

# Retrospective analysis of pediatric hepatoblastoma with tumor rupture: experience from a single center

**Yu-Tong Zhang**

the First Hospital of Jilin University

**Yu-fei Zhao**

the First Hospital of Jilin University

**Dian-fei Yang**

the First Hospital of Jilin University

**Jian Chang** (✉ [changjian@jlu.edu.cn](mailto:changjian@jlu.edu.cn))

the First Hospital of Jilin University

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## Research Article

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## Abstract

**Background** Hepatoblastoma (HB) tumor rupture is currently considered as a high-risk factor in some risk-stratification systems. This study aimed to investigate the value of HB tumor rupture in predicting the poor prognosis of child patients.

**Methods** The clinical data from children with high-risk HB or HB tumor rupture at our institution from October 2008 to October 2017 were retrospectively reviewed and analyzed.

**Results** Altogether 34 children with high-risk HB or HB tumor rupture were retrospectively reviewed, including 25 in the high-risk group and 9 in tumor rupture group. The 3-year overall survival (OS) rate in tumor rupture group was significantly higher than that in high-risk group (100% vs 60%,  $p=0.035$ ). In tumor rupture group, 7 (77.8%) out of 9 patients had the hemoglobin level  $\leq 8$  g/L and 3 (33.3%) had that  $\leq 6$  g/L at the time of diagnosis. Peritoneal perfusion with normal saline and interleukin-2 was implemented for each patient until the free fluid was under normal level. At the end of the treatment, 7 (77.8%) of 9 patients achieved complete response (CR). No patient died at the last follow-up.

**Conclusions** Tumor rupture is not predictive of poor prognosis with the risk of peritoneal dissemination/relapse.

## Introduction

Hepatoblastoma (HB) is still the most common subtype of liver tumor, which accounts for only 1% of pediatric malignancies(1). With the development of contemporary state-of-the-art management of pediatric solid tumor, the risk-stratification treatment strategy has been widely accepted. With regard to the outcome of pediatric HB, its 3-year overall survival (OS) reaches over 80%(2). Notably, an optimal risk-stratification strategy can improve the outcomes and quality of life of patients, while reducing the treatment-related toxicities. Therefore, it is necessary to identify the potential prognostic factor for HB to perfect the stratification system. But this is still a big challenge at present because HB is rare, the incidence of tumor rupture at diagnosis is low, and the available published data are lacking(3, 4). Since the International Childhood Liver Tumors Strategy Group (SIOPEL) 4 trial has been carried out, tumor rupture at diagnosis is considered as a high-risk factor by some international liver tumor study groups(2, 5, 6). Accordingly, patients with HB tumor rupture are treated by the high-risk protocol. Recently, the Children's Hepatic tumors International Collaboration (CHIC) reviews data from each of the cooperative group studies and defines a new risk stratification with a common set of definitions(7-9). Thus, this study re-evaluated the role of tumor rupture in predicting HB prognosis.

## Patients And Methods

### Patients

Children pathologically diagnosed with high-risk HB or HB tumor rupture at our institution from October 2008 to October 2017 were enrolled in this study. All clinical data were retrospectively collected by using a standard table form. Besides, the imaging data were reviewed by one radiologist. Risk-stratification was adopted from the SIOPEL-4 trial(2), but the tumor rupture factor was removed from the high-risk group in our study. Thereafter, patients were divided into 2 groups, including the high-risk group and the tumor rupture group. Biopsy was performed before chemotherapy.

### Definition of tumor rupture

The definition of tumor rupture was adopted from the Pediatric Hepatic International Tumor Trial (PHITT). To be specific, tumor rupture was defined as the presence of free fluid in the abdomen or pelvis at diagnosis with at least one of the following findings of hemorrhage: 1. internal complexity/septation within fluid; 2. high-density fluid on CT ( $>25$  Hounsfield units); 3. imaging characteristics of blood or blood degradation products on MRI; 4. heterogeneous fluid on ultrasound with echogenic debris; and 5. visible rupture/hepatic capsular defect on imaging(10).

