Expression Pattern of Apurinic/Apyrimidinic Endonuclease in Sinonasal Squamous Cell Carcinoma

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Abstract

Objective. To evaluate the apurinic/apyrimidinic endonuclease 1 (APE1) expression in sinonasal squamous cell carcinomas (SCC) and to examine the correlation between APE1 expression patterns and various clinicopathological factors associated with sinonasal SCC that include SCC with inverted papilloma (SCCwIP) and SCC alone.

Study Design. Case-control study.

Setting. Chungnam National University Hospital.

Subjects and Methods. The expressions of APE1 were analyzed by means of immunohistochemistry in 30 sinonasal SCC, including 14 SCC patients associated with IP and 16 patients with SCC alone. A total of 19 patients who had been diagnosed with chronic rhinosinusitis with nasal polyposis and who required endoscopic sinus surgery were used as the control group. The degrees of APE1 expression were analyzed with respect to the following clinicopathologic variables: age, sex, T stage, histologic differentiation, distant metastasis, and recurrence.

Results. Cytoplasmic staining of APE1 was significantly higher in SCC compared with SCCwIP (68.75% vs 14.29%). Cytoplasmic staining of APE1 was significantly associated with T stage (P = .044) in SCC and histologic grade (P = .0025) in sinonasal SCC. Nuclear staining of APE1 was significantly associated with distant metastasis (P = .022) in SCC.

Conclusion. These results suggest that the nuclear and cytoplasmic expression of APE1 may be related to tumor invasiveness and prognosis in sinonasal SCC. The suppression of APE1 expression can potentially be a new target for future sinonasal SCC therapies.

Keywords
squamous cell carcinoma, inverted papilloma, APE-1, tumor invasion, metastasis

Malignant sinonasal tumors are very rare, accounting for less than 1% of human malignant tumors and about 3% of malignant head and neck tumors.¹ Histologically, most malignant sinonasal tumors are squamous cell carcinomas (SCC). In general, they can be treated only by removing the tumor from the primary site. However, most of them when initially found are at an advanced stage, and many of them possess insufficient resection margins for operation or have tumor cells diagnosed as positive in the resection margin. Therefore, postoperative radiotherapy and chemotherapy, or combined treatment modalities, are commonly needed.² However, despite aggressive treatment modalities, patients with sinonasal SCC generally have high recurrence and low survival rates. As a result, there have been ongoing efforts to discover factors associated with malignancy, distant metastasis, and prognoses for sinonasal SCC.

Apurinic/apyrimidinic endonuclease 1 (APE1), which is a ubiquitous and remarkably multifunctional protein, is called a reductive activator of an activator protein-1 (AP-1) transcription factor or a redox effector factor 1 (Ref-1).³,⁴ Various types of base damages and DNA single-strand breaks caused by reactive oxygen species or alkylating agents may be removed through the process of base excision repair. In this processing, APE1 reportedly plays an important role in recognizing the damaged site and making selective removal together with glycosylase. APE1 is also found to play an important role in repairing damaged apurinic/apyrimidinic (AP) sites by activating several transcription factors.⁵-⁷

Many recent studies have tried to determine the roles of APE1 in several types of human malignant tumors. In pancreatic cancer, greater APE1 expression was found in pancreatic cancer cells than in normal ones, and greater APE1 expression led to greater resistance to chemotherapy and more tumor angiogenesis.⁸ Research observing APE1 expression in ovarian, gastro-esophageal, and pancreatic

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cancer found that APE1 expression differed between the nucleus and cytoplasm of tumor cells and that the degree of APE1 expression was associated with a patient’s prognosis. However, no research to date has assessed the degree of APE1 expression with the clinical features associated with sinonasal SCC.

Sinonasal SCCs include primary squamous cell carcinomas (SCCs) and SCC associated with inverted papilloma (SCCwIP). Very limited and controversial comparative research has been conducted on the clinical features and prognosis between the two conditions.9,10

In this study, we examined the differences in the degree of APE1 expression between sinonasal SCC and SCCwIP and assessed for any association between factors such as T stage, histological grades of differentiation, distant metastasis, locoregional recurrence, and APE1 expression.

