

**Esra Cobankent Aytekin<sup>1</sup>, Murat Araz<sup>2</sup>**

<sup>1</sup>Department of Pathology, Konya Numune Hospital, Konya, Turkey

<sup>2</sup>Department of Medical Oncology, Necmettin Erbakan University School of Medicine, Konya, Turkey

# Small cell neuroendocrine carcinoma of the bladder with synchronous Warthin’s tumor of the parotid gland: A rare case and overview of the literature

**Address for correspondence:**

Esra Cobankent Aytekin, MD  
 Department of Pathology, Konya Numune Hospital, Ferhuniye neighborhood  
 Hastaneler Street No:22,  
 42060 Selcuklu/Konya, Turkey  
 e-mail: esracobankent@hotmail.com

**ABSTRACT**

**Introduction.** Neuroendocrine tumors (NETs) develop from the epithelium rich in enterochromaffin cells. NETs most commonly originate from the gastrointestinal and respiratory tract. NETs rarely occur in the urinary bladder. Synchronous tumor is defined as having two different tumors growing at the same time in an organ. NETs are frequently associated with synchronous or metachronous second-primary malignancies. In this paper, we describe a synchronous tumor: a small cell neuroendocrine carcinoma (SCNEC) of the bladder and a Warthin's tumor (WT) of the parotid gland, both of which are highly rare in the literature.

**Case report.** A 79-year-old male patient was admitted to the hospital with gross hematuria and nodular mass involving the wall of the urinary bladder. The bladder neck resection and transurethral bladder resection (TURB) were performed. The tumor consisted of small, uniform, round, and spindled-shaped cells with chromatin dark nuclei and numerous mitotic figures. The cells were immunoreactive for CD56, synaptophysin (diffuse), and keratin (focal). The diagnosis of SCNEC with focal urothelial carcinoma in situ component was established. PET-CT was performed for staging purposes, and it showed a residual/recurrent tumor behind the lumen of the bladder floor and two nodular lesions with metabolic activity in the left parotid. After the biopsy of the parotid gland, it was diagnosed as WT. No metastasis of SCNEC was found at the time of diagnosis, and the patient received four cycles of induction chemotherapy (Etoposide combined with carboplatin chemotherapy) followed by chemoradiotherapy.

**Conclusion.** In this case report, an extremely rare case of primary SCNEC of the bladder with synchronous of the parotid gland is presented, along with a discussion on the clinical presentation, immunohistochemical and cytomorphological characteristics, management, biological behavior, and prognosis.

**Key words:** small cell bladder carcinoma, small cell carcinoma, synchronous cancers, Warthin's tumor, urothelial carcinoma in situ

Oncol Clin Pract 2022; 18, 2: 128–133

Oncology in Clinical Practice  
 DOI: 10.5603/OCP.2022.0002  
 Copyright © 2022 Via Medica  
 ISSN 2450–1654  
 e-ISSN 2450–6478

**Introduction**

Neuroendocrine tumors (NETs) develop from the epithelium rich in enterochromaffin cells. NETs comprise small cell neuroendocrine carcinoma (SCNEC), large cell neuroendocrine carcinoma (LCNEC),

well-differentiated neuroendocrine tumor, and paragangliomas [1]. NETs most commonly originate from the gastrointestinal and respiratory tract. NETs rarely occur in the urinary bladder.

NETs are frequently associated with synchronous or metachronous second primary malignancies [2].

Received: 12.08.2021

Accepted: 30.08.2021

Early publication date: 20.01.2022

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

Though the cause and developmental mechanisms of multiple primary tumors are not fully understood, various factors including immune deficiency, genetic instability, increased use of systemic chemotherapy and radiotherapy, increased survival, elderliness, and smoking have been implicated. SCNEC of the bladder is a quite rare neoplasm and comprises less than 1% of all bladder malignancies [1, 3].

SCNEC of the bladder has a strong male predilection and most commonly presents in the seventh decade, with a mean age of presentation at approximately 67 years [3].

Risk factors are not well-defined; however, these tumors are more prominent in smokers suffering from longstanding cystitis and bladder stones [4–5].

SCNEC of the bladder is a highly aggressive tumor, nevertheless, these tumors are chemotherapy-sensitive and are often managed with a multi-disciplinary approach due to their highly malignant potential.

