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## **The Influence of treatment intervals on prognosis in young breast cancer patients: Insights from the French national cohort**

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**Enora Laas** : conceptualization, methodology, data curation, formal analysis, writing original draft; **Elise Dumas** : data curation, software, validation, **Anne-Sophie Hamy** : conceptualization,resources, validation **Thomas Gaillard** : data curation, software, methodology, validation **Paul Gougis** : methodology, software, validation, **Fabien Reyat** : methodolgy, project administration **François Husson** : conceptualization, methodology, supervision **Anne-Sophie Jannot** : conceptualization, methodology, supervision

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1  
2 **The Influence of treatment intervals on prognosis in young breast cancer**  
3 **patients: Insights from the French national cohort**  
4

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31 treatment intervals  
32  
33

34 **Highlights**

- 35       • Increased treatment intervals are associated with poorer survival in young  
36       women with non-metastatic breast cancer (BC)
- 37       • The intervals between adjuvant chemotherapy and radiotherapy, and the  
38       interval between neoadjuvant chemotherapy and surgery had significant  
39       impacts on patient survival.
- 40       • Care delays optimization is associated with a 1.2-fold decreased risk for  
41       recurrence or mortality compared to non-optimal delays

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44 **Abstract**

45 **Background:** Suboptimal treatment delays is known to impact prognosis of patients  
46 with cancer but optimal timing in specific subgroups remains poorly studied. This study  
47 aimed to analyze treatment delays in young women treated for a breast cancer (BC)  
48 on and its impact on their prognosis using French Nationwide Data.

49 **Methods:** Using the CAREPAT-YBC Cohort based on the French National Healthcare  
50 System Database, we analyzed disease-free survival (DFS) in 22,093 young women  
51 (18-45 years) who underwent either surgery-chemotherapy-radiotherapy pathway  
52 (adjuvant setting, 15,433 patients) or chemotherapy-surgery-radiotherapy pathway  
53 (neoadjuvant setting, 6,660 patients), according to delays between the different  
54 pathways.

55 **Results:** For the adjuvant chemotherapy-radiotherapy interval, the best timing was 17-  
56 31 days with increased risk above this delay. For the neoadjuvant setting, the optimal  
57 neoadjuvant chemotherapy-surgery interval was 17-31 days, while  $\leq 15$  days (HR 1.44,  
58 95%CI 1.21-1.71) or  $\geq 62$  days (HR 2.07, 95%CI 1.36-3.15) showed poorer prognosis.  
59 Combining best timing into an "optimal pathway" was associated with respectively a  
60 1.2-fold decreased risk for recurrence or mortality.

61 **Conclusion:** Optimizing treatment intervals enhance BC survival in younger age.

## 62 INTRODUCTION

63 Breast cancer (BC) in women under 45 years-old represents up to 10% of all BC  
64 cases.[1] Younger age is associated with poorer prognosis in BC compared to their  
65 older counterparts[2–6]. It has been suggested that younger age could be associated  
66 with diagnostic delays that could explain poorer outcomes[7,8]. Indeed, young BC  
67 patients have to face care pathway challenges particularities compared to older  
68 patients: at cancer diagnosis, with the absence of organized screening and the  
69 frequent need of MRI and after diagnosis, for procedures such as oncogenetics  
70 consultation[9], fertility preservation discussions, oncoplastic surgery, immediate  
71 reconstruction. All these further steps could contribute to potential treatment delays.

72  
73 Despite its recognized importance, the impact of the different delays between  
74 treatments in young BC patients remains controversial[10–16]. European Society of  
75 Breast Cancer Specialists (EUSOMA) [17,18] recommend that the interval between  
76 each treatment steps should not exceed 8 weeks. However, this recommendation was  
77 developed using data from a cohort with a median age of 63 years and fails to capture  
78 the complexity of the relationship between delay and survival: a delay that is either too  
79 short or too long may have a negative impact. This highlights the need for a more  
80 precise consideration of delays between treatment steps in young BC patients.  
81 Moreover, BC is a heterogeneous disease with multiple subtypes, each characterized  
82 by distinct biological features, treatment pathways, and survival outcomes. This  
83 diversity necessitates subtype-specific approaches to treatment and pathways and  
84 underscores the importance of understanding how different therapeutic modalities  
85 impact prognosis across these varied forms of BC.

86 The French National Healthcare System Database (SNDS) compiles extensive  
87 medical and administrative data, providing a rich resource for analyzing cancer care,  
88 including treatment sequence impact on prognosis and its potential confounding in all  
89 patients having had BC in France[19,20].

90 Using this real-life population, we focused on young women with BC who underwent  
91 either surgery-chemotherapy-radiotherapy pathway (adjuvant setting) or  
92 chemotherapy-surgery-radiotherapy pathway (neoadjuvant setting). Our objective was  
93 to describe the time intervals between the treatment steps and its determinants and to

94 highlight the optimal timeframe for the different treatments regarding patients' disease-  
95 free survival.  
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## 97 METHODS

98 This cohort study was authorized by the French data protection agency (Commission  
99 nationale de l'informatique et des libertés) with registration number 920304. Written  
100 informed consent from patients was not required, in compliance with French  
101 regulations.

### 102 **Population selection**

103  
104 We performed a retrospective cohort study using data from the CAREPAT-YBC cohort,  
105 following the REporting of studies Conducted using Observational Routinely-collected  
106 Data (RECORD) statement[21].The CAREPAT-YBC cohort is a nearly exhaustive  
107 cohort of young women patients treated for BC in France, derived from the French  
108 National Health Data System. For data extraction, we used a specific methodology  
109 described elsewhere[19].

