World J Clin Cases 2020 November 6; 8(21): 5070-5495





#### **Contents**

Semimonthly Volume 8 Number 21 November 6, 2020

#### **REVIEW**

5070 Strategies and challenges in the treatment of chronic venous leg ulcers

Ren SY, Liu YS, Zhu GJ, Liu M, Shi SH, Ren XD, Hao YG, Gao RD

5086 Peripheral nerve tumors of the hand: Clinical features, diagnosis, and treatment

Zhou HY, Jiang S, Ma FX, Lu H

#### **MINIREVIEWS**

5099 Treatment strategies for gastric cancer during the COVID-19 pandemic

Kang WZ, Zhong YX, Ma FH, Liu H, Ma S, Li Y, Hu HT, Li WK, Tian YT

#### **ORIGINAL ARTICLE**

#### **Retrospective Cohort Study**

5104 Oncological impact of different distal ureter managements during radical nephroureterectomy for primary upper urinary tract urothelial carcinoma

Lai SC, Wu PJ, Liu JY, Seery S, Liu SJ, Long XB, Liu M, Wang JY

5116 Clinical characteristics and survival of patients with normal-sized ovarian carcinoma syndrome: Retrospective analysis of a single institution 10-year experiment

Yu N, Li X, Yang B, Chen J, Wu MF, Wei JC, Li KZ

#### **Retrospective Study**

5128 Assessment of load-sharing thoracolumbar injury: A modified scoring system

Su QH, Li YC, Zhang Y, Tan J, Cheng B

5139 Accuracy of endoscopic ultrasound-guided needle aspiration specimens for molecular diagnosis of nonsmall-cell lung carcinoma

Su W, Tian XD, Liu P, Zhou DJ, Cao FL

5149 Application of hybrid operating rooms for clipping large or giant intracranial carotid-ophthalmic aneurysms

Zhang N, Xin WQ

5159 Magnetic resonance imaging findings of carcinoma arising from anal fistula: A retrospective study in a single institution

Zhu X, Zhu TS, Ye DD, Liu SW

5172 Efficacy and safety of S-1 maintenance therapy in advanced non-small-cell lung cancer patients

Cheng XW, Leng WH, Mu CL

#### Contents

#### Semimonthly Volume 8 Number 21 November 6, 2020

- 5180 Analysis of 234 cases of colorectal polyps treated by endoscopic mucosal resection Yu L, Li N, Zhang XM, Wang T, Chen W
- 5188 Epidemiological and clinical characteristics of fifty-six cases of COVID-19 in Liaoning Province, China Wang JB, Wang HT, Wang LS, Li LP, Xv J, Xv C, Li XH, Wu YH, Liu HY, Li BJ, Yu H, Tian X, Zhang ZY, Wang Y, Zhao R, Liu JY, Wang W, Gu Y
- 5203 Radiomics model for distinguishing tuberculosis and lung cancer on computed tomography scans Cui EN, Yu T, Shang SJ, Wang XY, Jin YL, Dong Y, Zhao H, Luo YH, Jiang XR
- 5213 Influence of transitional nursing on the compliance behavior and disease knowledge of children with purpura nephritis

Li L, Huang L, Zhang N, Guo CM, Hu YQ

#### **Randomized Controlled Trial**

5221 Wavelet and pain rating index for inhalation anesthesia: A randomized controlled trial Zhang JW, Lv ZG, Kong Y, Han CF, Wang BG

#### **SYSTEMATIC REVIEWS**

5235 Essential phospholipids for nonalcoholic fatty liver disease associated with metabolic syndrome: A systematic review and network meta-analysis

Dajani AI, Popovic B

- 5250 Cardiovascular impact of COVID-19 with a focus on children: A systematic review Rodriguez-Gonzalez M, Castellano-Martinez A, Cascales-Poyatos HM, Perez-Reviriego AA
- 5284 Anterior bone loss after cervical disc replacement: A systematic review Wang XF, Meng Y, Liu H, Hong Y, Wang BY

#### **CASE REPORT**

5296 Submicroscopic 11p13 deletion including the elongator acetyltransferase complex subunit 4 gene in a girl with language failure, intellectual disability and congenital malformations: A case report

Toral-Lopez J, González Huerta LM, Messina-Baas O, Cuevas-Covarrubias SA

5304 Pancreatic panniculitis and elevated serum lipase in metastasized acinar cell carcinoma of the pancreas: A case report and review of literature

Miksch RC, Schiergens TS, Weniger M, Ilmer M, Kazmierczak PM, Guba MO, Angele MK, Werner J, D'Haese JG

5313 Diffusion-weighted imaging might be useful for reactive lymphoid hyperplasia diagnosis of the liver: A case report

Tanaka T, Saito K, Yunaiyama D, Matsubayashi J, Nagakawa Y, Tanigawa M, Nagao T

5320 Nafamostat mesylate-induced hyperkalemia in critically ill patients with COVID-19: Four case reports Okajima M, Takahashi Y, Kaji T, Ogawa N, Mouri H

П

#### Contents

#### Semimonthly Volume 8 Number 21 November 6, 2020

5326 Arthroscopic treatment of iliopsoas tendinitis after total hip arthroplasty with acetabular cup malposition: Two case reports

Won H, Kim KH, Jung JW, Kim SY, Baek SH

5334 Successful treatment of a high-risk nonseminomatous germ cell tumor using etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine: A case report

