cancers

MDPI

*Article*

# The Prognostic Value of Lymph Node Involvement after Neo-adjuvant Chemotherapy Is Different among Breast Cancer Sub-Types

**Lucie Laot [†,1], Enora Laas [†,1], Noemie Girard [1], Elise Dumas [2], Eric Daoud [2], Beatriz Grandal [2], Jean-Yves Pierga [3], Florence Coussy [3], Youlia Kirova [4], Elsy El Alam [5], Guillaume Bataillon [5], Marick Lae [6], Florence Llouquet [1], Fabien Reyal [1,2,*] and Anne-Sophie Hamy [2]**

**Table S1.** Post-NAC nodal involvement according to NAC regimen among HER-2 positive BC patients (n=295).

| | | NAC with trastuzumab | NAC without trastuzumab | *p* |
|---|---|---|---|---|
| n = | | 204 (69.2%) | 91 (30.8%) | |
| Post NAC node involvement | Negative | 158 (77.5%) | 47 (51.6%) | <0.00001 |
| | Positive | 46 (22.5%) | 44 (48.4%) | |

Abbreviations: NAC=neoadjuvant chemotherapy.

**Table S2.** Association between relapse free survival and pCR versus nodal status after neoadjuvant chemotherapy (Whole population, Luminal BC, TNBC and HER-2 positive BC).

| | | Whole population | | | | | Luminal BC | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **Class** | **Number** | **Events** | **HR** | **CI** | ***p*** | **Number** | **Events** | **HR** | **CI** | ***p*** |
| pCR | pCR | 285 | 39 | 1 | | | 33 | 5 | 1 | | |
| | No pCR | 911 | 332 | 2.87 | [2.06 - 4] | <0.001 | 493 | 179 | 2.16 | [0.89 - 5.24] | 0.09 |
| Nodal status | Negative | 682 | 144 | 1 | | | 197 | 49 | 1 | | |
| | Positive | 515 | 227 | 2.26 | [1.83 - 2.78] | <0.001 | 329 | 135 | 1.7 | [1.22 - 2.35] | 0.002 |
| | | **TNBC** | | | | | ***HER-2* positive BC** | | | | |
| **Variable** | **Class** | **Number** | **Events** | **HR** | **CI** | ***p*** | **Number** | **Events** | **HR** | **CI** | ***p*** |
| pCR | pCR | 139 | 20 | 1 | | | 113 | 14 | 1 | | |
| | No pCR | 236 | 96 | 3.48 | [2.15 - 5.64] | <0.001 | 182 | 57 | 2.82 | [1.57 - 5.06] | <0.001 |
| Nodal status | Negative | 280 | 60 | 1 | | | 205 | 35 | 1 | | |
| | Positive | 96 | 56 | 3.81 | [2.65 - 5.5] | <0.001 | 90 | 36 | 2.69 | [1.69 - 4.29] | <0.001 |

Abbreviations: pCR=pathological complete response.

**Table S3.** Association between clinical and pathological pre and post-NAC parameters with relapse-free survival (Luminal BC population, univariate and multivariate analysis).

