

Case Report

Primary thyroid extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type in a patient with breast cancer: a case report and review of literature

Xiao-Cong Zhou^{1,2*}, Meng Su^{3*}, Yi Jiang⁴, Pei-Zhen Huang⁵, Ying-Hai Ye¹, Qing-Si He²

Departments of ¹Surgery, ⁴Pathology, ⁵Ultrasonography, The Dingli Clinical Institute of Wenzhou Medical University (Wenzhou Central Hospital), Wenzhou, Zhejiang, P. R. China; ²Department of General Surgery, Qilu Hospital of Shandong University, Jinan, Shandong, P. R. China; ³Department of Radio-Chemotherapy Oncology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, P. R. China. *Equal contributors and co-first authors.

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Abstract: Background: Breast cancer coexisting with primary thyroid lymphoma is a very rare combination of multiple primary malignant neoplasms. We present an unusual case of primary thyroid extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) occurring in a patient with breast cancer. Case presentation: A 76-year-old female was admitted to our hospital with bilateral thyroid nodules, which were detected two years and eight months ago. In May 2006, she underwent modified radical mastectomy for invasive ductal carcinoma of the left breast. The patient was treated with total left thyroid lobectomy, isthmusectomy and subtotal right lobectomy. Histopathological and immunohistochemical (IHC) examination of surgical specimen confirmed the diagnosis of primary thyroid MALT lymphoma. She received chemotherapy and levothyroxine substitution therapy postoperatively. At the time of last follow-up (seven years and ten months after thyroid surgery), she was found to have a good prognosis (there was no recurrence). Conclusion: Clinical awareness of primary thyroid lymphoma in patients with malignant thyroid nodules should be increased. Surgery should be recommended for suspected malignant thyroid nodules in patients with a history of breast cancer. Post-operative histopathological and IHC examination of surgical specimen confirms the diagnosis. Early treatment is associated with a good prognosis.

Keywords: Thyroid neoplasms, extranodal marginal zone B-cell lymphoma, mucosa-associated lymphoid tissue type, breast neoplasms, multiple primary neoplasms

Introduction

Primary thyroid lymphoma is a rare tumor, which accounts for approximately 1-5% of all thyroid malignancies [1-4], and 1-2.5% of all lymphomas [1-3]. Primary thyroid lymphoma is a heterogeneous disease, which includes a wide spectrum of histological subtypes, and a predilection for middle-aged and elderly females [5, 6]. The majority of thyroid lymphomas are non-Hodgkin's lymphomas of B-cell origin [3, 7]. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) represents a distinct histological subtype of B-cell non-Hodgkin lymphoma [8]. Increased prevalence of thyroid

cancer in patients with breast cancer has been frequently reported in recent years [9, 10]; however, occurrence of thyroid MALT lymphoma in patients with breast cancer is exceedingly rare. Here we present a very rare case of breast invasive ductal carcinoma with thyroid MALT lymphoma.

Case presentation

A 76-year-old woman was admitted to our hospital with bilateral thyroid nodules in January 2009. The thyroid nodules were initially detected in May 2006 with ultrasonographic findings of bilateral thyroid enlargement, heterogeneous echoes, several small patchy hypoechoic areas,

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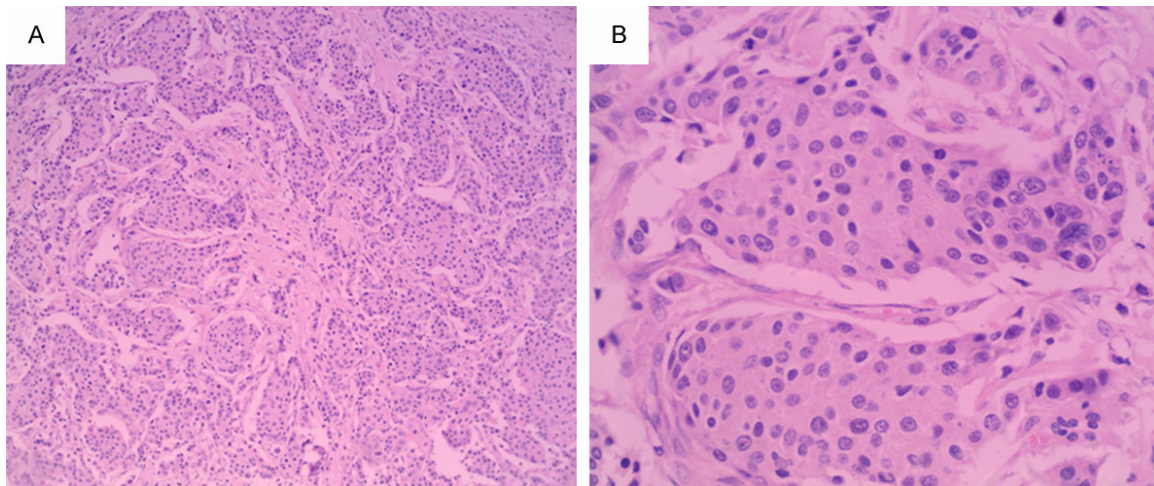


