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American Joint Committee on Cancer staging for resected perihilar cholangiocarcinoma: a comparison of the 6th and 7th editions

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Abstract

Objectives: This study was conducted to evaluate the prognostic value of, respectively, the 6th and 7th editions of the American Joint Committee on Cancer (AJCC) staging system for patients with resected perihilar cholangiocarcinoma (PHC).

Methods: Patients who underwent resection of PHC between 1991 and 2012 were identified from prospective databases at two centres. Overall survival was estimated using the Kaplan–Meier method and compared across stage groups with the log-rank test. The concordance index and Brier score were used to compare the prognostic accuracy of the staging systems.

Results: Data for a total of 306 patients were analysed. Staging according to the 7th edition upstaged 63% of patients in comparison with staging by the 6th edition. The log-rank *P*-value for both staging systems was highly statistically significant ($P < 0.001$). Staging according to the 6th edition categorized 93% of patients as having stage I or II disease, whereas staging according to the 7th edition distributed patients more equally across stages. Prognostic accuracy was similar between the staging systems: the concordance index was 0.59 and the Brier score 0.17 for both the 6th and 7th editions. The same prognostic accuracy was achieved using an alternative tumour–node–metastasis (TNM) stage grouping simplified to four rather than six stage groups.

Conclusions: The 6th and 7th editions of the AJCC staging system for PHC have similar prognostic accuracy. Other prognostic factors can potentially improve individual patient prognostication.

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Introduction

Perihilar cholangiocarcinoma (PHC) accounts for about 60% of all cases of cholangiocarcinoma and has an annual incidence of one to two cases per 100 000 population. It involves the occurrence of tumours at or near the biliary confluence, arising between the origin of the cystic duct and the confluence of the second-order bile ducts.[1] Tumours arising distal to the origin of the cystic duct are classified as lesions of distal cholangiocarcinoma, and tumours that are proximal to the left and right hepatic ducts are classified as lesions of intrahepatic cholangiocarcinoma. Patients with PHC typically present with symptoms arising from bile duct obstruction. Resection is the optimal treatment and facilitates a median overall survival (OS) of about 44 months.[2] Unfortunately, at presentation the majority of patients have metastatic or locally advanced disease and consequently do not benefit from resection.

Several systems for staging PHC have been published. The Bismuth classification and the Blumgart T-stage focus on determining resectability using preoperative imaging.[3,4] DeOliveira *et al.* recently introduced a new classification for PHC, including both radiologic and pathologic covariates.[5] This classification is

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comprehensive, but remains to be validated. The American Joint Committee on Cancer (AJCC) staging still represents the staging system most widely used to determine prognosis and appropriate treatment, and to compare outcomes among centres.

In the 6th edition (2003) of the AJCC staging system, all patients with extrahepatic bile duct tumours were covered by a single classification.[6] In the 7th edition (2010), perihilar (proximal) and distal cholangiocarcinoma were staged separately.[1] Two important changes from the 6th to 7th editions for PHC concern the definitions of T-stage (Table 1). Firstly, invasion of the liver parenchyma was downstaged to stage T2b in the 7th edition from stage T3. Secondly, T4 was expanded to include the bilateral involvement of second-order bile ducts (Bismuth 4), and the unilateral involvement of second-order bile ducts and contralateral vascular involvement. With respect to N-stage, N2 was introduced as a new N-stage for metastases to lymph nodes beyond those in the hepatoduodenal ligament, including the periaortic and pericaval lymph nodes and those at the superior mesenteric artery or the coeliac artery.

Other changes concerned the distribution of T- and N-stages across the stage groups. Firstly, invasion beyond the bile duct wall (T2) was upstaged from stage Ib to stage II. Secondly, invasion of the unilateral branches of the portal vein or hepatic artery (T3) was upstaged from stage IIa to stage IIIa. Thirdly, regional lymph node metastasis was upstaged from stage IIb to stage IIIb. Fourthly, stage IV was expanded to include disease of T4 (IVa) and N2 (IVb) status, in addition to that of M1 (IVb) status.