| | | Luminal | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Univariate | | | | Multivariate | | |
| **Variable** | **Class** | **Number** | **Events** | **HR** | **CI** | **p*** | ***p*** | **HR** | **CI** | **p** |
| Pre-NAC parameters | | | | | | | | | | |
| Age | [0 -50) | 304 | 101 | 1 | | | 0.345 | | | |
| | [50 -60) | 158 | 56 | 1.06 | [0.76 - 1.46] | | | | | |
| | 60+ | 64 | 27 | 1.37 | [0.9 - 2.1] | | | | | |
| Menopausal status | Pre | 338 | 111 | 1 | | | 0.212 | | | |
| | Post | 184 | 71 | 1.21 | [0.9 - 1.63] | | | | | |
| BMI | 18.5-24.9 | 289 | 91 | 1 | | | 0.053 | | | |
| | <18.5 | 24 | 10 | 1.63 | [0.85 - 3.14] | 0.141 | | | | |
| | 25-29.9 | 135 | 46 | 1.08 | [0.76 - 1.54] | 0.682 | | | | |
| | >=30 | 75 | 36 | 1.64 | [1.11 - 2.41] | 0.012 | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Smoking status | No | 297 | 107 | 1 | | | 0.952 | | | |
| | Yes | 113 | 38 | 1.01 | [0.7 - 1.46] | | | | | |
| BRCA mutation genes | BRCA1 | 8 | 2 | 1 | | | 0.997 | | | |
| | BRCA2 | 6 | 2 | 1.24 | [0.17 - 8.82] | | | | | |
| | others | 1 | 0 | | | | | | | |
| | No | 74 | 24 | 1.16 | [0.27 - 4.91] | | | | | |
| Clinical T stage (TNM) | T0-T1 | 21 | 10 | 1 | | | 0.01 | | | |
| | T2 | 358 | 111 | 0.59 | [0.31 - 1.14] | 0.115 | | | | |
| | T3-T4 | 147 | 63 | 0.93 | [0.48 - 1.81] | 0.824 | | | | |
| Clinical N stage (TNM) | N0 | 235 | 75 | 1 | | | 0.1 | | | |
| | N1-N2-N3 | 290 | 109 | 1.28 | [0.95 - 1.72] | | | | | |
| Histological type | NST | 444 | 150 | 1 | | | 0.08 | | | |
| | Others | 65 | 28 | 1.43 | [0.96 - 2.15] | | | | | |
| KI67 | [0-10) | 52 | 17 | 1 | | | 0.778 | | | |
| | [10-20) | 79 | 29 | 1.13 | [0.62 - 2.05] | | | | | |
| | >=20 | 157 | 58 | 1.21 | [0.71 - 2.08] | | | | | |
| SBR grade | Grade I-II | 324 | 119 | 1 | | | 0.643 | | | |
| | Grade III | 182 | 58 | 0.93 | [0.68 - 1.27] | | | | | |
| LVI | No | 144 | 59 | 1 | | | 0.162 | | | |
| | Yes | 84 | 27 | 0.72 | [0.46 - 1.14] | | | | | |
| DCIS component | No | 186 | 59 | 1 | | | 0.677 | | | |
| | Yes | 224 | 81 | 1.07 | [0.77 - 1.51] | | | | | |
| CT regimen (NAC) | anthra-taxans | 340 | 108 | 1 | | | 0.272 | | | |
| | anthra | 133 | 54 | 1.05 | [0.75 - 1.46] | | | | | |
| | taxanes | 8 | 1 | 0.37 | [0.05 - 2.64] | | | | | |
| | others | 45 | 21 | 1.49 | [0.93 - 2.38] | | | | | |
| Post-NAC parameters | | | | | | | | | | |
| pCR | No pCR | 493 | 179 | 1 | | | 0.09 | | | |
| | pCR | 33 | 5 | 0.46 | [0.19 - 1.13] | 0.09 | | | | |
| Post-NAC LVI | No | 237 | 75 | 1 | | | 0.046 | | | |
| | Yes | 189 | 78 | 1.38 | [1.01 - 1.9] | 0.046 | | | | |
| ypN | 0 | 197 | 49 | 1 | | | <0.001 | 1 | | |
| | [1-3] | 216 | 70 | 1.24 | [0.86 - 1.79] | 0.245 | | 1.18 | [ 0.82 - 1.71 ] | 0.377 |
| | 4 and more | 113 | 65 | 2.8 | [1.93 - 4.06] | <0.001 | | 2.68 | [ 1.84 - 3.89 ] | <0.001 |
| RCB class | RCB-0 | 11 | 3 | 1 | | | 0.172 | | | |
| | RCB-I | 18 | 2 | 0.41 | [0.07 - 2.43] | | | | | |
| | RCB-II | 109 | 33 | 1.12 | [0.34 - 3.64] | | | | | |
| | RCB-III | 84 | 36 | 1.58 | [0.48 - 5.13] | | | | | |

*p* represents the p-value for the Wald test, and p* represents the individual p-value versus reference class. Abbreviations: pCR=pathological complete response; BMI=body mass index ; NST= no special type ; ER=estrogen receptor; PR=progesterone receptor; NAC=neoadjuvant chemotherapy; AC=anthracyclines; TILs=tumor infiltrating lymphocytes; RCB=residual cancer burden; LVI=lymphovascular invasion.

