Biology and treatment of cervical adenocarcinoma: review

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Abstract: Uterine cervical adenocarcinoma (ADC) has been increasing in its prevalence world widely despite the decrease of squamous cell carcinoma (SCC). It comprises nearly 20–25% of the all cervical malignancy in developed countries. The worse biological behavior had been reported in patients with intermediate- and high risk factors after surgery, and in advanced stage over III, radiotherapy (RT) alone and concurrent chemo-radiotherapy (CCRT) with cisplatin was not always effective. As for chemotherapy (CT), the induction CT has not established, as well. Further molecular targeted therapy (MTT) has been studied. The targets of oncogenic driver mutations were vascular endothelial growth factor (VEGF) in SCC, or tyrosine kinase (TK) of endothelial growth factor receptor 2 (EGFR2, Her2/neu)-Ras-MAPK-ERK pathway. Bevacizumab (Bev, anti-VEGF monoclonal antibody) is considered as one of key agent with paclitaxel and carboplatin in SCC, but not for ADC. This article focuses on up-to-date knowledge of biology and possible specific therapeutic directions to explore in the management of cervical ADC.

Keywords: Cervical cancer; adenocarcinoma (ADC); atypical glandular cell (AGC); gastric type adenocarcinoma (GAS)

Introduction

From the point of treatment, for cervical squamous cell carcinoma (SCC), especially in patients with stage IB2–IVA, concurrent chemo-radiotherapy (CCRT) with cisplatin has been gold standard from 2001, in Japan. From the point of treatment, for cervical SCC, especially in advanced stage IB2–IVA, CCRT with cisplatin has been gold standard from 2001. As for CCRT in patients with cervical adenocarcinoma (ADC), there is no prospective study. Some retrospective studies revealed poorer overall survival (OS) than that of SCC (*Table 1*). To improve the OS in CCRT some trials that concomitant agent changed with platinum and paclitaxl, or the subsequent CT with full dose paclitaxel and carboplatin (1,2).

It is well known that ADC of cervix has radio-resistant and chemo-resistant, in general sated bellow. Bevacizumab with TP therapy is the gold standard for cervical cancer, nowadays, for SCC the response was effective significantly, but not significant for cervical ADC. As for new agents,

some new molecular targets were identified by full genomic analyses with new generation sequencing (NGS). In order to conquer the disease, new strategy or development of new agents must be mandatory.

This article focuses on up-to-date knowledge of biology and possible specific therapeutic directions to explore in the management of cervical ADC.

Etiology and prevalence

In China, cervical cancer mortality rate was reported as 9.2 per 100.000 in 2007–2008 (3).

In Japan, cervical cancer mortality was 4.1 per 100,000 in 2012–2013 (4).

In the world, cervical cancer is responsible for 10–15% of cancer-related deaths in women worldwide (data for cervical cancer are available for 602,225 women. A total of 192 registries in 51 countries provided data for1995–1999, 244 registries in 58 countries contributed data for 2000–2004, and 244 registries in 61 countries provided data

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Table 1 5-year survival in cervical cancer between subtypes, such as squamous, adenocarcinoma, and adenosquamous type

FIGO stage	SCC	AC	ASC
n*	10,381	2,988	966
IB1	88.2%	84.8%	81.7%
IB2	69.0%	68.3%	65.1%
IBNOS	77.9%	83.7%	77.5%
IIA	58.3%	45.5%	42.0%
IIB	55.1%	46.3%	55.2%
IIIA	33.7%	15.6%	33.8%
IIIB	31.3%	20.3%	24.6%
IVA	17.1%	8.0%	10.4%
IVB	5.9%	9.4%	8.7%
n#	2,206	527	129
I	93.4%	88.2% (P=0.0003)	88.0%
II	81.1%	67.7% (P=0.0002)	75.0%
III	59.3%	47.6% (P=0.0117)	44.4%
IV	33.2%	19.6% (P=0.0089)	26.7%

*, Galic *et al*.; Gynecologic Oncology 2012, 125.287 (cases which initiated treatments in 1988–2005); #, Japanese Society of Obstetrics and Gynecology: Gynecologic Tumor Committee Reports 2012, Jpn JSOG, patients who initiated treatments in 2005. SCC, squamous cell carcinoma.

for 2005–2009) (5). The percentage of cervical ADC was increasing in many countries especially in younger women than those in patient with SCC. In developed countries it accounts for 20–25% in all cervical cancer and it accounts for 22% in 2012 in Japan as well (6,7).