The objective of this study was to compare the prognostic accuracy of the 6th and 7th editions of the AJCC staging system in patients with resected PHC. Secondly, alternative stage distributions were evaluated to improve on the current AJCC staging.

Materials and methods

Patient population

This study included patients for whom prospective data had been collected in databases at two centres: the Academic Medical Centre (AMC) in Amsterdam, the Netherlands, and the Memorial Sloan–Kettering Cancer Center (MSKCC) in New York, USA. The institutional review boards of each centre approved the study. Consecutive patients with resected PHC were included. Perihilar cholangiocarcinoma was defined as cancer arising from the common hepatic duct (i.e. arising proximal to the origin of the cystic duct), biliary confluence, or main hepatic ducts (left or right) up to the confluence of the second-order bile ducts. Patients with papillary PHC and carcinoma *in situ* were also included. The study exclusion criteria excluded patients with final pathology indicative of a diagnosis other than PHC, patients who suffered in-hospital mortality, patients who underwent an R2 resection, and patients submitted to re-resection after initial resection in another hospital. Data on patient demographics, laboratory studies, preoperative imaging, preoperative biliary drainage, type of surgery, pathology and OS were collected.

Table 1 American Joint Committee on Cancer (AJCC) staging system by tumour–node–metastasis (TMN) stage

Stage	AJCC, 6th edition	AJCC, 7th edition
Tumour (T) stage		
T1	Tumour confined to the bile duct	Tumour confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumour invades beyond the wall of the bile duct	–
T2a	–	Tumour invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	–	Tumour invades adjacent hepatic parenchyma
T3	Tumour invades the liver, gallbladder, pancreas, and/or unilateral branches of the PV or HA	Tumour invades unilateral branches of the PV or HA
T4	Tumour invades main PV or its branches b/l, CHA, or other adjacent structures (such as colon, stomach, duodenum, abdominal wall)	Tumour invades main PV or its branches b/l, CHA, second-order bile ducts b/l, unilateral second-order bile ducts with contralateral PV or HA involvement
Node (N) stage		
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis: hilar (along the CBD, cystic duct, HA, PV), coeliac, periduodenal, peripancreatic, SMA	Regional lymph node metastasis: hilar (along CBD, cystic duct, HA or PV)
N2	–	Metastasis to periaortic, pericaval, SMA or coeliac lymph nodes.
Metastasis (M) stage		
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis

PV, portal vein; HA, hepatic artery; CHA, common hepatic artery; SMA, superior mesenteric artery; CBD, common bile duct; b/l, bilateral.

Patient management

Preoperative workup and patient selection for surgery were similar in both centres. Patients typically underwent cross-sectional imaging with computed tomography (CT) of the chest, abdomen and pelvis and magnetic resonance cholangiopancreatography (MRCP) of the liver at or before initial referral, ideally prior to biliary drainage. Imaging allowed for evaluation of distant metastases, the biliary extent of the tumour, and involvement of the portal vein and hepatic artery. In recent years, preoperative biliary drainage of the presumed remnant liver was carried out percutaneously rather than endoscopically in order to minimize the bacterial contamination of the biliary tract. However, many patients had undergone endoscopic drainage before referral. A brush was typically performed at the time of preoperative biliary drainage. However, pathologic confirmation of malignancy was not required to proceed with surgical resection. Diagnostic laparoscopy to rule out distant metastatic disease was performed often, but not in all patients, given the decreasing yield as preoperative imaging improved over time.[7] With some exceptions, patients with involvement of the main portal vein, the portal vein bilaterally, the common hepatic artery or the hepatic artery bilaterally were considered unresectable. Patients with involvement of the second-order bile ducts were considered resectable if clear margins at the segmental bile ducts were anticipated. Fewer than 5% of all patients underwent preoperative portal vein embolization if the size and function of the future liver remnant were considered to be insufficient. Fewer than 5% of all patients underwent neoadjuvant therapy.

