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ORIGINAL ARTICLE

Aquaporin 3 Expression in Endometrioid Carcinoma of the Uterine Body Correlated With Early Stage and Lower Grade

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Abstract

Aquaporins (AQPs) are a family of transmembrane water channel proteins distributed in various human tissues. Recent studies revealed that AQPs play important roles in cancer biology. Few studies have documented the relationship between the prognosis, stage, and histological grade of uterine endometrioid carcinoma, with AQP expression. Hence, the present study aimed to investigate this relationship between uterine endometrioid carcinoma and AQP expression. We retrospectively reviewed records of the patients who underwent surgery for uterine body cancer between 1990 and 2010 at the National Defense Medical College Hospital, Saitama, Japan. In 241 cases of endometrioid carcinoma, we immunohistochemically examined the expression of AQP 1, 2, 3, 4, and 5, and their relationship with clinicopathological parameters and the patients' prognosis. We investigated the relationship between the clinicopathological parameters and AQP3 expression, and found that as the FIGO stage and histological grade progressed, the percentage of AQP3 expression tends to decrease. Furthermore, we analyzed progression-free survival/overall survival (PFS/OS) using the log-rank test, and found that the AQP3-positive group had a better prognosis than AQP3-negative group (PFS: $P < 0.001$, OS: $P = 0.002$, respectively). Using Cox's univariate proportional hazard model, we revealed that AQP3 had a low hazard ratio. However, according to Cox's multivariate proportional hazard model, AQP3 was not an independent prognostic factor. Among the endometrioid carcinoma patients, the AQP3-positive group was associated with early stage and lower grade compared to the AQP3-negative group. Therefore, AQP3 has the potential to serve as a predictor of prognosis, although further investigation is necessary to elucidate the biological mechanism of AQP3 in endometrioid carcinoma.

Keywords Aquaporin · water channel · uterus · endometrioid carcinoma · immunohistochemistry

Introduction

In 2013, Japan reported 2107 deaths due to uterine cancer, and it was estimated that 13004 Japanese might have uterine body cancer. The morbidity rate per 100,000 was determined to be 19.9 for the total age, and 51.2 for women in the age range of 55–59 years [1]. Hence, uterine body cancer is a common disease among 50-year old women.

Aquaporins (AQPs) are water channel proteins, and 13 members (AQP0-12) have been identified in mammals [2]. They are subdivided into aquaporins and aquaglyceroporins, the latter transporting water and other small solutes such as glycerol [2, 3]. Recently, AQPs have been reported to be involved in cancer cell proliferation, migration, and angiogenesis; thus, AQPs-target inhibitors have the potential to become a therapeutic strategy [4, 5]. Currently, some aquaporins have been identified in male and female reproductive systems, and previous studies have demonstrated the importance of aquaporins in reproductive functions [6]. However, few studies have documented the relationship between prognosis, stage, and histological grade, with AQP expression in uterine body cancer. This study investigated the prognosis in patients diagnosed with uterine body cancer and who underwent surgery at the National Defense Medical College Hospital (NDMCH), Japan, and attempted to elucidate the relationship between prognosis, stage and histological grade, with AQP expression in uterine body cancer.

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Materials and Methods

Study On Setting and Population

We retrospectively reviewed records of 449 patients who underwent surgery for uterine body cancer between June 1990 and September 2010 at the NDMCH in Tokorozawa, Japan. Of the 449 patients, 186 were excluded because of the lack of data or specimens. In addition, 22 patients with special histological types were excluded. The remaining 241 patients with endometrioid carcinoma met the criteria for inclusion (Fig. 1). Clinicopathological features of the patients are shown in Table 1. Of the patients reviewed, 138 (57%) patients were under 60 years old, and 103 (43%) were 60 years old or older. According to the International Federation of Gynecology and Obstetrics (FIGO) system, there were 162 (67%) cases at FIGO stage I, 22 (9%) at stage II, 50 (21%) at stage III, and 7 (3%) at stage IV. Adjuvant chemotherapy was administered to 126 (52%) patients. The adjuvant chemotherapy composition was as follows: 62 patients received cyclophosphamide + adriamycin + cisplatin (CAP), 42 patients received paclitaxel + carboplatin (TC), 11 patients received tegafur + uracil (UFT), 3 patients received docetaxel + cisplatin (DP), 2 patients received cyclophosphamide + adriamycin + carboplatin (CAJ), 1 patient received cyclophosphamide + carboplatin (CJ), and 1 patient received etoposide + cisplatin (EP), respectively. The treatment administered to each patient was in accordance with the treatment guidelines, regimen of clinical study, or clinicians' choice. Progression-free survival (PFS) was defined as the interval between the completion of upfront treatment until death or disease progression. Overall survival (OS) was defined as the interval between the diagnosis or the start of treatment and death due to any cause. We also selected 12 cases of normal endometrial tissue (6 cases in the proliferative phase, 6 cases in the secretory phase) as normal controls. The research protocol was approved by the Institutional Ethical Review Board Committee of the National Defense Medical College.