The Warthin's tumor (WT) is the second most common benign salivary gland tumor and is located almost exclusively in the parotid gland [6]. Like SCNEC of the bladder, WT occurs between the sixth and seventh decades when the male gender is dominant and is associated with smoking [7].

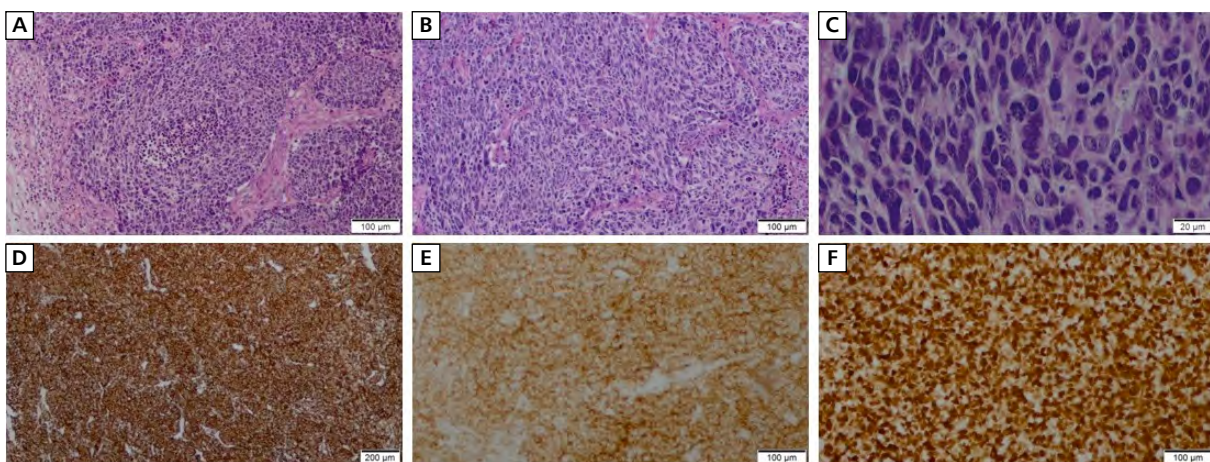
Nonetheless, the cases of small cell cancer of the bladder and synchronous tumors are rarely reported in the literature [2, 8–9].

In the present study, this rare case of SCNEC+ in situ urothelial carcinoma (UCI) of the bladder with synchronous WT of the parotid gland is presented, along with a discussion on the clinical presentation, immunohistochemical (IHC), and cytomorphological characteristics, management, biological behavior, and prognosis of this disease.