Yun J, Lee SW, Lim SH, Kim SH, Kim CK, Park SK

5341 Donepezil-related inadequate neuromuscular blockade during laparoscopic surgery: A case report Jang EA, Kim TY, Jung EG, Jeong S, Bae HB, Lee S

5347 Successful treatment of relapsed acute promyelocytic leukemia with arsenic trioxide in a hemodialysisdependent patient: A case report

Lee HJ, Park SG

5353 Treatment of afferent loop syndrome using fluoroscopic-guided nasointestinal tube placement: Two case

Hu HT, Ma FH, Wu ZM, Qi XH, Zhong YX, Xie YB, Tian YT

- 5361 Emergency surgical workflow and experience of suspected cases of COVID-19: A case report Wu D, Xie TY, Sun XH, Wang XX
- 5371 Seven-year follow-up of the nonsurgical expansion of maxillary and mandibular arches in a young adult: A case report

Yu TT, Li J, Liu DW

5380 Pancreatic cancer with ovarian metastases: A case report and review of the literature Wang SD, Zhu L, Wu HW, Dai MH, Zhao YP

5389 Early ultrasound diagnosis of conjoined twins at eight weeks of pregnancy: A case report

Liang XW, Cai YY, Yang YZ, Chen ZY

5394 Supermicroscopy and arterio-venolization for digit replantation in young children after traumatic amputation: Two case reports

Chen Y, Wang ZM, Yao JH

5401 Candidal periprosthetic joint infection after primary total knee arthroplasty combined with ipsilateral intertrochanteric fracture: A case report

Ш

Xin J, Guo QS, Zhang HY, Zhang ZY, Talmy T, Han YZ, Xie Y, Zhong Q, Zhou SR, Li Y

Aspiration pneumonia during general anesthesia induction after esophagectomy: A case report 5409 Tang JX, Wang L, Nian WQ, Tang WY, Xiao JY, Tang XX, Liu HL

5415 Large and unusual presentation of gallbladder adenoma: A case report

Cao LL, Shan H

5420 Rare narrow QRS tachycardia with atrioventricular dissociation: A case report

Zhu C, Chen MX, Zhou GJ

#### Contents

#### Semimonthly Volume 8 Number 21 November 6, 2020

5426 Synchronous parathyroid adenoma, papillary thyroid carcinoma and thyroid adenoma in pregnancy: A case report

Li Q, Xu XZ, Shi JH

5432 Pseudohyperkalemia caused by essential thrombocythemia in a patient with chronic renal failure: A case report

Guo Y, Li HC

5439 Acute leukemic phase of anaplastic lymphoma kinase-anaplastic large cell lymphoma: A case report and review of the literature

Zhang HF, Guo Y

5446 Chinese patient with cerebrotendinous xanthomatosis confirmed by genetic testing: A case report and literature review

Cao LX, Yang M, Liu Y, Long WY, Zhao GH

5457 Incomplete Kawasaki disease complicated with acute abdomen: A case report

Wang T, Wang C, Zhou KY, Wang XQ, Hu N, Hua YM

5467 Fanconi-Bickel syndrome in an infant with cytomegalovirus infection: A case report and review of the literature

Xiong LJ, Jiang ML, Du LN, Yuan L, Xie XL

5474 Benign symmetric lipomatosis (Madelung's disease) with concomitant incarcerated femoral hernia: A case report

Li B, Rang ZX, Weng JC, Xiong GZ, Dai XP

5480 Potential protection of indocyanine green on parathyroid gland function during near-infrared laparoscopic-assisted thyroidectomy: A case report and literature review

Peng SJ, Yang P, Dong YM, Yang L, Yang ZY, Hu XE, Bao GQ

5487 New treatment of patellar instability after total knee arthroplasty: A case report and review of literature Shen XY, Zuo JL, Gao JP, Liu T, Xiao JL, Qin YG

#### **CORRECTION**

5494 Erratum: Author's Affiliation Correction. Type II human epidermal growth factor receptor heterogeneity is a poor prognosticator for type II human epidermal growth factor receptor positive gastric cancer (World J Clin Cases 2019; Aug 6; 7 (15): 1964-1977)

ΙX

Kaito A, Kuwata T, Tokunaga M, Shitara K, Sato R, Akimoto T, Kinoshita T

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#### **RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Yan-Xia Xing Production Department Director: Yun-Xiaojian Wu; Editorial Office Director: Jin-Lei Wang.

#### **NAME OF JOURNAL**

World Journal of Clinical Cases

#### **ISSN**

ISSN 2307-8960 (online)

#### **LAUNCH DATE**

April 16, 2013

#### **FREQUENCY**

Semimonthly

#### **EDITORS-IN-CHIEF**

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

#### **EDITORIAL BOARD MEMBERS**

https://www.wjgnet.com/2307-8960/editorialboard.htm

#### **PUBLICATION DATE**

November 6, 2020

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https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/GerInfo/287

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https://www.wignet.com/bpg/gerinfo/240

#### **PUBLICATION ETHICS**

https://www.wignet.com/bpg/GerInfo/288

#### **PUBLICATION MISCONDUCT**

https://www.wjgnet.com/bpg/gerinfo/208

#### ARTICLE PROCESSING CHARGE

https://www.wjgnet.com/bpg/gerinfo/242

#### STEPS FOR SUBMITTING MANUSCRIPTS

https://www.wjgnet.com/bpg/GerInfo/239

#### **ONLINE SUBMISSION**

https://www.f6publishing.com

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World J Clin Cases 2020 November 6; 8(21): 5116-5127

