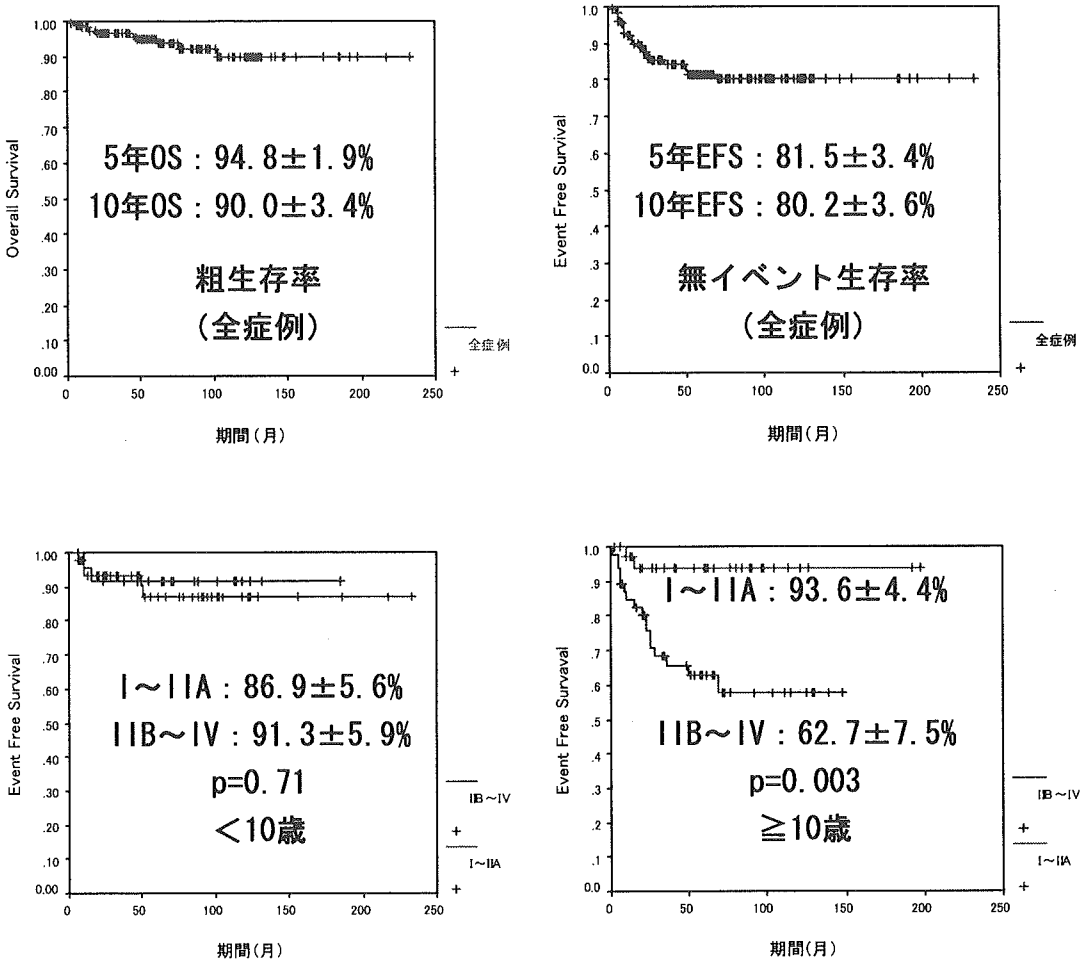
表8　予後因子の多変量解析

	予後不良因子	回帰係数	リスク比（CI　95%）	有意確率
全症例（n=157）				
性	男	0.88	2.4（0.95-6.2）	0.064
年齢	10歳以上	0.95	2.6（1.1-6.4）	0.036
治療年代	1994年以前	0.59	1.8（0.76-4.2）	0.18
病期	IIB以上	1.1	2.9（1.2-7.1）	0.023
巨大腫瘤	有り	-0.25	0.78（0.34-1.7）	0.56
照射の有無	有り	-0.035	0.97（0.31-3.0）	0.95
9歳以下（n=72）				
性	男	-0.61	0.54（0.1-2.9）	0.48
治療年代	1994年以前	1	2.8（0.31-26）	0.35
病期	IIB以上	0.057	1.1（0.2-5.7）	0.95
照射の有無	有り	1.9	6.4（0.75-54）	0.089
巨大腫瘤	有り	-13	0（Eventなしのため推計不能）	0.99
10歳以上(n=85)				
性	男	1.1	3.1（1-9.6）	0.045
治療年代	1994年以前	0.51	1.7（0.63-4.5）	0.3
病期	IIB以上	1.8	5.8（1.3-26）	0.021
照射の有無	無し	1.3	3.7（1.0-13）	0.05
巨大腫瘤	有り	0.7	2.4（0.6-9.3）	0.22