### General work-up of HB tumor rupture

Abdominal and thoracic CT scans and/or abdominal MRI examination were performed at diagnosis, before biopsy, and after every 2 cycles of chemotherapy. Also, ultrasound was a useful and convenient approach to monitor bleeding. At the same time, the following general biochemical indexes were measured, including AFP, peripheral blood cell count, vital organ functions, coagulation function, and serum electrolytes.

### Treatment

Operative intervention was not the preferred choice to manage tumor rupture, unless there was uncontrolled active bleeding. Peritoneal perfusion with normal saline and interleukin-2 (IL-2,  $4.0-6.0 \times 10^6$  IU/m<sup>2</sup>, maximum dose  $10.0 \times 10^6$  IU) was implemented for each patient for no more than 4 times at the intervals of 2 days, until the free fluid was under normal level.

The vital indicators in patients were continuously monitored, so as to maintain hemoglobin level  $\geq 8$  g/L, balanced serum electrolyte, normal coagulation and organ functions. Operative intervention was necessary when the hemoglobin level was not maintained by blood transfusion for over 3 days or the blood pressure (BP) continued to be  $\leq 90/60$  mmHG or the vital organ function was lost. Moreover, a biopsy was needed after tumor rupture was under control.

As for chemotherapy regimen, all children were treated by the SIOPEL3 high-risk protocol(11) or the SIOPEL4 protocol(2).

### Treatment response

The tumor response was assessed based on the imaging findings and the serum AFP level before operation according to the SIOPEL3/4 criteria. Complete response (CR) was defined as no evidence of disease with normal AFP level after adjusting for age, partial response (PR) was defined as any shrinkage of

tumor volume with the AFP level decreasing by over 1 log below the original measurement, stable disease (SD) was deemed as no change in tumor volume and no change or less than 1 log decrease in AFP level, while progression disease (PD) was regarded as the unequivocal increase in AFP concentration.

## Statistical analysis

Treatment outcomes were assessed by event-free survival (EFS) and overall survival (OS). The survival curves were plotted by the Kaplan-Meier method, and the confidence intervals (CIs) were calculated according to the Rothman method.

## Results

The available data of 34 children with high-risk HB or HB tumor rupture at our institution from October 2008 to October 2017 were collected, including 25 in high-risk group and 9 in tumor rupture group. The age of patients in high-risk group, including 11 males and 14 females, ranged from 0.2 to 15 (median, 3.8) years, while that in tumor rupture group including 3 males and 6 females was 0.7-13 (median, 5.1) years. There was no statistical difference in age between the two groups ( $p=0.23$ ). The 3-year EFS and OS in tumor rupture group were higher than those in high-risk group ( $47.64\pm 26.0\%$  and  $60.13\pm 18.4\%$  vs  $35.86\pm 26.6\%$  and  $38.86\pm 23.38\%$ , respectively). Difference in OS was statistically significant ( $p=0.0345$ ). More details are shown in Fig1.

In tumor rupture group, 7 (77.7%) patients had the hemoglobin level less than 8 g/L, 3 (33.3%) had that less than 6 g/L at diagnosis. Typically, the decline of hemoglobin level  $\geq 2$  g/L/day was suggestive of active bleeding. Additionally, 3 (33.3%) patients suffered from hypofibrinogenemia and 2 (22.2%) had thrombocytopenia. The clinical characteristics of these patients are presented in Table 1(Fig2). Meanwhile, 2 (22.2%) patients received operative intervention due to the uncontrolled peritoneal active bleeding for over 3 days, of them, one developed peritoneal seeding at 4 months after the emergency operation. Besides, 2 (22.2%) patients had slightly declined blood platelet count, while 3 (33.3%) had mildly decreased serum fibrinogen concentration. There was no evident imbalance of serum electrolytes. No patient was diagnosed with tumor cell lysis syndrome. Before chemotherapy, a needle biopsy was performed in 7 (77.8%) patients. At the end of the treatment, 7 (77.8%) patients achieved CR, 2 (22.2%) had mildly increased AFP (of them, Case3 experienced intrahepatic relapse at 6 months after the completion of chemotherapy, whereas case2 had normal AFP level in one year). In total, 2 events (including 1 PD and 1 relapse) occurred during the median follow-up of 5.7 years. No patient died till the last follow-up.

