Immunohistochemical Expression Status of HER2/neu and E-cadherin in Prostate Adenocarcinoma: A Cross-sectional Study

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ABSTRACT

Introduction: Prostate cancer is a common tumour, accounting for 92% of malignancies in the male genital tract. Due to the high recurrence rate, it is important to identify prognostic markers in prostate cancer. Human Epidermal Growth Factor Receptor 2 (HER2) and Epithelial cadherin (E-cadherin) are speculated to be associated with carcinogenesis, but the literature has provided controversial results.

Aim: To investigate the expression of HER2/neu and E-cadherin in prostatic adenocarcinoma and its correlation with clinicopathological parameters.

Materials and Methods: A retrospective cross-sectional study was conducted at the Department of Pathology, SDM University, Dharwad, Karnataka, India. The study duration was one year and five months, from October 2020 to March 2022. A total of 45 cases diagnosed as prostatic adenocarcinoma between October 2016 and September 2019 were included. Clinicopathological parameters such as age, Prostate-Specific Antigen (PSA) levels, metastasis, perineural invasion, Gleason score, Gleason grade, and two-year survival were retrieved from hospital records and through telephone interviews. Immunohistochemistry (IHC) staining for HER2 and E-cadherin was performed and assessed by pathologists. Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 20.0, and the Chi-square test was applied.

Results: The mean age of the study participants was 69.6 years, ranging from 52 to 95 years. The rates of HER2/neu overexpression/positivity and reduced E-cadherin expression were 25 (55.5%) and 14 (31.1%), respectively. No statistically significant associations were found between HER2 and E-cadherin expression and age, PSA levels, perineural invasion, Gleason score, Gleason grade, and two-year survival (p>0.05). However, a statistically significant association was observed between HER2 expression and distant metastasis (p-value=0.006), whereas no significant association was found with E-cadherin (p-value=0.81).

Conclusion: The study demonstrated a significant association between HER2/neu overexpression and tumour metastasis, suggesting that HER2/neu could serve as a prognostic parameter to assist surgeons. In contrast, E-cadherin showed no association with clinicopathological parameters, raising questions about its involvement in the progression of prostatic adenocarcinoma.

INTRODUCTION

In India, prostate cancer accounts for more than 92% of malignancies in the male genital tract [1]. The recurrence rate of the disease is estimated to be 15%-30% [2,3]. Clinicopathological parameters play a crucial role in prognostication prostate cancer, as most cases are diagnosed at an advanced stage with metastasis. Unlike breast cancer, there are no specific Immunohistochemical (IHC) markers available to predict disease progression. Although androgen deprivation therapy and surgery are the primary treatments for prostate cancer, there are numerous issues associated with androgen therapy. Many advanced or metastatic tumours do not respond to androgen therapy [4]. Therefore, there is a need for alternative hormonal therapies, such as anti-HER2/neu therapy, for such cases.

HER2/neu and E-cadherin are the most widely studied markers for their potential as prognostic tools in prostate cancer. The HER2/neu oncogene is a transmembrane tyrosine kinase receptor of the epidermal growth factor receptor family, and it is involved in the proliferation and differentiation of epithelial cells [5]. While HER2/neu is not expressed in normal tissues, it has been found to be expressed in epithelial tumours of the bladder, prostate, ovary, and gastric mucosa, making it a unique candidate for prognostication of the disease. However, the literature reveals contradictory results regarding HER2/neu expression in prostate cancer, with positivity rates ranging from 0% to 87% [6,7].

Another protein of interest is E-cadherin, a cell-to-cell adhesion molecule responsible for maintaining tissue integrity [8]. Decreased E-cadherin expression has been observed in prostatic carcinoma, leading to the hypothesis that it may be a predictor of prostate cancer progression. However, there are controversial findings regarding E-cadherin and its expression in different studies [9,10]. Therefore, the present study aimed to evaluate the immune expression status of HER2/neu and E-cadherin and compare it with clinicopathological parameters in prostate adenocarcinoma.