図1　生存曲線



D.　考察

1. 欧米の標準的治療と問題点

欧米で用いられている治療法は、①化学療法＋リンパ節領域照射（Involved Field：IF照射）（ドイツ[5]、米国POG[4]、フランス[6]など）、②化学療法±IF照射（完全寛解：CRなら照射を省略）（ドイツ[7]、米国CCG[8]）③化学療法のみ（オランダ[9]）、の3法である。これらのうち多くの研究グループで採用されてきたものは①の化学療法と放射線照射の併用療法である。その中で最も良好な成績はドイツから報告されている[5]。報告では、低危険群：OEPA/OPPA×2（男児にはOEPA、女児にはOPPAを用いて男児の性腺障害の軽減を図る）＋IF照射（25Gy～35Gy）、5年EFS：94%、5年OS：99%、中間危険群：OEPA/OPPA×2＋COPP×2+IF照射（25Gy～35Gy）、5年EFS：93%、5年OS：97%、高危険群：OEPA/OPPA×2＋COPP×4+IF照射（20Gy～35Gy）、5年EFS：86%、5年OS：94%、という非常に良好な成績であった。この治療法における問題点は、全症例に照射が行われる点である。

化学療法±IF照射の例としては、ドイツ[7]と米国CCG[8]の報告がある。ドイツの治療法は前記の治療[5]と同一の化学療法を用い

て、化学療法終了後に完全寛解なら照射を省略するというものである。その結果、短い観察期間ながら非照射群は照射群とほぼ同等の治療成績であったと報告した。この治療法の問題点は、完全寛解率が22%と低値であること、すなわち照射群の割合が78%と高いことである。米国CCG[8]では、化学療法により完全寛解となった症例を2群に分け、比較試験が行われた。中間危険群を例に挙げると、化学療法はCOPP/ABV×6、IF照射21Gyである。この治療での完全寛解率は55%とドイツの報告に比べて高いことが評価されるが、問題点は、プロカルバジンによる男児の性腺障害[10]、中間危険群にも関わらず比較高用量（300mg/m2）のアドリアマイシンが投与されることである。化学療法のみの例としては、オランダからの報告[9]が挙げられる。この報告では、腫瘍径4cm未満の全病期の症例に対して3つの化学療法が試みられ、MOPP×6（症例数21例、I/IIA：14例、IV：0）では、EFS：91%、ABVD×6（症例数17例、I/IIA：11例、IV：2）では、EFS：70%、MOPP×3＋ABVD×3（症例数21例、I/IIA：11例、IV：1）では、EFS：91%であった。この治療法の問題点は、MOPP×6、MOPP/ABVD×6では性腺障害が必発と考えられること[10]、ABVD単独では成績が不良であることである。照射を省略する治療については、過去に大規模な臨床試験の報告がなく、エビデンスレベルは低い。

以上から、現時点での標準治療は化学療法とリンパ節領域照射の併用と考えられるが、寛解例での照射の省略が今後の多くの研究グループで採用されるものと考えられた。

2. 新規レジメンの考え方と課題

わが国のアンケート調査結果と欧米の報告を検討した結果、以下の考え方を基本とすることが提案された。①高いEFSを目指し、再発後の救済を前提としない。②化学療法で完全寛解なら照射を省略する。③化学療法の選択においては不妊、心筋障害を避けることを第一に考える。④10歳未満の症例では放射線照射の影響がより強く、また、わが国では非照射群の予後が良好であったことから、この群の照射を減弱する。

