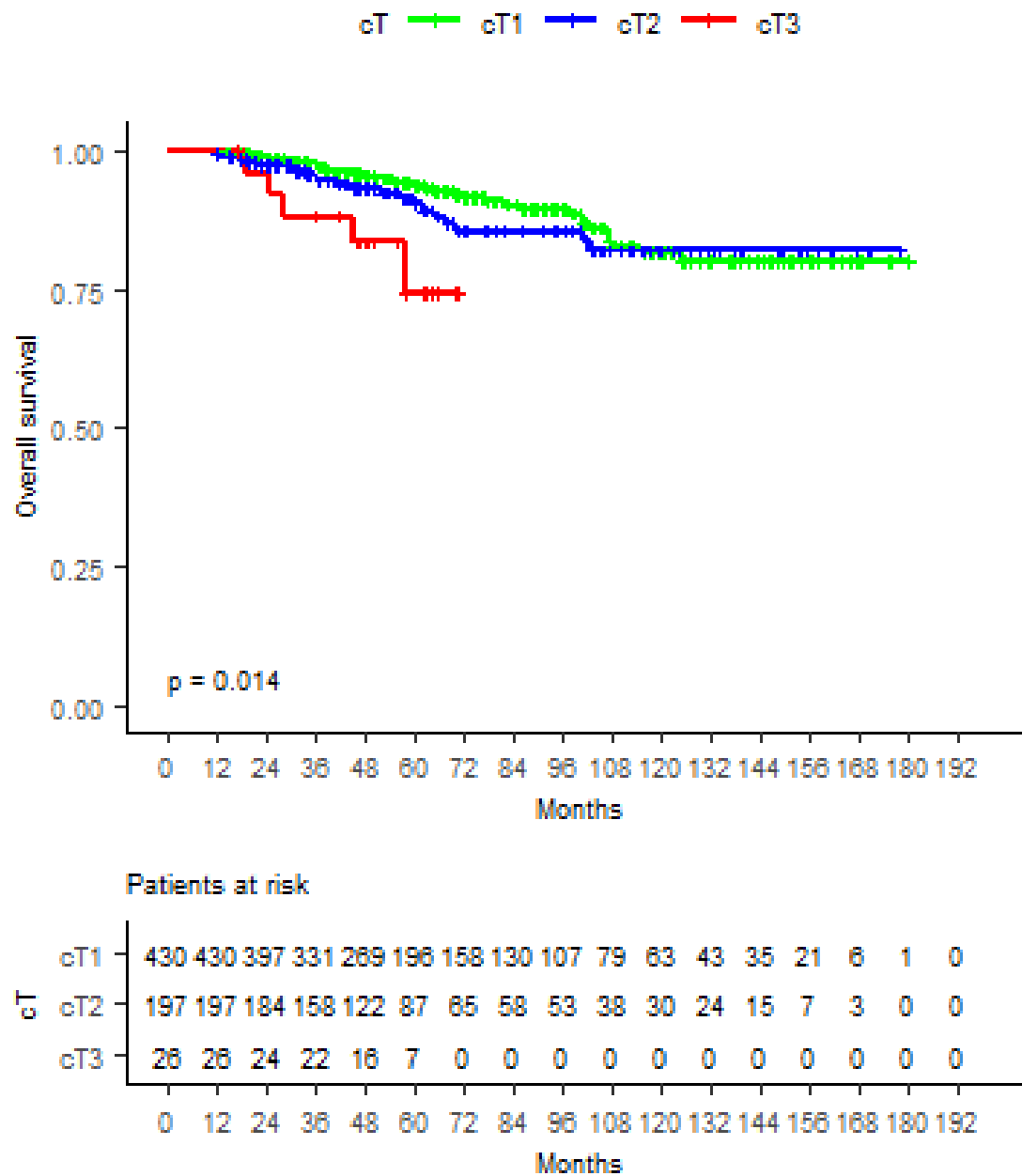


Figure 3. Overall survival according to cN.

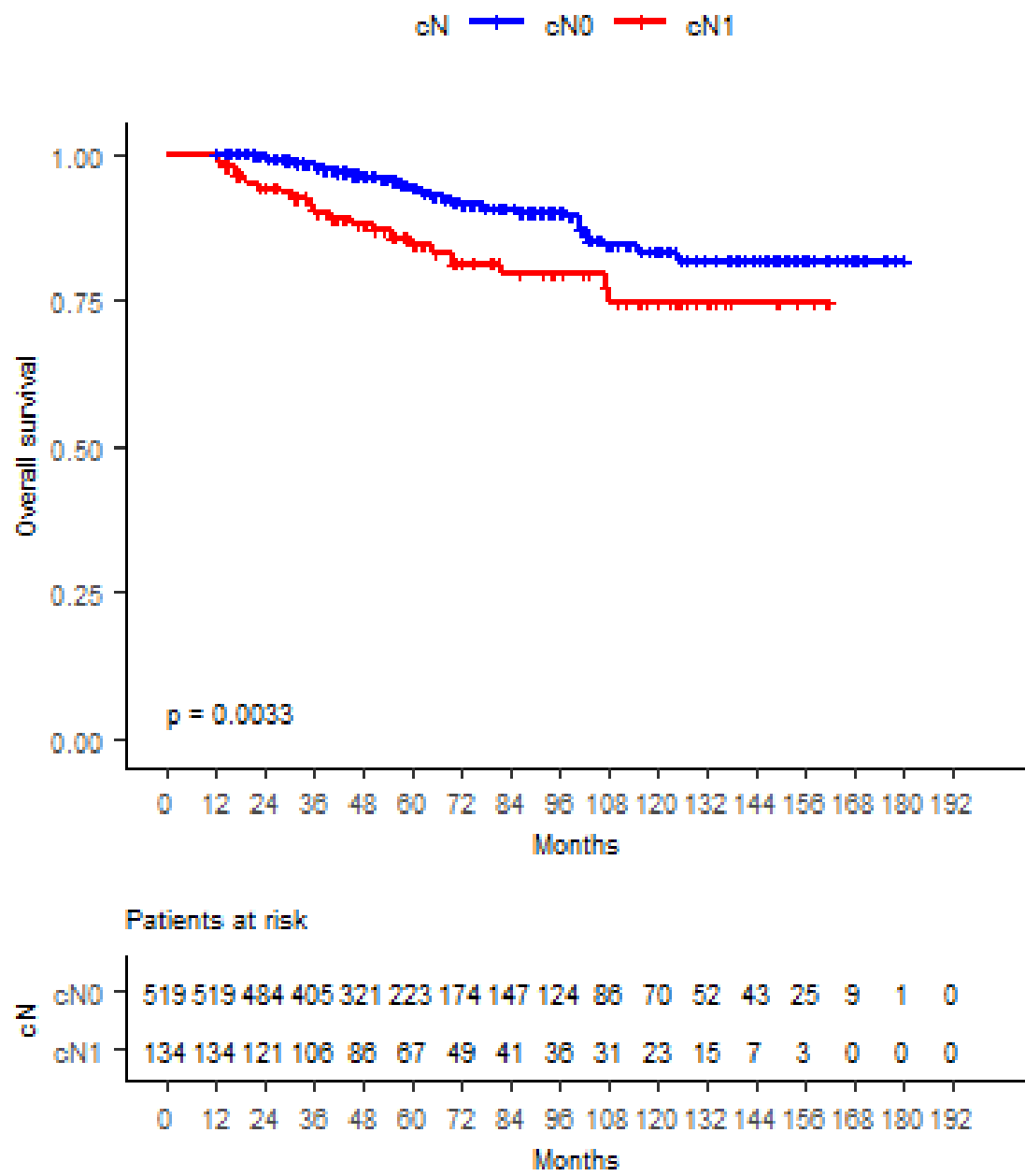


Figure 4. Overall survival according to stage.

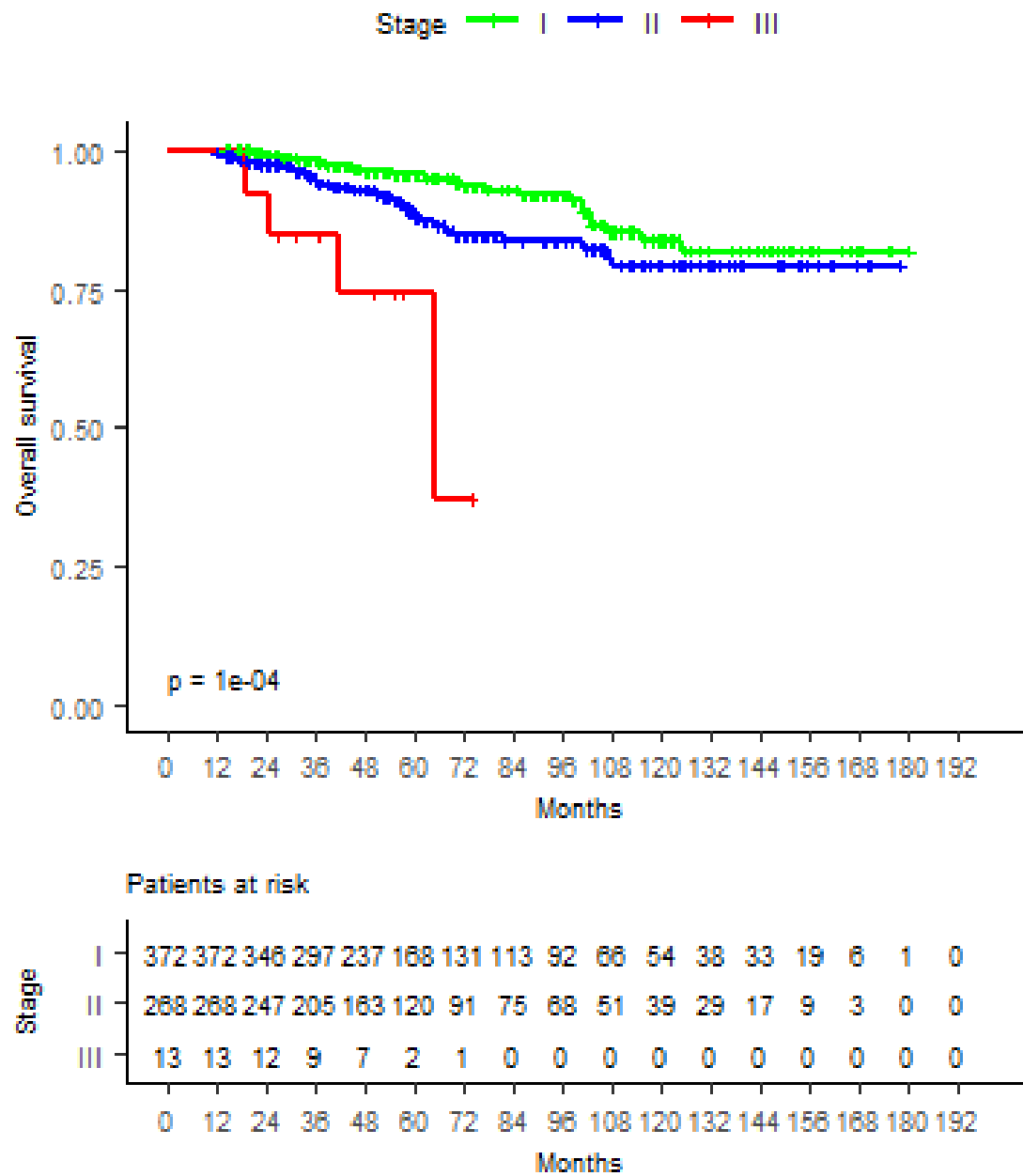


Figure 5. Overall survival with and without hormone therapy.

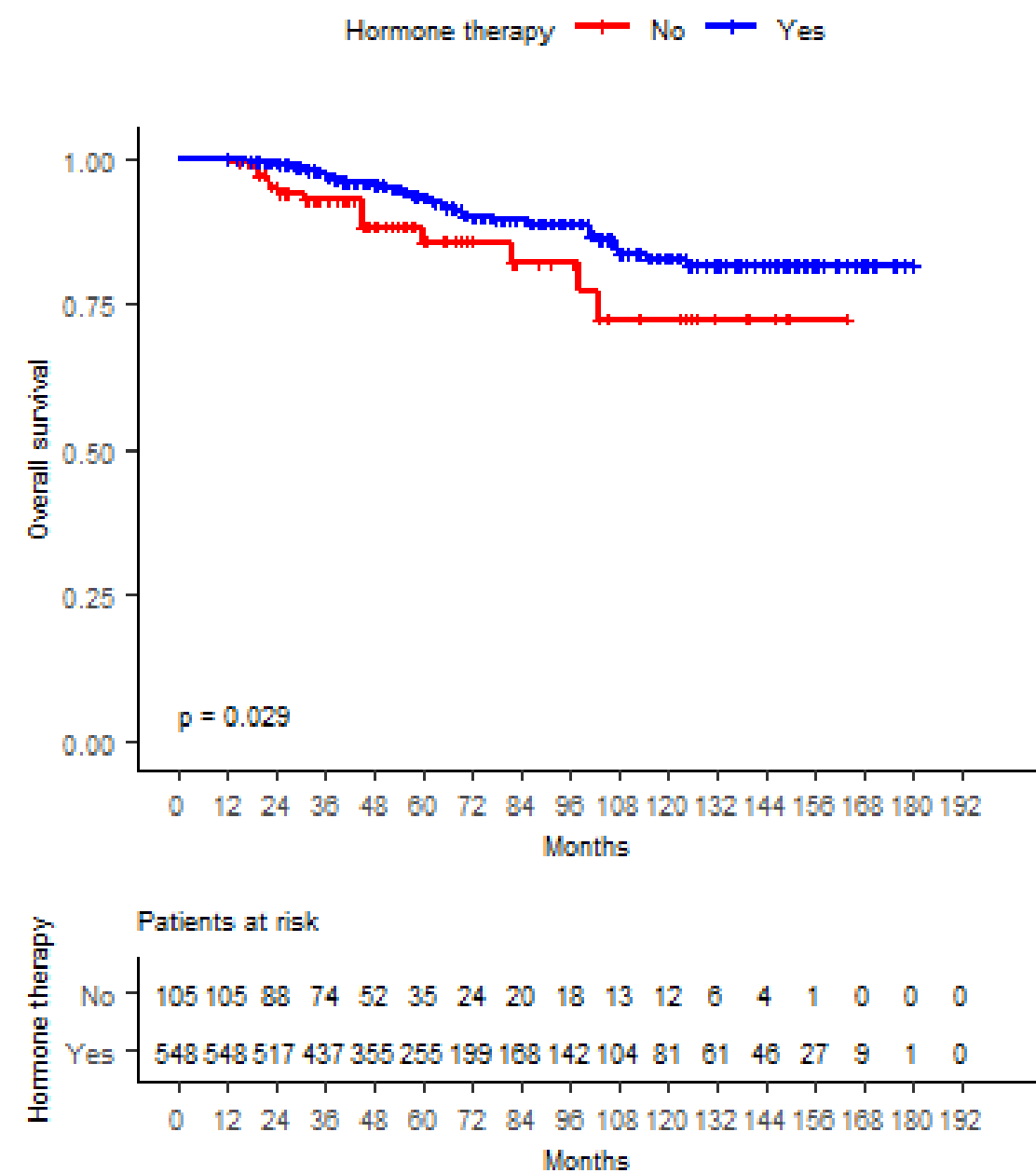


Figure 6. Overall survival with and without adjuvant chemotherapy.