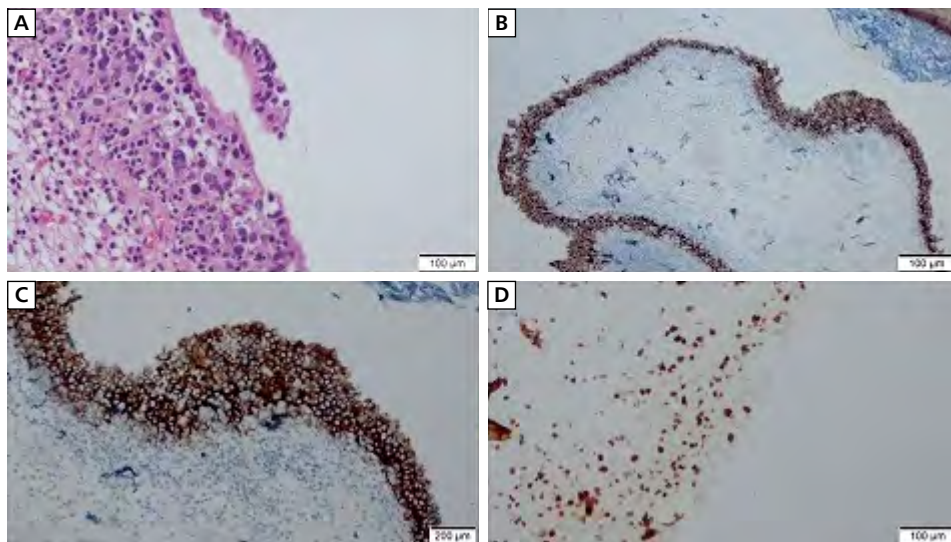
## Case report

A 79-year-old ex-smoker man who had complained for 6 months of intermittent painful gross hematuria was admitted to the hospital in December 2020. A 60 x 30 mm homogeneously contrasted mass extending to the ureterovesical junction at the bladder floor and right grade-3/4 hydroureteronephrosis were detected in Ultrasonography and contrast-enhanced computed tomography (CT). Bladder neck resection and transurethral bladder resection (TURB) with deep muscle biopsy were performed because the bladder neck was completely closed at cystoscopy. Histopathological (HP) examination revealed tumor tissue infiltrating into the lamina propria and deep muscles in all sections (Fig. 1A). A tumor is composed of nests of small round malignant cells with pyknotic round to oval nuclei and evenly dispersed salt and pepper chromatin and a scant amount of cytoplasm (Fig. 1B). Few comedo necrosis foci and increased atypical mitosis were also noted (Fig. 1C). Lymphovascular and perineuronal tumor invasion was observed. IHC studies showed positivity for CD56 (Fig. 1D) and synaptophysin (Fig. 1E). However, the tumor was negative for chromogranin, CD45, TTF-1, and GATA3. Ki-67 labeling index showed a very high proliferation fraction of virtually 95% (Fig. 1F).

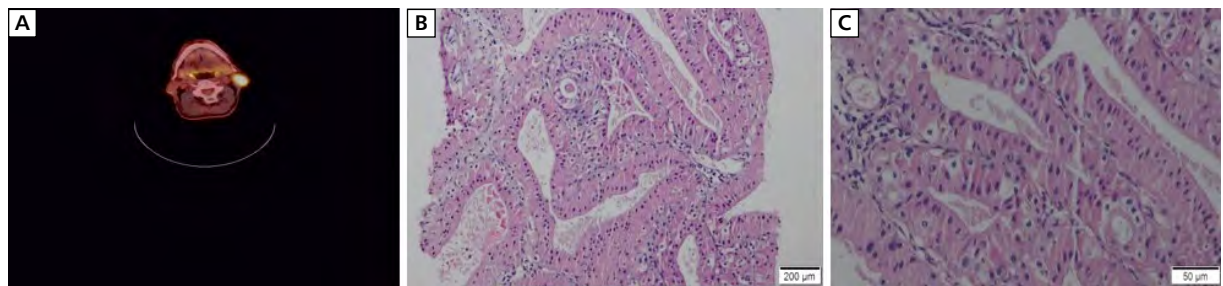
In addition, UCI, which is the second lesion consisting of cells with large irregular hyperchromatic nuclei in one area, was observed. Significant nuclear pleomorphism, a high N/C ratio, and mitotic figures in the upper epithelium were observed in this area. There was full-thickness atypia (Fig. 2A). IHC studies showed positivity for CK20 full-thickness (Fig. 2B–2C), and Ki-67 positivity was seen extending to the upper



**Figure 1.** SCNEC of bladder; **A.** Comedonecrosis, apoptotic debris, muscle invasion (H&E  $\times 10$ ); **B.** Tumor composed of nests of malignant small round/spindle cells arranged in sheets (H&E,  $\times 10$ ); **C.** High power showing oval to spindle-shaped nucleus with salt and pepper chromatin with many pyknotic nuclei and atypical mitotic figures (H&E  $\times 40$ ); **D.** Tumor cells with synaptophysin positivity ( $\times 4$ ); **E.** CD 56 positivity ( $\times 10$ ) and **F.** Ki-67 labelling index of 95%



**Figure 2.** Carcinoma in situ; A. H&E; B, C. CK20; D. Ki-67



**Figure 3.** Warthin's tumor; A. Parotid gland PET-CT; B. Tubular masses of cells; C. With a two rows of pink (eosinophilic) epithelial cells (with cuboidal basal cells and columnar luminal cells)

level of the epithelium (Fig. 2D). The final pathological outcome was diagnosed as muscle-invasive SCNEC of the bladder.

PET-CT was performed for staging purposes for the patient. Residual/recurrent tumor growing posteriorly to the lumen of the bladder floor, approximately 3 cm in diameter (SUVmax: 16.06) (Fig. 4A–4B), two nodular lesions in the left parotid gland (SUVmax: 20.76) with metabolic activity (SUVmax: 20.76) (Fig. 3A), the left preauricular 9 mm diameter (SUVmax: 5.67), and the left parotid gland inferior to 9 mm diameter (SUVmax: 7.28) nodular lesions were detected on the PET-CT. No metastasis was identified in on other organ systems.