これらの考え方をもとに以下のレジメン案をJPLSGリンパ腫委員会に提案した。

治療レジメン案：①ドイツレジメン[5]を基本に、同療法の問題点である完全寛解率の低さ（＝照射群の割合の高さ）を改善すべく、毒性の重ならない化学療法を各危険群のレジメンに加える（例：ABVD2コースを各リスク群の化学療法に加える）。②完全寛解例には照射の省略を行う。③若年発症例には照射線量の減量あるいは照射野の縮小を行う。

このレジメンにおける問題点、課題として、①後方視的調査であるアンケート調査結果を治療にどこまで加味するべきか。②完全寛解の判定基準（PET、シンチグラム、生検）をどのように設定するか。③化学療法をさらに強化して完全寛解率（＝非照射の割合）を上げるべきか。④症例数を考慮すると臨床試験として成立するのか。などがあげられ、現在検討中である。

E. 結論

小児ホジキンリンパ腫に対する治療法を欧米の報告とわが国のアンケート調査に基づいて考察した。化学療法により完全寛解に

導入された症例に対して放射線照射を省略するという方向は妥当と考えられたが、照射の対象の選定、年齢因子を層別化に用いるかどうかは重要な問題であり、種々の治療が混在している後方視的調査の結果の重み付けには、さらに慎重な議論が必要である

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F. 健康危険情報

該当事項なし

G. 研究発表

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2. 学会発表：

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H. 知的財産権の出願・登録状況

なし

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ. 研究成果の刊行物・別刷

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Case Report

Recurrent yolk sac tumor following resection of a neonatal immature gastric teratoma

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Abstract Gastric teratomas are very rare and usually benign. Only a few cases of gastric teratomas with malignant components have been reported. This report describes recurrence of a yolk sac tumor following resection of a neonatal immature gastric teratoma. Gastric teratoma recurring as a malignant lesion has not been previously reported. Recurrence of immature gastric teratomas should be considered, and a periodic follow-up check with alpha-fetoprotein level should be mandatory.

Keywords Gastric teratoma - Immature teratoma - Yolk sac tumor

Introduction

Gastric teratomas are very rare, with a reported incidence of less than 1% of all pediatric teratomas [1]. As of 2002, only 107 cases had been reported in the English literature [2–7] and 54 cases in the Japanese literature [8, 9]. Gastric teratoma patients exhibit characteristic differences in gender (90% are male), age (less than 1 year of age), and malignant behavior compared with patients with teratomas originating in other organs. Malignant gastric teratomas are especially rare, with only a few cases reported [10–12]. We describe a case of immature gastric teratoma that recurred as yolk sac tumor (YST) 2 years after the resection. To our knowledge, this report is the first of its kind in the literature.

Case report

A 4-day-old male infant was admitted with vomiting and fever. Abdominal examination revealed a firm, elastic, mobile mass with an irregular contour in the left upper quadrant. Upper gastrointestinal tract contrast radiography revealed a gastric tumor with irregular contour (Fig. 1). Computed tomography (CT) showed a calcified, low-density tumor involving the stomach wall and extending toward the retroperitoneum. The serum alpha-fetoprotein (AFP) level was appropriate for age at 80,050 ng/ml, beta human chorionic gonadotropin concentration was <0.1 ng/ml (standard <0.1 ng/ml), and a neuron-specific enolase level was 13.2 ng/ml (standard <10.0 ng/ml) (Table 1).