## Discussion

HB tumor rupture at diagnosis is rare, and its incidence greatly varies among different cooperative study groups (COG, GPLT, JPLT, and SIOPEL), ranging from 5% to 15%(2, 6). This may be explained by the fact that no common definition of tumor rupture is available at present. According to the latest 2017 PRETEXT staging system that provides a new and common set of definitions available in clinical trials, tumor rupture is clearly defined as the presence of free fluid in the abdomen or pelvis with at least one imaging criteria of hemorrhage after excluding biopsy-related hemorrhage, intraoperative rupture, non-hemorrhagic ascites and subcapsular fluid(10)(Fig3). Today, no consensus is reached on the predictive role of HB tumor rupture. In the CHIC database, tumor rupture is shown to be significantly associated with the poor outcome in univariate analysis. However, it is not taken as a high-risk factor in the JPLT and the COG groups(12, 13). Considering the potential risk of peritoneal seeding after tumor rupture, patients with HB tumor rupture at diagnosis receive the high-risk protocol in the SIOPEL group(2).

In our retrospective study, promising results were achieved in tumor rupture group, in which no patient died and only 2 events occurred. The 3-year EFS and OS in tumor rupture group were higher than those in high-risk group, and the difference in OS was statistically significant. These results suggested that HB tumor rupture at diagnosis was not a poor prognostic factor in our cohort. However, there was a noticeable clue in tumor rupture group, in which the strong poor prognostic factor of lung metastasis was not found in any patient. This might partly explain the superior outcome in tumor rupture group to high-risk group where some patients suffered from lung metastasis. Additionally, in the absence of tumor rupture, some patients in tumor rupture group had standard-risk HB (3 PRETEXT<sup>III</sup>). In tumor rupture group, 7 (77.8%) patients achieved CR at the end of the treatment, and only 2 showed mildly increased AFP level without residual disease on imaging. Of these 2 patients, one elder patient developed intrahepatic relapse, while the other infant patient gradually had normal AFP level. Obviously, such findings further confirmed that tumor rupture at diagnosis was not a risk factor of peritoneal seeding and relapse.

The management of hepatic trauma has changed significantly from the early compulsory operative approach to the non-operative management approach(14). In our cohort, we adopted the far more conservative management. After tumor rupture, in addition to the increased risk of peritoneal seeding, the injury to the biliary tree and the hepatic vasculature will result in bile and blood leakage, which present with ascites and peritonitis. It has been confirmed that intraperitoneal instillation of IL-2 inhibits the formation of malignant ascites(14). Therefore, in our management protocol of HB tumor rupture, peritoneal perfusion with normal saline and IL-2 was an obligatory procedure to protect patients from peritonitis and peritoneal seeding. In our cohort, only one patient (1/9, 11.1%) suffered from peritoneal seeding, which was partly because that his postoperative chemotherapy was delayed for 4 months. After salvage chemotherapy and the second operation, the patient remained disease-free until the follow-up of 7.5 years. None of our patients experienced peritonitis or hematoma. Based on these results, conservative management with peritoneal perfusion of IL-2 and normal saline was an effective approach to prevent peritoneal seeding and peritonitis.

In the case of tumor rupture, blood loss to varying degrees was the most common presentation. 3 (33.3%) of our patients suffered from severe anemia. Additionally, the drop of hemoglobin level  $\geq 2$  g/L/day was closely associated with the potential active bleeding. The hemoglobin levels of all patients were dynamically monitored, and 2 (22.2%) of them received operative intervention to control bleeding. In some severe cases, the patients concomitantly presented with mild to moderate thrombocytopenia and/or hypofibrinogenemia. In our patients, the presentation of imbalanced serum electrolytes was rare, and no patient developed tumor lysis syndrome (TLS) based on the laboratory criterion. TLS results from the rapid destruction of malignant cells and the abrupt release of intracellular components into the extracellular space, thus causing metabolic disorders(15). Therefore, in HB tumor rupture, the tumor cell

destruction rate and the intracellular component release rate should be mild and they are under the normal metabolic homeostasis of the body. The major challenge in HB tumor rupture should be the management of active bleeding.

