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XPA expression is a predictive marker of the effectiveness of neoadjuvant chemotherapy for locally advanced uterine cervical cancer

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Abstract. The standard treatment for locally advanced uterine cervical cancer is concurrent chemoradiotherapy. Successful neoadjuvant chemotherapy (NAC) may reduce tumor size and facilitate a hysterectomy, thereby improving the prognosis for patients with locally advanced cervical cancer. In contrast, unsuccessful NAC may worsen the prognosis because if a hysterectomy is not possible, the change in treatment plan may delay the initiation of core treatment. Therefore, there is a need to identify biomarkers that predict the efficacy of NAC in patients with uterine cervical cancer. The xeroderma pigmentosum complementation group A (XPA) protein serves a major role in nucleotide excision repair, which is a key DNA damage response pathway involved in cisplatin resistance. In the present study, the association between XPA expression in tumor tissue and the efficacy of NAC for locally advanced uterine cervical cancer was investigated. Data from 56 patients aged <70 years with locally advanced uterine cervical cancer (FIGO stages IIIA or IIIB) who were classified into two groups based on effective (n=31) and ineffective (n=25) responses to NAC treatment was evaluated. Tumor tissue samples were obtained by punch biopsy prior to NAC and XPA expression was examined immunohistochemically and scored using a weighted scoring system. In addition, the effects of RNA interference-mediated downregulation of XPA on the cisplatin sensitivity of uterine cervical cancer cells was investigated *in vitro*. It was revealed that the NAC effective group had significantly lower weighted XPA scores than the NAC ineffective group (P=0.001). Similarly, low tumor expression of XPA was significantly associated with higher sensitivity to NAC (P=0.001). Additionally, the downregulation of XPA expression in cervical cancer cells significantly increased their sensitivity to cisplatin *in vitro*. The results of the present study suggest that low XPA expression may be a predictive biomarker of NAC efficacy for patients with locally advanced uterine cervical cancer, which may be helpful for improving their prognosis.

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Key words: uterine cervical cancer, xeroderma pigmentosum complementation group A, neoadjuvant chemotherapy, platinum resistance, predictive marker

Introduction

Cervical cancer is a frequent cause of cancer death among women worldwide (1). The standard treatment for locally advanced uterine cervical cancer including International Federation of Gynecology and Obstetrics (FIGO) stage IIIA, IIIB, and IVA cancer consists Platinum-based concurrent chemoradiotherapy (CCRT) (2-4). However, the prognosis of these patients is poor, and the 5-year survival is <60% (5,6).

Successful neoadjuvant chemotherapy (NAC) can reduce tumor size in patients with locally advanced cervical cancer, thereby facilitating hysterectomy and improving the prognosis (7). However, the prognosis worsens if NAC is unsuccessful, because hysterectomy may no longer be practicable and the switch to radiotherapy may delay the initiation of the core treatment (8-10). Therefore, there is an urgent need to identify predictive biomarkers of NAC efficacy for patients with locally advanced uterine cervical cancer (10-14).

The antineoplastic activity of cisplatin is primarily due to its ability to induce DNA damage, particularly intrastrand DNA crosslinks, which leads to apoptosis (15). Nucleotide excision repair (NER) is a pathway that identifies and repairs intrastrand DNA crosslinks. Tumor sensitivity to cisplatin has been associated with a decrease in the induction of DNA repair (16). Consistent with this, overexpression of NER proteins confers resistance to platinum-based drugs (17,18). The xeroderma pigmentosum complementation group A (XPA) protein is an indispensable factor for NER. Several reports have shown that XPA recognizes and verifies DNA damage sites, stabilizes repair intermediates, and contributes to the induction of other NER-associated factors (19-24). XPA expression has been reported to correlate with the resistance

of nasopharyngeal carcinoma and lung cancer cell lines to platinum drugs (17-25). However, the role of XPA in the response of uterine cervical cancer cell lines and uterine cervical cancer patients to cisplatin is not clear.

Here, we sought to determine the utility of XPA expression as a predictive biomarker by investigating the relationship between tumor expression of XPA and the efficacy of NAC for locally advanced uterine cervical cancer.