Materials and Methods

Subjects

The research was conducted on 30 patients who had been diagnosed with sinonasal SCC and had an operation for sinonasal SCC in the Department of Otorhinolaryngology in Chungnam National University Hospital between April 1992 and April 2010. Patients could go through follow-up for more than 10 months. Median follow-up periods were 30.2 months (range, 2 months-224 months) in SCC and 57 months (range, 2 months-123 month) in SCCwIP. During the study period, 16 patients were diagnosed with SCC, and 14 were diagnosed with SCCwIP. In patients with SCCwIP, 2 patients were considered as metachronous tumor, and 12 patients were synchronous tumor. Factors such as demographics, stage of tumors, treatment, and the recurrence rate were retrospectively analyzed for each patient on the basis of medical records.

Table 1 shows age and sex distribution for the patients.

<table>
<thead>
<tr>
<th>Age and Sex Distributions of the Patients</th>
<th>Age, y</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Cases</td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>NP</td>
<td>19</td>
<td>44.84</td>
</tr>
<tr>
<td>SCCwIP</td>
<td>14</td>
<td>56.86</td>
</tr>
<tr>
<td>SCC</td>
<td>16</td>
<td>64.31</td>
</tr>
</tbody>
</table>

Abbreviations: NP, nasal polyps; SCCwIP, inverted papilloma with squamous cell carcinoma; SCC, squamous cell carcinoma.

Clinicopathologic Analysis

T staging of patients was implemented according to the classification set forth by the American Joint Committee on Cancer in 2011. The SCCwIP group had 3, 1, 7, and 3 patients at T1, T2, T3, and T4, respectively, while the SCC group had 1, 0, 5, and 10 patients at T1, T2, T3, and T4, respectively.

The grades of tumor cells were divided into 3 stages according to the World Health Organization (WHO) classification: poor, moderate, and well differentiated. As a result, the SCCwIP group had 3 patients with well differentiation, 11 with moderate differentiation, and no patient with poor differentiation. The SCC group had no patient with well differentiation, 7 with moderate differentiation, and 9 with poor differentiation. To put both groups together, there were 3 patients with well differentiation, 18 with moderate differentiation, and 9 with poor differentiation.

H&E Staining

Serial sections 3 μm in thickness were made with the 10% neutral formalin-fixed and paraffin-embedded tissues. For H&E staining, they were deparaffined with 100% xylene and then each treated with 100%, 95%, 90%, 80%, 75%, and 50% ethanol for 2 minutes to hydrate. They were then treated with the hematoxyline solution for 3 minutes and with the eosin solution for 10 minutes followed by dehydration and mounting.

Immunohistochemistry for APE1

For immunohistochemistry, they were deparaffined with 100% xylene and each treated with 100%, 95%, 90%, 80%, 75%, and 50% ethanol for 2 minutes to hydrate. To inhibit activity of endogenous peroxidase, they were treated with 3% hydrogen peroxide for 10 minutes, cleansed with distilled water, and washed with the 50mM Tris buffer solution (TBS, pH7.5). After nonspecific reactions were removed, they were made to react to the primary antibody (rabbit polyclonal antibody against human-APE1, Novus Biologicals Inc., Littleton, Colorado), which was diluted in a 1:500 ratio Tris buffer solution at 4°C overnight. After the reaction to the primary antibody, they were washed with the Tris buffer solution and made to react to the secondary antibody (EnVision anti-rabbit polymer, Dako, Glostrup, Denmark) at room temperature for 30 minutes. They were then washed with the Tris buffer solution, made to react to the color coupler or the 3,3-diаминобензидин tetrachloride solution, and observed for color reaction for 5 minutes, followed by mounting.