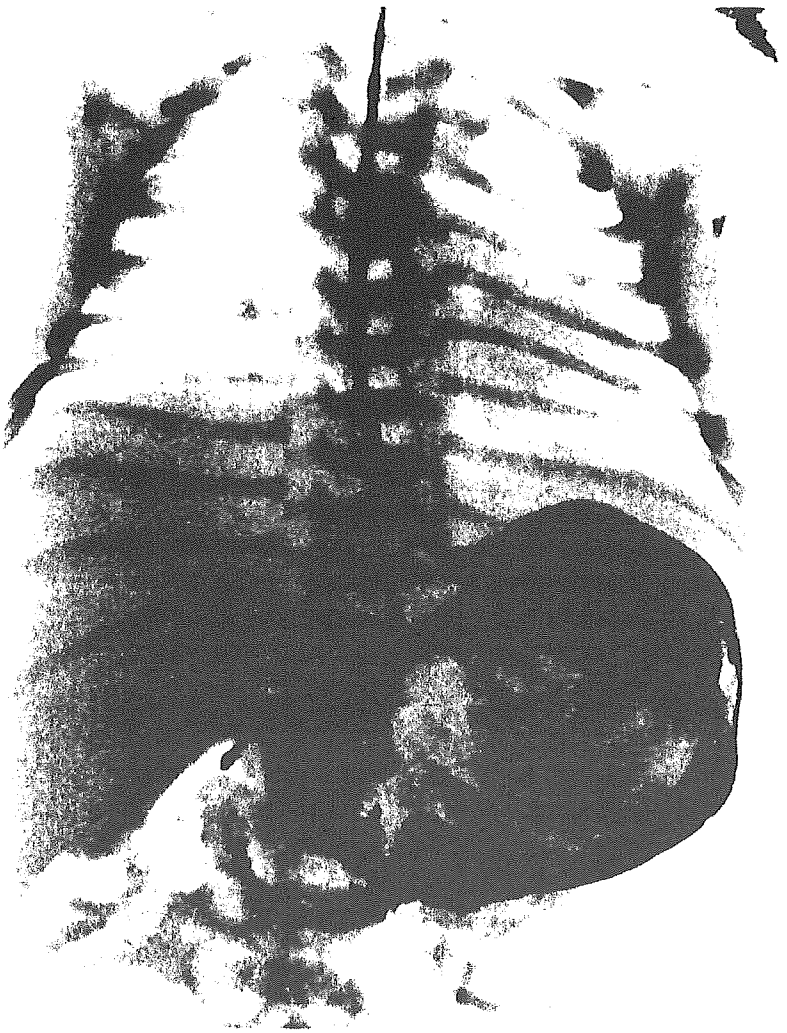

Fig. 1 Upper gastrointestinal contrast study shows a large space-occupying mass with irregular contour in the stomach

Table 1 Serum tumor marker levels on admission (*AFP* alpha-fetoprotein, *HCG* human chorionic gonadotropin, *Beta-HCG* beta human chorionic gonadotropin, *NSE* neuron-specific enolase, *VMA* vanillylmandelic acid, *Cr* creatinine, *HVA* homovanillic acid, *CEA* carcinoembryonic antigen)

	This case	Standard
AFP(day 5)	80,050.0 ng/ml	
HCG	<0.4 mIU/ml	<0.7 mIU/ml

Beta-HCG	<0.1 ng/ml	<0.1 ng/ml
NSE	13.2 ng/ml	<10.0 ng/ml
VMA/Cr	7.7 mg/gCr	
HVA/Cr	18.9 mg/gCr	
CEA	<0.9 ng/ml	<2.5 ng/ml
Ferritin	96.1 ng/ml	3120 ng/ml

Laparotomy confirmed a well-encapsulated solid tumor arising from the lesser curvature of the stomach and extending into the lumen and retroperitoneum. The tumor was not adherent to adjacent structures. Resection of the tumor was performed, with a 0.5-cm gastric wall margin taken. The tumor was positive in the surgical margin near the esophagogastric junction (EGJ) by intraoperative pathological assessment. Additional resection was performed for the margin. The tumor was 5.5×4.4×4.0 cm in size and weighed 70 g. Histological examination demonstrated an immature teratoma with a variety of components derived from endoderm, ectoderm, and mesoderm, including mature cartilage, alimentary tract epithelium, and immature central nervous system. No yolk sac histology was observed.

The infant 's postoperative course was uneventful. Serum AFP levels decreased to <10 ng/ml by 7 months after the operation and were maintained at 7.3 ng/ml for 12 months. However, at the child 's 24-month check-up, AFP had risen to 356.2 ng/ml. CT and magnetic resonance imaging (MRI) revealed an enhanced tumor under the left lobe of the liver and the right side of the spleen (Fig. 2). These findings prompted a second-look laparotomy, which was performed 26 months after the initial surgery. The recurrent tumor originated from the greater curvature of the stomach, locally invading the lumen and more growing toward the retroperitoneum surrounding the stomach. The recurrent tumor origin was near the surgical margin of the first operation. It was adherent to the spleen and the left lateral lobe of the liver. The tumor was removed en bloc with the spleen, the left lateral lobe of the liver, and regional lymph nodes. The pathologic diagnosis was YST without any area of immature teratoma (Fig. 3). By standard histologic microscopic evaluation, no invasion was observed to the spleen or the liver. Likewise, no metastasis was seen to any regional lymph nodes.

