

Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Surgical resection of splenic metastasis from the adenosquamous gallbladder carcinoma: A case report



Masashi Utsumi*, Hideki Aoki, Tomoyoshi Kunitomo, Yutaka Mushiake, Nobuhiko Kanaya, Isao Yasuhara, Takashi Arata, Kou Katsuda, Kohji Tanakaya, Hitoshi Takeuchi

Department of Surgery, National Hospital Organization Iwakuni Clinical Center, Iwakuni, Japan

ARTICLE INFO

Article history:

Received 20 October 2015
Received in revised form 24 January 2016
Accepted 24 January 2016
Available online 2 February 2016

Keywords:

Adenosquamous carcinoma
Gallbladder carcinoma
Splenic metastasis

ABSTRACT

INTRODUCTION: Splenic metastasis of gallbladder carcinoma is extremely rare. Specific anatomical, histological, and functional properties of spleen are believed to be responsible for the rarity of solitary splenic metastasis.

PRESENTATION OF CASE: We present the case of a 62-year-old female who developed metachronous splenic metastasis of adenosquamous carcinoma of the gallbladder. We performed central bisegmentectomy of the liver for gallbladder carcinoma. The patient subsequently presented 3 months later with isolated splenic metastasis and liver metastasis. Splenectomy and partial hepatectomy was performed at this time. Histological examination confirmed metastatic adenosquamous carcinoma of the gallbladder. No signs of recurrence were observed at 3 months after the second surgery.

DISCUSSION: Although splenectomy provides a potential means of radical treatment in patients with isolated splenic metastases, it should be performed with caution as splenic metastatic lesions may represent the initial clinical manifestation of systemic metastases at multiple sites. In this case, radical surgery was performed following the confirmation of no new unresectable metastatic lesions or systemic dissemination.

CONCLUSION: This is the first report on the adenosquamous splenic metastasis from the gallbladder carcinoma. Curative resection may be the treatment of choice for prolonging survival in patients with the splenic metastasis of gallbladder carcinoma.

© 2016 The Authors. Published by Elsevier Ltd. on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Splenic metastases are rare, comprising 0.96% of reported cases of metastatic cancer [1]. Specific anatomical, histological, and functional properties of the spleen are believed to be responsible for the rarity of solitary splenic metastasis. As majority of splenic metastases are detected concurrently with multi-organ metastases, isolated splenic metastasis is extremely rare. Gallbladder (GB) carcinoma commonly metastasizes to the liver and regional lymph nodes and rarely the spleen. Adenosquamous carcinoma of GB is a relatively rare (<10%) type of gallbladder carcinoma, defined as being comprised of 25–99% squamous cells [2,3].

Abbreviations: GB, gallbladder; CT, computed tomography; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; SCC, squamous cell carcinoma antigen.

* Corresponding author at: Iwakuni Clinical Center, Department of Surgery, 1-1-1 Atago-machi, Iwakuni-shi, Yamaguchi 740-8510, Japan. Fax: +81 827 35 5600.

E-mail address: masashi11232001@yahoo.co.jp (M. Utsumi).

In this study, we report a case of splenic metastasis of adenosquamous carcinoma of GB occurring 3 months after initial curative treatment which was treated by splenectomy.

2. Presentation of case

We report the case of a 62-year-old female who presented with right hypochondralgia and was subsequently diagnosed with gallbladder cancer by abdominal ultrasonography before referral to our hospital for possible surgery. Computed tomography (CT) revealed an irregular gallbladder mass involving the liver (Fig. 1). A pre-operative diagnosis of stage T3N0M0 gallbladder carcinoma was made according to the UICC classification [4]. Serum levels of tumor biomarkers, including carcinoembryonic antigen and carbohydrate antigen 19-9 (CA19-9), were within the normal limits. However, squamous cell carcinoma antigen (SCC) was higher than the normal range (6.5 ng/ml; reference values, 0–1.5 ng/ml). Central bisegmentectomy of the liver with partial resection of transverse colon, as performed as laparotomy, revealed liver metastasis in segment 8 and invasion into the transverse colon. Lymph node dissection at