In China, even in patients with early stages (stage IB–IIB), a retrospective study of 255 patients (including 36 patients of non-squamous histology) revealed a poor prognosis of ADC.

Biology of cervical adenocarcinoma (ADC)

Recently, genomic alteration of cervical carcinoma (SCC and ADC) was demonstrated by whole exon sequence in 79 SCC and 24 ADC including 79 transcriptome sequence and 14 whole genome sequence. The somatic mutations were detected in PIK3CA, PTEN, TP53, STK11, ERBB2 and KRAS in SCC, ELF3, PIK3CA, ERBB2, STK11, and CBFB were detected in ADC (8). Further precise evaluation will be necessary about the co-relation between the gene mutations for targeting therapy.

Pathogenesis and classification

The oncogenesis of ADC has not been elucidated in precise. In speculation, HPV 18 and 16 and their proteomes thought to be responsible for oncogenesis with estrogens which stimulate the endometrioid type's and endocervical type's proliferation, but recently new entity of gastric type adenocarcinoma (GAS) was detected and its prognosis is worst among subtypes of ADC (9). GAS, which driver gene has not been elucidated, had somatic gene mutations such as ERBB2 (Her2/neu2), k-Ras, PIK3CA, STKII, ELF3, and CBFB (8).

On the other hand, Harvard group, Wright *et al*. (10) reported the comparison of the spectrum of cancer-related gene mutations in the two main subtypes of cervical cancer ADC and SCC.

They found that 31 percent of the samples had *PIK3CA* mutations; 17.5 percent of the ADC (and non-SCC) had *KRAS* mutations; and 7.5 percent of the SCC (but none of the ADC) had a rare mutation in the gene *EGFR*. Patients with the ADC subtype of cervical cancer may benefit from targeted agents known as MEK inhibitors, which have shown some success in clinical trials (9). In one case of ADC, Ojesina *et al*. revealed EGFR mutation but, Wright *et al*. reported no case of EGFR mutation in their data set. There might unknown heterogeneity of EGFRs' dimerizations.

Among them, STK11 was suspected as a responsible gene mutation of GAS.

Germ line mutations in this gene have been associated with Peutz-Jeghers syndrome (PJS). Patients with PJS have a cancer risk in cervix, such as lobular endocervical glandular hyperplasia (LEGH), or minimal deviation adenocarcinoma (MDA) and mutinous ADC, which depends on STK11 mutation (11).

STK11 (LKB1) is a member of serine/threonine kinase family and regulates cell polarity and suppresses tumor genesis via adenine monophosphate-activated protein kinase (AMPK) which is member of PI3K-mTOR pathway. Activation of AMPK by SKT11 suppresses tumor growth and proliferation when energy and nutrient levels are scarce. Activation of AMPK-

Table 2 Risk factors of adenocarcinoma of cervix

Factors	Intermediate-high	High-risk
LVSI	Positive	Positive
Tumor size	<40 mm	More than 40 mm
LN metastases	Negative	Positive
Stage	IB–IIB	IIIB
Extra uterine lesion	Negative	Positive

LVSI: lymph-vascular space invasion,

related kinases by LKB1 plays vital roles maintaining cell polarity thereby inhibiting inappropriate expansion of tumor cells.

WHO 2014 classification has involved GAS as new subtype of ADC which had SKT11 mutation (WHO 2014) (12).

As for cytology, the expression of atypical glandular cells (AGC) by PAP smear test such as AGC is unstable and the subsequent re-examination or endocervical curettage reveals often negative, and further precise absolute examination must be excisional conization or hysterectomy.

Clinical risks

It is controversy whether subtype of histology such as ADC had poor prognosis in some randomized clinical trial (RCT) in some setting of trials (1). In general point of view, there were few RCTs in this field of disease. From some retrospective trials the prognostic factors had been extracted and clinical risks were selected as intermediate-high risk or high risk (*Table 2*).

