Prognostic Role of the Ratio between Cyclooxygenase-2 in Tumor and Stroma Compartments in Cervical Cancer

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Departments of 1 Obstetrics and Gynecology, 2 Histology, and 3 Pathology, Catholic University of the Sacred Heart, Rome, Italy.

ABSTRACT

Purpose: The aim of this study was to analyze the clinical role of cyclooxygenase (COX)-2 in a large series of 175 cervical cancer patients. Experimental Design: Immunohistochemistry was performed on paraffin-embedded sections by using rabbit antiserum against COX-2. The tumor:stroma (T/S) ratio of COX-2 expression was used to define the overall COX-2 content in the tumor.

Results: The T/S COX-2 ratio values ranged from 0.03 to 48.2 (mean ± SE, 3.7 ± 0.5). A total of 95 of 175 patients (54.3%) were scored as having a high (>1) T/S COX-2 ratio. In locally advanced cervical cancer patients who underwent neoadjuvant treatment, the percentage of cases showing a high T/S COX-2 ratio was greater in patients who did not respond to treatment (26 of 29 patients, 89.7%) than in patients with a partial (32 of 50 patients, 64.0%) or complete (19 of 44 patients, 43.2%) response (P = 0.0003). When logistic regression was applied, International Federation of Gynecologists and Obstetricians (FIGO) stage (χ2 = 11.3; P = 0.0008) and T/S COX-2 ratio (χ2 = 5.3; P = 0.021) retained an independent role in predicting a poor response of cases with a high T/S COX-2 ratio had a shorter overall survival (OS) [2-year OS, 61% (95% confidence interval 75–83)] than cases with a low T/S COX-2 ratio (2-year OS, 90%; 95% confidence interval, 81–99; P = 0.0001). In multivariate analysis, the status of T/S COX-2 IDV ratio, together with advanced stage, retained an independent negative prognostic role for OS.

Conclusions: The assessment of COX-2 status in both tumor and stroma compartment could provide valuable information to identify cervical cancer patients endowed with a very poor chance of response to neoadjuvant treatment and unfavorable prognosis.

INTRODUCTION

Several reports have recently highlighted the biological and clinical role of cyclooxygenase (COX)-2, the key enzyme in the conversion of arachidonic acid to prostaglandins (1, 2), in the pathogenesis and natural history of human cancer.

In particular, COX-2 overexpression is involved in the inhibition of apoptosis, increased metastatic potential and neoangiogenesis, and impairment of host immune responses (3–6). Moreover, COX-2 has been associated with parameters of tumor aggressiveness and unfavorable prognosis in several solid tumors including colorectal, breast, ovarian, and cervical cancer (7–10).

Recent reports by us and others (10–13) have shown that high COX-2 expression in tumor cells characterizes cervical cancer patients with poor survival regardless of the type of primary treatment.

We recently showed that (a) COX-2 is also expressed in the cellular elements of the stroma in cervical tumors, (b) an inverse relationship exists between COX-2 expression in tumor cells and COX-2 expression in the stroma inflammatory compartment, and (c) the ratio between COX-2 expression in tumor versus COX-2 in the stroma might play a relevant prognostic role in this neoplasia (14).

In this context, it is worth noting that high COX-2 staining in tumor cells is associated with a lower proportion of CD3+, CD4+, and CD25+ T cells in the stroma (14) of cervical cancer, suggesting that the involvement of COX-2 in the inhibition of host immune functions could influence clinical outcome.

We were then prompted to analyze the clinical role of the tumor:stroma (T/S) ratio of COX-2 expression in a large series of cervical cancer patients.

The correlation with conventional prognostic parameters such as clinicopathological factors and circulating levels of squamous cell carcinoma (SCC) antigen (15) was also investigated.

PATIENTS AND METHODS

The study included 175 stage IB–IV cervical cancer patients consecutively admitted to the Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Catholic University of Rome between November 1995 and December 2002. Median age was 52 years (range, 24–80 years). Fifty-five patients had stage IB disease, 9 patients had stage IIA disease, and 70 patients had stage IIB disease, whereas advanced stage of disease was observed in 41 patients. Most tumors were SCC.
(n = 144), 20 were adenocarcinomas, and 11 were adenosquamous carcinomas. The other clinicopathological characteristics are summarized in Table 1.

