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The Sensitivity and Specificity of Preoperative Staging of Axillary Nodes in Cancer Breast Patients

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AA and MS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors NC and SS managed the analyses of the study. Author MB managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Metastasis to axillary lymph nodes is an important prognostic factor in carcinoma breast patients, with implications on overall survival and progression-free survival. To evaluate the accuracy of pre-operative clinical palpation and USG axilla in patients with carcinoma breast, using histopathology as the gold standard.
Study Design: Cross-sectional observational study.
Place and Duration of Study: This was a retrospective study, carried out at Cancer Research Institute, SRHU, India, between January 2015 and December 2018.
Methodology: Data was collected from Case records and Hospital Information System for patients

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having undergone surgery for breast cancer. Pre-treatment clinical, ultrasound axilla, and final histopathology details were recorded. Taking histopathology as the gold standard test, diagnostic accuracy of clinical palpation and ultrasound axilla was calculated.

Results: 256 patients were enrolled in the study. Clinically, 70.7% of patients were T1/T2 stage, 53.9% were node-positive, on USG axilla 59% had abnormal nodes, pathologically 53.52% had nodal metastasis. The sensitivity, specificity for clinical palpation was 77.86% and 75%, for USG was 90.71% and 79.31%. Sensitivity and specificity of USG in c T1/2 was 88.64% and 80.21%; in c T3/4 94.23% and 65.22%; in c N negative 87% and 72.16%; in c N positive 91.74% and 75.86%.

Conclusion: The diagnostic accuracy of clinical palpation of axilla alone was low; Ultrasound axilla had high sensitivity but low specificity across all T stages of breast tumor. The ultrasound had a high negative predictive value in clinically non-palpable nodes and a high positive predictive value in clinically palpable nodes.

Keywords: Axillary lymph node evaluation; axillary ultrasound; sensitivity; pre-operative axillary evaluation; lymph node metastasis in carcinoma breast.

1. INTRODUCTION

Metastasis to axillary lymph nodes is an important prognostic factor in carcinoma breast patients, with implications on overall survival and progression-free survival. The survival rate for breast cancer at 5 years is 82% for node-negative disease, 73% for 1-3 positive nodes, 46% for 4-12 positive nodes, and 28% for 13 or more positive nodes [1]. Accurate pre-operative evaluation of axillary nodes is important, as there are multiple options for axillary surgery. The histological examination of axillary nodes is the gold standard for evaluation of axilla, this could be either axillary node sampling, sentinel lymph node biopsy (SLNB), or an axillary lymph node dissection (ALND). The decision to go for an axillary dissection or less is usually based on pre-operative evaluation of the axilla. Clinically node-negative axilla is defined as- non-palpable nodes and normal nodes on mammographic examination. In T1/2 disease clinically node-negative patients, SLNB is recommended; whereas in clinically node-positive patients, and ALND level I, II, or clearance upto level III (if involved) is recommended [2]. The use of ALND is limited by its adverse effects like varying degrees of pain, shoulder dysfunction, and lymphedema. Clinical palpation of the axilla is known for high false negative and false-positive results, especially in early-stage breast cancer. Ultrasound (USG) evaluation of axillary nodes is a good adjunct to palpation to diagnose abnormal nodes that may be normal in size, as it utilizes morphological features too. Any test should have a high sensitivity and specificity to be clinically useful. A high false-negative rate (FNR) may lead to higher conversion from SLNB to ALND; a high false-positive rate (FPR) may subject node-negative patients to ALND and its associated adverse effects. Thus, this study was planned to evaluate the accuracy of pre-operative clinical palpation and USG axilla in patients with carcinoma breast, using histopathology as the gold standard.

2. METHODOLOGY

2.1 Aim of the Study

To determine the sensitivity, specificity, positive and negative predictive value of preoperative evaluation of axillary nodes in cancer breast patients, using Histopathology as the gold standard.

2.2 Inclusion Criteria

1. Patients operated for diagnosed breast cancer in this institute with pre-treatment mammography report.

2.3 Exclusion Criteria

1. Previous axillary surgery.
2. Mammography done elsewhere
3. Patients having received neoadjuvant chemotherapy with no pre-treatment pathological evaluation of the axilla

2.4 Methods

Data was collected from Case records and Hospital Information System with regards to the following variables

1. Patient demographics.
2. Pre-treatment clinical tumor, nodal details, and stage of the disease.
3. Pre-treatment X-ray and Sono-mammography report of the tumor and the axilla.