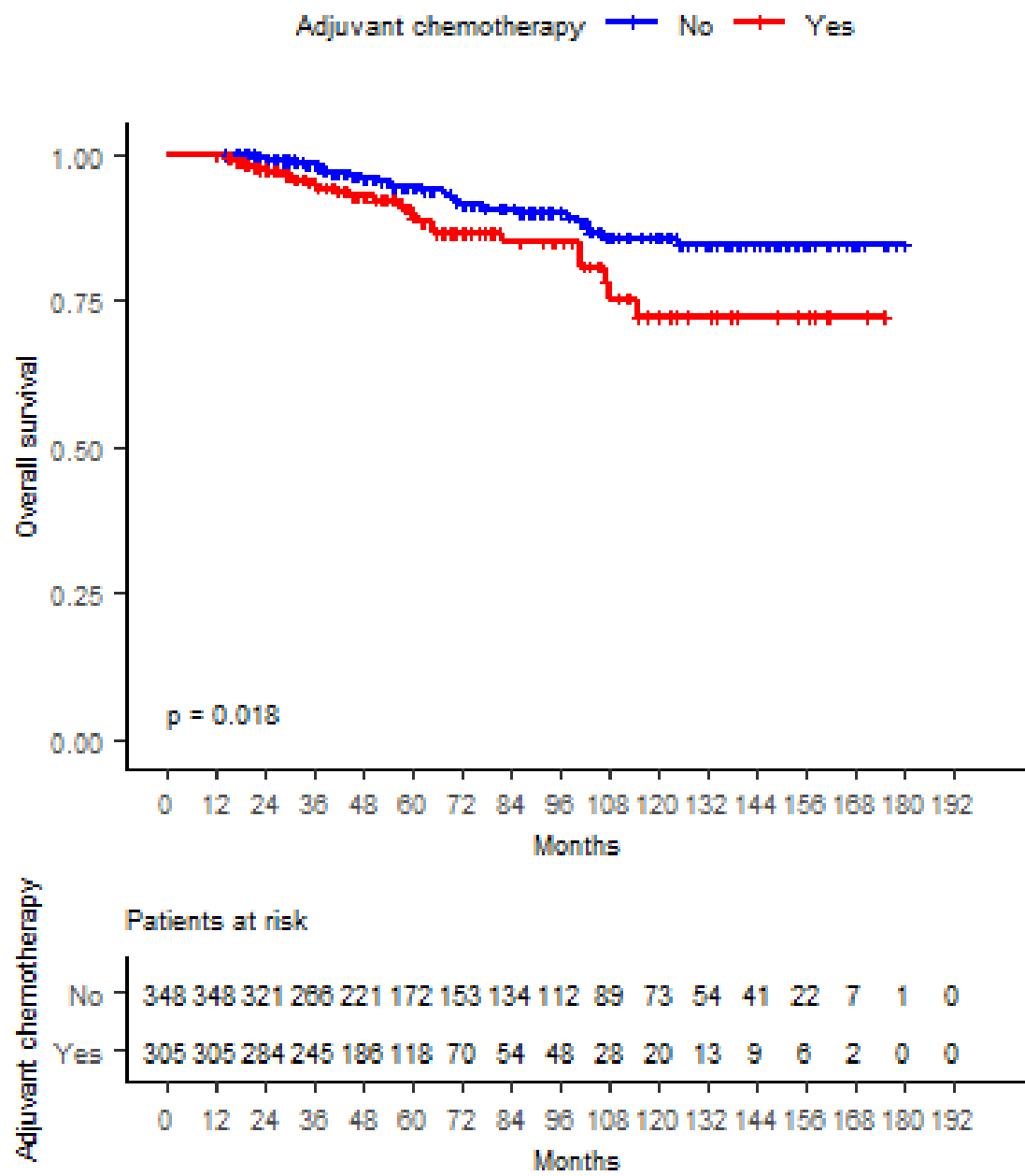


Figure 7. Overall survival according to pN.

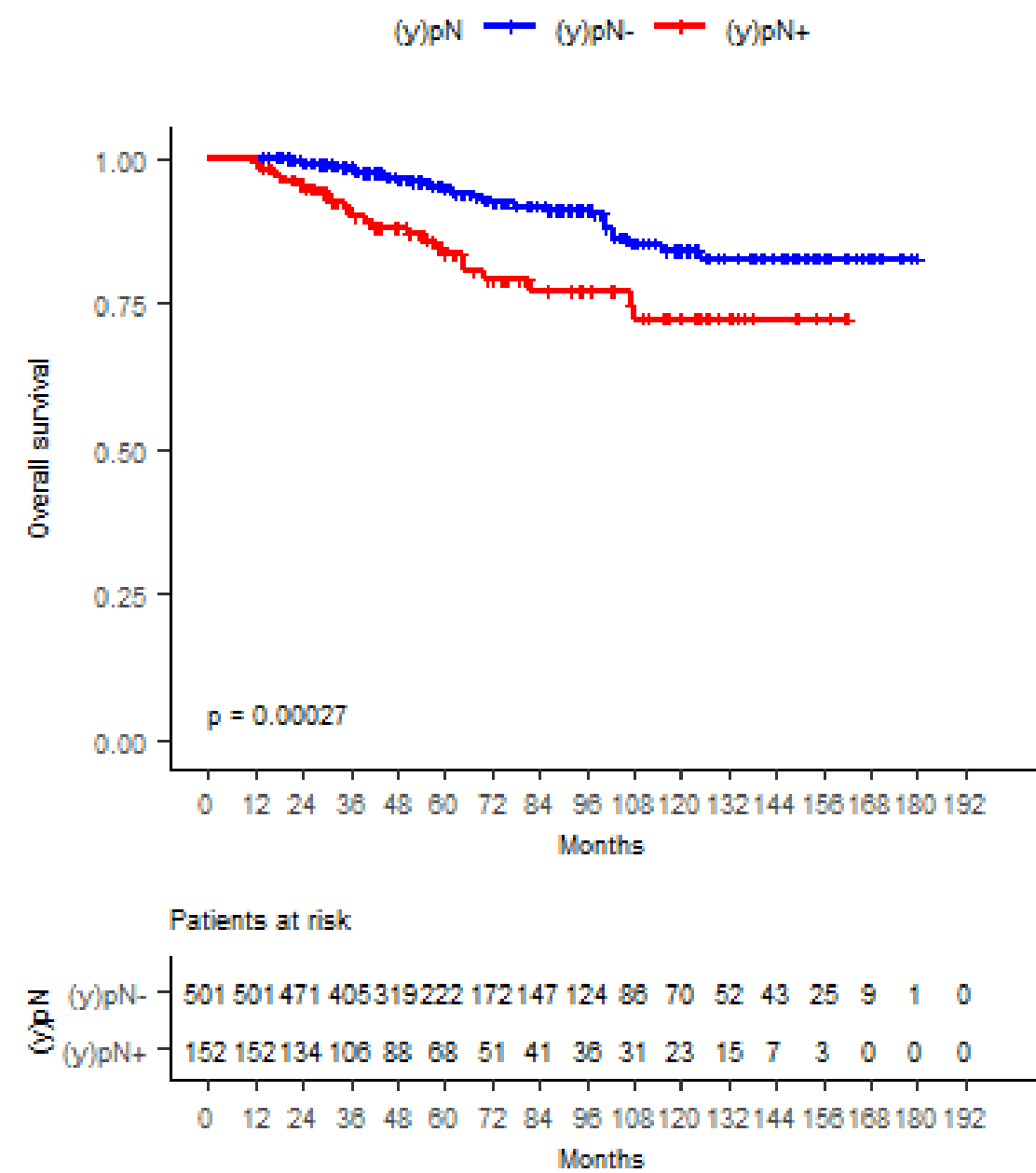


Figure 8. Overall survival according to grade.

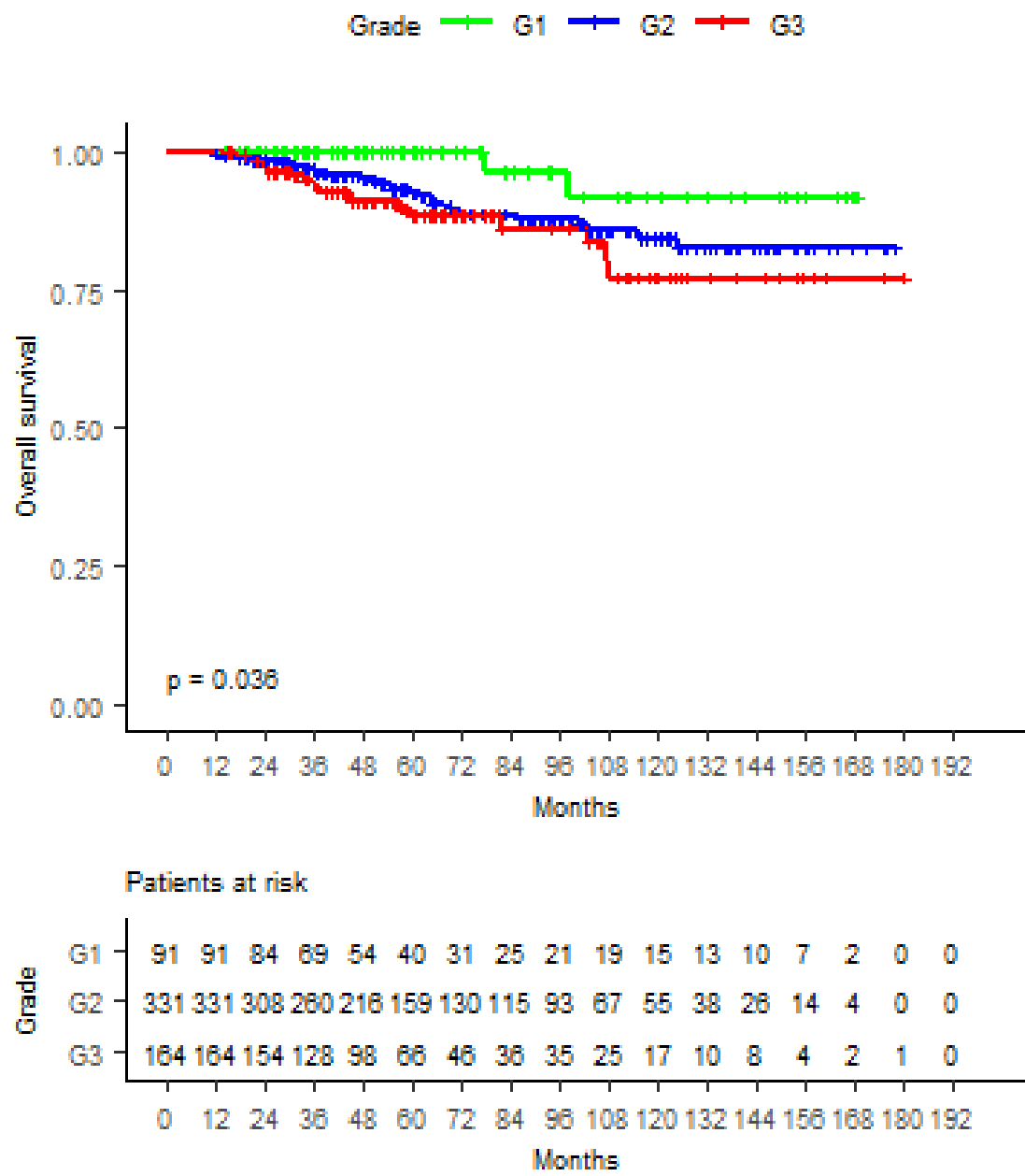


Figure 9. Overall survival according to estrogen receptors.

