Oncology and Translational Medicine
DOI 10.1007/s10330-017-0233-3

October 2017, Vol. 3, No. 5, P197–P202

ORIGINAL ARTICLE

Papillary serous carcinoma of the uterine cervix: a clinicopathological analysis of 4 cases and a literature review

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Abstract

Objective To investigate the clinicopathological characteristics and clinical treatment outcomes of patients with papillary serous carcinoma of the uterine cervix (PSCC).

Methods In this study, 4 patients with histologically confirmed papillary serous carcinoma of the uterine cervix were retrospectively investigated. Pap smears, human papillomavirus (HPV) screening, tumor marker status, biopsy analysis, and relevant imaging examinations were conducted for the confirmation of primary diagnosis and recurrence. Patients underwent surgery, chemotherapy, or radiotherapy, and survival were the main endpoint.

Results The 4 patients were diagnosed with IB1, IB1, IIA, or IIIB disease. Two patients (2/4) presented with recurrence within 18 months after primary therapy. Compared with chemotherapy alone (progression-free survival (PFS): 11 months), radiotherapy combined with adjuvant chemotherapy showed favorable PFS rates (PFS: 20, 36, 13 months in 3 cases), although valid statistical analysis was not feasible because of the small sample size. The 5-year survival rate was 0%, and the 3-year survival rate was 75%. Our data, in agreement with the literature evidence, showed that the number of moderate-risk and high-risk factors in patients diagnosed with PSCC at an early stage was higher than that in patients diagnosed with common adenocarcinoma/squamous carcinoma of the uterine cervix.

Conclusion PSCC has a poor clinical prognosis, and compared with chemotherapy alone, radiotherapy combined with adjuvant chemotherapy may lead to improved PFS.

Key words: papillary serous carcinoma of uterine cervix (PSCC); clinicopathological features; prognosis analysis

Received: 16 June 2017
Revised: 23 August 2017
Accepted: 27 September 2017

Papillary serous carcinoma commonly arises in the ovary, fallopian tube, or the peritoneum and is a rare pathological variant of cervical adenocarcinoma [1]. Papillary serous carcinoma of the uterine cervix (PSCC) is usually mixed with other types of adenocarcinomas and is characterized by its aggressive nature and poor sensitivity to radiotherapy and chemotherapy [2]. The literature pertaining to PSCC comprises predominantly of case reports, and the largest study published has been by Zhou, who described the clinicopathological features of 17 patients diagnosed with PSCC in Canada in 1998 [3]. Only three PSCC cases of Chinese have been reported [5]. In our study, we analyzed the pathological features and assessed the clinical prognosis of 4 cases of PSCC. We also reviewed published literature pertaining to PSCC, and performed a comparative analysis of outcomes of different treatment regimens.

Materials and methods

Clinical records and pathological evidences of patients with PSCC who visited the National Cancer Center / Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, between January 1, 1999 and June 31, 2016, were collected. This study was approved by the Institutional Review Board of National Cancer Center / Cancer Hospital, Chinese Academy of Medical Sciences. Written consent was obtained from each participant or legal offspring.

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The diagnosis of PSCC conformed to the histological criteria of World Health Organization International Histological Classification of Tumors. At least two pathologists reviewed immunohistochemical data and participated in the diagnosis of papillary serous carcinoma of the uterine cervix. Six patients met the study criteria, but only 4 patients were included in the study because of limited follow-up of 2 patients. The follow-up ended on December 31, 2016.

Comprehensive testing was carried out to exclude the possibility of cervical metastasis originating from the ovaries, the fallopian tubes, or the peritoneum, and to rule out any cervical infiltration extending from a uterine papillary serous carcinoma. The initial examination included Pap smears, a vagino-recto-abdominal examination, human papilloma virus (HPV) screening, tumor marker status assessment (cancer antigen 19-9 (CA19-9), cancer antigen 125 (CA125), and carcinoembryonic antigen (CEA)), a biopsy, and relevant medical imaging examinations (computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography–computed tomography (PET-CT), or ultrasound). On the basis of the disease recurrence status, some or all of the above-mentioned diagnostic techniques were employed to evaluate the therapeutic efficacy, and facilitate decisions regarding further treatment.