Figure 1. Histopathological examination revealed a 1.5 × 0.8 cm invasive ductal breast carcinoma of histological grade 3 (hematoxylin-eosin stain): original magnification × 100 (A), original magnification × 400 (B).

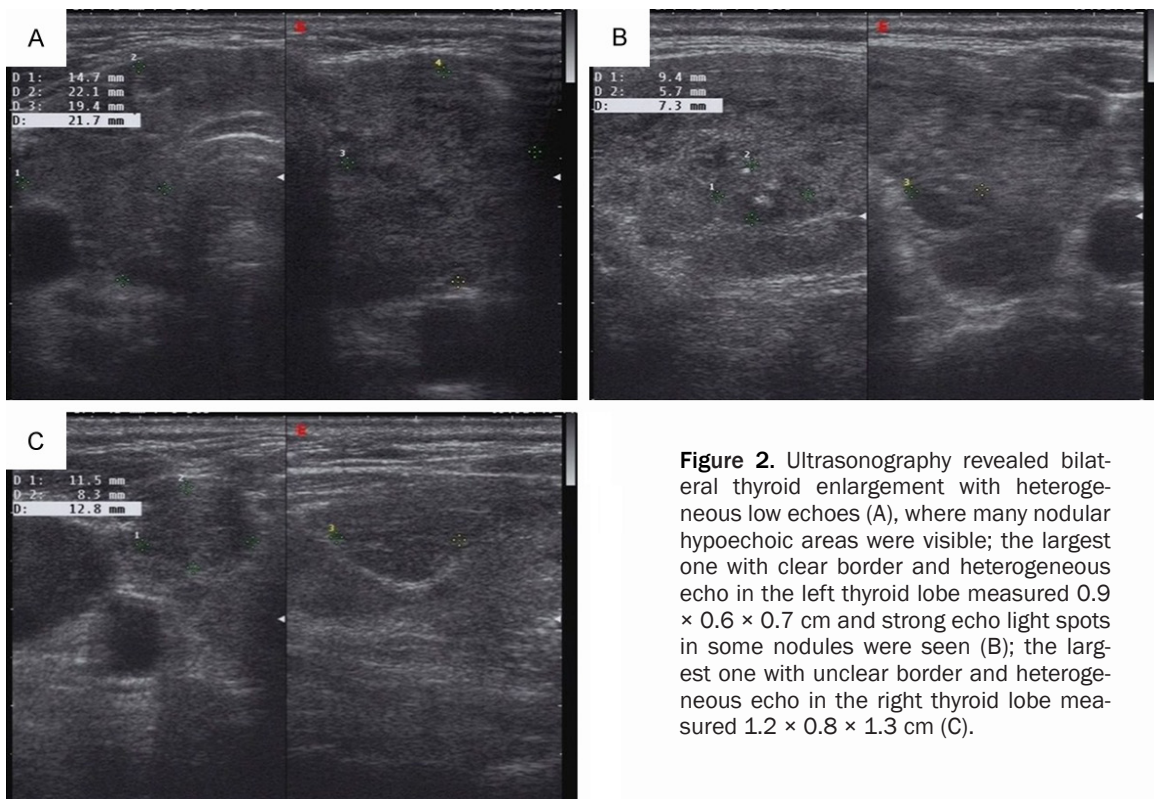


Figure 2. Ultrasonography revealed bilateral thyroid enlargement with heterogeneous low echoes (A), where many nodular hypoechoic areas were visible; the largest one with clear border and heterogeneous echo in the left thyroid lobe measured 0.9 × 0.6 × 0.7 cm and strong echo light spots in some nodules were seen (B); the largest one with unclear border and heterogeneous echo in the right thyroid lobe measured 1.2 × 0.8 × 1.3 cm (C).

