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Tumoral CD10 Expression Correlates with Aggressive Histology and Prognosis in Patients with Malignant Pleural Mesothelioma

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Abstract

Background—Currently, tumor-node-metastasis stage and histologic type are the established prognostic factors for malignant pleural mesothelioma, whereas no prognostic markers have been established for clinical practice. We investigated the prognostic value of CD10, a metalloproteinase that can promote cancer aggressiveness through enzymatic degradation and intracellular signaling crosstalk, in malignant pleural mesothelioma.

Methods—CD10 immunostaining was performed for 176 cases of malignant pleural mesothelioma (epithelioid, 148; biphasic, 14; sarcomatoid, 14), and its expression was dichotomized as negative (no staining) or positive (any staining). Epithelioid tumors were classified as pleomorphic subtype when cytologic pleomorphism was ≥10 % of the tumor. Overall survival (OS) was analyzed by log-rank tests and Cox proportional hazard models.

Results—Tumoral CD10 expression was identified in 42 % of epithelioid non-pleomorphic tumors, 57 % of epithelioid pleomorphic tumors, 79 % of biphasic tumors, and 93 % of sarcomatoid tumors ($p < 0.001$). Positive CD10 expression was correlated with higher mitotic count ($p = 0.002$). Overall survival for patients with positive CD10 expression was significantly shorter than that for patients with negative CD10 expression in all patients ($p = 0.001$) and in patients with epithelioid tumor ($p = 0.04$). On multivariate analysis, CD10 expression was an independent prognostic factor for all patients (hazard ratio 1.48; $p = 0.019$).

DISCLOSURE: Kyuichi Kadota, Jonathan Villena-Vargas, Jun-ichi Nitadori, Camelia S. Sima, David R. Jones, William D. Travis, and Prasad S. Adusumilli do not have any commercial interests to disclose.

Conclusions—Tumoral CD10 expression correlated with aggressive histologic types and higher mitotic activity and is an independent prognostic factor for patients with malignant pleural mesothelioma.

Malignant pleural mesothelioma is an uncommon but aggressive tumor. Despite improvements in surgical management, chemotherapy, and radiotherapy, the prognosis for malignant pleural mesothelioma remains poor, with a median survival of <2 years.[1–3] Even though several prognostic markers have been proposed (including specific histologic patterns, tumor markers, immune cell infiltrates, and radiologic findings),[4–9] at present, tumor-node-metastasis (TNM) stage and histologic type (epithelioid, biphasic, and sarcomatoid) are the most established factors for determination of clinical management.[1–3] However, the prognostic utility of TNM staging is limited to differentiating between early- (I–II) and late-stage (III–IV) disease.[1,2] Even among patients with epithelioid mesothelioma, survival outcomes remain variable. Therefore, further prognostic factors are necessary to optimize treatment options, as well as to better stratify patients in clinical trials.

CD10 (neutral endopeptidase), a zinc-dependent metalloproteinase, is expressed in various normal tissues[10] and is capable of efficiently degrading various peptides and cytokines.[11,12] CD10 is also expressed in malignant tumors and has been identified as a predictor of tumor biological aggressiveness through extracellular enzymatic degradation and intracellular signaling crosstalk.[13–23] Although CD10 is expressed in malignant pleural mesothelioma,[24] its prognostic significance for malignant pleural mesothelioma is not known.

In this study, we investigate whether CD10 expression can be used to stratify patients with respect to survival and whether it correlates with clinicopathologic factors in patients with malignant pleural mesothelioma.

MATERIALS AND METHODS

Patients

The current retrospective study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center. We reviewed all patients who were diagnosed with malignant pleural mesothelioma at our institution between 1989 and 2009. A total of 305 cases had tumor slides available for histologic evaluation. Of these, 198 had tumor blocks available for construction of tissue microarrays. Clinical data were collected from the prospectively maintained malignant pleural mesothelioma database. Disease stage was based on the reported imaging findings, the surgeon's intraoperative findings, and the pathologic evaluation of the resected specimens, according to the 6th edition of the American Joint Committee on Cancer Staging Manual.[25]

The cases in this study have been included in previous reports from our group; the pathologic diagnosis of malignant mesothelioma was confirmed by histologic, histochemical, and immunohistochemical examination.[4,5]

