Feasibility of Tailored Axillary Surgery (TAS) in Patients with Clinically Node-Positive Breast Cancer in the Upfront Surgery Setting: Results of a Prospective, Single-Arm, Multicenter Phase II Trial

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JCOG Breast Cancer Study Group

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Introduction

Axillary lymph node dissection (ALND), while historically the standard of care for clinically node-positive (cN+) breast cancer (BC), is associated with impaired quality of life and has been progressively **de-escalated**.

In the upfront surgery setting for cN+ disease, ALND remains the standard of care, and evidence supporting its omission is lacking.

Tailored axillary surgery (TAS)[1,2] is a novel approach that targets suspicious nodes while omitting ALND, aiming to reduce **morbidity**.

We conducted **a prospective phase II study to assess the feasibility of TAS**, ensure procedural consistency, and evaluate associations between clinicopathologic factors and residual tumor burden.

Tailored Axillary Surgery (TAS)

After general anesthesia, mark* one lymph node(LN) with pathologically diagnosed metastasis before surgery.

(*: wire, dye or tattoo, clip + dye or tattoo, , clip + wire)

Removal of the marked LN, sentinel node, and palpable LN.

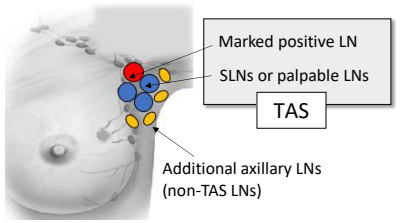
Invasive breast cancer 1-3 suspicious LNs

↓

Registration

↓

Breast surgery + TAS and ALND



Major Eligibility Criteria

- Histologically diagnosed invasive breast cancer in the primary tumor
- Surgery is scheduled as **initial treatment**
- The lymph node most suspected of metastasis is pathologically diagnosed as metastasis by cytology or needle biopsy
- There are **1 - 3** lymph nodes in level I suspected of metastasis in diagnostic imaging
- No suspicion of metastasis in level II, III, Rotter, internal mammary and supraclavicular LNs
- The clinical classification of the primary tumor is **T1 - 3**
- Women who are at least 18 years old and 74 years of age or younger

Patients and Methods

- This single-arm, prospective, multicenter phase II trial was conducted across 42 institutions in Japan within the JCOG Breast Cancer Study Group. (jRCT s061220113)
  - This feasibility trial was conducted to inform the design of our planned subsequent randomized clinical trial by identifying appropriate eligibility and exclusion criteria.

Actual period: April 2023– March 2025

Primary endpoint: non-TAS LNs positive rate

Factors to be considered for the percentage of non-TAS LN metastases

1. Number of lymph node metastases suspected on preoperative imaging (1, 2, 3)
2. Number of lymph nodes removed by TAS (1, 2, 3, 4 or more)
3. Number of metastases in lymph nodes removed by TAS
4. Tumor size (cT1, cT2, cT3)
5. Invasive lobular carcinoma (yes, no)

Secondary endpoints:

- Identification rate of TAS (at least 1 metastatic LN included in lymph nodes removed by TAS / all eligible cases)
- Identification rate of marked metastatic lymph node
- Identification rate of metastatic lymph nodes among lymph nodes removed by TAS
- Percentage of upper extremity lymphedema*
- QOL (Quick DASH, FACT-B+4 ARM subscale)* *: Under follow-up

Table 1. Patient characteristics

		No. (%)
Age	Median (range)	53.5(27-77)
cT	1	58(27.4)
	2	140(66.0)
	3	14(6.6)
No. of suspicious LNs	1	58(27.4)
	2	140(66.0)
	3	14(6.6)
Imaging modalities for axillary staging	US	211(99.5)
	CT	110(51.9)
	PET-CT	117(55.2)
Type of breast surgery	Bt	166(78.3)
	Bp	46(21.7)
Tumor type	Ductal	194(91.5)
	Lobular	5(3.3)
	Others	11(5.2)
Tumor subtype	ER+/HER2-	186(87.7)
	ER+/HER2+	11(5.1)
	ER-/HER2+	1(0.5)
	ER-/HER2-	10(4.7)
Grade	1-2	140(66.0)
	3	63(29.7)
pN	1	138(65.1)
	2	56(26.4)
	3	18(8.5)
pStage	IIA	50(23.6)
	IIB	101(47.6)
	IIIA	51(24.0)
	IIIB	2(0.9)
	IIIC	8(3.7)

Table 2. TAS procedure.