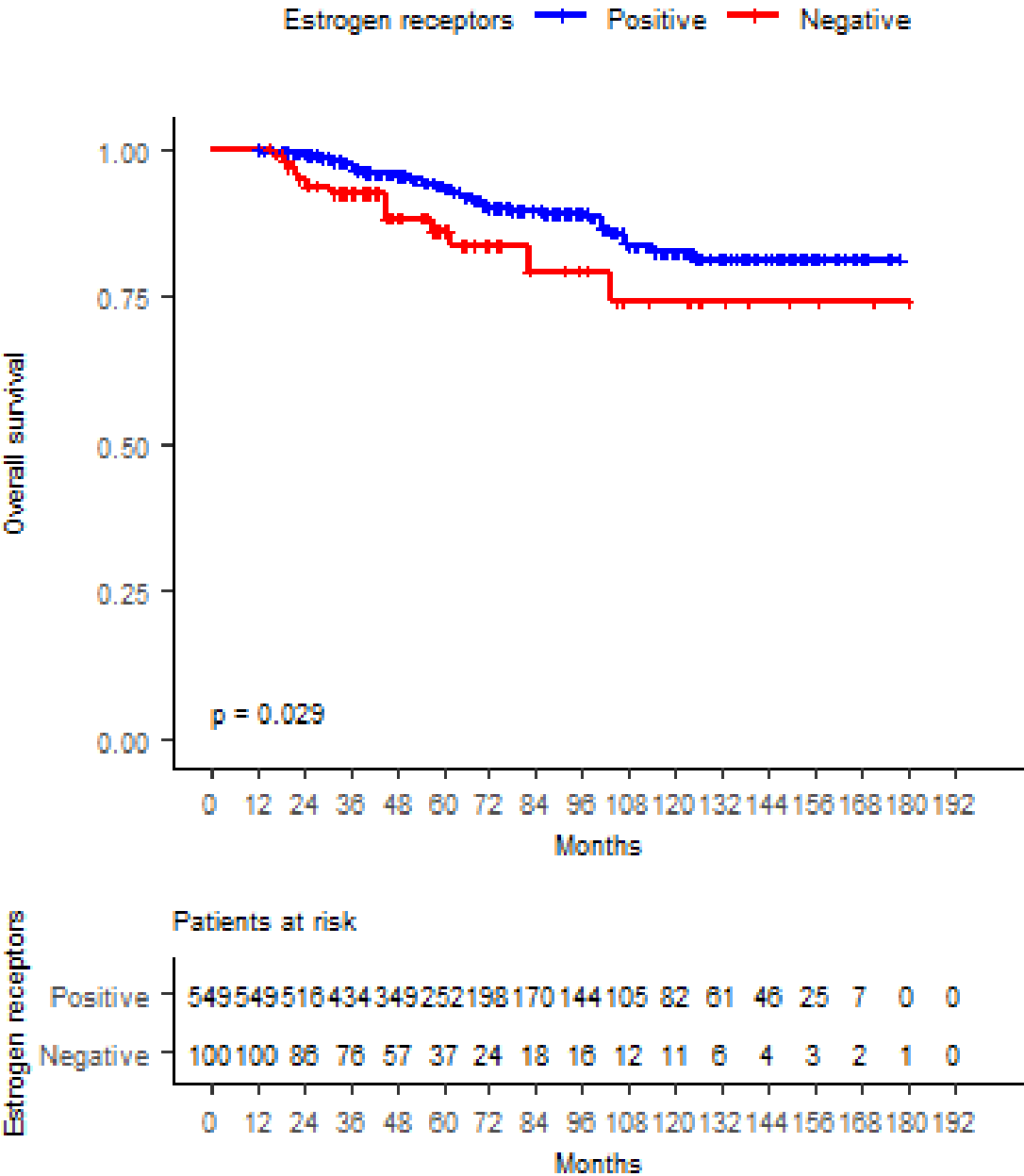


Figure 10. Overall survival according to progesterone receptors.

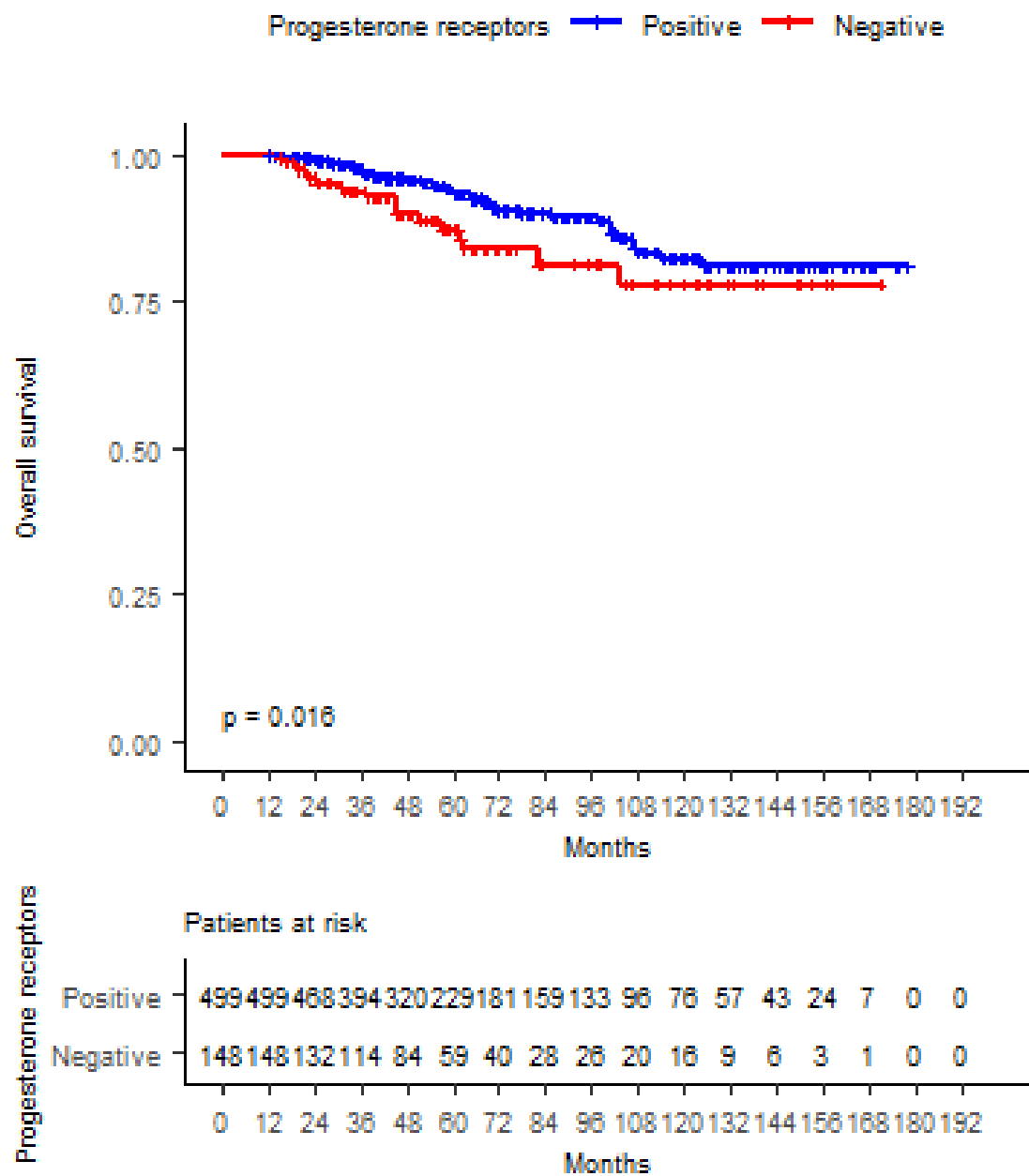


Table 2. Cox regression analysis of characteristics predicting time to death.

Characteristics	HR not adjusted	95% CI	p	HR adjusted*	95% CI	p
cT						
cT1	Ref.			Ref.		
cT2	1.25	0.73-2.15	0.413	1.03	0.53-2.01	0.923
cT3	3.57	1.38-9.26	0.009	3.55	1.16-10.88	0.027
cN						
cN0	Ref.					
cN1	2.13	1.27-3.56	0.004			
Stage						
I	Ref.			Ref.		
II	1.72	1.02-2.88	0.041	1.17	0.48-2.85	0.728
III	7.68	2.64-22.33	<0.05	2.92	0.61-13.94	0.179
Hormone therapy						
No	Ref.			Ref.		
Yes	0.52	0.29-0.94	0.032	0.66	0.27-1.60	0.359
Adjuvant chemotherapy						
No	Ref.			Ref.		
Yes	1.84	1.10-3.06	0.019	0.98	0.52-1.86	0.954
(y)pN (evaluarlo)						
(y)pN-	Ref.			Ref.		
(y)pN+	2.48	1.50-4.11	<0.05	3.22	1.04-9.94	0.042
Grade						
G1	Ref.					
G2	3.86	0.92-16.14	0.065			
G3	5.51	1.28-23.68	0.022			
Estrogen receptors						
Positive	Ref.			Ref.		
Negative	1.92	1.06-3.49	0.032	1.61	0.56-4.61	0.375
Progesterone receptors						
Positive	Ref.			Ref.		
Negative	1.74	1.01-2.99	0.046	1.06	0.481-2.342	0.883

* No included grade.

Table 3. Cumulative local recurrence rate by patient's characteristics.

	Cumulative local recurrence rate, %				p
	N (events)	12m	60m	120m	
All patients	653 (22)	0.3	2.3	7.9	
Age, years					
<50	159 (13)	0.6	7.7	12.9	
≥50	494 (9)	0.2	0.5	6.1	<0.05
cT					
cT1	430 (15)	0.5	1.9	7.6	
cT2	197 (5)	0.0	2.2	7.5	
cT3	26 (2)	0.0	8.5		0.032
cN					
cN0	519 (16)	0.2	1.5	8.0	
cN1	134 (6)	0.7	5.3	8.0	0.24
Stage					
I	372 (10)	0.0	0.9	6.5	
II	268 (11)	0.7	3.9	9.3	
III	13 (1)	0.0	8.3		0.031
Frozen section before IORT?					
Yes	596 (21)	0.3	2.2	7.8	
No	53 (1)	0.0	2.2		0.39
Was margin extension performed after IORT?					
Yes	151 (6)	0.0	1.4	13.2	
No	495 (16)	0.4	2.6	6.6	0.61
Final paraffin situation					
R0	600 (20)	0.3	2.2	7.2	
R1	52 (2)	0.0	3.2	27.4	0.54
Applicator diameter, cm					
≤3	100 (4)	0.0	4.2	7.1	

≥3.5	509 (13)	0.4	1.9	4.7	0.2
Hormone therapy					
No	105 (6)	0.0	5.0	13.9	
Yes	548 (16)	0.4	1.9	7.1	0.034
Adjuvant chemotherapy					
No	348 (10)	0.0	0.4	7.4	
Yes	305 (12)	0.7	4.5	6.6	0.071
Fractionation					
Hypofractionation (>2Gy/Fx)	159 (1)	0.0	1.8		
Normofractionation (1.8- 2Gy/Fx)	492 (21)	0.4	2.5	8.1	0.34
(y)pT					
(y)pT0	28 (1)	0.0	9.1		
(y)pT1	435 (15)	0.5	1.7	7.4	
(y)pT2	190 (6)	0.0	2.9	8.3	0.89
(y)pN					
(y)pN(-)	501 (14)	0.0	1.1	7.8	
(y)pN(+)	152 (8)	1.3	6.2	8.8	0.003
Grade					
G1	91 (1)	0.0	0.0	4.2	
G2	331 (13)	0.6	2.2	8.5	
G3	164 (7)	0.0	4.8	10.1	0.33
In situ component					
Yes	131 (4)	0.0	3.9	17.6	
No	468 (16)	0.4	2.3	6.9	0.23
Margins from in situ component, mm					
≥2	239 (8)	0.4	1.7	4.5	
<2	162 (5)	0.0	3.8	8.6	0.4
Estrogen receptors					
Positive	549 (19)	0.4	2.1	8.4	
Negative	100 (3)	0.0	3.1	3.1	0.88

Progesterone receptors					
Positive	499 (17)	0.2	2.2	8.5	
Negative	148 (5)	0.7	2.8	4.7	0.69
HER2					
Positive	105 (3)	0.0	1.3	8.8	
Negative	540 (19)	0.4	2.5	7.7	0.75
Subtype					
Triple negative	69 (3)	0.0	4.7	4.7	
Luminal A	395 (13)	0.3	2.0	7.1	
Luminal B	81 (3)	1.2	2.9		
HER2,Luminal/HER2	105 (3)	0.0	1.3	8.8	0.3

Figure 11. Cumulative local recurrence rate.

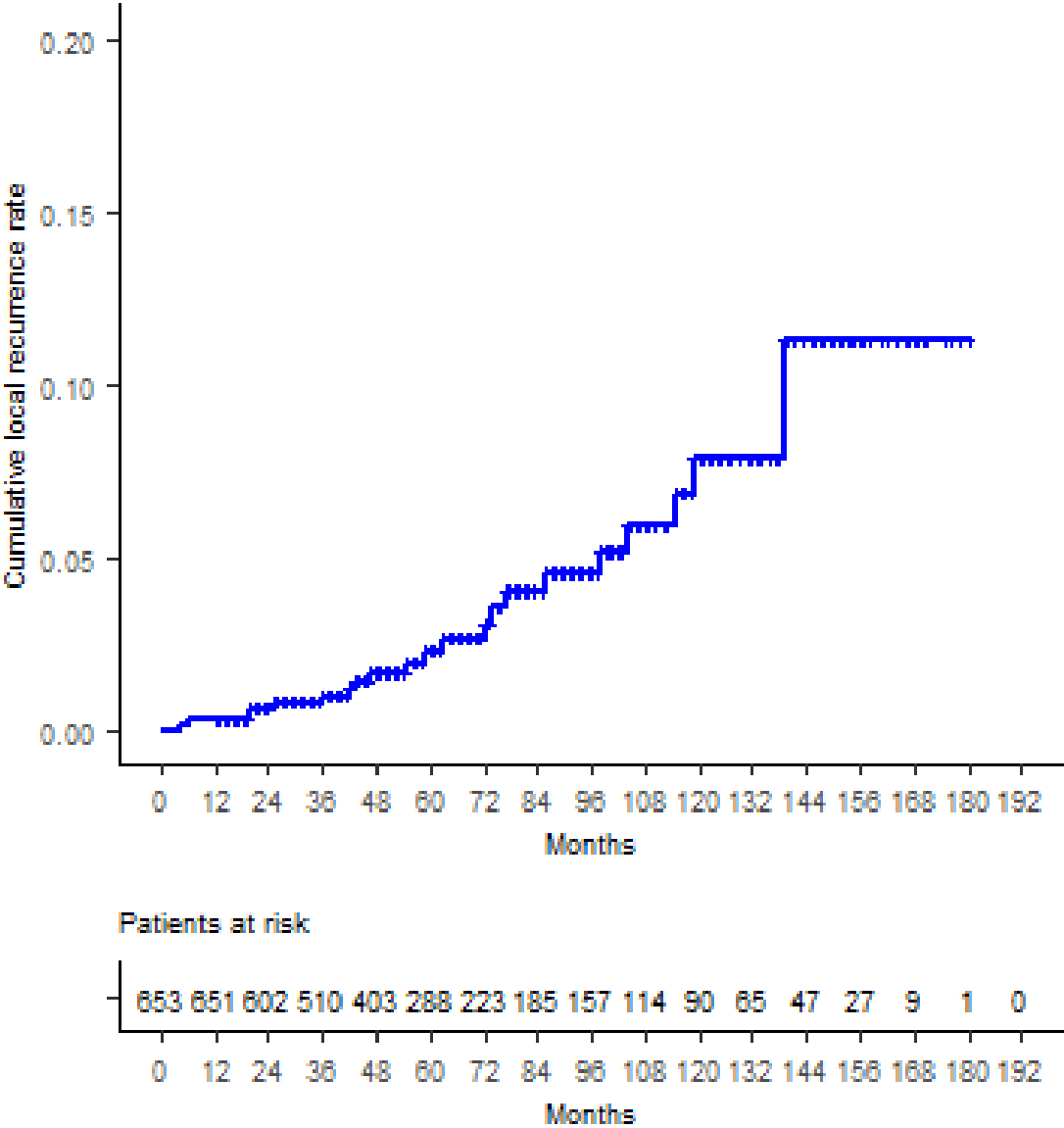


Figure 12. Cumulative local recurrence rate according age.