Staging

Table 2 presents the AJCC staging classification for both the 6th and 7th editions. Tumour stage was determined based on macroscopic and microscopic evaluations of the resected specimen. Evaluation of the biliary extent of the tumour was necessary to determine T4 stage in the 7th edition of the AJCC staging system. In fewer than 5% of patients, preoperative cross-sectional imaging was used if the pathology report was insufficiently detailed to determine the biliary extent of the tumour: isolated second-order biliary bile ducts were considered to be involved by the tumour. Evaluation of the vascular involvement of the tumour (portal vein or hepatic artery) was necessary to determine stages T3 and T4 according to both editions. In fewer than 5% of all patients, preoperative cross-sectional imaging was used if the pathology report was insufficiently detailed to determine vascular involvement: the portal vein and hepatic artery were considered to be involved in cases of occlusion, obvious narrowing or tumour abutment of ≥180 degrees.

Table 2 American Joint Committee on Cancer (AJCC) staging system

AJCC, 6th edition				AJCC, 7th edition			
Stage	**T**	**N**	**M**	**Stage**	**T**	**N**	**M**
0	is	0	0	0	is	0	0
Ia	1	0	0	I	1	0	0
Ib	2	0	0	–			
IIa	3	0	0	II	2	0	0
IIb	1–3	1	0	–			
III	4	Any	0	IIIa	3	0	0
–	–			IIIb	1–3	1	0
IV	Any	Any	1	IVa	4	Any	0
–				IVb	Any	2	0
–					Any	Any	1

Alternative tumour–node–metastasis stage groupings

Two regroupings of tumour–node–metastasis (TNM) stages were compared across the 6th and 7th editions of the AJCC staging system. A regrouping of TNM stages was recently proposed by a Japanese multicentre study (Ebata staging).[8] In this staging system, bilateral second-order bile duct involvement (Bismuth 4) was removed from the T4 definition. Moreover, T4N0 patients were downstaged to stage IIIb, and TanyN1 patients were upstaged to stage IVa.

An alternative simplified regrouping of TNM stages was evaluated with only four stages: stage I represented disease that was confined to the bile duct (T1N0); stage II represented disease that extended beyond the bile duct (T2–4N0); stage III represented node-positive disease (TanyN1), and stage IV represented disease that included N2 nodes or distant metastasis (TanyN2 or TanyNanyM1).

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows Version 21.0 (IBM Corp., Armonk, NY, USA) and R (a language and environment for statistical computing) Version 3.0.2 for Mac (R Foundation for Statistical Computing, Vienna, Austria). Survival was measured from the date of surgery to the date of death or date of last contact prior to 1 January 2014. Survival probabilities were estimated using the Kaplan–Meier method and compared with the log-rank test. Overall survival was the primary outcome.

The concordance index and Brier score were used to compare the staging systems.[9] The concordance index is a measure of discrimination used to evaluate whether a staging system can discriminate between two patients at different stages of disease. It is calculated as the probability that for a random pair of patients at different stages of disease, the patient at the lower stage has a longer observed survival. A concordance index of 0.5 means that the predictive ability is no better than guessing; a concordance index of 1 means perfect prediction. Other AJCC staging systems were found to have a concordance index of about 0.70.[10] When stage-specific survival is consistently higher or lower than the observed survival, this would be expected to remain undetected by the concordance index. Therefore, the Brier score is often used in combination with the concordance index. The Brier score is a

Table 3 Characteristics of 306 patients with resected perihilar cholangiocarcinoma assessed in the present study

