# An isolated metachronous metastasis to the adrenal gland from a pancreatic neuroendocrine tumor: A case report

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### ABSTRACT

INTRODUCTION: Pancreatic neuroendocrine tumors are rare. Treatment includes aggressive local management of the primary lesion and metastases, and systemic somatostatin. This is the first report of an isolated metachronous metastasis to the adrenal gland from a pancreatic neuroendocrine tumor that presented 90 months after the primary tumor.
PRESENTATION OF CASE: The patient presented as a 53yo man with a left upper quadrant mass and synchronous metastases to the spleen and liver (pancreatic neuroendocrine tumor T4N0M1, Stage IV), which were resected (CD56-, synaptophysin+, chromogranin+, Ki-67 < 1%). Over the next 90 months, he underwent five procedures to treat hepatic recurrences (2 liver resections and 3 percutaneous radiofrequency ablations). Serum PIVKA levels were elevated prior to treatment of four of six lesions and returned to baseline after therapy. He presents now, asymptomatic, with a right adrenal mass found on routine imaging and no other lesions. Serum PIVKA was elevated to 44 mg/dL. The adrenal gland was resected and shown to be a metastasis (CD56+, synaptophysin+, chromogranin+, Ki-67 15–20%).
DISCUSSION: This patient's clinical course reflects aggressive local therapy of the primary lesion and multiple metastatic lesions to three organs (liver, spleen, adrenal) over nearly eight years. The utility of serum PIVKA levels in patients with pancreatic neuroendocrine tumors is not previously reported and needs further investigation.
CONCLUSION: This patient has a pancreatic neuroendocrine tumor with metastases to the spleen, liver and adrenal gland and elevated PIVKA levels with recurrent disease. These unique clinical features add to the diversity of clinical presentation of these rare tumors.

## 1. Introduction

Pancreatic neuroendocrine tumors (pNET) are rare, presenting with synchronous metastases in up to 65% of patients. There are few reports of patients with metachronous metastases from NETs although prolonged survival is well-known [1]. Aggressive local management (surgery, radio-frequency ablation [RFA], etc.) is advocated for both the primary tumor and metastases [1–5]. Most metastatic lesions from pNETs are in the liver. In a series of NETs from a national registry in Spain, including 837 patients, synchronous metastases were found in 44% of patients, including in the liver (42%), lymph nodes, peritoneal surface, bone, lung, central nervous system and adrenal gland. All four patients with synchronous adrenal tumors had metastatic disease in other sites [6].

The present patient has been previously reported as the first patient with a metastasis to the spleen from a primary pNET, approximately 90 months prior to this presentation [1]. The patient has been followed closely at a major university hospital with imaging at regular intervals, and has remained asymptomatic, but presents now with a right adrenal gland mass. This is the first report of an isolated metachronous metastasis from a pNET to the adrenal gland.

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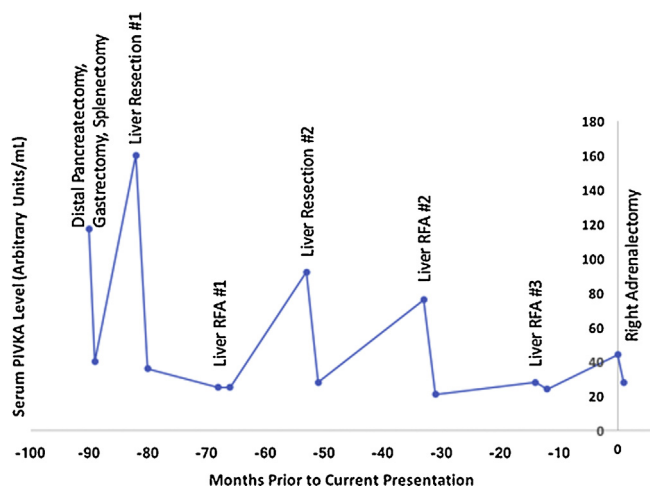  E-mail address: alefor@jichi.ac.jp (A.K. Lefor).

**Fig. 1.** Treatment history and serum PIVKA levels for 90months prior to the current presentation. Each intervention is marked by a serum PIVKA level before and after. Serum PIVKA levels are elevated for five of seven recurrences, and then return to normal after treatment. Serum PIVKA was not elevated before two of the radiofrequency ablation (RFA) procedures.