MATERIALS AND METHODS

A cross-sectional study was conducted in the Department of Pathology, SDM University, Dharwad, Karnataka, India. The study duration was one year and five months, from October 2020 to March 2022. A total of 45 cases diagnosed with prostate adenocarcinoma at the Department of Pathology, SDM Hospital, Dharwad, were included. This retrospective study included cases diagnosed as prostate adenocarcinoma between October 2016 and September 2019. The study was approved by the Institutional Ethics Committee- SDMCDS IEC. No. 2021/Medical/Pathology/PG/07.

Inclusion criteria: All cases of prostate adenocarcinoma diagnosed in the Department of Pathology between October 2016 and September 2019 were included in the study.

Exclusion criteria: Cases with inadequate samples for further processing with IHC and cases where the cause of death was unrelated to prostate cancer were excluded from the study.

Study Procedure

With defined inclusion criteria, the authors included 45 cases of prostatic adenocarcinoma diagnosed through Transurethral Resection of the Prostate (TURP) and trucut biopsies. Haematoxylin and Eosin (H&E) slides for each case were reviewed, and the histopathological score and descriptive factors about the tumour were noted. Clinical and biochemical data were obtained from the laboratory information system, and two-year survival was investigated through telephone interviews. Prostate-Specific Antigen (PSA) levels upto 4 ng/mL were considered normal, 4-10 ng/mL as the borderline range, and >10 ng/mL as a high risk for prostate cancer. Therefore, the patients were divided into groups with PSA levels <10 ng/mL and >10 ng/mL [11]. Gleason scoring and grading were based on [Table/Fig-1] [12]. Distant metastasis was evaluated based on radiological evidence. Patients without radiological evidence of distant metastasis were considered to have early-stage disease, while those with radiological evidence of distant metastasis were considered to have advanced prostatic adenocarcinoma.

Risk group	Grade groups	Gleason score
Low/very low	1	<6
Intermediate	2	7 (3+4)
	3	7 (4+3)
High/very high	4	8
	5	9-10

[Table/Fig-1]: Gleason score and grading in prostate cancer [12].

Immunohistochemistry staining and interpretation: Paraffin-embedded blocks were retrieved from the Department of Pathology. A 4 µm thick section was taken on positively charged slides. Benign Prostatic Hyperplasia (BPH) was used as a positive control. The PolyExcel Horseradish Peroxidase (HRP)/Diaminobenzidine (DAB) detection system was used for IHC staining. After overnight incubation at 37ºC and deparaffinization with repeated washes of xylene (10 minutes each) followed by rehydration of tissues with graded alcohol, the slides were washed under running water (10 minutes) and distilled water (5 minutes). Antigen retrieval was done with citrate or Ethylenediamine Tetraacetic Acid (EDTA) buffer at 95ºC, followed by cooling at room temperature. A peroxide block was carried out for 10-15 minutes, and the slides were washed in Phosphate Buffer Solution (PBS) for five minutes. They were then incubated with the primary antibody (clone: E-cadherin-EP6, HER2/neu-EP3) for 45 minutes. Subsequently, tissues were incubated with the PolyExcel target binder for 15 to 20 minutes, washed with PBS for five minutes, and incubated with PolyExcel poly HRP for 15 to 20 minutes. After another wash with PBS for five minutes, the slides were developed with DAB chromogen for 5-8 minutes. Sections were counterstained with haematoxylin, washed under running water for 1-2 minutes, and mounted with Dibutylphthalate Polystyrene Xylene (DPX).

The IHC expression of both immune markers was noted, with HER2/neu being scored as normal/overexpressed and E-cadherin as normal/negative, and associated with various parameters such as age, metastasis, perineural invasion, PSA levels, Gleason score, Gleason grade, and two-year survival. IHC interpretation of HER2/neu and E-cadherin was performed [Table/Fig-2]. The following cut-off score was used for calculation: HER2/neu overexpression assessment was categorised as 0 (negative), 1 (weakly positive), 2 (moderately positive), 3 (strongly positive) [5]. E-cadherin expression was categorised as 0 (no/weak expression), 1 (moderate expression), 2 (intense staining) [10].