Covariate	*n*	All	AMC (*n* = 133)	MSKCC (*n* = 173)
Gender, male, *n* (%)	306	179 (58%)	79 (59%)	100 (58%)
Age, years, mean (range)	306	63 (30–89)	62 (30–82)	64 (34–89)
Weight loss of >5 kg, *n* (%)	266	169 (64%)	69 (62%)	100 (65%)
Jaundice, *n* (%)	303	215 (71%)	104 (80%)	111 (64%)
Preoperative bilirubin, ml/dl, mean (range)	270	3.0 (0.2–35.6)	1.2 (0.2–8.7)	4.0 (0.2–35.6)
Bismuth stage, *n* (%)	306			
1		58 (19%)	20 (15%)	38 (22%)
2		39 (13%)	18 (14%)	21 (12%)
3a		79 (26%)	39 (29%)	40 (23%)
3b		64 (21%)	26 (20%)	38 (22%)
4		43 (14%)	18 (14%)	25 (14%)
Left or right bile duct, *n* (%)		23 (8%)	12 (9%)	11 (6%)
Lobar atrophy, *n* (%)	300			
No		211 (70%)	104 (81%)	107 (63%)
Right		38 (13%)	15 (12%)	23 (13%)
Left		51 (17%)	10 (8%)	41 (24%)
Portal vein involvement, *n* (%)	272			
No		176 (65%)	68 (67%)	108 (63%)
Right		36 (13%)	11 (11%)	25 (15%)
Left		54 (20%)	19 (19%)	35 (20%)
Main		2 (1%)	1 (1%)	1 (1%)
Bilateral		2 (1%)	2 (2%)	0
Preoperative drainage, *n* (%)	304			
No		61 (20%)	17 (13%)	44 (25%)
PTC		51 (17%)	11 (8%)	40 (23%)
ERCP		156 (51%)	84 (64%)	72 (42%)
Both		36 (12%)	19 (15%)	17 (10%)
Type of resection, *n* (%)	306			
Bile duct resection only		53 (17%)	21 (16%)	32 (19%)
Left hepatectomy		88 (29%)	37 (28%)	51 (30%)
Right hepatectomy		24 (8%)	8 (6%)	16 (9%)
Extended left hepatectomy		25 (8%)	15 (11%)	10 (6%)
Extended right hepatectomy		90 (29%)	32 (24%)	58 (34%)
Central hepatectomy		26 (8%)	20 (15%)	6 (3%)
Caudate resection[a], *n* (%)	302	137 (45%)	74 (57%)	63 (36%)
Papillary tumour, *n* (%)	306	57 (19%)	18 (14%)	39 (23%)
Positive margin, *n* (%)	306	84 (28%)	39 (29%)	45 (26%)
Differentiation, good, *n* (%)	297	69 (23%)	29 (23%)	40 (24%)
Lymphovascular invasion, *n* (%)	299	78 (26%)	24 (19%)	54 (31%)
Perineural invasion, *n* (%)	306	211 (69%)	91 (68%)	120 (69%)

[a]The caudate resection rate is relatively low because 19% of the study population had a Bismuth 1 tumour: these patients typically did not undergo any liver resection. Moreover, in the early 1990s, caudate resections were less commonly performed.
AMC, Academic Medical Centre (Amsterdam, the Netherlands); MSKCC, Memorial Sloan–Kettering Cancer Center (New York, NY, USA); PTC, percutaneous transhepatic cholangiography; ERCP, endoscopic retrograde cholangiopancreatography.

measure of the average difference between observed survival and predicted stage-specific survival. Lower Brier scores are better; a Brier score of 0 is perfect. Other AJCC staging systems were found to have Brier scores of about 0.16.[10]

Results

Patients

A total of 306 consecutive patients submitted to surgery between 1991 and 2012 were identified. These included: 133 (43.5%) patients at AMC and 173 (56.5%) patients at MSKCC. No patients were excluded for missing data on staging. Patient characteristics are summarized in Table 3. Median OS was 40 months (95% confidence interval: 34–46 months). A total of 103 patients (33.7%) were censored at a median follow-up time of 38 months.

Stage transitions

Table 4 is a cross-tabulation presenting transitions for T-stages, N-stages and AJCC stages for the 6th and 7th staging editions.