Analysis of Immunohistochemistry

From the slides going through immunohistochemistry, 10 sites were randomly selected and observed with a magnifying power of 400 by using an optical microscope to measure the percentage of the tumor cells showing an immune reaction to APE1. The results of the immunohistochemistry were read by 3 pathologists who had no clinical information about the patients.
Analysis of nuclear staining. To set the criteria for positive staining of SCC for APE1, immunohistochemistry was conducted by using nasal polyps from 19 patients with chronic rhinosinusitis with nasal polyposis as the control group. Of all the epithelial cells of the nasal polyps, those with the positive nuclear staining accounted for 19.21% on average. The case with less than 20% positive nuclear staining was determined as negative (grade 0), 20% to 50% tumor cells with nuclear staining as grade 1, 50% to 75% tumor cells with nuclear staining as grade 2, and more than 75% tumor cells with nuclear staining as grade 3 (Figure 1).

Analysis of cytoplasmic staining. As for cytoplasmic expression of APE1, cases where cytoplasmic staining was similar to or deeper than nuclear staining were determined as being positive, and the opposite as negative (Figure 2).

Statistical Analysis
SPSS (version 18.0, SPSS, Inc., Chicago, Illinois) was used to carry out t test and Pearson chi-square test. If the P value was less than .05, it was regarded as statistically significant.

Results

Immunohistochemical Findings

Nuclear staining. Nuclear expression of APE1 was found to be more vivid and be associated with a larger number of positively stained cells in both the SCCwIP and SCC groups compared with the nasal polyp control group (Figure 3). Regarding nuclear staining, the SCC group had 4, 4, 4, and 4 patients at grades 0, 1, 2, and 3, respectively, while the SCCwIP group had 2, 3, 5, and 4 patients, respectively (Table 2).

Cytoplasmic staining. For cytoplasmic staining, 11 out of 16 patients (68.75%) had APE1 stained positively in the SCC group, and 2 out of 14 patients (14.29%) had APE1 stained positively in the SCCwIP group, showing statistical significance (P = .003) (Table 3).

Correlation between APE1 Expression and T Stage

Both SCCwIP and SCC groups had no statistically significant correlation between the degree of nuclear APE1 expression and T stage (Table 4). The SCCwIP group had no statistically significant correlation between T stage and the cytoplasmic APE1 staining rate, while a higher T stage led to a statistically significantly higher intracytoplasmic APE1 staining rate in the SCC group (P < .05) (Table 5).

Correlation between APE1 Expression and Distant Metastasis or Locoregional Recurrence

There was no statistically significant correlation between the degree of nuclear APE1 expression and distant metastasis in the SCCwIP group. In contrast, an increase in nuclear expression of APE1 was associated with a significantly larger number of patients showing distant metastasis (P = .022) (Table 4).

Both groups had no statistically significant correlation between cytoplasmic expression of APE1 and distant metastasis or locoregional recurrence (Table 5).

Correlation between APE1 Expression and Histological Grades

There was no significant correlation between the degree of nuclear APE1 expression and histological grades. However, greater cytoplasmic expression of APE1 led to a statistically significantly lower histological grade (P = .0025) (Table 6).

Discussion

SCC arising in inverted papilloma (IP) has been reported in the literature for more than 50 years and has a reported incidence between 5% and 15%.11 The incidence of SCCwIP in our institute during the study period was 8.4% (17 cases of SCCwIP from 202 cases of IP).

SCCwIP is not simply an intermingling of 2 separate primary tumors, but rather a malignant transformation of the IP.12 Some reports suggest that the development of SCCwIP is heralded by a reduced cellular apoptosis, which is triggered by human papilloma virus infection.13 Because of the rarity of SCCwIP, limited information on the natural history...
and treatment of SCCwIP is available. Although it is well known that sinonasal SCC is etiologically related to smoking and occupational exposure to wood, leather, and other types of organic dust, the tumorigenesis of these tumors is still poorly understood. However, molecular genetic analysis is becoming increasingly important in characterizing the genetic “signatures” of tumors and in aiding clinical management by novel anti-cancer treatments.

