Original Research Article

International Journal of Science and Healthcare Research
[Indexed, Peer-Reviewed Journal]
Vol. 11; Issue: 3; July-Sept. 2026
Website: ijshr.com
ISSN: 2455-7587

Pattern of Axillary Lymph Node Metastasis at Different Levels, Rotter's Nodes and Skip Metastasis in Node-Positive Breast Cancer: A Prospective Observational Study

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DOI: https://doi.org/10.52403/ijshr.20260334

Received: 03/04/2026; Revised: 02/08/2026; Accepted: 10/09/2026

ABSTRACT

Background: The extent of axillary lymph node dissection (ALND) in node-positive breast cancer remains controversial, particularly regarding routine assessment of level III and interpectoral (Rotter's) nodes. This study evaluated the distribution of metastatic disease across axillary levels and the prevalence of skip metastasis, while exploring clinicopathological factors associated with non-level-I disease.

Methods: This prospective observational study was conducted at the Department of Surgical Oncology, Tertiary Cancer Centre, from July 2019 to November 2020. Patients aged 18–70 years with biopsy-proven breast cancer undergoing modified radical mastectomy or breast-conserving surgery with ALND were eligible; patients with recurrent or metastatic disease and those declining participation were excluded. Level I, level II, level III and Rotter's nodes were dissected and labelled separately. Clinicopathological variables and postoperative morbidity were recorded. Associations were assessed using chi-square/Fisher's exact tests and logistic regression as reported in the study; $p<0.05$ was considered significant.

Results: Among 146 recruited patients, 59 were pathologically node-positive and constituted the analysis cohort. Mean age was 52.5±8.5 years; 42.4% received neoadjuvant chemotherapy. Level I nodes were positive in 58/59 (98.3%) patients. Level III metastasis was identified in 5/59 (8.5%), Rotter's node metastasis in 6/59 (10.2%), and skip metastasis in 1/59 (1.7%). Four patients (6.8%) had metastases involving levels I, II and III. Tumour location in the outer quadrant was independently associated with level III positivity (multivariable $p=0.04$). Grade 1/2 tumours, outer-quadrant location and HER2-negative status were independently associated with Rotter's node positivity. Clinical examination and axillary ultrasonography had sensitivities of 45.7% and 74.5%, respectively, for detecting pathological nodal disease in this node-positive cohort. Seroma occurred in 23.7% and subjective upper-limb lymphedema symptoms in 8.5%.

Conclusions: In this small prospective cohort, skip metastasis was uncommon, whereas level III and Rotter's node metastases occurred in a clinically relevant minority of node-positive patients. The findings support selective level III dissection based on suspicious level II disease or a high level-I nodal burden rather than routine level III clearance, while careful assessment of the interpectoral space may identify additional metastatic nodes. Larger studies with longer follow-up are required.

Keywords: breast cancer; axillary lymph node dissection; level III lymph nodes; Rotter's nodes; skip metastasis; axillary metastasis; neoadjuvant chemotherapy

1. INTRODUCTION

Breast cancer is the most common malignancy among women worldwide and has become the most common cancer overall in many populations. The burden of breast cancer in India is substantial, with a comparatively high proportion of patients presenting at younger ages and with advanced disease **[1]**. Axillary nodal status remains an important component of staging and prognostication in breast cancer.

The role of ALND has progressively narrowed with the adoption of sentinel lymph node biopsy and trials demonstrating that selected patients with limited sentinel-node disease can safely avoid completion ALND**[2–4].** Nevertheless, ALND remains relevant in clinically node-positive disease and in settings where sentinel node biopsy is unavailable or unsuitable. The optimal extent of ALND is less certain. Conventional teaching describes sequential lymphatic spread from level I to level II and level III nodes, but discontinuous or skip metastases and involvement of interpectoral (Rotter's) nodes have also been reported **[5–8]**.

Level III involvement has implications for pathological staging because apical/infraclavicular nodal disease represents advanced regional nodal involvement. Previous series have reported substantial variation in the prevalence of level III and Rotter's node metastases, and the relevance of these findings may differ according to tumour burden, neoadjuvant treatment and patient population**[5,8–10]**. In particular, Indian series have described considerable axillary nodal burden, raising questions about whether data derived from lower-risk Western cohorts can be directly extrapolated to all patients in resource-constrained settings.