## 2. Case presentation

The patient initially presented as a 53y old white male with anemia and fatigue. Past medical history, social history and family history are unremarkable. Physical exam showed a left upper quadrant fullness and was otherwise negative. Computed tomography (CT) scan of the abdomen showed a 24 cm left upper quadrant mass with multiple liver lesions, splenomegaly and a 1 cm mass in the spleen. Treatment over the next 78 months is described in detail elsewhere. (Fig. 1) [1]. Briefly, he underwent gastrectomy, splenectomy, distal pancreatectomy and resection of small bowel and colon. The spleen contained a 1.0 cm metastatic lesion [1]. The final pathology showed a pNET, well differentiated, stage T4N0M1 with 0/13 lymph nodes containing tumor and an isolated metastasis to the spleen. There were three mitoses per 50 high power fields, and Ki-67 < 1%. Immunostains for chromogranin A and synaptophysin are positive. Immunostains for CD56, OCGH1E5, AFP, glucagon, insulin, somatostatin, pancreatic polypeptide, alpha 1-anti trypsin, alpha 1 anti-chymotrypsin and lipase were negative. Blood chemistry studies showed that this was a non-functional tumor.

Over the next 90 months, the patient underwent a left lateral segmentectomy of the liver to resect synchronous metastatic disease (82 months previously), RFA of a central hepatic lesion (68 months previously), resection of multiple hepatic nodules (53 months previously), RFA of another liver mass (33 months previously), and RFA of a liver mass (14 months previously). CT scans have been obtained at three-month intervals and serum PIVKA levels checked monthly (Fig. 1). The patient receives somatostatin, long acting release, 20 mg/month. All recurrences were initially identified on imaging studies. Lesions (three) treated with RFA had no pathologic confirmation, but resected liver lesions (two) were histologically confirmed as metastases.

At 90months after resection of the primary tumor, routine CT scan showed a mass in the right adrenal gland (Fig. 2). The patient is asymptomatic, and physical examination is unremarkable. Laboratory studies show no elevated serum hormone levels. Serum PIVKA level was 44 Arbitrary Units (AU)/ml (Reference <40 AU/ml). Magnetic resonance imaging showed a 3 cm lesion in the right adrenal gland, enhanced on T2 weighted images (Fig. 3). There are no other lesions in the abdomen, including the liver. The patient underwent a laparoscopic right adrenalectomy (with hand-assist because of

dense adhesions to the liver). There were no postoperative complications.

In summary, the patient is a 60yo man who presented 90 months previously with a pNET Stage IV, T4N0M1, Ki-67 index <1%, CD56 −, synaptophysin+ and chromogranin A+, with synchronous metastases to the spleen and liver. In addition to resection of the primary lesion and synchronous spleen metastasis, he has undergone two open liver resections, and three episodes of percutaneous RFA for liver metastases. He presented with a metachronous metastatic lesion in the right adrenal gland (Fig. 4), which was resected, measuring $3 \times 2 \times 2$ cm, with a Ki-67 index of 15–20%, and is CD56+, synaptophysin+ and chromogranin A+.

## 3. Discussion

This is the first report of a metachronous metastasis from a pNET to the adrenal gland, 90 months after initial presentation. There are previous reports of five patients with synchronous metastases to the adrenal gland [6,7]. Of these, details are available for one patient, and the adrenal lesion was found with widely disseminated disease [7]. The other four patients were reported as aggregate data in patients with synchronous metastases [6], and were also seen with disseminated disease. In a review of a single-center experience over 30 years with 464 patients with adrenal gland metastases, the mean latent period was seven months [8]. Lung was the most common primary tumor (35%) with other sites including stomach (14%), esophagus (12%) and liver/bile ducts (10%. There were no NET primary tumors in this large series.

In a study of rare sites of metastases from NETs, investigators found lesions in the heart, breast, retro-orbital, uterus, skin, brain, spleen, testes, seminal vesicle and peripheral muscle [9]. There were no lesions of the adrenal gland in this series. Several reports have described the treatment of metastases to the adrenal gland, from primary tumors such as the lung [10], colon [11] and kidney [12,13]. In an early review of the treatment of isolated metastases to the adrenal gland, resection was recommended in patients with a disease-free interval of greater than 6 months [14]. This collective review reviewed 37 patients with primary tumors of the lung, kidney and colon. The overall 5-year survival of the group was 24%, with a median survival of 21 months. In a retrospective review of 41 patients who underwent open or laparoscopic adrenalectomy for isolated metastatic disease, investigators concluded that laparoscopic adrenalectomy should be offered to patients with a disease-free interval of more than 6 months [15].