Intermediate-high risks thought to be lymph vascular space invasion (LVSI) (13,14), tumor size no less than 40 mm (13,14), cervical muscle-layer invasion less than 1/3 (14).

High risk had lymph-nodes metastases (13-15), positive of surgical margin (13), distal metastases (13), vaginal metastases (14).

Issues of diagnosis

Cytology and histology

The issue of diagnosis depends on the location of foci. If the foci located near squamous-columnar junction (SCJ), it is easy to biopsy, but most of the cases the abnormal lesion located deep in glands along with narrow cervical canal. The macroscopic observation is often impossible

even if endoscopy. From this issue, even if blush-taken cytology, or endocervical curettage, it is very difficult to diagnose AIS, or micro invasive ADC. Only frank invasive ADC serves easily the specimen diagnosed malignant.

Minimal deviation ADC (adenoma malignum: MDA) and its related endocervical tumors such as lobular glandular endocervical hyperplasia (LEGH), atypical LEGH, and ADC in situ including endocervical dysplasia had been classified in 2014 WHO classification. The differential diagnosis by cytology or endocervical curettage was very difficult because of its location of disease exists deep in endocervical gland generally. Only conization (excisional conization) or extirpation of uterus revealed by negative for HPV18 analysis, HIK1038 staining, p16 ink4 immunoblotting, mib-1 (Ki-67) staining, MUC6, and carbonic anhydrase type IX (16-19).

Issues of imaging

Magnetic resonance imaging (MRI) is a high-resolution diagnostic modality of tissue (water concentration)-dependent quality in tumors. Comparing the T1, T2 (conventional images), weighted images, the feature of the tumor (both cystic or solid) was depicted specific signal intensities as low to high deserved serous to mucinous (according to viscosity: free degree of proton spins). Furthermore, using enhancer of A gadolinium with diethylenetriaminepentaacetate (Gd-DTP) the nature of blood flow (arterial phase), blood dissemination (capillary phase) and blood drainage (venous return phase) was depicted as an angiography, the consume rate of blood in the foci and around the micro environment of the tumor would be elucidated (dynamic MRI).

Diffusion weighted image (DWI) was depended on proton diffusion in magnetic gradient. DWI positive images were often obtained in malignancy.

The images of minimal deviation of cervical ADC and its related tumors was depicted accumulation of small to large sized high signal intensity on T2, and low on T1, lesions at deep cervical stroma. It is called cosmos flower sign (20).

Issues of treatment

Surgery (radical hysterectomy)

Up to stage IB (FIGO stage), Korea group reported a

retrospective study as a difference between ADC and ADSQ, in factors of clinical risk. ADC and ADSQ showed that mean size of tumor and percentage of LVSI were 2.3 *vs.* 2.7 mm (P=0.019) and 14.7% *vs.* 29.2% (P=0.008). Both recurrent disease and death of the disease were 15.3% *vs.* 12.5% (P=0.47), and 18.1% and 14.7% (P=0.56), respectively. Five-year recurrent free disease was 85% *vs.* 89%, respectively, and it was no significant difference (21).

Yamauchi *et al*. reported a retrospective study for early stage of cervical ADC, as well. Ninety one ADC and 364 SCC were enrolled and the prognosis of ADC was poorer than that of SCC significantly (P=0.001). As for prognostic factors, LVSI (P=0.008), stromal invasion (P=0.024) and adnexal metastasis (P=0.032) were the shorter survival by multivariate analyses in ADC (22).

Pelvic exenteration

Pelvic exenteration has an important role in the treatment of advanced or recurrent cervical cancer to obtain a complete cure or longer survival. Pelvic exenteration comprises of three types that is anterior exenteration, posterior exenteration and total exenteration. Reconstruction is necessary, i.e., urinary tracts re construction for anterior exenteration, rectal anastomosis for posterior exenteration, and both for total exenteration (23-26).