The clinical management of our patient population was as described previously (10, 13): as summarized in Fig. 1, cases with early-stage disease [International Federation of Gynecologists and Obstetricians (FIGO) Stage IB–IIA, major tumor diameter of <4 cm] were primarily subjected to radical surgery (n = 52), whereas locally advanced cervical cancer (LACC) cases (n = 123) were first given neoadjuvant treatment including neoadjuvant platinum-based chemotherapy (100 mg/m² cisplatin every 3 weeks for 2–3 courses; n = 71) or neoadjuvant chemoradiation (n = 52), as described previously (16).

In case of clinical response, as assessed by the above-described procedures and recorded according to WHO response evaluation criteria (17), LACC patients were subjected to radical surgery (n = 94): operative technique consisted of type II–IV radical hysterectomy and systematic pelvic lymphadenectomy. An anterior exenteration was performed in three cases with persisting involvement of the bladder after neoadjuvant treatment. Para-aortic lymphadenectomy up to the level of inferior mesenteric artery was performed in high-risk patients as reported previously (18).

Patients showing no clinical change/progression during neoadjuvant treatment were subjected to salvage treatment, with the exception of 7 patients in whom, despite clinically documented evidence of no response to treatment, surgery was attempted due to their young age and resulted predominantly (n = 6) in the impossibility of proceeding to remove the tumor due to the extension of disease (explorative laparotomy).

**Table 1** Distribution of T/S* COX-2 ratio according to clinicopathological characteristics of cervical cancer population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
<th>T/S COX-2 ratio no. (no.)</th>
<th>P</th>
<th>T/S COX-2 ratio (mean ± SE)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>175</td>
<td>95 (54.3)</td>
<td>3.7 ± 6.9</td>
<td>0.0001</td>
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<tr>
<td>Age (yrs)</td>
<td></td>
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<tr>
<td>&lt;50</td>
<td>82</td>
<td>44 (53.7)</td>
<td>3.4 ± 0.7</td>
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<tr>
<td>≥50</td>
<td>93</td>
<td>51 (54.8)</td>
<td>3.9 ± 1.1</td>
<td>0.5</td>
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<tr>
<td>FIGO stage</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IB–II</td>
<td>134</td>
<td>65 (48.5)</td>
<td>3.4 ± 0.6</td>
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<td></td>
</tr>
<tr>
<td>III–IV</td>
<td>41</td>
<td>30 (73.2)</td>
<td>4.6 ± 1.1</td>
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<tr>
<td>Histotype</td>
<td></td>
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<tr>
<td>Squamous</td>
<td>144</td>
<td>70 (48.6)</td>
<td>2.9 ± 0.5</td>
<td>0.0013d</td>
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</tr>
<tr>
<td>Other</td>
<td>31</td>
<td>25 (80.6)</td>
<td>7.5 ± 1.9</td>
<td>0.0001d</td>
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<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1–2</td>
<td>69</td>
<td>41 (59.4)</td>
<td>3.8 ± 0.7</td>
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<tr>
<td>3</td>
<td>91</td>
<td>54 (59.3)</td>
<td>3.5 ± 0.7</td>
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<tr>
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<td>Tumor size (cm)</td>
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<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>71</td>
<td>28 (39.4)</td>
<td>1.8 ± 0.3</td>
<td>0.0005</td>
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<tr>
<td>≥4</td>
<td>104</td>
<td>67 (64.4)</td>
<td>5.0 ± 0.8</td>
<td>0.0005</td>
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<td>Clinical response*</td>
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<tr>
<td>Complete</td>
<td>44</td>
<td>19 (43.2)</td>
<td>2.7 ± 0.8</td>
<td>0.0003</td>
<td>0.0008</td>
</tr>
<tr>
<td>Partial</td>
<td>50</td>
<td>32 (64.0)</td>
<td>3.9 ± 0.8</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>No change/progression</td>
<td>29</td>
<td>26 (89.7)</td>
<td>8.5 ± 2.3</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

* T/S, tumor:stroma; COX, cyclooxygenase; FIGO, International Federation of Gynecologists and Obstetricians.