STATISTICAL ANALYSIS

The quantitative variables were expressed as means and percentages. Due to the small sample size, two groups were formed for statistical purposes, and the association of parameters in the two groups was

| HER2/neu staining pattern [5]	Score
No staining or membrane staining observed in <10% of tumour cells	0-Negative
Faint or barely perceptible membrane staining detected in >10% of tumour cells: cells are stained only in part of their membrane	1±Negative
Weak to moderate, complete membrane staining observed in >10% of tumour cells	2±Weakly positive
Strong complete membrane staining observed in >10% of tumour cells	3±Strongly positive
E-cadherin staining pattern [10]	
No expression, no detectable staining in < 10% of the membrane	0-No expression
Weak, but detectable discontinuous staining present in 10%-39% of the membranes	1±Weak
Moderate, clearly positive discontinuous staining present in 40-90% of the membranes	2±Moderate
Intense continuous staining of the membranes create a honeycomb pattern	3±Intense

[Table/Fig-2]: Immunohistochemistry (IHC) interpretation of HER2/neu and E-cadherin.

tested using the Chi-square test. A p-value <0.05 was considered statistically significant (SPSS software version 20.0).

- Group 1: The association of HER2 expression with age, distant metastasis, perineural invasion, PSA, Gleason score, Gleason grade, and two-year survival was examined.

- Group 2: The association of E-cadherin with age, distant metastasis, perineural invasion, PSA, Gleason score, Gleason grade, and two-year survival was examined.

RESULTS

A total of 45 cases were studied. Prostate cancer was most commonly seen in the mean age group of 69.6 years, ranging from 52 to 95 years, in the present study. On histomorphological examination, prostatic adenocarcinoma showed a Gleason score of more than seven in 39 (86.6%) cases. Perineural invasion was seen in 23 (51.1%) out of the 45 cases. Distant metastasis was observed in 15 (33.3%) cases. A total of 14 (31.1%) patients expired [Table/Fig-3].
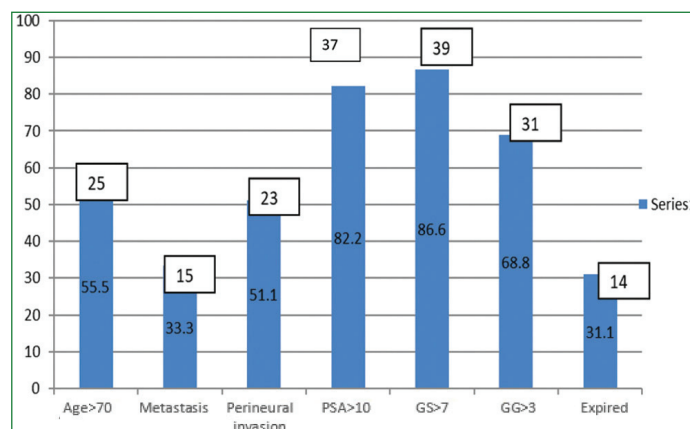

[Table/Fig-3]: Prostate cancer and clinicopathological parameters.
Numbers inside the bar- percentage; Numbers outside the bar- No. of patients

The expression of HER2/neu immunostaining in prostatic adenocarcinoma was examined with various parameters. A total of 45 cases diagnosed with prostate adenocarcinoma were studied for HER2/neu expression [Table/Fig-4]. HER2 scores of 0, 1, 2, and 3 were found in 5, 15, 21, and 4 cases, respectively. Out of these 45 cases, 25 (55.5%) showed HER2 overexpression/positivity (2+, 3+) [Table/Fig-5,6].

Stage of the disease: Out of the 45 cases, 15 (33.3%) presented in the advanced stage (with metastasis). Among these, 3 (20%) cases showed HER2 overexpression/positivity. Out of the 30 cases that presented in the early stage (without metastasis), 22 (73.3%)

Clinicopathological parameters	Overexpression/ positive (2+,3+)	Negative (0,1+)	No. of cases (n)	p-value
Age (in years)				
<70	8	12	20	0.06
>70	17	8	25	
Metastasis				
Absent	22	8	30	0.006
Present	3	12	15	
Perineural invasion				
Present	12	11	23	0.64
Absent	13	9	22	
PSA				
<10	3	5	8	0.25
>10	22	15	37	
Gleason score				
5-7	4	2	6	0.55
>7	21	18	39	
Gleason grade				
<3	8	6	14	0.88
>3	17	14	31	
Two year survival				
Survived	19	12	31	0.24
Expired	6	8	14	