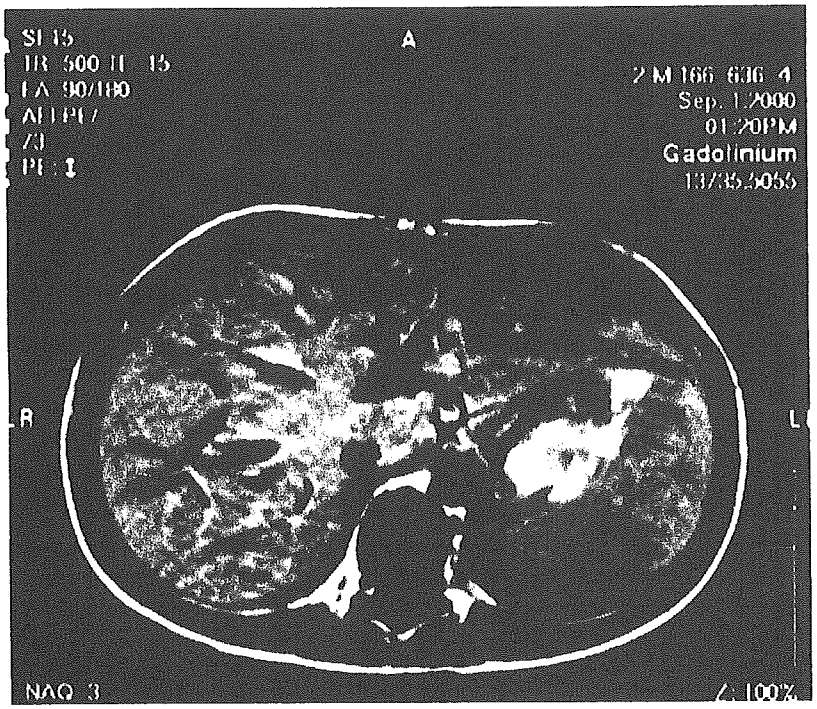

Fig. 2 Magnetic resonance imaging clearly outlines a tumor of high signal intensity on gadolinium-enhanced T1-weighted images (*T1WI*) 2 years after the first operation

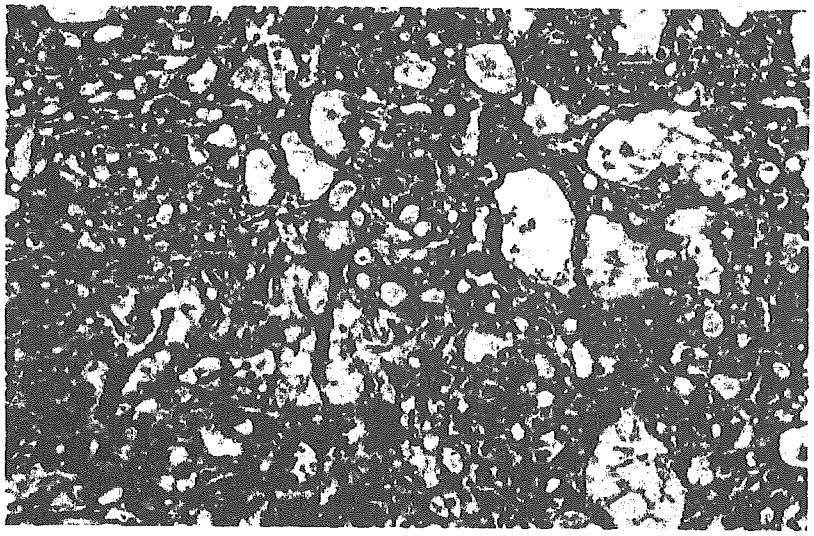

Fig. 3 Photomicrograph of the tumor resected at the second operation. The pathological diagnosis was pure yolk sac tumor (*YST*) without immature teratoma components (hematoxylin and eosin staining, original magnification ×100)

After the operation, chemotherapy with four courses of PVB regimen (cisplatin, 20 mg/m^2 ×5 days; vinblastine, 0.2 mg/kg ×2 days; bleomycin, 15 mg/m^2 ×1 day) was administered. No recurrence has been observed 3.5 years after the second operation and 3 years after the end of chemotherapy.