Survival across stages

Figure 1(a) and (b) presents Kaplan–Meier curves for OS for the four main stage groups of the 6th and 7th editions. Findings of the log-rank test for both staging systems were highly statistically significant ($P = 0.002$ and $P < 0.001$, respectively). Figure 1(c) and (d) demonstrates that when all sub-stages were compared, separation of the curves further improved for both editions ($P < 0.001$ for both). Table 5 presents stage-specific median OS in patients staged according to both the 6th and 7th editions of the AJCC staging system. Figure 2a presents OS curves according to the Ebata staging, and Fig. 2b according to the alternative staging.

Table 4 Cross-tabulation of the 6th and 7th editions of the American Joint Committee on Cancer (AJCC) staging system: (a) T-stage, (b) N-stage and (c) AJCC stage. Each row shows how many patients at a specific 6th edition stage transitioned to other stages according to the 7th edition. Numbers in red refer to patients who moved to a different stage from the 6th to the 7th edition

(a)

T-stage		7th edition						
		is	1	2a	2b	3	4	Total
6th edition	is	11						11 (4%)
	1		36				1	37 (12%)
	2			90			5	95 (31%)
	3			3	92	32	29	156 (51%)
	4						7	7 (2%)
	Total	11	36	93	92	32	42	306
	%	4	12	30	30	10	14	100

(b)

N-stage		7th edition			
		0	1	2	total
6th edition	0	228			228 (75%)
	1		74	4	78 (25%)
	Total	228	74	4	306
	%	75	24	1	100

(c)

AJCC stage		7th edition							
		0	I	II	IIIa	IIIb	IVa	IVb	total
6th edition	0	11							11 (4%)
	Ia		35				1		36 (12%)
	Ib			70			3		73 (24%)
	IIa			63	20		17		100 (33%)
	IIb					58	13	4	75 (25%)
	III						7		7 (2%)
	IV							4	4 (1%)
	Total	11	35	133	20	58	41	8	306
	%	4	11	43	7	19	13	3	100