Laterally extended endopelvic resection (LEER)

Hockel (27) and Caceres *et al*. (24) reported the efficacy of LEER. To demonstrate the therapeutic potential of the (LEER), phase 2 study was conducted especially for patients with recurrent cervical carcinomas involving the side wall of an irradiated pelvis. These patients, suffering from the most common situation of local failure, have so far no longer been considered for curative therapy. The procedures in general were as follows: extending the lateral resection plane of pelvic exenteration to the medial aspects of the lumbosacral plexus, sacrospinous ligament, acetabulum, and obturator membrane enables the complete removal of a subset of locally advanced and recurrent tumors of the lower female genital tract fixed to the pelvic wall with free margins (R0).

Thirty-six patients with recurrent (n=29) or primary advanced (n=7) gynecologic malignancies involving the side wall of the lesser pelvis underwent LEER from July 1996 until October 2002. The majority of the patients suffered from cervical carcinoma (n=29) and had received previous pelvic irradiation (n=24). Tumor-free (R0) lateral margins were obtained in 34 patients. Severe postoperative complications occurred in 14 patients with one treatment-related death (TRD). Five-year survival probability is 49% for the whole group and 46% for those patients considered only for palliation with current treatment options. Most patients without evidence of disease at least 1 year after LEER achieved good quality of life (24). Fourteen treatment derived severe adverse events (including one TRD) deserves nearly 40% of the cases. The comparisons of survivals were shown in *Table 3*. It might be reduced under 5.0% by using new energy devices or MRI-guided operation in near future.

Surgery and adjuvant radiotherapy (RT)

A retrospective study of stage IB–IIA cervical cancer with adjuvant RT showed 83.7%, 66.5% and 79.6%, in 5-year survival of SCC, AD, ADSQ, respectively. ADC was significantly poor prognosis compared to SCC (P<0.0001) (14).

From Japanese study, Shimada *et al*. reported a retrospective study adjuvant RT after radical hysterectomy, comparing the efficacy of RT in different histology. Eight hundred and twenty patients were enrolled (280ADC and 540SCC). Among them 139 ADC and 327 SCC patients were received adjuvant RT.

The histological type did not affect the outcome for patients with stage I disease. However, in stage II disease, ADC was significantly worse prognosis than SCC. Patient with SCC exhibited significantly higher lymph node involvement in stage IB, but not in IB2 and II. Among patients with lymph node involvement patients with ADC exhibited a significantly worse 5-year survival rate compared to those with SCC (46.4% *vs.* 72.3%, respectively, P=0.0005). Among the patients receiving the adjuvant RT, those with ADC showed higher recurrence rate of central recurrence (pelvic and stump) than those with SCC (24.6% *vs.* 10.5%, P=0.0022). As for distant recurrence and paraaortic recurrence there was no difference between histological subtypes (2).

Okazawa *et al*. reported a retrospective study in patients with stage IB1–IIB for efficacy of CCRT *vs.* RT as an adjuvant therapy for intermediate-risk or high-risk. Both PFS and OS of CCRT were superior to those of RT.

Issues of chemotherapy (CT)

Bevacizumab with TP therapy is the gold standard for

Table 3 Comparison of survival times pelvic exenteration and LEER

Author	Reference	Patients (disease and numbers)	Median survival time or 5 years survival	Comments
Chiantera et al.	Int J Gynecol Cancer 2014;24(5):916	Advanced: 27 pts; persistent 34 pts	5 y OS 38%	CR surgery 72.5%
Tanaka et al.	Int J Clin Oncol	12 pts; stage IVA, 2 pts; recurrent, 61 pts	5 y OS 42%	5 pts NED, 4 pts recurrence
Hockel et al.	Gynecol Oncol 2012;127(2):297	91 pts (30 pts primary), 61 pts recurrent	5 y OS 61%	
Fotopoulou et al. (26)	J Surg Oncol 2010;101:507	47 pts, 10 pts primary, 37 pts recurrent	23 pts (49%) R0, mOS 22 months, mPFS 12 months	
Caceres et al. (24)	Int J Gynecol Ongol 2008;18:1139	Recurrent	71% 22 months	78 % CR
Morley et al. (23)	Obstet Gynecol 1989;74(6):934			SCC 77%, ADC 22%

LEER, laterally extended endopelvic resection; pts, patients; OS, overall survival; CR, complete response; PFS, progression free survival; SCC, squamous cell carcinoma; ADC, adenocarcinoma.

cervical cancer, nowadays, for SCC the response was effective significantly, but not significant in cervical ADC. As for CCRT in patients with cervical ADC, only few prospective studies were reported. Some retrospective studies revealed poorer OS than that of SCC. To improve the OS in CCRT some trials that concomitant agent changed with platinum and paclitaxel, or the subsequent CT with full dose paclitaxel and carboplatin.