Type of Marking	No. (%)
Dye or black ink	138(65.1)
Clip + dye or black ink	38(17.9)
Wire	13(6.1)
Clip + wire	5(3.3)
Clip + dye or black ink + wire	4(1.9)
Wire + dye or black ink	2(0.9)
Clip	1(0.5)

SLNB procedures	No. (%)
Dye	95(44.8)
Dye＋RI	81(38.2)
Fluorescence	35(16.5)
RI	1(0.5)

Table 3. Technical outcomes of TAS

No. of TAS nodes retrieved (median)	4 (IQR, 3-6; range, 1-11)
No. of metastatic nodes among TAS	2 (IQR, 1-3)
Marking success rate (%)	100.0
Marked LN retrieval rate (%)	100.0
Marked LN positivity rate (%)	95.8
Tracer-positive rate in marked LNs (%)	70.0
Identification rate of TAS (%)	100.0

Table 4. Residual axillary tumor burden after TAS

	No. (%)
non-TAS LN positivity rate	**82/212 (38.7)**
No. of additional positive nodes	
None	130 (61.3)
One	35(16.5)
Two	19(9.0)
Three	6(2.8)
Four	3(1.4)
Five or more	19(9.0)

Table 5. Multivariable logistic regression analysis of factors associated with non-TAS positive nodes

Variable	Odds Ratio	95% CI	p-value
No. of suspicious nodes on imaging	1.318	0.867–2.003	0.197
No. of TAS nodes retrieved	**0.848**	**0.728–0.988**	0.035
No. of metastatic TAS LNs	**1.502**	**1.167–1.935**	0.0016
Clinical T stage	1.188	0.695–2.030	0.529

Results

A total of 212 patients were enrolled.

Patient characteristics are summarized in Table 1.

Technical outcomes of TAS (Table 3):

- The median number of TAS nodes retrieved was 4 (IQR, 3-6; range, 1-11), including 2 metastatic nodes (IQR, 1-3).
- Marked node retrieval was achieved in 100% of patients.
- Thirty percent of the marked nodes lacked SLN tracer uptake.
- The identification rate of TAS was 100%.
- Median number of LNs retrieved by ALND was 18 nodes (IQR 14-24).

Residual axillary tumor burden after TAS (Table 4):

- The non-TAS LN positivity rate was 38.7% (82/212).
- In multivariable analysis (Table 5),
  - a smaller number of TAS LNs retrieved (OR 0.85; 95% CI 0.73-0.99)
  - more positive TAS LNs (OR 1.50; 95% CI 1.17-1.94)

  were associated with higher non-TAS LN positivity.
  - clinical T stage and number of suspicious nodes on imaging were not significant.

Safety: The major complications included post-operative bleeding (4.3%) and infection (3.7%).

Conclusions

- **TAS was feasible** in **cN+** breast cancer undergoing **upfront surgery**, with acceptable safety.
- Multivariable analysis alone did not provide definitive criteria to determine eligibility or exclusion for our upcoming phase III RCT.
- The non-TAS LN positivity rate (38.7%) was slightly higher but comparable to the false-negative rates reported in cN0 SLN-positive trials (27-34.5%)[3,4,5].
- The axillary tumor burden in this cN+ cohort was higher than in previous studies, highlighting the need to understand how this burden contributes to axillary recurrence risk and worsened prognosis.
- Overall, these findings indicate that moving forward to an RCT within this feasibility cohort is reasonable, with minor refinements to eligibility potentially warranted—particularly for patients with higher residual axillary tumor burden.
- Taken together, these findings support the evaluation of ALND omission as a rational next step, supported by systemic therapy and radiotherapy, and provide the basis for **our planned Phase III trial** within the framework of **stepwise axillary de-escalation**.

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