Radical hysterectomy is a widely adopted treatment option for patients diagnosed with IA1-IB1 or IIA1 disease. According to the guidelines of the National Comprehensive Cancer Network (NCCN), patients at high risk for recurrence should receive postoperative adjuvant therapy. Accordingly, radical radiotherapy or concurrent radiochemotherapy was recommended for patients diagnosed with stage IB2, IIA2, and ≥ IIB disease in this study.

Results

Clinical features

The clinical stages, pathological features, therapy protocols and recurrence status of patients are shown in Table 1. The median follow-up period was 33.5 months (34 to 45 months) without loss to follow-up. Abnormal vaginal bleeding and watery vaginal discharge were predominant symptoms and were commonly cited as reasons for medical consultation. According to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging system, the clinical stage of the four patients was IB1, IB1, IIA, or IIIB.

Case 1 was a 62 year-old patient with FIGO stage IB1. Tumor progression was observed 11 months after the administration of 7 cycles of chemotherapy. The main clinical symptoms after recurrence were pharyngalgia, trachyphonia, and choking cough. A CT examination revealed neoplasm located in the mediastinum, left lung, and the chest wall. The pathological result of a biopsy of the left lung supported the diagnosis of a poorly differentiated squamous cancer. Because the preliminary pathological analysis showed a low proportion of squamous components, and the X-ray examination results of the lung prior to surgery and chemotherapy were negative, the neoplasm in the lung was determined to be a distant metastasis of the cervical cancer. The patient underwent 3 cycles of chemotherapy (300 mg of paclitaxel plus 500 mg of carboplatin, intravenous, day 1; 300 mg of paclitaxel plus 130 mg of nedaplatin, intravenous, day 1; and 60 mg of doxorubicin hydrochloride plus 130 mg of oxaliplatin, intravenous, day 1). The efficacy of chemotherapy was limited and the regimen was modified at each cycle. With a continual deterioration of his physical condition, the patient was unable to tolerate further treatment and died in June, 2015.

Case 2 was a 50 year-old patient with FIGO stage IIIB disease, who underwent concurrent chemoradiotherapy (CCRT). The prescription dosage (95% planned target volume (PTV)) of external beam radiotherapy was 45 Gy/1.8 Gy/25 f, and the prescription dosage (95% PTV) of vaginal radiotherapy was 40 Gy/8 f. The disease deteriorated with local recurrence 13 months after radiotherapy, and the overall survival was 45 months.

Case 3 was a 55 year-old patient with FIGO stage IB1 disease, who received sequential chemotherapy and radiotherapy (SCRT). The chemotherapy protocol was paclitaxel plus carboplatin (175 mg/m^2 paclitaxel plus carboplatin at an area under the curve of 5, intravenous, day 1). The protocol was repeated every 21 days and the patient received 4 cycles of chemotherapy in total. The prescription dosage (95% PTV) of external radiotherapy was 4500 cGy/180 cGy/25 fractions (f). Twenty months post-SCRT, a metastasis in the pelvic bone was discovered. The patient suffered from pathological fractures, and a reconstruction of the pelvic bone was performed; however, thrombotic complications of lower limbs developed after the surgery. The pathological results of a pelvic bone lesion biopsy confirmed the diagnosis of an adenocarcinomatous metastasis. The overall survival was 41 months.