Materials and methods

Patients and tissue samples. We evaluated 56 patients with locally advanced uterine cervical cancer (FIGO stages IIIA and IIIB). All patients were <70 years of age and were first treated at Osaka City University Hospital (Osaka, Japan) between April 1995 and March 2010. Tumor tissue samples were obtained by punch biopsy before NAC. Patients were classified into two groups based on the response to NAC: Patients who were successfully treated with NAC, underwent hysterectomy, and received radiation therapy (NAC + OP+ R group; n=31), and patients who were unsuccessfully treated with NAC and received only radiation therapy (NAC + R group; n=25). Balloon-occluded arterial infusion chemotherapy for NAC is performed for all patients. We infused Cisplatin (Bristol-Myers Squibb, Tokyo, Japan) intra-arterially through the catheters over 30 min. Cisplatin was administered three times at doses of 50, 75 or 100 mg/m^2, depending on the patient's age and renal function (26).

Written informed consent was obtained from all patients prior to tumor biopsy. The study was approved by the institutional review board of Osaka City University Hospital (IRB no. 3526).

Immunohistochemical staining. XPA protein expression was examined in four-micrometre sections from paraffin-embedded tissue samples using a mouse monoclonal antibody against XPA (cat no. sc-28353; Santa Cruz Biotechnology, Inc., Dallas, TX, USA) and a Dako LSAB2 Peroxidase kit (cat no. K0675; Agilent Technologies, Santa Clara, CA, USA). After routine deparaffnization and rehydration, sections were immersed in 3% hydrogen peroxide at room temperature for 10 min to block endogenous peroxidase activity. Heat-mediated antigen retrieval was performed with 10 mM citrate buffer (pH 6.0) by an autoclave at 110˚C for 20 min. After washing with phosphate-buffered saline (PBS), tumor tissue sections were incubated with a 1:100 dilution of the anti-XPA antibody overnight at 4˚C. Next, sections were washed in PBS for 15 min and then incubated for 10 min with biotinylated goat anti-mouse and anti-rabbit immunoglobulin G secondary antibody (Dako; Agilent Technologies), followed by an incubation with a streptavidin-peroxidase complex, and color was developed using 3,3'-diaminobenzidine used as the chromogen. Finally, tissue sections were counterstained with hematoxylin. A specificity control was prepared in the same manner except the primary antibody was omitted.

The expression levels of XPA were quantitatively analyzed using the weighted score method of Sinicrope *et al* (27). The mean percentage of stained tumor cells was scored on a scale of 0 to 4 as follows: 0, ≤5%; 1, 5-25%; 2, 25-50%; 3, 50-75%; and 4, >75%. Staining intensity was classified into three categories: 1+, weak; 2+, moderate; and 3+, intense. The weighted score for each tissue specimen was determined by multiplying the score of percentage of stained tumor cells by that of staining intensity.

Cell culture. The human uterine cervical cancer cell line Ca Ski (cat no. IFO50007; Japanese Collection of Research Biosources Cell Bank, Osaka, Japan) was cultured in RPMI medium (Gibco; Thermo Fisher Scientific, Waltham, MA, USA) containing 10% fetal bovine serum (Gibco; Thermo Fisher Scientific) and 1% penicillin and maintained in a humidified atmosphere with 5% CO_2 at 37˚C.

RNA interference. Small interfering RNA (siRNA) targeted to XPA (5'-GUACCGUAAGACUUGUACUtt, 5'-AGUACAAGU CUUACGGUACtt; cat. no. sc-36853) and a negative control sequence (cat. no. sc-37007) were obtained from Santa Cruz Biotechnology. Cells were seeded in 6-well plates overnight and then transfected with siRNAs using Lipofectamine RNAiMax (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. The culture medium was changed 24 h after transfection and cells were used for experiments 24 h after transfection.

RNA extraction and reverse-transcription-quantitative polymerase chain reaction (RT-qPCR). Total RNA was extracted from the Ca Ski cells using an RNeasy Mini kit (QIAGEN GmbH, Hilden, Germany) according to the instruction of the manufacturer. RNA was reverse transcribed using a High Capacity cDNA Reverse Transcription kit (Applied Biosystems; Thermo Fisher Scientific). PCR was performed using a TaqMan Gene Expression Assay (Applied Biosystems; Thermo Fisher Scientific) and an Applied Biosystems 7500 Fast Real-Time PCR System. XPA mRNA levels were normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) mRNA in the same samples. TaqMan probes were Hs00902270_m1 for XPA and Hs99999905_m1 for GAPDH.