Histologic Evaluation

All available hematoxylin and eosin (H&E)-stained tumor slides [median 9 slides/case (range 1–43 slides/ case)] were reviewed by two pathologists (KK and WDT) blinded to the patients' clinical outcomes, by use of an Olympus BX51 microscope (Olympus Co., Tokyo, Japan) with a standard 22-mm diameter eyepiece. Epithelioid mesothelioma can be composed of one or more of the following five histologic patterns, which were recorded in 5 % increments: trabecular, tubulopapillary, micropapillary, solid, and pleomorphic, as previously reported.[5] Tumors were classified as pleomorphic subtype when cytologic pleomorphism made up at least 10 % of the tumor. The remaining tumors were classified according to the predominant histologic pattern.[5]

Mitotic counts were determined with a high-power field (HPF) of 400× magnification (0.237 mm^2), as previously reported.[4,26] Mitoses were evaluated in 50 HPF areas, with the highest mitotic activity after scanning through all tumor slides being used, and were recorded as the average number of mitotic figures per 10 HPFs.

Tissue Microarray

Formalin-fixed, paraffin-embedded tumor blocks were used for construction of tissue microarrays. For epithelioid tumors, six representative tumor areas and three tumor-related stromal areas were marked on H&E-stained slides. For biphasic and sarcomatoid tumors, six representative areas of sarcomatoid morphologic pattern were marked on H&E-stained slides. Cylindrical 0.6-mm tissue cores were arrayed from the marked areas of corresponding paraffin blocks into a recipient block by use of an automated tissue arrayer (ATA-27; Beecher Instruments, Sun Prairie, WI, USA), resulting in five tissue microarray blocks.

Immunohistochemical Analysis and Scoring of CD10

In brief, 4-μm-thick sections from the blocks were deparaffinized. The standard avidin-biotin-complex per-oxidase technique was used for immunostaining of anti-CD10 antibody [56C6; diluted at 1:50] (Vector Laboratories, Burlingame, CA, USA). Sections were stained using a Ventana Discovery XT automated immunohistochemical stainer (Ventana, Tucson, AZ, USA) in accordance with the manufacturer's guidelines.

CD10 expression was observed in the cytoplasm of tumor cells, tumor-related stromal cells, and granulocytes in tumoral and stromal areas (Fig. 1), as previously observed in other solid tumors.[17,18] In addition, CD10 was expressed in the interstitial stromal cells of normal lung tissue, which was used as an internal positive control.[10] The intensity score (0, no expression; 1, mild; 2, intermediate; 3, strong) and distribution score (0, 0 %; 1, 1–50 %; 2, 51–100 %) for immunostaining were summed into a total score for each tumor and stromal core (total score, 0–5),[27,28] which was dichotomized as negative (score 0) or positive (score >0). The prevalence of CD10-positive granulocytes was scored in tumoral and stromal cores semiquantitatively: score 0 (CD10-positive granulocytes = 0), score 1 (1–2), score 2 (3–9), score 3 (10–29), and score 4 (≥30). The average score for the tumor or stromal core was considered to be the score for each patient. In total, 176 tumors (epithelioid, 148; biphasic,

14; sarcomatoid, 14) had adequate cores available for immunohistochemical analysis of tumoral CD10.

Statistical Analysis

Associations between clinicopathologic factors and CD10 expression were analyzed using the Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables. Overall survival (OS) following surgery was estimated using the Kaplan–Meier method, with patients censored if they were alive at the time of the last follow-up. Non-parametric group comparisons were performed using the log-rank test. Multivariate analyses were performed using the Cox proportional hazard regression model to study the effects of different variables on OS. All p values were based on two-tailed statistical analysis, and $p < 0.05$ was considered to indicate statistical significance. All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA).

RESULTS

Clinicopathologic Demographic Characteristics of Patients with Epithelioid Malignant Pleural Mesothelioma and Their Association with Overall Survival (OS)

The median age of all patients with epithelioid mesothelioma ($n = 148$) was 63 years (range 29–83 years). Most patients were men ($n = 106$), and most had stage III disease ($n = 85$). In total, 32 patients received preoperative chemotherapy, and 136 had undergone surgical resection (Table 1). Median OS was 15.4 months. On univariate analysis, nodal metastasis ($p = 0.016$), advanced disease stage (stage III–IV; $p = 0.006$), lymphatic invasion ($p = 0.007$), vascular invasion ($p = 0.001$), and pleomorphic subtype ($p < 0.001$) were associated with shorter OS (Table 1).