DOI: 10.12998/wjcc.v8.i21.5116 ISSN 2307-8960 (online)

ORIGINAL ARTICLE

#### **Retrospective Cohort Study**

## Clinical characteristics and survival of patients with normal-sized ovarian carcinoma syndrome: Retrospective analysis of a single institution 10-year experiment

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Author contributions: Yu N and Li KZ contributed to protocol/project development, data collection and management, data analysis, and manuscript writing/editing; Li X, Chen J, and Wei JC contributed to protocol/project development and manuscript writing/editing; Yang B contributed to data collection and management and manuscript writing/editing; Wu MF contributed the manuscript writing/editing.

Supported by National Key Technology R&D Program of China, No. 2019YFC1005200, and No. 2019YFC1005202; National Natural Science Foundation of China, No. 81501530, No. 81802896, and No. 81701530; Natural Science Foundation of Hubei Province, No. 2017CFB800; and Hubei Province Health and Family Planning Scientific Research Project, No. WJ2017Z013, and No. WJ2019M127.

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#### **Abstract**

#### **BACKGROUND**

Normal size ovarian cancer syndrome (NOCS) is a challenge for clinicians regarding timely diagnosis and management due to atypical clinical and imaging features. It is extremely rare with only a few cases reported in the literature. More data are needed to clarify its biological behavior and compare the differences with abnormal size ovarian cancer.

#### **AIM**

To assess the clinical and pathological features of NOCS patients treated in our institution in the last 10 years and to explore risk factors for relapse and survival.

#### **METHODS**

Patients who were pathologically diagnosed with NOCS between 2008 and 2018 were included. Papillary serous ovarian carcinoma (PSOC) patients were initially randomly recruited as the control group. Demographics, tumor characteristics, treatment procedures, and clinical follow-up were retrospectively collected. Risk factors for progression-free survival and overall survival were assessed.

A total of 110 NOCS patients were included; 80 (72.7%) had primary adnexal carcinoma, two (1.8%) had mesotheliomas, 18 (16.4%) had extraovarian peritoneal serous papillary carcinoma, and eight (7.3%) had metastatic tumors. Carbohydrate antigen (CA)125 and ascites quantity were lower in the NOCS cohort than in the PSOC group. The only statistically significant risk factors for worse overall survival (P < 0.05) were the levels of CA199 and having fewer than six chemotherapy cycles. The 1-year, 3-year, and 5-year survival rates were 75.5%, 27.7%, and 13.8%, respectively.

#### Institutional review board

statement: The Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology approved this study protocol.

Informed consent statement: In accordance with the rules of the ethics committee, this study applied for exemption from informed consent.

Conflict-of-interest statement: None declared.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at tjkeke@126.com.

STROBE statement: The authors have read the STROBE Statement - checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Manuscript source: Unsolicited manuscript

Specialty type: Obstetrics and gynecology

Country/Territory of origin: China

#### Peer-review report's scientific quality classification

Grade A (Excellent): 0 Grade B (Very good): B Grade C (Good): C Grade D (Fair): 0 Grade E (Poor): 0

#### **CONCLUSION**

The clinical symptoms of the NOCS group are atypical, and the misdiagnosis rate is high. Ascites cytology and laparoscopic exploration are valuable in the early diagnosis to avoid a misdiagnosis. The level of CA199 is the most important predictor of overall survival, and more than six cycles of chemotherapy contributes to the increased survival rates of NOCS patients.

**Key Words:** Normal-sized ovarian carcinoma syndrome; Ovarian cancer; Survival; Prognostic factors; Epithelial ovarian carcinomas; Carbohydrate antigen 125

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**Core Tip:** Normal size ovarian cancer syndrome is a rare and aggressive disease with poor prognosis. Carbohydrate antigen 199 may be an effective marker to monitor disease progression, and adequate adjuvant chemotherapy should be recommended for all patients following surgery, as patients with more than six cycles of chemotherapy have increased survival rates.

Citation: Yu N, Li X, Yang B, Chen J, Wu MF, Wei JC, Li KZ. Clinical characteristics and survival of patients with normal-sized ovarian carcinoma syndrome: Retrospective analysis of a single institution 10-year experiment. World J Clin Cases 2020; 8(21): 5116-5127

URL: https://www.wjgnet.com/2307-8960/full/v8/i21/5116.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v8.i21.5116

#### INTRODUCTION

Epithelial ovarian carcinomas, which originate from the surface epithelium of the ovary, are usually found as a large ovarian mass at diagnosis[1]. However, ovaries of normal size with disseminated peritoneal spread are clinically rare. Feuer et al<sup>[2]</sup> in 1989 first proposed the original diagnostic criteria of "normal-sized ovary carcinoma syndrome (NOCS)" as a diffuse metastatic malignant disease of the abdominal cavity of the female, with normal-sized ovaries and no site of origin assigned definitively by preoperative or intraoperative evaluation.

