

Impact in delay of start of chemotherapy and surgery on pCR and survival in breast cancer – a pooled analysis of individual patient data from six prospectively randomized neoadjuvant trials

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Background

In the adjuvant setting a delay in starting treatment has been shown to have an impact on patients' outcome. The time interval between diagnostic biopsy and start of neoadjuvant chemotherapy (NACT) and its impact on disease-free (DFS) and overall survival (OS) has not been analyzed. To our knowledge, only one study assessed the relationship between this time interval and pathological complete response (pCR). In particular no difference was found in terms of pCR if patients started treatment before or after 28 days from diagnosis.¹

Patients could experience treatment-related toxicities and the waiting time for resolution could delay surgery. Moreover, scheduling surgery in a timely fashion after NACT may be a challenge for some hospitals due to organizational issues. It has been demonstrated that patients with NACT to surgery intervals of up to 8 weeks had equivalent OS, relapse-free survival and local relapse-free survival.² It is still unclear whether a delay of systemic therapy or surgery impacts patients outcome.

Materials and Methods

Overall 9127 patients with early breast cancer (BC) from 6 German neoadjuvant trials receiving an anthracycline-taxane based NACT were included. pCR (ypT0/is ypN0), disease free survival (DFS) and overall survival (OS) were compared according to the **time interval from diagnostic biopsy to NACT (TBC)** start and from **last chemotherapy application to surgery (TCS)** length (cut-off of ≤28 vs >28 days (d)). The analysis has been conducted in the overall cohort and in subgroups (BC subtypes [luminal, HER2+, triple-negative breast cancer (TNBC)] and pCR [yes vs no] for survival endpoints), adjusted by study.

Objectives

1. Describe the median (range) time to NACT (TBC) and time to surgery after NACT (TCS)
2. Analyse the frequency of TBC and TCS length ≤28d vs >28d (predefined cut-off)
3. Analyse the impact of TBC length on pCR and of TBC and TCS length on DFS and OS

Results

Table 1: Baseline characteristics

CHARACTERISTICS	N	%*
AGE (median [range])	49 [21-80]	
BMI		
<18.5 (underweight)	135	1.5
18.5-<25 (normal weight)	4409	48.4
25-<30 (overweight)	2826	31.0
≥30 (obese)	1745	19.1
cT		
cT1	1130	12.4
cT2	5637	62.0
cT3-4	2329	25.6
cN		
Negative	4635	51.4
Positive	4382	48.6
HISTOLOGICAL TYPE		
Ductal invasive	7508	82.3
Lobular invasive	919	10.1
Other	692	7.6
GRADING		
G1-2	4965	55.9
G3	3912	44.1
BIOLOGICAL SUBTYPE		
Luminal	3657	46.0
Triple-negative	2099	26.4
HER2+	2194	27.6
CT DENSITY		
Conventional	8086	88.6
Dose-dense	1041	11.4
TARGETED THERAPY		
None	6127	67.1
Anti-HER2	1729	18.9
Anti-VEGF	1271	13.9
pCR (ypT0/is ypN0)		
No	6749	73.9
yes	2378	26.1