Discussion

At birth, teratomas present mainly as coccygeal tumors, whereas in the first 6 months teratomas are predominantly localized in the testis. Later, between the ages of 9 and 15 years, ovarian teratomas are seen [*13*]. Gastric teratomas are very rare and exhibit distinguishing characteristics compared with teratomas from other organ sites. For example, most gastric teratoma patients are male (90%) [*2*], whereas the other teratomas predominate in females. Most gastric teratomas described in previous papers were in infants less than 1 year of age. In addition, gastric teratomas have predominantly exhibited benign behavior. Only a few cases of gastric teratomas with malignant components have been reported [*10–12*]. A case of malignant transformation in an adenocarcinoma arising from immature teratoma in an 83-year-old male was reported [*14*]. Gastric teratoma recurring as a malignant lesion has never been reported.

Our patient's teratoma was diagnosed as an immature teratoma. Immature teratomas are the most controversial and least well-characterized germ cell tumors in children [*15*]. The prevalence of microscopic foci of YST is said to be directly related to the grade of the malignant potential and to be the only valid predictor of recurrence in pediatric immature teratoma. Researchers have reported that elevations of serum AFP concentration greater than 100 ng/dl almost always indicated the presence of foci of YST [*15*]. In our case, the concentration of serum AFP was 80,050.0 ng/ml, within the normal range for a 5-day-old patient. Positive AFP immunoreactivity was not found in the tumor resected at the first operation. However, because clusters of YST cells may be very small or associated intimately with immature neural tissue, or both, and because they frequently do not stain positively for AFP, they are easily overlooked [*16*]. In one series, half of relapsing patients showed highly malignant tumor histology at relapse (mainly YST and in a few cases embryonal

carcinoma) [13]. Relapses were observed for patients with mature as well as immature teratomas. Tumors have had foci of YST in immature teratoma. The recurrent YST in our patient originated near the initial surgical margin but was apart from the EGJ that was positive by intraoperative pathological assessment.

The most common germ cell tumors of childhood are sacrococcygeal teratomas, which have been reported to have a malignant potential of 17% [17]. A case of sacrococcygeal teratoma with immature elements was reported with local recurrence as malignant teratoma [18]. Without coccygectomy, local recurrence of sacrococcygeal teratomas has been reported and was postulated to have arisen from the microscopic remnants of the primary tumors [19]. Our observations suggest that this mechanism may have led to relapse in our patient. This is the first time gastric teratoma has been reported to recur locally with a malignant histology.

The serum concentration of AFP was a good indicator for tumor recurrence in our patient. The AFP concentration—which had been 7.3 ng/ml 12 months after the operation, indicating normal range for the patient's age—was abnormally elevated compared with age-appropriate normal controls when found to be 356.2 ng/ml 24 months later, and CT and MRI confirmed tumor recurrence. MRI was useful in that it made the tumor contour stand out against surrounding viscera. MRI clearly indicated a tumor of low T1 but high T2 signal intensity, with gadolinium enhancement (Fig. 2). A gallium and bone scintigram were negative.

For treating the recurrent tumor, we selected en bloc surgical resection together with surrounding viscera firmly adherent to the tumor. Complete surgical resections are recommended as the most effective treatments for teratomas with or without malignant elements [20].

After the surgery, we chose the PVB (cisplatin, vinblastine, and bleomycin) regimen as an antineoplastic chemotherapy. Vincristine, actinomycin D, vinblastine, bleomycin, doxorubicin, cisplatin, and etoposide have proved effective in treating various tumors of germ cell origin [16]. Cisplatin and its incorporation into combination regimens has resulted in a substantial increase in disease-free survival. VP16 may cause secondary leukemia [21], and ifosfamide may cause severe multiorgan toxicity [22]. Thus, we chose PVB, expecting stronger effects than regimens without cisplatin and weaker side effects than regimens with VP16 or ifosfamide. Four courses of the same PVB regimen that we used are the standard therapy for stage 1 YST in Germany, where favorable outcomes are reported [23].

Our patient has been free of recurrence for 3.5 years after the second operation. Although immature gastric teratomas are considered to have benign behavior, a pediatric surgeon should consider the possibility of recurrence, and periodic follow-up checks with AFP tumor marker measurement should be mandatory.

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