It has been known that sinonasal tumors are comprised of various histologies, including squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma (ACC), melanoma, and esthesioneuroblastoma. Each of these specific neoplasms, in turn, is unique in its clinical behavior and aggressiveness, with overall 5-year survivals reported from 22% to 67%. The authors also had experienced various types of malignant tumors during the study period. However, these malignancies are very rare and numbers of each case are too small to compare the expression of APE1 with clinicopathologic parameters of these tumors. And recent studies indicated that the expression pattern or location of APE1 could be different according to histological types of tumor. Therefore, we included only sinonasal SCC patients for this study.

As expression of APE1 is controlled by p53 genes; p53 genetic abnormalities frequently found in tumor cells lead to over-expression of APE1, causing over-activation of the DNA base excision repair (BER) pathway. This process is known as an important mechanism that allows tumor cells to become resistant to anti-cancer treatment. This is supported by the result that an increase in APE1 expression might lead to greater resistance to anti-cancer treatment for teratocarcinoma, malignant melanoma, and nonsmall cell lung cancer. The result that APE1 inhibition using gene combination leads to an increase in cytotoxicity of cisplatin in nonsmall cell lung cancer suggests that APE1 inhibition can be an effective method for tumor treatment.

In our series, 9 patients (64.3%) received adjuvant radiotherapy (RTx, 7 patients) or chemotherapy and radiotherapy (CTx + RTx, 2 patients) in SCCwIP group. Among them, 1 patient died of distant metastasis at 5 months after treatment, and this patient showed high grade of nuclear staining (grade 3) and positive cytoplasmic staining for APE1.

### Table 2. Distribution of Patients according to Grade of Nuclear Staining for Apurinic/Apyrimidinic Endonuclease 1 (APE1)

<table>
<thead>
<tr>
<th>Grade of Nuclear Staining for APE1</th>
<th>SCCwIP</th>
<th>SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: SCCwIP, inverted papilloma with squamous cell carcinoma; SCC, squamous cell carcinoma.

*p = .852.

Figure 2. Degree of cytoplasmic staining for apurinic/apyrimidinic endonuclease 1 (APE1) in sinonasal squamous cell carcinomas (SCC). A, negative; C, positive. B and D = H&E staining of A and C (original magnification, ×200).
mean grades of nuclear staining for APE1 in the failure group and survival group were 1.56 and 1.75, respectively. The number of patients who showed positive cytoplasmic staining for APE1 was 8 in the failure group (61.5%) and 2 in the survival group (50%). We presumed that there were no significant differences between failure group and survival group in APE1 expression after adjuvant therapy because the number of cases in the present study was too small to investigate APE1 expression with respect to adjuvant therapy response.

Many researchers suggest that an increase in nuclear expression of APE1 is associated with poorer prognosis. Some suggested that the patients at the advanced stage of ovarian cancer, which could hardly be removed operatively, or those showing a low survival rate had nuclear expression

Table 3. Distribution of Patients according to Cytoplasmic Staining of Apurinic/Apyrimidinic Endonuclease 1 (APE1)*

<table>
<thead>
<tr>
<th>Cytoplasmic Staining</th>
<th>SCCwIP</th>
<th>SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Positive</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: SCCwIP, inverted papilloma with squamous cell carcinoma. SCC, squamous cell carcinoma. *P = .003.

Table 4. Correlation of Degree of Nuclear Staining for Apurinic/Apyrimidinic Endonuclease 1 (APE1) with T Stage, Distant Metastasis, and Locoregional Recurrence in SCCwIP and SCC