A tumor consisting of papillary and tubular structures containing cystic spaces was observed in the biopsy of the parotid gland. The tumor consisted of papillary structures lined by bi-layered oncocytic epithelium and enclosing a scant amount of lymphocytic infiltrate (Fig. 3B–3C).

The multidisciplinary tumor board planned induction chemotherapy followed by concurrent chemoradiotherapy treatment for the non-metastatic SCNEC of the

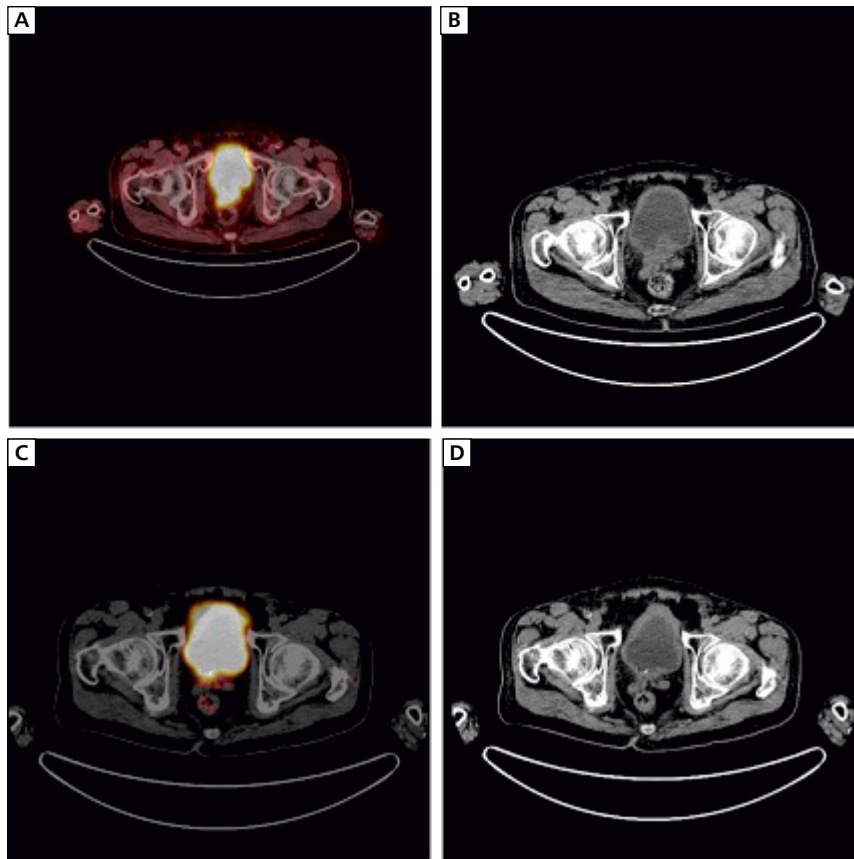
bladder, and it was decided to follow the synchronous WT of the parotid gland.

Etoposide combined with carboplatin chemotherapy was planned for the patient with ECOG (Eastern Cooperative Oncology Group), the performance status was 2.

After 3 cycles of chemotherapy, the mass in the bladder in the previous PET-CT disappeared, and other findings were stable (Fig. 4C–4D). After 4 courses of chemotherapy were completed, definitive weekly carboplatin (AUC: 2) concurrent radiotherapy was started and the patient's treatment is still ongoing. After finishing the bladder treatment, if there is still no progression, parotid tumor surgery will be planned.

## Discussion

SCNEC of the bladder is a rare aggressive malignant neoplasm with a high incidence of local recurrence and metastasis. Smoking is the most important risk factor [3]. No consensus exists regarding the origin and



**Figure 4.** Positron emission tomography-computed tomography (PET-CT) mass in the posterior wall of the urinary bladder; A. PET-CT with FDG; B. PET-CT without FDG, the image where the mass in the bladder disappeared after post-chemotherapy treatment; C. PET-CT with FDG; D. PET-CT without FDG

histogenesis of SCNEC of the urinary bladder. Yet, metaplastic differentiation from transitional cell carcinoma has been suggested. The most common clinical presentation is hematuria, which might be accompanied by pain and dysuria.