Association between CD10 Expression and OS in Patients with Epithelioid Malignant Pleural Mesothelioma

Positive tumoral CD10 expression was observed in 45 % (66/148) of patients with epithelioid malignant pleural mesothelioma. Among these patients, there were 22 cases with a total score of 0–1, 19 cases with a total score of 1–2, 14 cases with a total score of 2–3, 6 cases with a total score of 3–4, and 5 cases with a total score >4. The OS for patients with positive tumoral CD10 expression ($n = 66$) was significantly shorter (median OS 14.5 months) than that for patients with negative CD10 expression ($n = 82$; 17.4 months; $p = 0.04$) (Fig. 2a). Among the patients with early-stage disease (stage I–II; $n = 46$), OS was significantly shorter for patients with positive CD10 expression ($n = 21$; median OS 16.3 months) than for patients with negative CD10 expression ($n = 25$; 36.4 months; $p = 0.008$), although this result was determined from a small number of patients.

On multivariate analysis of patients with epithelioid mesothelioma, a trend was observed between tumoral CD10 expression and shorter OS [hazard ratio (HR) 1.41; $p = 0.052$]. Advanced disease stage (stage III–IV; HR 1.49; $p = 0.045$) and pleomorphic subtype (HR 1.89; $p = 0.018$) were independent predictors of OS (Table 2).

In total, 23 % of cases had CD10 expression in tumor-related stroma. Tumoral CD10 + granulocytes and stromal CD10 + granulocytes were observed in 57 % (10 % with a score ≥3) and 42 % (3 % with a score ≥3) of cases, respectively; however, these parameters had no association with clinicopathological factors, including OS.

Association between Tumoral CD10 Expression and Histologic Types or Clinicopathologic Factors in Patients with Malignant Pleural Mesothelioma

CD10 expression was positively correlated with higher-grade histologic types ($p < 0.001$); it was identified in 42 % (53/125) of epithelioid non-pleomorphic tumors, 57 % (13/23) of epithelioid pleomorphic tumors, 79 % (11/ 14) of biphasic tumors in the sarcomatoid area, and 93 % (13/14) of sarcomatoid tumors (Fig. 3a). Among epithelioid non-pleomorphic tumors, tumoral CD10 expression was identified in 37 % (11/30) of tubulopapillary tumors, 25 % (5/20) of trabecular tumors, 50 % (30/60) of solid tumors, and 47 % (7/15) of micropapillary tumors.

Mitotic counts (mitoses per 10 HPFs) were significantly higher in CD10-positive tumors than in CD10-negative tumors [median 6 (range 0–42) vs. 3 (range 0–64); $p = 0.002$] (Fig. 3b); however, tumoral CD10 expression did not correlate with other clinicopathologic factors, including TNM stage.

Association between Tumoral CD10 Expression and OS in All Patients with Epithelioid and Non-Epithelioid Mesothelioma

Among all patients with epithelioid and non-epithelioid mesothelioma ($n = 176$), OS for patients with positive CD10 expression ($n = 90$) was significantly shorter (median 9.8 months) than that for patients with negative CD10 expression ($n = 86$; 16.9 months; $p = 0.001$) (Fig. 2b). On multivariate analysis of all patients, positive CD10 expression was an independent factor of prognosis (HR 1.48; $p = 0.019$) (Table 3).

DISCUSSION

We have demonstrated that tumoral CD10 expression correlates with aggressive histologic types and higher mitotic activity, and is an independent prognostic factor of OS in patients with malignant pleural mesothelioma.