<table>
<thead>
<tr>
<th>Variable Factors</th>
<th>SCCwIP</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>SCC</th>
<th></th>
<th></th>
<th></th>
<th>P Value</th>
<th></th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>.349</td>
<td>.677</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
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<td>2</td>
<td>0</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>.442</td>
<td>.022*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td></td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Distant metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.442</td>
<td>.022*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/2</td>
<td>0/3</td>
<td>0/5</td>
<td>1/4</td>
<td></td>
<td></td>
<td>0/4</td>
<td>1/4</td>
<td>1/4</td>
<td>4/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>0/2</td>
<td>0/3</td>
<td>1/5</td>
<td>2/4</td>
<td></td>
<td>1/4</td>
<td>1/4</td>
<td>2/4</td>
<td>2/4</td>
<td>.346</td>
<td></td>
<td>.785</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SCCwIP, inverted papilloma with squamous cell carcinoma; SCC, squamous cell carcinoma. The asterisk represents statistically significant data (P < .05).
of APE1 increased in their tumor cells. Also, nuclear expression of APE1 was increased in the tumor cells that remained even after anti-cancer treatment.6 The research on SCC in the head and neck found that an increase in nuclear expression of APE1 was associated with lymph node metastasis, resistance to treatment, lower survival rate, and poorer prognosis.22 In the presenting study, it was found that there was no difference in the degree of expression between SCCwIP and SCC groups, but both groups had nuclear expression of APE1 increased as compared with the control group of nasal polyps. While comparison was made for the degree of nuclear APE1 expression in relation to T stage, no statistical correlation was found between T stage and the degree of nuclear APE1 expression. However, an increase in the degree of nuclear APE1 expression led to a statistically significant increase of distant metastasis in the SCC group in prior studies.6

For colorectal cancer, tumor cells have higher cytoplasmic APE1 staining rates than normal cells, and a higher cytoplasmic APE1 staining rate leads to an increase in tumor cell invasiveness.23 For gastro-esophageal cancer, an increase in nuclear and cytoplasmic expression of APE1 leads to a lower histological grade of differentiation and a lower survival rate.6 However, some hold that a decrease in cytoplasmic expression of APE1 leads to more perineural and vascular invasion and a lower histological grade of differentiation in pancreatic cancer.6

In this study, the SCC group showed a significantly higher cytoplasmic APE1 staining rate than the SCCwIP group (Table 3), and an increase in T stage led to higher cytoplasmic APE1 staining rates in the SCC group (Table 5). It was therefore found that an increase in nuclear and cytoplasmic expression of APE1 was associated with distant metastasis and invasiveness of tumors in the SCC group. However, no correlation between the increase in APE1 expression and T stage, distant metastasis, or locoregional recurrence was found for the SCCwIP group. This difference between SCCwIP and SCC may be due to the differences in the causes and mechanisms between the 2 conditions.11 Further comparative research on these conditions is needed since some show that better prognosis are found for SCCwIP than for SCC in terms of the survival rate after treatment, while others suggest that there is no significant difference in prognosis between the two conditions.9,10

In this study the SCC group showed that an advanced T4 stage (62.5% vs 21%), greater distant metastasis (37.5% vs 7.1%), and more frequent locoregional recurrence (37.5% vs 21.4%) displayed greater nuclear and cytoplasmic expression of APE1 compared to the SCCwIP group. Although we did not find significant differences between these 2 groups because of a small number of cases, this result indicated that APE1 expression could be associated with invasiveness and prognosis for sinonasal SCC.

For the histological grade of differentiation for tumors, the SCCwIP group had no patients with poor differentiation, and the SCC group had a few patients with poorly differentiated tumors (Table 6). For colorectal cancer, tumor cells have higher cytoplasmic APE1 staining rates than normal cells, and a higher cytoplasmic APE1 staining rate leads to an increase in tumor cell invasiveness.23 For gastro-esophageal cancer, an increase in nuclear and cytoplasmic expression of APE1 leads to a lower histological grade of differentiation and a lower survival rate.6 However, some hold that a decrease in cytoplasmic expression of APE1 leads to more perineural and vascular invasion and a lower histological grade of differentiation in pancreatic cancer.6

### Table 5. Correlation of Degree Cytoplasmic Staining for Apurinic/Apyrimidinic Endonuclease 1 (APE1) with T stage, Distant Metastasis, and Locoregional Recurrence in SCCwIP and SCC