[Table/Fig-4]: HER2/neu expression in prostate cancer.
PSA: Prostate specific antigen
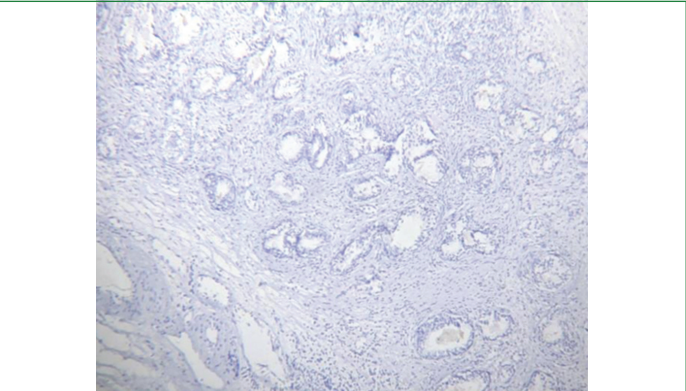
[Table/Fig-5]: HER2/neu expression in prostate adenocarcinoma (400x, IHC)-negative.
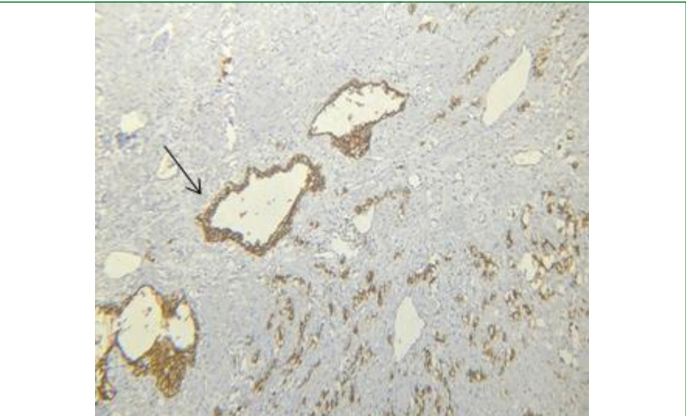
[Table/Fig-6]: HER2/neu expression in prostate adenocarcinoma (400x, IHC)-overexpression/positive.

showed HER2 overexpression/positivity. This result was statistically significant (p-value=0.006). Gleason score, Gleason grade, and HER2 expression: High Gleason scores (>7) were observed in 39 (86.6%) cases. Out of the 25 cases that showed HER2 overexpression/positivity, 21 cases had a Gleason score >7, and only four cases had a score of <7. Similarly, 17 cases had a Gleason grade >3, while eight cases had a grade of <3.

PSA with HER2 expression: Preoperative PSA levels were collected and compared with HER2 expression. High PSA levels (>10 ng/mL) were seen in 37 (82.2%) cases, out of which 22 (59.4%) cases showed HER2 overexpression/positivity.

Perineural invasion and HER2 expression: Out of the 23 cases with perineural invasion, 12 (52.17%) cases showed HER2 overexpression/positivity.
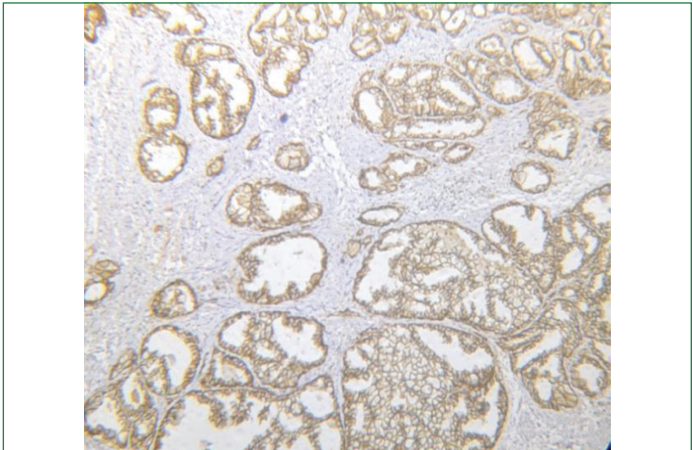
Age with HER2 expression: Out of the 25 patients aged more than 70 years, 17 (68%) cases showed HER2 overexpression/positivity.