110 Patients with suspected locoregional or distant metastases at diagnosis, or with  
111 concomitant or previous cancer, were excluded. We included from this cohort all  
112 women who have undergone surgery for BC between 18-45 yo between January 1,  
113 2010, and December 31, 2018 and who underwent either surgery-chemotherapy-  
114 radiotherapy pathway (adjuvant setting) or chemotherapy-surgery-radiotherapy  
115 pathway (neoadjuvant setting). Treatment data were used to infer the BC subtype, as  
116 no histological information was available in the database. Tumors were classified as  
117 *HER2*-positive if patients received anti-*HER2* therapy, as luminal if treated with ET,  
118 and triple-negative (TNBC) if receiving chemotherapy without ET or anti-*HER2*  
119 therapy. Tumors treated only with surgery and/or radiotherapy were labeled as having  
120 an undefined subtype.

### 121 **Variables definition**

122 The following variables were extracted or reconstructed according to the specific  
123 methodology described elsewhere: age at surgery, BC subtype, diagnostic procedure,  
124 breast surgery type, care structure for breast surgery, axillary surgery, targeted  
125 therapy, endocrine therapy, fertility preservation, immediate BC reconstruction and  
126 type. Median income of the patient's residential area were retrieved from census data  
127 as a proxy for socio-economic environment. We also extracted 58 health conditions

128 (grouped into 15 categories) using the algorithms that have been previously developed  
129 from the medical information available in SNDS[22]

130 The Aarhus checklist, which ensures precision and transparency in both definitions  
131 and methods in early cancer treatment interval research, has been completed[23].

132

133 We analyzed pathways according to two different setting, corresponding to the  
134 standard of care in early breast cancer management.

135 Regarding the neoadjuvant setting, diagnosis-neoadjuvant chemotherapy (NAC)  
136 interval was estimated as the time between the diagnostic procedure and the first  
137 session of chemotherapy, NAC-surgery interval as the time between the last session  
138 of chemotherapy and the date of the first surgery for BC and surgery-radiotherapy  
139 interval as the time between the last surgery for BC and the first session of  
140 radiotherapy.

141 Regarding the adjuvant setting, diagnosis-surgery interval was estimated as the time  
142 between the diagnostic procedure and the first surgery for BC, surgery-adjuvant  
143 chemotherapy (adj CT) interval as the time between the last surgery for BC and the  
144 first session of chemotherapy and adj CT-radiotherapy interval as the time between  
145 the last session of chemotherapy and the first session of radiotherapy.

146 Recurrence events (local or distant) were identified as a new treatment (chemotherapy,  
147 radiotherapy, or surgery) for a BC code, occurring more than 6 months after the last  
148 treatment or a diagnostic code indicating metastasis or a molecule specific to the BC  
149 metastatic treatment.

## 150 **Study endpoints**

151 We implemented a one-year landmark after diagnosis to help addressed the wait time  
152 paradox, where the most severe cases are treated more quickly, and to ensure that  
153 most patients had completed their treatment.

154 Disease-free survival (DFS) was defined as the time from the diagnosis to recurrence  
155 or death. Patients were censored on December 31, 2018.

**156 Statistical analysis**

157

158 Quantitative variables were presented as median (IQR) and qualitative variable as  
159 counts (frequency). Associations between patient's characteristics and treatment  
160 intervals were assessed using an ANOVA. We cut intervals into 15-days periods ("1-  
161 16 days", "17-31 days", "32-46 days", "47-61 days", "62-76 days", "77-91 days" and  
162 "more than 91 days") and considered these intervals as an ordinal variable. This  
163 decision balances granularity and statistical power, ensuring that each interval is large  
164 enough for robust analysis while maintaining the clinical relevance of the findings. The  
165 "17-31 days" interval was chosen as the reference, as it was the most clinically  
166 relevant, acknowledging that an interval that is too short could be as detrimental as  
167 one that is too long.

168 Univariable and multivariable Cox model analyses were performed to assess the  
169 association between each interval and survival, after adjustment for confounding  
170 factors, using a stepwise regression approach based on the Akaike Information  
171 Criterion, employing backward selection.

172 An "optimal pathway" was defined as the combination of optimal treatment intervals  
173 (i.e. the one giving the best survival) in each treatment sequence and compared to all  
174 other pathways.

175 Analyses were further stratified by BC subtypes, care structure and age.

176 Analyses were performed with R software, version 4.0.1[24].

## 177 RESULTS

### 178 Population description

179 From 2010 to 2018, 22,093 patients aged 18 to 45 were treated for non-metastatic BC,  
180 15,433 patients (70%) had an adjuvant setting, while 6,660 (30%) underwent a  
181 neoadjuvant setting (Table 1).

### 182 Treatment intervals description and determinants

183 The distribution of the different care intervals is displayed on Figure S1.

#### 184 *Neoadjuvant Setting* (Figure S2-S4)

##### 185 Diagnosis-NAC interval

186 In the neoadjuvant setting (n = 6,660), over 97% of patients experienced a diagnosis-  
187 NAC interval of 8 weeks or less, consistently across patients' characteristics. Older  
188 patients (41-45 yo) were more likely to experience a diagnosis-NAC interval of more  
189 than 4 weeks (44.7% vs. 37.3% at 18-25 yo, 35.8% at 26-30 yo, 36.9% at 31-36 yo,  
190 39.4% at 36-40 yo,  $p < 0.001$ ). Patients with luminal tumors experienced a longer  
191 interval with 44.1% of patients treated after 4 weeks vs. 37.5% in *HER2*-positive  
192 patients and 38.7% in TNBC,  $p < 0.001$ . Patients treated in cancer care centers,  
193 private or semi-private structures were more likely to be treated within 4 weeks (61%,  
194 60% and 62% respectively vs. 52% in university hospitals and 55% in general  
195 hospitals,  $p < 0.001$ )(Figure S2).