<table>
<thead>
<tr>
<th>Variable Factors</th>
<th>SCCwIP</th>
<th></th>
<th></th>
<th>SCC</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td>P Value</td>
<td>Negative</td>
<td>Positive</td>
<td>P Value</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>T1</td>
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<td>1</td>
<td>0</td>
<td>.044†</td>
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<td>T2</td>
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<td></td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>2</td>
<td>1</td>
<td></td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>1/12</td>
<td>0/2</td>
<td>.672</td>
<td>1/5</td>
<td>4/11</td>
<td>.330</td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>2/12</td>
<td>1/2</td>
<td>.287</td>
<td>1/5</td>
<td>4/11</td>
<td>.330</td>
</tr>
</tbody>
</table>

Abbreviations: SCCwIP, inverted papilloma with squamous cell carcinoma; SCC, squamous cell carcinoma. The asterisk represents statistically significant data (P < 0.05).

### Table 6. Correlation of Degree of Nuclear or Cytoplasmic Staining for Apurinic/Apyrimidinic Endonuclease 1 (APE1) with Histologic Grade

<table>
<thead>
<tr>
<th>Variable Factors</th>
<th>WD</th>
<th>MD</th>
<th>PD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
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<td>Grade of nuclear staining</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
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<td>3</td>
<td></td>
</tr>
<tr>
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<td>0</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Cytoplasmic staining</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
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<td></td>
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<tr>
<td>Positive</td>
<td>0</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: WD, well differentiation; MD, moderate differentiation; PD, poor differentiation.

†R = 0.06175 (95% CI, –0.3054 to 0.4129).
‡R = 0.4933 (95% CI, 0.1617–0.7248).
11 with moderate differentiation, and 3 with well differentiation. The SCC group had no patients with well differentiation, 7 with moderate differentiation, and 9 with poor differentiation. It is believed that such a histological grade of differentiation can also be a feature to differentiate the 2 conditions. However, as both groups are sinonasal SCC and so far there is no definite finding concerning the difference in the causes and mechanisms between the 2 groups, it will also be meaningful to compare the degree of APE1 expression by histological grades of differentiation without the division into SCCwIP and SCC. Based on our findings, no significant correlation was found between nuclear expression of APE1 and histological grades of differentiation. However, a lower histological grade led to a statistically significant increase in cytoplasmic expression of APE1 (Table 6). This is consistent with the result for gastro-esophageal cancer showing that an increase in cytoplasmic expression of APE1 leads to a lower histological grade.6

Recently, many studies suggested the possibility that for malignant tumors with poor prognosis, such as ovarian, gastro-esophageal, pancreatic, and lung cancer, inhibition of APE1 expression can help treatment.6,8,21 Over-expression of APE1 is induced by DNA damaging agents and is associated with treatment resistance. Constitutional or engineered down-regulation of APE1 confers sensitivity to treatment and can overcome chemo-resistance. A number of inhibitors of the APE1 DNA repair domain are currently under development, showing promise in vitro in their ability to potentiate the actions of agents causing alkylating or oxidation damage and overcome treatment resistance. Further development of these inhibitors into clinically relevant compounds is an important and expanding area of cancer therapeutics. It is therefore believed that research to development therapy targeting APE1 as a method for inhibiting invasion and metastasis of tumors is needed for sinonasal SCC.

Conclusion

Based on our findings, an increase in nuclear and cytoplasmic expression of APE1 in sinonasal SCC may be associated with distant metastasis of tumors, advanced T stages, and poorer prognosis. Since this is a retrospective study on a small number of patients, molecular biological research is needed on a larger number of patients to validate our findings. Research is needed to develop potential therapies for inhibiting APE1 in the nucleus and cytoplasm of tumor cells without affecting APE1 metabolism in normal cells in patients with sinonasal SCC.

Author Contributions

Jin Woo Lee, write manuscript and statistic analysis; Jun Jin, immunohistochemistry and analysis; Ki-Sang Rha, study plan and patient collection; Yong Min Kim, study plan and write manuscript.

Disclosures

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