and a well-defined (0.5 × 0.5 cm) hypoechoic nodule with a few strong echo light spots in the lower pole of the left thyroid lobe. Ultrasonic diagnosis was bilateral thyroid enlargement with echo changes, and left thyroid nodule with microcalcification. Thyroid function tests showed no significant abnormalities at that time. The patient had also undergone modified radical mastectomy for invasive ductal carcinoma

of the left breast in May 2006. Histopathological examination revealed a 1.5 × 0.8 cm invasive ductal breast carcinoma of histological grade 3 (Figure 1) with skin infiltration; one resected axillary lymph node was positive for carcinoma. Immunohistochemical (IHC) examination showed that the left breast cancer was negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth

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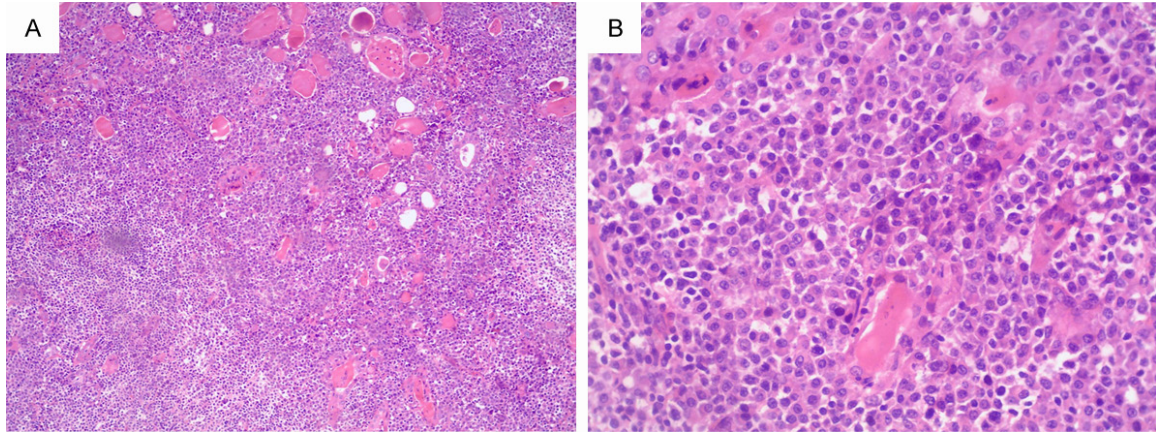


Figure 3. Postoperative examination of paraffin section of surgical specimen revealed primary thyroid MALT lymphoma: The lesion was characterized by diffuse hyperplasia of small-to medium-sized lymphocytes with slight irregular nuclei, occasional small nucleoli, and abundant pale-stained cytoplasm. Monocytoïd-like cells, plasma-like cells and lymphoepithelial lesions can also be seen in the lesion. (Hematoxylin-eosin stain): original magnification $\times 100$ (A), original magnification $\times 400$ (B).