The early clinical manifestations of NOCS are not obvious and easy to be ignored, and the late clinical manifestations are not representative and usually include signs and symptoms like bloating and abdominal pain, which reflect a diffuse progressive abdominal condition caused by ascites[3]. Threshold for surgical exploration of an ovarian mass is currently set as a mass diameter greater than 5 cm; however, the pelvic masses of NOCS patients are less than 5 cm. Because NOCS patients have small masses and mild accompanying symptoms, which often are easily overlooked by clinicians, most patients have elevated tumor markers and massive ascites at the time of diagnosis, with the disease having reached advanced stages when treatment is initiated. Therefore, the definite diagnosis of benign ovarian lesions and tumor-like lesions and timely surgical exploration are extremely important<sup>[4]</sup>. However, it is difficult to find primary lesions by imaging examination due to its mass size (less than 5 cm × 5 cm)<sup>[5]</sup>. It was reported that computer tomography (CT) and magnetic resonance imaging showed normal-appearing ovaries, ascites, peritoneal thickening, and mesenteric or omental involvement, which was atypical [6-9]. A recent study has demonstrated that positron emission tomography/CT (PET/CT) has a relatively high detectability of ovarian cancer and other abdominal primary cancers. PET/CT may be able to discern the site of origin, but it is expensive and not widely used[6,7]. NOCS is difficult to diagnose clinically because of its atypical clinical manifestations and imaging examination, and the misdiagnosis rate is very high. It was previously reported to be 38.2%-100%[5], which makes clinical diagnosis and selection of effective treatment very difficult[10]. Therefore, early diagnosis and timely treatment are of utmost importance to guarantee the life safety of NOCS patients, which is an urgent problem to be solved.

Primary ovarian carcinoma usually exhibits biological behavior; its growth is local at the primary lesion at first, then metastasizing to distant sites. The histology of Received: June 28, 2020 Peer-review started: June 28, 2020 First decision: August 8, 2020 Revised: August 16, 2020 Accepted: October 1, 2020 Article in press: October 1, 2020 Published online: November 6,

P-Reviewer: Vetvicka V S-Editor: Wang JL L-Editor: Filipodia P-Editor: Li JH



2020

NOCS was reported to be the same as common epithelial ovarian cancer with variable degrees of differentiation, but it has a great tendency to spread externally with no local increase<sup>[3,11]</sup>. What is the difference between the development, occurrence, and prognosis of NOCS and the abnormal size ovarian carcinoma? As NOCS is rare, studies are scarce and have relatively small sample sizes and/or short follow-up periods. Furthermore, because of its low incidence, treatment is temporarily referred to ordinary ovarian cancer, but its clinical characteristics and prognosis and the differences with abnormal size ovarian cancer are not clear. Therefore, although NOCS has been named for nearly 30 years, its biological behavior still needs evidence-based medical data for confirmation.

Therefore, we presented a retrospective review of all cases of NOCS in our medical center. Our aim was to describe the presentation and management of this rare disease and to identify important prognostic features in this cohort, in order for clinicians to achieve early accurate diagnosis and treatment for such patients in the clinic.

#### MATERIALS AND METHODS

#### Selection of patients

Between 2008 and 2018, 110 patients were diagnosed with NOCS at our institution. The Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology approved this study protocol. In accordance with the rules of the ethics committee, this study applied for exemption from informed consent. The histological criteria of NOCS, which was modified from the criteria of Hata[5], are as follows: First, there are extensive abdominal tumors and bilateral ovaries of normal size, the surface with or without vegetation by laparotomy or transventral operation; Second, postoperative pathological examination of the ovaries or salpinx as primary carcinoma or metastasis of other organs; Third, no other primary lesions were found by preoperative imaging and surgical exploration; Fourth, no ovarian disease patient received chemotherapy or radiotherapy before surgery nor had ovarian surgery performed recently.

As a control for comparison, a total of 152 papillary serous ovarian carcinoma (PSOC) patients were recruited between 2008 and 2018 according to the following criteria: (1) There are abdominal tumors or unilateral or bilateral ovarian masses more than 5 cm before surgery; (2) Postoperative pathological examination of the ovaries as primary papillary serous ovarian carcinoma; (3) Postoperative clinic stage II to IV; and (4) No ovarian disease received chemotherapy or radiotherapy before surgery nor had ovarian surgery performed recently.

#### Clinical characteristics

The collected clinical data included: Age, parity, symptoms, amount of ascites, preoperative carbohydrate antigen 125 (CA125) and CA199 (U/mL), surgical stage, surgery method, type of chemotherapy, and date of tumor recurrence or progression. Progression-free survival was defined as the number of months in which there was no evidence of disease upon pelvic examination and imaging examination and during which the CA125 levels had also become normal. The overall survival time was measured in months from the time of diagnosis to the date of the last follow-up or death.

#### Pathological analysis

All the surgical pathology slides were reviewed by two gynecologic pathologists. Tumors were reclassified according to the World Health Organization classification, and grading was conducted using the Universal Grading System by Silverberg[12,13]. The same grading system was applied to both ovarian and extraovarian peritoneal tumors.

#### Statistical analysis

Descriptive summary statistics were used to evaluate the demographics. Statistical analyses of the frequency data and continuous variables were performed using Fisher's exact test, Kaplan-Meier method, and Cox regression method. A P-value of less than 0.05 was considered significant. SPSS 22.0 (SPSS Inc., Armonk, NY, United States) was used for the statistical analyses.