**Table S4.** Association between clinical and pathological pre and post-NAC parameters with relapse-free survival (TNBC population, univariate and multivariate analysis).

| | | | **TNBC** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | **Univariate** | | | | **Multivariate** | | |
| **Variable** | **Class** | **Number** | **Events** | **HR** | **CI** | **p*** | ***p*** | **HR** | **CI** | **p** |
| Pre-NAC parameters | | | | | | | | | | |
| Age | [0 -50) | 205 | 60 | 1 | | | 0.723 | | | |
| | [50 -60) | 115 | 38 | 1.17 | [0.78 - 1.77] | | | | | |
| | 60+ | 56 | 18 | 1.13 | [0.67 - 1.91] | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Menopausal status | Pre | 229 | 70 | 1 | | | 0.991 | | | |
| | Post | 143 | 44 | 1 | [0.69 - 1.46] | | | | | |
| BMI | 18.5-24.9 | 211 | 65 | 1 | | | 0.238 | | | |
| | <18.5 | 12 | 1 | 0.22 | [0.03 - 1.58] | | | | | |
| | 25-29.9 | 103 | 31 | 1.01 | [0.66 - 1.54] | | | | | |
| | >=30 | 49 | 19 | 1.4 | [0.84 - 2.33] | | | | | |
| Smoking status | No | 238 | 73 | 1 | | | 0.565 | | | |
| | Yes | 66 | 18 | 0.86 | [0.51 - 1.44] | | | | | |
| BRCA mutation genes | BRCA1 | 22 | 6 | 1 | | | 0.673 | | | |
| | BRCA2 | 5 | 2 | 1.43 | [0.29 - 7.1] | | | | | |
| | No | 83 | 18 | 0.79 | [0.31 - 1.98] | | | | | |
| Clinical T stage (TNM) | T0-T1 | 31 | 7 | 1 | | | 0.001 | 1 | | |
| | T2 | 243 | 65 | 1.23 | [0.56 - 2.69] | 0.6 | | 1.28 | [0.58 - 2.8] | 0.544 |
| | T3-T4 | 102 | 44 | 2.42 | [1.09 - 5.38] | 0.03 | | 2.29 | [1.03 - 5.09] | **0.043** |
| Clinical N stage (TNM) | N0 | 171 | 49 | 1 | | | 0.282 | | | |
| | N1-N2-N3 | 205 | 67 | 1.22 | [0.85 - 1.77] | | | | | |
| Histological type | NST | 340 | 101 | 1 | | | 0.367 | | | |
| | Others | 6 | 1 | 0.4 | [0.06 - 2.9] | | | | | |
| KI67 | [0-10) | 10 | 2 | 1 | | | 0.558 | | | |
| | [10-20) | 16 | 6 | 2.18 | [0.44 - 10.81] | | | | | |
| | >=20 | 141 | 52 | 2.18 | [0.53 - 8.93] | | | | | |
| SBR grade | Grade I-II | 53 | 17 | 1 | | | 0.917 | | | |
| | Grade III | 314 | 97 | 1.03 | [0.61 - 1.72] | | | | | |
| LVI | No | 82 | 28 | 1 | | | 0.121 | | | |
| | Yes | 38 | 18 | 1.6 | [0.88 - 2.9] | | | | | |
| DCIS component | No | 282 | 86 | 1 | | | 0.219 | | | |
| | Yes | 51 | 21 | 1.35 | [0.84 - 2.18] | | | | | |
| CT regimen (NAC) | anthra-taxanes | 287 | 86 | 1 | | | 0.728 | | | |
| | anthra | 63 | 24 | 1.2 | [0.76 - 1.89] | | | | | |
| | taxanes | 1 | 0 | | | | | | | |
| | others | 24 | 6 | 0.73 | [0.32 - 1.69] | | | | | |
| Post-NAC parameters | | | | | | | | | | |
| pCR | No pCR | 236 | 96 | 1 | | | <0.001 | | | |
| | pCR | 139 | 20 | 0.29 | [0.18 - 0.47] | <0.001 | | | | |
| Post-NAC LVI | No | 170 | 48 | 1 | | | <0.001 | | | |
| | Yes | 64 | 38 | 2.65 | [1.73 - 4.06] | <0.001 | | | | |
| ypN | 0 | 280 | 60 | 1 | | | <0.001 | 1 | | |
| | [1-3] | 55 | 29 | 3.19 | [2.05 - 4.98] | <0.001 | | 3.17 | [2.03 - 4.95] | **<0.001** |
| | 4 and more | 41 | 27 | 4.83 | [3.06 - 7.63] | <0.001 | | 4.52 | [2.85 - 7.17] | **<0.001** |