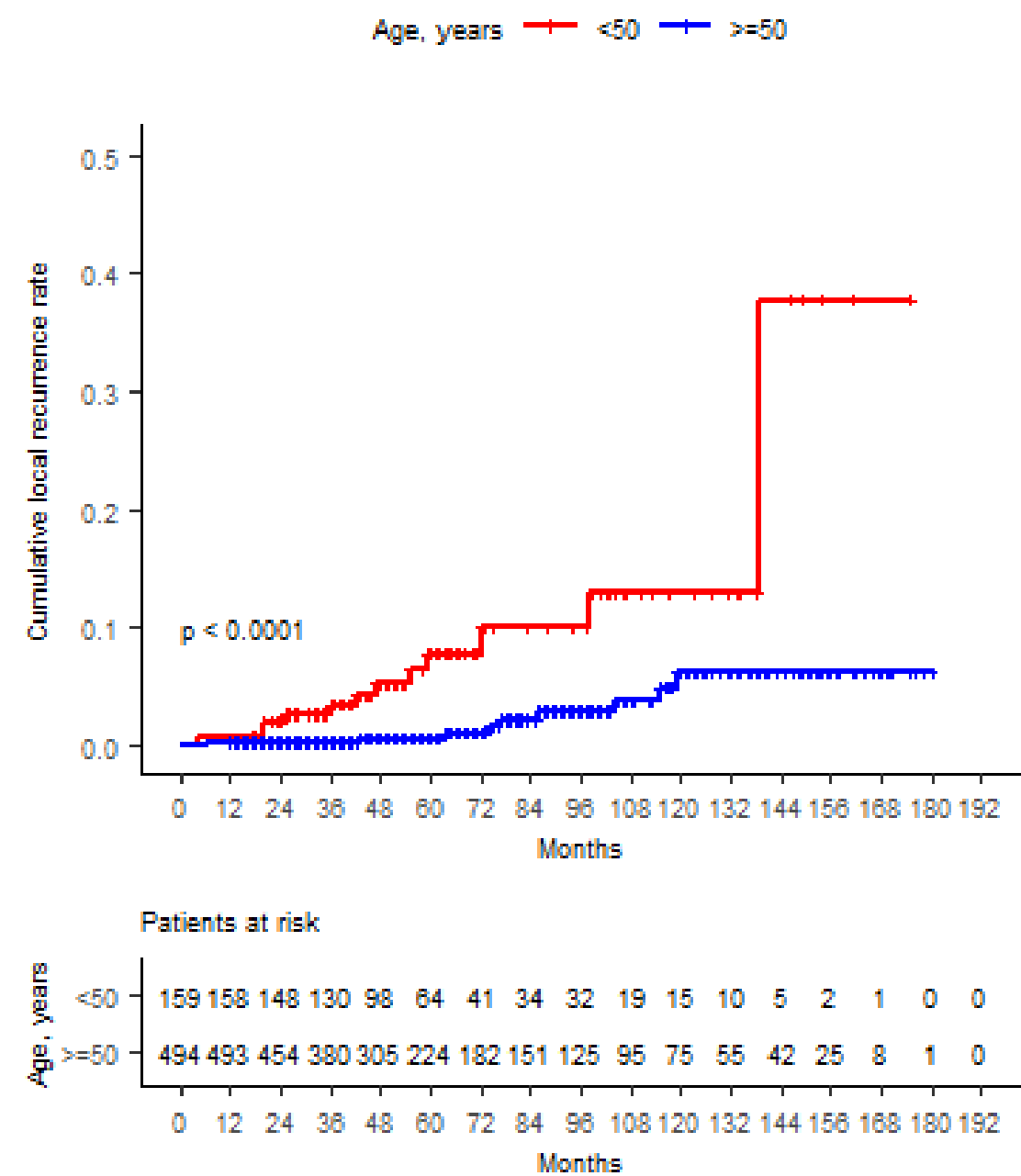


Figure 13. Cumulative local recurrence rate according cT.

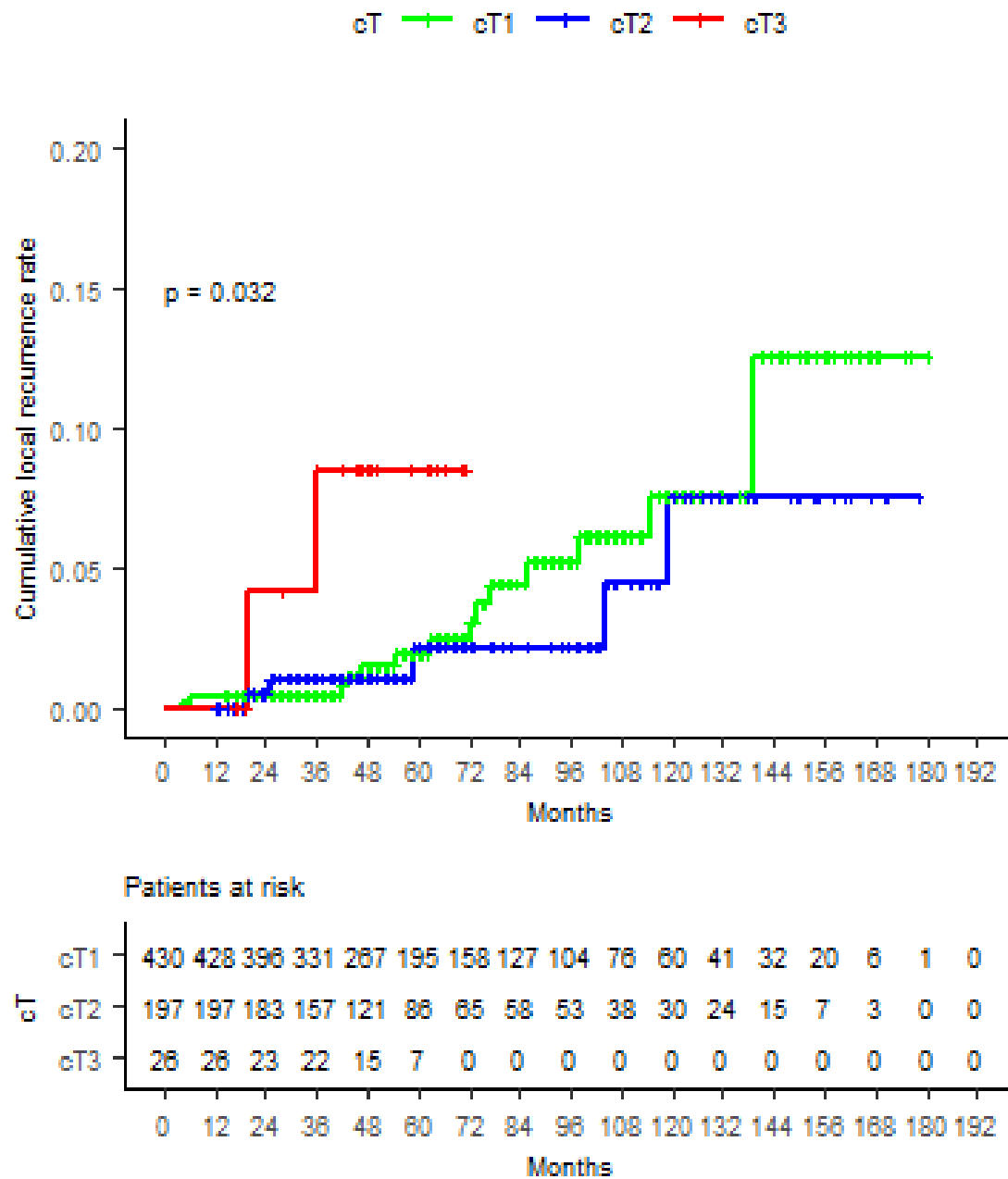


Figure 14. Cumulative local recurrence rate according stage.

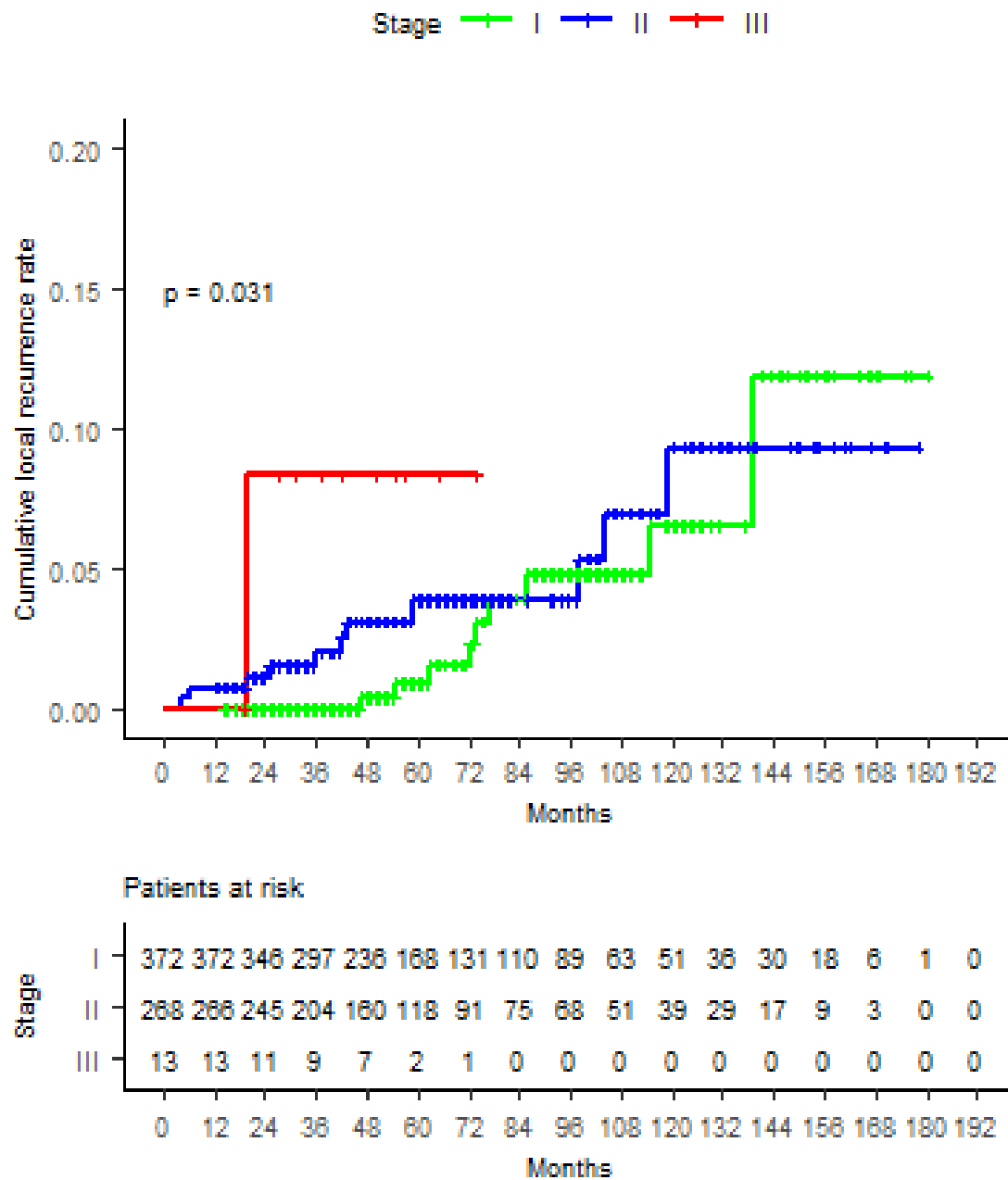


Figure 15. Cumulative local recurrence rate with and without hormone therapy.

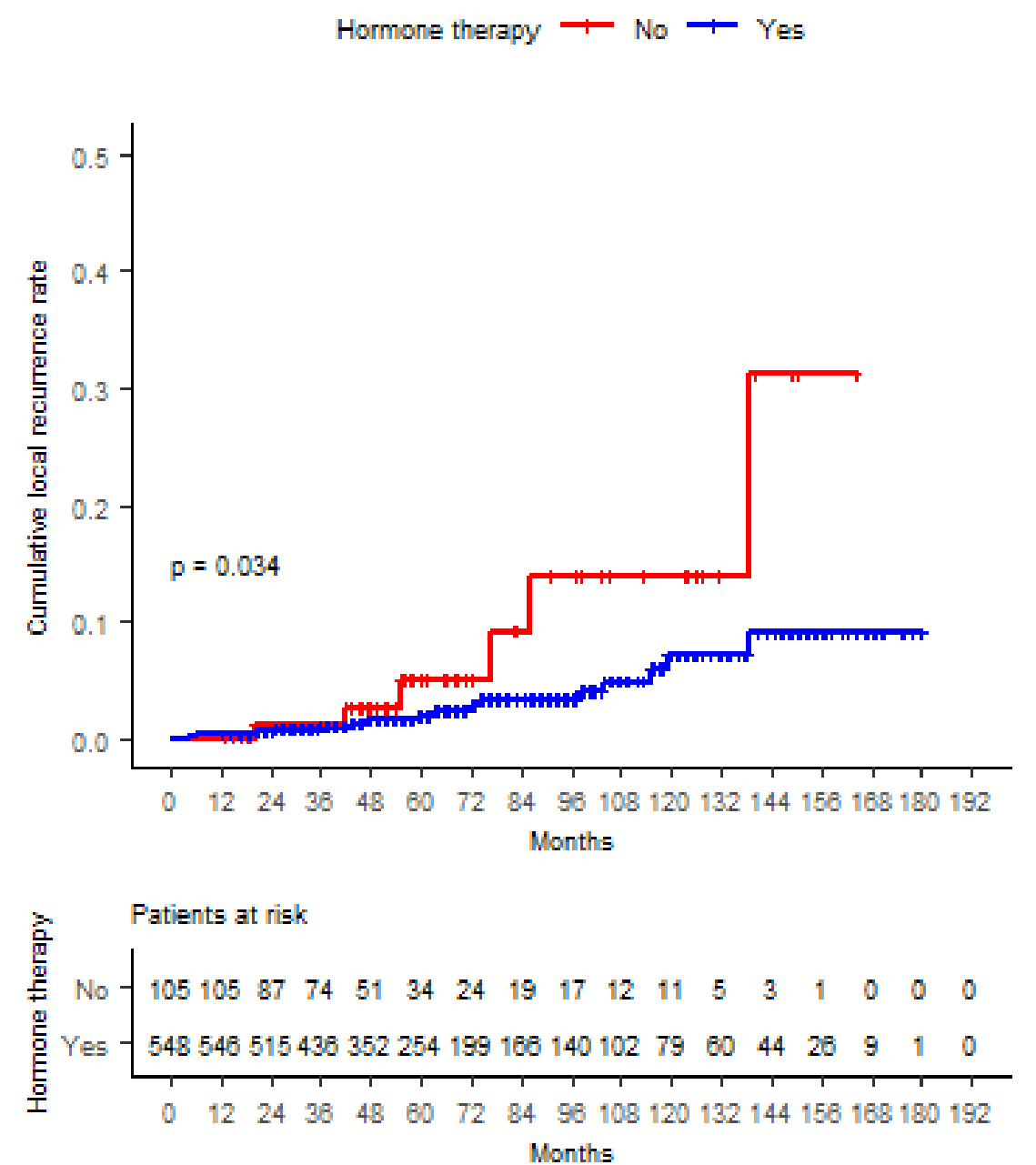


Figure 16. Cumulative local recurrence rate according to pN.