Immunohistochemical Staining

We investigated the expression of AQP 1, 2, 3, 4, and 5 by immunohistochemistry. Primary antibodies used were rabbit polyclonal antibodies for AQP1 (dilution 1:300; Bioss bs-1506R, Boston, MA, USA), AQP2 (dilution 1:100; Abcam ab78230, Cambridge, UK), AQP3 (dilution 1:200; Bioss bs-1253R), AQP4 (dilution 1:300; Bioss bs-0634R), and AQP5 (dilution 1:400; Bioss bs-1554R). Using the formalin-fixed paraffin-embedded tissue blocks stored in the Department of Laboratory Medicine, NDMCH, 2-mm diameter cancer tissue cores were enucleated from each case, and subjected to the construction of tissue microarray (TMA) blocks. Each TMA block was sliced into 4 μm-thick sections and mounted on silane-coated slides, and deparaffinized. Antigen retrieval treatment was conducted in Tris-EDTA buffer pH 9.0 (DAKO, Tokyo, Japan) at 98 in a water bath for 1 h. The endogenous peroxidase was blocked with 3% hydrogen peroxide in methanol for 5 min. After rinsing the slides with phosphate-buffered saline pH 7.4 (PBS) (TaKaRa, Kusatsu, Japan) for 15 min, the slides were incubated with the primary antibodies for AQP1, AQP3, AQP4, and AQP5 at 4 °C overnight, and then exposed to the DAKO REAL EnVision system/HRP, containing Rabbit/Mouse secondary antibodies for 60 min at 18 °C. Specific antigen-antibody reactions were visualized with Dako REAL DAB + chromogen from the kit, and counterstained with Mayer hematoxylin.

We evaluated intensity score (0, negative; 1, weakly positive; 2, strongly positive) and proportion score (0, < 1% of

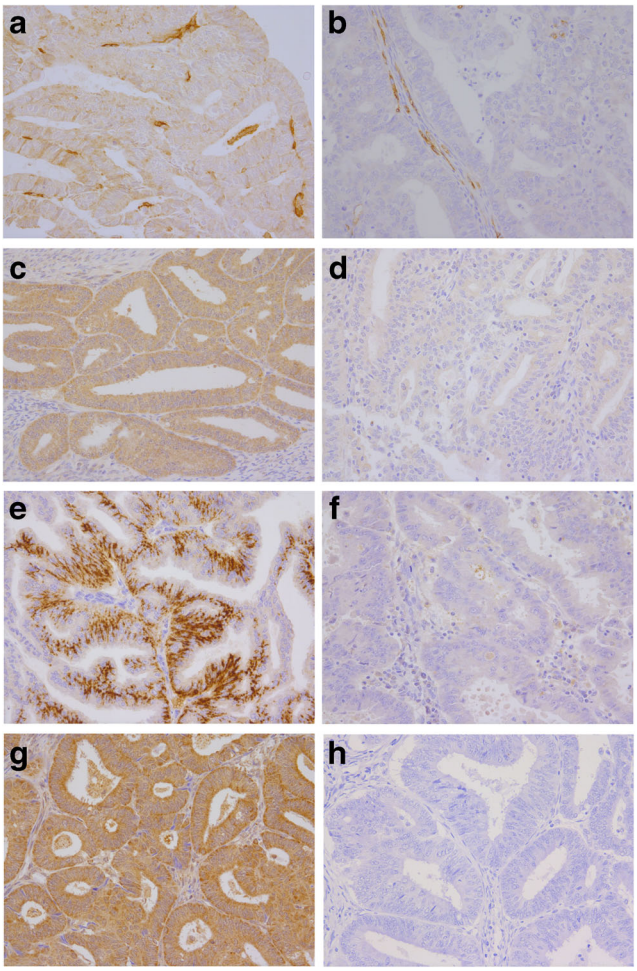

Fig. 1 Representative photomicrographs of immunohistochemical staining for AQP1-5 in endometrioid carcinoma (A-H) and normal endometrial tissue (H). The membrane and cytoplasm were stained. **A** AQP1 positive, **B** AQP1 negative, **C** AQP3 positive, **D** AQP3 negative, **E** AQP4 positive, **F** AQP4 negative, **G** AQP5 positive, **H** AQP2 negative. (H) Most cases were AQP3 negative in normal endometrial tissues