| | | | | | | |
|---|---|---|---|---|---|---|
| RCB class | RCB-0 | 1 2 3 | 18 | 1 | | <0.001 |
| | RCB-I | 2 3 | 4 | 1.22 | [0.41 - 3.61] | 0.717 |
| | RCB-II | 1 3 1 | 50 | 3.09 | [1.8 - 5.29] | <0.001 |
| | RCB-III | 4 2 | 30 | 9.16 | [5.08 - 16.54 ] | <0.001 |

*p* represents the p-value for the Wald test, and p* represents the individual p-value versus reference class. Abbreviations: pCR=pathological complete response; BMI=body mass index ; NST= no special type ; ER=estrogen receptor; PR=progesterone receptor; NAC=neoadjuvant chemotherapy; AC=anthracyclines; TILs=tumor infiltrating lymphocytes; RCB=residual cancer burden; LVI=lymphovascular invasion.

**Table S5.** Association between clinical and pathological pre and post-NAC parameters with relapse-free survival (*HER-2* BC population, univariate and multivariate analysis).

| ***HER2*-positive** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | **Univariate** | | | | **Multivariate** | | |
| **Variable** | **Class** | **Number** | **Events** | **HR** | **CI** | **p*** | ***p*** | **HR** | **CI** | **p** |
| Pre-NAC parameters | | | | | | | | | | |
| **Age** | [0 -50) | 169 | 49 | 1 | | | 0.066 | | | |
| | [50 -60) | 79 | 12 | 0.48 | [0.25 - 0.9] | **0.022** | | | | |
| | 60+ | 47 | 10 | 0.74 | [0.37 - 1.46] | 0.386 | | | | |
| **Menopausal status** | Pre | 179 | 51 | 1 | | | **0.039** | 1 | | |
| | Post | 115 | 20 | 0.58 | [0.35 - 0.97] | **0.039** | | 0.44 | [ 0.23 - 0.84 ] | **0.013** |
| **BMI** | 18.5-24.9 | 180 | 37 | 1 | | | 0.253 | | | |
| | <18.5 | 12 | 4 | 1.74 | [0.62 - 4.89] | | | | | |
| | 25-29.9 | 66 | 19 | 1.52 | [0.87 - 2.64] | | | | | |
| | >=30 | 35 | 11 | 1.71 | [0.87 - 3.37] | | | | | |
| **Smoking status** | No | 186 | 41 | 1 | | | 0.563 | | | |
| | Yes | 54 | 14 | 1.2 | [0.65 - 2.2] | | | | | |
| **BRCA mutation genes** | BRCA1 | 1 | 1 | 1 | | | 0.423 | | | |
| | BRCA2 | 3 | 0 | 0 | [0 - Inf] | | | | | |
| | No | 63 | 17 | 0.26 | [0.03 - 1.96] | | | | | |
| **Clinical T stage (TNM)** | T0-T1 | 18 | 1 | 1 | | | 0.167 | | | |
| | T2 | 196 | 47 | 4.69 | [0.65 - 34] | 0.126 | | | | |
| | T3-T4 | 80 | 22 | 6.06 | [0.82 - 44.95] | 0.078 | | | | |
| **Clinical N stage (TNM)** | N0 | 119 | 24 | 1 | | | 0.208 | | | |
| | N1-N2-N3 | 176 | 47 | 1.37 | [0.84 - 2.24] | | | | | |
| **Histological type** | NST | 276 | 66 | 1 | | | 0.645 | | | |
| | Others | 3 | 1 | 1.59 | [0.22 - 11.48] | | | | | |
| **KI67** | [0-10) | 3 | 2 | 1 | | | 0.244 | | | |
| | [10-20) | 15 | 3 | 0.22 | [0.04 - 1.3] | | | | | |
| | >=20 | 108 | 34 | 0.42 | [0.1 - 1.76] | | | | | |
| **SBR grade** | Grade I-II | 100 | 34 | 1 | | | **0.006** | 1 | | |
| | Grade III | 182 | 33 | 0.51 | [0.32 - 0.83] | **0.006** | | 0.39 | [ 0.23 - 0.68 ] | **0.001** |
| **LVI** | No | 41 | 11 | 1 | | | 0.085 | | | |
| | Yes | 49 | 21 | 1.91 | [0.91 - 3.99] | 0.085 | | | | |
| **DCIS component** | No | 136 | 20 | 1 | | | **0.006** | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Yes | 114 | 33 | 2.19 | [1.25 - 3.82] | **0.006** | |
| **CT regimen (NAC)** | anthra-taxanes | 218 | 40 | 1 | | | **<0.001** |
| | anthra | 39 | 19 | 3.2 | [1.85 - 5.54] | **<0.001** | |
| | taxanes | 16 | 3 | 1.12 | [0.35 - 3.63] | 0.848 | |
| | others | 22 | 9 | 2.64 | [1.28 - 5.45] | **0.009** | |
| Post-NAC parameters | | | | | | | |
| **pCR** | No pCR | 182 | 57 | 1 | | | **<0.001** |
| | pCR | 113 | 14 | 0.35 | [0.2 - 0.64] | **<0.001** | |
| **Post-NAC LVI** | No | 124 | 20 | 1 | | | **<0.001** |
| | Yes | 49 | 28 | 4.93 | [2.77 - 8.78] | **<0.001** | |
| **ypN** | 0 | 205 | 35 | 1 | | | **<0.001** |
| | [1-3] | 70 | 28 | 2.7 | [1.64 - 4.43] | **<0.001** | |
| | 4 and more | 20 | 8 | 2.69 | [1.24 - 5.8] | **0.012** | |
| **RCB class** | RCB-0 | 68 | 2 | 1 | | | **0.002** |
| | RCB-I | 24 | 1 | 1.52 | [0.14 - 16.78] | 0.732 | |
| | RCB-II | 69 | 19 | 10.35 | [2.41 - 44.46] | **0.002** | |
| | RCB-III | 15 | 6 | 16.53 | [3.33 - 81.99] | **<0.001** | |