<http://dx.doi.org/10.1016/j.ijscr.2016.01.032>

2210-2612/© 2016 The Authors. Published by Elsevier Ltd. on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

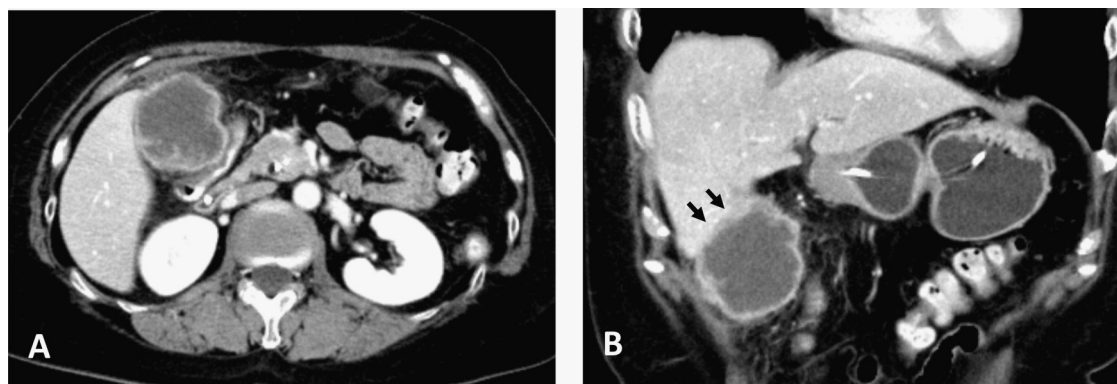


Fig. 1. Abdominal computed tomography reveal the gallbladder carcinoma.

(A) The axial view of contrast-enhanced CT. (B) The coronal view of contrast-enhanced CT. Contrast-enhanced CT demonstrating increased gallbladder wall thickness and a low density irregular mass within the gallbladder. The mass was diagnosed as gallbladder cancer with invasion into the liver (arrows).

the hepatoduodenal ligament and along the common hepatic artery was also performed.

Macroscopically, the GB tumor was 8.0 cm in size with massive invasion into the liver and transverse colon. Histopathological examination of the specimen demonstrated adenosquamous carcinoma with liver metastases in segment 8 and lymph node metastases along the common bile duct. Therefore, the final pathological stage was determined as pT4N1M1, pStage IV, according to the UICC system [4]. Serum SCC levels decreased to 0.6 ng/ml during the early postoperative period. Two courses of adjuvant chemotherapy consisting of TS-1 80 mg/day for 14 days were administered with a 7-day interval.

Three months after initial surgery, serum SCC levels elevated to 8.7 ng/ml. Enhanced CT imaging revealed a low density mass in the spleen (Fig. 2A). Fluorodeoxyglucose positron emission tomography (FDG-PET) demonstrated abnormal FDG accumulation in the spleen (Fig. 2B). Other remote organ metastases were not observed on either CT or FDG-PET imaging. The previous history of GB carcinoma contributed to a presumptive diagnosis of metachronous isolated splenic metastases.

Two courses of intravenous chemotherapy consisting of gemcitabine (1200 mg) and cisplatin (30 mg)/day were administered due to early metastasis after the initial surgery. However, serum SCC levels gradually increased to 65.8 ng/ml. Five months after the initial surgery, CT imaging revealed an enlarging splenic tumor and new liver metastasis in segment 6, indicating a poor response to chemotherapy (Fig. 2C). No other intra-abdominal organ metastases or peritoneal dissemination were observed at this time. Therefore, splenectomy and partial liver resection were performed for the treatment of splenic and liver metastases. Upon laparotomy, intraoperative lavage cytology was negative and no recurrence of nodular masses was observed except in the spleen and liver. As the splenic tumor had invaded into the left diaphragm, combined partial resection of the left diaphragm was performed.