Table 1 Clinicopathological characteristics of the patients

Parameters		Number of patients (%)
Age (years old)	< 60	138 (57)
	≥ 60	103 (43)
FIGO stage	I	162 (67)
	II	22 (9)
	III	50 (21)
	IV	7 (3)
Histological grade	G1	138 (57)
	G2	66 (27)
	G3	37 (15)
Lymph node metastasis	-	178 (74)
	+	29 (12)
	Not evaluable	34 (14)
Surgical therapy	TH + BSO	21 (9)
	TH + BSO + LN dissection	35 (15)
	TH + BSO + LN dissection + partial omentectomy	15 (6)
	SRH + BSO	5 (2)
	SRH + BSO + LN dissection	134 (56)
	SRH + BSO + LN + partial omentecomy	22 (9)
	Others	9 (4)
Adjuvant therapy	None	115 (48)
	Chemotherapy	110 (46)
	Chemotherapy + radiation	10 (4)
	Radiation alone	6 (2)

FIGO, The International Federation of Gynecology and Obstetrics; TH, total hysterectomy; BSO, bilateral salpingooophorectomy; LN, lymph node; SRH, semiradical hysterectomy

tumor area stained; 1, 1–50% stained; 2, > 50% stained). Then, we applied H-score (0, 1, 2, 3, 4) by adding intensity score and proportion score. Except for AQP5, there were many negative cases, therefore we divided the negative (score 0) and positive (score 1, 2, 3, 4) groups by applying the median.

Statistical Analysis

All statistical analyses were performed with the JMP Pro software version 14 (SAS Institution Inc., Cary, NC, USA). The chi-square test and Fisher's exact test were used to evaluate differences in the correlation between the expression of AQPs and clinicopathological parameters. If the number of cases was five or less in each parameter, we applied Fisher's exact test. Cumulative survival curves were drawn using the Kaplan-Meier method and compared with the log-rank test. Cox's univariate and multivariate proportional hazard model analyses were used to identify prognostic factors. In univariate analyses, we included age, FIGO stage, histological grade, and AQPs expression. In multivariate analysis, we chose the parameters that were statistically significant in the univariate analyses.

Results

The representative photomicrographs of AQPs immunoreaction are shown in Fig. 1. AQP1, AQP2, AQP3, AQP4 and AQP5 were positive in 4 (1.7%), 0 (0%), 137 (56.8%), 39 (16.2%), and 241 (100%) of endometrioid carcinomas, respectively. The number of AQP3-negative cases was significantly higher in the FIGO stage II/III/IV groups (47 of 79, 59.5%) than in FIGO stage I group (57 of 162, 35.2%) ($P = 0.0003$) (Table 2). Similarly, the number of AQP3-negative cases was significantly higher in G2/G3 cases (89 of 103, 86.4%) than in G1 cases (15 of 138, 10.9%) ($P < 0.0001$). The AQP3-negative cases were also significantly higher in the older (≥ 60) age group (53 of 103, 51.5%) than in the younger (< 60) age group (51 of 138, 37.0%) ($P = 0.025$). The number of patients receiving adjuvant therapy (72 of 126, 57.1%) was higher than those receiving no adjuvant therapy (32 of 115, 27.8%) (Table 2). However, this appeared to be secondary to the stage and grade, with patients at advanced stages or with higher grade tumors receiving adjuvant chemotherapy more frequently than those at earlier stages or with lower grade tumors. The expression rates of AQP1 and AQP4 were not statistically correlated with these parameters.

Comparisons of the survival curves showed that there were significant differences in PFS and OS between AQP3-positive and negative groups (PFS: $P < 0.001$, OS: $P = 0.002$) (Fig. 2). The 10-year PFS ratios of AQP3-positive and negative groups were 92.3% and 67.8%, respectively. The 10-year OS ratios of AQP3-positive and negative groups were 96.9% and 83.2%, respectively. However, with respect to AQP 1 and 4, survival curves did not differ in PFS and OS between the positive and negative groups (Fig. 2).