Chemosensitivity assay. The sensitivity of Ca Ski cells to cisplatin was examined using a Cell Counting kit-8 (CCK-8; Dojindo Molecular Technologies, Kumamoto, Japan). Cells were transfected with negative control or XPA-specific siRNAs as described above and then seeded into 96-well tissue culture plates at 2x10^3 cells/well. After 24 h, the culture medium was removed and vehicle or cisplatin (0-10 μg/ml) was added for 48 h. Subsequently, 10 μl/well CCK-8 was added and the plates were incubated for 2 h. The absorbance at 450 nm was then assesed with a microplate reader (Corona Electric, Ibaraki, Japan). Dose-response curves were constructed of the percentage viable cells compared with untreated cells.

Statistical analysis. All statistical analyses were conducted with SPSS software version 21.0 (IBM SPSS, Armonk, NY, USA). Data are presented as the mean ± standard deviation in the tables and as the mean ± standard error in the figures. Kaplan-Meier plots and log-rank analyses were used for prognostic analysis. Weighted scores were compared using the Mann-Whitney

Table I. Characteristics of the patients in the NAC effective and ineffective groups.

Characteristic	NAC effective	NAC ineffective	P-value
No. of patients	31	25	
Age (years)			0.317[a]
Mean ± SD	48.9±13.2	52.3±11.5	
Range	24-69	36-68	
FIGO stage			0.397[b]
IIIA	1	0	
IIIB	30	25	
Histology			0.433[b]
SCC	27	21	
A	4	3	
AS	0	1	
Tumor size (mm)			0.956[a]
Mean ± SD	41.1±22.7	41.4±23.8	

[a]Student's t-test; [b]χ^2 test; NAC, neoadjuvant chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; A, adenocarcinoma; AS, adenosquamous carcinoma; SD, standard deviation. Data are the number of patients, unless indicated.

Table II. Weighted scores for XPA expression in the NAC effective and ineffective groups.

	No. of patients	
Weighted score	NAC effective[a]	NAC ineffective[b]
0	3	0
1	4	1
2	4	1
3	4	0
4	6	6
6	5	4
8	2	5
9	3	3
12	0	5
Total	31	25
Weighted score (mean)	3.90	7.12

[a]The NAC effective group underwent neoadjuvant chemotherapy, surgery, and radiotherapy. [b]The NAC ineffective group underwent neoadjuvant chemotherapy and radiotherapy only. NAC, neoadjuvant chemotherapy.

U test. Student's t-test was used for comparison of significant differences between group means, and χ^2 tests were used for identification of the association between group categorical variables. $P<0.05$ was considered to indicate a statistically significant difference.