Diagnosis of primary SCNEC of the bladder mainly depends on histopathology, immunohistochemistry, and cytomorphological characteristics, which is similar to SCNEC in the lung and other tissues. The differential diagnosis includes high-grade urothelial carcinoma (lymphoma-like variant), lymphoma, and metastatic malignant neoplasms.

Our case was an elderly male smoker, who presented with hematuria and dysuria as reported in the literature. HP and IHC findings were similar to small cell lung cancer. Cancers included in the differential diagnosis were ruled out with IHC findings, and the final diagnosis was made as SCNEC of bladder including UCI of the bladder.

Wang et al. performed clinicopathological and IHC analysis of 81 cases of SCNEC of the bladder. They reported 66% of SCNEC to be mixed with other carcinomas, most commonly urothelial carcinoma (UC) (40%) and UCI (32%) [3].

Chen et al. [10] found these rates as UC 56.3% and UCI 5.3% in the 128 Chinese patients with SCNEC of the bladder. On the other hand, in the report of Nicholas W. et al. [11], 61.4% of forty-four patients with primary bladder SCNEC had pure SCNEC.

Cheng et al. [12] analyzed the heterozygous loss patterns of SCNEC of bladder with the comparable UC and concluded that SCNEC of bladder and UC had nearly identical allelic loss patterns, implying a common clonal precursor origin. Nevertheless, further genetic and molecular studies are required to explore the oncogenesis of bladder SCNEC.

Wang et al. [3] found no significant difference in survival rates between patients with pure SCNEC of bladder and mixed histology in their study. A similar result was reported in the 2020 review by Vericco et al. [2] On the contrary, publications are suggesting pure SCNEC of bladder is associated with a worse prognosis than SCNEC of bladder mixed with other histology [13, 14].

Since SCNEC of the bladder is a clinically rare tumor, no standard treatment exists. In the study of Wang et al., the median survival time for patients who received neoadjuvant chemotherapy before cystectomy

was longer (38 months) than for patients who did not (12 months), and longer survival (> 60 months) has been reported in patients with the bladder-localized disease who received neoadjuvant chemotherapy [3]. Similarly, Lynch et al. [15] reported in 16 patients with long-term survival that radical cystectomy after neoadjuvant chemotherapy is an effective approach in the treatment of patients with bladder-localized SCNEC. In our case, the tumor was muscle-invasive, and distant organ metastasis was not observed. In the treatment response evaluation after 3 cycles of neoadjuvant chemotherapy, the mass has disappeared and other findings were stable.

Verrico et al. showed an increased risk of second cancer following NETs in their study evaluating the incidence of additional malignancies in patients with NETs. In this single-institution retrospective review, the incidence of additional malignancies in patients with NETs was 11.4% [2]. Although few similar studies exist, these studies also reported similar results [16, 17]. However, in these studies, very few or no reports of synchronous or metachronous tumors with Neuroendocrine tumors of the bladder were reported. To date, five cases of multiple primary tumors with synchronous/metachronous with bladder NETs have been reported in the literature. Three of these case reports involved multiple primary tumors with SCNEC of bladder: one with squamous cell carcinoma of the lung and esophagus [9], one with prostatic ductal adenocarcinoma, and penile squamous cell carcinoma [8], and one with Chronic lymphocytic leukemia [18]. Two of these cases were multiple primary tumors with non-subtype specified neuroendocrine tumors [2, 17].

Although multiple primary tumors might emerge at any age, they are reported to be more common in elder patients [16]. This result can be explained by reasons such as the duration of carcinogenesis, the insensitivity of aged tissues to carcinogens, and weakening of immunity with aging [19]. Synchronous tumors are associated with organ-specific carcinogens, such as smoking and alcohol. Hence, synchronous tumors tend to involve the aerodigestive and urinary tract (head-neck, lung, and upper esophagus) and are usually associated with smoking.

In our case, the WT was present in the parotid gland as the synchronous second primary tumor. Synchronized SCNEC of bladder + UCIS/WT is not associated with any known syndrome. The causal risk factors we could identify were smoking and elderliness, which could explain synchronous bladder and WT. Although high-grade NETs of the bladder determined the prognosis and survival as in our case, second primary tumors of the bladder NETs should be kept in mind as in other organ NETs, and further diagnostic evaluations should be made in suspicious lesions.