##### 196 NAC-Surgery interval

197 For the NAC-surgery interval, 99% of patients experienced an interval within 8  
198 weeks. 91% of patients with *HER2*-positive tumors underwent surgery within 4  
199 weeks, vs. 56.7% in TNBC and 54.7% in luminal cancer ( $p < 0.001$ ). This interval was  
200 consistent across different care structures (Fig S3).

##### 201 Surgery-Radiotherapy interval

202 Radiotherapy was predominantly (71.5%) administered between 4 and 8 weeks,  
203 unaffected by age ( $p = 0.2$ ). Patients with postoperative complications were more  
204 likely to receive radiotherapy after 8 weeks (49% vs. 32.6% if no postoperative  
205 complication,  $p=0.001$ ) (FigS4).

206 *Adjuvant Setting* (Figure S5-S7)

207 Diagnosis-Surgery interval

208 In the adjuvant setting ( $n = 15,644$ ), 95% of patients had a diagnosis-surgery interval  
209 within 8 weeks. Patients aged 18-25 yo were more likely to be treated within 4 weeks  
210 (69%), compared to patients aged 40-45 yo (57%,  $p>0.001$ ) (FigS5).

211 Surgery-Adj CT interval

212 93.1% of patients experienced a surgery-adj CT interval up to 8 weeks. This interval  
213 increased with age, with 37% of patients managed within 4 weeks at ages 18-25 and  
214 25.8% at 41-45 yo. Patients with luminal tumors were also more likely to receive their  
215 chemotherapy more than 8 weeks after surgery (75.1% vs. 64.9% in *HER2*-positive  
216 tumors and 64.2% in TNBC,  $p<0.001$ ). Patients receiving immediate breast  
217 reconstruction with a free-flap had a higher likelihood of an interval of more than 8  
218 weeks after surgery before receiving chemotherapy (38% vs. 6.2% for patients with  
219 no reconstructive surgery) (FigS6).

220 Adj CT-Radiotherapy interval

221 Seventy-nine percent of patients had an adjuvant chemotherapy-radiotherapy interval  
222 between 2 and 8 weeks with no clinically significant differences based on patient  
223 characteristics (FigS7).

224 **Impact of treatment intervals on prognosis**

225 During the study period, 1,272 deaths occurred, 672 in the neoadjuvant setting and  
226 600 in the adjuvant setting. Age, molecular subtype, breast surgery type, salary level,  
227 and care structure showed significant associations with prognosis, with poorer  
228 prognosis for younger patients, TNBC, or patients managed in university hospital  
229 (FigureS8).

230 Univariate analysis showed significant associations between each treatment interval  
231 and prognosis (Figure 1). After adjusting for confounding factors (age, care structure,  
232 surgical procedure, income environment, post-operative complications, obesity,  
233 comorbidities, psychiatric disease and year of diagnosis), the chemotherapy-  
234 radiotherapy interval in the adjuvant setting, as well as the NAC-surgery interval in the  
235 neoadjuvant setting, remained significantly associated with prognosis (Figure 2).

236

### 237 *Adjuvant setting*

238 No impact on DFS was found for the interval between diagnosis and surgery, nor for  
239 the interval between surgery and adjuvant chemotherapy.

240 Regarding the interval between adj CT and radiotherapy, a longer interval was  
241 associated with a poorer prognosis. Compared to patients managed within 17-31-days,  
242 prognosis increased by 1.14 (adjusted aHR 1.14 95%CI: 1.09-1.29) for patients  
243 managed between 31-46-days and further increased to 1.85 (95%CI: 1.51-2.27) for  
244 patients managed after 3 months. These findings remained consistent across  
245 molecular subtypes, care structures and age classes (Figures S9-S19).

246

### 247 *Neoadjuvant setting*

248 In the neoadjuvant setting, only NAC-surgery interval was significantly associated to  
249 prognosis with the optimal timing for the NAC-surgery interval within the 17–31-day  
250 period. Prognosis was adversely affected when surgery was performed either too soon  
251 (within the first 15 days, aHR 1.31, 95%CI 1.09-1.58) or too late (aHR 2.16, 95%CI  
252 1.42-3.30 for surgery between 62-76 days). These results were consistent across  
253 molecular subtypes, care structures, and age groups (Supplemental Figures S20-28).