#### **RESULTS**

#### Patient characteristics

The clinical characteristics of patients with NOCS are summarized in Table 1. There was no significant difference in mean age at diagnosis, median menopause times, preoperative CA199 values, and positive rate of ascites cytology between the NOCS and PSOC groups. The presenting symptoms were most commonly abdominal distension (63.6%) or abdominal pain (18.2%) in the NOCS group. However, only five women (4.5%) experienced abdominal masses in the NOCS group (mass size was less than 5 cm). Of all patients in the NOCS group, 15 patients (15.6%) were asymptomatic and diagnosed during routine gynecological examination, imaging procedures, or from high levels of CA125. In the PSOC group, the proportion of abdominal masses of patients was higher (35.5% vs 4.5%, P < 0.05), whereas those with abdominal distension and abdominal pain were fewer (58.6% vs 81.8%, P < 0.05). The preoperative CA125 values and the volume of ascites in the NOCS group were significantly lower than that in PSOC patients (1318.04 U/mL vs 1863.38 U/mL; 1658.63 mL vs 2302.24 mL, P < 0.05). In the NOCS group, 82 (74.5%) had stage III, and 28 (25.5%) had stage IV diseases.

#### Tumor pathological characteristics

Tumor pathological characteristics are reported in Table 2, and pathological hematoxylin-eosin staining images are shown in Figure 1. NOCS was surgically and histologically reconfirmed in 110 patients. A total of 80 patients (72.7%) had primary adnexal carcinoma (65 cases of ovarian carcinoma, nine cases of salpinx carcinoma, and six cases of adnexal carcinoma), two patients (1.8%) had malignant peritoneal mesothelioma (MPM), 18 patients (16.4%) had extraovarian peritoneal serous papillary carcinoma (EPSPC), and eight patients (7.3%) had metastasis. We found that there was no significant difference in the mean age at diagnosis, menopausal status, initial symptoms, positive rate of ascites cytology preoperative, the volume of ascites, and stage in four histological subtypes. However, the preoperative CA125 values were not elevated significantly in MPM patients (36.81 U/mL) and metastatic patients (205.40 U/mL) compared to primary adnexal patients (1465.40 U/mL) and EPSPC patients (1308.14 U/mL). The preoperative CA199 values were elevated in EPSPC patients (83.87 U/mL) and metastatic patients (244.63 U/mL).

#### Treatment characteristics

All patients in the NOCS group underwent surgical treatment (Table 3). The majority of the patients underwent complete surgery (55.5%) with residual tumors (60.9%) in the NOCS group, and there was no significant difference between NOCS and PSOC. Sixty-one patients underwent laparoscopy surgery in the NOCS group, which was more than that in the PSOC group. In the NOCS group, adjuvant chemotherapy treatment was given to 89 patients, platinum-based chemotherapy was given to 86 patients (96.6%), nonplatinum-based chemotherapy was given to three patients, including FolFox, and so on. The majority of patients (65.9%) had more than six rounds of chemotherapy.

#### Outcomes and survival analysis

5119

The mean survival period was 29.02 mo (median, 20.00 mo; range, 5-81 mo) in the NOCS group. As of the date of the follow-up, 60 patients (54.5%) were alive, 34 (30.9%) had died of NOCS, and 16 patients were lost to follow-up. In the whole series, the overall 1-, 3-, and 5-year survival rates were 75.5%, 27.7%, and 13.8%, respectively (Table 1). There was no statistically significant difference in survival rate among the primary ovarian group, EPSPC group, and metastatic group. With the exception of the MPM group, the number of patients was too small (Table 2 and Figure 2).

In the univariate Cox regression analysis (Table 4), decreased overall survival was associated with preoperative CA199 values more than 35 and having fewer than six chemotherapy cycles, whereas lower preoperative CA125 value, the volume of ascites, operation method, platinum-based chemotherapy, and residual tumors were associated with a more favorable outcome (but not significantly different). In the multivariate analysis, preoperative CA199 values more than 35 and having had fewer than six chemotherapy cycles were significant risk factors (Table 5). In addition, Kaplan-Meier curves illustrate survival outcomes (Figure 2).

Table 1 Clinical characteristics of the patients with normal size ovarian cancer syndrome and papillary serous ovarian carcinoma, n (%)

Characteristic, patients with data available	NOCS	PSOC	P value
Age in yr	53.76 (110)	52.61(152)	0.400
Menopausal status			0.579
Premenopausal	39 (35.4)	59 (38.8)	
Postmenopausal	71 (64.6)	93 (61.2)	
Initial symptoms			0.003
Abdominal distension	70 (63.6)	63 (41.4)	
Abdominal pain	20 (18.2)	26 (17.1)	
Mass	5 (4.5)	54 (35.5)	
Other	15 (15.6)	9 (5.9)	
CA125 in U/mL	1318.04	1863.38	0.039
CA199 in U/mL	51.41	28.52	0.202
Ascites cytology			0.057
Positive	47 (88.6)	34 (73.9)	
Negative	6 (11.3)	12 (26.1)	
Ascites in mL	1658.63	2302.24	0.025
Misdiagnosis rate	23.6%	1.32%	0.000
Survival rates			0.179
1-year	75.5%	64.5%	
3-year	27.7%	23.0%	
5-year	13.8%	9.9%	

CA: Carbohydrate antigen; NOCS: Normal size ovarian cancer syndrome; PSOC: Papillary serous ovarian carcinoma.