Systemic chemotherapy (CT)

From ESMO Clinical Practice Guideline (28), CT for advanced or metastatic/recurrent cervical cancer is palliative. Cisplatin is considered as the single most active cytotoxic agent. Only cisplatin combination doublet which had OS advantage than cisplatin single agent was cisplatin + topotecan regimen, but no significant difference among cisplatin + paclitaxel, cisplatin + gemcitabine, cisplatin + vinorelbine, and cisplatin + topotecan. Carboplatin had an advantage in lower adverse event such as nephrotoxicity. Japanese Clinical Oncology Group (JCOG) trial of the RCT (JCOG0505) revealed no inferiority to cisplatin + paclitaxel regimen (29,30).

Issues of adjuvant chemotherapy (CT) and CCRT

Shimada et al. reported a retrospective study of cervical

ADC in comparing adjuvant RT (including CCRT) and adjuvant CT. It revealed favorable 5-year survival in CT rather than RT (+ CCRT) such as 79.2%, 70.9%, respectively. RT followed by CT group had worst 5-year survival such as 66.2% (31). Chinese study of 424 pts revealed adjuvant CT had longer recurrence free survival time (15).

Issues of neo-adjuvant chemotherapy (NACT)

He et al. reported a meta-analysis of 2 RCTs and 9 observational studies about the efficacy of NACT in different histological types of cervical cancer. The results were as follows: the short-term efficacy estimated by response [complete response (CR) + partial response (PR) or CR alone] was no difference between SCC and non-SCC, and in RCTs higher response in SCC than that of non-SCC. Long-term outcome of NACT, SCC had a significant longer 5-year OS (HR =1.47, 95% CI, 1.06–2.06) and PFS (HR =1.96, 95% CI, 1.61–2.38) than those of non-SCC. It became more obvious if the stage in IIB in subgroup analysis (HR =2.06, 95% CI, 1.79–2.36), but stage IB–IIB it became no significant (HR =1.33, 95% CI, 0.99–2.38). In conclusion, in early stages such as IB and IIB, there was no significant difference in OS between SCC and non-SCC (32). Italian group, Landoni et al. reported a retrospective study of efficacy of neo-adjuvant

CT followed by radical hysterectomy. The optimal responders by NACT and surgery in FIGO stage IB–IIB cervical cancer do not need any further treatment, and for patient with suboptimal response and intra-cervical residual disease, additional cycles of CT would be of benefit (33).

A RCT of CCRT with CDDP *vs.* CDDP and tirapazamine (TPZ) in patients with advanced ADC revealed no superiority of additional TPZ. Three-year PFS for the TPZ/CIS/RT and CIS/RT arms were 63.0% and 64.4% (log-rank P=0.7869). Three-year OS for the TPZ/CIS/RT and CIS/RT arms were 70.5% and 70.6%, respectively (log-rank P=0.8333) (34).

Tang *et al.* reported in patients with stage IIB–IVA cervical ADC a randomized phase III study comparing CCRT alone *vs.* one cycle of paclitaxel + cisplatin (TP) therapy before CCRT followed by two cycles of TP therapy. The disease free survival of CCRT alone and CCRT with adjuvant CT were 60.4% *vs.* 71.4% (P<0.05). Recurrence were 39.6% *vs.* 28.6% (P<0.05), respectively. OS were about 60% *vs.* 73% (P<0.04, log-rank test: data were not elucidated in true value, only Kaplan-Meier curves were demonstrated) (35).