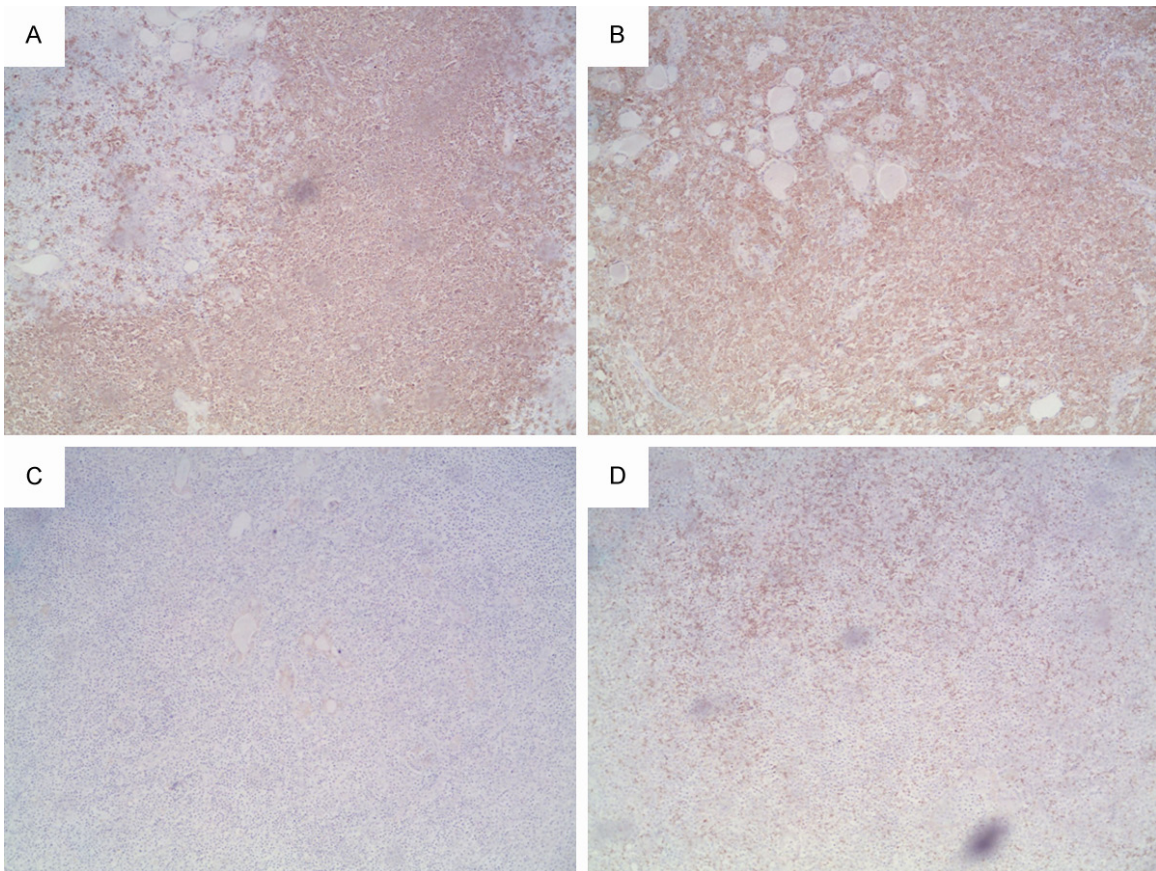


Figure 4. Immunohistochemical examination showing tumor cells positive for CD20 (A) and CD79 α (B), and negative for CD5 (C) and CD3 (scattered CD3-positive cells are reactive T cells) (D) (original magnification $\times 100$).

factor receptor-2 (HER-2). The patient had received adjuvant chemotherapy postoperatively.

During the intervening period of two years and eight months, she was free of disease except for the presence of thyroid nodules, until

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January 2009, when ultrasonography (**Figure 2**) revealed bilateral thyroid enlargement with heterogeneous low echoes, where many nodular hypoechoic areas were visible, the largest one with clear border and heterogeneous echo in the left thyroid lobe measured $0.9 \times 0.6 \times 0.7$ cm and strong echo light spots were seen in some nodules. The largest one with unclear border and heterogeneous echo in the right thyroid lobe measured $1.2 \times 0.8 \times 1.3$ cm. Ultrasonic diagnosis was bilateral thyroid enlargement with echo changes, bilateral thyroid nodules, and suspected calcification in the left thyroid nodules. A pre-operative thyroid function test showed elevated levels of thyroid-stimulating hormone (TSH) ($13.71 \mu\text{IU/mL}$; normal, $0.27\text{-}4.2 \mu\text{IU/mL}$) and thyroid peroxidase antibody (TPOAb) (294.50 IU/mL ; normal, $0\text{-}34 \text{ IU/mL}$). Serum levels of triiodothyronine (T3), thyroxine (T4), free T3 (FT3), free T4 (FT4) and serum thyroglobulin antibody (TgAb) were within the normal range.

