Research Square

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Outcomes of children with hepatoblastoma managed at a tertiary hospital in China

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Abstract

Objective: To summarise our experiences in hepatoblastoma management in South China

Methods: We diagnosed 135 children with hepatoblastoma at our institution between January 2010 and December 2017. Information regarding demographics, clinical data, and outcomes were retrospectively collected and analysed.

Results: Ninety-three patients underwent liver resection and were enrolled in this study. Thirty-six, 23, 3, and 31 patients had PRETEXT stages II, III, IV, and unspecified tumours, respectively. Seven patients had ruptured tumour, 9 had lung metastasis, and 1 had portal vein thrombosis. Sixteen patients underwent primary liver resection, 22 received neoadjuvant chemotherapy and delayed surgery, 25 received preoperative transarterial chemoembolisation and delayed surgery, and 30 received a combination of neoadjuvant chemotherapy, transarterial chemoembolisation, and delayed surgery. Forty patients had both PRETEXT and POST-TEXT information available for analysis. Twelve cases were downstaged after preoperative treatment: 2 from stage IV to III, 8 from stage III to II, and 2 from stage II to I. Ten patients with unspecified PRETEXT stage were confirmed to have POST-TEXT stages II (n=8) and I (n=2) tumours. The PRETEXT and POST-TEXT stages were significantly different. Seven tumours were associated with positive surgical margins, and 12 patients had microvascular involvement. During a median follow-up period of 30.5 months, 84 patients survived without relapse, 9 experienced tumour recurrence, and 4 died. The two-year EFS and OS rates were significantly better among patients without metastasis. The two-year EFS and OS rates were similar among patients treated with different preoperative strategies.

Conclusion: The outcomes of hepatoblastoma after resection were excellent.

Introduction

Hepatoblastoma is the most common childhood liver malignancy, and has a prevalence of 1 per 1 000 000 population[1,2]. The incidence of hepatoblastoma has increased in the past two decades, and this upward trend has been correlated with an increasing survival rate among premature and low-birth-weight infants[3]. Hepatoblastoma usually affects children younger than 3 years, and presents as a large abdominal mass. Some patients may present with sudden abdominal pain and haemorrhagic shock in the scenario of tumour rupture. A combination of elevated α-fetoprotein protein (AFP) level and radiographically identified hepatic mass suffices for the clinical diagnosis of hepatoblastoma in children with ages between 6 months and 3 years. However, biopsy, preferably via ultrasound-guided core needle biopsy is recommended for patients of all age groups [4,5].

The treatment of hepatoblastoma is multidisciplinary; a combination of platinum-based chemotherapy and complete surgical removal is the mainstay of treatment. Cisplatin monochemotherapy and delayed surgical resection provide standard-risk patients with a five-year overall survival (OS) probability of more than 90%[6]. Primary hepatic resection is recommended for patients with PRETEXT stages I and II tumours with no additional annotative risk factors. Otherwise, patients should undergo neoadjuvant

chemotherapy and delayed surgery. Orthotopic liver transplantation is an ideal treatment option for patients with PRETEXT stage IV hepatoblastomas and other forms of unresectable hepatoblastomas, and can provide them with a five-year OS probability of more than 70%[7].

Nonetheless, the outcomes of hepatoblastoma in developing countries are still far more inferior to those in developed countries[8]. Treatment abandonment among children with cancer is not an unusual phenomenon in developing countries, particularly among those with advanced stage cancers[9]. Furthermore, patients in developing countries have far more limited access to liver transplantation. In order to improve the management and outcomes of hepatoblastoma in developing countries, such experiences are worth summarising. Herein, we described our experiences in treating hepatoblastoma at a tertiary hospital in South China.

Methods

The diagnosis of hepatoblastoma was initially made based on an elevated AFP level and radiographic detection of a liver mass, and confirmed via pathological examination of samples obtained via either biopsy or primary liver resection. Patients with hepatocellular carcinoma and other liver malignancies were excluded from this analysis.