In conclusion, SCNEC of bladder is a rare aggressive malignant neoplasm with the diagnosis mainly depending on histopathology and immunohistochemistry.

After the diagnosis of NETs, second cancer formation should be kept in mind and monitored closely.

Despite the poor prognosis associated with SCNEC of the bladder, a good response to chemotherapy is obtained.

## Conflict of interest

The authors have declared no conflicts of interest.

## References

- Kouba E, Cheng L. Neuroendocrine Tumors of the Urinary Bladder According to the 2016 World Health Organization Classification: Molecular and Clinical Characteristics. *Endocr Pathol.* 2016; 27(3): 188–199, doi: [10.1007/s12022-016-9444-5](https://doi.org/10.1007/s12022-016-9444-5), indexed in Pubmed: [27334654](https://pubmed.ncbi.nlm.nih.gov/27334654/).
- Verrico M, Rossi L, Tomao S, et al. Metachronous and Synchronous Cancers in Patients with Neuroendocrine Tumors. *Oncology.* 2020; 98(1): 10–15, doi: [10.1159/000502384](https://doi.org/10.1159/000502384), indexed in Pubmed: [31505502](https://pubmed.ncbi.nlm.nih.gov/31505502/).
- Wang G, Xiao Li, Zhang M, et al. Small cell carcinoma of the urinary bladder: a clinicopathological and immunohistochemical analysis of 81 cases. *Hum Pathol.* 2018; 79: 57–65, doi: [10.1016/j.humphath.2018.05.005](https://doi.org/10.1016/j.humphath.2018.05.005), indexed in Pubmed: [29763719](https://pubmed.ncbi.nlm.nih.gov/29763719/).
- Alijo Serrano F, Sánchez-Mora N, Angel Arranz J, et al. Large cell and small cell neuroendocrine bladder carcinoma: immunohistochemical and outcome study in a single institution. *Am J Clin Pathol.* 2007; 128(5): 733–739, doi: [10.1309/HTREM6QYQDYGWYA](https://doi.org/10.1309/HTREM6QYQDYGWYA), indexed in Pubmed: [17951193](https://pubmed.ncbi.nlm.nih.gov/17951193/).
- Li Z, Lin C, Wang D, et al. Primary small-cell neuroendocrine carcinoma of the urinary bladder: A rare case and a review of the literature. *Mol Clin Oncol.* 2018; 9(3): 335–338, doi: [10.3892/mco.2018.1679](https://doi.org/10.3892/mco.2018.1679), indexed in Pubmed: [30155256](https://pubmed.ncbi.nlm.nih.gov/30155256/).
- Dżaman K, Pietniczka-Załęska M, Piskadlo-Zborowska K, et al. Parotid gland tumours in the ENT Department in Międzyzyleski Hospital in Warsaw between 2007 and 2014. *Otolaryngol Pol.* 2016; 70(1): 34–40, doi: [10.5604/00306657.1193068](https://doi.org/10.5604/00306657.1193068), indexed in Pubmed: [26926306](https://pubmed.ncbi.nlm.nih.gov/26926306/).
- Peter Klusmann J, Wittekindt C, Florian Preuss S, et al. High risk for bilateral Warthin tumor in heavy smokers--review of 185 cases. *Acta Otolaryngol.* 2006; 126(11): 1213–1217, doi: [10.1080/00016480600740605](https://doi.org/10.1080/00016480600740605), indexed in Pubmed: [17050316](https://pubmed.ncbi.nlm.nih.gov/17050316/).
- Ogawa S, Yasui T, Taguchi K, et al. The probability of involvement of human papillomavirus in the carcinogenesis of bladder small cell carcinoma, prostatic ductal adenocarcinoma, and penile squamous cell carcinoma: a case report. *BMC Res Notes.* 2014; 7: 909, doi: [10.1186/1756-0500-7-909](https://doi.org/10.1186/1756-0500-7-909), indexed in Pubmed: [25512116](https://pubmed.ncbi.nlm.nih.gov/25512116/).
- Tamura K, Inoue K, Fukata S, et al. Small cell carcinoma of the urinary bladder with synchronous esophageal cancer and incidental lung cancer: a case report. *Hinyokika kyo Acta urologica Japonica.* 2001; 47(4): 273–276.
- Chen Z, Liu Q, Chen R, et al. Clinical analysis of small cell carcinoma of the bladder in Chinese: nine case reports and literature reviews. *World J Surg Oncol.* 2017; 15(1): 33, doi: [10.1186/s12957-016-1079-y](https://doi.org/10.1186/s12957-016-1079-y), indexed in Pubmed: [28125986](https://pubmed.ncbi.nlm.nih.gov/28125986/).
- Choong NWW, Quevedo JF, Kaur JS. Small cell carcinoma of the urinary bladder. The Mayo Clinic experience. *Cancer.* 2005; 103(6): 1172–1178, doi: [10.1002/cncr.20903](https://doi.org/10.1002/cncr.20903), indexed in Pubmed: [15700264](https://pubmed.ncbi.nlm.nih.gov/15700264/).
- Cheng L, Jones TD, McCarthy RP, et al. Molecular genetic evidence for a common clonal origin of urinary bladder small cell carcinoma and coexisting urothelial carcinoma. *Am J Pathol.* 2005; 166(5): 1533–1539, doi: [10.1016/S0002-9440\(10\)62369-3](https://doi.org/10.1016/S0002-9440(10)62369-3), indexed in Pubmed: [15855652](https://pubmed.ncbi.nlm.nih.gov/15855652/).
- Pasquier D, Barney B, Sundar S, et al. Small Cell Carcinoma of the Urinary Bladder: A Retrospective, Multicenter Rare Cancer Network Study of 107 Patients. *Int J Radiat Oncol Biol Phys.* 2015; 92(4): 904–910, doi: [10.1016/j.ijrobp.2015.03.019](https://doi.org/10.1016/j.ijrobp.2015.03.019), indexed in Pubmed: [26104942](https://pubmed.ncbi.nlm.nih.gov/26104942/).
- Cheng L, Pan CX, Yang XJ, et al. Small cell carcinoma of the urinary bladder: a clinicopathologic analysis of 64 patients. *Cancer.* 2004;