*p* represents the p-value for the Wald test, and p* represents the individual p-value versus reference class. Abbreviations: pCR=pathological complete response; BMI=body mass index ; NST= no special type ; ER=estrogen receptor; PR=progesterone receptor; NAC=neoadjuvant chemotherapy; AC=anthracyclines; TILs=tumor infiltrating lymphocytes; RCB=residual cancer burden; LVI=lymphovascular invasion.

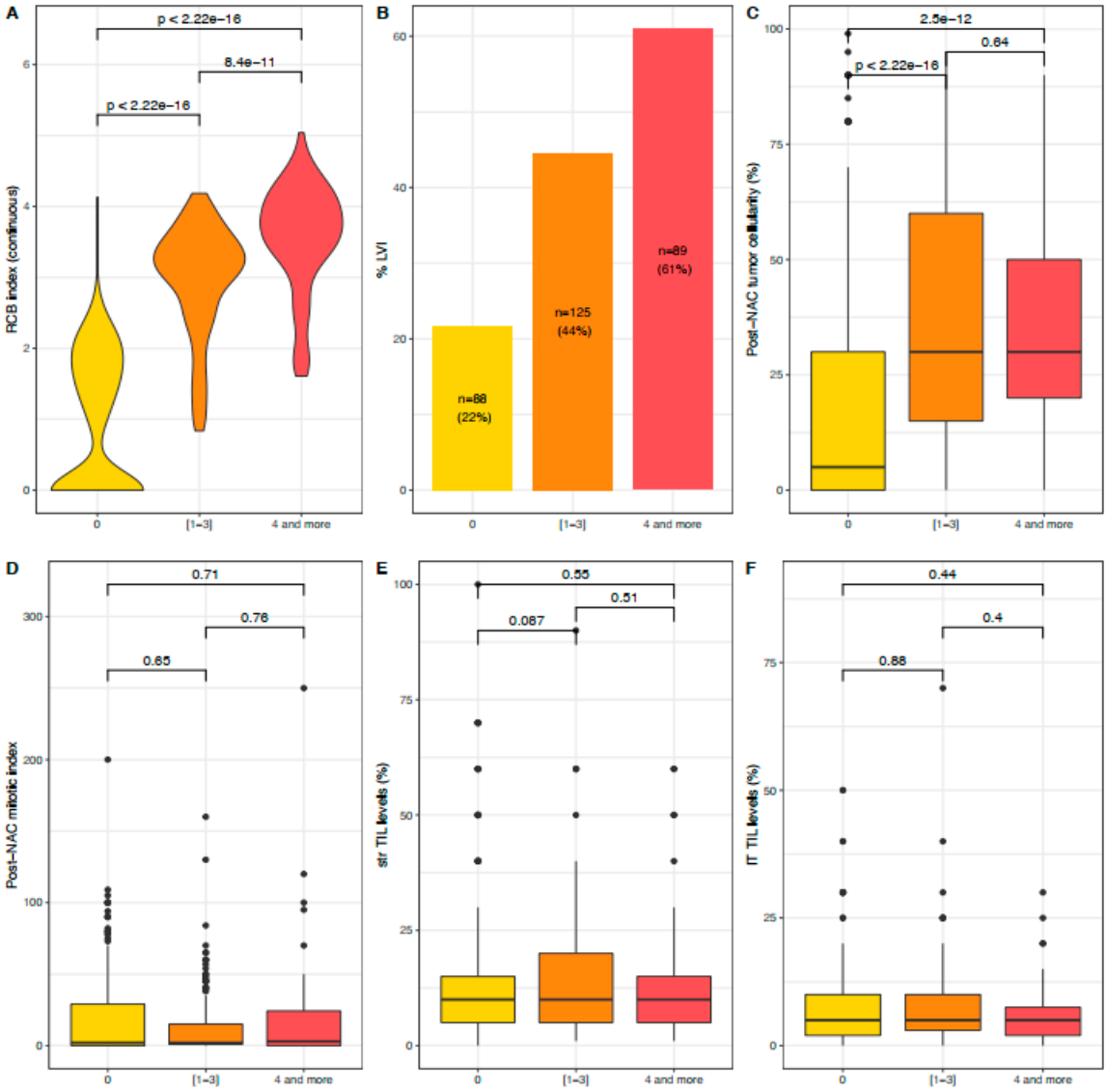


**Figure S1.** Association between post-NAC involvement and tumor characteristics in the whole population: RCB index (A); Lymphovascular invasion (B); Tumor cellularity (C); Post-NAC mitotic index (D); Stromal TIL levels (E). Intra tumoral (IT) TIL levels (F).