4. The final Histopathology report of the breast cancer surgery specimen.

2.5 Statistical Analysis

The data was analyzed using SPSS version 22. To calculate the diagnostic accuracy, Histopathology was used as the *gold standard test* and a two by two table was made taking tests in question, i.e., clinical examination and Ultrasound axilla.

3. RESULTS

A total of 925 patient's medical records were screened, 256 patients met all the inclusion criteria and were included in the final analysis. All patients were female, with a mean age of 50.5 years (± 12.82 SD, range 22-78 years).

3.1 Baseline Data

The demographic, patient, and clinical disease details are enumerated in Table 1. The majority of patients 53.9% (138/256) were in the age group of 40-59 years, with 20.8% (53/256) 20-39 years and 25.39% (65/256) 60-79 years. In this study population, only 9.8% (25/256) had received neoadjuvant chemotherapy, 22.7% (58/256) underwent breast conservation surgery and the majority 69.9% (179/256) had a level III axillary dissection. Clinically, 70.7% (181/256) patients were in T1/T2 stage, 46.1% (118/256) were node-negative.

3.2 Mammography and Histopathology Results

On Ultrasound mammography of the axilla, abnormal nodes were found in 59% (151/256) patients with a mean overall lymph node size of 13.34 mm(±14.83 SD, range- 2.2-50 mm) (Table 2). Pathologically, 98% (251/256), 1.6% (4/256) and 0.4% (1/256) patients had infiltrating ductal carcinoma, infiltrating lobular carcinoma and Paget's disease respectively; 61% (155/256) patients were T2 stage (Fig. 1), 46.48% (119/256) were node-negative (Fig. 2) and 36% (91/256) had extranodal extension of tumor metastasis (Fig. 3).

3.3 Diagnostic Accuracy of Clinical Palpation and Ultrasound in Pre-Treatment Evaluation of Axilla

For clinical palpation of axilla, the overall sensitivity and specificity were low (77.86% and 75%, respectively). Sensitivity was even lower in clinical T1/T2 stage (67.05%) but high in T3/T4 stage (96.15%) with FNR of 32.95% and 3.85% respectively. For USG evaluation of axilla, the overall sensitivity and specificity was 90.71% and 79.31%; FNR of 9.29% and FPR of 20.69%. In clinical T1/T2 stage FNR found to be 11.36% and FPR 19.79%; in clinical T3/T4 FNR 5.77% and FPR 34.78%. The overall diagnostic accuracy of clinical palpation was 76.56% and Ultrasound was 85.55% (Table 3).

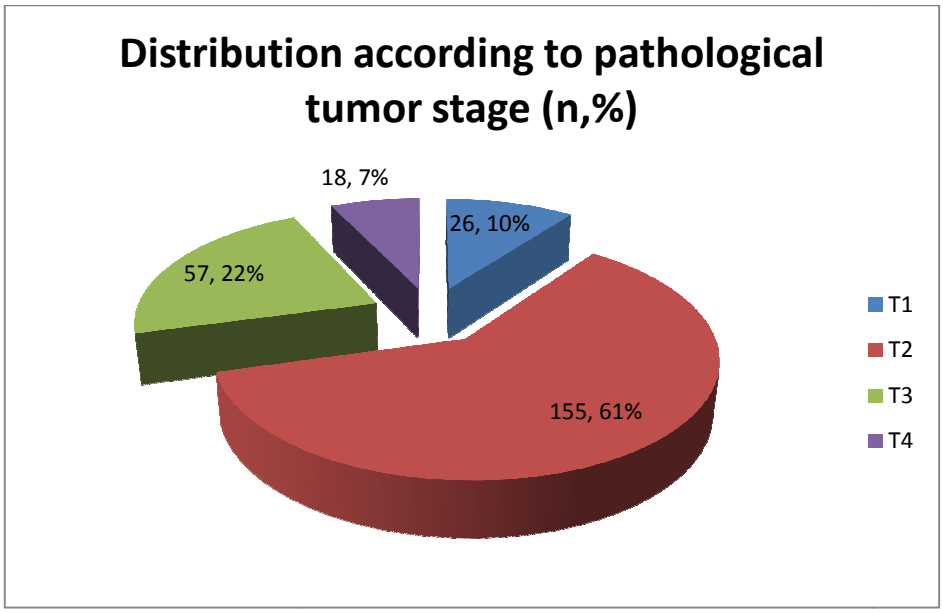

Fig. 1. The pathological tumor stage of patients (n=256)