It is of interest in this patient that while the primary tumor had a Ki-67 index of <1%, the adrenal metastasis has a Ki-67 index of 15–20%. Ki-67 is a cell surface antigen expressed in proliferating cells. It has been shown that tumor size and increased Ki-67 index are independent factors which correlate with a poor prognosis [16]. Ki-67 level was recently added to the standard grading system of NETs. Other important tumor markers in NETs include CD56, synaptophysin, and chromogranin A. While the primary tumor in this patient was CD56-, the metastasis to the adrenal gland is CD56+, which is typical in NETs. The role of these three cellular markers in the diagnosis of NETs has been investigated and a new marker, INSM1 has been identified for NET of the chest [17]. The role of this new marker in gastrointestinal tract NETs is undefined.

Serum PIVKA levels have been described for the diagnosis and follow-up of patients with hepatocellular carcinoma (HCC). They have also been used in conjunction with chromogranin A as markers for HCC [18]. The value of PIVKA as an early diagnostic marker was established in 2002 [18]. In one study, investigators found that PIVKA has a sensitivity of 75% in the initial diagnosis of HCC, and 74% for the diagnosis of recurrent disease [19]. However, there have been no reports of elevated PIVKA levels in patients with NET. The
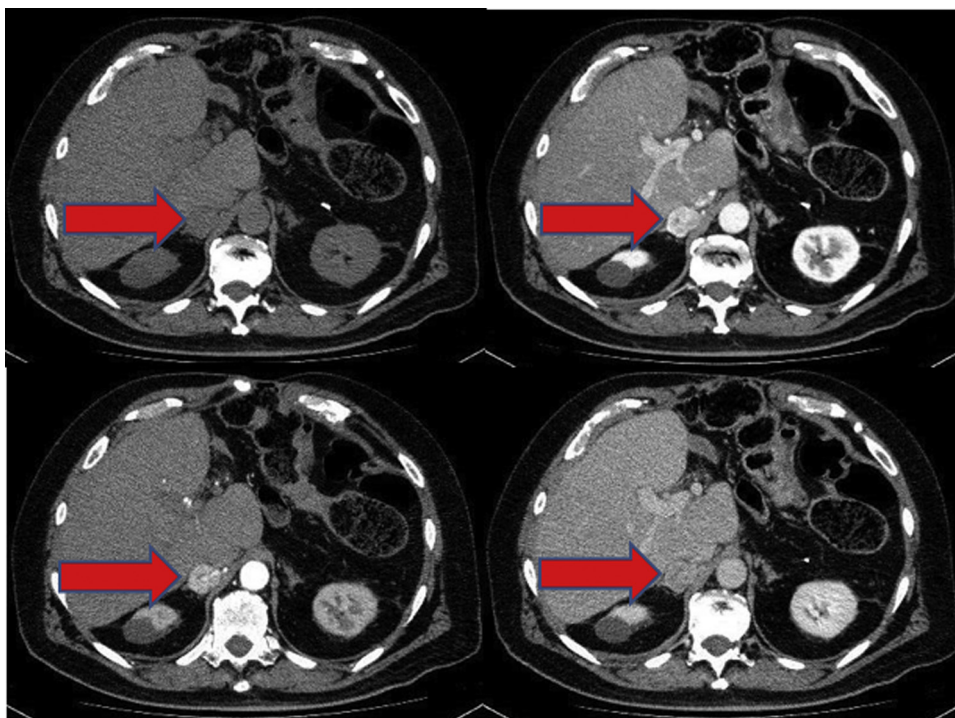
**Fig. 2.** Computed tomography scans of the abdomen show a 2.5 cm mass in the right adrenal gland (arrow). Left upper image: non-enhanced, left lower: early arterial phase, right upper: late arterial phase, right lower: late portal phase. The tumor is markedly enhanced in the early arterial phase but not in the portal phase.
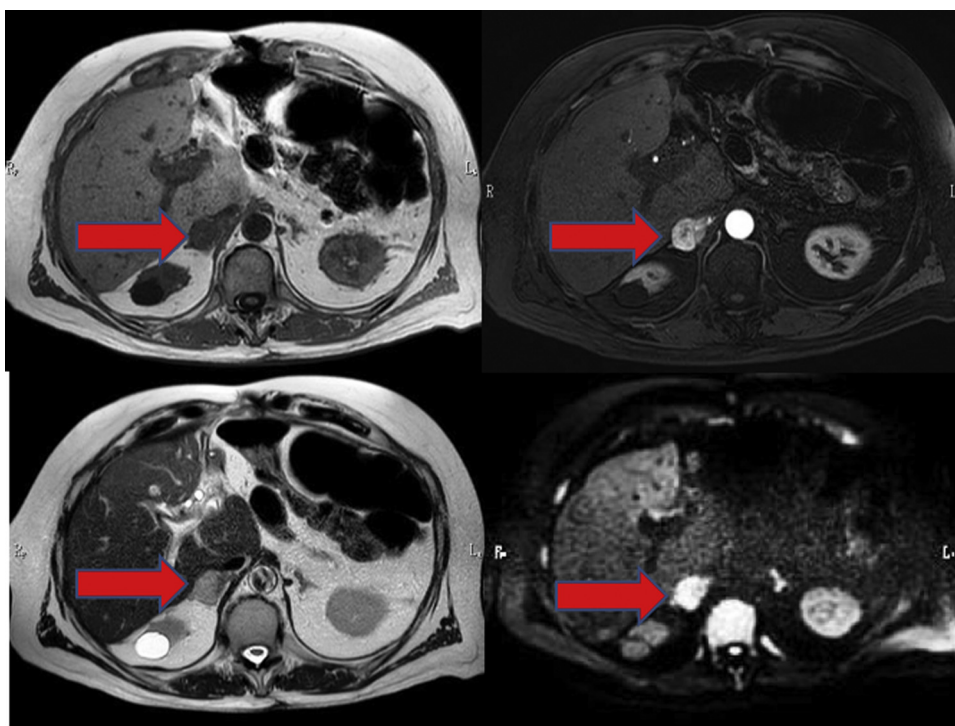