One hundred and thirty-five children were diagnosed with hepatoblastoma at our institution between January 2010 and December 2017. Our study included 93 cases that were treated according to the institutional protocol and underwent liver resection. Forty-two cases were excluded from the analysis mainly due to treatment abandonment, including 6 cases who died due to aggressive tumour progression prior to treatment and 36 cases that received no further treatment information after diagnosis. The patients were followed up at the clinic and via regular telephone calls. The OS duration was defined as the interval between the time of diagnosis and the time of death, and event-free survival (EFS) as the interval between the time of diagnosis and the time of the first occurrence of tumour progression, relapse, or death, whichever occurred first.

We collected information regarding patients' demographic data, including age and gender; clinical data including AFP level, radiographic findings, pre-treatment extent of disease (PRETEXT) and post-treatment extent of disease (POST-TEXT) staging, preoperative management strategy (neoadjuvant chemotherapy and transarterial chemoembolisation [TACE]), and liver resection technique; pathological findings including pathological subtype, surgical margin status, microvascular involvement, and lymph node involvement; and clinical outcomes including disease relapse and death.

A standard data extraction form with a logical organisation similar in flow to the format of the original medical charts, was used to collect data. Two trained data abstractors, who were blinded to the study hypothesis, independently reviewed the original medical charts and collected data. Explicit criteria for extracting data regarding variables were applied. Any discrepancies between the abstractors were reviewed jointly and discussed to clarify any issues[10].

A senior radiologist, who was blinded to the study objective, retrospectively reviewed patients' computed tomography (CT) and magnetic resonance imaging (MRI) data. The radiologist defined the PRETEXT/POST-TEXT system and annotation factors according to the PRETEXT staging system[11]. Not all patients had CT/MRI images stored in the electronic database; only patients who underwent CT/MRI scans at our institution had their radiographic images stored.

The study protocol was approved by the institutional review board of Guangzhou Women and Children's Medical Center. The need for informed consent was waived on account of the retrospective nature of the demographic, clinical, and outcome data. All patients' data were de-identified prior to the analysis.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as medians and ranges. The PRETEXT and POST-TEXT stages were compared using the McNemar chi-square test. The probabilities of OS and EFS were computed using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was set at $p<0.05$. All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patients' demographic and clinical characteristics

Of the 93 patients who underwent liver resection, 66 (60.2%) were male and 37 (39.8%) were female (Table 1). The median age at diagnosis was 11 (range, 1.7–87) months. The median AFP level was 76,131 (range, 5–1,881,360) ng/ml and the median tumour diameter was 10.6 (range, 5.1–15.8) cm. Fifty-seven (61.3%) patients had unifocal tumours, 7 (7.5%) had multifocal tumours, and 29 (31.2%) had tumours with unspecified focality.

Thirty-six (38.7%) patients had PRETEXT stage II tumours, 23 (24.7%) had stage III tumours, 3 (3.2%) had stage IV tumours, and 31 (33.3%) had tumours with unspecified stages. Seven (7.5%) patients had ruptured tumours, 9 (9.7%) had lung metastasis, and 1 (1.1%) had portal vein thrombosis. Sixteen (17.2%) patients underwent primary liver resection. Twenty-two patients (23.7%) received neoadjuvant chemotherapy and delayed surgery, 25 (26.9%) received preoperative TACE and delayed surgery, and 30 (32.3%) received a combination of neoadjuvant chemotherapy, TACE, and delayed surgery. The median number of treatment cycles was 2.5 (range, 1–8) for neoadjuvant chemotherapy and 2 (range, 1–7) for preoperative TACE. Forty patients had information regarding both PRETEXT and POST-TEXT stages available for analysis. Twelve cases were downstaged after preoperative treatment, including 2 from stage IV to III, 8 from stage III to II, and 2 from stage II to I. Furthermore, 10 patients with unspecified PRETEXT stage were confirmed to have POST-TEXT stages II (n = 8) and I (n = 2) tumours. There was a statistically significant difference between the PRETEXT and POST-TEXT stages ($p<0.001$).

