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Role of a pre-operative radiological scoring system in determining resectability for potentially resectable hilar cholangiocarcinoma

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ABSTRACT

Aims: Cholangiocarcinoma is a rare cancer arising from the biliary tree. Case series indicate that 25–40% of all borderline resectable primary tumours are potentially resectable. The Memorial Sloane Kettering System (MSKCC) stratifies patients for resectability by longitudinal and radial extension of the hilar tumour. The Bismuth-Corlette system describes the longitudinal extension of the tumour within the biliary duct system. We sought to validate and, if possible, augment these two scores within an independent validation cohort.
Methods: Patients diagnosed with hilar cholangiocarcinoma between January 2009 and December 2016 were analysed from a prospectively held database. Patients with distal cholangiocarcinoma, peripheral cholangiocarcinoma and gallbladder cancer were excluded. Comparison of surgical findings to pre-operative radiological imaging was undertaken at the time of surgery.
Results: The validation cohort was formed of 198 patients, of which, 55 (27.8%) patients underwent resection. Logistic regression analyses identified that BC score, MSKCC score, age at diagnosis and left artery involvement were all significant independent predictor's univariately. BC score explained 28% of the variability in resectability compared to 26% explained by MSKCC. In combination, the model consisting of BC score, age at diagnosis and left artery involvement explained 39% of variability in resectability compared to the 34% explained same model including MSKCC score instead of BC score.
Conclusion: In this cohort an augmented BC score, incorporating left hepatic artery involvement, is more discriminative in predicting resectability than the current MSKCC system.

Introduction

Rationale

Cholangiocarcinoma is a rare cancer arising from the biliary tree. Currently the only curative option is R0 surgical resection of the primary tumour [1]. Case series indicate that 25–40% of all borderline resectable primary tumours are potentially resectable [2–9].

Two systems are used to describe anatomical location of the primary tumour. The Bismuth-Corlette (BC) classificatory system stratifies patients by longitudinal extension of the tumour along the biliary ducts and radicals (Fig. 1). Series have demonstrated that the BC system has limited utility in determining potential resectability [10–12]. The Blumgart-Jarnagin Memorial Sloane Kettering System (MSKCC), initially proposed in 1997 and subsequently modified, stratifies patients for resectability by longitudinal and radial extension of the hilar tumour (Fig. 2) [5,11]. Radial extension is determined by the extension of tumour in to the hilar vascular structures. The MSKCC system also utilises surrogate indicators of radial tumour extension, such as ipsilateral or contralateral lobar atrophy, to infer resectability. The MSKCC system has been internally validated but lacks external assessment of validity.

Abbreviations: BC, Bismuth-Corlette; MSKCC, Memorial Sloane Kettering Cancer Centre; PVR, Portal Vein Reconstruction; PVI, Portal Vein Involvement.
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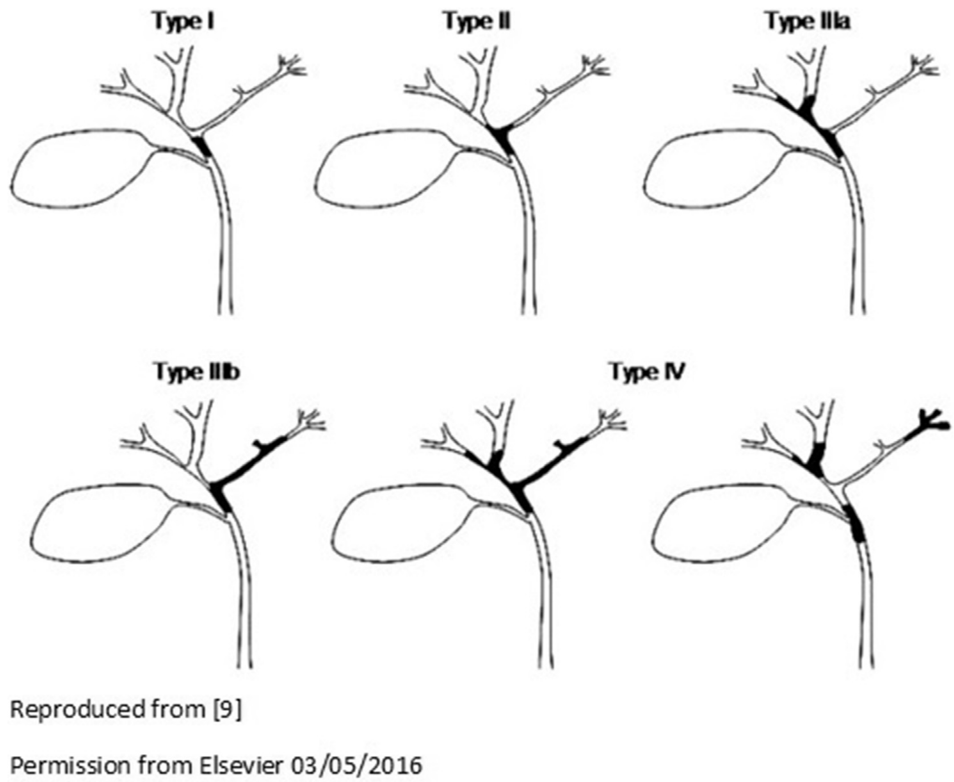