A fine needle aspiration (FNA) of the thyroid was not routinely performed in our institution at that time, so it was not done. Total left thyroid lobectomy, isthmusectomy and subtotal right lobectomy were performed. Postoperative examination of paraffin section of surgical specimen (**Figure 3**) showed diffuse hyperplasia of small-to medium-sized lymphocytes with slightly irregular nuclei, occasional small nucleoli, and abundant pale-stained cytoplasm. Monocytoid-like cells, plasma-like cells and lymphoepithelial lesions were also observed. On IHC examination (**Figure 4**), the tumor cells were positive for CD20 and CD79 α , but negative for CD5, CD10, CD23, cyclinD1, CD3 and Bcl-2. The plasma cells were positive for CD79 α , and the follicular dendritic cells were also positive for CD21. The thyroid lesion was, therefore, diagnosed as primary thyroid MALT lymphoma. The patient received seven cycles of chemotherapy with CHOP (cyclophosphamide, adriamycin, vincristine, and prednisone) and levothyroxine substitution therapy postoperatively. At the time of last follow-up (seven years and ten months after thyroid surgery), no clinical or radiographic evidence of recurrence was found, and she continues to have a favorable prognosis.

Discussion

Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)

was first described by Isaacson and Wright in 1983 [11]. It is a distinct clinicopathological entity included in the Revised European-American Classification of Lymphoid Neoplasms [12] and the World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues [13]. This sub-group of lymphomas is classified as low-grade MALT lymphomas, and includes a number of extranodal B-cell lymphomas. The extranodal B-cell lymphomas are largely composed of small cells characterized by similar clinicopathological and molecular characteristics [14]. These include monocytoid-like or centrocyte-like cells, lymphoepithelial lesions, often with plasmacytoid differentiation and plasma cell infiltration, reactive lymphoid follicles, and occasional follicular colonization [4, 12, 15].

Gastrointestinal tract is the most common site of extranodal organ involvement for MALT lymphomas [16-18]. MALT lymphomas have also been described in various nongastrointestinal sites, including salivary gland, lung, ocular adnexa, skin, thyroid, breast, kidney and prostate [19-25]. Thyroid MALT lymphoma is extremely rare, owing to the lack of native lymphoid tissue in the thyroid gland. Intrathyroid lymphoid tissue is occurred in various pathological conditions in the setting of chronic inflammation or autoimmune thyroid disease, such as Hashimoto's thyroiditis or lymphocytic thyroiditis [1, 7, 26]. Histologically, the acquired lymphoid tissue bears a close resemblance to MALT and can evolve into lymphoma (including MALT lymphoma) [1, 21]; however, the exact mechanism underlying this malignant transformation is not yet clear [4, 27]. In our case, microscopic examination revealed thyroid MALT lymphoma in the presence of Hashimoto's thyroiditis. The pre-operative thyroid function test showed significantly elevated levels of serum TSH and TPOAb, which was consistent with the clinical diagnosis of Hashimoto's thyroiditis.

MALT lymphoma is the second most common histological type of thyroid lymphomas after diffuse large B-cell lymphoma [1, 7, 28], and both these lymphomas account for more than 70% of all thyroid lymphomas. Other types include follicular lymphoma, Hodgkin's disease, small lymphocytic lymphoma, Burkitt's lymphoma, plasmacytoma and T-cell lymphoma [1, 29]. Methods for treatment of primary thyroid lymphoma

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Table 1. Similar published cases of primary thyroid MALT lymphoma