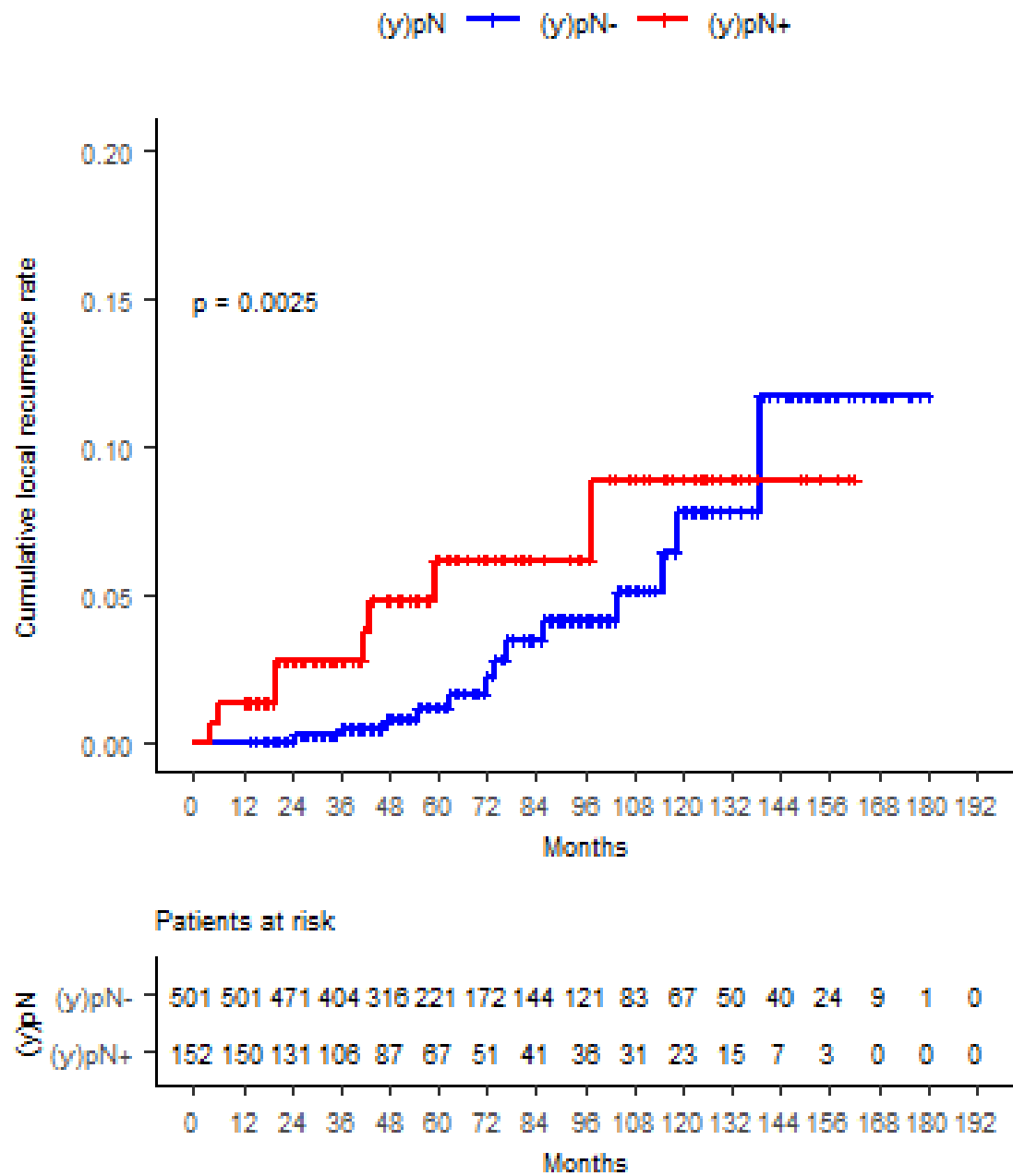


Table 4. Cox regression analysis of characteristics predicting time to local recurrence.

Characteristics	HR not adjusted	95% CI	p	HR adjusted	95% CI	p
Age, years						
<50	Ref.			Ref.		
≥50	0.18	0.07-0.41	<0.05	0.19	0.08-0.47	<0.05
cT						
cT1	Ref.			Ref.		
cT2	0.72	0.26-1.97	0.518	0.63	0.23-1.75	0.379
cT3	4.84	1.03-22.66	0.045	2.29	0.48-10.99	0.300
Stage						
I	Ref.					
II	1.57	0.67-3.71	0.300			
III	6.46	0.80-52.47	0.081			
Hormone therapy						
No	Ref.			Ref.		
Yes	0.37	0.15-0.96	0.041	0.47	0.18-1.21	0.117
(y)pN						
(y)pN-	Ref.					
(y)pN+	2.05	0.85-4.89	0.108			

Table 5. Cumulative regional recurrence rate by patient's characteristics.

	N (events)	Cumulative regional recurrence rate, %			p
		12m	60m	120m	
All patients	653 (9)	0.5	1.2	2.1	
Age, years					
<50	159 (4)	0.6	2.9	2.9	
≥50	494 (5)	0.4	0.7	1.7	0.1
cT					
cT1	430 (4)	0.5	0.8	1.4	
cT2	197 (4)	0.5	1.7	3.2	
cT3	26 (1)	0.0	4.2		0.24
cN					
cN0	519 (6)	0.4	0.8	1.9	
cN1	134 (3)	0.7	2.7	2.7	0.28
Stage					
I	372 (3)	0.0	0.9	6.5	
II	268 (6)	0.7	3.9	9.3	
III	13 (0)	0.0	8.3		0.28
Frozen section before IORT?					
Yes	596 (9)	0.5	1.3	2.2	
No	53 (0)	0.0	0.0		0.5
Was margin extension performed after IORT?					
Yes	151 (3)	0.7	1.4	3.3	
No	495 (6)	0.4	1.2	1.7	0.5
Final paraffin situation					
R0	600 (8)	0.5	1.1	1.9	
R1	52 (1)	0.0	3.6	3.6	0.58
Applicator diameter, cm					
≤3	100 (1)	0.0	1.0	1.0	

≥3.5	509 (7)	0.6	1.0	2.2	0.83
Hormone therapy					
No	105 (2)	0.0	1.8	6.1	
Yes	548 (7)	0.5	1.1	1.6	0.5
Adjuvant chemotherapy					
No	348 (2)	0.0	0.0	1.3	
Yes	305 (7)	1.0	2.6	2.6	0.038
Fractionation					
Hypofractionation (>2Gy/Fx)	159 (0)	0.0	0.0		
Normofractionation (1.8- 2Gy/Fx)	492 (9)	0.6	1.5	2.4	0.16
(y)pT					
(y)pT0	28 (0)	0.0	0.0		
(y)pT1	435 (5)	0.5	1.1	1.6	
(y)pT2	190 (4)	0.5	1.7	3.4	0.54
(y)pN					
(y)pN(-)	501 (6)	0.2	0.9	2.0	
(y)pN(+)	152 (3)	1.3	2.4	2.4	0.35
Grade					
G1	91 (1)	1.1	1.1	1.1	
G2	331 (5)	0.6	1.4	2.1	
G3	164 (2)	0.0	0.7	3.0	0.96
In situ component					
Yes	131 (1)	0.0	0.9	0.9	
No	468 (8)	0.6	1.4	2.5	0.61
Margins from in situ component, mm					
≥2	239 (3)	0.0	0.5	2.3	
<2	162 (4)	1.2	3.0	3.0	0.14
Estrogen receptors					
Positive	549 (7)	0.5	1.2	1.6	
Negative	100 (2)	0.0	1.2	6.2	0.47

Progesterone receptors					
Positive	499 (7)	0.6	1.3	1.8	
Negative	148 (2)	0.0	0.8	4.0	0.94
HER2					
Positive	105 (2)	0.0	2.1	2.1	
Negative	540 (7)	0.6	1.0	2.1	0.54
Subtype					
Triple negative	69 (1)	100.0	100.0	92.3	
Luminal A	395 (5)	99.5	98.8	98.3	
Luminal B	81 (1)	98.8	98.8		
HER2,Luminal/HER2	105 (2)	100.0	97.9	97.9	0.92

Figure 17. Cumulative regional recurrence rate.

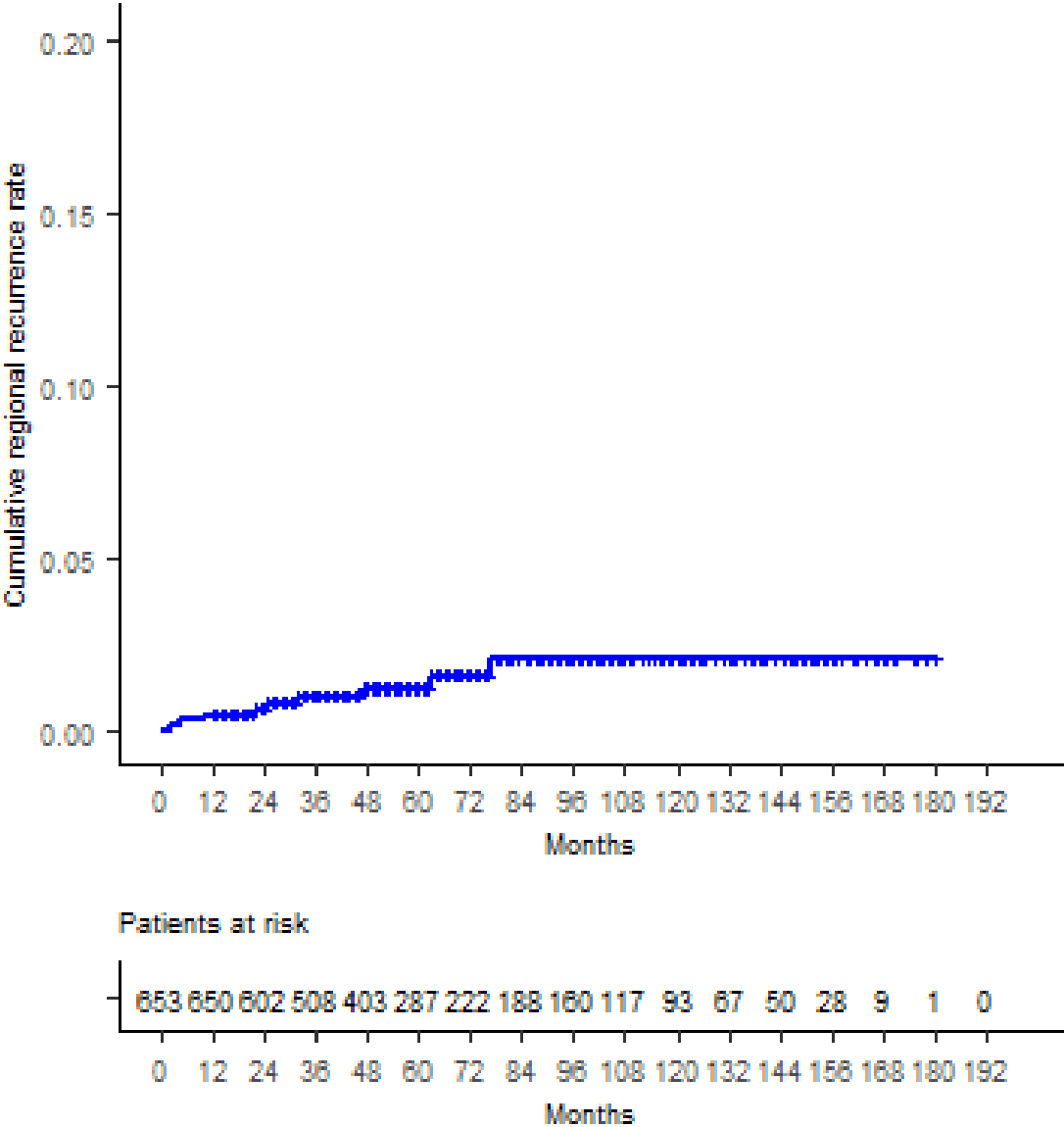


Figure 18. Cumulative regional recurrence rate with and without adjuvant chemotherapy.