Fig. 1. Bismuth-corlette classificatory system.

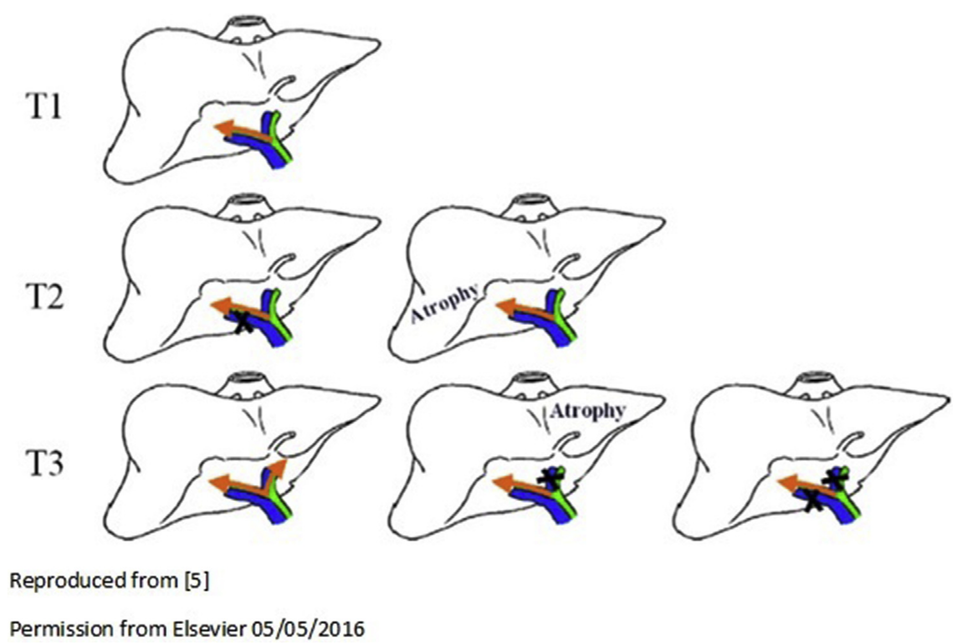

Fig. 2. Memorial sloane kettering cancer centre scoring system.

Objectives

Primary end-point of study was to determine the utility of the MSKCC system in predicting resectability within a large European cohort of hilar cholangiocarcinoma patients.

Secondary end-point of study was to determine if there were any novel co-variates which could be utilised to augment either of the scoring systems to improve their predictive accuracy.

Materials and methods

Inclusion criteria

Patients diagnosed with hilar cholangiocarcinoma, referred to a supra-regional tertiary referral centre between January 2009 and December 2016, were extracted from a prospectively held database linked to Hospital Episode Statistics data. Patients with distal cholangiocarcinoma, peripheral (true intrahepatic) cholangiocarcinoma and gallbladder cancer were excluded from analysis. Central mass-forming tumours, demonstrated on radiological imaging, which appeared to be predominantly intra-hepatic malignancies were excluded from analysis. All patients with computed tomography (CT) or endoscopic evidence of tumour originating at the biliary confluence and extending in to the biliary radicles were included. Any patients with tumour arising in the common hepatic duct were included if the tumour extended to the confluence or in to the radicles.

Multi-disciplinary team assessment

All patients were assessed at our centre as previously described [13,14]. The Bismuth-Corlette (BC) classification was applied to patients with radiologically proven hilar disease as a means of description of anatomical location. Allocation of the MSKCC resectability score was undertaken by a Consultant Radiologist and a Consultant Hepato-biliary Surgeon retrospectively and blinded to outcome. Comparison of surgical findings to pre-operative radiological imaging was undertaken at the time of surgery.