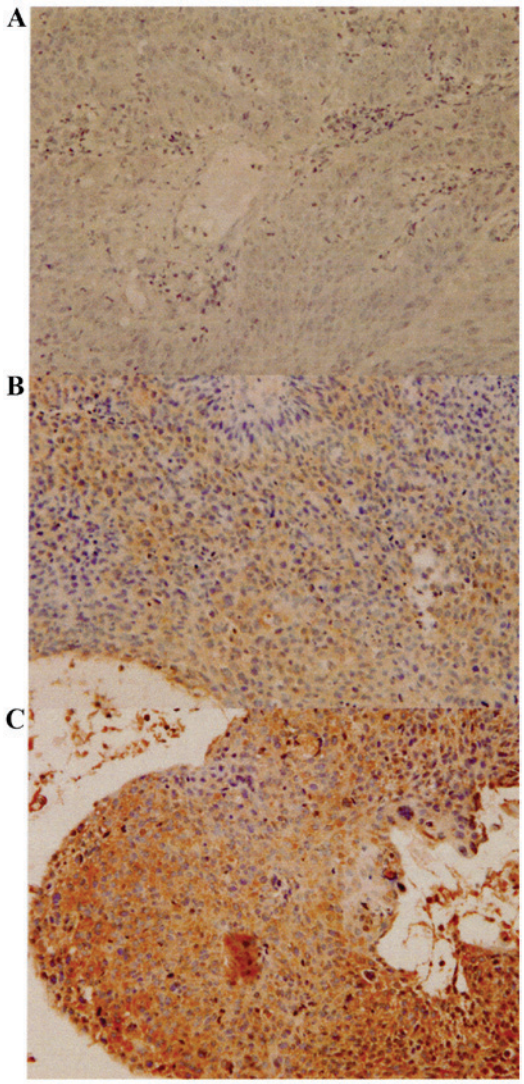

Figure 1. Immunohistochemical staining of XPA in locally advanced cervical cancer. (A) Negative control staining performed without primary antibody. (B and C) Representative sections stained with a primary antibody against XPA showing scores of 6 (B) and 12 (C). Sections were counterstained with hematoxylin. Magnification, x400. XPA, xeroderma pigmentosum complementation group A.

Results

Patient characteristics. A total of 56 patients with locally advanced uterine cervical cancer were divided into two groups based on their response to therapy: The NAC effective group (NAC + OP + R group; n=31) and the NAC ineffective group (NAC + R group; n=25). Table I shows the patients' clinicopathological characteristics. No statistically significant differences were observed between the two groups.

XPA expression in uterine cervical cancer tissue. XPA was expressed in both the nuclei and cytoplasm of the tumor cells (Fig. 1). Table II shows the weighted scores for XPA tissue staining. The mean weighted score of the NAC ineffective group was significantly higher than that of the NAC effective group (7.12 and 3.90, respectively; P=0.001) (Fig. 2 and Table II). Of the 56 patients, 17 had weighted scores of 0-3 (designated low expression) and 39 had weighted scores of

Table III. Characteristics of patients in the low and high XPA expression groups.

Characteristic	XPA expression (≤3 score)	XPA expression (≥4 score)	P-value
Number of patients	17	39	
Age (years)			0.808[a]
Mean ± SD	49.8±13.6	49.8±13.6	
Range	24-68	24-69	
FIGO stage			0.505[b]
IIIA	0	1	
IIIB	17	38	
Histology			0.759[b]
SCC	15	33	
A	2	5	
AS	0	1	
Tumor size (mm)			0.470[a]
Mean ± SD	44.6±18.5	39.8±24.8	

[a]Student's t-test; [b]χ^2 test; XPA, xeroderma pigmentosum complementation group A; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; A, adenocarcinoma; AS, adenosquamous carcinoma; SD, standard deviation. Data are the number of patients, unless indicated.

Table IV. Number of patients with low and high XPA expression in the NAC effective and NAC ineffective groups.

	Number of patients (%)		
XPA expression	NAC + OP + R n=31	NAC + R n=25	P-value
Low expression (≤3 score)	15 (88%)	2 (12%)	0.001[a]
High expression (≥4 score)	16 (41%)	23 (59%)	

[a]χ^2 test; NAC+OP+R, neoadjuvant chemotherapy + surgery + radiotherapy; NAC+R, neoadjuvant chemotherapy + radiotherapy; XPA, xeroderma pigmentosum complementation group A.

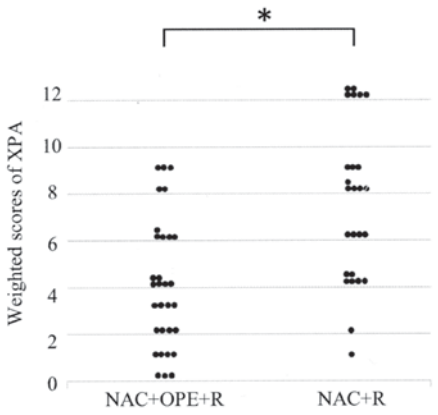

Figure 2. Weighted scores for XPA expression in tumor samples from patients with locally advanced cervical cancer. *P=0.001 (Mann-Whitney U test). NAC + OP + R, neoadjuvant chemotherapy + surgery + radiotherapy; NAC + R, neoadjuvant chemotherapy + radiotherapy; XPA, xeroderma pigmentosum complementation group A.

4-12 (high expression). There were no significant differences in patient characteristics between these two groups (Table III).