Macroscopically, the splenic tumor was solitary and homogeneous. The cut surface of the resected specimen revealed a whitish splenic mass with a diameter of 6.7 cm (Fig. 3). Histopathologically, the splenic and liver tumors were found to be adenosquamous carcinoma, consistent with metastasis of the primary GB carcinoma (Fig. 4). The postoperative course was uneventful. SCC levels decreased to within normal limits. The patient was discharged on postoperative day 13. Chemotherapy consisting of TS-1 or gemcitabine and cisplatin was not effective. Therefore, we administered adjuvant chemotherapy consisting of docetaxel and nedaplatin, which we expected to be effective. There was no sign of recurrence at 3 months after the second surgery.

3. Discussion

Splenic metastases from non-hematologic malignancies account for only 0.96% of the metastatic carcinoma and 2.9–4.4% of the autopsied carcinoma specimens [5,6]. In majority of cases, the spleen is involved as a part of diffuse carcinomatosis with the presence of splenic metastases usually indicating widespread tumor dissemination [7,8]. Very few splenic metastases are observed as isolated splenic lesions, synchronous or metachronous to the primary tumor. There have been few case reports and reviews of isolated splenic metastases from carcinoma of the colorectum, stomach, kidney, or ovary [9–14]. Splenic metastasis from GB cancer is extremely rare. Taki et al. first reported isolated splenic metastasis from adenocarcinoma of GB [15]. Therefore, this presents the second reported case of the splenic metastasis of GB successfully treated by surgical resection. According to histopathological diagnosis, to the best of our knowledge, this is the first report of splenic metastasis of adenosquamous cancer of the gallbladder.

The rarity of splenic metastases is believed to be due mechanical factors and the splenic microenvironment [16]. Mechanical factors related to the spleen, such as constant blood flow through the spleen, rhythmic contraction of the splenic capsule, the sharp angle of the splenic artery after branching from the celiac trunk, and the lack of afferent lymphatic vessels, may protect against tumor cells infiltration and the development of metastases [17]. Further, the splenic microenvironment may inhibit cancer cell proliferation [17,18]. Although the precise mechanisms underlying the inhibition of cancer cell growth has yet to be fully elucidated, the immunological environment of the spleen may be particularly hostile to tumor cells.

Adenosquamous carcinoma of GB is a relatively rare type of gallbladder carcinoma associated with worse prognosis. Primary GB carcinoma includes the following histological types in a decreasing order of incidence: adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma, and oat cell carcinoma [19]. In GB carcinoma, tumor stages of adenosquamous and squamous cell carcinoma are significantly advanced at presentation, compared to adenocarcinoma [3,20,21]. The overall prognosis of adenosquamous GB carcinoma appears to be worse, with most patients dying within few months of diagnosis [2]. However, curative surgical resection of adenosquamous or squamous cell carcinoma might result in disease-free survival rates comparable to those for adenocarcinoma [3,20,21].

A metastatic origin should be suspected for all isolated splenic tumors found during oncologic follow-up. Serum tumor marker levels reportedly have predictive value in detecting isolated splenic