Cox's univariate proportional hazard model analysis revealed that age, the FIGO stage, grade and AQP3 expression was statistically significant in PFS. Similarly, FIGO stage, grade, and AQP3 expression were statistically significant in OS (Table 3). Cox's multivariate proportional hazard model analysis of PFS, including age, FIGO stage, histological grade and AQP3 expression, revealed that age, FIGO stage and histological grade were statistically significant ($P = 0.018$, $P = 0.0001$, and $P = 0.008$, respectively) (Table 4). Likewise, the Cox's multivariate analysis of OS, including FIGO stage, grade and AQP3, revealed that FIGO stage and histological grade were independent prognostic factors ($P < 0.0001$, $P = 0.022$, respectively) (Table 4). However, AQP3 was not an independent prognostic factor.

In normal endometrial tissues, the expression of AQPs was as follows: AQP1 (proliferative phase: negative 6/positive 0; secretory phase: negative 6/positive 0), AQP3 (proliferative phase: negative 5/positive 1; secretory phase: negative 6/positive 0), AQP4 (proliferative phase: negative 4/positive 2; secretory phase: negative 3/positive 3), and AQP5 (proliferative phase: negative 4/positive 2, secretory phase: negative 3/positive 3). Therefore, no differential expression of each AQP between proliferative and secretory phase was observed. All cases were AQP1 negative, and most cases were AQP3 negative in normal endometrial tissues (Fig. 2H).

Discussion

AQPs are closely involved in tumor biology, and expressed in more than 20 types of tumors [7]. AQPs are considered to play a role in tumor cell proliferation, migration, and angiogenesis, and hence, AQP-targeted inhibitors have the potential to function as therapeutic agents [3, 4]. In a previous study, AQP1 expression in endometrioid carcinoma was investigated, and it was suggested that AQP1 overexpression in the microvessels and small vessels may be involved in the tumor neogenesis and the progression of endometrioid carcinoma [8]. However, AQP3 expression of endometrioid carcinoma and its clinical implications have not been investigated.

Table 2 Expression of AQPs and clinicopathological characteristics

Number of patients (%) Parameters	AQP1		*P*-value	AQP3		*P*-value	AQP4		*P*-value
	+ (n = 04) (1.7%)	- (n = 237) (98.3%)		+ (n = 137) (56.8%)	- (n = 104) (43.2%)		+ (n = 39) (16.2%)	- (n = 202) (83.8%)	
Age (years old)									
< 60	3 (2.2)	135 (97.8)	0.638	87 (63.0)	51 (37.0)	**0.025***	21 (15.2)	117 (84.8)	0.638
≥ 60	1 (1.0)	102 (99.0)		50 (48.5)	53 (51.5)		18 (17.5)	85 (82.5)	
FIGO stage									
I	3 (1.9)	159 (98.2)	1.000	105 (64.8)	57 (35.2)	**0.0003***	24 (14.8)	138 (85.2)	0.409
II, III, IV	1 (1.3)	78 (98.8)		32 (40.5)	47 (59.5)		15 (19.0)	64 (81.0)	
Histological grade									
G1	1 (0.7)	137 (99.3)	0.316	123 (89.1)	15 (10.9)	**< 0.0001***	22 (15.9)	116 (84.1)	0.907
G2, G3	3 (2.9)	100 (97.1)		14 (13.6)	89 (86.4)		17 (16.5)	86 (83.5)	
Adjuvant therapy									
Done	2 (1.6)	124 (98.4)	1.000	54 (42.9)	72 (57.1)	**< 0.0001***	18 (14.3)	108 (85.7)	0.403
Not done	2 (1.7)	113 (98.3)		83 (72.2)	32 (27.8)		21 (18.3)	94 (81.7)	
Lymph node metastasis									
-	3 (1.7)	175 (98.3)	0.456	105 (59.0)	73 (41.0)	**0.034***	25 (14.0)	153 (86.0)	0.581
+	1 (3.5)	28 (96.6)		11 (37.9)	18 (62.1)		5 (17.2)	24 (82.8)	
Not evaluable	0 (0)	34 (100)		21 (61.8)	13 (38.2)		9 (26.5)	25 (73.5)	