NAC effectiveness correlates with XPA expression. Of the 17 patients with low XPA expression, 15 (88%) were in the NAC effective group and 2 (12%) were in the NAC ineffective group. In the high XPA expression group, 16 patients (41%) were in the NAC effective group and 23 (59%) were in the NAC ineffective group. Thus, patients in the low XPA expression group were more sensitive to NAC than those in the high XPA expression group (P=0.001, Table IV).

Survival. Overall survival was significantly longer for the NAC effective group than for the NAC ineffective group (P<0.001) (Fig. 3) and was significantly longer for the low XPA expression group than for the high XPA expression group (P=0.01) (Fig. 4).

Knockdown of XPA enhances the sensitivity of a uterine cervical cancer cell line to cisplatin treatment. qRT-PCR analysis of Ca Ski cells confirmed that XPA expression was effectively suppressed by transfection with a specific targeting siRNA but not by a non-targeting control siRNA (Fig. 5). Cells transfected with XPA-specific siRNA were significantly more sensitive to cisplatin than were the control cells (P<0.05) (Fig. 6).

Discussion

CCRT is considered the standard treatment for patients with locally advanced uterine cervical cancer. Effective NAC can reduce the tumor size, allowing the patient to undergo hysterectomy and potentially improving their prognosis (7). However, the prognosis can worsen if NAC is unsuccessful because the change in treatment plan from surgery to radiotherapy can delay implementation of the core treatment (8-10). Therefore, it is important to identify biomarkers that can predict the efficacy of NAC in patients with locally advanced uterine cervical cancer.

The antitumor mechanism of platinum-containing drugs such as cisplatin results from covalent binding to DNA and formation of platinum-DNA adducts, which interfere with DNA replication and ultimately induce apoptosis (28). Although platinum-based chemotherapy often has good initial efficacy, cancer cells may acquire resistance to this therapy. Some of the potential mechanisms of resistance are reduced intracellular accumulation of cisplatin (29-31), inactivation of apoptotic pathways (32), increased DNA damage repair capacity (18,33), increased detoxification of cisplatin (34), and other epigenetic changes occurring at the molecular and cellular levels (35,36). Among these, NER, which mediates DNA damage repair, is believed to be one the most crucial determinants (18). XPA is an indispensable factor for

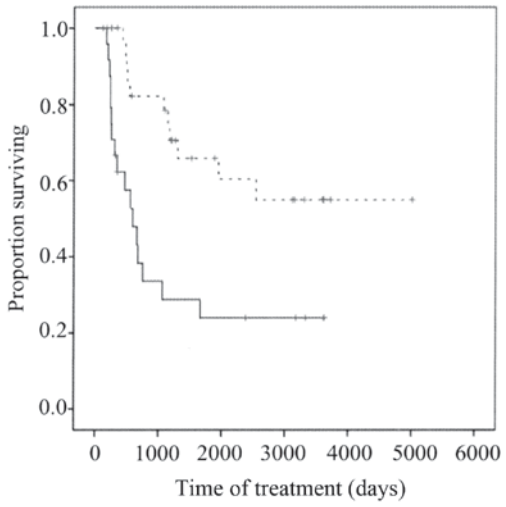

Figure 3. Overall survival rate of the NAC effective group (dashed line, n=31) and NAC ineffective group (solid line, n=25). P<0.001 (Kaplan-Meier and log-rank tests). NAC, neoadjuvant chemotherapy.

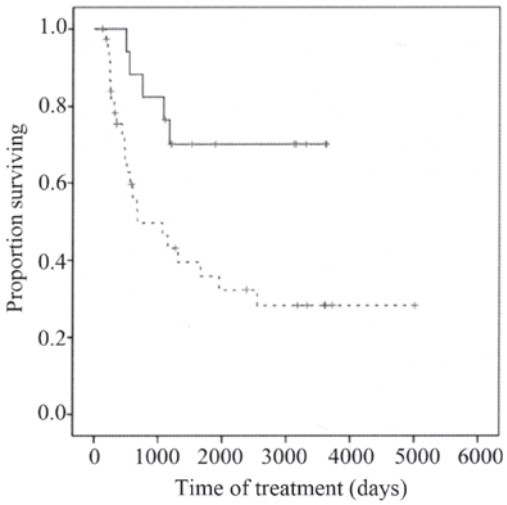

Figure 4. Overall survival of the low XPA expression group (solid line, n=17) and high XPA expression group (dashed line, n=39). P=0.01 (Kaplan-Meier and log-rank tests). XPA, xeroderma pigmentosum complementation group A.