Two-year survival and HER2 expression: Out of the 14 cases that expired, only six cases showed HER2 overexpression/positivity, while eight cases showed negative HER2 expression.

The expression of E-cadherin immunostaining in prostatic adenocarcinoma was examined with various parameters. A total of 45 cases diagnosed with prostate carcinoma were studied for E-cadherin expression [Table/Fig-7]. E-cadherin scores of 0, 1, 2, and 3 were found in 0, 14, 17, and 14 cases, respectively. Most of the cases showed normal E-cadherin expression, and only 14 (31.1%) cases showed negative E-cadherin expression (scores 0 and 1) [Table/Fig-8,9].
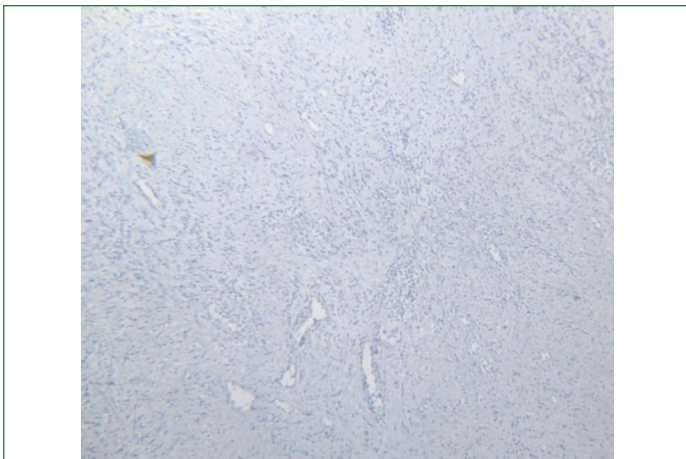
Clinicopathological parameters	Normal/strong expression (2+,3+)	Negative/weak expression (0,1+)	No. of cases (n)	p-value
Age (in years)				
<70	15	5	20	0.42
>70	16	9	25	
Metastasis				
Absent	21	9	30	0.81
Present	10	5	15	
Perineural invasion				
Present	14	9	23	0.23
Absent	17	5	22	
PSA				
<10	5	3	8	0.66
>10	26	11	37	
Gleason score				
5-7	4	2	6	0.89
>7	27	12	39	
Gleason grade				
<3	9	5	14	0.65
>3	22	9	31	
Two-year survival				
Survived	24	7	31	0.06
Expired	7	7	14	

[Table/Fig-7]: E-cadherin expression in prostate cancer.
PSA: Prostate specific antigen

[Table/Fig-8]: E-cadherin expression in prostate adenocarcinoma (400x, IHC) normal/strong expression.

[Table/Fig-9]: E-cadherin expression in prostate adenocarcinoma (400x, IHC) negative/weak expression.

Age with E-cadherin expression: Out of the 14 cases that showed reduced E-cadherin expression, nine cases were >70 years of age, and five cases were <70 years of age.

Gleason score, Gleason grade, and E-cadherin expression: High Gleason scores (>7) were observed in 39 cases, out of which 12 (30.7%) cases showed negative E-cadherin expression. Most of the cases with high Gleason scores showed normal E-cadherin expression, i.e., 27 cases. Out of the 31 cases that showed high Gleason grade (>3), most of the cases showed normal E-cadherin expression, i.e., 22 cases.

Metastasis and E-cadherin expression: Distant metastasis was seen in 15 cases, out of which E-cadherin was negative in 5 (33.3%) cases and normally expressed in 10 (66.6%) cases.

Perineural invasion and E-cadherin expression: Out of the 14 cases that showed negative E-cadherin expression, perineural invasion was found in nine cases and absent in five cases.

PSA and E-cadherin expression: Out of the 37 cases with PSA levels >10 ng/mL, only 11 cases showed negative E-cadherin expression, while 26 cases showed normal E-cadherin expression.