Chart 1. Clinical examination and ultrasound axilla

Test in question	Histopathology node-positive	Histopathology node-negative	Total
Test positive	a (true positive)	b (false positive)	a+b (all positives)
Test negative	c (false negative)	d (true negative)	c+d (all negatives)
Total	a+c (disease present)	b+d (disease absent)	

The sensitivity, specificity, negative and positive predictive value was calculated using the following formulas-
Sensitivity= a / a+c (true positives / disease present)
Specificity= d / b+d (true negatives / disease absent)
Negative predictive value= d / c+d (true negatives / all negatives)
Positive predictive value= a / a+c (true positives / all positives)
False negative rate= 1- Sensitivity
False positive rate= 1- Specificity

Table 1. The baseline clinical data of patients (n=256)

Variable		Number	Percentage
Age group (years)	20-29	5	2.0
	30-39	48	18.8
	40-49	74	28.9
	50-59	64	25.0
	60-69	41	16.0
	70-79	24	9.4
Side	Left	127	49.6
	Right	129	50.4
NACT	No	231	90.2
	Yes	25	9.8
Surgery for primary	BCS	58	22.7
	Mastectomy	198	77.3
Surgery for axilla	Level I	29	11.3
	Level I, II	48	18.8
	Level I, II III	179	69.9
cT	1	25	9.8
	2	156	60.9
	3	38	14.8
	4	37	14.5
cN	0	118	46.1
	1	120	46.9
	2	17	6.6
	3	1	0.4

NACT- neoadjuvant chemotherapy, BCS- breast conserving surgery, cT- clinical tumor stage, cN- clinical nodal stage

Table 2. Outcome data of pre-treatment Mammography (n=256)

Variable		Number	Percentage
Mean lymph node size (mm)		13.34(±14.83 SD, range- 2.2-50)	
USG report of axillary lymph nodes	Normal	105	41
	Abnormal	151	59

(SD- standard deviation, USG- ultrasonography)

The sensitivity and specificity of USG axilla in clinically node negative patients was 87% (FNR=13%) and 72.16% (FPR=27.84%); in clinically node positive patients 91.74% (FNR=8.26%) and 75.86% (FPR=24.14%). The sensitivity of USG axilla in cT1/2,N negative, cT1/2,N positive, cT3/4,N negative and cT3/4,N positive was 86.21%, 89.83%, 100% and 94% respectively; specificity being 83.56%, 80%, 64.29% and 66.67% respectively (Table 4).

For USG axilla, the positive predictive value (PPV) was higher in clinically node-positive, cT1/2,N positive, and cT3/4,N positive patients (93.46%, 92.98%, and 94%) as compared to clinically node-negative patients. Conversely, the negative predictive value (NPV) was higher in clinically node-negative, cT1/2,N negative, and cT3/4,N negative patients (94.59%, 93.85%, and 100%) than in the clinically node-positive patients (Table 4).