Surgery and outcomes

Thirty-seven (39.8%) patients underwent hemihepatectomy, 17 (18.3%) underwent wedge resection, 13 (14.0%) underwent trisectionectomy, 9 (9.7%) underwent bisegmentectomy (left lateral sectionectomy), and 2 (2.2%) underwent central hepatectomy. Fifteen (16.1%) patients underwent tumour resection at other institutions. The operative time, estimated volume of blood lost, and volume of red blood cells transfused were 290 (range, 100–510) minutes, 100 (range, 20–1,000) ml, and 1 (range, 0–6) units, respectively. There were 24 (25.8%) cases of epithelial variant hepatoblastoma, 11 (11.8%) cases of mixed epithelial hepatoblastoma, and 41 (44.1%) cases of mixed epithelial and mesenchymal hepatoblastoma, and 17 cases were not subclassified. Seven (7.5%) cases had positive surgical margins, 69 (74.2%) had negative surgical margins, and 17 (18.3%) had unspecified surgical margin status. Twelve (12.9%) patients had microvascular involvement, 43 (46.2%) had no microvascular involvement, and 38 (40.9%) cases had unspecified microvascular status. Thirty-one patients underwent lymph node dissection, none of whom had positive lymph node involvement.

Sixty-three (67.7%) patients received postoperative chemotherapy, with a median of 6 (range, 1–12) cycles. Twenty-seven (29.0%) patients received no postoperative chemotherapy. During a median follow-up duration of 30.5 (range, 0.7–105.1) months, 84 (90.3%) cases survived without relapse, 9 (9.7%) experienced disease recurrence, and 4 (5.4%) died.

Failure among patients with tumour recurrence

Among the 9 patients with tumour recurrence, the median time from diagnosis to recurrence was 8.5 (range, 0.7–22.4) months. Among the 4 patients who died as a result of tumour recurrence, the median time from diagnosis to death was 11.3 (range, 3.6–21.4) months. Their treatment and outcome information is summarised in Table 3. Five patients underwent wedge resection, and 1 underwent left hepatectomy associated with a positive surgical margin. However, one patient with PRETEXT stage II disease who underwent complete tumour removal died about two years after diagnosis.

Survival

The two-year EFS and OS rates were 89.4±0.03%, and 95.2±0.02% (Figs. 1A and 2A), respectively. The two-year EFS and OS rates were significantly better among patients without metastasis (no metastasis vs metastasis: 93.5±0.04% vs 46.7±0.19%, $p = 0.005$ and 97.6±0.02% vs 61.0±0.18%, $p = 0.003$, respectively) (Figs. 1C and 2C). The two-year EFS and OS rates of patients with PRETEXT stage IV hepatoblastoma, positive surgical margins, and microvascular involvement were lower compared to those of their counterparts, but the differences were not statistically significant (all $p>0.05$). The two-year EFS and OS rates were similar among patients treated with different preoperative strategies (Figs. 1F and 2F).

Discussion

Here, we reported the outcomes of patients with hepatoblastoma treated at a tertiary children's institution in South China. The OS rates among patients who underwent hepatic resection were satisfactory. The two-year EFS and OS rates were approximately 90% and >90%, respectively. Cases associated with distant metastasis had a poor prognosis, with two-year EFS and OS rates of about 46.7±0.19% and 61.0±0.18%, respectively. However, because a large portion of patients discontinue or abandon treatment, and patients with advanced stage tumours might be more likely to give up on treatment, it is unlikely that the OS and EFS probabilities in this cohort reflect the true status of the overall hepatoblastoma patient population.

Both neoadjuvant chemotherapy and preoperative TACE were used at our institution as preoperative strategies to shrink the tumour and downstage the tumour[12]. However, our results showed no significant differences regarding the effect of neoadjuvant chemotherapy and TACE on the OS and EFS. Similarly, a previous study showed that TACE was as effective as neoadjuvant chemotherapy in shrinking and downstaging tumours; however, the OS was inferior to that of those who underwent neoadjuvant chemotherapy[13]. TACE is considered a challenging technique in most children's hospitals. Furthermore, the evidence from experiences among adult patients showed that TACE was not without complications[14]. Generally speaking, neoadjuvant chemotherapy should be considered the first choice for the preoperative management of hepatoblastoma. However, these two preoperative strategies would be best compared in a randomised controlled trial. Until now, no such prospective study had been conducted for the comparison of these two strategies in the preoperative management of hepatoblastoma. TACE could be an option for patients who fail to respond to neoadjuvant chemotherapy. Furthermore, TACE is particularly useful for patients who experience tumour rupture[15].