The present study was undertaken to characterize the pattern of axillary nodal metastasis in node-positive breast cancer by separately evaluating levels I–III and Rotter's nodes, to determine the prevalence of skip metastasis, and to identify clinicopathological factors associated with level III and Rotter's node involvement. The study also assessed the sensitivity of clinical examination and axillary ultrasonography and documented morbidity associated with extensive axillary dissection.

2. MATERIALS AND METHODS

2.1 Study design and setting

This was a prospective observational study conducted in the Department of Surgical Oncology, Tertiary Cancer Centre, India, from July 2019 to November 2020. The study was undertaken after approval from the Institutional Thesis Review and Ethical Committee with number AS/11/IEC/ SVIMS/2017. Written informed consent was obtained from participants.

2.2 Eligibility criteria

Patients aged 18–70 years with biopsy-proven breast cancer who were willing to participate and underwent modified radical mastectomy or breast-conserving surgery with axillary dissection during the study period were eligible. Receipt of neoadjuvant chemotherapy (NACT) was not an exclusion criterion. Patients who refused participation, had recurrent breast cancer, or had metastatic breast cancer/toilet mastectomy were excluded.

2.3 Preoperative assessment and treatment

Routine preoperative evaluation was performed according to institutional protocol. Clinical tumour characteristics, tumour size and location, histology, Scarff–Bloom–Richardson/Nottingham grade, lymphovascular invasion and relevant pathological variables were recorded. All patients underwent preoperative axillary ultrasonography/sonomammography, and the findings were compared with postoperative histopathology. Patients requiring NACT were treated by the medical oncology team and subsequently underwent surgery.

2.4 Axillary dissection and pathological assessment

During ALND, level I, level II, level III and Rotter's/interpectoral nodal tissue were dissected separately, labelled individually and submitted for histopathological examination. Level III dissection was performed through a transpectoral approach. Following lateral retraction of the pectoralis minor, the pectoralis major was split along the direction of its muscle fibres when required to expose the apical axilla; in breast-conserving procedures, the Auchincloss approach was used without splitting pectoralis major. The number of lymph nodes harvested and involved at each level, extracapsular extension, lymphovascular emboli, and pathological T and N categories were recorded.

2.5 Definitions and outcomes

The primary outcomes were the prevalence of metastatic disease in levels I, II and III and in Rotter's nodes, and the prevalence of skip metastasis, defined as metastasis to level II, level III or Rotter's nodes in the absence of level-I involvement. Secondary outcomes included associations between nodal patterns and clinicopathological variables, preoperative axillary assessment versus histopathology, and perioperative/postoperative morbidity.

2.6 Statistical analysis

Categorical variables were summarized as frequencies and percentages; continuous variables were summarized using mean ± standard deviation or median with range, as appropriate. Associations between categorical variables were assessed using Pearson's chi-square test or Fisher's exact test. Multivariable logistic regression was used for selected subgroup analyses. Receiver operating characteristic (ROC) analysis was used to identify thresholds of positive level-I and level-II nodes associated with level III metastasis. A p value <0.05 was considered statistically significant. The original thesis calculated a target sample size of 126 pathological node-positive patients; because of the study period and COVID-19-related constraints, all eligible patients were included, resulting in 59 node-positive cases for analysis.

3. RESULTS

3.1 Study population and baseline characteristics

A total of 163 patients underwent surgery for breast cancer during the study period. Of these, 146 consented and were recruited; 59 were pathologically node-positive and formed the study cohort. The remaining 87 patients were pathologically node-negative and were excluded from the primary analysis. The mean age was 52.5±8.5 years. Thirty patients (50.8%) were premenopausal and 29 (49.2%) were postmenopausal. Two patients underwent breast-conserving surgery, 56 underwent modified radical mastectomy and one underwent axillary dissection alone. Twenty-five patients (42.4%) received NACT and 34 (57.6%) underwent upfront surgery (Table 1).

