Targeted Axillary Dissection after Neoadjuvant Systemic Chemotherapy in patients with Early Breast Cancer: Estimating the Real-World Impact of Omitted Axillary Lymph Node Dissection using the CANTO Cohort

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INTRODUCTION

Targeted Axillary Dissection (TAD), which combines sentinel lymph node biopsy with excision of a pre-marked target lymph node, has been shown to improve staging accuracy and reduce false-negative rates in patients with early breast cancer (EBC) and clinically positive lymph nodes (cN+) undergoing neoadjuvant systemic therapy (NAST). By identifying NAST responders with limited residual nodal burden, TAD would enable omission of axillary lymph node dissection (ALND) in selected cases, thus reducing surgical morbidity. However, its potential applicability and impact in unselected real-world populations remain unclear.

METHODS AND MATERIALS

Using data from the CANTO cohort (NCT01993498)[1], a large French prospective study including patients with stage I-III EBC, we consecutively identified patients with cT1–T4 cN+ EBC treated with NAST between May 2012 and August 2022 who underwent ALND according to national guidelines implemented during the same period.

The primary outcome of this exploratory study was the proportion of patients who would have avoided ALND if TAD had been available, defined as the percentage of patients with cN+ EBC treated with NAST who achieved axillary pCR, according to changes in surgical management of the axilla consistent with ongoing international trials and future guideline proposals[2-5]. Additional outcomes included 3-year rate of axillary recurrence, any invasive recurrence and the impact of ALND on quality of life (QoL) using arm symptom score on QLQ BR23.

RESULTS

In total, 370 patients with cN+ EBC treated with NAST in the CANTO cohort were included (tab1-2).

Pathological complete axillary node response (N-pCR) was achieved in 46,3% pts, pathological complete breast response (B-pCR) in 27.8% pts (tab3).

The lobular subtype shows the lowest pCR rate compared to ductal histology in both the axilla (N-pCR 30,0% vs 49,1%) and breast (B-pCR 10,0% vs 30,3%- data not shown).

At a median follow-up (FU) of 101 months, 3-year DFS was 78.3% (95%CI,73.8%;82.2%) with higher rates for total pCR (T-pCR: 90,9%), 83,5% when N-pCR, 75,0% when B-pCR and lowest for total non-pCR (74,0%). DFS was highest for the HER2+ subtype (90,4%), followed by HR+/HER2- (83,1%) and lowest for HR-/HER2- subtype (57,4%).

When N-pCR, 46,9% patients experienced distant relapse, 15,6% locoregional or contralateral, 12,5% both; without N-pCR, 50,6% pts had distant relapse, 22.2% locoregional or contralateral, 14,8% both. Similarly, no difference was seen between distant relapse rate if B-pCR (53,3%) vs non-B-pCR (49,0%), locoregional/contralateral relapse if B-pCR (20,0%) vs non-B-pCR (20,0%) and both distant and locoregional (6,7% B-pCR vs 15,0% non-B-pCR) (data not shown).

Overall, 117 of 340 patients (35.5%) developed lymphedema after ALND within 36 months. Arm pain was significantly higher ($p < 0.05$) in 72 of 358 patients with lymphedema one year after surgery.

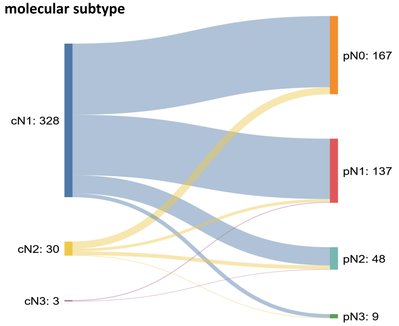
Table 1: Patient and tumor characteristics

	N (%)
Age at diagnosis	**N=370**
Median[min - max]	46.6 [24.3 - 83.8]
cT stage	**N=370**
T1	56 (15.1%)
T2	220 (59.5%)
T3	94 (25.4%)
cN stage	**N=370**
N1	335 (90.6%)
N2	32 (8.6%)
N3	3 (0.8%)
Molecular subtype	**N=370**
HR+/HER2+	85 (23.0%)
HR-/HER2+	40 (10.8%)
HR+/HER2-	143 (38.8%)
HR-/HER2-	101 (27.4%)
Missing	1
Pathology	**N=370**
Ductal	329 (89.4%)
Lobular	10 (2.7%)
Mixed (ductal&lobular)	29 (7.9%)
Missing	2

Table 2: Treatments

Type of NAST	**N=370**
Antracyclines-Taxanes	345 (93.2%)
Other	25 (6.8%)
Adjuvant chemotherapy	**N=370**
No	343 (92.7%)
Yes	27 (7.3%)
Type of adjuvant CT	**N=27**
Capecitabine	9 (33.3%)
TC/T/FEC-T	10 (37.0%)
Other	8 (29.7%)
Radiotherapy	**N=370**
No	14 (3.8%)
Yes	355 (96.2%)
Missing	1
Endocrine therapy	**N=370**
No	145 (39.3%)
Yes	224 (60.7%)
Missing	1
Trastuzumab	**N=370**
No	242 (65.4%)
Yes	128 (34.6%)
Other Targeted therapy	**N=370**
No	314 (91.8%)
Yes	28 (8.2%)
Missing	28
Immunotherapy	**N=370**
No	369 (99.7%)
Yes	1 (0.3%)

Figure 1 : Sankey diagram cN ->ypN and % according to molecular subtype



	Total	HER2+	HR-/HER2-	HR+/HER2-
cN1 -> pN0	152 (46.1%)	64 (56.1%)	45 (52.9%)	43 (32.8%)
cN2 -> pN0	15 (50.0%)	6 (85.7%)	5 (45.5%)	4 (33.3%)
cN3 -> pN0	0 (0.0%)			0 (0.0%)