Poujade *et al.* studied about neo-adjuvant (NAC) CCRT for stage IB2 to IIIB ADC of the cervix, and revealed the pathological CR was obtained 33% of the patients. Prognostic factors of residual viable tumor were patients with post menopause, parametrial invasion (PMI), LVSI, and mucinous subtype (36). A total of 66.7% of patients treated CCRT had residual disease at least. Shibata *et al.* reported 26% of pathological CR after NAC CCRT with 70 mg/m^2 cisplatin and 700 mg/m^2 5-FU 5 days continuous infusion. A total of 74% had residual viable tumors, as well (37). Here we can find the limitation of CCRT with cisplatin.

For advanced stage, Katanyoo *et al.* reported retrospective study for the treatment outcomes in patients with advanced (stage IIB–IVA) ADC of cervix compared with the same stage-matched SCC of cervix. It revealed that the significant worse CR rate of ADC than that of SCC (P=0.004). Complete pathological response rates were 42.1% and 73.7% in ADC and SCC, respectively, it seemed less effective in ADC, as well. As for CCRT, used agents were cisplatin alone, carboplatin alone, and carboplatin with 5-FU, so more precise information such as dosage and course number was not shown, 37% of the patients were treated such CCRT (38).

Radiotherapy (RT) and CCRT

Adeno- and adenosquamous carcinomas of the cervix are associated with worse OS when treated with radiation alone but with similar progression-free and OS compared to SCCs of the cervix when treated with cisplatin based chemoradiation (1).

In Japan, Niibe *et al.* reported that the stage IIIB cervical ADC treated with RT alone revealed 20.2% in 5-year survival (39).

In Asia, from Taiwan, retrospective study of CCRT for stage IB–IIB cervical cancer was performed and ADC/ADSQ (n=21) showed worse 5-year progression free survival (PFS) (30.0% *vs.* 47.6%, P=0.044), worse 5-year distant metastasis-free survival (41.5% *vs.* 69.9%, P=0.005), and trends toward worse 5-year local recurrence-free survival (64.4% *vs.* 76.2%, P=0.165), and worse 5-year OS (41.3% *vs.* 58.1%, P=0.090) than patients with SCC (n=109) (40).

In summary, it is very difficult to diagnose in precancerous neoplasia such as AIS or LEGH by cytology or curettage. AGC in Bethesda system is one of trial of screenings for early diagnosis with the measurement of CAIX, or HPV18, p16INK4, and Ki-67. It has been a GOG0237 study which has been on going, would be useful to improve the diagnostic accuracy.

Oncogene mutation would be detected by cytology in future and it would be useful to make differential diagnosis between usual ADC between GAS.

New entity of GAS was chemo-resistant rather than usual ADC.

If the ADC were able to diagnose in early stage, surgical treatment with or without CCRT is selected, which are effective for early stages in treatment of ADC.

Which is better CCRT or RT alone as adjuvant RT? The answer has not been determined. Now, we are accruing GOG 263 trial, the RCT of RT alone or CCRT with cisplatin for intermediate risk in patients with stage IB-IIA cervical cancer. The result of GOG263 would be informative first randomized study as for adjuvant CCRT in patients with intermediate-risk of cervical cancer.

For advanced, metastatic, and recurrent disease, there was no effective treatment except for exenteration and LEER.

CCRT was the standard treatment without distant metastasis but it was not necessary appropriate treatment. Sometimes further therapy such as CT or extended RT was necessary. To investigate more effective treatments, neo-

adjuvant systemic chemotherapy (NACT), or following systemic CT (paclitaxel + carboplatin) was tried. RCT has not been performed yet.

Possibility of molecular targeted therapy (MTT) for ADC

ADC specific gene mutations were detected by Genome Wide Association Study. From the two datasets, ADC specific gene mutations were ELF3, CBFB, STKII, and Kras mutations. Both SCC and ADC had ERBB2, P53and PIK3CA mutations.

From these knowledges, new targeted therapy would be planed.

In conclusion, few RCTs were conducted and some improvements were demonstrated in this disease, but the prognoses in advanced patients were still poorer. Further randomized study will be mandatory including new molecular targeted agents.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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