Patients with tumour metastasis had significantly lower two-year EFS and OS probabilities. Our data supported the fact that patients with metastatic hepatoblastoma have far more inferior OS and EFS. The EFS and OS probabilities for patients with metastatic disease were only about 46.7±0.19% and 61.0±0.18%, respectively. We failed to demonstrate that patients with PRETEXT stage IV tumours had significantly worse EFS and OS probabilities than those with tumours of other stages. However, our cohort only had 3 cases with PRETEXT stage IV tumours. Two cases were downstaged to POST-TEXT stage III, and the other died. Again, this cohort would have selection bias due to treatment abandonment.

The two-year EFS and OS probabilities for patients with positive surgical margins or microvascular involvement were lower than those of their counterparts, but the differences were not statistically significant. The evidence suggested that positive surgical margin might not affect the EFS and OS probabilities in the setting of neoadjuvant chemotherapy[16]. However, this might not be true in the setting of primary resection. Complete resection with a negative resection margin should always be pursued. Microvacular involvement was suggested to be a poor prognostic factor in a retrospective study[17]. In our cohort, twelve (12.9%) patients had microvascular involvement, 43 patients had no microvascular involvement, and 38 patients had tumours with unspecified microvascular status. Our data

suggested that although patients with microvascular involvement had lower two-year EFS and OS probabilities than did those without microvascular involvement, the differences were non-significant.

Hepatoblastoma seemed not to spread through the lymph nodes. None of the 31 patients who underwent lymph node biopsy had positive lymph node involvement.

Five out of 9 patients who experienced relapse or died underwent wedge resection. This suggests that wedge resection might be associated with worse outcomes. Standard hepatic resection should always be pursued in any possible scenario.

Due to the retrospective nature of this study, we were unable to retrieve some of the important information. For example, some of the patients did not undergo preoperative CT or MRI scans for PRETEXT staging. Furthermore, a large proportion of the patients abandoned or discontinued treatment after the establishment of the diagnosis. These patients will most likely fall into the high-risk group. Treatment abandonment is not an unusual phenomenon in developing countries, which underscores the need for more attention and funding for this vulnerable population[18,19]. The follow-up duration was not long enough, and the probability might either be overestimated if patients abandoned treatment due to poor results or underestimated if patients abandoned treatment because their parents prematurely assumed they were cured. An assessment of the interactions between different characteristics requires more stable follow-up with larger samples.

In conclusion, the outcomes of patients with hepatoblastoma who underwent resection were excellent. However, a large proportion of patients discontinued treatment after the diagnosis. A large effect is needed to secure a satisfactory survival probability for patients managed for hepatoblastoma, and decrease the rate of abandonment.

Declarations

Conflict of interest statement

All authors declare no conflict of interest

Acknowledgments

None

Abbreviations

CTcomputed tomography

EFS event-free survival

MRImagnetic resonance imaging

OSoverall survival

AFPalpha-fetoprotein

PRETEXTpre-treatment extent of disease system

TACEtransarterial chemoembolisation

POST-TEXTpost-treatment extent of disease system

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Tables

TABLE 1: Demographic, clinical, radiological, and pathological characteristics of the study cohort

Characteristics	Number or as shown	Proportion (%)
All	93	100
Gender		
Male	56	60.2
Female	37	39.8
Age [median (range)], months	11 (1.7–87)	-
AFP level [median (range)], ng/ml	76,131 (5–1,881,360)	-
Maximum tumour diameter [median (range)], cm	10.6 (5.1–15.8)	-
Focality		
Unifocal	57	61.3
Multifocal	7	7.5
Unknown	29	31.2
PRETEXT stage		
I	0	0.0
II	36	38.7
III	23	24.7
IV	3	3.2
Unknown	31	33.3
Rupture		
Yes	7	7.5
No	56	60.2
Unknown	30	32.3
Metastasis		
Yes	9	9.7
No	55	59.1
Unknown	29	31.2
Portal vein thrombosis		
Yes	1	1.1
No	63	67.7
Unknown	29	31.2
Hepatic vein thrombosis		
Yes	0	0.0
No	64	68.8
Unknown	29	31.2
Primary resection		
Yes	16	17.2
No	77	82.8
Neoadjuvant chemotherapy		
Yes [n, median (range)]	52, 2.5 (1–8)	55.9
No	41	44.1
Preoperative TACE, cycles		
Yes [n, median (range)]	55, 2 (1–7)	59.1
No	38	40.9
POSTTEXT[a] stage (n=77)		
I	4	5.2
II	36	46.8
III	9	11.7
IV	1	1.3
Unknown	27	35.1