Source	Gender (No.)	Age (years)	Treatment	Prognosis (No.)
Thieblemont C et al. [1]	Male/female: 0/6	Median: 62	Total thyroidectomy in 6 patients (including one patient with a stage IV disease received an adjuvant chemotherapy)	CR: 5 (treated with surgery alone)
Binesh F et al. [4]	Male: 1	69	Right thyroid lobectomy and radiotherapy	CR
Derringer GA et al. [7]	Male/female: 10/20	(Range, 34-84) Mean: 63.1	Surgery in 16 patients; surgery and radiotherapy in 5 patients; surgery and chemotherapy in 3 patients; surgery and combined therapy in 6 patients	CR
Zucca E et al. [8]	Male+female: 10	NA	Surgery with or without chemotherapy or radiotherapy	CR: 6, 5-year OS, CSS, and PFS were 100%
Thieblemont C et al. [21]	Male+female: 6	NA	Surgery, radiotherapy or chemotherapy	NA
Oh SY et al. [26]	Male/female: 10/17	(Range, 25-82) Median: 53	Surgery in 7 patients; surgery and radiotherapy in 5 patients; surgery and chemotherapy in 5 patients; surgery, chemotherapy and radiotherapy in 3 patients; radiotherapy in 1 patient; radiotherapy and chemotherapy in 1 patient; chemotherapy in 4 patients; observation in 1 patient	CR: 24, PR: 1, SD: 1, NE: 1
Serefhanoglu S et al. [30]	Female: 1	56	Total thyroidectomy and chemotherapy	CR
Sasai K et al. [32]	Male/female: 5/8	(Range, 28-82) Median: 71	Radiotherapy and chemotherapy in 12 patient; radiotherapy in 1 patient	CR

CR = complete response; PR = partial response; SD = stable disease; NE = not evaluable; NA = not available; OS (Overall survival) was defined as the time from diagnosis to death from any cause or last follow-up; CSS (Cause-specific survival) was defined as the time from diagnosis to death from disease or treatment-related causes. PFS (Progression-free survival) was defined as the time from diagnosis to primary treatment failure, relapse/progression, or death [8].

phomas included various surgical modalities, radiotherapy and chemotherapy. The choice of treatment in primary thyroid lymphomas is based on the histological subtype and the stage of the disease [1, 29]. For thyroid MALT lymphoma, when localized to the thyroid (stage IE), total thyroidectomy or radiation has a good response rate [1, 30]. In our case, radiation therapy was not administered. Instead, (because the bilateral thyroid nodules were considered suspicious of thyroid cancer by our clinicians before surgery, and the intraoperative frozen section of surgical specimen only showed lymphocytic thyroiditis and therefore the diagnosis of lymphatic sarcoma could not be completely excluded) surgery (total left thyroid lobectomy, isthmusectomy and subtotal right lobectomy), followed by systemic chemotherapy was administered to ensure that the occult disease had been treated adequately. Previous similar cases of primary thyroid MALT lymphoma were shown in **Table 1**.

MALT lymphoma is generally associated with good prognosis [1, 30, 31]; however, malignant transformation of MALT lymphoma into aggressive lymphoma worsens the prognosis [4, 6, 19, 32]. Clinicians often assume that malignant primary thyroid nodules in a patient with breast cancer are likely to be thyroid carcinoma (especially papillary subtype). Since patients with papillary thyroid carcinoma usually have

better outcomes [33] than those with breast cancer, comprehensive treatment of breast cancer tends to take precedence over other conditions. Due to the limited awareness about thyroid lymphoma (compared to thyroid carcinoma), breast cancer patients may not receive timely treatment for thyroid lymphoma. In our case, the thyroid nodules had been detected for two years and eight months. Luckily, after two years and eight months, the postoperative histopathological results of thyroid specimen confirmed the phenotype of MALT lymphoma. At the time of last follow-up (seven years and ten months after thyroid surgery) there was no recurrence and the patient continues to have a favorable prognosis.

Conclusion

Primary thyroid lymphoma is a rare thyroid malignancy, which as a clinical entity may be easily misdiagnosed as a thyroid carcinoma. The clinical awareness of primary thyroid lymphoma must be increased. We conclude that surgery should be recommended for suspected malignant thyroid nodules in patients with a history of breast cancer. The importance of early diagnosis should be recognized. Histopathological and immunohistochemical examination of surgical specimen confirms the diagnosis, thus treating the disease effectively and improving the prognosis.

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Disclosure of conflict of interest

None.

Address correspondence to: Ying-Hai Ye, Department of Surgery, The Dingli Clinical Institute of Wenzhou Medical University (Wenzhou Central Hospital), Wenzhou, Zhejiang, P. R. China. Tel: 86-577-88053100; Fax: 86-577-88070100; E-mail: yyh100161@163.com; Qing-Si He, Department of General Surgery, Qilu Hospital of Shandong University, Jinan, Shandong, P. R. China. Tel: 86-531-82166331; Fax: 86-531-82166331; E-mail: heqsurgeon@163.com

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