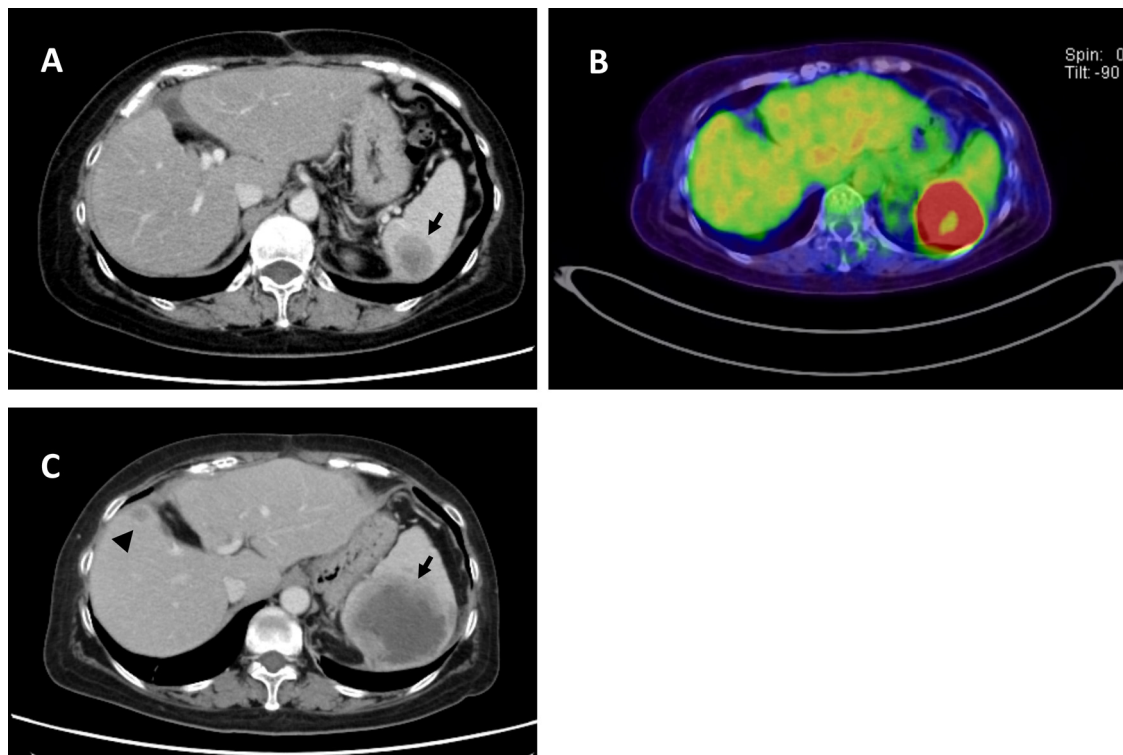


Fig. 2. Abdominal computed tomography and PET-CT reveal a splenic tumor.

(A) Contrast-enhanced CT demonstrating a 4-cm low density splenic mass (arrow) considered to represent splenic metastasis 3 months after initial surgery. (B) PET-CT demonstrated uptake of FDG in the spleen. No other intra-abdominal organ metastases or peritoneal dissemination were observed. The mass was diagnosed as a solitary splenic metastasis. (C) Contrast-enhanced CT demonstrating a 6.5-cm enlarging splenic mass (arrow) and a 1-cm nodule (arrowhead) in the liver segment 8, 5 months after initial surgery.

metastases prior to confirmation by imaging [13,22]. There are currently no diagnostic criteria for the detection of splenic metastasis by imaging modalities. Although multi-modal imaging techniques, including CT [23], MRI [24], and FDG-PET [24], have diagnostic utility in such cases, the differentiation of a primary splenic tumor from lymphoma, vascular tumors, or infectious disorders can be challenging.

In this case, elevated serum SCC levels, CT imaging, abnormal FDG accumulation on PET, and a history of gallbladder carcinoma were all highly suggestive of splenic metastasis. Though chemotherapy was initiated immediately after the initial surgery, liver metastasis developed two months later. Splenectomy with partial liver resection was performed at this time. Pathological examination of the surgical specimen demonstrated adenosquamous carcinoma with morphology resembling the primary gallbladder carcinoma confirming our initial clinical diagnosis.

Although splenectomy provides a potential means of radical treatment in patients with isolated splenic metastases, it should be performed with caution as splenic metastatic lesions may represent the initial clinical manifestation of systemic metastases at multiple sites [9]. Under such circumstances, surgical stress from splenectomy may cause severe adverse clinical effects. Accordingly, following the discovery of the splenic lesion, two cycles of chemotherapy were administered in this case, rather than immediate splenectomy, which also allowed for an observational period. Radical surgery was performed following the subsequent confirmation of no new unresectable metastatic lesions or systemic dissemination. A widely understood complication of splenectomy is the asplenic patient's susceptibility to infection [25], particu-

larly to the pathogens, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Prophylactic vaccinations against these bacteria should ideally be given to patients about 2 weeks before the planned surgery or roughly 2 weeks after the surgery. Furthermore, intraperitoneal hemorrhage is a fatal complication of splenectomy [26,27]. Some medical conditions, such as use of anticoagulant agents to prevent thrombosis and pancreatic injury during surgery, have been identified and might be one of the risk factors leading to hemorrhage after splenectomy [28].