254

### 255 *Optimal pathway*

256

257 An optimal pathway was subsequently defined, incorporating the optimal intervals for  
258 each treatment setting. In the adjuvant setting, this pathway was defined as an adj CT-  
259 radiotherapy interval of 16-31-days, irrespective of the interval between diagnosis and  
260 surgery and surgery and adj CT. Seventy-five percent of patients had a sub-optimal

261 adjuvant pathway, which was associated with a 1.25-fold increased risk for recurrence  
262 or mortality compared to an optimal pathways (95%CI 1.13-1.38)(Fig3AB).  
263 In the neoadjuvant setting, the optimal pathway was defined by a neoadjuvant  
264 chemotherapy (NAC) to surgery interval of 17-31-days, regardless of the duration of  
265 other treatment intervals. Eighty-six percent of patients had a sub-optimal neoadjuvant  
266 pathway, which resulted in a 1.2-fold increased risk for recurrence or mortality  
267 compared to an optimal pathways(HR 1.2 95%CI 1.09-1.36)(Fig3CD).  
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269 **DISCUSSION**

270 Using a nationwide database covering nearly the entire population of young French  
271 women with BC between 2010 and 2018, we found that certain time intervals  
272 between treatments significantly affect prognosis: notably, the adj CT-radiotherapy  
273 interval in the adjuvant setting, as well as the NAC-surgery interval. Our analysis  
274 revealed that an optimal care pathway could result in a 1.2-fold decreased risk for  
275 recurrence or mortality. Socioeconomic and healthcare-related factors, such as a  
276 patient's income environment and the type of care structure, were identified as  
277 significant influences on these treatment intervals. Patients from more deprived  
278 backgrounds and those attending private facilities experienced longer intervals,  
279 although this relationship varied across different types of intervals.

280 Our findings align with several studies suggesting that not all treatment intervals are  
281 associated with prognosis. The time in initiating NAC within six months of  
282 diagnosis[14], or the timing of surgery following NAC do not seem to significantly  
283 affect prognosis[25]. Similarly, while some research suggests that time intervals in  
284 adjuvant chemotherapy could lead to worse prognosis[26,27], other studies found  
285 that chemotherapy remain equally effective up to 12 weeks post-surgery[15].

286 In our study, the interval between adj CT and radiotherapy showed a significant and  
287 clinically relevant impact on patient prognosis, consistent with literature indicating  
288 that starting radiotherapy within up to 8 weeks is associated with better DFS and  
289 OS[28,29].

290 An optimal interval of 16-31-days for the NAC-surgery interval aligns with previous  
291 guidelines, suggesting 2-4 weeks post-NAC as the most suitable timing for  
292 surgery[30] and emphasizing the risk associated with performing surgery too soon  
293 after chemotherapy. A meta-analysis by Su et al. demonstrated that an interval  
294 longer than 4 weeks had a negative impact on prognosis[31]. This interval is crucial  
295 as longer waiting times could negatively impact prognosis due to potential tumor  
296 growth, despite data suggesting otherwise[32].

297 The rationale for an optimal period, neither too early nor too late, could be based on  
298 a compromise between the immunosuppression after chemotherapy in early cases

299 and the risk of developing micro-metastases in later cases. Initiating treatment too  
300 early may not allow sufficient time for patients to recover from previous treatment or  
301 for comprehensive evaluations to be completed, potentially leading to complications  
302 or inappropriate treatment choices. The fact that a shorter delay does not necessarily  
303 lead to a better prognosis has already been raised by Hanna et al. In their study, a  
304 4% excess mortality was found for patients who had their surgery within 2 weeks,  
305 although this may be due to the biased fact that patients with the most serious  
306 conditions are treated more quickly [33]. Aside from this point, this study consistently  
307 found that longer delays result in worse outcomes for BC.

308 Our study corroborates that care structures and income levels have a significant  
309 impact on treatment intervals. Most treatment intervals are predictable and modifiable  
310 with better healthcare coordination. Knowing the chemotherapy end date in advance  
311 allows for the scheduling of subsequent treatments, and having a planned surgery  
312 date makes organizing subsequent treatments straightforward.

313 Income disparities contribute to longer treatment intervals, highlighting persistent  
314 socioeconomic inequities in healthcare access and delivery. Xiaofang et al. identified  
315 that black race, rural residence, mastectomy, and single status were risk factors  
316 associated with delay in adjuvant chemotherapy among non-metastatic patients[34].

317 To the best of our knowledge, this is the first study focusing on the impact of delays  
318 between steps in young women treated for early BC. Younger patients experienced  
319 specific situations such as the absence of a screening program, which could lead to a  
320 longer diagnostic interval, or specific exams (genetic, fertility, MRI) that could affect the  
321 delay. Recent studies suggest that a younger age was not associated with a delay in  
322 diagnosis[7,8]. The notion that delays could yield varying impacts according to age is  
323 not substantiated by our study, as the results are analogous to those found for older  
324 women in the literature.

325 This real-life population study reflects actual delays and potential influencing factors,  
326 such as care structure, BC subtype, age, salary level, living area... The SNDS is one  
327 of the largest exhaustive nationwide aggregated health data resources globally[35]. Its  
328 accuracy and reliability have been established for a broad range of medical conditions,

329 including BC[36–38]. By ensuring homogeneous treatment among patients, we  
330 enhanced the comparability of our groups and minimized indication bias.

331 One limitation lies in the accuracy of reimbursement indicators as proxies for the  
332 medical condition, leading to potential discrepancies or errors in coding methods  
333 across different centers, which could affect the validity of the results[39]. Our strict  
334 criteria for patient inclusion, while ensuring high-quality data, may also introduce a  
335 selection bias, potentially limiting the generalizability of our findings[40]. Most of the  
336 exclusions were due to the absence of chemotherapy or radiotherapy for medical  
337 reasons. Only 734 patients were excluded due to aberrations in treatment or coding,  
338 with a minimal impact on the surgery-radiotherapy interval.