Discussion of potential resectability incorporating longitudinal and radial extension of the tumour, involvement of hilar vasculature and presence of radiologically proven metastases was undertaken. Encasement of the hilar structures precluded surgical assessment and was defined as representing in-operable locally advanced disease. Patients with these radiological characteristics were allocated to palliative treatment for locally advanced disease. Involvement of any vascular structure was considered to occur when greater than 180° of the vessel were incorporated by the tumour. Qualitative assessment of lobar atrophy was undertaken. Comparison to previous CT scans was undertaken to determine chronology of lobar atrophy. Functional volumetric assessment of liver volume was undertaken on all patients considered to be potentially resectable. Nodal status was not used to stratify patients to palliation pre-operatively unless there were concomitant metastases present. Patients considered not fit for surgery or chemotherapy were excluded from further analysis. Radiologically proven metastatic disease stratified patients for palliative gemcitabine-cisplatin chemotherapy as per ABC-02 trial [15], rather than further surgical investigation.

Surgical assessment

All patients considered potentially resectable underwent surgical assessment to stratify patients for resection as described by Bird and colleagues [14]. Surgical assessment was a two-stage process requiring initial assessment for radiologically occult intra-abdominal metastases by staging laparoscopy (SL). During SL thorough inspection of the entire abdominal cavity was undertaken to exclude peritoneal metastases. Suspicious lesions were biopsied and sent for full histopathological assessment. Histopathological evidence of metastatic disease was used to stratify the patients and precluded further exploratory laparotomy (EL) with trial dissection. If coeliac lymph nodes were found to be enlarged, biopsies were taken and specimens sent for frozen section analysis. An examination of the hilum was then undertaken to determine local resectability with emphasis upon viability of the hilar vasculature being the main determinant of progression to resection. Encasement of the hilar structures was determined to occur when the primary tumour circumferentially encapsulated all the hilar structures. Patients deemed un-resectable at this stage were referred for palliative chemotherapy [15].

Intra-operative frozen-section was utilised routinely on all attempted resections. Negative margins on frozen section were considered to indicate successful resection of the tumour at the time of surgery. Full histo-pathological assessment of the specimens was undertaken to determine resection status (R0/R1). R1 resection status was defined as microscopic involvement of the longitudinal and circumferential resection margins. Only patients with histo-pathologically proven cholangiocarcinoma were included for analysis.

Statistical analysis

Resection was treated as a binary outcome, coded as 1 if resection occurred and 0 if it did not. Logistic regression modelling was undertaken to determine correlation between covariates and resection status.

Both the BC and MSKCC scores were treated as factors, with the highest severity of score being set as the reference factor. Demographic covariates included age at diagnosis (measured in years), sex (coded as 1 if male; 0 if female). Binary indicators were used for the involvement of the following: right artery, left artery, hepatic artery, hepatic veins, main portal vein, right portal vein, left portal veins. Binary indicators were also used for ipsilateral lobar and contralateral lobar atrophy.

All analyses were performed in the software package R (R Foundation for Statistical Computing, Vienna, Austria) with the library packages MASS (Modern Applied Statistics with S. 4th edition) and RMS (Regression Modelling Strategies, https://CRAN.R-project.org/package=rms).

For logistic regression analyses, covariates were investigated against outcomes univariately. Covariates with suggestive significance ($p < 0.1$) were combined in a multivariable model and stepwise selection was utilised to derive the maximal model for each outcome. The pseudo-R^2 of models was calculated using the log likelihoods of alternative compared to null models.

Results

Patient stratification and demographics

The results of the MDT assessment are shown in Fig. 3. A total of 341 patients records were retrieved of those with hilar cholangiocarcinoma who were referred un-selected (all-comers) for assessment for resection at a supra-regional referral centre.

Of these 341 patients record, 115 indicated the patient as being medically unfit for either surgical assessment or palliative treatment. Further, 36 patient records were identified to be serial entries for those patients who had been referred more than once, for these, the latter entry was removed. Ten patients were removed due to having an incomplete set of covariates. The remaining 198 patients were assessed for suitability for surgery. The demographics, resectability scores and anatomical covariates are presented in Table 1. Twenty-nine patients with Bismuth-Corlette (BC) class 1 anatomy demonstrated on CT radiography were excluded from MSKCC sub-group analysis due to non-involvement of the biliary duct confluence. One hundred and seventy patients were stratified to the MSKCC sub-group.