Previous studies identified CD10 as a predictor of biological aggressiveness in various malignant tumors.[13–23] In breast carcinoma, CD10 expression in tumor-related stroma is correlated with worse survival, with a greater risk of lymph node metastasis and higher tumor grade.[13–15] In colorectal carcinoma, tumoral CD10 expression is correlated with a greater risk of liver metastasis.[16,17] In addition, in colorectal carcinoma, CD10 expression was observed in tumor-infiltrating granulocytes, which was correlated with worse survival.[18] In prostate carcinoma, tumoral CD10 expression identifies a subset of patients with a poor prognosis, with a higher risk of lymph node metastasis and a higher Gleason grade.[19–21] In contrast, in hematopoietic tumors such as malignant lymphoma, tumoral CD10 expression is correlated with improved survival.[22,23] In our study, tumoral CD10 expression identified a subset of patients with malignant pleural mesothelioma with a poor prognosis. CD10 was also expressed in tumor-related stroma and tumor-infiltrating immune

cells (granulocytes) in patients with malignant pleural mesothelioma, although this finding did not have prognostic significance.

We identified that tumoral CD10 expression was more frequently observed in non-epithelioid tumors (79 % of biphasic tumors, 93 % of sarcomatoid tumors) than in epithelioid tumors (45 %). Among epithelioid tumors, the pleomorphic subtype, which we recently identified as the epithelioid mesothelioma subtype with the worst prognosis,[5] was more likely to express CD10 (57 %) compared with non-pleomorphic tumors (42 %). Even though tumoral CD10 expression was significantly associated with the non-epithelioid histologic type, which has been considered a poor prognostic type, tumoral CD10 expression was an independent prognostic factor for survival in our multivariate model that adjusted for histologic subtype (epithelioid vs. non-epithelioid). Furthermore, even among patients with epithelioid tumors, CD10 expression showed potential as an independent prognostic factor.

At present, cisplatin combined with pemetrexed is the standard first-line regimen for the treatment of malignant pleural mesothelioma.[29,30] Recently, CD10 was demonstrated to be a novel marker of cisplatin resistance and cancer stem cells using cell lines from other solid malignancies.[31] In addition, CD10 has been reported to cleave and activate a peptidic prodrug of doxorubicin,[32,33] and recent clinical trials suggest that chemotherapy with doxorubicin could be effective in patients with malignant pleural mesothelioma, with improvements in quality of life and an acceptable level of toxicity.[34,35] Therefore, CD10 is a potential marker for investigating chemotherapy sensitivity or resistance in patients with malignant pleural mesothelioma.

A limitation of the present study is that we used a cohort that was heterogeneous in terms of TNM stage. However, tumoral CD10 expression remained a prognostic factor in patients with early-stage disease, and was an independent prognostic factor on multivariate analysis after adjustment for TNM stage (early vs. advanced). Another potential limitation in this study, which used a tissue microarray, is that CD10-negative tumors might be focally positive if they are stained with whole-tissue blocks; however, when whole-tissue blocks were used in a previous study, the total rate of CD10 positivity was 54 % for malignant mesothelioma.[24] This is similar to that in the present study using tissue microarray analysis (51 % in all patients with mesothelioma). Therefore, we believe that our conclusions would not be significantly changed if a whole-tissue block was used to confirm tumoral CD10 positivity.

CONCLUSIONS

In malignant pleural mesothelioma, expression of CD10 correlates with aggressive histologic types and high mitotic activity, and is an independent predictor of patient survival. As immunohistochemical analysis has become routine clinical practice, prognostic stratification using CD10 immunostaining can be readily implemented to potentially select treatment options for patients with malignant pleural mesothelioma.

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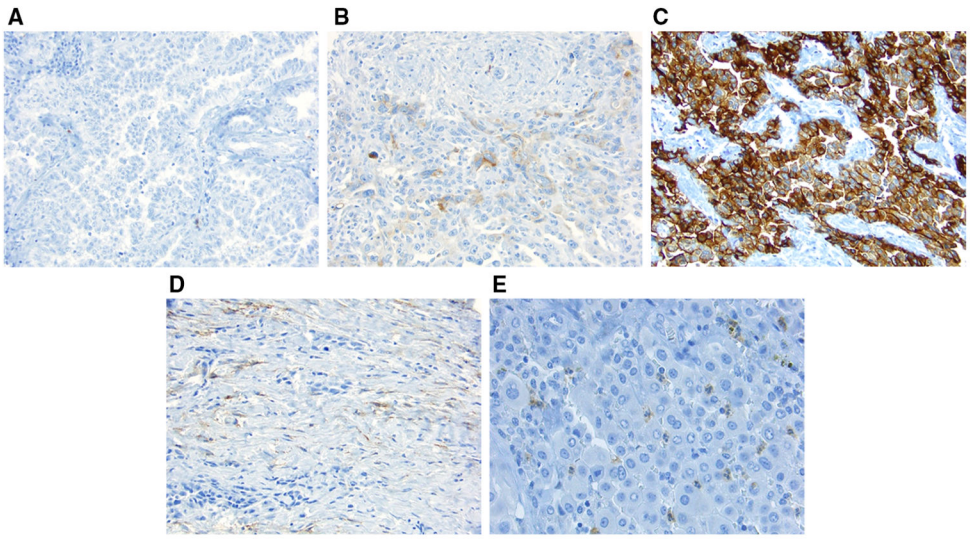