Previous studies have reported long-term remission following the detection of isolated splenic metastasis indicating this finding may not necessarily be a sign of widespread, terminal cancer [9–14,29]. Although the clinical course of splenic metastasis is challenging to predict, surgical resection may offer a feasible treatment option. As an alternative treatment, chemotherapy might be indicated for patients who had a relapse after surgery; however, no standard treatment with solid evidence of a survival benefit has yet been established for such patients. Gemcitabine plus cisplatin has become an established standard therapeutic regimen for advanced biliary cancer [30,31]. New therapeutic modalities, such as molecular-targeted therapies have recently been used for unresectable disease, and randomized controlled trials are under way to establish standard adjuvant chemotherapy for the resectable disease [32–34].

We were unable to identify any reports of the splenic metastasis of GB carcinoma, or adenosquamous carcinoma of the gallbladder, in previous literature. Further accumulation of reports of this rare condition are therefore required to determine the efficacy of splenectomy in increasing survival and to define the role postoperative chemotherapy.



Fig. 3. Macroscopic view of the cut specimen reveal the splenic tumor. Cut surfaces of resected and fixed specimen from the second operation. The splenic tumor was found to have a diameter of 6.7 cm.

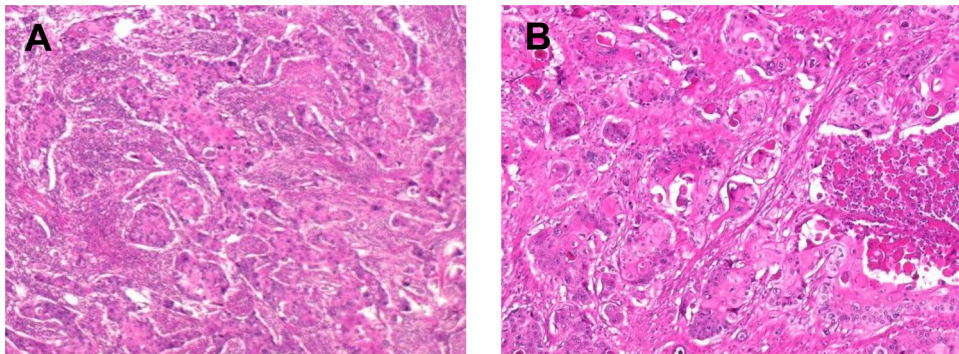


Fig. 4. Histopathologically demonstrated the primary gallbladder adenosquamous carcinoma and splenic tumor. Representative histological images of (A) the primary gallbladder adenosquamous carcinoma and (B) the splenic metastasis (hematoxylin–eosin stain, $\times 40$). Both had features consistent with adenosquamous carcinoma.

4. Conclusion

Splenic metastasis of GB carcinoma is an extremely rare finding during follow-up of GB carcinoma. Curative resection may represent the treatment of choice for prolonging survival in patients with splenic metastasis of GB carcinoma.

Conflict of interest

All authors declare no potential conflict of interest.

Funding

None.

Author's contribution

MU performed literature review and wrote the manuscript. MU, HA and TK were involved in the clinical management of the patient. YM, NK, IY, KK, KT, and HT participated in literature review. HA and KT revised the manuscript. All authors were involved in the management of the patient. All authors read and approved the final manuscript.

Consent

Written informed consent was obtained from the patient for the information to be included in our manuscript. The information has been de-identified to the best of our ability to protect his privacy.

Guarantor

Hideki Aoki M.D., Ph.D (aoki@iwakuni-nh.go.jp). Department of Surgery, National Hospital Organization. Iwakuni Clinical Center, Iwakuni, Japan.

Ethical approval

Ethical approval not needed.

Acknowledgement

The authors wish to thank Rie Yamasaki for the pathological diagnosis.