**Fig. 3.** Magnetic resonance imaging shows an enhanced 3 cm mass in the right adrenal gland (arrow). Left upper image: T1-weighted image, left lower: T2-weighted image, right upper: dynamic sequence, right lower: Diffusion weighted image (DWI) sequence (b = 1000). The adrenal gland tumor is markedly enhanced in the early arterial phase (similar to the computed tomography images). The T2-weighted image shows a high intensity signal and diffusion restriction is noted in the DWI sequences.

present patient underwent seven procedures to treat the primary lesion and six recurrences (Fig. 1). Serum PIVKA levels were elevated before treatment of five of these lesions (primary + spleen, liver resection, liver resection, liver RFA and adrenal gland) and were not elevated before two sessions of RFA. It is impossible to calculate the sensitivity since there were no specimens obtained after all three RFA treatments. This observation suggests that serum PIVKA levels should be further investigated as a potentially useful tumor marker in patients with pNETs.
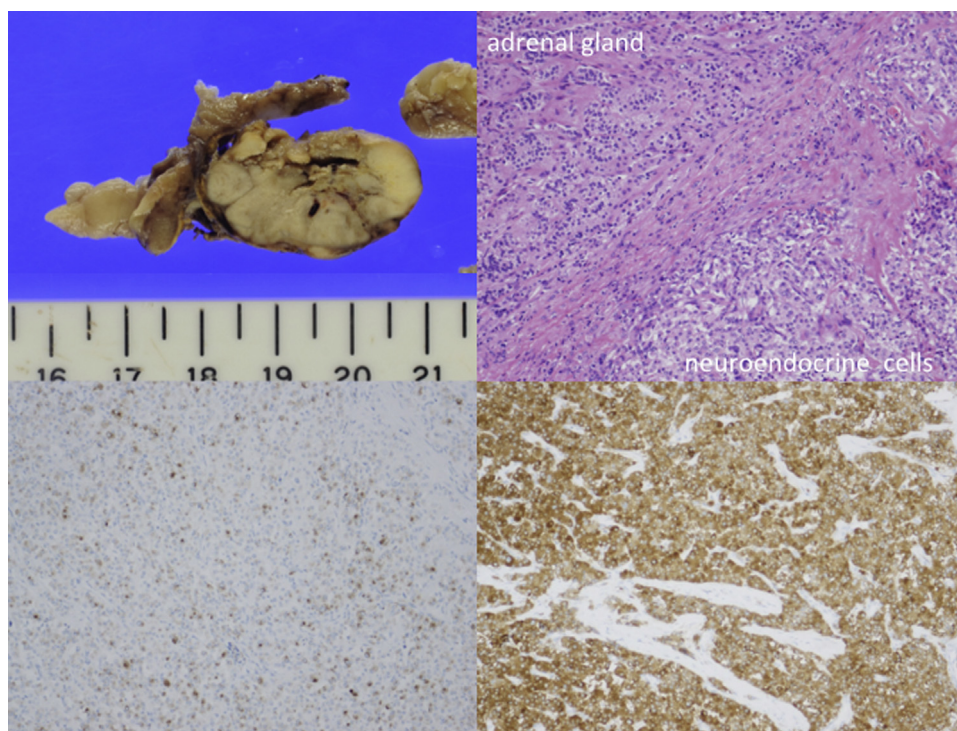
**Fig. 4.** Histology of the right adrenal mass. Left Upper: Macroscopic image shows a 3 cm tumor in the right adrenal gland. Right Upper: Microscopic findings (Hematoxylin and eosin stain, ×100) shows the border of the adrenal gland tissue with a nest of neuroendocrine cells. Left Lower: The tumor cells were weakly positive for chromogranin A by immunohistochemical staining (×100) while strongly positive for synaptophysin (Right Lower, ×100).