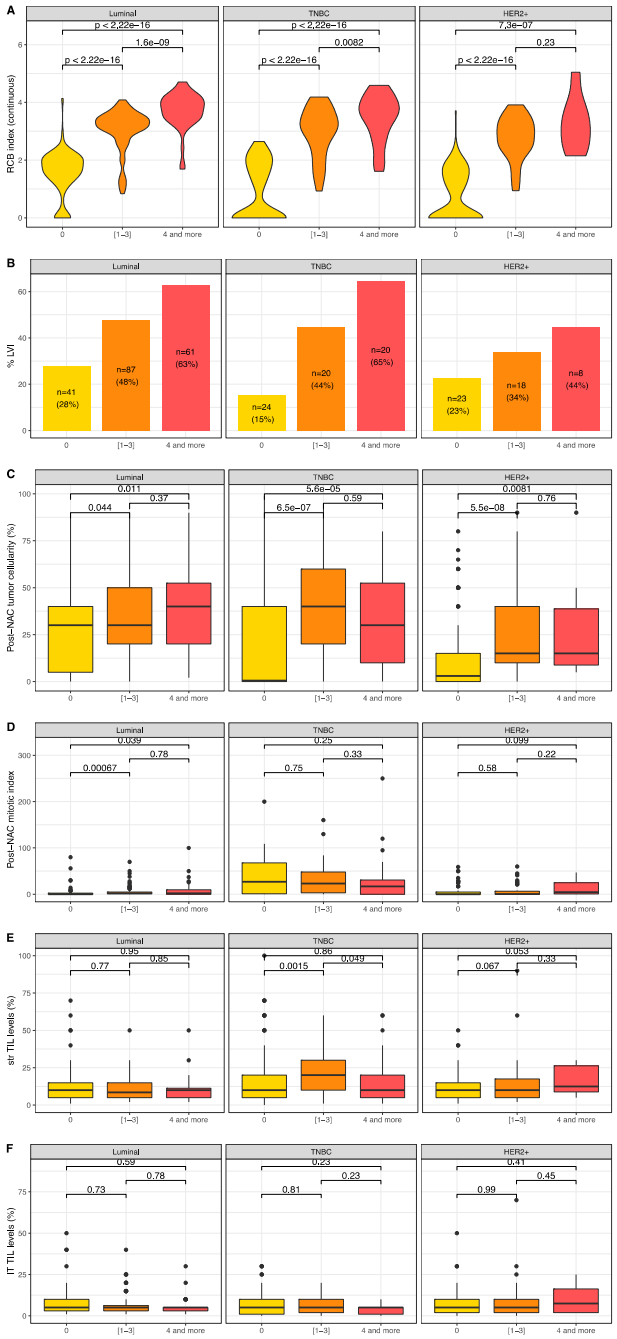


**Figure S2.** Association between post-NAC involvement and tumor characteristics according to BC subtype: RCB index (A); Lymphovascular invasion (B); Tumor cellularity (C); Post-NAC mitotic index (D); Stromal TIL levels (E). Intra tumoral (IT) TIL levels (F).

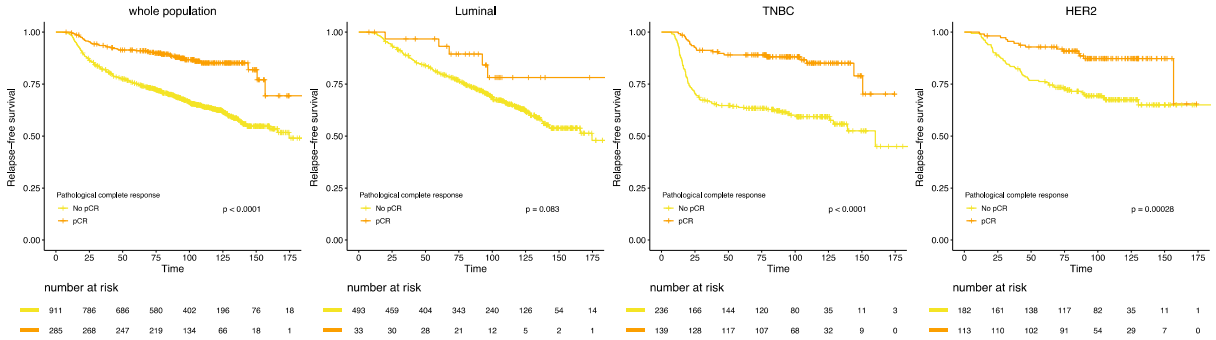