Calculated by χ² test.

Calculated by Kruskal-Wallis nonparametric test.

Squamous versus other histotypes.

Results are relative to locally advanced cervical cancer patients.

Fig. 1 Flow chart of our patient population. *, in seven cases, surgery was attempted, resulting in six explorative laparotomies.
then simultaneously processed for immunohistochemistry on the TechMate Horizon automated staining system (DAKO) using the Vectastain ABC peroxidase kit (Vector Laboratories, Burlingame, CA). Endogenous biotin was saturated by a biotin blocking kit (Vector Laboratories). Sections were incubated with normal non-immunized rabbit serum for 15 min and then incubated with rabbit antiserum against COX-2 (20), diluted 1:300, for 1 h. Negative controls were performed using nonimmunized rabbit serum, omitting the primary antibodies. As a positive control for COX-2 antibody, COX-2-positive Hep-2 squamous cancer cells and COX-2-positive squamous cancer tissue specimens (21) were always run in the assay.

Quantification of Immunohistochemical Staining. The intensity of immunohistochemical staining was evaluated using image analysis based on Photoshop (Version 5.0; Adobe System, San Jose, CA) together with The Image Processing Toolkit version 3.0 (CRC Press, Boca Raton, FL) according to the method reported previously (14), with some modifications. Briefly, the technical set up included a Zeiss Axioskop (Zeiss, Jena, Germany) equipped with a Nikon Coolpix 950 digital camera (Nikon Corp., Tokyo, Japan). Three ×20 fields were chosen form each section so as to best reflect the overall immunostaining of the tumor contained on the entire slide. After acquisition with a digital camera, the files were saved in tagged-image file format, which allows LZW compression without discarding any data. The files were opened in Photoshop using a Macintosh 400 MHz G3 workstation (Apple, Cupertino, CA). The immunostained regions of interest in the tumor and stromal compartments were automatically selected and highlighted using the “Magic Wand” tool and an appropriate color tolerance level. The mean density value and the area (in pixels) of the immunostained regions were measured by the “Brightness filter” tool and a built-in calibration curve constructed from the “Brightness filter” readings and the known absorbance values of calibrated wedges digitized with the same camera. The rest of the tumor tissue was subsequently selected using the “Invert” tool, and the relative area in pixels was calculated with the “Brightness filter” tool and added to the immunostained area to obtain the total measured area. Then, the integrated density of the immunostaining was calculated as the product of the mean density value of the immunoreactive regions by the percentage of immunostained tumor tissue. The computerized image analysis of all tissue sections was done by two different pathologists (F. O. R. and M. G.) without any prior knowledge of the clinical and biological parameters.

Statistical Analysis. The χ² test was used to analyze the distribution of cases with a high (>1) T/S COX-2 ratio according to several clinicopathological features. The Kruskal-Wallis nonparametric test was used to analyze the distribution of T/S COX-2 integrated density values according to clinicopathological variables. Overall survival (OS) was calculated from the date of diagnosis to the date of death or date last seen. Medians and life tables were computed using the product-limit estimate by the Kaplan-Meier method (22), and the log-rank test was used to assess statistical significance (21). The prognostic role of COX-2 as a continuous variable was also analyzed by means of the Cox proportional hazard model (20). A Cox’s regression model with stepwise variable selection (20) and multiple logistic analysis (23) were used to analyze the role of clinicopathological parameters and COX-2 staining as prognostic factors and predictors of response to neoadjuvant treatment. Statistical analysis was carried out using SOLO (BMDP Statistical Software, Los Angeles, CA) and Statview survival tools (Abacus Concepts Inc., Berkeley, CA).