The development of another recurrent lesion in this patient who receives monthly injections of long acting somatostatin brings into question the value of continued therapy. This is a difficult question, for which there is little data to evaluate. However, since a number of studies have concluded that somatostatin is a worthwhile adjunct, it will be continued in this patient [1,2,5]. This patient has been asymptomatic through the development of multiple sites of recurrent disease which have been diagnosed by routine CT scans. Octreotide scans have only recently become available in Japan and may be a useful follow-up modality. Follow-up for this patient will include serum PIVKA levels and CT scans.

## 4. Conclusions

This patient presented 90 months previously with a Stage IV (T4N0M1) pNET. He has undergone four open resections and three sessions of percutaneous RFA to treat the primary tumor (with a synchronous spleen metastasis) and six recurrences (five in the liver and one in the adrenal gland). Features unique to this patient illustrate major teaching points including the first reported metastases from a pNET to the spleen [1] and adrenal gland, and elevated serum PIVKA levels as a potential tumor marker. This patient has undergone aggressive local treatment as well as monthly administration of somatostatin [1–5]. The appearance of an adrenal mass underscores the need for close follow-up.

## Conflicts of interest

All authors report no conflicts of interest or competing interests.

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None.

## Ethical approval

Review of this case report was waived by the Jichi Medical University Institutional Review Board.

## Consent

Written and signed consent was given by the patient for this case report.

## Authors contribution

Yasunaru Sakuma: Acquisition and analysis of data, critical revisions of the article, approval of final version.

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Yuuki Kawarai Shimada: Analysis of data, critical revisions of the article, approval of final version.

Chieko Kawarai Lefor: Acquisition of data, drafting and critical revisions of the article, approval of final version.

Alan Kawarai Lefor: Conception of Study, Acquisition and analysis of data, drafting and critical revisions of the article, approval of final version.

## Registration of research studies

Not Applicable.

## Guarantor

Alan Kawarai Lefor MD MPH PhD FACS.

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This case report conforms to the SCARE criteria [20].

## References

[1] Y. Sakuma, Y. Yasuda, N. Sata, Y. Hosoya, A. Shimizu, H. Fujii, D. Matsubara, N. Fukushima, A. Miki, M. Maeno, A.K. Lefor, Pancreatic neuroendocrine tumor with metastasis to the spleen: a case report, BMC Cancer 17 (2017) 37–45, PMID: 28068959.

[2] G.B. Deutsch, J.H. Lee, A.J. Bilchick, Long term survival with long acting somatostatin analogues plus aggressive cytoreductive surgery in patients with metastatic neuroendocrine carcinoma, J. Am. Coll. Surg. 221 (2015) 26–36.

[3] J.G. Touzios, J.M. Kiely, S.C. Pitt, W.S. Rilling, E.J. Quebbemann, S.D. Wilson, H.A. Pitt, Neuroendocrine hepatic metastases: does aggressive management improve survival, Ann. Surg. 241 (2005) 776–785.

[4] R. Rossi, S. Massironi, D. Conte, M. Perrachi, Therapy for metastatic pancreatic neuroendocrine tumors, Ann. Trans. Med. 2 (2014) 8–15, http://dx.doi.org/10.3978/j.issn.2305-5839.2013.03.01.

[5] M. Pavel, E. Baudin, A. Couvelard, E. Krenning, K. Oberg, T. Steinmuller, et al., ENETS consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut and unknown primary, Neuroendocrinology 95 (2012) 157–176.