*Statistically significant

AQP, aquaporin; FIGO, The International Federation of Gynecology and Obstetrics

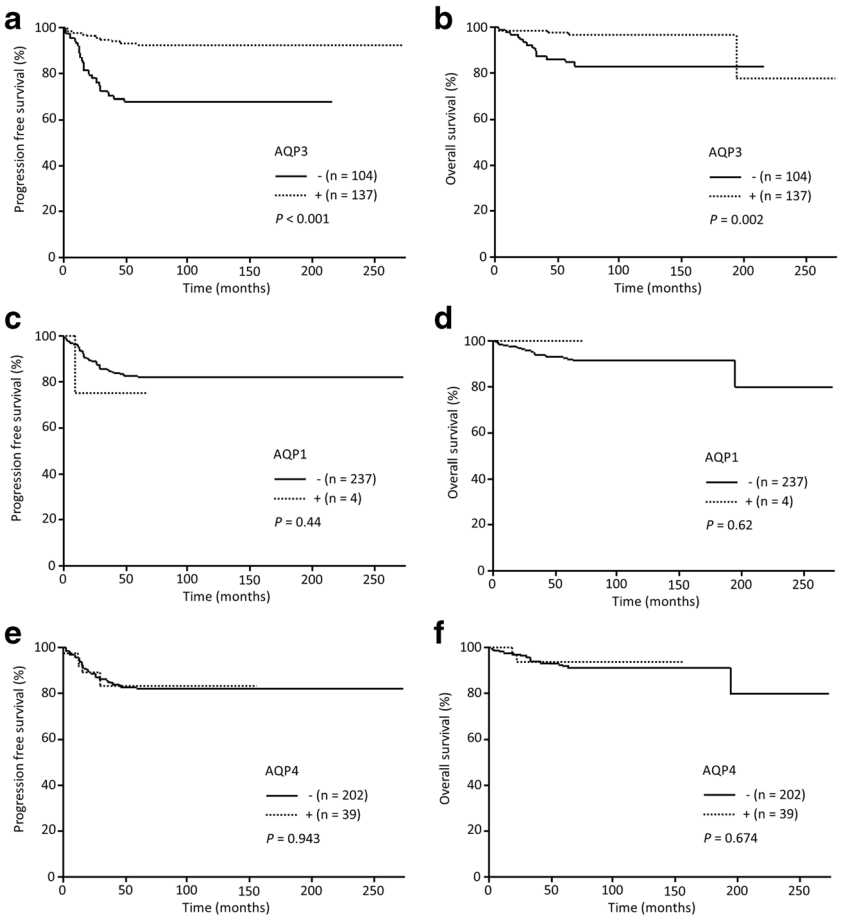

Fig. 2 Progression-free survival (PFS) and overall survival (OS) curves for patients with endometrial carcinomas with respect to expressions of AQPs. **A** AQP3 expression and PFS, **B** AQP3 expression and OS, **C** AQP1 expression and PFS, **D** AQP1 expression and OS, **E** AQP4 expression and PFS, **F** AQP4 expression and OS

In this study, we examined the relationship between FIGO stage, histological grade and patients' prognosis of uterine body cancer and AQPs expression. By using the chi-square test, we found that AQP3 expression was significantly correlated with an earlier FIGO stage and a lower histological grade. Furthermore, by the log-rank test, the AQP3-positive group was found to have a better prognosis than the AQP3-negative group. Cox's univariate analysis demonstrated that the expression of AQP3 had a low hazard ratio (0.203 for PFS, 0.226 for OS). However, Cox's multivariate analysis showed that the expression of AQP3 was not an independent prognostic factor.

AQP3 was reported to be overexpressed in lung, colon, and esophageal cancers, oral squamous cell, breast invasive ductal, bladder, and hepatocellular carcinomas, and pancreatic ductal and gastric adenocarcinomas [9]. Furthermore, the relationship of AQP3 with stage and histological grade was reported in lung adenocarcinoma [10], urothelial carcinoma [11, 12], breast cancer [13], and gastric carcinoma [14]. In lung adenocarcinomas, AQP3 expression was found to be more frequent in well-differentiated tumors than in less-differentiated tumors, and was more frequent in the cases at clinical stage I, than in those at clinical stages II and III [10]. Similarly, in urothelial carcinoma, AQP3 expressions were reported to be reduced or lost according to the progression of grades and stages [11, 12]. In addition, in a study conducted on ovarian cancers [15], the rate of AQP3 expression was lower in the FIGO stage III and IV groups than in the stage I and II groups. These results suggested that AQP3 expression might be decreased with progress of cancer in various organs. The present findings in uterine endometrioid carcinoma demonstrated the same tendency.