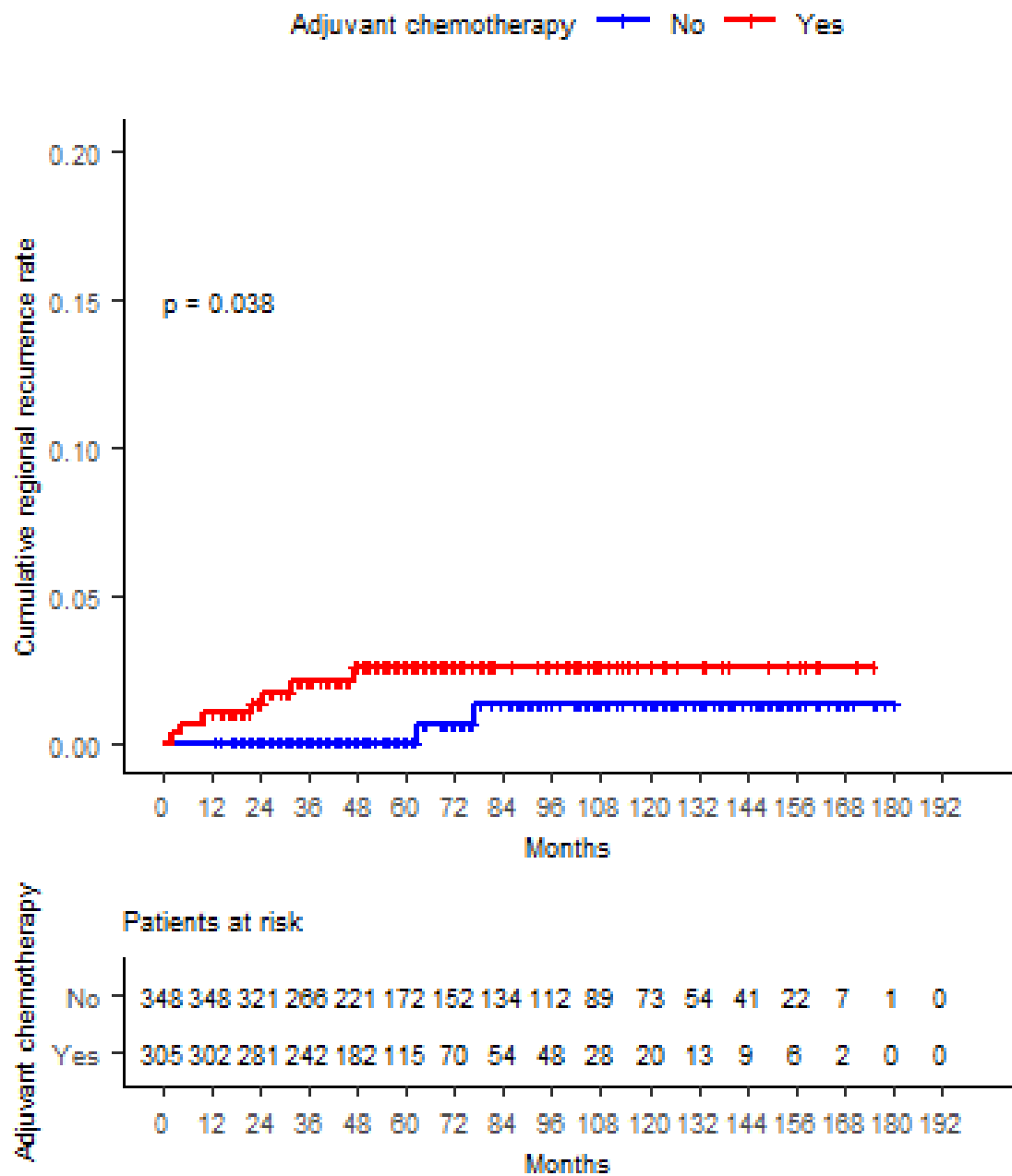


Table 6. Cumulative distant recurrence rate by patient's characteristics.

	Cumulative distant recurrence rate, %				p
	N (events)	12m	60m	120m	
All patients	653 (45)	0.6	6.9	13.2	
Age, years					
<50	159 (13)	0.0	7.8	18.1	
≥50	494 (32)	0.8	6.4	12.0	0.36
cT					
cT1	430 (25)	0.2	5.5	11.5	
cT2	197 (16)	1.5	8.1	15.3	
cT3	26 (4)	0.0	16.4		0.032
cN					
cN0	519 (24)	0.0	4.8	10.3	
cN1	134 (21)	3.0	14.7	23.1	<0.05
Stage					
I	372 (15)	0.0	4.1	8.8	
II	268 (28)	1.5	10.1	18.7	
III	13 (2)	0.0	17.9		0.001
Frozen section before IORT?					
Yes	596 (43)	0.7	6.8	13.1	
No	53 (1)	0.0	2.0		0.79
Was margin extension performed after IORT?					
Yes	151 (8)	0.0	7.7	7.7	
No	495 (37)	0.8	6.6	14.6	0.37
Final paraffin situation					
R0	600 (40)	0.7	6.3	12.8	
R1	52 (5)	0.0	15.2	15.2	0.11
Applicator diameter, cm					
≤3	100 (7)	0.0	8.8	8.8	

≥3.5	509 (33)	0.8	6.4	13.4	0.58
Hormone therapy					
No	105 (7)	1.0	6.1	14.4	
Yes	548 (38)	0.5	6.9	13.0	0.69
Adjuvant chemotherapy					
No	348 (14)	0.0	4.1	7.5	
Yes	305 (31)	1.3	10.0	23.7	<0.05
Fractionation					
Hypofractionation (>2Gy/Fx)	159 (1)	0.0	2.6		
Normofractionation (1.8- 2Gy/Fx)	492 (44)	0.8	7.9	14.2	0.021
(y)pT					
(y)pT0	28 (1)	0.0	3.6		
(y)pT1	435 (28)	0.2	6.3	12.1	
(y)pT2	190 (16)	1.6	8.5	15.9	0.65
(y)pN					
(y)pN(-)	501 (23)	0.0	4.6	10.1	
(y)pN(+)	152 (22)	2.6	14.8	23.2	<0.05
Grade					
G1	91 (1)	0.0	2.5	2.5	
G2	331 (23)	0.9	6.9	12.3	
G3	164 (12)	0.6	7.0	15.6	0.1
In situ component					
Yes	131 (5)	0.0	6.0	10.5	
No	468 (37)	0.9	7.8	13.9	0.55
Margins from in situ component, mm					
≥2	239 (22)	1.3	9.1	15.9	
<2	162 (10)	0.6	8.1	8.1	0.64
Estrogen receptors					
Positive	549 (38)	0.5	6.6	13.2	
Negative	100 (7)	1.0	8.8	11.9	0.68

Progesterone receptors					
Positive	499 (32)	0.4	6.3	11.8	
Negative	148 (13)	1.4	9.2	19.1	0.18
HER2					
Positive	105 (15)	1.9	14.4	26.3	
Negative	540 (30)	0.4	5.3	10.6	0.002
Subtype					
Triple negative	69 (3)	0.0	4.0	9.1	
Luminal A	395 (22)	0.5	4.8	10.0	
Luminal B	81 (5)	0.0	9.4		
HER2,Luminal/HER2	105 (15)	1.9	14.3	26.2	0.011

Figure 19. Cumulative distant recurrence rate.

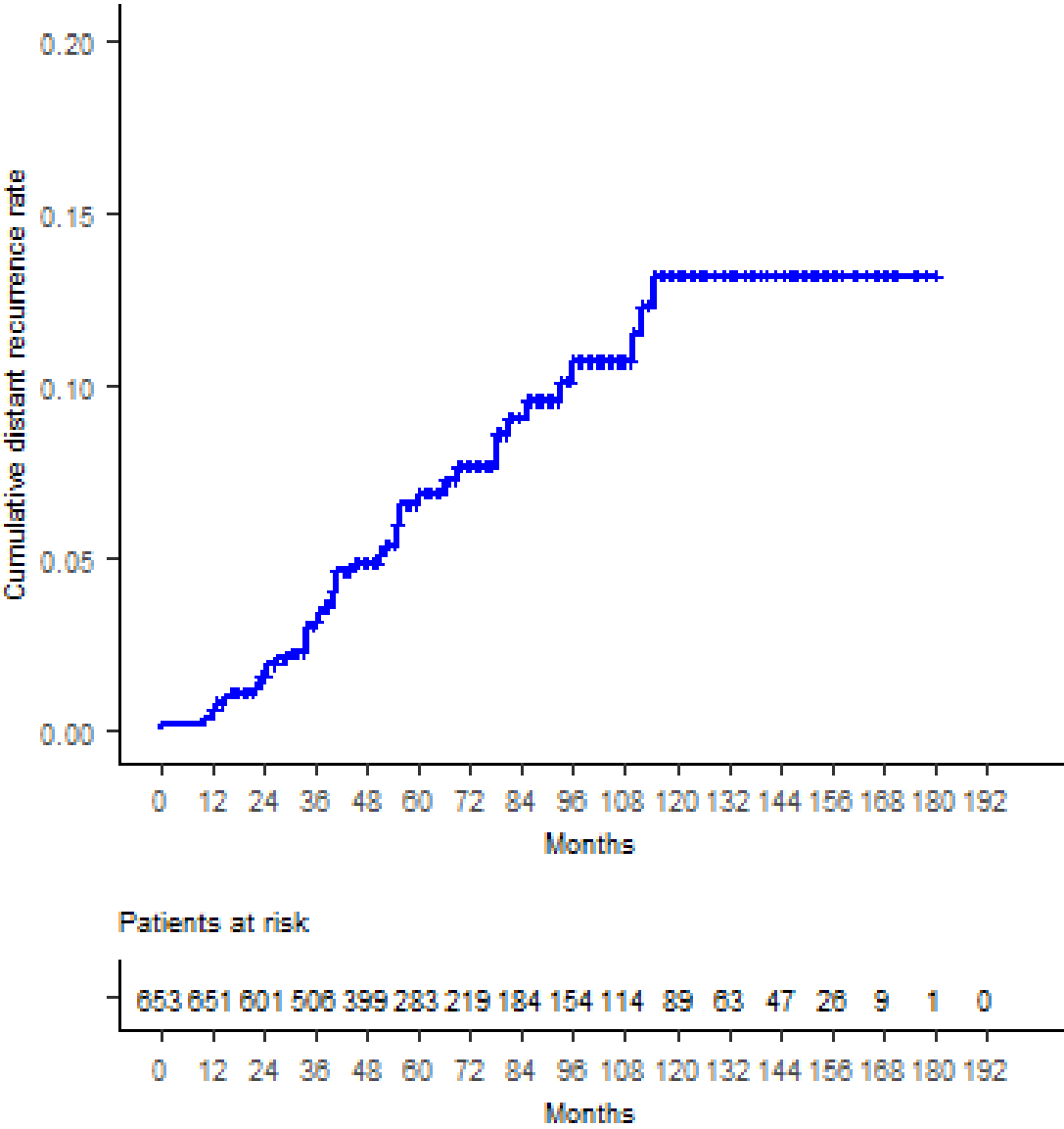


Figure 20. Cumulative distant recurrence rate according to cT.

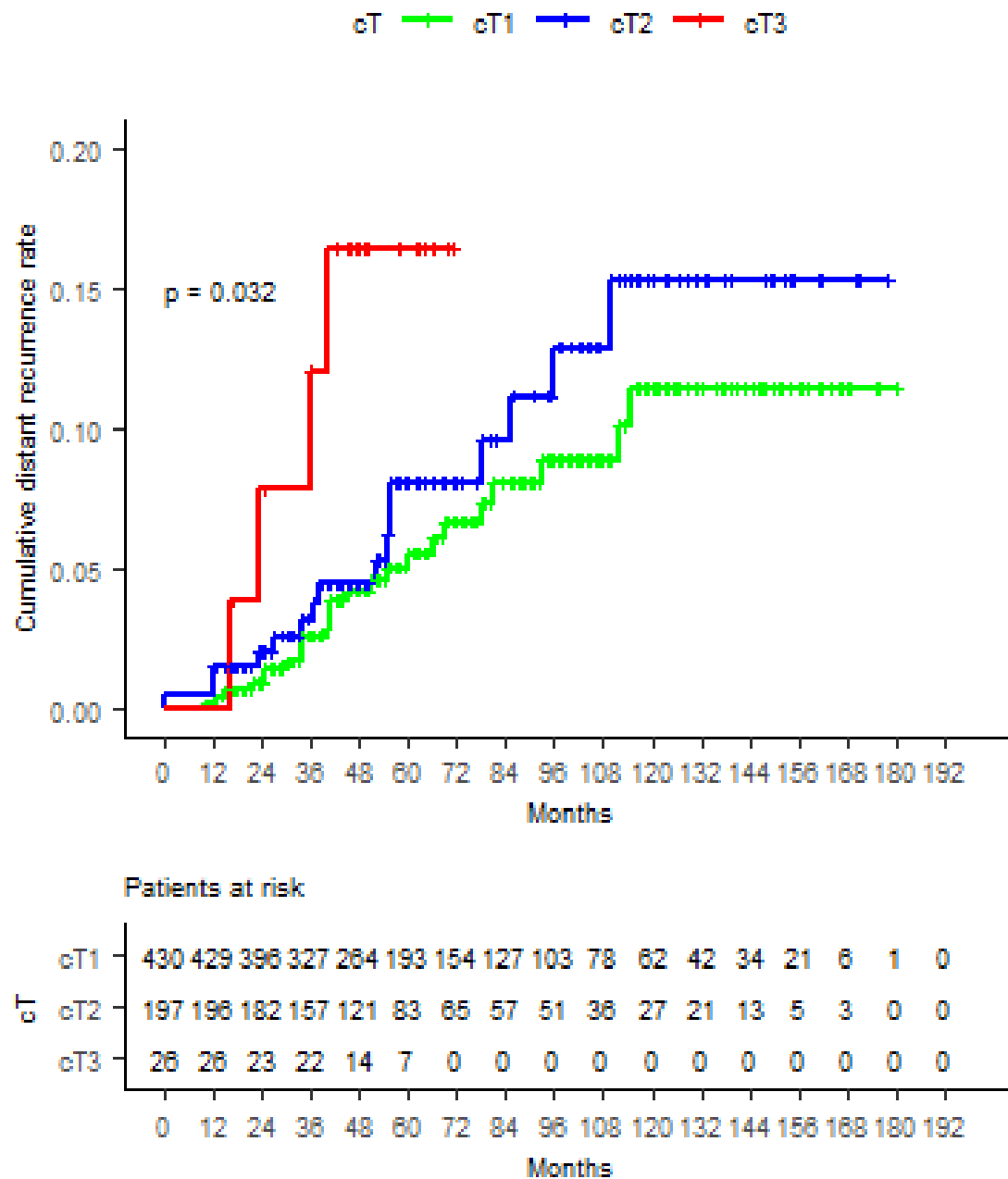


Figure 21. Cumulative distant recurrence rate according to cN.