[6] R. Garcia-Carbonero, J. Capdevila, G. Crespo-Herrero, J.A. Diaz-Perez, M.P. Martinez del Prado, V. Alonso Orduna, et al., Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National cancer Registry of Spain, Ann. Oncol. 21 (2010) 1794–1803, PMID 20139056.

[7] T. Ochiai, S. Komiyama, H. Ikoma, T. Kubota, M. Nakanishi, D. Ichikawa, S. Kikuchi, H. Fujiwara, C. Sakakura, Y. Kokuba, T. Sonoyama, E. Otsuji, A case report of metastatic neuroendocrine carcinoma of the right adrenal gland successfully treated with chemotherapy and surgery, Int. J. Clin. Oncol. 15 (2010) 423–427.

[8] K.Y. Lam, C.Y. Lo, Metastatic tumours of the adrenal glands: a 30 year experience in a teaching hospital, Clin. Endocrinol. 56 (2002) 95–101.

[9] C. Carreras, H.R. Kulkarni, R.P. Baum, Rare metastases detected by 68Ga-somatostatin receptor PET/CT in patients with neuroendocrine tumors, Recent Results Cancer Res. 194 (2013) 379–384.

[10] T. Tanvetyanon, L.A. Robinson, M.J. Schell, V.E. Strong, R. Kapoor, D.G. Coit, G. Bepler, Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small cell lung cancer: a systematic review and pooled analysis, J. Clin. Oncol. 26 (2008) 1142–1147, http://dx.doi.org/10.1200/JCO.2007.14.2091.

[11] M. Uemura, H. Kim, M. Ikeda, J. Nishimura, T. Hata, I. Takemasa, et al., Long term outcome of adrenalectomy for metastasis from colorectal cancer with other metastatic sites: a report of 3 cases, Oncol. Lett. 12 (2017) 1649–1654, http://dx.doi.org/10.3892/ol.2016.4897.

[12] M. Kuczyk, G. Wegener, U. Jonas, The therapeutic value of adrenalectomy in case of solitary metastatic spread originating from primary renal cancer, Eur. Urol. 48 (2005) 252–257, http://dx.doi.org/10.1016/j.eururo.2005.04.004.

[13] I. Peters, M. Hora, T.R. Herrmann, C. von Klot, G. Wegener, P. Stransky, O. Hes, M.A. Kuczyk, A.S. Merseburger, Incidence of synchronous and metachronous adrenal metastases following tumor nephrectomy in renal cell cancer patients: a retrospective bi-center analysis, SpringerPlus 2 (2012) 293–302.

[14] S.H. Kim, M.F. Brennan, P. Russo, M.E. Burt, D.G. Coit, The role of surgery in the treatment of clinically isolated adrenal metastasis, Cancer 82 (1998) 389–394.

[15] A.I. Sarela, I. Murphy, D.G. Coit, K.C. Conlon, Metastasis to the adrenal gland: the emerging role of laparoscopic surgery, Ann. Surg. Oncol. 10 (2003) 1191–1196.

[16] N.A. Hamilton, T.C. Liu, A. Cavatiao, K. Mawad, L. Chen, S.S. Strasberg, D.C. Linehan, D. Cao, Ki-67 predicts disease recurrence and poor prognosis in pancreatic neuroendocrine tumors, Surgery 152 (2012) 107–113, http://dx.doi.org/10.1016/j.surg.2012.02.011.

[17] L.M. Rooper, R. Sharma, Q.K. Li, P.B. Illei, W.H. Westra, INSM1 demonstrates superior performance to the individual and combined use of synaptophysin, chromogranin and CD56 for diagnosing neuroendocrine tumors of the thoracic cavity, Am. J. Surg. Pathol. 41 (2017) 1561–1569, PMID:28719469.

[18] N.M. El-Assaly, N. El Ashry, I. Mostafa, M. El Ghanman, M. Attia, Serum chromogranin-A and serum PIVKA as useful complementary diagnostic markers for HCC, Res. J. Med. Med. Sci. 4 (2008) 391–401.

[19] D.Y. Kim, Y.H. Paik, S.H. Ahn, Y.J. Youn, J.W. Choi, J.K. Kim, et al., PIVKA-II is a useful tumor marker for recurrent hepatocellular carcinoma after surgical resection, Oncology 72 (Suppl. 1) (2007) 52–57, http://dx.doi.org/10.1159/000111707.

[20] R.A. Agha, A.J. Fowler, A. Saetta, I. Barai, S. Rajmohan, D.P. Orgill, for the SCARE Group, The SCARE statement: consensus-based surgical case report guidelines, Int. J. Surg. 34 (2016) 180–186.