FIG. 1.

CD10 immunohistochemical analysis using a tissue micro-array (original magnification, ×200). **a** Tumor cells are negative for CD10; **b** tumor cytoplasm is weakly positive for CD10; **c** tumor cytoplasm is strongly positive for CD10; **d** tumor-related stroma is positive for CD10; **e** granulocytes infiltrating in tumor cells are positive for CD10

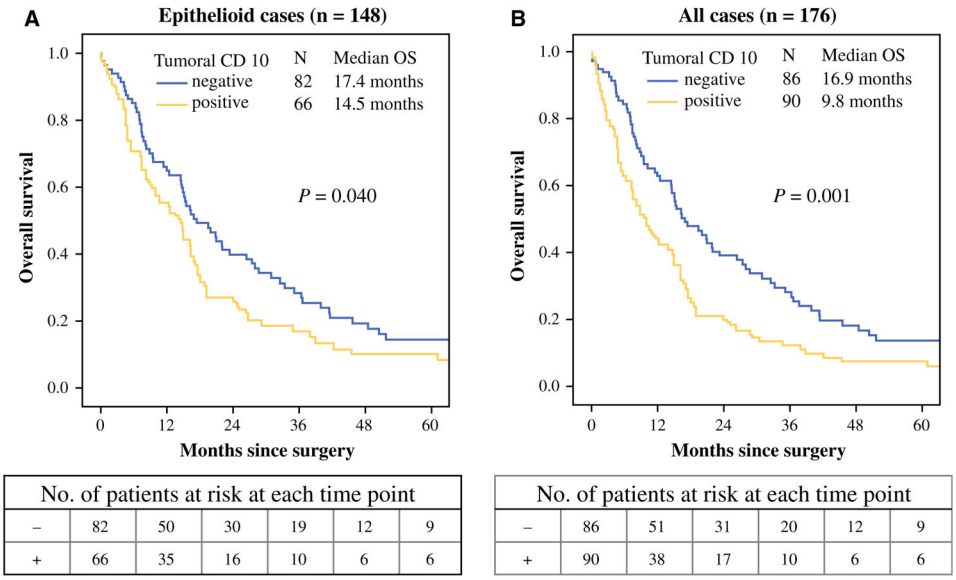

FIG. 2.

Association between CD10 expression and OS in patients with epithelioid and all malignant pleural mesotheliomas. **a** In patients with epithelioid malignant pleural mesothelioma, the OS for patients with positive tumoral CD10 expression (n = 66) was significantly shorter (median OS 14.5 months) than that for patients with negative CD10 expression (n = 82; 17.4 months; p = 0.04). **b** For all patients with epithelioid and non-epithelioid tumors, the OS for patients with positive tumoral CD10 expression (n = 90) was significantly shorter (median OS 9.8 months) than that for patients with negative CD10 expression (n = 86; 16.9 months; p = 0.001). *OS* overall survival