In conclusion, the current goals of pediatric solid tumor management focus on minimizing toxicity while maintaining the excellent outcomes in low-risk disease, and improving outcomes in patients with high-risk disease. In this regard, it is necessary to progressively refine the risk-stratification systems and evaluate every potential annotation factor in HB. Frankly, our results are obtained from a small sample size. Hopefully, our findings can be tested in a randomized, multi-center clinical trial in the future.

## List Of Abbreviations

blood pressure	BP
Complete response	CR
confidence intervals	CI
event-free survival	EFS
Hepatoblastoma	HB
International Childhood Liver Tumors Strategy Group	SIOPEL
overall survival	OS
partial response	PR
Pediatric Hepatic International Tumor Trial	PHITT
progression disease	PD
stable disease	SD
tumor lysis syndrome	TLS

## Declarations

**Ethics approval and consent to participate** Approved by the Ethical Institution of the first hospital of Jilin university. Because of its retrospective manner, informed consent was waived by the Ethical Institution of the first hospital of Jilin university

**Statement:** All methods were carried out in accordance with relevant guidelines and regulations.

**Consent to Participate** Because of its retrospective manner, informed consent was waived by the Ethical Institution of the first hospital of Jilin university

**Consent for publication:** Not applicable

**Availability of data and materials** Patient's data were available in medical records room of the first hospital of Jilin university. The datasets generated and/or analysed during the current study are not publicly available due to they are files in medical records room in our hospital, but are available from the corresponding author on reasonable request.

**Competing interests** The authors indicated no potential conflicts of interest.

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### Authors' contributions

1) YTZ: Dr. Z made substantial contributions to design of the work; drafted the manuscript; agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the manuscript.

2) YFZ: Dr. Z made substantial contributions to design of the work; drafted the manuscript; all authors have read and approved the manuscript; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

3) DFY: Dr. Y made substantial contributions to the design of the work revised the manuscript critically; all authors have read and approved the manuscript; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

4) JC: Dr. C made substantial contributions to design of the work; drafted the manuscript; agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the manuscript.

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## Table

**Table 1. Clinical characteristics of patient with HB tumor rupture**

Patient	Gender/age(y)	PRETEXT number	Vascular involvement	Histology subtype	AFP at Diagnosis (ng/mL)	Tumor site	Extra-hepatic metastasis	Tumor size (mm)	Operative intervention for tumor rupture	TP or HFn	Nadir of Hb (g/L)	CR after the first-line treatment
1	M/12	0	V1-P0	Epi/Mix	79941	Ll/Lm	N	163×138×109	Y	HFn (+)	5.7	Y
2	F/0.6	0	V1-P1	Mix/Tera	2450	Ll/Lm/Ra	N	68×51×72	Y	TP (+) HFn (+)	2.8	N
3	F/5	0	V2- P0	Epi/Em	>120000	All sections	N	103×64×119	N	TP (+)	65	N
4	F/8	0	V0- P0	Epi/ Mix	52929	Ra/Lm	AN	92×52×94	N	-	77	Y
5	F/3	0	V1-P1	Epi/ Fet	>120000	Lm/Ll	N	93×62×104	N	-	73	Y
6	F/0.9	0	V0- P0	Epi/ Fet	85000	Ra/Rp	N	30×40×37	N	-	8.5	Y
7	M/6.7	0	V1- P0	Epi/ Fet	103000	Ra/Rp/Ll	AN	101×64×78	N	HFn (+)	5.8	Y
8	F/4.1	0	V0- P0	Epi/ Em	45300	Ra/Lm	N	85×60×67	N	-	7.5	Y
9	M/5.3	0	V1- P0	Epi/ Mix	57600	Ra	N	67×52×71	N	-	9.0	Y

Abbreviations: M, male; F, female; V, hepatic vein; P, portal vein; Epi, epithelial; Mix, mixed; Tera, teratoid; Em, embryonal; Fet, fetal; Ll, left lateral section; Lm, left medial section; Ra, right anterior section; Rp, right posterior section; RL, right lateral section; Y, yes; N, no; AN,