339 One of the main biases of retrospective studies, including our own, is the waiting time  
340 paradox, where patients treated later often have a better prognosis due to physicians'  
341 implicit adaptation to the severity of the disease. In our study, we addressed this by  
342 selecting only patients who had received chemotherapy, aiming to mitigate this  
343 paradox by focusing on the most severe cases with homogeneous treatment and  
344 conditions[41,42]. A landmark analysis was also carried out to take into account and  
345 reduce the effect of this bias. Another limitation of this study is the use of treatment  
346 receipt as an eligibility criterion, which confines the generalizability of our findings to  
347 patients with similar treatment regimens and characteristics. While this approach may  
348 introduce immortal time bias, it does not result in bias between groups, as all patients  
349 received the same standardized treatment protocol. However, this limitation may  
350 restrict the extrapolation of our results to broader patient populations. The immortality  
351 bias was then addressed using a landmark analysis.

352

353 Additionally, we defined BC subtypes based on treatment, which may not accurately  
354 represent all patients. Finally, the absence of clinical parameters limited the ability to  
355 adjust for potential confounding factors.

356 In conclusion, the management timeline of BC influences patient prognosis.

357 Identifying and addressing the factors contributing to these delays could potentially  
358 enhance outcomes for patients. This strategy is not only more straightforward and  
359 quicker but also less costly than many expensive treatments. Given our findings on  
360 the effects of care structures and socioeconomic status, strategies should be

361 developed to address these disparities and ensure equitable access to timely and  
362 effective cancer care.

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365 Declaration of Generative AI and AI-assisted technologies in the writing process’.  
366  
367 During the preparation of this work the authors used ChatGPT in order to correct english  
368 grammar. After using this tool, the authors reviewed and edited the content as needed and  
369 take full responsibility for the content of the publication.  
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Variable	Overall, N = 22,093 <sup>1</sup>	Adjuvant chemotherapy, N = 15,433 <sup>1</sup>	Neoadjuvant chemotherapy, N = 6,660 <sup>1</sup>
<b>Age</b>	40.1 (36.3, 42.8)	40.5 (36.9, 43.0)	39.1 (34.9, 42.3)
<b>Age (class)</b>			
18-25	129 (0.6%)	71 (0.5%)	58 (0.9%)
26-30	1,017 (4.6%)	585 (3.8%)	432 (6.5%)
31-35	3,096 (14%)	1,890 (12%)	1,206 (18%)
36-40	6,543 (30%)	4,456 (29%)	2,087 (31%)
41-45	11,308 (51%)	8,431 (55%)	2,877 (43%)
<b>BC Subtype</b>			
Luminal	12,159 (55%)	9,352 (61%)	2,807 (42%)
HER2-positive	4,651 (21%)	2,918 (19%)	1,733 (26%)
TNBC	5,283 (24%)	3,163 (20%)	2,120 (32%)
<b>Diagnosis procedure</b>			
Biopsy + cytology	2,800 (13%)	1,487 (9.6%)	1,313 (20%)
Biopsy alone	17,781 (80%)	12,783 (83%)	4,998 (75%)
Cytology alone	492 (2.2%)	379 (2.5%)	113 (1.7%)
Imaging	1,020 (4.6%)	784 (5.1%)	236 (3.5%)
<b>Breast surgery</b>			
Lumpectomy	14,250 (65%)	10,451 (68%)	3,799 (57%)
Mastectomy	7,843 (35%)	4,982 (32%)	2,861 (43%)
<b>Radiotherapy</b>			
Yes	22,093 (100%)	15,433 (100%)	6,660 (100%)
<b>Chemotherapy</b>			
Yes	22,093 (100%)	15,433 (100%)	6,660 (100%)
<b>Targeted therapy</b>	4,651 (21%)	2,918 (19%)	1,733 (26%)
<b>Endocrine therapy</b>	15,371 (70%)	11,432 (74%)	3,939 (59%)
<b>Fertility preservation</b>	2,128 (9.6%)	1,462 (9.5%)	666 (10%)
<b>Income environment</b>	18,465 (16,640, 21,084)	18,473 (16,667, 21,004)	18,457 (16,595, 21,350)
Unknown		834	584
			250
<b>Care structure</b>			
University hospital	2,687 (13%)	1,842 (13%)	845 (13%)
General hospital	3,037 (14%)	2,287 (16%)	750 (12%)
Cancer care center	8,500 (40%)	5,274 (36%)	3,226 (50%)
Private structure	6,081 (29%)	4,632 (32%)	1,449 (22%)
Semi private structure	697 (3.3%)	525 (3.6%)	172 (2.7%)
Unknown		1,091	873
			218
<b>Post operative complication</b>	450 (2.0%)	337 (2.2%)	113 (1.7%)
<b>Immediate reconstructive surgery</b>			
IBRS	866 (3.9%)	604 (3.9%)	262 (3.9%)
No IBRS	21,227 (96%)	14,829 (96%)	6,398 (96%)
<b>Diagnosis-surgery (days)</b>	27 (19, 37)	27 (19, 37)	-
<b>Surgery - Adj CT (days)</b>	38 (29, 47)	38 (29, 47)	-

<b>Adj CT - RT (days)</b>	34 (26, 48)	34 (26, 48)	-
<b>Diagnosis-NAC (days)</b>	27 (18, 38)	-	27 (18, 38)
<b>NAC- Surgery (days)</b>	27 (19, 34)	-	27 (19, 34)
<b>Surgery - RT (days)</b>	51 (41, 65)	-	51 (41, 65)

<sup>1</sup> Median (IQR); n (%)

Adj : adjuvant; BC Breast cancer; CT: Chemotherapy, IBRS : Immediate Breast reconstructive surgery;NAC : Neoadjuvant chemotherapy; RT : Radiotherapy