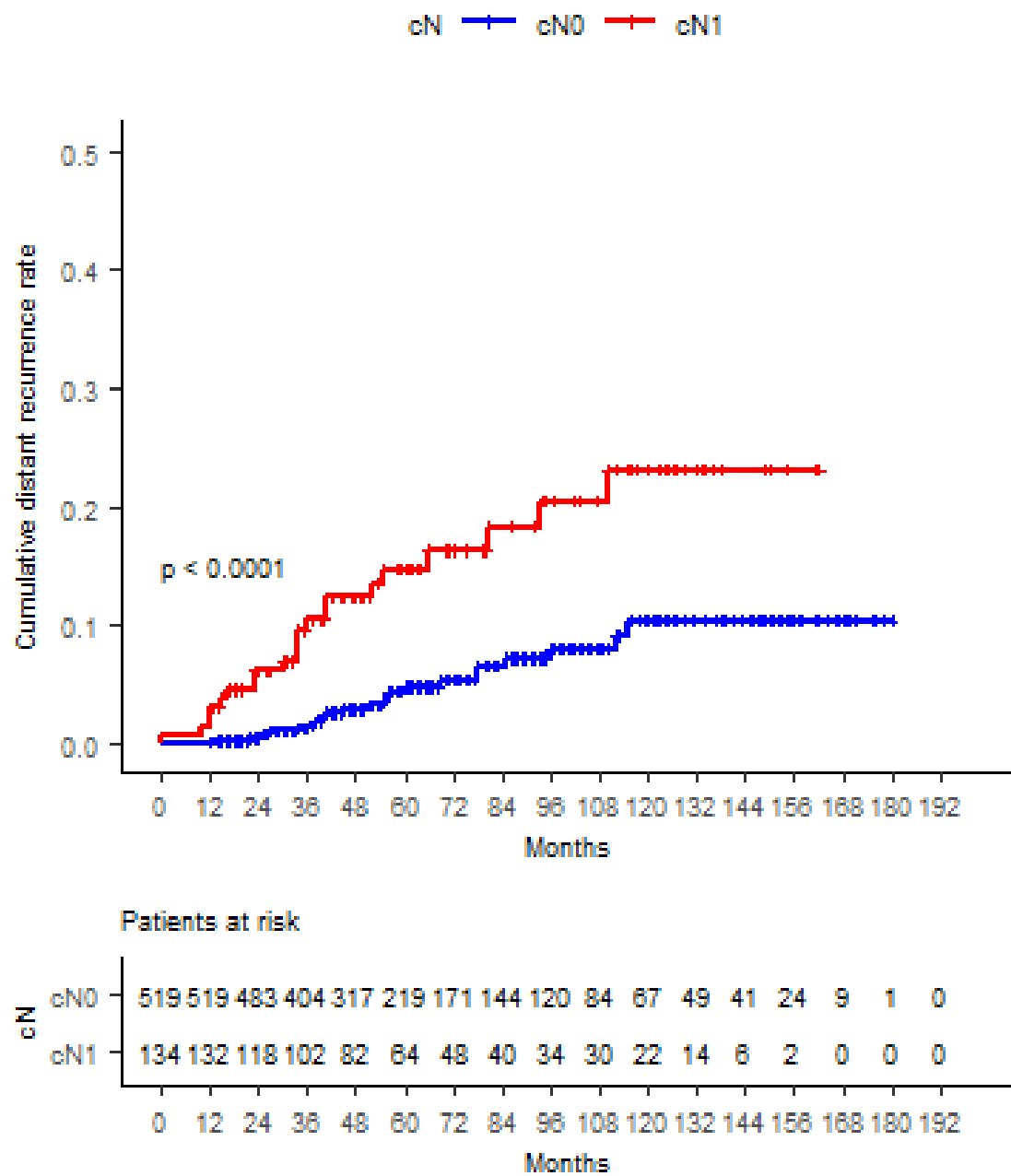


Figure 22. Cumulative distant recurrence rate according to stage.

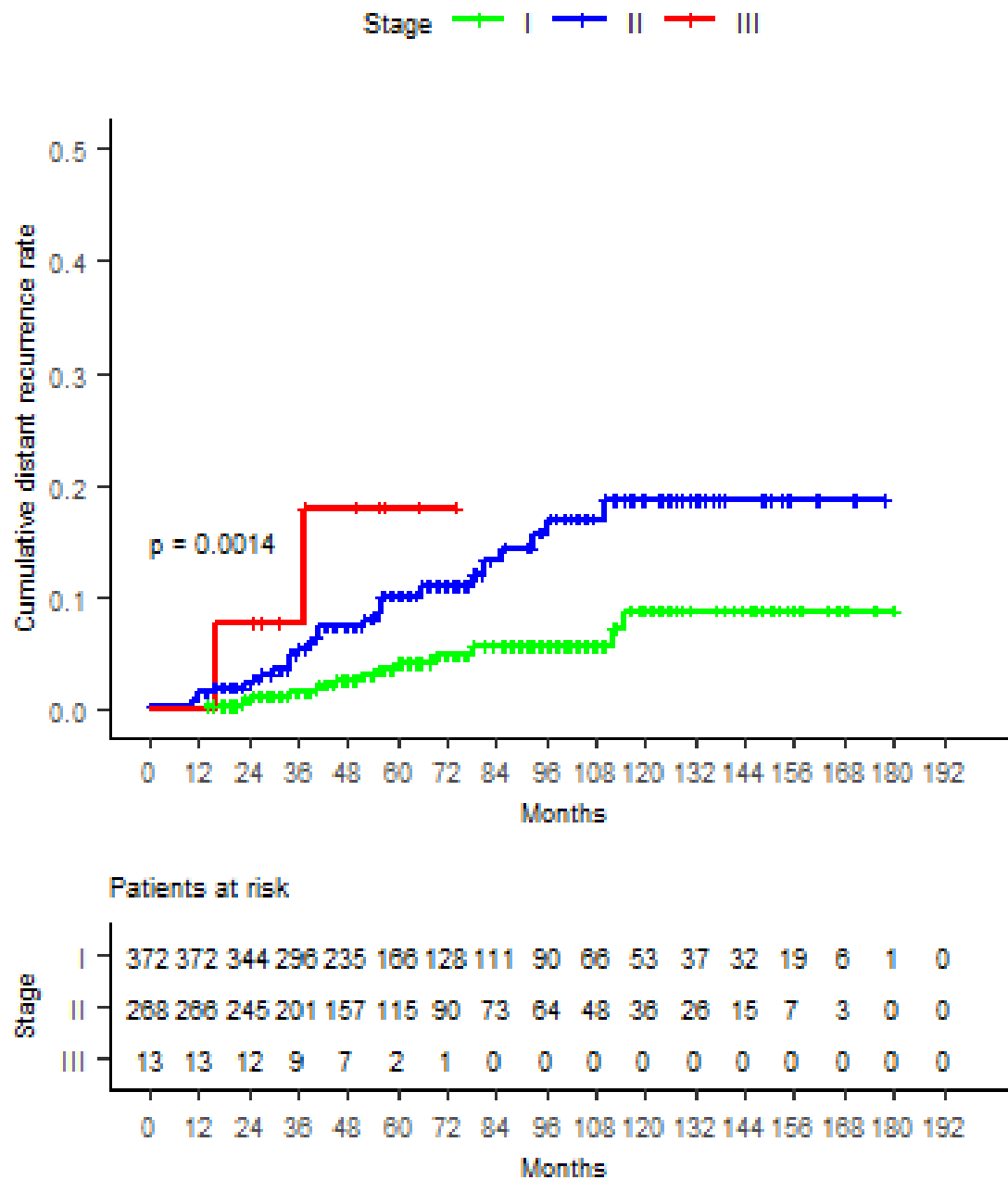


Figure 23. Cumulative distant recurrence rate with and without adjuvant chemotherapy.

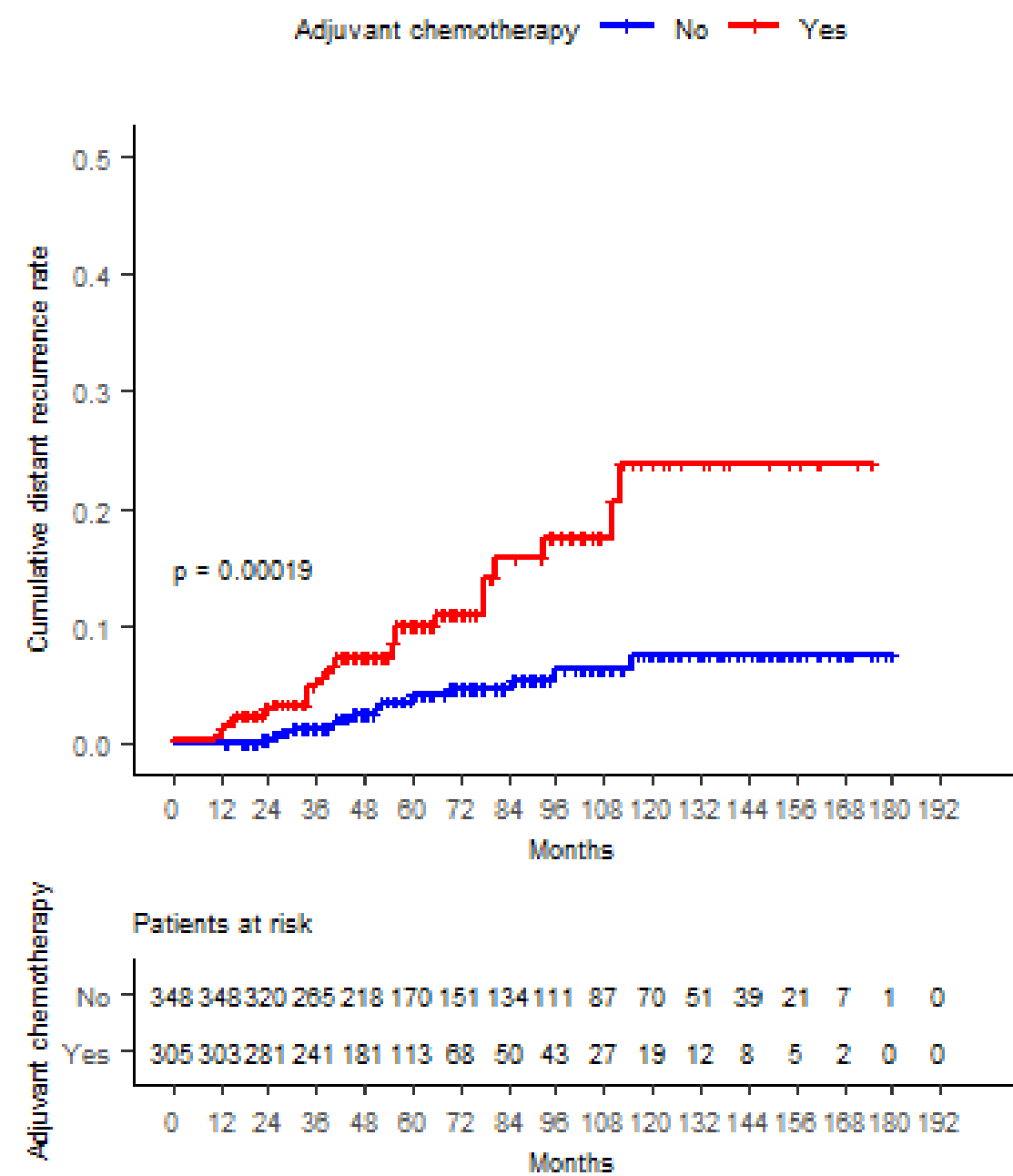


Figure 24. Cumulative distant recurrence rate according to fractionation.

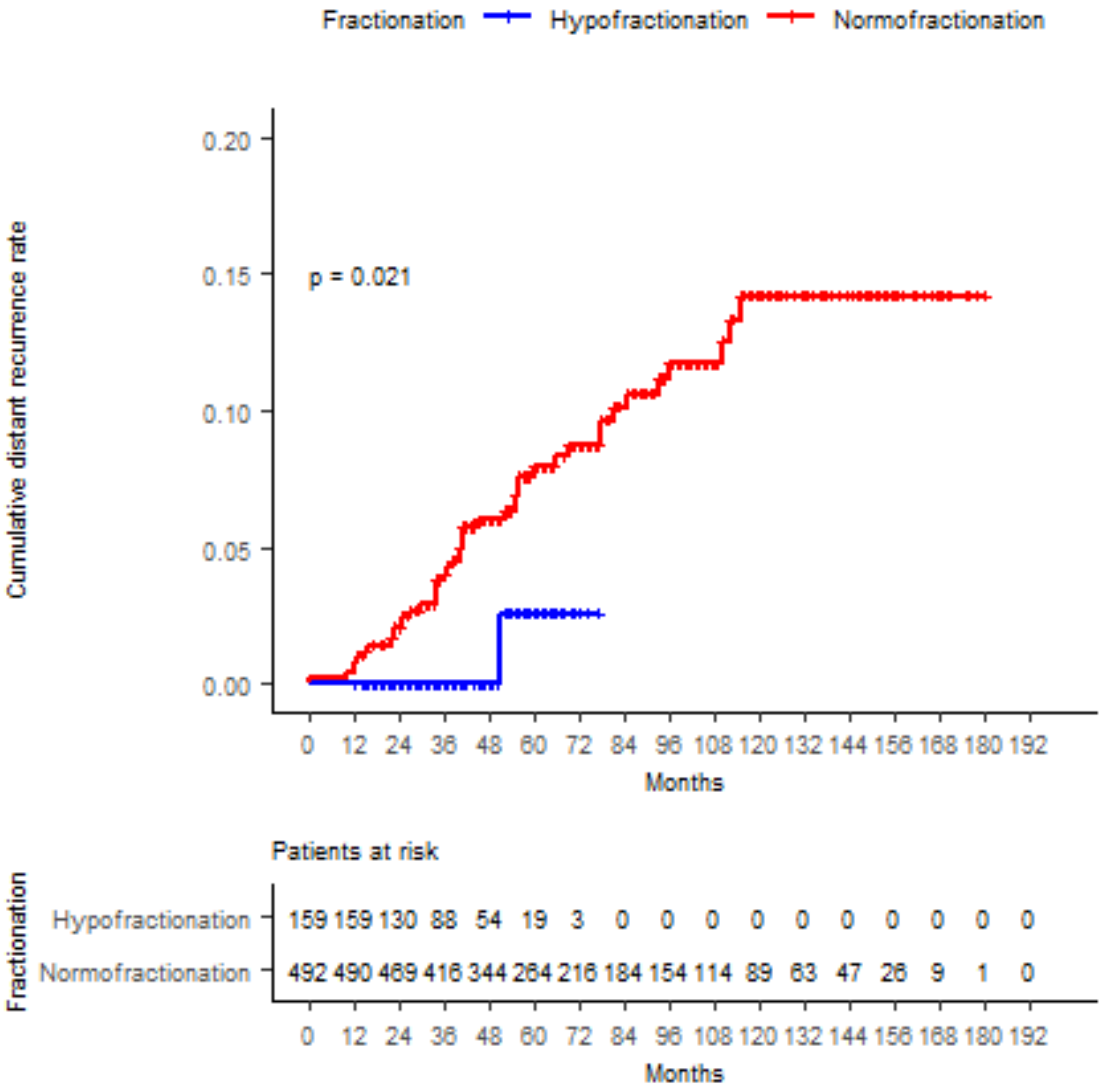


Figure 25. Cumulative distant recurrence rate according to pN.