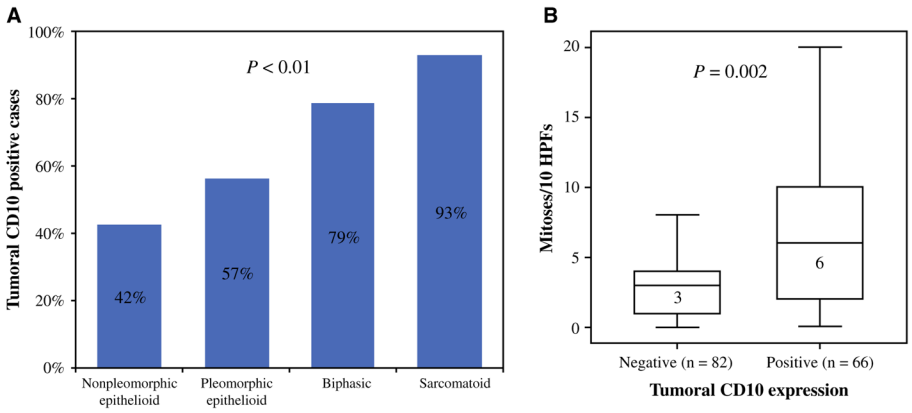

FIG. 3.

Association between CD10 expression and histologic types and mitotic count. **a** Tumoral CD10 expression was positive in 42 % (53/125) of epithelioid non-pleomorphic tumors, 57 % (13/23) of epithelioid pleomorphic tumors, 79 % (11/14) of biphasic tumors, and 93 % (13/14) of sarcomatoid tumors ($p < 0.001$). **b** Mitotic counts (mitoses per ten HPFs) were significantly higher in CD10-positive tumors than in CD10-negative tumors [median 6 (range 0–42) vs. 3 (range 0–64); $p = 0.002$]. *HPFs* high-power fields

TABLE 1

Associations between clinicopathologic factors and overall survival in patients with epithelioid tumors

Variable	*n*	%	Median OS (months)	*p* value
Total	148	100	15.4	
Age (years)				0.63
≤65	85	57	16.3	
>65	63	43	15.1	
Sex				0.43
Female	42	28	18.9	
Male	106	72	15.0	
Preoperative chemotherapy				
No	116	78	15.2	0.55
Yes	32	22	16.3	
Disease laterality				0.82
Left	62	42	16.1	
Right	86	58	15.1	
Surgical procedure				0.17
Extrapleural pneumonectomy	81	55	14.5	
Pleurectomy-decortication	55	37	18.9	
Other	12	8	7.9	
T stage				0.050
T1 + T2	6 + 60	45	16.3	
T3 + T4	69 + 13	55	14.5	
N stage				**0.016**
N0	89	60	18.1	
N1 + N2	12 + 47	40	9.5	
TNM stage				**0.006**
I + II	5 + 41	31	19.2	
III + IV	85 + 17	69	12.5	
Lymphatic invasion				**0.007**
Absence	77	52	20.9	
Presence	71	48	12.3	
Vascular invasion				**0.001**
Absence	114	77	17.0	
Presence	34	23	9.7	
Histologic subtype				**< 0.001**
Non-pleomorphic	125	84	16.3	
Pleomorphic	23	16	8.1	

Significant *p* values ($p < 0.05$) are shown in bold

OS overall survival, *TNM* tumor-node-metastasis

TABLE 2

Multivariate model in patients with epithelioid tumors (n = 148)

Variable	HR	95 % CI	*p* value
Tumoral CD10: positive vs. negative	1.41	0.99–2.00	0.052
TNM stage: III–IV vs. I–II	1.49	1.00–2.19	**0.045**
Lymphatic invasion: presence vs. absence	1.26	0.84–1.88	0.26
Vascular invasion: presence vs. absence	1.29	0.78–2.12	0.33
Histologic subtype: pleomorphic vs. non-pleomorphic	1.89	1.12–3.18	**0.018**

Significant p values (p <0.05) are shown in bold

HR hazard ratio, *CI* confidence interval, *TNM* tumor-node-metastasis

TABLE 3

Multivariate model in all patients (n = 176)

Variable	HR	95 % CI	*p* value
Tumoral CD10: positive vs. negative	1.48	1.07–2.04	**0.019**
TNM stage: III–IV vs. I–II	1.45	1.00–2.09	**0.046**
Lymphatic invasion: presence vs. absence	1.32	1.93–1.85	0.12
Vascular invasion: presence vs. absence	1.34	0.90–1.99	0.15
Histologic type: non-epithelioid vs. epithelioid	2.27	1.43–3.62	**<0.001**

Significant p values (p <0.05) are shown in bold

HR hazard ratio, *CI* confidence interval, *TNM* tumor-node-metastasis