Table 1 Description of the population according to the treatment setting

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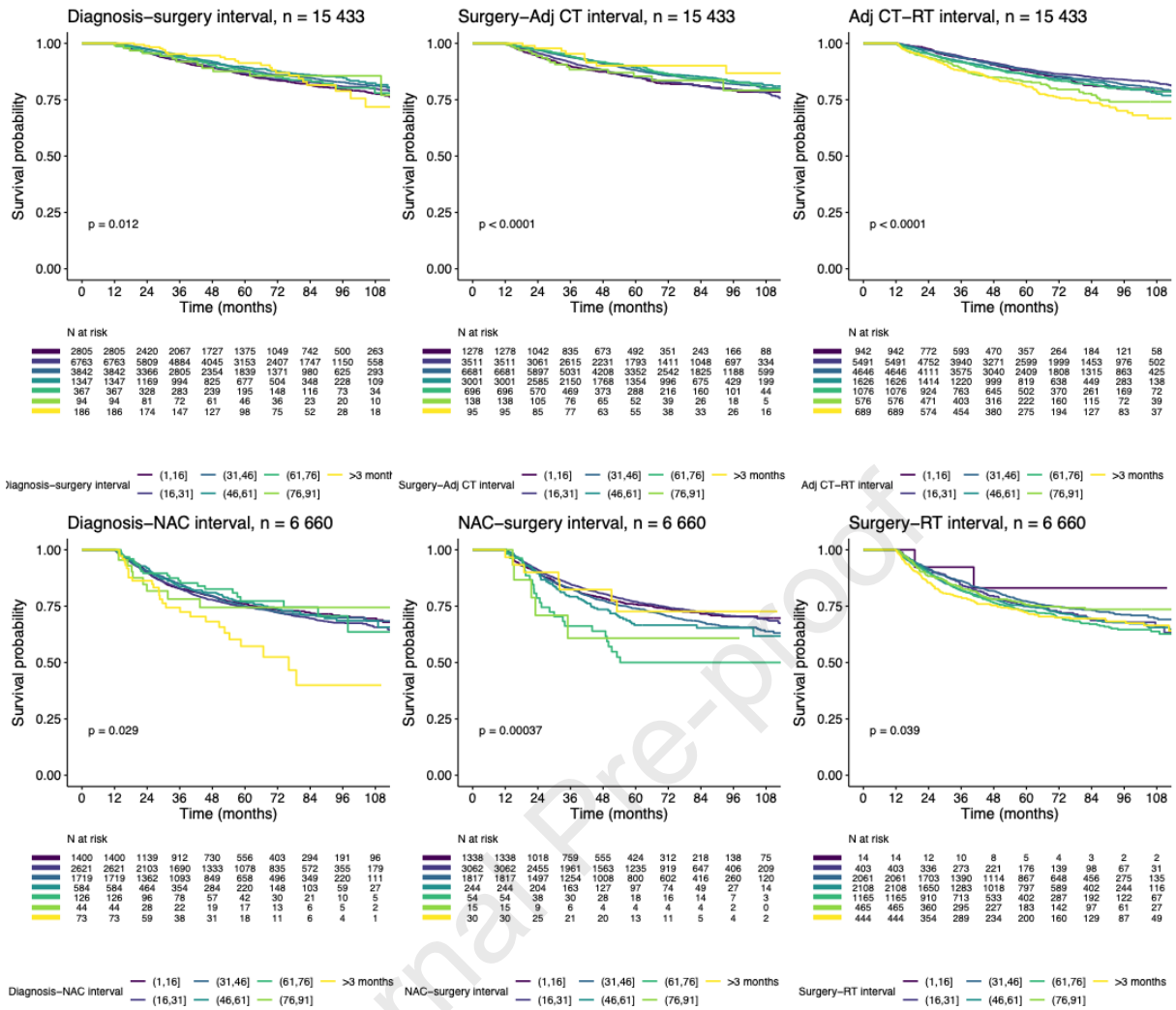
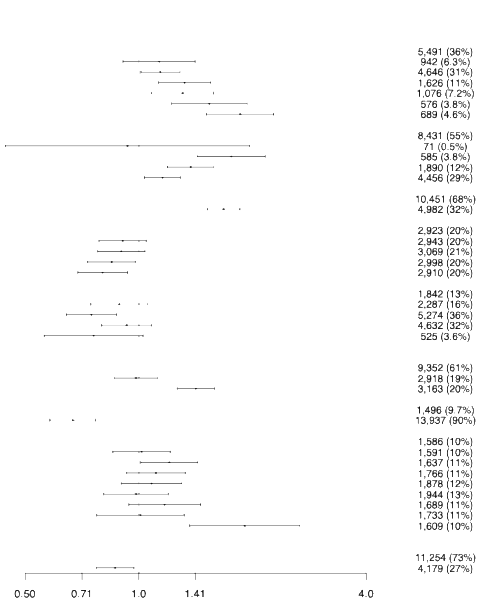