RESULTS

COX-2 Immunostaining. In the whole series, COX-2 integrated density values in the tumor component ranged from 1.2 to 82.3 with mean ± SE values of 24.5 ± 1.5. COX-2 integrated density values in the stroma component range from 0.9 to 96.0 with mean ± SE values of 19.9 ± 1.2. Given the statistically significant inverse relation between COX-2 of tumor versus COX-2 in the stroma compartment (r = −0.38; P < 0.0001; data not shown), the T/S COX-2 ratio was used to normalize COX-2 expression in each case and to categorize tumors according to low versus high T/S COX-2 ratio values of content.

The T/S COX-2 ratio ranged from 0.03 to 48.2 (mean ± SE, 3.7 ± 0.5). Given the inverse relation between COX-2 in the tumor and stroma, a value of ≤1 was chosen a priori because it best represented the equivalence in terms of COX-2 expression between the tumor and stroma compartments. According to the chosen cutoff value, 95 of 175 patients (54.3%) were scored as having a high (>1) T/S COX-2 ratio.

Correlation with Clinicopathological Parameters. The distribution of cases with high T/S COX-2 ratio according to clinicopathological characteristics is shown in Table 1.

The percentage of cases with a high T/S COX-2 ratio was greater in stage III–IV cases than in stage I–II cases (73.2% versus 48.5%; P = 0.0069). Similarly, higher T/S COX-2 ratio values were found in stage III–IV cases as compared with stage I–II cases (P = 0.024).

The percentage of cases with a high T/S COX-2 ratio was greater in tumor with adenocarcinoma/adenosquamous histotype than in squamous tumors (80.6% versus 40.6%; P = 0.0013). Similarly, mean ± SE T/S COX-2 ratio values were higher in adenocarcinoma/adenosquamous tumor (mean ± SE, 7.5 ± 1.9) than in squamous tumors (mean ± SE, 2.9 ± 0.5; P = 0.0001).

Moreover, cases with a high T/S COX-2 ratio were observed more frequently in tumors of ≥4 cm than in smaller tumors (64.4% versus 39.4%; P = 0.001). Similarly, higher T/S COX-2 ratio values were observed in cases with tumor volume ≥ 4 cm (mean ± SE, 5.0 ± 0.8) than in smaller tumors (mean ± SE, 1.8 ± 0.3; P = 0.0001).

No association with age or grade of differentiation was found (data not shown).

At imaging, metastatic lymph node involvement was found in 71 of 175 (40.6%) cases: the percentage of COX-2 tumor positivity was 62.7% in lymph node-positive cases with respect to 49.5% in lymph node-negative cases (difference not significant; data not shown).

COX-2 Status and Response to Neoadjuvant Treatment. As far as clinical response to treatment is concerned, the percentage of cases with a high T/S COX-2 ratio was significantly greater in patients who did not respond to treatment.
In the univariate analysis, advanced FIGO stage and high T/S COX-2 ratio proved to be associated with poor chance of response to neoadjuvant treatment (complete/partial response versus no response). When logistic regression was applied, FIGO stage ($\chi^2 = 11.3; P = 0.0008$) and T/S COX-2 ratio ($\chi^2 = 5.3; P = 0.021$) retained an independent role in predicting a poor chance of response to treatment. Similar results were obtained when T/S COX-2 ratio was analyzed as a continuous variable (data not shown).

As far as pathological response to treatment is concerned, the percentage of cases showing a high T/S COX-2 ratio was significantly greater in patients who did not respond to treatment (12 of 14, 85.7%) as compared with patients with partial (29 of 56, 51.8%) and complete (11 of 25, 44.4%) responses ($P = 0.049$). Similar results were found considering the mean ± SE COX-2 ratio values according to clinical response (Table 1).

**Correlation with SCC Levels.** Serum SCC levels were measured in 136 patients and ranged from 0 to 4.34 (median, 1.85). The correlation analysis between T/S COX-2 ratio values and SCC levels did not reveal any significant trend ($r = 0.1; P = 0.8$).

**Survival Analysis.** Follow-up data were available for 175 patients. As of May 2003, the median follow-up was 29 months (range, 4–88 months). During the follow-up period, 38 of 175 (21.7%) patients died of disease.