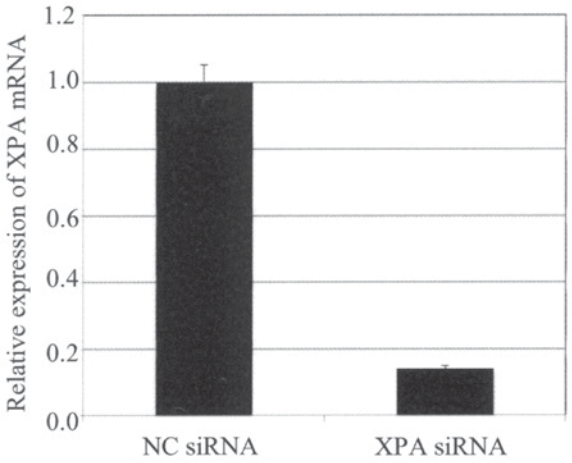

Figure 5. Reverse transcription-quantitative polymerase chain reaction analysis of *XPA* mRNA expression levels in the uterine cervical cancer cell line Ca Ski after transfection with control or *XPA*-targeting siRNAs. mRNA levels were normalized to *GAPDH*. NC, negative control; XPA, xeroderma pigmentosum complementation group A; siRNA, small interfering RNA; *GAPDH*, glyceraldehyde 3-phosphate dehydrogenase.

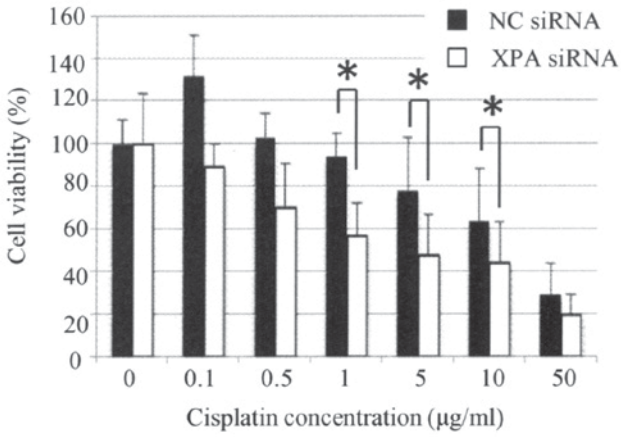

Figure 6. Cell viability of Ca Ski cells transiently transfected with control or *XPA*-targeting siRNAs and then incubated with the indicated concentrations of cisplatin for 24 h. *P<0.05 (Student's t-test). NC, negative control; XPA, xeroderma pigmentosum complementation group A; siRNA, small interfering RNA.

NER (17,18). Several reports have shown that XPA mediates the initial recognition and verification of DNA lesions, stabilizes repair intermediates, and is involved in the induction of other NER factors (19-24). Therefore, it is likely that upregulation of XPA expression would increase platinum resistance. Indeed, XPA expression has been reported to correlate with the resistance of nasopharyngeal carcinoma and lung cancer cell lines to platinum-based therapy (17,18,25).

The present study reveals a significant relationship between XPA expression and the effectiveness of NAC in patients with locally advanced uterine cervical cancer. Patients with low XPA expression tended to be more sensitive to NAC and underwent surgery after NAC. This is consistent with the longer overall survival times of the low XPA expression group and NAC effective group compared with the high XPA expression group and NAC ineffective group, respectively. We also found that downregulation of XPA expression increased the cisplatin sensitivity of cultured uterine cervical cancer cells, suggesting that XPA is a cisplatin-resistance factor. This is the first report of a correlation between XPA expression and NAC efficacy for locally advanced uterine cervical cancer. However, this study included only 56 patients. One of the limitations of this study was the small number of patients. We need further investigations with a larger number of cases to know the critical fact.

In summary, XPA expression may be a predictive marker of the effectiveness of NAC for patients with locally advanced uterine cervical cancer. This finding could help to improve the prognosis of these patients.

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