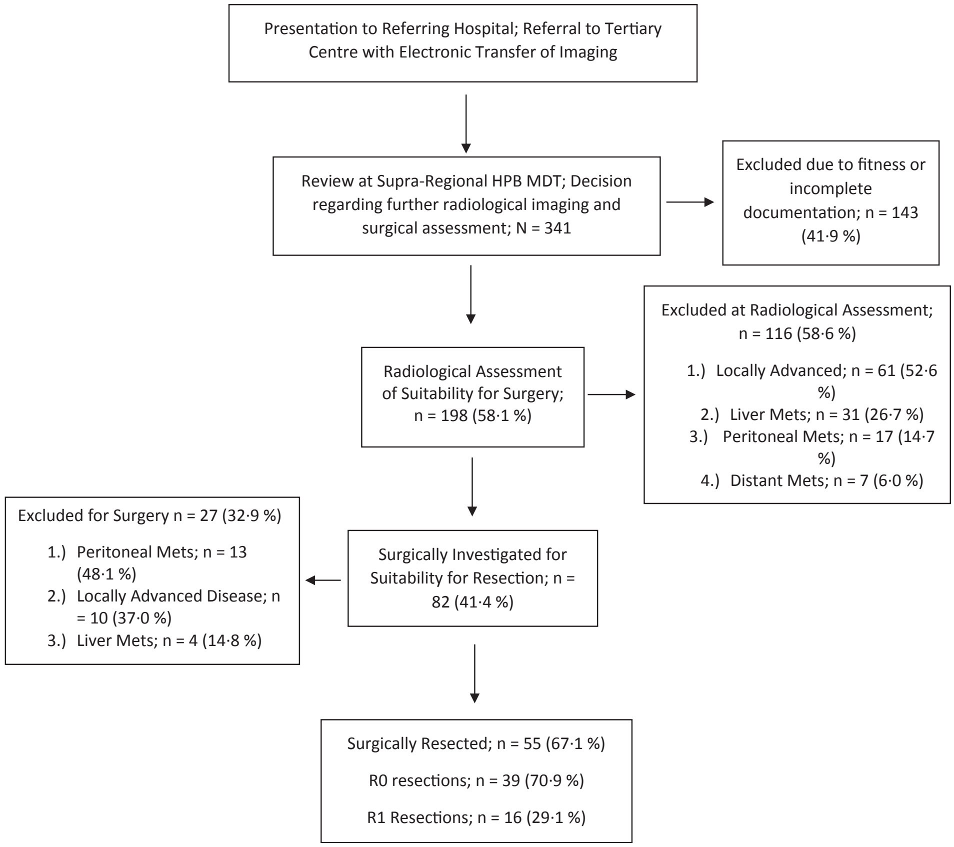

Fig. 3. Flow diagram demonstrating MDT assessment of hilar cholangiocarcinoma patients.

Table 1
Demographics, resectability scores and anatomical covariates of study population.

Covariate	Descriptor				
Sex	Male: 104 (52%)			Female: 95 (48%)	
Age	Mean ± SD: 68.3 ± 10.4 years				
BC Classification	1: 29 (14%)	2: 33 (16%)	3A: 37 (19%)	3B: 43 (22%)	4: 57 (29%)
Radiological MSKCC Score	N/A: 29 (14%)		T1: 51 (26%)	T2: 45 (23%);	T3: 74 (37%)
Right Artery	Not Involved: 175 (88%)			Involved: 24 (12%)	
Left Artery	Not Involved: 152 (76%)			Involved: 24 (24%)	
Hepatic Artery	Not Involved: 192 (96%)			Involved: 7 (4%)	
Hepatic Veins	Not Involved: 198 (99%)			Involved: 1 (1%)	
Portal Vein Main	Not Involved: 191 (96%)			Involved: 8 (4%)	
Right Portal Vein	Not Involved: 174 (87%)			Involved: 25 (13%)	
Left Portal Vein	Not Involved: 146 (73%)			Involved: 53 (27%)	
Ipsilateral Lobar Atrophy	Not Involved: 144 (72%)			Involved: 55 (28%)	
Contralateral Lobar Atrophy	Not Involved: 189 (95%)			Involved: 9 (5%)	

Table 2
Cases stratified by system category.