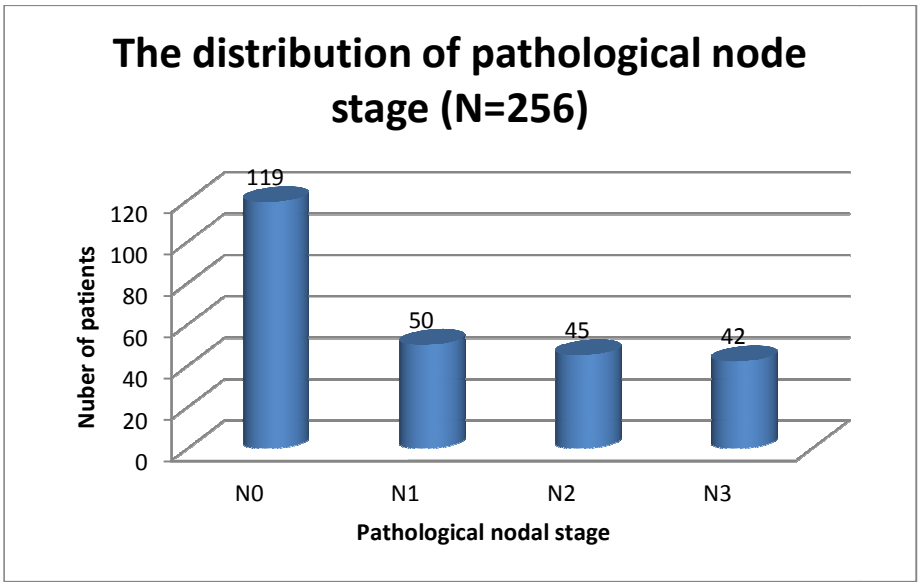

Fig. 2. The pathological nodal stage of patients (n=256)

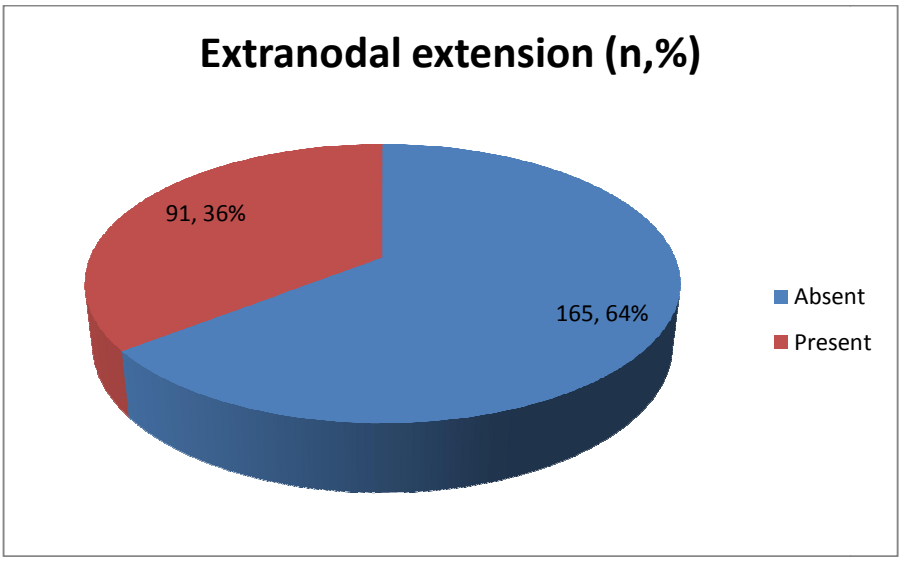

Fig. 3. The presence of extranodal extension of tumor metastasis in the nodes on histopathology (n=256)

Table 3. Diagnostic accuracy of pre-treatment clinical palpation and ultrasound evaluation of axilla (n=256)

Test		Number of patients	Sensitivity	Specificity	PPV	NPV	Accuracy
Clinical palpation	**Overall**	**256**	**77.86**	**75.00**	**78.99**	**73.73**	**76.56**
	cT1, T2	181	67.05	78.49	74.68	71.57	72.93
	cT3, T4	75	96.15	60.87	84.75	87.5	85.33
Ultrasound axilla	**Overall**	**256**	**90.71**	**79.31**	**84.11**	**87.62**	**85.55**
	c T1, T2	181	88.64	80.21	80.41	88.51	84.24
	c T3, T4	75	94.23	65.22	85.96	83.33	85.33

PPV- positive predictive value, NPV- negative predictive value, c- clinical stage

Table 4. Diagnostic accuracy of pre-treatment Ultrasound evaluation of axilla in different clinical tumor and node stage (N=256)

Test	Clinical stage	Number of patients	Sensitivity	specificity	PPV	NPV	Accuracy
USG axilla	c N negative	118	87	72.16	50	94.59	75.78
	c N positive	138	91.74	75.86	93.46	70.97	88.41
	cT1/2,N negative	102	86.21	83.56	67.57	93.85	84.31
	cT1/2,N positive	79	89.83	80	92.98	72.73	87.34
	cT3/4,N negative	16	100	64.29	28.57	100	68.25
	cT3/4,N positive	59	94	66.67	94	66.67	89.83