Table 1: Baseline characteristics of study population

Characteristic	n (%)
Age 31–40 years	2 (3.4%)
Age 41–50 years	28 (47.5%)
Age 51–60 years	18 (30.5%)
Age 61–70 years	11 (18.6%)
Premenopausal	30 (50.8%)
Postmenopausal	29 (49.2%)
Upfront surgery	34 (57.6%)
Neoadjuvant chemotherapy	25 (42.4%)
Modified radical mastectomy	56 (94.9%)
Breast-conserving surgery	2 (3.4%)
Axillary dissection alone	1 (1.7%)

3.2 Tumour characteristics

All patients presented with a breast lump; the median duration of symptoms was 4 months (range, 0.5–18 months). The primary tumour was left-sided in 30 patients and right-sided in 29. Tumour size was <5 cm in 43 (72.9%), >5 cm in 11 (18.6%), and not measurable in 5 (8.5%) because of complete pathological response or previous lumpectomy elsewhere. The tumour was located in the outer quadrants in 29 (49.2%), inner quadrant in 11 (18.6%), central quadrant in 9 (15.3%), and was multicentric in 6 (10.2%); location was unavailable in 4 patients.

Invasive ductal carcinoma was the predominant histology (52/59, 88.1%). Other histologies included mucinous carcinoma (1.7%), metaplastic carcinoma (1.7%) and carcinoma with apocrine differentiation (1.7%); three patients (5.1%) had complete pathological response of the breast primary and one had unavailable final histology because surgery was performed elsewhere. Molecular subtypes were luminal A (17, 28.8%), luminal B (11, 18.6%), HER2-enriched (18, 30.5%) and triple-negative (13, 22.0%).

The primary tumour was pT2 in 36 patients (61.0%), pT1 in 8 (13.6%), pT3 in 7 (11.9%), pT4 in 3 (5.1%), pT0 in 3 (5.1%) and unknown in 2 (3.4%). Nottingham grade was grade 1 in 17 (28.8%), grade 2 in 29 (49.2%), grade 3 in 8 (13.6%) and unavailable in 5 (8.5%).

3.3 Distribution of axillary nodal metastasis

Level I nodal metastasis was present in 58/59 patients (98.3%). The median number of nodes harvested from level I was 11 (range, 3–21), with a median of 2 involved nodes (range, 0–12). The median number of level II nodes harvested was 2 (range, 0–15), with a median of 0 involved nodes (range, 0–7). For level III, the median number harvested was 1 (range, 0–9) and the median number involved was 0 (range, 0–5). Rotter's nodal tissue yielded a median of 0 nodes (range, 0–21), with a median of 0 involved nodes (Table 2).

Table 2: Distribution of Axillary Nodes

Nodal group	Median nodes harvested (range)	Median nodes involved (range)	Patients with metastasis
Level I	11 (3–21)	2 (0–12)	58/59 (98.3%)
Level II	2 (0–15)	0 (0–7)	Not reported as a standalone patient-level prevalence
Level III	1 (0–9)	0 (0–5)	5/59 (8.5%)
Rotter's nodes	0 (0–21)	0 (0–21)	6/59 (10.2%)

Sixteen patients had metastatic disease in both levels I and II, while 5/59 (8.5%) had metastases involving all three axillary levels. Four patients (6.8%) were reported as having positivity across all levels in the subgroup analysis; the source documents contain a discrepancy between this count and the broader narrative description, so the manuscript retains the consistently reported level III denominator of 5/59 and reports the all-level subgroup separately.

3.4 Skip metastasis and predictors of level III involvement

Skip metastasis was identified in 1/59 patients (1.7%), consisting of level III involvement without level-I or level-II metastasis; no isolated level-II or Rotter's-node skip metastasis was observed. The single patient had received NACT for T4b disease and had not undergone axillary FNAC/biopsy before chemotherapy, limiting certainty that this represented a true biological skip metastasis.

Among the 5 patients with level III metastasis, all had outer-quadrant tumours. On univariate analysis, tumour location was significantly associated with level III involvement (p=0.003), and the association remained significant on multivariable logistic regression (p=0.04). Age, tumour size, grade, NACT, number of positive level-I/II nodes, hormone receptor status, HER2 status, extracapsular extension and lymphatic emboli were not statistically significant in this small cohort (Table 3).