#### DISCUSSION

We represent a fairly large cohort of patients with the rare NOCS. This group mirrors the characteristics and behavior of a typical NOCS population. Feuer et al<sup>[2]</sup> subdivided NOCS in to four categories: MPM, EPSPC, metastatic tumors, and primary ovarian carcinoma. Our study is the first large sample study examining the clinical characteristics and prognosis of NOCS.

The clinical characteristics and prognosis of the 110 patients with NOCS and 152 patients with PSOC in our study reflect the complexity of studying these diseases. As our study demonstrates, the patient characteristics of the two groups were very similar, such as age, menopausal status, preoperative CA199 values, and ascites quantity. The exception between the two groups was preoperative CA125 value. CA125 levels were elevated in most NOCS patients (89.72%) and all PSOC patients in this study, and the level in patients with NOCS was significantly lower than that in PSOC patients (median level of 1318.04 U/mL and 1863.38 U/mL, respectively). The possible explanation is that tissue sources and pathological types in the NOCS group were different; not all of them were derived from epithelial cells. Moreover, CA-125 is not tumor specific and is not typically best used to monitor disease recurrence or progression in those with a confirmed diagnosis, which is different from previous studies about PSOC[14,15]. The main initial symptoms of the NOCS group were abdominal distension (63.6%), with only 4.5% with abdominal masses (< 5 cm). In addition, the ascites quantity in the NOCS group was significantly lower than that in the PSOC group; therefore, the clinical symptoms of the NOCS group were atypical. The preoperative CA199 values were increased in some NOCS patients, but it was lower than that in the gastrointestinal tumors (51.41 U/mL vs 132.34 U/mL).

In this study, from 110 patients according to Feuer's criteria, 80 patients (72.7%) had primary adnexal carcinoma, two patients (1.8%) had MPM, 18 patients (16.4%) had EPSPC, and eight patients (7.3%) had metastasis. There was no significant difference in

Table 2 Clinical characteristics of the patients with normal size ovarian cancer syndrome in four histological subtypes

Characteristic	Primary adnexal	MPM	EPSPC	Metastatic
n (%)	80 (72.7)	2 (1.8)	19 (17.3)	9 (8.2)
Age in yr	53.28 (24-67)	51.50 (45-58)	56.42 (44-72)	53.00 (35-66)
Menopausal status				
Premenopausal	13	0	1	2
Postmenopausal	67	2	18	7
Initial symptoms				
Abdominal distension	52	2	12	4
Abdominal pain	14	0	5	1
Mass	3	0	1	1
Other	11	0	1	3
CA125 in U/mL	1465.40	36.81	1308.14	205.40
CA199 in U/mL	22.61	13.2	83.87	244.63
Ascites cytology	62	1	14	6
Positive, n (%)	37 (59.7)	1 (100)	8 (57.1)	4 (66.7)
Negative, n (%)	25 (40.3)	0 (0)	6 (42.9)	2 (33.3)
Ascites in mL	1717.87	1000	1500	1480
Stage, n (%)				
III	58 (72.5)	2 (100)	12 (63.2)	6 (66.7)
IV	22 (27.5)	0 (0)	7 (36.8)	3 (33.3)
Survival rates				
1-year	79.5%	100%	64.7%	66.7%
3-year	32.1%	100%	23.5%	33.3%
5-year	20.5%	50%	5.9%	22.2%

CA: Carbohydrate antigen; EPSPC: Extraovarian peritoneal serous papillary carcinoma; MPM: Malignant peritoneal mesothelioma.

age, menopausal status, clinic symptoms, and ascites quantity among the four groups, which suggested that the characteristics of the four groups were very similar. Moreover, as in previous literature, our study showed that the prognosis of the four groups was similar<sup>[3,11,16,17]</sup>. The difference of the four groups was preoperative CA125 and CA199 values and histological patterns. Preoperative CA125 was notably elevated in the primary adnexal carcinoma group and EPSPC group but not elevated in the other two groups. In addition, preoperative CA199 was elevated in the metastatic and EPSPC groups, which was not significantly elevated in the other two groups. The reason may be that the source of each group was different. However, the specificity of preoperative CA125 and CA199 was not high, and it is very limited in helping the clinical diagnosis.

We found that ascites cytology is very meaningful with high accuracy (88.6%) and easy operation. We also found that all NOCS patients were at advanced stages (III/IV) at the time of diagnosis, likely because the main clinical signs and symptoms of NOCS patients are not representative, and the primary lesions were very difficult to find by imaging examination. Therefore, it is difficult to diagnose at early stages, and the misdiagnosis rate is very high. In this study, the misdiagnosis rate was 23.6%, and the preoperative hospitalization time was 15.76 d (2-60 d), which was lower than that in previous studies<sup>[5]</sup>. This may be associated with advanced detection methods such as PET/CT, growing number of laparoscopic procedures, and physicians' increased emphasis on this disease. In NOCS, surgery remains critical as a first approach in both diagnosis and treatment, as it could reduce preoperative hospitalization time and inspection costs. It is recommended that patients with these symptoms, including bloating and abdominal pain caused by ascites as well as elevated tumor markers,

Table 3 Treatment characteristics of primary normal size ovarian cancer syndrome and papillary serous ovarian carcinoma, n (%)