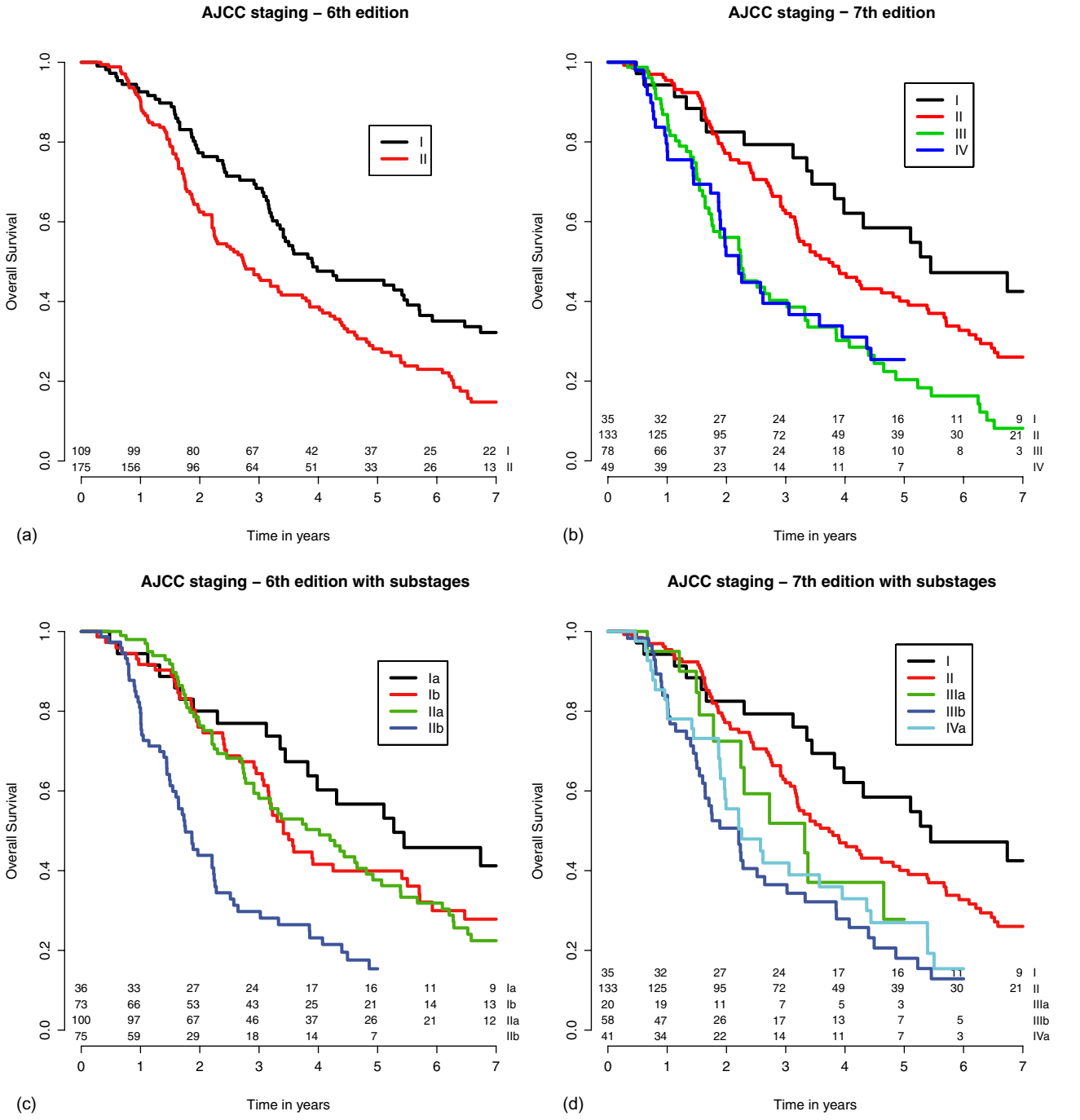

Figure 1 Overall survival by stage without sub-stages according to the (a) 6th edition of the American Joint Committee on Cancer (AJCC) staging system main stage groups [data for patients with stage III ($n = 7$) and IV ($n = 4$) disease are not presented], and (b) 7th edition of the AJCC four main stage groups. Overall survival by stage and sub-stage according to the (c) 6th edition of the AJCC staging system, including subgroups [data for patients with stage III ($n = 7$) and IV ($n = 4$) disease are not presented], and (d) 7th edition of the AJCC staging system, including subgroups [data for patients with stage IVb ($n = 8$) disease are not presented]

Table 5 Stage-specific median overall survival (OS) in months according to the 6th and 7th editions of the American Joint Committee on Cancer (AJCC) staging system. Median OS is not presented for 6th edition stages III ($n = 7$) and IV ($n = 4$). Differences in OS between the four main stage groups of the 6th and 7th editions were highly statistically significant (log-rank $P = 0.002$ and $P < 0.001$, respectively), as well as when sub-stages were considered (both $P < 0.001$)

	6th edition AJCC			7th edition AJCC		
	n	Median OS	95% CI	*n*	Median OS	95% CI
0	**11**	**80**	**26–135**	**11**	**80**	**26–135**
I	**109**	**48**	**26–70**	**35**	**65**	**33–97**
Ia	36	65	33–98	–	–	–
Ib	73	41	32–49	–	–	–
II	**175**	**33**	**25–41**	**133**	**46**	**30–61**
IIa	100	48	35–61	–	–	–
IIb	75	21	18–24	–	–	–
III	**–**	**–**	**–**	**78**	**27**	**22–32**
IIIa	–	–	–	20	40	25–55
IIIb	–	–	–	58	26	19–34
IV	**–**	**–**	**–**	**49**	**24**	**19–28**
IVa	–	–	–	41	26	17–35
IVb	–	–	–	8	17	3–31

Results for the main stage groupings are shown in bold.
95% CI, 95% confidence interval.