Figure 1 - Survival curves according to treatment intervals

A	is-surgery interval - Adj CT interval - RT interval		p-value
	1,16]	31,46]	
(16,31]	1.13	0.91, 1.41	0.4
(1,16]	1.14	1.01, 1.29	0.12
(31,46]	1.32	1.13, 1.55	<0.001
(46,61]	1.31	1.08, 1.58	
(61,76]	1.34	1.22, 1.94	
(76,91]	1.85	1.51, 2.27	
>3 months			
Age			<0.001
41-45			
18-25	0.93	0.44, 1.97	
26-30	1.76	1.43, 2.16	
31-35	1.37	1.19, 1.58	
36-40	1.15	1.03, 1.29	
Breast surgery type			<0.001
Lumpectomy			
Mastectomy	1.68	1.52, 1.85	
Income environment			0.054
(7820,16200]			
(16200,17600]	0.91	0.78, 1.05	
(17600,19300]	0.90	0.78, 1.04	
(19300,22000]	0.85	0.73, 0.98	
(22000,44600]	0.80	0.69, 0.93	
Care structure			<0.001
University hospital			
General hospital	0.89	0.75, 1.06	
Cancer care center	0.75	0.64, 0.87	
Private structure	0.93	0.80, 1.08	
Semi private structure	0.76	0.56, 1.03	
Post operative complication			>0.9
Molecular subtype			<0.001
Luminal			
HER2-positive	0.98	0.86, 1.12	
TNBC	1.42	1.26, 1.59	
Obesity			<0.001
Yes			
No	0.67	0.58, 0.77	
Year of diagnosis			0.011
2010			
2011	1.02	0.85, 1.21	
2012	1.20	1.01, 1.43	
2013	1.11	0.93, 1.33	
2014	1.08	0.90, 1.30	
2015	0.98	0.81, 1.20	
2016	1.17	0.94, 1.46	
2017	1.01	0.77, 1.32	
2018	1.91	1.36, 2.67	
Comorbidities			0.4
Psychiatric disease			0.013
No			
Yes	0.87	0.77, 0.97	

B



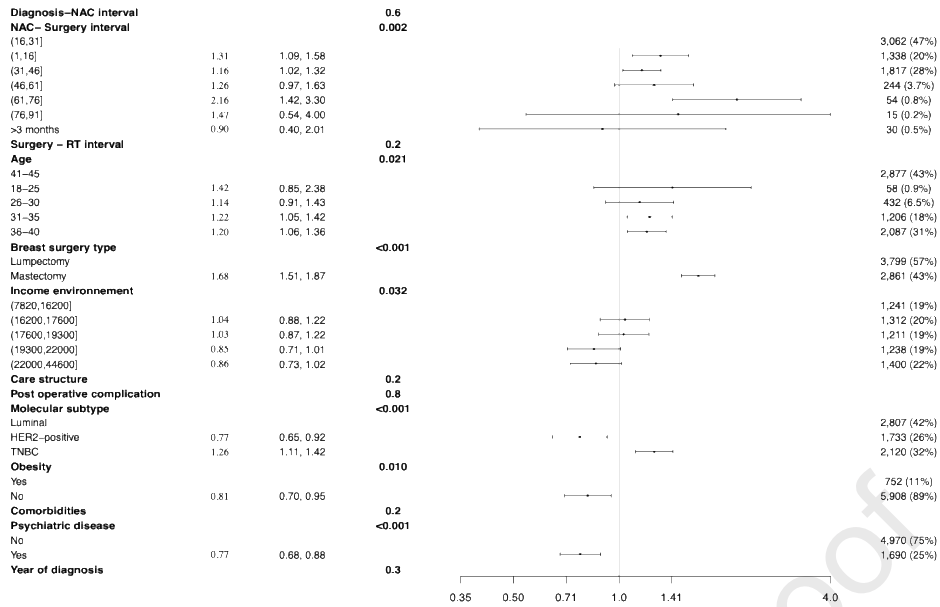
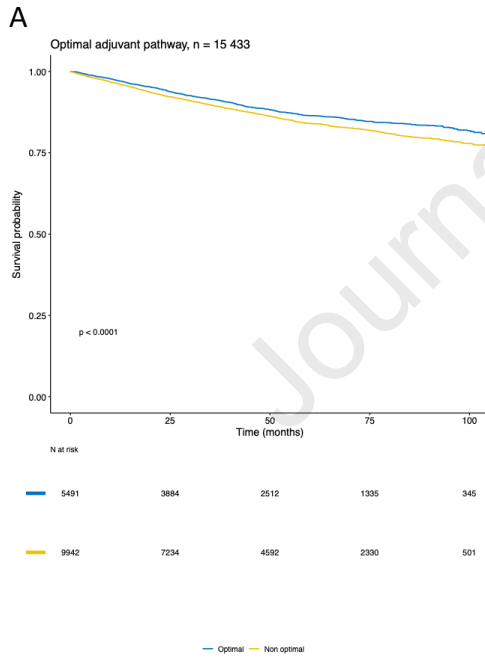
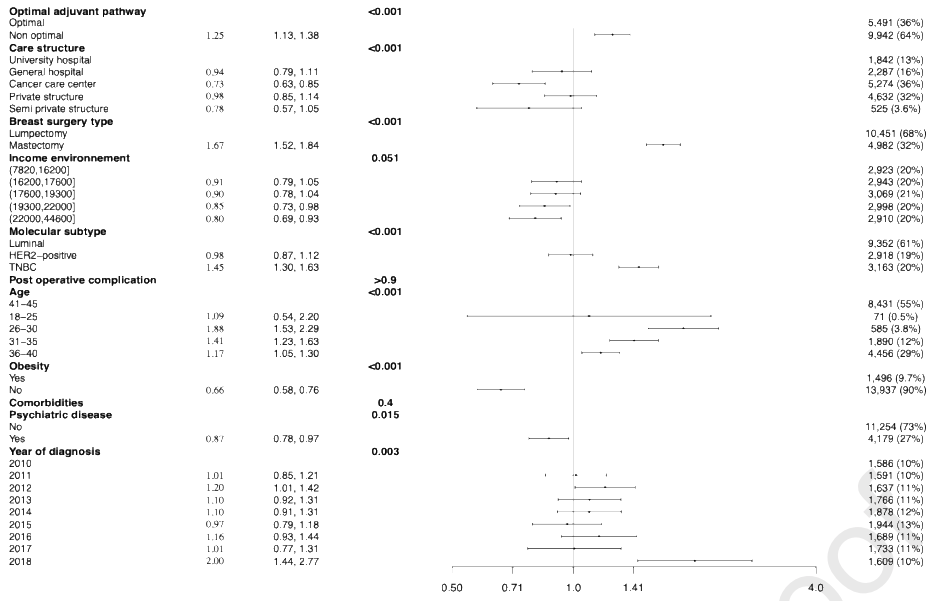