Case 4 was a 52 year-old patient, and the chief clinical finding was a pelvic mass, 7 cm × 6 cm in size. The patient received simple hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and resection of the pelvic mass at a local hospital. Postoperative pathology indicated PSCC, and the patient visited our hospital for further treatment. Postoperative chemotherapy and radiotherapy were recommended. The chemotherapy regimen was paclitaxel (175 mg/m^2, intravenous, day 1) plus carboplatin (at an area under the

curve of 5, intravenous, day 1). The protocol was repeated every 21 days, and the patient received 4 cycles of chemotherapy in total. Prescription dosage (95% PTV) of external radiotherapy was 4500 cGy/180 cGy/25 f. There was no evidence of recurrence 36 months post-SCRT.

Histological characteristics

The neoplasms of the cervix were categorized as endophytic (2 cases), exophytic (1 case), or ulcerative type (1 case). The pathological type of case 1 was mixed, consisting of moderately or poorly differentiated papillary serous adenocarcinoma (80%), and endometrioid and poorly differentiated squamous carcinoma (20%). The tumor invaded less than half of the intramural cervix, and showed involvement of the lymph-vascular space. The margins of the vagina and parametrial tissues were normal, and there was no evidence of infiltration into the vagina, ovaries, fallopian tubes, or the lymph nodes. The pathological type of the tumors in the remaining three patients was absolutely moderately differentiated papillary serous carcinoma.

Recurrence and survival

Disease recurred in two patients (50%) within 18 months of initial therapy. We observed that the combination of radiotherapy and chemotherapy showed favorable PFS (PFS: 20, 36, 13 months in 3 patients) compared with chemotherapy alone (PFS: 11 months); however, statistical analysis was not feasible because of the small sample size. For the first 3 patients, the 5-year survival rate was 0% and 3-year survival rate was 66.67%.

Tumor markers

The CA19-9, CA125, SCC, and CEA expression status was periodically tested to evaluate the disease status, treatment outcomes, recurrence, and prognosis. Case 1 with a mixed pathological pattern displayed normal levels of CA125 at first visit. The levels of CA125 were normal until the appearance of the lung neoplasm. Sustained high levels of CA125 were observed for over four months, and the peak level of 350.3 U/mL was detected at one month after the last chemotherapy cycle. After recurrence, chemotherapy showed poor efficacy, and the patient refused to continue treatment after 3 cycles with different protocols. Even without further therapy, the levels of CA125 gradually returned normal within two months after the peak. Pathological results of the biopsy of the lung lesion revealed a poorly differentiated squamous carcinoma, accompanied by high levels of CA125, although no squamous cell carcinoma antigen (SCC) elevation was observed. The decrease in CA125 levels could not be explained, and was probably not due to chemotherapy. Without effective chemotherapy, the status of this patient continued to deteriorate, and the overall survival time was 45 months.

A slightly higher level of CA125 (41.1 U/mL) was detected at preliminary diagnosis in case 3. After surgery, the CA125 levels decreased and continued to be normal for 20 months even with a confirmed bone metastasis. Tumor marker status (CA125, CA19-9 and CEA) during a further 2½ year-period was available as part of 21 records, and showed that the patient displayed normal levels of these biomarkers. The accumulated number of records was 17 and 13 for case 1 and case 2, respectively, and no abnormal levels of CA125, CEA, and CA 19-9 were recorded.

IHC

Three samples were tested by immunohistochemical analysis. Two among the 3 cases were P53-positive, and the P53 condition in one patient was not clear. The estrogen receptor (ER) and progesterone receptor (PR) status was negative in all 3 cases.

Discussion

Cervical adenocarcinoma mainly includes mucinous, serous, endometrioid, clear cell, and transitional cell subtypes [6]. As a rare variant of cervical adenocarcinoma, the incidence of papillary serous carcinoma is very low, and only 52 cases of PSCC have been reported since 1992. Even though the biological behavior of PSCC is distinct, treatment decisions for PSCC are based on the guidelines for cervical adenocarcinoma, as PSCC has not been well studied [4–17].