Table 3: Predictors of level III involvement

Predictor of level III positivity	Univariate p	Multivariable p	Interpretation
Outer-quadrant tumour location	0.003	0.04	Significant association
Age	0.548	0.962	Not significant
Tumour size	0.548	0.43	Not significant
Grade	0.072	0.63	Not significant
>4 positive level I/II nodes	0.072	0.636	Not significant
NACT	0.548	0.709	Not significant
HER2 status	0.072	0.636	Not significant

3.5 ROC analysis

ROC analysis suggested that >6 positive level-I nodes predicted level III metastasis with an area under the curve (AUC) of 0.763, sensitivity of 80.0% and specificity of 88.9%. For level II, the AUC was 0.835, with sensitivity of 80.0% and specificity of 77.8% at a threshold of >0 involved node. Given the small number of level III-positive cases, these thresholds should be considered exploratory rather than definitive (Figure 1).

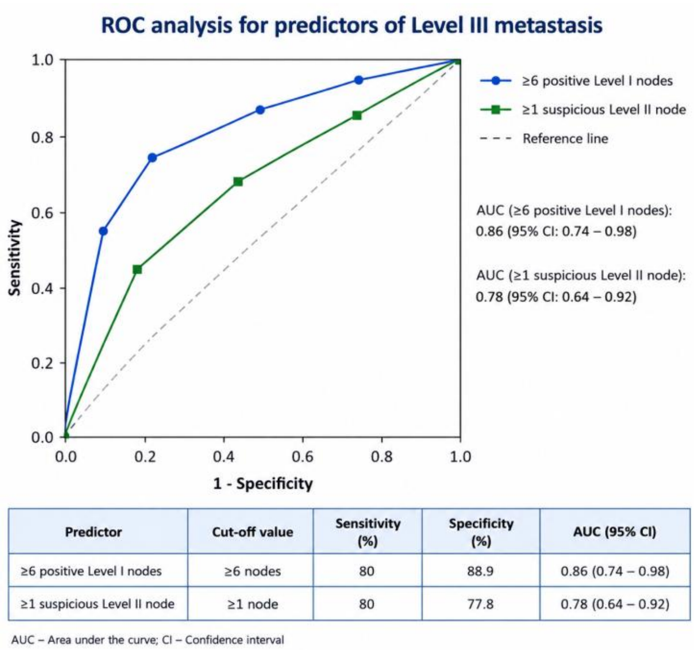

Figure 1. ROC Analysis for predictors of level III Metastasis

3.6 Rotter's node involvement

Rotter's node metastasis was present in 6/59 patients (10.2%). On univariate analysis, tumour grade (p=0.03), outer-quadrant location (p=0.03), ≥4 positive level-I/II nodes (p=0.0009) and HER2-negative status (p=0.03) were associated with Rotter's node positivity. On multivariable analysis, grade 1/2, outer-quadrant location and HER2-negative status remained statistically significant, with p values of 0.04, 0.02 and 0.02, respectively. The study also observed lymphatic emboli in all six Rotter's-node-positive cases, although the reported multivariable association was not statistically significant.

3.7 All-level nodal positivity and residual nodal disease after NACT

Four patients (6.8%) had metastatic disease involving all axillary levels in the subgroup analysis. Outer-quadrant tumour location, >4 positive level-I/II nodes, HER2-negative status and lymphatic emboli were associated with all-level positivity (p=0.008 for each in the reported analysis). Among three patients with breast-only pathological complete response after NACT, tumour size <5 cm, absence of extracapsular extension and absence of lymphatic emboli were associated with breast-only response (p=0.02 for each); these analyses are based on very small numbers and should be interpreted cautiously.

3.8 Preoperative axillary assessment

Clinical examination identified palpable axillary nodes in 27/59 patients, while 32/59 had clinically occult nodal metastasis. Axillary ultrasound detected suspicious/abnormal nodes in 44/59 patients and missed 15. In this pathologically node-positive cohort, the sensitivity of clinical examination was 45.7% and that of ultrasound was 74.5%. Because the analysis cohort contained only pathologically node-positive patients, specificity and negative predictive value could not be estimated from the reported data.