[a]Sixteen children underwent primary tumour resection (with no neoadjuvant chemotherapy and no preoperative TACE), and did not need to undergo POST-TEXT stage evaluation. Abbreviations: AFP, alpha-fetoprotein; PRETEXT, pre-treatment extent of disease system; TACE, transarterial chemoembolisation; POST-TEXT, post-treatment extent of disease system

TABLE 2: Surgical and pathological outcomes of patients managed for hepatoblastoma

Characteristics	Number or as shown	Proportion (%)
Liver resection		
Hemihepatectomy (left hepatectomy + right hepatectomy)	37	39.8
Wedge resection	17	18.3
Trisectionectomy (left trisectionectomy + right trisectionectomy)	13	14.0
Bisegmentectomy (left lateral sectionectomy)	9	9.7
Central hepatectomy	2	2.2
Others	15	16.1
Operative time [median (range)], minutes	290 (100–510)	-
Estimated blood loss [median (range)], ml	100 (20–1000)	-
Volume of red blood cells transfused [median (range)], units	1 (0–6)	-
Pathologic subtype	93	
Epithelial variants	24	25.8
Pure foetal variant with low mitotic activity	3	-
Foetal variant, mitotically active	10	-
Unspecified	11	-
Epithelial mixed	11	11.8
Mixed epithelial and mesenchymal	41	44.1
Without teratoid features	2	-
With teratoid features	15	-
Unspecified	24	-
Unknown	17	18.3
Surgical margin		
Positive	7	7.5
Negative	69	74.2
Unknown	17	18.3
Microvascular involvement		
Yes	12	12.9
No	43	46.2
Unknown	38	40.9
Lymph node status (n=31)		
Positive	0	0.0
Negative	31	100.0
Postoperative chemotherapy		
Yes [n, median (range)]	63, 6 (1–12)	67.7
No	27	29.0
Unknown	3	3.2
Outcomes		
Survived without relapse	84	90.3
Survived with relapse	5	5.4
Died from relapse	4	4.3
Median follow-up duration [median (range)], months	30.5 (0.7–105.1)	-

TABLE 3: Detailed information of patients who experienced tumour relapse or death

[a]null, unknown; -, no need to fill in; [b]W, wedge resection; LH, left hepatectomy; B, bisegmentectomy; RT, right trisectionectomy; [c]N^-, negative; P^+, positive; [d]EV, epithelial variant; With TF, with teratoid features; MEM, mixed epithelial and mesenchymal; EM, epithelial mixed; [e]C, chemotherapy; TACE,

Characteristics	Patients[a]								
	P1	P2	P3	P4	P5	P6	P7	P8	P9
Age, months	7	24	9	5	19	41	46	6	87
Gender	Female	Female	Male	Male	Male	Female	Female	Male	Male
PRETEXT stage	II	III	II	II	IV	II	Null	Null	II
Multifocal tumour	No	No	No	No	Yes	No	Null	Null	No
Metastasis	Yes	Yes	No	Yes	Yes	No	Null	Null	No
Neoadjuvant chemotherapy, cycles	0	2	0	8	4	4	2	0	0
Preoperative TACE	0	2	3	0	7	1	4	5	0
POSTTEXT stage	-	III	II	II	III	II	Null	Null	-
Surgical resection[b]	W	W	B	LH+W	LH	W	RT	Null	W
Surgical margin status[c]	N^-	P^+	N^-	N^-	P^+	N^-	Null	Null	N^-
Postoperative pathologic subtype[d]	Foetal	With TF	EV	MEM	EV	EM	Null	Null	EM
Postoperative chemotherapy, cycles	3	0	6	4	2	Null	Null	4	4
Relapse	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time from diagnosis to relapse, months	0.7	3.3	13.4	8.5	11.3	6.4	14.1	7.3	22.4
Further anti-tumour treatment[e]	C	Not appropriate	C	Gave up	C	S	TACE	C	S
Death	Yes	Yes	Yes	Yes	No	No	No	No	No
Time from diagnosis to death, months	7.7	3.6	21.4	14.8	-	-	-	-	-

transarterial chemoembolisation; S, surgery

P8 was operated at another institution.