*Valid percent

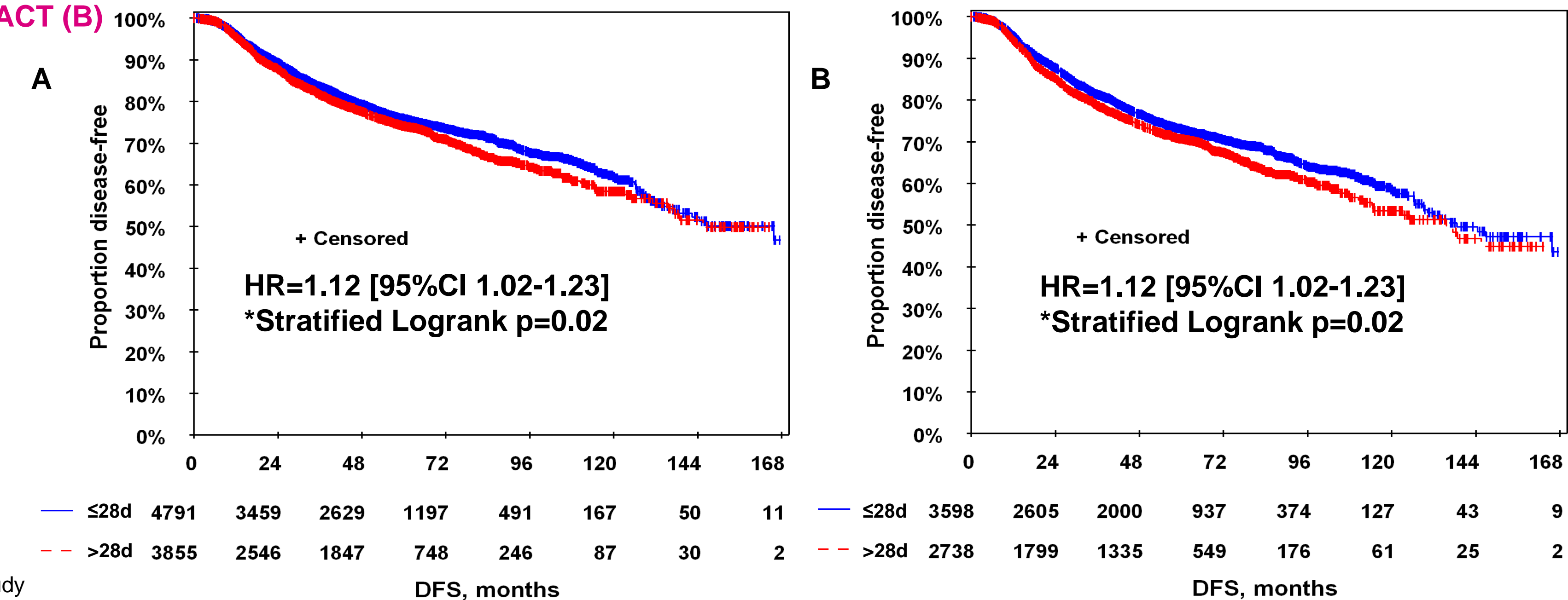
Table 2: Interval from diagnostic biopsy to NACT (TBC) and to surgery after NACT (TCS)

	TBC N=8075	TCS N=8646
MEDIAN [RANGE], days	23 [0-228]	28 [0-204]
INTER-STUDY VARIABILITY*, days	14-32	24-29
INTERVAL LENGTH		
≤28 days	67.6%	55.4%
>28 days	32.4%	44.6%

*Ranging from the oldest to the most recently conducted study

Median follow-up was 65 months (range 0-201). **TBC** did not influence the pCR rate, neither overall nor in subgroups. In the multivariable logistic regression analysis TBC length did also not independently predict pCR. TBC did not influence DFS or OS, neither in all patients nor in subgroups. **TCS>28d** was associated with worse DFS overall (>28d vs ≤28d HR adjusted for study=1.12 [95%CI (1.02-1.23)], p=0.02) and in patients not achieving a pCR (>28d vs ≤28d HR adjusted for study=1.12, [95%CI (1.02-1.23)], p=0.02) (Figure 1). No difference was observed within BC subtypes. OS was not impacted by TCS length. In the multivariable Cox regression analysis neither TBC nor TCS ≤28d vs >28d did independently influence DFS or OS.

Figure 1: DFS according to the time of surgery after NACT (TCS) ≤28d vs >28d in the overall cohort (A) and in patients without pCR after NACT (B)



Conclusions

A delay in starting NACT does neither impact the pCR rate nor DFS or OS. Delay in surgery after NACT in patients without pCR seems to influence outcome. Our analysis is explorative, but indicates for the first time, that time interval of starting NACT might be uncritical, but timing of surgery seems to be relevant especially for those patients not achieving a pCR.

References

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