USG- Ultrasound, PPV- positive predictive value, NPV- negative predictive value, c- clinical stage

4. DISCUSSION

The perfect investigation or test should be sensitive, specific with high positive and negative predictive value. Accuracy depends on, among other things, skill and experience of the professional performing the test in question. Thus, the accuracy of evaluation of axilla may vary at every cancer treating center. A sensitive test usually helps to rule out disease, i.e., if the test is negative then the nodal metastases are probably absent. A high sensitivity means a low false negative rate. An FNR of ≤ 10% is usually acceptable in a clinical scenario. In early breast cancer patients, a highly sensitive test is required to rule out axillary nodal metastasis, so that the patient need not undergo unwarranted ALND. The sensitivity of combining clinical palpation with USG axilla increased from 70% to 82% as reported by Vaidya et al. [3]. Kubilay E et al, in their retrospective study, found a sensitivity of 31.6% for clinical palpation and 58% in combination with USG [4]. Other studies (Table 5) have reported sensitivity for USG axilla ranging from 54 to 90% [3-15]. In our study, the sensitivity for clinical palpation and USG axilla were 77.86% and 90.71% respectively. Clinical palpation yields high FNRs, 22.14% in our study, thus not being a reliable tool in isolation. When combined with USG the FNR dropped to 9.29%, making this a valuable pre-operative test. A patient with normal nodes on USG axilla could be managed with SLNB alone, improving the functional long term outcomes in terms of limb mobility and lymphedema rates.

The high specificity of a test points to a high probability of disease being present if the test is positive. Conversely, FPR drops as specificity increases. A low FPR is required in the pre-operative evaluation of the axilla, or else, breast cancer patients may undergo excessive axillary surgery in the form of ALND. The specificity of clinical palpation of the axilla, in our study, was very low (75%), combining with USG, specificity increased only marginally (79.31%). In various retrospective studies (Table 5) specificity of USG axilla has ranged from 88.7% to 98% (3-15) and prospective studies 73% to 97.1% [3-15]. The studies which had a high specificity combined USG evaluation with either fine need cytology or needle biopsy of the abnormal node. In our study, due to the retrospective nature, this could not be achieved. To reduce the proportion of patients undergoing an unnecessary ALND, either a USG guided cytology/ biopsy or SLNB should be performed, especially in patients with early breast cancer.

In patients with early breast cancer (cT1/2), pre-operative assessment of the axilla is of utmost importance in determining the surgical plan for the axilla. In the present study, for patients with clinically T1/2, any N breast cancer; the sensitivity for clinical palpation was low (67.05%) and for USG was 88.64%. The sensitivity of USG in patients with cT1/2, cN negative was 86.21% and cT1/2, cN positive 89.93%. Thus, in early breast cancer, FNR for USG axilla was lower for clinically palpable nodes than non-palpable nodes. Similar results were demonstrated in a study by KubilayErtan et al, sensitivity for USG in clinically node-positive patients being 96% and clinically node-negative 40% [4]; Natalia ST et al found a sensitivity as low as 70% in cT1/T2 cN0 patients [12]. In the present study, the negative predictive value (NPV) of the USG axilla was 88.51% in cT1/2 any N, 93.85% in cT1/2, cN negative, and 72.73% in cT1/2, cN positive patients. Caudle AS et al have mentioned NPV of 96% when USG was combined with microbiopsy of abnormal nodes [16]; Schipper RJ et al have demonstrated an NPV of 98% for diagnosing normal axilla, in a study with 577 patients [17]. A high NPV of more than 95%, USG in combination with microbiopsy helps in ruling out bulky nodal disease and utilization of SLNB approach in early breast cancer patients, reducing the need for second axillary surgery after SLNB [18]. The PPV of USG axilla in cT1/2, any N was 80.41%,

Table 5. Comparison of sensitivity and specificity for Ultrasound axilla in various studies with the present study