Two-year survival and E-cadherin expression: Two-year survival was better in patients with normal E-cadherin expression, irrespective of the stage of the tumour. Out of the 14 patients who expired, an equal number of patients showed negative (50%) and normal (50%) E-cadherin expression [Table/Fig-9].

DISCUSSION

In India, prostate cancer represents more than 92% of malignancies in the male genital tract [1]. The identification of markers helps in understanding the molecular mechanisms involved in carcinogenesis and invasion. HER2 has gained significance in breast carcinoma, as its expression is associated with poor prognosis. Additionally, the development of anti-p185neu antibody (trastuzumab) has become important in the field of HER2/neu and various cancers [13]. Early identification of the E-cadherin molecule helps in identifying neoadjuvant therapy, as seen in breast carcinoma, and aids in early containment of the tumour. Adhesion molecules play a role in epithelial tumours. Studies have shown that reduced E-cadherin promotes invasion and metastasis [14]. E-cadherin is assessed only in epithelial cells and is associated with Epithelial-Mesenchymal Transition (EMT). Fan L et al., speculated that loss of E-cadherin promotes prostate cancer metastasis via upregulation [14]. E-cadherin expression is inversely proportional to high Gleason score and distant metastasis [14]. EMT, stimulated by Transforming Growth Factor-beta 1 (TGFβ1), leads to downregulation of E-cadherin. E-cadherin is a key regulator of EMT switching. After the loss of E-cadherin, cells undergo EMT and demonstrate the potential to invade [14]. E-cadherin is an easily available and cost-effective marker in most tertiary care hospitals. The presence or absence of this protein will aid in prognostication of

the disease. A combined testing strategy to detect E-cadherin and HER2/neu will help in identifying high-risk cases and for follow-up of the same.

Prostate carcinoma and HER2/neu: In the present study, a total of 45 cases were analysed. The rate of HER2 overexpression/positivity was 55.5%. Various studies have reported HER2 overexpression rates ranging from 0% to 87% [6,7]. Zahir ST et al., and Sadasivan R et al., showed HER2 overexpression in only 16% and 36% of cases, respectively [15,16], while Morote J et al., reported a higher incidence of HER2 overexpression [6]. In the present study, no significant associations were found between HER2 expression and any of the clinicopathological factors, except for metastasis. The authors referenced a study by Moghadasniyat M, where the authors concluded that HER2 expression can be considered an indicator of mortality rate in patients with metastatic prostate cancer, similar to the findings of the present study [17]. A similar study by Nishio Y et al., on HER2 expression in prostate cancer did not show any association with clinical data [18]. However, Ross JS et al., found an association with tumour grade [19]. In our study, age >70 years, high PSA levels, high Gleason score, and early-stage prostatic carcinoma showed HER2 overexpression/positivity. Patients with androgen-independent prostate cancer express high levels of HER2 protein [20]. The present study did not analyse the androgen status of the patients, so it is possible that HER2 plays an important role in the carcinogenesis of androgen-independent tumours. This finding is supported by the present study, in which patients aged >70 years showed HER2 overexpression/positivity. Increasing age is known to lead to decreased levels of androgen [21]. As the incidence of prostate cancer is higher in older age, it is suggested that there may be another mechanism for the development of prostatic carcinoma, in which HER2 protein plays a role. Zahir ST et al., found that HER2 expression was higher in younger patients [15], whereas the present study showed the opposite. Zahir ST et al., also reported that elevated PSA levels were associated with increased HER2 expression, similar to the present study [15]. Furthermore, Jorda M et al., emphasise that HER2 is distributed focally and has weak intensity compared to breast cancer [22]. Present study supports this finding.

The present study showed that tumours with no perineural invasion and early/non metastatic lesions had increased expression of HER2. This suggests that early cases express more HER2 protein and there may be silencing of HER2 protein in advanced/invasive prostate cancer cases. Therefore, it is important to identify a HER2-negative set of tumours for administrating adjuvant analogues that can prevent metastasis and follow them up for high-grade transformation of malignancy. Ross JS et al., showed an association of HER2 expression with tumour grade, which contradicted the findings of the present study. Ross JS et al., stated that "High Gleason score is associated with increased HER2 expression" [19]. However, the authors emphasise that Gleason score is based on morphology patterns and architecture and is not associated with the extent of invasion or metastasis. Even advanced tumours can have a Gleason grade of 6 or below, while exhibiting bone metastasis and perineural invasion [23]. A meta-analysis by Neto AS et al., showed that HER2 overexpression was observed in patients with recurrence and an increased risk of death [24]. Since the follow-up period in the present study was restricted to two years, significant data on the risk of death could not be obtained.