- 101(5): 957–962, doi: [10.1002/cncr.20456](https://doi.org/10.1002/cncr.20456), indexed in Pubmed: [15329903](https://pubmed.ncbi.nlm.nih.gov/15329903/).
15. Ismaili N, Lynch SP, Shen Yu, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the MD Anderson Cancer Center. *Eur Urol.* 2013; 64(2): 307–313, doi: [10.1016/j.eururo.2012.04.020](https://doi.org/10.1016/j.eururo.2012.04.020), indexed in Pubmed: [22564397](https://pubmed.ncbi.nlm.nih.gov/22564397/).
16. Tsai HJ, Wu CC, Tsai CR, et al. Second cancers in patients with neuroendocrine tumors. *PLoS One.* 2013; 8(12): e86414, doi: [10.1371/journal.pone.0086414](https://doi.org/10.1371/journal.pone.0086414), indexed in Pubmed: [24392036](https://pubmed.ncbi.nlm.nih.gov/24392036/).
17. Reina JJ, Serrano R, Codes M, et al. Second primary malignancies in patients with neuroendocrine tumors. *Clin Transl Oncol.* 2014; 16(10): 921–926, doi: [10.1007/s12094-014-1174-x](https://doi.org/10.1007/s12094-014-1174-x), indexed in Pubmed: [24788817](https://pubmed.ncbi.nlm.nih.gov/24788817/).
18. Vaidyanathan S, Mansour P, Soni BM, et al. Chronic lymphocytic leukaemia, synchronous small cell carcinoma and squamous neoplasia of the urinary bladder in a paraplegic man following long-term phenoxybenzamine therapy. *Spinal Cord.* 2006; 44(3): 188–191, doi: [10.1038/sj.sc.3101789](https://doi.org/10.1038/sj.sc.3101789), indexed in Pubmed: [16130025](https://pubmed.ncbi.nlm.nih.gov/16130025/).
19. Balducci L, Beghe' C. Cancer and age in the USA. *Crit Rev Oncol Hematol.* 2001; 37(2): 137–145, doi: [10.1016/s1040-8428\(00\)00109-8](https://doi.org/10.1016/s1040-8428(00)00109-8), indexed in Pubmed: [11166587](https://pubmed.ncbi.nlm.nih.gov/11166587/).