Cases with a high T/S COX-2 ratio had a shorter OS than cases with a low T/S COX-2 ratio: in particular, the 2-year OS was 61% (95% confidence interval, 50–83) in cases with high T/S COX-2 ratio as compared with cases with a low T/S COX-2 ratio (2-year OS, 90%; 95% confidence interval, 81–99; $P = 0.0001$; Fig. 2). Similar results were observed in the subgroup of LACC patients: the 2-year OS was 54% (95 confidence interval, 42–66) in cases with high T/S COX-2 ratio as compared with cases with a low T/S COX-2 ratio (2-year OS, 90%; 95 confidence interval, 81–99; $P = 0.0001$; data not shown).

The use of an arbitrary cutoff to distinguish cases with high versus low T/S COX-2 ratio is unlikely to have introduced any bias because a direct association between T/S COX-2 ratio values and risk of death was found in the overall series ($\chi^2 = 8.3; P = 0.0039$) as well as in the LACC patients ($\chi^2 = 3.9; P = 0.047$) using the ratio as continuous covariate (data not shown). The estimated probability of 1- and 2-year OS in the LACC series as function of T/S COX-2 ratio values is shown in Fig. 3.

We also investigated whether the prognostic role of the T/S COX-2 ratio could vary according to the type of primary treatment. Fig. 4 shows that regardless of whether patients received concomitant chemoradiation (Fig. 4A) or platinum-based chemotherapy (Fig. 4B) before surgery, the status of T/S COX-2 ratio retained its negative prognostic significance.

In multivariate analysis, the status of the T/S COX-2 IDV ratio together with advanced stage of disease retained an independent negative prognostic role for OS (Tables 2 and 3). Similar results were obtained in multivariate analysis considering the values of T/S COX-2 ratio as a continuous covariate in the LACC and overall series (data not shown).

**DISCUSSION**

This study confirms in a large series that the T/S COX-2 ratio is a very effective tool for the identification of cervical cancer patients endowed with a poor chance of response to neoadjuvant treatment and at high risk of death of disease.

Potential advantages in using this parameter instead of the measurement of COX-2 separately in each compartment deserve to be underlined. (a) The combination in a single measurement of the prognostic information deriving from the assessment of tumor and stroma COX-2 expression might support a better role of T/S COX-2 ratio in the prognostic characterization of cervical cancer patients than a separate evaluation of COX-2 in the two compartments. (b) This observation could also be supported by biological considerations: we showed that the presence of high COX-2 expression in cervical tumor cells is associated with a low proportion of CD3+, CD4+, and CD25+ T cells in the stroma (14). Indeed, high COX-2 levels in tumor cells might play a role in inhibiting host immune functions, as reported.
recently (6, 24, 25). In this context, T/S COX-2 could better represent the interplay between tumor and host cells rather than the separate evaluation of each compartment. (c) Finally, from a practical point of view, the ratio would be able to normalize COX-2 content for each case on the basis of its stromal component, providing a parameter no longer susceptible to variations once assigned to that specific patient.

T/S COX-2 ratio was shown to be strictly associated with large tumor volume, advanced disease, and more aggressive histotype, confirming our previous data in a smaller series (14) and results reported in other solid tumors (26). On the other hand, we failed to find any relation between T/S COX-2 ratio values and serum SCC levels, as also reported recently (27).

It is unlikely that the association between high T/S COX-2 ratio and clinicopathological parameters of tumor aggressiveness might be the only determinant of the role of T/S COX-2 ratio in predicting poor response to treatment because multivariate analysis by logistic regression demonstrated that T/S COX-2 ratio, together with advanced stage, retained an independent unfavorable significance even when matched with the other parameters. However, models generated by multivariate analysis must always be taken with caution, and the analysis of the predictive/prognostic role of COX-2 ratio should also be conducted after stratification according to relevant clinicopathological parameters such as FIGO stage.