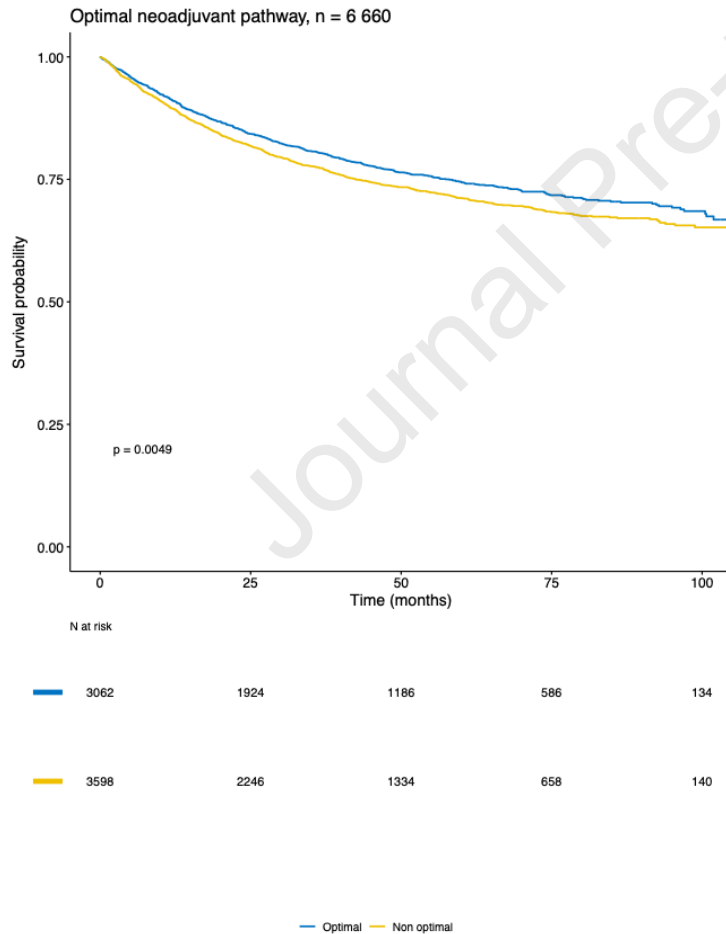
Figure 2 - Impact of time intervals on survival  
 A - Neoadjuvant setting (multivariable analysis)  
 B- Adjuvant setting (multivariable analysis)



**B**



C



D

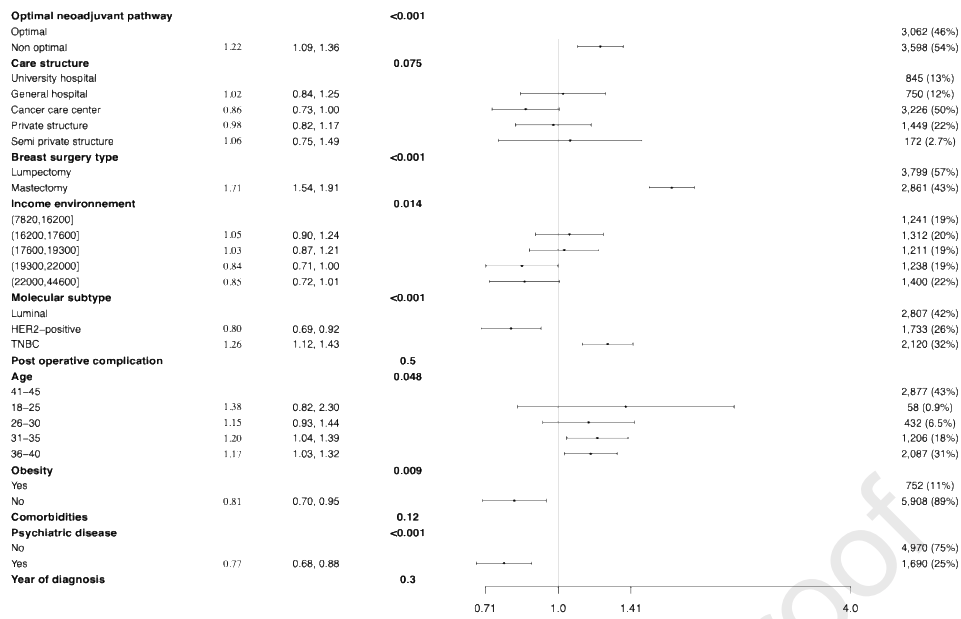


Figure 3 - Impact of optimal pathways on survival  
 A- Survival curve in neoadjuvant setting  
 B- After adjustment for cofounding factors in neoadjuvant setting  
 C- Survival curve in adjuvant setting  
 D- After adjustment for cofounding factors in adjuvant setting

**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for *[Journal name]* and was not involved in the editorial review or the decision to publish this article.

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