Study	Year	Type of study	Number of patients	Sensitivity	Specificity
Vaidya et al [3]	1996	Prospective	200	82	90
Yang et al [5]	1996	Prospective	114	84.1	97.1
Bonnema et al [6]	1997	Prospective	148	87	95
Strauss et al [7]	1998	Prospective	74	90	91.7
Kebudi et al [8]	2005	Prospective	42	79.1	77.7
Mills et al [9]	2010	Retrospective	653	59	-
Jung et al [10]	2010	Prospective	189	54	91
Garcia-Ortega et al [11]	2011	Retrospective	675	63	88.7
Kubilay et al [4]	2013	Retrospective	172	58	91.6
Natalia S et al [12]	2016	Prospective	647	70	73
Laura LS et al [13]	2016	Retrospective	620	40.8	92.7
Rashpal S et al [14]	2019	Prospective	100	61.7	75.47
Tugba HY et al [15]	2019	Retrospective	156	69.2	98
Present study	2020	Retrospective	256	90.91	79.31

cT1/2, cN negative was 67.57% and cT1/2, cN positive was 92.98% in the present study. Abe H et al found PPV of 82% for USG axilla in case of N2/3 disease in 500 patients [19]. PPV of USG axilla can be improved to 100% if fine needle cytology or microbiopsy is added to the procedure, thereby reducing the number of patients who have to undergo a secondary ALND after metastatic nodes on SLNB [16,18].

In patients with clinically T3/4 disease, axillary evaluation is important to determine the level of ALND in patients planned for upfront surgery; and pre-treatment axillary stage in patients planned for neoadjuvant systemic therapy (NST), to determine the need for axillary radiotherapy after mastectomy. For cT3/4 patients, the sensitivity of palpation and USG axilla was 96.15% and 94.23% respectively; specificity 60.87% and 65.22% respectively in the present study. Thus, the FNR was low and FPR was high for pre-operative axillary evaluation. For USG axilla, Belinda Lee et al reported a sensitivity of 67% in cT3 tumors [20], KubilayErtan et al reported a sensitivity of 62% and specificity of 100% in cT3/4 tumors [4]. In the present study, in patients with cT3/4,N negative disease the sensitivity was as high as 100%, and cT3/4,N positive disease it was 94%, although the specificity was low (64.29% and 66.67% respectively). Mainiero MB et al have indicated a 42% more use of microbiopsy with USG axilla in patients with tumors 2-5 cm [21] to increase specificity and thus reduce chances of secondary ALND following a positive SLNB. Oruwari JUN et al reported PPV of 100% in cT3/4 disease when USG axilla was combined with microbiopsy of abnormal nodes [22].

In the present study, for USG axillary evaluation, we found a high NPV if there were no clinically palpable nodes and high PPV if there were palpable nodesin all cT stages. This finding was supported by a study on 172 patients published in 2013 [4].

As of now, the mammography does not have high enough sensitivity or negative predictive value that a histopathological examination of the axilla could be avoided [23]. In other words, a pre-operative evaluation of the axilla with mammography does not preclude axillary surgery but may determine the extent of surgery. Pinheiro DJPC et al, in their review of literature, have concluded that USG axilla helps in identifying the extent of disease and aids in microbiopsy of abnormal nodes, but is of limited help in patients with minimal axillary disease in the form of micrometastasis [24]. USG axilla still plays a significant role in pre-treatment axillary staging, especially when combined with microbiopsy, and is a relatively non-invasive diagnostic tool. A clinical trial is underway to compare the outcome of two groups- sentinel lymph node biopsy versus observation, for USG negative axilla patients with early breast cancer [25]. Vidya et al, suggested that USG had a lower specificity in tumors which were grade III, Hormone receptor negative, HER-2 receptor positive, triple negative and larger size [26].

5. CONCLUSION

The diagnostic accuracy of clinical palpation of axilla alone is low with high false negative and false positive rates. Ultrasound axilla had high sensitivity but low specificity. In this study, for USG axilla highest sensitivity and negative predictive value was found in the subgroup cT3/4,N negative patients; highest specificity and positive predictive value in cT1/2,N negative, and cT3/4,N positive patients respectively. The limitation of this study was its retrospective nature.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties).

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee (SRHU/HIMS/ETHICS/2019/34)".

This was a retrospective observational study, carried out at Cancer Research Institute, Swami Rama Himalayan University, Dehradun, India, between January 2015 and December 2018, after institutional ethics committee clearance (SRHU/HIMS/ETHICS/2019/34).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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