Characteristic, patients with data available	NOCS	PSOC	P value
Initial surgery			0.892
Complete	79 (71.8)	108 (71.1)	
Incomplete	31 (28.2)	44 (28.9)	
Operation method			0.000
Laparotomy	49 (44.5)	112 (73.7)	
Laparoscopy	61 (55.5)	40 (26.3)	
Residual tumor			0.136
Yes	67 (60.9)	106 (69.7)	
No	43 (39.1)	46 (30.3)	
Chemotherapy			0.000
Platinum-based	86 (77.3)	142 (93.4)	
Nonplatinum-based	3 (2.7)	0 (0.0)	
Without	22 (20)	10 (6.6)	
Chemotherapy numbers			0.051
≥6	58 (65.2)	74 (52.1)	
<6	31 (34.8)	68 (47.9)	

Complete: Standard ovarian tumor staging operation (hysterectomy + bilateral appendage resection + omentectomy + pelvic lymph node dissection + tumor cell reduction); Incomplete: Non-standard ovarian tumor staging operation. NOCS: Normal size ovarian cancer syndrome; PSOC: Papillary serous ovarian carcinoma.

> should undergo laparoscopic exploration as soon as possible in order to determine a definite diagnosis to provide early treatment.

> Our study is the first report of a large population-based study that showed 1-, 3-, and 5-year survival rates of 75.5%, 27.7%, and 13.8%, respectively, further confirming the overall poor prognosis of NOCS. In addition, these tumor patients quickly relapsed; the average recurrence time was 17.83 mo. The most important prognostic indicator was the preoperative CA199 values at presentation (hazard ratio 2.546, P <0.05). This finding is in accordance with prior studies, which have shown a significant positive association between the levels of CA199 and mortality. A possible explanation is that patients with NOCS had advanced tumors, and the gastrointestinal tract was invaded in most of the cases or had metastatic tumors of the gastrointestinal tract. Hence, the level of CA199 is typically best used to monitor disease progression or used for prognosis.

> The number of chemotherapy cycles was another important prognostic factor in this study; having more than six chemotherapy cycles was associated with a hazard ratio for mortality of 0.307 compared to having fewer than six cycles. This finding suggested that systemic chemotherapy is highly effective in NOCS patients achieving excellent survival outcomes, even during metastasis.

> However, this study has several limitations. First, some statistical analyses were limited due to low numbers. Second, prospective cohorts could be performed to collect relevant data and standardize the management of these rare diseases to conceal evaluation biases related to retrospective studies performed in rare diseases[18]. Third, although our study included a large sample, some of the sub-categories had limited numbers of samples. Despite these limitations, this study is among the largest population-based studies of this rare form of cancer to date.

#### CONCLUSION

NOCS is a rare and aggressive disease with poor prognosis. The clinical symptoms of the NOCS group is atypical, and the misdiagnosis rate is high. Ascites cytology and laparoscopic exploration are valuable in early diagnosis to avoid a misdiagnosis. The

Table 4 The Cox regression models for normal size ovarian cancer syndrome-specific survival prognostic factors in the univariate analysis

Factors	Overall survival			Progression-free survival		
raciois	Hazard ratio	95%CI	P value	Hazard ratio	95%CI	P value
Age ≥ 50 yr	1.314	0.594-2.906	0.500	0.736	0.290-1.871	0.520
CA125 ≥ 100 in U/mL	3.751	0.898-15.664	0.070	1.163	0.333-4.058	0.813
CA199 ≥ 35 in U/mL	2.546	1.156-5.608	0.020	1.778	0.483-6.543	0.387
Ascites ≥ 1000 in mL	1.954	0.987-3.870	0.055	1.248	0.567-2.747	0.582
Stage III vs IV	1.517	0.688-3.347	0.302	0.617	0.238-1.603	0.322
Residual tumor	2.348	0.969-5.691	0.059	1.059	0.431-2.599	0.901
Complete surgery	1.632	0.948-3. 061	0.512	0.842	0.267-2.134	0.534
Differentiation	0.047	0.000-42.817	0.512	0	0	0
Histological subtype	1.023	0.818-2.342	0.342	0.736	0.278-1.899	0.365
Operation method	0.541	0.268-1.091	0.086	1.114	0.512-2.424	0.785
Platinum-based CT	0.355	0.083-1.522	0.163	0.682	0.085-5.474	0.719
Chemotherapy numbers ≥ 6	0.307	0.138-0.684	0.004	0.384	0.117-1.261	0.115

CA: Carbohydrate antigen; CI: Confidence interval; CT: Computed tomography.

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Table 3 THE COX IS	gression models for norm	ai Size Ovaliali Galicei Syli	iui oille-specific sui vi	val in the multivariate analysis

Factors	Overall survival			
raciois	HR	95%CI	P value	
CA125 ≥ 100 in U/mL	0.785	0.093-6.589	0.823	
CA199 ≥ 35 in U/mL	3.004	1.133-7.960	0.027	
Ascites ≥ 1000 in mL	1.935	0.814-4.599	0.135	
Residual tumor	1.417	0.492-4.078	0.518	
Chemotherapy numbers ≥ 6	0.313	0.127-0.770	0.012	
Histological subtype	1.124	0.744-3.451	0.235	
Stage	0.769	0.642-3.477	0.176	
Operation method	1.213	0.984-3.461	0.115	

5123

CA: Carbohydrate antigen; CI: Confidence interval.

level of CA199 is the most important predictor of overall survival, and more than six cycles of chemotherapy contributes to the increased survival rates of NOCS patients.