Figures

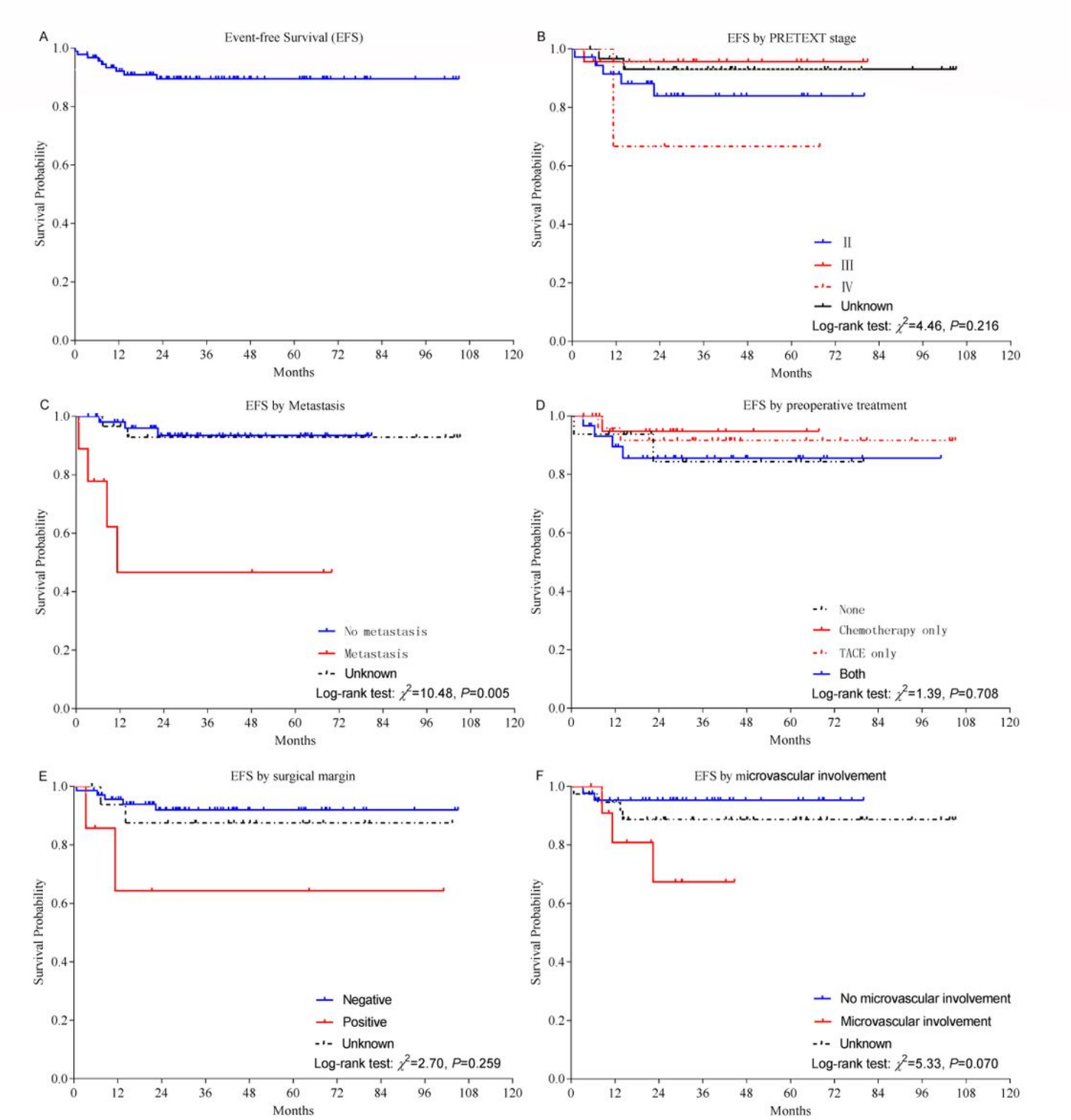

Figure 1

Kaplan-Meier estimates of event-free survival probabilities