## Figures

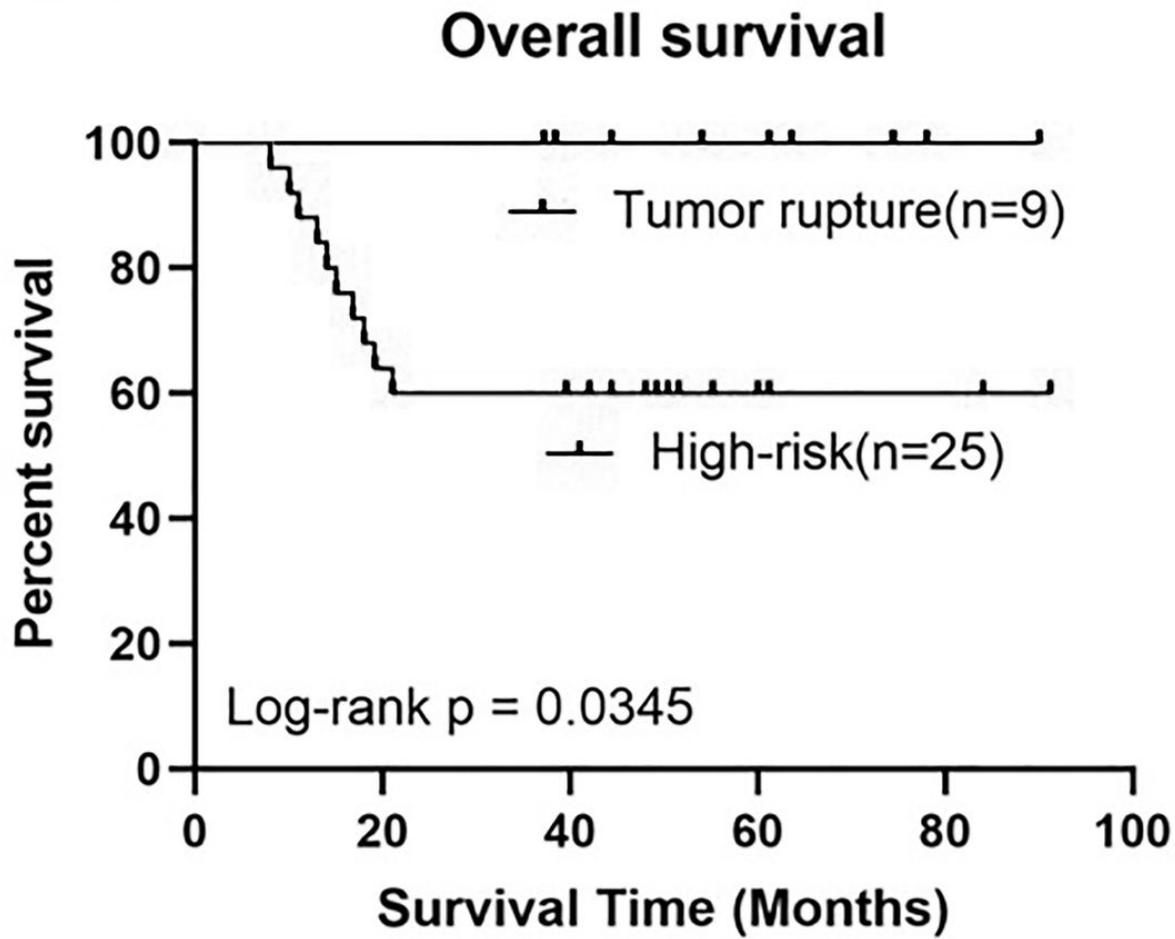


Figure 1

Kaplan-Meier estimates showed a significant difference of 3-year OS between HB tumor rupture group and high-risk HB group,  $p=0.0345$ .