**Figure S3.** Relapse Free Survival (RFS) according to pCR after neoadjuvant chemotherapy in the whole population and according to breast cancer subtype.

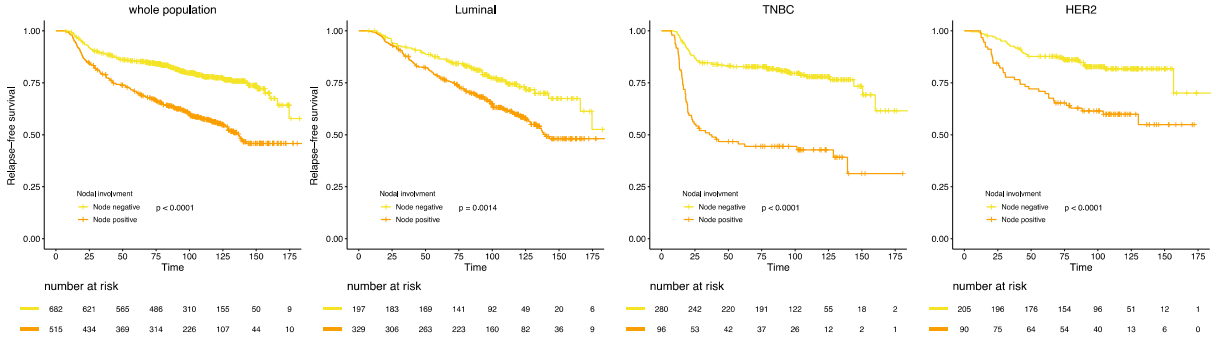


**Figure S4.** Relapse Free Survival (RFS) according to nodal status after neoadjuvant chemotherapy in the whole population and according to breast cancer subtype.