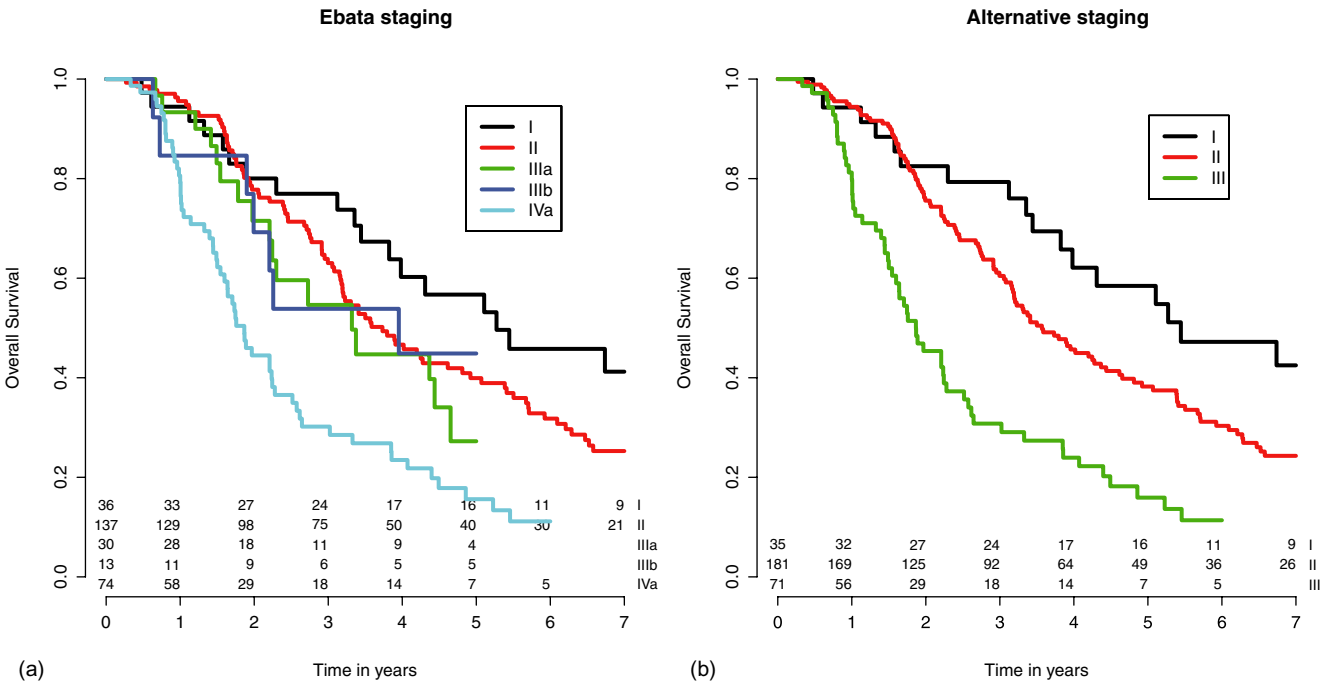

Figure 2 Overall survival by stage in patients staged according to (a) Ebata staging [data for patients with stage IVb ($n = 5$) disease are not presented], and (b) an alternative staging system [data for patients with stage IV ($n = 8$) disease are not presented]

Prognostic accuracy

Table 6 presents the concordance indices and Brier scores for all evaluated staging systems. Prognostic accuracy was remarkably similar across the AJCC staging systems. Expanding the 6th edition of the AJCC staging system with sub-stages did not improve prognostic accuracy; the 7th edition improved with sub-stages but its prognostic accuracy was similar to that of the 6th edition. The prognostic accuracy of both the Ebata staging system and the alternative staging system was similar to that of the AJCC staging systems.