References

- [1] J. Sauer, K. Sobolewski, K. Dommisch, Splenic metastases—not a frequent problem, but an underestimate location of metastases: epidemiology and course, *J. Cancer Res. Clin. Oncol.* 135 (2009) 667–671.
- [2] J.C. Roa, O. Tapia, A. Cakir, O. Basturk, N. Dursun, D. Akdemir, et al., Squamous cell and adenocarcinomas of the gallbladder: clinicopathological analysis of 34 cases identified in 606 carcinomas, *Mod. Pathol.* 24 (2011) 1069–1078.
- [3] R. Kalayarsan, A. Javed, P. Sakhuja, A.K. Agarwal, Squamous variant of gallbladder cancer: is it different from adenocarcinoma, *Am. J. Surg.* 206 (2013) 380–385.
- [4] Sobin LH GM, Witterkind C, editors., ed. Tnm classification of malignant tumors. New York : Wiley-Backwell, 2009.
- [5] D.A. Nash Jr., C.C. Sampson, Secondary carcinoma of the spleen: its incidence in 544 cases and a review of the literature, *J. Natl. Med. Assoc.* 58 (1966) 442–446.
- [6] T. Berge, Splenic metastases: frequencies and patterns, *Acta Pathol. Microbiol. Scand. A* 82 (1974) 499–506.
- [7] M.L. Gemignani, D.S. Chi, C.C. Gurin, J.P. Curtin, R.R. Barakat, Splenectomy in recurrent epithelial ovarian cancer, *Gynecol. Oncol.* 72 (1999) 407–410.
- [8] K.Y. Lam, V. Tang, Metastatic tumors to the spleen: a 25-year clinicopathologic study, *Arch. Pathol. Lab. Med.* 124 (2000) 526–530.
- [9] Y.P. Zhu, Y.P. Mou, J.J. Ni, Y.C. Zhou, J.W. Jiang, Z.N. Jiang, et al., Isolated splenic metastases from gastric carcinoma: a case report and literature review, *World J. Gastroenterol.* 19 (2013) 5199–5203.
- [10] K.K. Kamaleshwaran, B. Sivanesan, D. Shibu, A.S. Shinto, Rare case of isolated splenic metastases from gastric cancer detected with fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography, *Indian J. Nucl. Med.* 28 (2013) 119–120.
- [11] M. Popovic, G. Barisic, Z. Krivokapic, Isolated splenic metastases of colorectal carcinoma—case report and review of literature, *Acta Chir. Iugosl.* 55 (2008) 73–76.
- [12] T. Okuyama, M. Oya, H. Ishikawa, Isolated splenic metastasis of sigmoid colon cancer: a case report, *Jpn. J. Clin. Oncol.* 31 (2001) 341–345.
- [13] R. Gencosmanoglu, F. Aker, G. Kir, N. Tozun, Isolated metachronous splenic metastasis from synchronous colon cancer, *World J. Surg. Oncol.* 4 (2006) 42.
- [14] T.F. Nunes, D. Szejnfeld, L.N. Mijji, S.M. Goldman, Isolated metachronous splenic metastasis from renal cell carcinoma after 5 years, *BMJ Case Rep.* (2012) 2012.
- [15] Y. Taki, T. Sugiura, K. Matsunaga, H. Kanemoto, T. Mizuno, Y. Okamura, et al., Postoperative isolated splenic metastasis from gallbladder cancer: report of a case, *Clin. J. Gastroenterol.* 6 (2013) 480–484.
- [16] E. Comperat, A. Bardier-Dupas, P. Camparo, F. Capron, F. Charlotte, Splenic metastases: clinicopathologic presentation, differential diagnosis, and pathogenesis, *Arch. Pathol. Lab. Med.* 131 (2007) 965–969.
- [17] J.C. Kim, C.S. Jeong, H.C. Kim, C.S. Yu, G.H. Kang, M.G. Lee, Isolated splenic metastasis from colorectal carcinoma: a case report, *J. Korean Med. Sci.* 15 (2000) 355–358.
- [18] J.N. Miller, G.W. Milton, An experimental comparison between tumour growth in the spleen and liver, *J. Pathol. Bacteriol.* 90 (1965) 515–521.