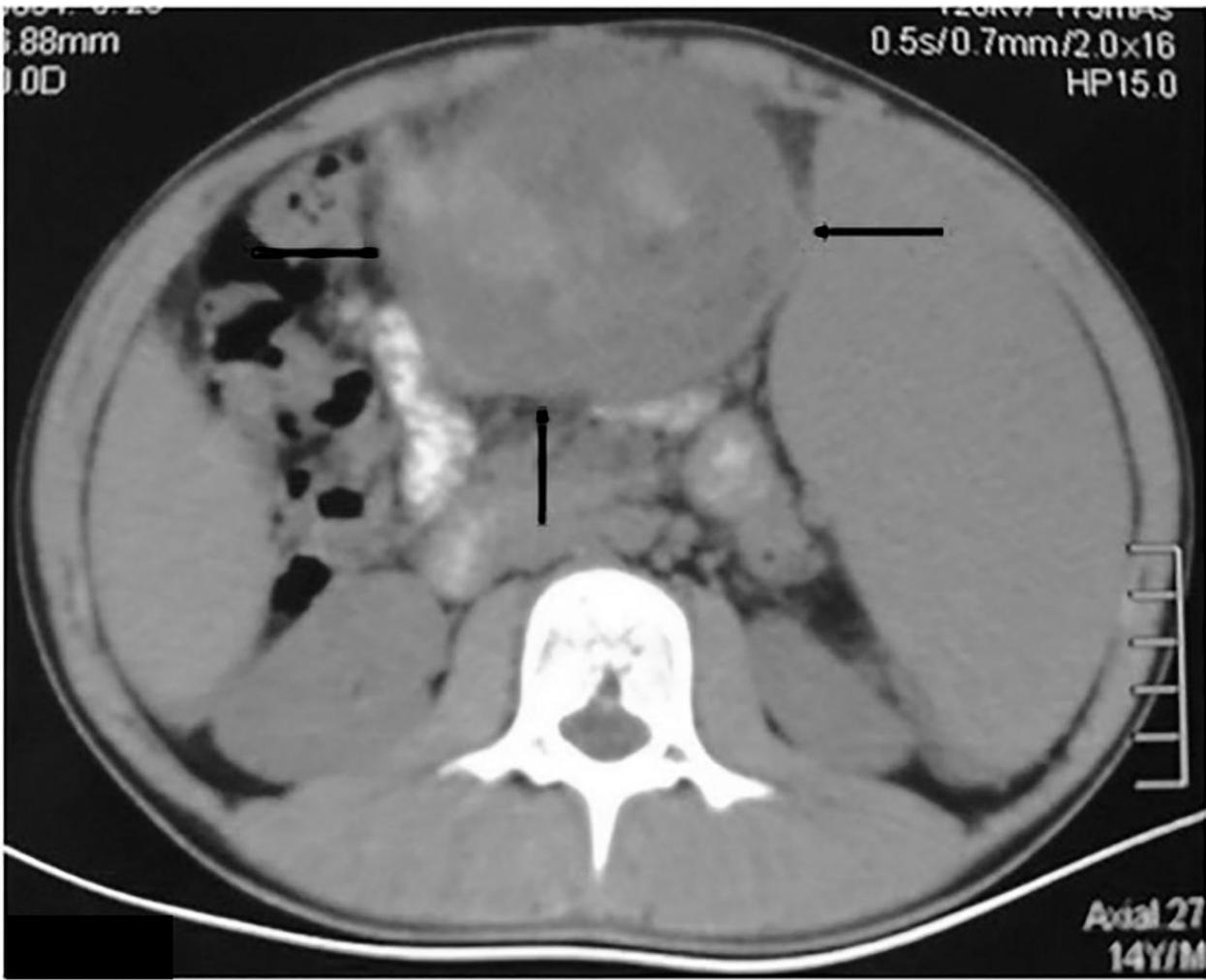


Figure 2  
After tumor rupture, a CT scan showed peritoneal metastasis mass of HB. There was a huge tumor mass in the omentum majus (between arrows, patient 1).



**Figure 3**

An enhanced CT scan showed a right lobe HB with a discontinuity of tumor edge (arrow a). High density peritoneal effusion (>25 Hounsfield units) was seen (between arrow b and arrow c).