In contrast, a study on estrogen receptor-positive breast cancer reported that the AQP3 expression could be correlated with higher histological grade and larger number of lymph node metastasis [13]. In another study investigating gastric carcinoma, high AQP3 expression was correlated with poor prognosis in patients, as well as with epithelial-mesenchymal transition (EMT)-related proteins such as E-cadherin and vimentin [14]. These results suggest that AQP3 may play different biological and clinical roles in different cancers. Estrogen and epidermal growth factor (EGF) have been suggested to be upstream regulators of AQP3 expression [13, 16]. In breast cancer cells expressing the estrogen receptor, stimulation with estrogen transcriptionally upregulated the expression of AQP3 [13]. In cultured ovarian cancer cells, EGF treatment increased AQP3 expression [16]. Therefore, it is possible that these factors influence AQP3 expression to various degrees in each cancer.

Table 3 Results of Cox's univariate proportional hazard model

	Parameters	Category	Hazard ratio (95% CI)	*P*-value
PFS	Age	< 60	1	
		≥ 60	2.398 (1.279–4.655)	**0.006***
	FIGO stage	I	1	
		II/III/IV	4.625 (2.449–9.111)	**< 0.0001***
	Histological grade	G1	1	
		G2/G3	6.607 (3.197–15.42)	**< 0.001***
	AQP1	-	1	
		+	2.146 (0.121–9.902)	0.502
	AQP3	-	1	
		+	0.203 (0.094–0.401)	**< 0.0001***
	AQP4	-	1	
		+	0.969 (0.366–2.145)	0.943
OS	Age	< 60	1	
		≥ 60	2.468 (0.992–6.638)	0.052
	FIGO stage	I	1	
		II/III/IV	9.466 (3.404–33.47)	**< 0.0001***
	Histological grade	G1	1	
		G2/G3	8.099 (2.688–34.88)	**< 0.0001***
	AQP1	-	1	
		+	< 0.001	0.485
	AQP3	-	1	
		+	0.226 (0.073–0.592)	**0.002***
	AQP4	-	1	
		+	0.731 (0.115–2.569)	0.663

*Statistically significant

CI, confidence interval; FIGO, The International Federation of Gynecology and Obstetrics; AQP, aquaporin

Table 4 Results of Cox's multivariate proportional hazard model

	Parameters	Category	Hazard ratio (95% CI)	*P*-value
PFS	Age	< 60	1	
		≥ 60	2.168 (1.142–4.259)	**0.018***
	FIGO stage	I	1	
		II/III/IV	3.535 (1.845–7.061)	**0.0001***
	Histological grade	G1	1	
		G2/G3	4.175 (1.437–12.64)	**0.008***
	AQP3	-	1	
		+	0.840 (0.287–2.172)	0.734
OS	FIGO stage	I	1	
		II/III/IV	7.767 (2.633–29.62)	**< 0.0001***
	Histological grade	G1	1	
		G2/G3	6.043 (1.286–32.77)	**0.022***
	AQP3	-	1	
		+	1.055(0.240–3.515)	0.937

*Statistically significant

CI, confidence interval; FIGO, The International Federation of Gynecology and Obstetrics; AQP, aquaporin

He et al. previously published preclinical study confirmed potential regulatory role of AQP2 in human endometrium [17]. In that study, they showed that the highest expression of AQP2 was observed in the late proliferative and mid-secretory phases, but the level was lowest in the early proliferative and late secretory phases [17]. We could not find AQP2 expression in endometrioid carcinoma in the present study. Molecular mechanisms that downregulate AQP2 expression in endometrioid carcinoma remains to be seen.

The limitation of this study was that only a retrospective immunohistochemistry analysis was performed. Although we believe that the semi-quantitative analysis using immunohistochemistry has significance, quantitative analysis should be performed for a more reliable evaluation.

Nonetheless, the present results indicate that in endometrioid carcinomas, AQP3 expression is involved in the growth of tumors in the early stage, and that loss of AQP3 expression may lead to a poor prognosis. Thus, AQP3 possesses the potential to serve as a predictor of prognosis, necessitating further investigation to reveal the biological mechanism of AQP3 in endometrioid carcinoma.

Conclusions

Among endometrioid carcinoma patients, AQP3 expression was correlated with earlier clinical stage and lower histological grades. In addition, the AQP3 positive group showed better prognosis than the AQP3 negative group in the log-rank test. Further studies are required to utilize AQP3 in evaluating the prognosis of uterine endometrioid carcinomas.

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