- [19] D.E. Henson, J. Albores-Saavedra, D. Corle, Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates, *Cancer* 70 (1992) 1493–1497.
- [20] K.M. Chan, M.C. Yu, W.C. Lee, Y.Y. Jan, M.F. Chen, Adenosquamous/squamous cell carcinoma of the gallbladder, *J. Surg. Oncol.* 95 (2007) 129–134.
- [21] W.S. Kim, K.T. Jang, D.W. Choi, S.H. Choi, J.S. Heo, D.D. You, et al., Clinicopathologic analysis of adenosquamous/squamous cell carcinoma of the gallbladder, *J. Surg. Oncol.* 103 (2011) 239–242.
- [22] E. Opocher, R. Santambrogio, P. Bianchi, U. Cioffi, M. De Simone, S. Vellini, et al., Isolated splenic metastasis from gastric carcinoma: value of cea and ca 19-9 in early diagnosis: report of two cases, *Am. J. Clin. Oncol.* 23 (2000) 579–580.
- [23] S. Senturk, M. Karcaaltincaba, D. Akata, Ct diagnosis of intrasplenic metastasis from ovarian carcinoma, *Eur. J. Radiol.* 81 (2012) 1094–1099.
- [24] M. Soussan, G. Pop, M.J. Ouvrier, A. Neuman, P. Weinmann, Diagnosis of synchronous isolated splenic metastasis from lung adenocarcinoma: complementary role of FDG PET/CT and diffusion-weighted MRI, *Clin. Nucl. Med.* 36 (2011) 707–709.
- [25] A. Cadilli, C. de Gara, Complications of splenectomy, *Am. J. Med.* 121 (2008) 371–375.
- [26] K. Kojouri, S.K. Vesely, D.R. Terrell, J.N. George, Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications, *Blood* 104 (2004) 2623–2634.
- [27] Winslow ER, Brunt LM. Perioperative outcomes of laparoscopic versus open splenectomy: A meta-analysis with an emphasis on complications. *Surgery* 2003;134:647-653; discussion 654-645.
- [28] Y. Qu, S. Ren, C. Li, S. Qian, P. Liu, Management of postoperative complications following splenectomy, *Int. Surg.* 98 (2013) 55–60.
- [29] Z.K. Otrock, M.A. Seoud, M.J. Khalifeh, J.A. Makarem, A.I. Shamseddine, Laparoscopic splenectomy for isolated parenchymal splenic metastasis of ovarian cancer, *Int. J. Gynecol. Cancer* 16 (2006) 1933–1935.
- [30] J.W. Valle, H. Wasan, P. Johnson, E. Jones, L. Dixon, R. Swindell, et al., Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study—the UK ABC-01 study, *Brit. J. Cancer* 101 (2009) 621–627.
- [31] J. Valle, H. Wasan, D.H. Palmer, D. Cunningham, A. Anthony, A. Maraveyas, et al., Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer, *N. Engl. J. Med.* 362 (2010) 1273–1281.
- [32] T. Takada, H. Amano, H. Yasuda, Y. Nimura, T. Matsushiro, H. Kato, et al., Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma: a phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma, *Cancer* 95 (2002) 1685–1695.
- [33] P.A. Philip, M.R. Mahoney, C. Allmer, J. Thomas, H.C. Pitot, G. Kim, et al., Phase II study of erlotinib in patients with advanced biliary cancer, *J. Clin. Oncol.* 24 (2006) 3069–3074.
- [34] J. Lee, S.H. Park, H.M. Chang, J.S. Kim, H.J. Choi, M.A. Lee, et al., Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study, *Lancet Oncol.* 13 (2012) 181–188.

Open Access

This article is published Open Access at sciendo.com. It is distributed under the [IJSCR Supplemental terms and conditions](#), which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.