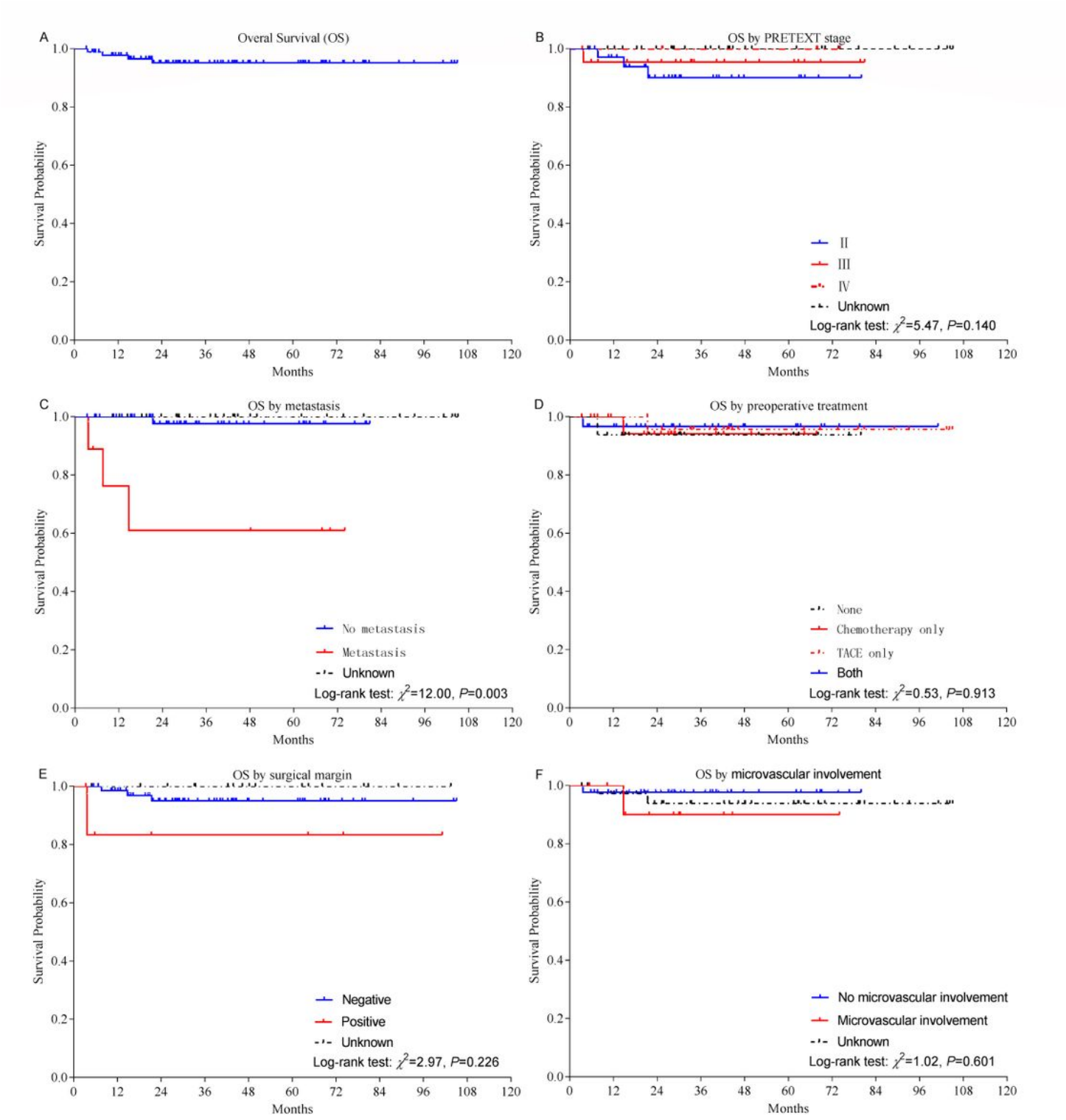

Figure 2

Kaplan-Meier estimates of overall survival probabilities