3.9 Perioperative and postoperative morbidity

Mean operative time was 136.3±19.4 minutes (range, 100–200), and mean blood loss was 71.2±24.9 mL (range, 50–100). Blood transfusion was required in 5 patients (8.5%), and pectoral vessel injury occurred in 5 (8.5%) during level III dissection. Median drain outputs on postoperative days 1, 2 and 3 were 100, 100 and 50 mL, respectively; median drain removal was reported as 15 days (Figure 2). Postoperative complications occurred in 29/59 patients (49.2%), including seroma in 14 (23.7%), subjective lymphedema symptoms in 5 (8.5%), high drain output in 2 (3.4%), flap necrosis along the suture line in 7 (11.9%), and combined high drain output and flap necrosis in 1 (1.7%). The documented early nerve/vessel-related morbidity resolved within one month. Lymphedema was assessed subjectively for only three months.

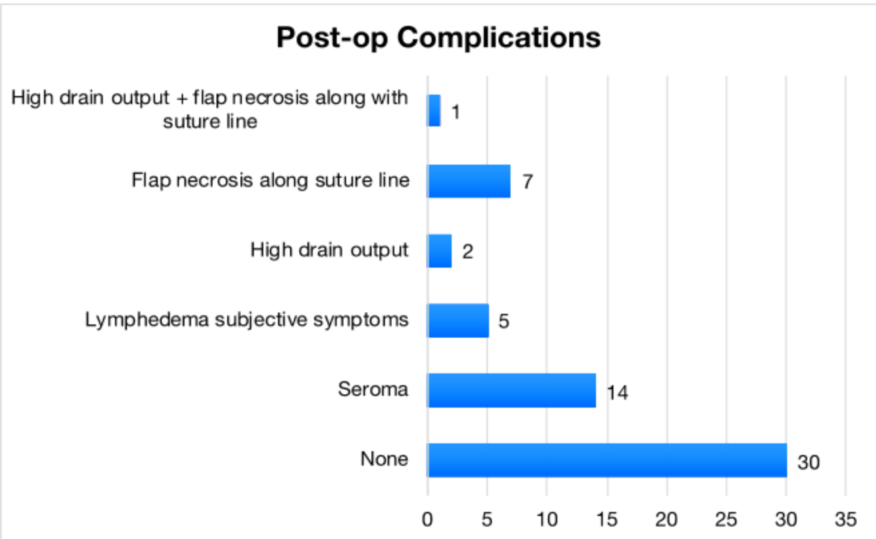

Figure 2. Postoperative complications.

4. DISCUSSION

This prospective study examined the anatomical distribution of nodal metastases in 59 pathologically node-positive breast cancer patients undergoing ALND, with separate pathological assessment of levels I–III and Rotter's nodes. The principal findings were a very high prevalence of level-I involvement (98.3%), level III involvement in 8.5%, Rotter's-node involvement in 10.2%, and skip metastasis in only 1.7%. The low prevalence of isolated skip metastasis does not support routine extension of ALND to level III solely to identify discontinuous disease in every patient, whereas the observed frequency of level III and Rotter's-node metastasis indicates that these nodal groups can contain clinically relevant disease in selected node-positive patients.

The observed 8.5% prevalence of level III involvement is lower than that reported in several earlier series. Veronesi et al. reported level III involvement in 22.2% of 839 cases, while Khafagy et al. reported 50.8% among 59 node-positive patients**[5,10]**. Joshi et al., in a large Indian prospective single-institution series of 1,591 node-positive patients, reported level III involvement in 27.3%**[8]**. Differences in patient selection, tumour burden, surgical technique, pathological processing and use of neoadjuvant therapy may account for variation between cohorts.

In the present study, outer-quadrant tumour location was the only factor independently associated with level III involvement. This differs from the large series by Joshi et al., in which higher nodal burden, extranodal extension, lymphovascular emboli and inner/central tumour location were independently associated with level III metastasis**[8]**. The discrepant findings may reflect the small number of level III-positive cases in the present study, which substantially limits statistical power and makes estimates vulnerable to sparse-data effects. The ROC-derived threshold of more than six positive level-I nodes had reasonably high sensitivity and specificity within this dataset, but should be regarded as hypothesis-generating.

Rotter's nodes were positive in 10.2% of patients, higher than the 1.7% reported by Khafagy et al. and the 4.7% reported by Joshi et al**[8,10].** Interpectoral nodes are anatomically variable and may be overlooked if the fibrofatty tissue between the pectoral muscles is not examined carefully. Previous work has demonstrated prognostic relevance of interpectoral nodal involvement, supporting deliberate inspection of this compartment when ALND is performed**[9]**. In the present study, whenever identifiable interpectoral nodes were present, they were frequently metastatic, although the number of harvested nodes was low.