System Category	(N) Discussed at MDT	Explored (n; %)	Resected (n; %)
T1	51	34; 66•7	19; 36•5
T2	45	29; 64•4	27; 60•0
T3	74	12; 16•2	9; 12•2
BC 1	29	7; 17•2	0
BC 2	33	12; 36•3	11; 33•3
BC 3A	37	26; 70•3	15; 40•5
BC 3B	43	27; 62•8	22; 51•2
BC 4	57	10; 17•5	8; 14•0

Resected cohort

Eighty-two (41 4%) patients considered to have potentially resectable disease underwent surgical assessment of resectability (Fig. 3 and Table 2). Of these 82 patients, 55 (67 1%) went onto to have attempted curative resections. Potentially curative R0 resection was achieved in 39 (70 9%) patients. Potentially curative R0 resection was therefore achieved in 19 7% (39/198) of the unselected MDT cohort. There were no R2 resections. The 55 resections consisted of 13 left hemi-hepatectomies, 12 left tri-sectionectomies, 12 right hemi-hepatectomies, 11 right tri-sectionectomies and 7 bile duct excisions (all resections had concomitant caudate lobe resections). Sixteen (29 1%) of the patients underwent vascular resection and

Table 3
Table demonstrating 30/90 day mortality for resected cohort.

Gender	Age at Operation	Radiological MSKCC Score	BC Classification	Operation	Vascular Reconstruction	Complication	Re-Intervention	Survival (Days)	Cause of Death
M	47	T1	3a	Right Tri + Caudate	Portal vein	P.V.* + H.A.** Thrombosis	Laparotomy	8	Liver Failure
M	70	T1	2	Right Tri + Caudate	N/a****	G.A.*** Branch bleed	2 × Laparotomy	14	Liver Failure
M	68	T3	4	Right hemi + Caudate	Portal Vein	P.V.s Thrombosis	N/a	6	Liver Failure
F	61	T1	2	Right Tri + Caudate	Portal Vein	Post-op Bleed	Laparotomy	21	Chest Sepsis
F	69	T1	3A	Right Tri + Caudate	Portal Vein	P.V. Thrombosis	Radiological	9	CVA*****
M	53	T1	3A	Right hemi + Caudate	N/a	Intra-operative Haemorrhage	Laparotomy	4	Multi-Organ Failure
M	71	T2	3b	Left hemi + Caudate	Portal Vein	Chest Sepsis	N/a	33	Chest Sepsis

*Abbreviation - Portal Vein; **Abbreviation – Hepatic Artery; ***Abbreviation – Gastro-Duodenal Artery; ****Not Applicable; *****Abbreviation – Cerebro-Vascular Accident.

reconstruction. There were 13 portal vein reconstruction's (PVR) and 3 inferior vena cava re-construction's (IVCR) with 2 of the cases consisting of concomitant PVR and IVCR. Seven PVR's (46 7%) resulted in R0 resection compared to 32 of the 39 (82 1%; p = 0 04; χ^2) patients undergoing hepatectomy alone.

Mortalities in resected cohort

There were 6 30-day mortality's producing a 30-day mortality rate of 10 9% (49/55). There was 1 mortality at 33 days, 26 days following initial discharge and 8 days following re-admission, producing an overall 90 day mortality rate of 12 7% (48/55). Five of the 7 patients who died before 90 day's post-op had PVR's (Table 3). Of these 5 patients only 1 PVR had pre-operative radiology demonstrating portal vein involvement (PVI). Only 2 of the 40 patients (5 0%) whom underwent extrahepatic biliary duct resection and hepatectomy without PVR suffered a 90 day post-operative mortality ($p = 0.02$; χ^2).

Factors influencing resectability

Univariate logistic regression of demographic, resectability scores and anatomical covariates against resectability demonstrated that contralateral lobar atrophy was significantly negatively associated with resection. Age at diagnosis, BC score, MSKCC score, and left artery involvement were all suggestively associated with resection (Table 4).

For multivariable logistic regression, we began with two different base models, one with BC score and one with MSKCC score due to the correlation of the two scores (Spearman's rho 0.77, $p < 0.001$). The pseudo-R^2 of the BC and MSKCC base models was 0.28 and 0.26, indicating the models explain 28% and 26% of the variability in resectability respectively. In comparison to the reference value of BC score of 4, a BC score of 3A ($\beta = 2.02$; $p < 0.001$) and 3B ($\beta = 1.73$; $p < 0.001$) were both associated with increased resectability. Similarly, in comparison to the reference value of MSKCC score of 3, a MSKCC score of 2 ($\beta = 1.78$; $p < 0.001$) and 1 ($\beta = 1.36$; $p = 0.003$) were both associated with increased resectability.