A very strong association between T/S COX-2 ratio values and shorter OS was shown in the overall patient group and the subset of LACC patients. Interestingly enough, a direct correlation between T/S COX-2 ratio values and risk of death from disease was found, indicating that the use of the cutoff values in Kaplan-Meier analysis of OS is unlikely to have introduced any bias (28). Indeed, the application of the Cox’s proportional hazard analysis enabled us to model the probability of OS for each patient according to her own T/S COX-2 ratio value, although the practical implications of this data require validation in a larger series.

Another interesting finding of our study is that the adverse

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Another interesting finding of our study is that the adverse

Table 2 Univariate and multivariate analysis of clinicopathological parameters and T/S COX-2 ratio as predictive factors of treatment response in LACC patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariatea</th>
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<tbody>
<tr>
<td>Stage</td>
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<tr>
<td>I–II</td>
<td>14.6</td>
<td>11.3</td>
</tr>
<tr>
<td>III–IV</td>
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<td>0.0008</td>
</tr>
<tr>
<td>Histotype</td>
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<td></td>
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<tr>
<td>Squamous</td>
<td>9.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Other</td>
<td>0.0017</td>
<td>0.057</td>
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<tr>
<td>Tumor size</td>
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<tr>
<td>&lt;4 cm</td>
<td>2.3</td>
<td>0.12</td>
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<tr>
<td>≥4 cm</td>
<td>0.025</td>
<td>0.021</td>
</tr>
<tr>
<td>T/S COX-2 ratio</td>
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<tr>
<td>Low (≤1)</td>
<td>9.1</td>
<td>5.3</td>
</tr>
<tr>
<td>High (&gt;1)</td>
<td>0.0025</td>
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</tr>
</tbody>
</table>

a T/S, tumor:stroma; COX, cyclooxygenase; LACC, locally advanced cervical cancer; n.s., nonsignificant.
b Only variables with $p < 0.20$ in the univariate analysis were included in the multivariate analysis.

Table 3 Univariate and multivariate analysis of clinicopathological parameters and T/S COX-2 IDV ratio as prognostic factors in LACC patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
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<tbody>
<tr>
<td>Stage</td>
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<tr>
<td>High (&gt;1)</td>
<td>0.0025</td>
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</table>

a T/S, tumor:stroma; COX, cyclooxygenase; IDV, integrated density value; LACC, locally advanced cervical cancer; n.s., nonsignificant.
b Only variables with $p < 0.10$ in the univariate analysis were included in the multivariate model.
The prognostic value of high T/S COX-2 ratio was retained in the group of patients given concurrent chemoradiation or platinum-based chemotherapy, suggesting that the impact of the T/S COX-2 ratio on prognosis is not restricted to a specific clinical setting.

In conclusion, our study showed that assessment of COX-2 status in both the tumor and stroma compartments could provide valuable information to identify cervical cancer patients endowed with a very poor chance of response to neoadjuvant therapy and unfavorable prognosis. In this context, COX-2 can reasonably be considered a potential target for therapeutic approach, also taking advantage of the commercial availability of selective COX-2 inhibitors that have already been approved for treatment of familial colorectal adenomatous polyposis (29) and entered several Phase II–III trials.

We have recently shown (30) that short-term treatment with celecoxib is able to modulate the expression of prostaglandin E<sub>2</sub>, Ki67 apoptosis-related marker, and microvessel density in human cervical cancer, suggesting that inhibition of COX-2 could affect critical aspects of cervical tumor biology.

Moreover, data showing that COX-2 inhibition may potentiate cytotoxic agents and radiation effects in “in vitro” and preclinical models (31–33) provide the rationale for investigating the combination of selective COX-2 inhibitors with chemotherapy and/or radiotherapy in cervical cancer patients, as emphasized by the recently launched National Cancer Institute-sponsored Phase I–II trial (RTOG-C-0128) combining celecoxib with external beam radiotherapy plus brachytherapy in LACC.

The general interest in the therapeutic potential of selective COX-2 inhibition is also demonstrated by the growing availability of newly developed selective COX-2 inhibitors (34, 35), whose potential antitumor activity and safety profile are under investigation.

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Prognostic Role of the Ratio between Cyclooxygenase-2 in Tumor and Stroma Compartments in Cervical Cancer

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