The largest study of PSCC was conducted by Zhou et al, who described 17 cases of PSCC in 1997. A bimodal age distribution was described by Zhou, with the first peak occurring before the age of 40 years and the second peak occurring after the age of 65 years [3]. In our study, the age of the patients ranged from 50 to 62 years, in agreement with prior studies conducted in Japan and Ireland (reported peak range: 50 to 65 years). The reported peak age was lower in Canada and America, and the diagnosis in published case studies was familial papillary serous carcinoma (the genetic background of these patients was not disclosed). Because of the low incidence of the disease, the prognostic divergence of the two groups in the bimodal distribution has not been well studied.

Costa *et al* found serous differentiation to be a poor prognostic predictor in stage I and II adenocarcinomas and adenosquamous carcinoma. In this study, 4 of 6 patients diagnosed with PSCC (5 stage I patients and 1 stage II patient) experienced distant metastasis [18]. Table 2 lists detailed information about FIGO stages, surgeries, and prognosis reported in relevant literature published since 1992, that was retrieved from the PubMed online database. Combined with the clinical data from our study,

the proportion of stage IA, IB, II, III, and IV patients was 3.03%, 66.67%, 15.15%, 9.09%, and 6.06%, respectively. Since PSCC is characteristically aggressive, several patients presented with extensive metastases at first visit. Endophytic growth pattern a common feature, which made early screening and diagnosis difficult.

Ayhan *et al* analyzed the prognosis of FIGO stage IB adenocarcinoma and squamous cell carcinoma and reported that CCRT was indicated in 5.5% of squamous cell carcinoma patients and in 11.9% of adenocarcinoma patients. Simple postoperative chemotherapy was performed in 26.0% and 25.4% of patients with squamous cell carcinoma and adenocarcinoma, respectively [19]. According to the clinical information presented in tables 1 and 2, 80% (12 in 15) of patients diagnosed with IB1 stage PSCC received radiotherapy after surgery due to the presence of high-risk factors (85%, 17 in 20). The proportion of moderate-risk and high-risk factors in IB1 patients diagnosed with PSCC was higher than that in patients diagnosed with common adenocarcinoma/ squamous carcinoma of the uterine cervix [20]. The presence of these risk factors was associated with aggressive biological behavior and poor prognosis of PSCC.

In a study by Eifel *et al*, multivariate analysis revealed that adenocarcinoma showed poorer prognosis than squamous carcinoma, and the overall 5-year survival rates of patients with squamous cell carcinoma (SCC) and adenocarcinoma (AC) were 81% and 72%, respectively. Compared with squamous carcinoma, adenocarcinoma was regarded as an independent risk factor for disease recurrence in patients with stage IB carcinoma [20]. In our study, both patients with stage IB1 disease died within five years of receiving chemotherapy or sequential chemotherapy and radiotherapy. Kaplan *et al* have described the case of a patient with IB1 disease who developed extensive peritoneal metastasis within 24 months after laparoscopy-assisted vaginal hysterectomy (LAVH) and SCRT [6]. In a study of 9 IB1 patients by Zhou *et al*, three patients died in 5 years and one patient developed malignant ascites 24 months after surgery. The clinical prognosis of PSCC was poorer than that of common adenocarcinoma.

Costa *et al* [18] have reported poor clinical outcomes in stage I and II patients with serous differentiation of adenocarcinoma, and Zhou *et al* have proposed that differences in treatment regimens may have led to such outcomes. In the study by Costa *et al*, patients received simple hysterectomy, while most of the patients with unfavorable prognostic factors received hysterectomy and radiotherapy in the study by Zhou *et al* [3]. In spite of receiving standard surgery and postoperative adjuvant therapy, Zhou *et al* reported that 4 in 12 cases with stage IB disease showed extensive metastasis and died within five years. It was interesting to note that though 8 cases were classified as "no evidence of metastasis or recurrence", the follow-up time was 6 months to 11 years, and individual follow-up periods were not delineated for patients. It was possible that recurrences or metastases occurring post-study in patients with a short follow-up period could not be reported, leading to an observation of an overall better prognosis. In our study, two patients with stage IB disease received radical hysterectomy and postoperative adjuvant therapy (chemotherapy or SCRT), and both patients developed distant metastases in two years, and died within four years. As shown in Tables 1 and 2, clinical findings in our study included depression, and shorter time-to-recurrence was noted in patients with multiple risk factors. The prognosis of patients with advanced stage III and IV disease was not poor. One patient survived for more than 5 years, and died 64 months after the initial diagnosis. All other patients showed either early recurrence (within 6 months) or limited survival (< 60 months), in spite of receiving adjuvant therapy and/or debulking surgery.