Table 6 Predictive accuracy of the various staging systems. A high concordance index is better; a low Brier score is better

Accuracy	Concordance index	Brier score
AJCC sub-stages – 6th edition	0.59	0.17
AJCC sub-stages – 7th edition	0.59	0.17
AJCC main stages – 6th edition	0.60	0.17
AJCC main stages – 7th edition	0.54	0.17
Ebata staging	0.59	0.17
Alternative staging	0.60	0.17

AJCC, American Joint Committee on Cancer.

Discussion

This study compared the 6th and 7th editions of the AJCC staging system in patients with resected PHC using prospective databases from two centres. The log-rank *P*-value across all sub-stages was highly statistically significant for both the 6th and 7th editions ($P < 0.001$). Prognostic accuracy was similar for both editions, with a concordance index of 0.59 and a Brier score of 0.17. The same prognostic accuracy was achieved using an alternative TNM stage grouping simplified to four rather than six stage groups (Fig. 2b, alternative staging).

A study from Germany compared the 6th and 7th editions of the AJCC system.[11] The authors of this study analysed data for all patients ($n = 195$) who underwent exploratory laparotomy for PHC with or without resection between 1998 and 2010. A disadvantage of including unresected patients is that the T-stage (with particular reference to vascular involvement and the biliary extent of the tumour) was determined on preoperative imaging and intraoperative assessment, without histologic verification. The authors of the study compared *P*-values derived from Cox proportional hazards modelling ($P = 0.44$ for the 6th edition and $P = 0.0093$ for the 7th edition) and concluded that the 7th edition better separated the survival curves of patients with stage II and III disease, respectively.

A study from Japan evaluated the 7th edition of the AJCC staging system and found that patients with T4 tumours (stage IVa) had better survival than patients with regional node-positive disease (stage IIIb), a finding confirmed in the present study.[8] They proposed a modified staging system that was considered superior based on a higher chi-squared value. Validation using the data in the present study found the prognostic accuracy of this modified staging system to be similar to that of the 6th and 7th editions of the AJCC staging system (Table 5, Ebata staging). However, a higher proportion of patients in the Japanese series with Bismuth 4 or involvement of the main portal vein may have caused suboptimal validation.

The present study has several limitations. Firstly, this study is one of the largest Western series of patients with resected PHC ($n = 306$) to be reported in the literature, but its sample size is still insufficient to allow for the drawing of definitive conclusions about small modifications in the staging system. Secondly, this study included only resected patients. The advantage of this is that pathological confirmation of the TNM stage was available for all patients. The disadvantage is that the results cannot be extrapolated to patients who do not undergo resection because of distant metastasis or locally advanced disease. Only resected patients were included in this study because the assessment of both T-stage and N-stage is inaccurate without microscopic evaluation of the resected specimen. The evaluation of N-stage based on size criteria on cross-sectional imaging has been shown to be very inaccurate: only 37% of lymph nodes of >3 cm in diameter were found to be positive.[12] Thirdly, in the present series, relatively few patients showed involvement of the main portal vein or common hepatic artery that required vascular resection and reconstruction. Centres around the world disagree about resectability criteria for patients with PHC. Some centres have published higher resection rates for patients with main or bilateral portal vein involvement.[13,14] Consequently, OS in stage IV patients in the present study differs from that in stage IV patients reported in studies that include more stage T4 patients.

Historically, the AJCC staging is based mainly on the anatomic extent of the tumour. Although non-anatomic factors have been introduced into the staging of some cancers (e.g. mitotic rate in melanoma), with reference to PHC, the 6th and 7th editions of the AJCC staging system adhered to the anatomic extent of the tumour, as in all other hepatobiliary and pancreatic cancers.[1] Several series of patients with PHC have identified independent prognostic factors, such as margin status, tumour differentiation and perineural invasion.[14] Future research should investigate whether a combination of AJCC staging and non-anatomic independent prognostic factors can further improve individual patient prognostication.

Conflicts of interest

None declared.

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