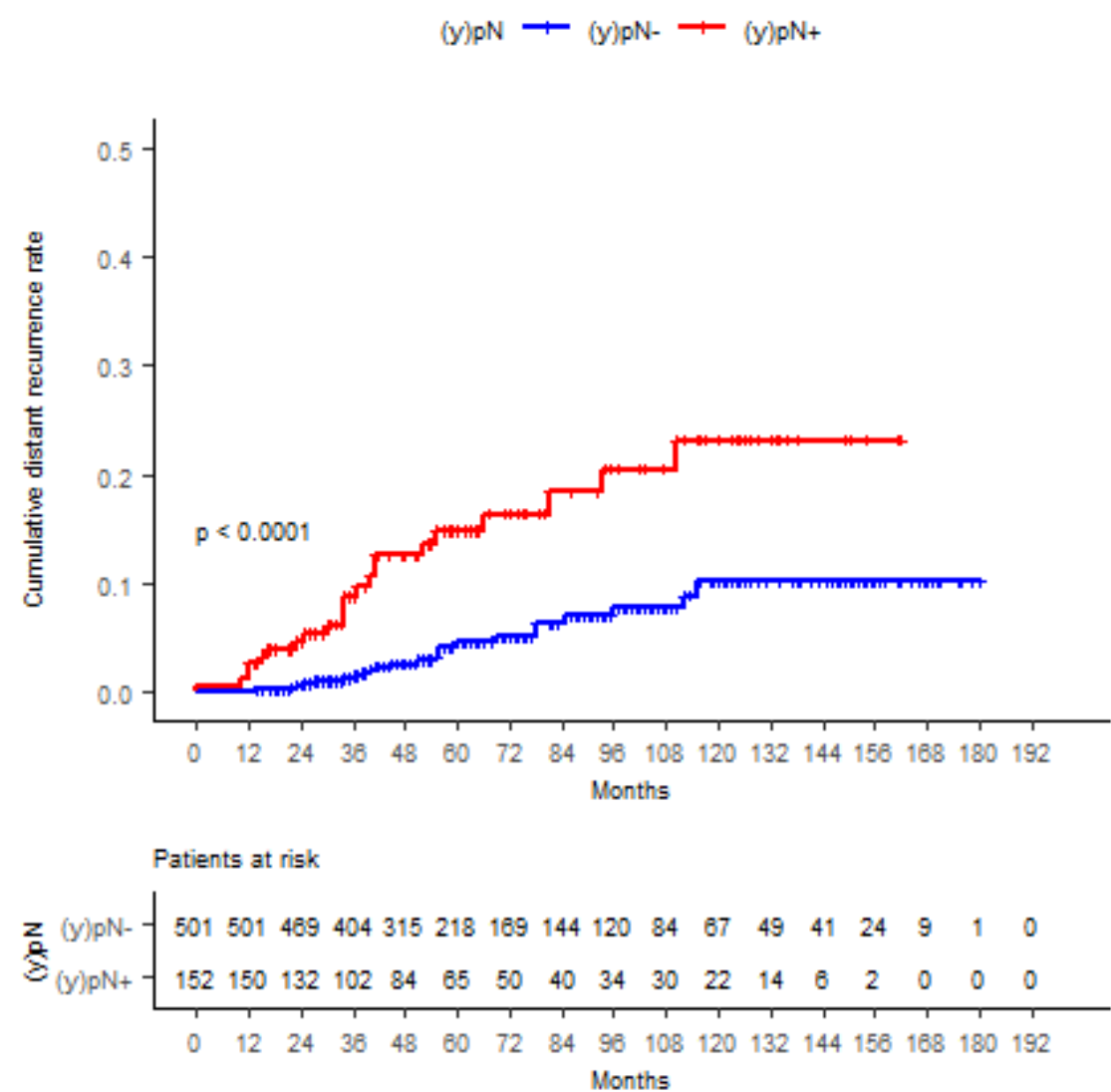


Figure 26. Cumulative distant recurrence rate according to HER2.

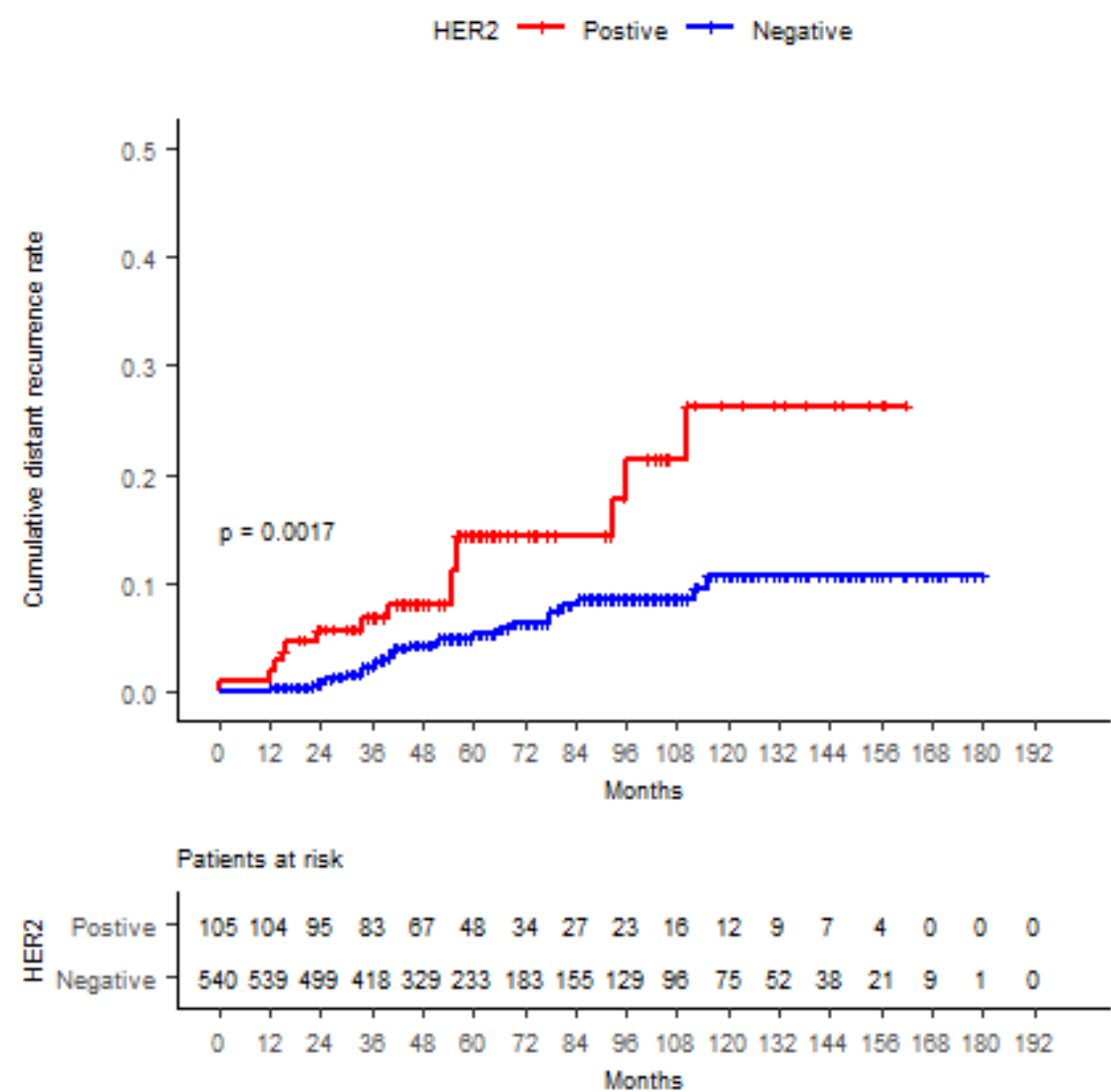


Figure 27. Cumulative distant recurrence rate according to subtype.

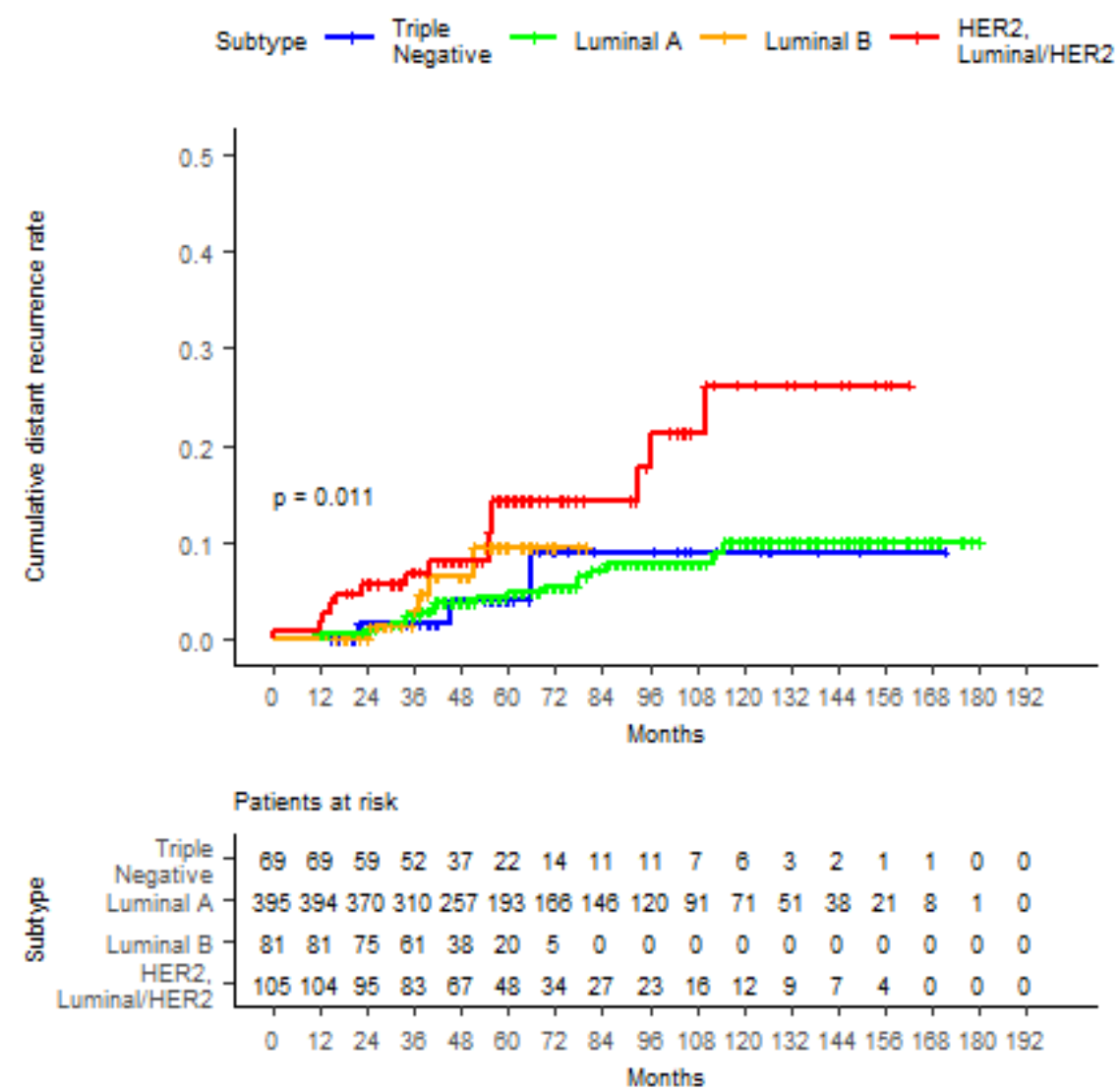


Table 7. Cox regression analysis of characteristics predicting time to distant metastasis.

Variables	HR not adjusted	95% CI	p	HR adjusted*	95% CI	p
cT						
cT1	Ref.			Ref.		
cT2	1.38	0.73-2.58	0.319	0.91	0.44-1.86	0.789
cT3	3.79	1.30-11.06	0.015	2.85	0.80-10.11	0.106
cN						
cN0	Ref.					
cN1	3.29	1.83-5.91	<0.05			
Stage						
I	Ref.			Ref.		
II	2.66	1.42-4.98	0.002	1.60	0.59-4.29	0.348
III	5.88	1.33-25.96	0.020	2.23	0.33-15.29	0.415
Adjuvant chemotherapy						
No	Ref.			Ref.		
Yes	3.2	1.69-6.08	<0.05	1.69	0.79-3.62	0.180
Fractionation						
Hypofractionation (>2Gy/Fx)	Ref.					
Normofractionation (1.8- 2Gy/Fx)	7.41	1.01-54.31	0.049			
(y)pN						
(y)pN-	Ref.			Ref.		
(y)pN+	3.39	1.89-6.08	<0.05	2.14	0.65-7.04	0.212
HER2						
Positive	Ref.			Ref.		
Negative	0.38	0.21-0.72	0.003	0.47	0.25-0.89	0.020
Subtype						
Triple Negative	Ref.					
Luminal A	0.99	0.30-3.35	0.998			
Luminal B	1.77	0.42-7.45	0.435			
HER2,Luminal/HER2	2.83	0.82-9.77	0.101			