Firstly, the reasons for the varied results may include differences in the type of primary antibody used (polyclonal/monoclonal), heterogeneity in case selection, and whether patients are androgen dependent, androgen refractory, or metastatic. Secondly, the phenotypic heterogeneity of prostate cancer with respect to HER2 expression has not been studied. Jorda M et al., suggested that prostate cancer is phenotypically heterogeneous, similar to breast cancer. Therefore, HER2 protein expression is not consistent and

uniform. Jorda M et al., found that 1-2 tumour cores showed HER2 expression while other cores were negative [22].

Prostate carcinoma and E-cadherin: In a total of 45 cases of prostatic adenocarcinoma, negative expression of E-cadherin was found in 14 (31.1%) cases. Among these, 5 (35.7%) cases had distant metastasis, 12 (85.7%) cases had a high Gleason score, 11 (78.5%) cases had high PSA levels, 9 (64.2%) cases showed perineural invasion, and 7 (50%) cases had poor two-year survival on follow-up. The present study did not find any statistical significance between E-cadherin expression and the clinicopathological parameters. Studies conducted by De Marzo AM et al., and Abdallah RA et al., also did not find a significant association between E-cadherin expression and clinicopathological features, similar to the findings of the present study [25,26]. Similarly, Arenas MI et al., did not show any association of E-cadherin loss with tumour progression or invasion, in line with the present study [27]. However, a study by Rubin MA et al., found aberrant E-cadherin expression in tumours with higher Gleason scores, positive surgical margins, and PSA recurrence [28].

Sommers CL suggested that the loss of E-cadherin expression suggests non-invasiveness, similar to the findings of the present study [29]. Therefore, the present study concludes that the absence of E-cadherin alone is not sufficient to cause distant metastasis. Firstly, the reasons for the varied results could be attributed to the type of primary antibody used, as mentioned earlier. Secondly, E-cadherin mutation is considered to be "transient" in most primary tumours, and studies have found that metastasis "re-expresses" E-cadherin. It is also postulated that the down-regulation of E-cadherin in some cases may be due to epigenetic alterations and is reversible [30]. Similar to HER2, E-cadherin also exhibits heterogeneous protein expression [31]. De Marzo AM et al., and Rubin MA et al., reported that most metastatic carcinomas showed E-cadherin expression. They hypothesised that E-cadherin down-regulation is transient during the process of metastasis [25,28]. Although metastatic tumours in the present study showed E-cadherin expression, as did localised tumours, there was no significant difference in E-cadherin expression between localised and metastatic tumours. The reason for this may be post-translational modification and truncation of E-cadherin, which inactivates it and converts it into a 97 kd protein [32]. Such cases may progress to metastasis but still show E-cadherin expression. This is because the commercial IHC E-cadherin kits bind to both the normal E-cadherin (120 kd) and the truncated (97 kd) forms of E-cadherin, resulting in staining. Metastatic carcinoma lesions actually show truncated E-cadherin [32]. Given that prostate cancer heterogeneously expresses E-cadherin, the study recommends evaluating different areas of prostate cancer and increasing the number of tissue samples.

Limitation(s)

A limitation of the present study was its small sample size. The study also did not evaluate the preoperative androgen therapy status. Furthermore, the study did not assess the role of HER2 and E-cadherin in the carcinogenesis of prostate adenocarcinoma.

CONCLUSION(S)

The study demonstrated a significant association between the overexpression of HER2/neu and tumour metastasis. Therefore, HER2/neu can be utilised as a prognostic parameter to assist surgeons. On the other hand, E-cadherin exhibited no association with the clinicopathological parameters. Consequently, its role in the progression of prostatic adenocarcinoma is questionable.

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