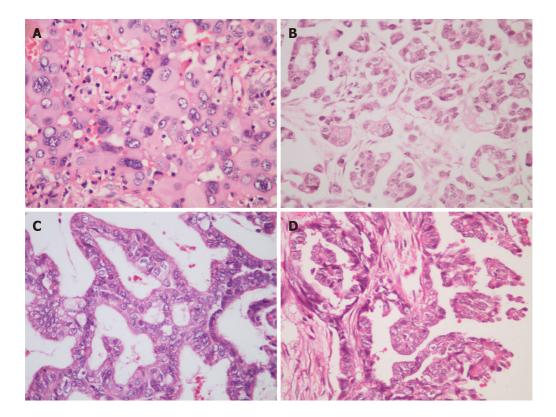


Figure 1 Pathological hematoxylin-eosin staining pictures of the four histological subtypes. A: Primary ovarian group; B: Malignant peritoneal mesothelioma group; C: Extraovarian peritoneal serous papillary carcinoma group; D: Metastatic group. Magnification: (A-D), × 400.

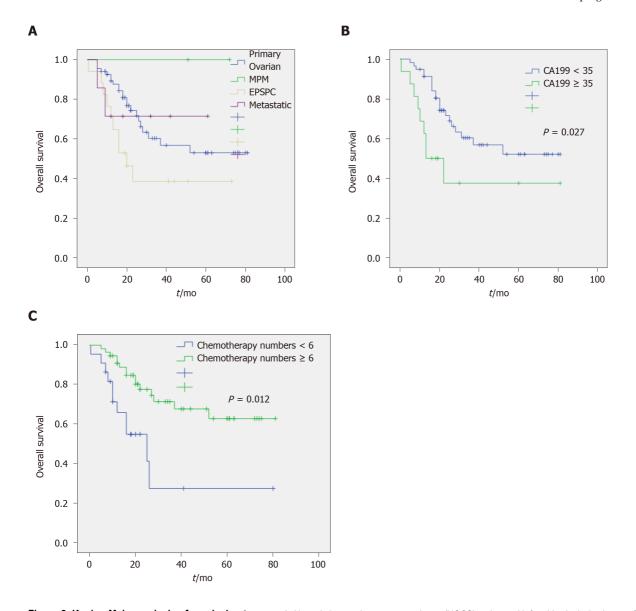


Figure 2 Kaplan-Meier analysis of survival outcomes. A: Normal size ovarian cancer syndrome (NOCS) patients with four histological subtypes; B: NOCS patients with carbohydrate antigen 199 (CA199) values < 35 and CA199 values ≥ 35; C: NOCS patients with chemotherapy numbers < 6 and chemotherapy numbers ≥ 6. CA199: Carbohydrate antigen 199; EPSPC: Extraovarian peritoneal serous papillary carcinoma; MPM: Malignant peritoneal mesothelioma.

5125

#### **ARTICLE HIGHLIGHTS**

#### Research background

Epithelial ovarian cancer is known as one of the most serious gynecologic cancers and shows a higher incidence in developed countries. The general presentation of late stage epithelial ovarian cancer includes increased ovarian tumor size, however, clinicians sometimes encounter cases of advanced stage ovarian cancer without definite ovarian enlargement, known as "normal-sized ovarian carcinoma syndrome (NOCS)".

#### Research motivation

NOCS is difficult to diagnose clinically due to its atypical clinical manifestations and imaging examination, and the misdiagnosis rate is very high. Therefore, early diagnosis and timely treatment are of utmost significance to guarantee the life safety of NOCS patients.

#### Research objectives

We describe clinical characteristics, management, and prognosis of NOCS and compare it with abnormal size ovarian cancer.

#### Research methods

We included the NOCS patients who were pathologically diagnosed between 2008 and 2018. Papillary serous ovarian carcinoma patients were initially randomly recruited as the control group. Demographics, tumor characteristics, treatment procedures, and clinical follow-up were retrospectively collected. Risk factors for progression-free survival and overall survival were assessed.

#### Research results

A total of 110 NOCS patients were included, and we found that carbohydrate antigen (CA)125 and ascites quantity were lower in the NOCS cohort than in the papillary serous ovarian carcinoma group. The only statistically significant risk factors for worse overall survival (P < 0.05) were the levels of CA199 and having fewer than six chemotherapy cycles. The 1-, 3-, and 5-year survival rates were 75.5%, 27.7%, and 13.8%, respectively.

#### Research conclusions

The clinical symptoms of the NOCS group are atypical, and the misdiagnosis rate is high. Ascites cytology and laparoscopic exploration are valuable in early diagnosis to avoid a misdiagnosis. The level of CA199 is the most important predictor of overall survival, and more than six cycles of chemotherapy contributes to the increased survival rates of NOCS patients.

#### Research perspectives

Our study is the first large sample study on the clinical characteristics and prognosis of NOCs in the literature, providing evidence for clinical diagnosis and treatment and clinical guidance for subsequent basic research.

#### **ACKNOWLEDGEMENTS**

The authors thank everyone in the Department of Obstetrics and Gynecology in the Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology for their scientific advice and encouragement.

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5126

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