In contrast to our findings, most prior studies have reported a positive CA125 marker status in PSCC patients, and high CA125 levels usually implied a poor clinical prognosis. Zhou *et al* reported that 75% patients (9 in 12) were CA125-positive [3]. Togami and group, in 2015, described the immunohistochemical profile of several patients with serous adenocarcinoma of uterine cervix (SACC), including some with PSCC (the exact number of PSCC cases was not mentioned). A strongly positive CA125 status was detected in 92% (11/12) of SACC, with similar expression patterns observed in ovarian serous adenocarcinoma (100%), uterine papillary serous carcinoma (90%), and mucinous endocervical adenocarcinoma (90%) [4]. However, these data by Togami *et al* cannot completely reflect the immune profile of PSCC, as the tumors studied were histologically heterogeneous. In our study, CA125 showed poor sensitivity and specificity as a tumor marker, and the correlation between CA125 and prognosis was not clear. The limited sample number and differences in target population were considered as possible reasons for this observation. Serous carcinomas of the ovaries usually display mutations in genes such as *BRCA1/BRCA2*, and *HER-2* amplification has also been reported in uterine papillary serous cancer [21]. Genetic profiling of PSCC has not been performed till date, and such data might provide insight into the aggressive biological behavior of PSCC, paving the way for the development of new targeted drugs to improve clinical prognosis.

Our data demonstrated improved recurrence-free survival advantage in patients who received postoperative adjuvant therapy (PFS: 20 months, 36 months, and 13 months in 3 patients) than in those who received chemotherapy alone (PFS: 11 months in 1 patient),

Table 1 Pathological features and clinical treatment details of 4 cases with papillary serous carcinoma of the uterine cervix (PSCC)

Age (years)	FIGO stages	Pathological pattern	Grade	CI	VI	PI	LVSI	LNI	Operation	IHC	Adjuvant therapy	Recurrent site	Recurrent pathological type	Recurrent interval (months)	Status(OS)
62	IB1	Mixed	1, 2	< 1/2	No	No	YES	No	RH	–	CT	Lung	SC	11	DOD (45)
55	IB1	Pure	2	< 1/2	No	No	No	No	RH	P53 (+) ER (–)	SCRT	Pelvic Bone	AC AC	20	DOD (41)
50	IIIB	Pure	2	–	Yes	–	–	–	No	ER (–) ER (–) PR (–)	CCRT	Pelvic cavity	SAC	13	DOD (34)
52	IIA1	Pure	2	2/2	No	No	No	No	SH	P53 (+) ER (–) PR (–) Ki (> 50% +)	SCRT	No	–	36	NED (36)

PSCC, papillary serous carcinoma of the uterine cervix; CI, cervical invasion (depth ratio); VI, vaginal invasion; PI, parametrial invasion; LVSI, lymph-vascular space involvement; LNI, lymph node invasion; IHC, immunohistochemical analysis; SAC, serous adenocarcinoma; AC, adenocarcinoma; SC, squamous cancer; CT, chemotherapy; SCRT, sequential chemotherapy and radiotherapy; CCRT, concurrent radiochemotherapy; RH, radical hysterectomy; SH, simple hysterectomy; DOD, dead of disease; NER, no evidence of recurrence; OS, overall survival

Table 2 Review of published articles and summation of relevant clinical features and prognosis