Skip metastasis was uncommon in this cohort. Only one patient had level III disease without level-I/II involvement, compared with reported rates of 8.4% in the Khafagy series, 10% in the Keskek series and 14.6% in the Sun series, although definitions differed across studies**[5,10,11]**. The isolated skip case in the present study occurred after NACT without pretreatment axillary biopsy, so treatment-related nodal downstaging cannot be excluded. Consequently, it should not be interpreted as unequivocal biological skip metastasis.

The preoperative assessment findings highlight the limitations of clinical staging. Clinical examination had a sensitivity of 45.7% and ultrasound 74.5% for pathological nodal disease in the present node-positive cohort. These findings are consistent with the concept that physical examination alone is insufficient for reliable axillary staging. Alvarez et al. reported a sensitivity of 47.6% for axillary ultrasonography in a systematic review and noted improved performance when suspicious nodes undergo ultrasound-guided biopsy**[12]**. The present study did not include sufficient data to calculate specificity or the incremental value of biopsy.

The morbidity profile was acceptable despite additional level III dissection. Pectoral vessel injury occurred in 8.5%, and subjective lymphedema symptoms were reported in 8.5% at three months. The authors used a transpectoral approach, which has previously been described as providing access to the axillary apex while minimizing injury to important pectoral structures**[13]**. However, the short follow-up is important because clinically significant breast-cancer-related lymphedema often develops beyond the first three postoperative months**[14].**

The study has practical relevance in settings where ALND remains commonly used. The data suggest that routine level III clearance in every patient may not be justified solely because of the possibility of skip metastasis. Instead, the study findings support selective level III assessment when level II disease is suspicious or when there is a high level-I nodal burden. The authors' original threshold of six or more positive level-I nodes should not be interpreted as a universal clinical rule because it was derived from only five level III-positive patients. Similarly, the observed Rotter's-node positivity supports careful examination of the interpectoral compartment during ALND, but does not establish that routine excision improves survival.

Importantly, this study cannot determine whether removal of additional level III or Rotter's nodes improves oncological outcomes. The cohort was small, included patients receiving NACT without pretreatment axillary biopsy in some cases, and had only three months of postoperative surveillance. No disease-free or overall survival analysis was available. These limitations substantially restrict causal and prognostic inference.

Limitations

The study included only 59 pathologically node-positive patients, substantially below the calculated target sample size of 126.

The study was conducted at a single institution over a relatively short period, limiting generalizability.

Patients receiving NACT were not uniformly evaluated with pretreatment axillary FNAC/biopsy, limiting interpretation of post-NACT skip metastasis and residual nodal disease.

Postoperative follow-up was limited to three months, which is insufficient for robust assessment of lymphedema and other late morbidity.

Disease-free survival and overall survival could not be assessed.

The very small numbers of patients with level III, Rotter's-node and skip metastases limit the reliability of multivariable modelling and ROC-derived thresholds.

CONCLUSIONS

In this prospective cohort of 59 pathologically node-positive breast cancer patients, level-I nodal involvement was almost universal, while level III and Rotter's-node metastases occurred in 8.5% and 10.2%, respectively. Skip metastasis was rare (1.7%) and occurred in a patient treated with NACT without pretreatment axillary biopsy, making true biological skip spread uncertain. Outer-quadrant tumour location was independently associated with level III positivity, while grade, tumour location and HER2 status were associated with Rotter's-node positivity. These findings favour selective rather than routine level III dissection, particularly in patients with suspicious level II disease or a high level-I nodal burden. Larger, adequately powered studies with standardized pretreatment axillary assessment and long-term follow-up are needed before these observations can be translated into definitive surgical recommendations.

Declaration by Authors

Ethical Approval: Approved
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Praneeth CS, Kushala P, Chandu YS. Pattern of axillary lymph node metastasis at different levels, rotter's nodes and skip metastasis in node-positive breast cancer: a prospective observational study. *Int. J. Sci. Healthc. Res.* 2026; 11(3): 310-318. DOI: *https://doi.org/10.52403/ijshr.20260334*

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