Table 3 : Pathological responses (pCR) by molecular subtype

	Total	HER2+	HR+/HER2-	HR-/HER2-	P value
Axillary node pCR	**N=370**	**N=125**	**N=143**	**N=101**	**0.0002**
No complete response	194 (53.7%)	53 (43.1%)	95 (66.9%)	46 (47.9%)	
Complete response	*167 (46.3%)*	*70 (56.9%)*	*47 (33.1%)*	*50 (52.1%)*	
Missing	9	2	1	5	
Breast pCR	**N=370**	**N=125**	**N=143**	**N=101**	**0.0424**
No complete response	262 (72.2%)	81 (65.3%)	113 (79.0%)	68 (70.8%)	
Complete response	*101 (27.8%)*	*43 (34.7%)*	*30 (21.0%)*	*28 (29.2%)*	
Missing	7	1		5	
Dissociated pCR	**N=370**	**N=125**	**N=143**	**N=101**	**0.0214**
No	269 (74.5%)	86 (69.9%)	117 (82.4%)	66 (68.8%)	
Yes	*92 (25.5%)*	*37 (30.1%)*	*25 (17.6%)*	*30 (31.3%)*	
Missing	9	2	1	5	
If yes, presence of residual cancer	**N=92**	**N=37**	**N=25**	**N=30**	
in axilla	13 (14.1%)	5 (13.5%)	4 (16.0%)	4 (13.3%)	
in breast	79 (85.9%)	32 (86.5%)	21 (84.0%)	26 (86.7%)	

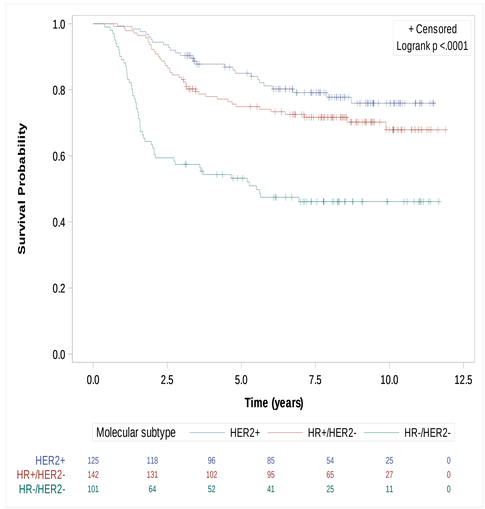


Figure 2 : Disease-Free Survival according to molecular subtype

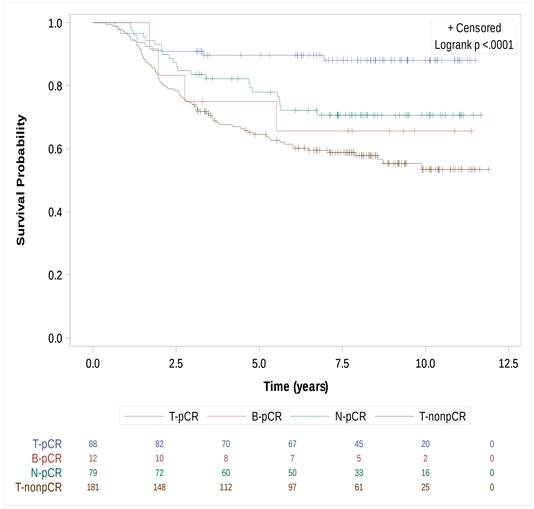


Figure 3 : Disease-Free Survival according to pCR

DISCUSSION

In CANTO cohort, pCR followed the expected hierarchy by molecular subtype (tab3). The pathological response by histological subtype confirms lobular histology chemo resistance (data not shown).

We observed pCR discordance between breast and axilla in 25.5% (92/361) of assessable cases, aligning with reports that nodal and breast responses may diverge.

N-pCR rate is consistently higher than the B-pCR rate across all breast cancer subtypes after NAST and it is more common when the breast also achieves pCR. In cases of dissociated response, residual disease is more frequently observed in the breast when the axilla achieves pCR. This pattern is probably influenced by nodal tumor burden, microenvironmental factors, higher baseline proliferation and immune interactions, resulting in higher axilla chemo sensibility[6-7].

N-pCR following NAST is not dependent on the initial N (Fig1). This highlights the prognostic significance of tumor subtype and therapeutic regimen over nodal stage in predicting N-pCR and guiding treatment decisions.

In CANTO cohort, 3-year DFS was strongly associated with molecular subtype (Fig2) and pCR (Fig3), with residual disease in the breast after NAST emerging as the primary prognostic factor for recurrence risk. Patients with or without N-pCR predominantly experience distant metastases rather than locoregional recurrences.

ALND, performed in 100% of cN+ patients in this series, is associated with a high incidence of lymphedema, as evidenced by arm symptom scores (BR23) and arm volume measurements at 0, 12, and 36 months.

This study is limited by its retrospective design and short follow-up. Not all HER2-positive cancers received double blockage therapy, and treatment strategies for HR-/HER2- EBC have evolved since the study period with the arrival of immunotherapy. Data completeness was suboptimal with some pCR assessments and patient-reported outcomes unavailable. Any patient underwent TAD, so the axillary pCR rates reflect hypothetical eligibility to omit ALND rather than observed practice.

CONCLUSION

This analysis showed that TAD could have been considered instead of ALND in around one third of patients treated with NAST, particularly those with HR-/HER2- or HER2+ EBC, having a higher likelihood of N-pCR. Comprehensive breast and axillary staging before and after NAST remains essential, given the risk of discordant pCR. Even though ALND remains essential in patients with residual nodal disease, axillary de-escalation is a rational strategy that allows tailored surgical management and reduces morbidity in selected patients.

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