	Age (years)	FIGO	Grade	Risk factors	CA125 (U/mL)	Therapy	Recurrence Site	Status(month)	Country
Power *et al* 2016	64	IIIB	2	M(3)H(3)	2580	DO + ICT	No(24)	DOD(64)	Ireland
	59	IVB	2	–	242	DO + CT	Bone(0)	DOD(10)	
W-W Tang *et al* 2013	53	IIA		M(3)H(1)	3460	RH + CCRT	LN(n)(2)	DOD(17)	China
Ueda *et al* 2012	56	IVB	–	–	2480	CT	LN(n)(0)	AWD(6)	Japan
Batistatou *et al* 2000	63	IB1	–	–	–	RH + CRT	Lung(36)	DOD(36)	
Kaplan *et al* 1998	39	IB1	–	M(2)	Normal	LAVH + SCRT	Peritoneum(24)	AWD(24)	America
Zhou *et al* 1998	–	IB1(9)	–	–	40–10000 (4 in 9)	RH + RT(5), RH + CRH(1) RH(2), VH + RT(1)	EM(3) < 60 MA(1)(24)	DOD(3) < 60	
		IB2(3)	–	–		CRT(3)		DOD(2) < 60	
		II(2)	–	–		RRT(2)	EM(2) < 60	DOD(1) < 60	
		III(1)	–	–		RRT(1)	EM(1) < 60		
Rose *et al* 1993	30	IB	–	–	–	RH	No(35)	NED(35)	
		IB	–	–		RT	Uterosacral ligament(X)		
Shintaku *et al* 1993	66	IIA	–	M(2)H(1)	695	RH + RT	Peritoneum(8)	DOD(8)	Japan
Gilks *et al* 1992	32	IB1	3	H(1)	–	RH + RT	No	NED(60)	Canada
	33	IB1	3	H(1)	–	RT + cervicectomy	No	NED(60)	

Moderate risk factors: LVSI, deep stromal Invasion, primary tumor size; High risk factors: positive margins, parametrial invasion, lymph nodes infiltration; RH, radical hysterectomy; DO, debulking operation; VH, vaginal hysterectomy; ICT, intermittent chemotherapy; CT, chemotherapy; RRT, radical radiotherapy; SCRT, sequential chemotherapy and radiotherapy; CCRT, concurrent chemoradiotherapy; LN(n), Lymph node(neck); EM, extensive metastasis; MA, malignant ascites; DOD, dead of disease; NER, no evidence of recurrence; AWD, alive with disease; LAVH: laparoscopic-assisted vaginal hysterectomy, PSCC was occasionally discovered after operation; X, unknown

although the statistical significance of these data could not be established.

Conclusions

As a variant of cervical adenocarcinoma, radical hysterectomy is recommended as the primary therapy protocol for PSCC. Our data indicate that a combination of chemotherapy and radiotherapy may lead to more favorable survival outcomes, although further studies with larger sample sizes are needed to confirm our results. A combination of chemotherapy and radiotherapy may address the biologically distinct nature of PSCC and may be a superior treatment option. More endeavors should be focused on studying the genetic background pertaining to PSCC (such as HER-2 amplification status), to evaluate the value of targeted therapy.

Ethics approval and consent to participate

This study was approved by Institutional Review Board of the Cancer Hospital, Chinese Academy of Medical Sciences, and all patients provided informed consent.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Li Ge, Lingying Wu, Hongwen Yao, Rong Zhang, and Xiaoguang Li contributed to the acquisition of clinical data. Li Ge was a major contributor in writing the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

We thank workers in Archive Department for the accumulation of records.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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DOI 10.1007/s10330-017-0233-3
Cite this article as: Ge L, Yao HW, Zhang R,*et al*. Papillary serous carcinoma of the uterine cervix: a clinicopathological analysis of 4 cases and a literature review. Oncol Transl Med, 2017, 3: 197–202.