Using the BC score base model, stepwise selection included age at diagnosis ($\beta = -0.06$; $p = 0.004$) and left artery involvement ($\beta = -1.41$; $p = 0.006$) in the final model (pseudo-$R^2 = 0.39$). Using the MSKCC score base model, stepwise selection included age at diagnosis ($\beta = -0.06$; $p = 0.001$) in the final model (pseudo-$R^2 = 0.34$).

Table 4
Univariate logistic regression of the resected outcome.

Covariate		β Effect Size	Standard Error	p-value
Sex		−0.0035	0.063	0.95
Age		−0.014	0.0028	<0.0001
BC Classification (Reference: 4)	1	−0.12	0.092	0.18
	2	0.089	0.088	0.31
	3A	0.39	0.085	<0.0001
	3B	0.32	0.081	0.0001
Radiological MSKCC Score	T1	−0.14	0.090	0.14
(Reference T3	T1	0.35	0.074	<0.0001
	T2	0.24	0.077	0.0018
Right Hepatic Artery		−0.06	0.096	0.53
Left Hepatic Artery		−0.12	0.073	0.10
Hepatic Artery		−0.27	0.17	0.11
Hepatic Veins		−0.26	0.44	0.55
Portal Vein Main		−0.14	0.16	0.37
Right Portal Vein		−0.021	0.094	0.82
Left Portal Vein		−0.022	0.071	0.76
Ipsilateral Lobar Atrophy		−0.11	0.070	0.12
Contralateral Lobar Atrophy		−0.28	0.14	0.05

Discussion

This study validated the use of both MSKCC and BC scores in an external cohort, demonstrating that BC score is the stronger predictor of resectability within our cohort. This study has identified a novel anatomical co-variate, left hepatic artery involvement, to augment the predictive capabilities of the BC score.

Blumgart and co-workers derived the MSKCC resectability score to improve surgical determination of resectability which was initially based on the Bismuth-Corlette system [5,16]. However, in this cohort both scoring systems demonstrate utility in pre-operatively stratifying patients for likelihood of resection. Both systems also explain a comparable percentage of the variability in resectability in this cohort.

The augmented BC system incorporating left hepatic artery involvement substantially increases the quantification of variability in resectability. Left-sided tumours appear to represent more challenging disease to surgically resect than right-sided disease [17,18]. Typically the extrahepatic course of the right hepatic duct, portal vein and hepatic artery are comparatively shorter than the left-sided biliary duct/vasculature complex. Resection of the left-sided system leaves a shorter right-side vascular pedicle to isolate, resect and reconstruct. The associated increased complexity of resection of the left-sided hilar anatomy reduces the resectability of tumours involving these structures. Left hepatic artery involvement may potentially be a surrogate indicator of radial extension due to its typically medial spatial relation to the left portal vein [19].

Limitations of radiological sensitivity affect the utility of both systems by potentially pre-operatively under-staging disease [20–23]. This is a particularly important consideration when unexpected PVI is determined at exploratory surgery. PVR is a technically demanding procedure undertaken to ensure adequate R0 resection margins in patients with locally advanced disease [24,25]. While R0 resection is feasible in this subset of patients, comparison with patients undergoing R0 resection without PVR demonstrates that it is significantly less achievable [26]. Patients undergoing hepatectomy and PVR compared to hepatectomy alone are known to have significantly increased risk of mortality [27]. This correlates with the experience of patients within this cohort. Four mortalities occurred in patients undergoing PVR and hepatectomy with no PVI demonstrated on pre-operative imaging. Unexpected PVI in potentially surgically resectable patients appears to thereby confer a substantial risk of mortality. For patients without obvious PVI on pre-operative imaging utilising the augmented BC-left hepatic artery system as an adjunct stratifying system may improve predictability of resection and improve peri-operative outcomes.

Age has been identified as a factor predicting un-resectable disease within this series. Age can act as a surrogate marker for frailty and co-morbidities. A clinical review of oncological practice has suggested that chronological age alone has been used to inappropriately limit treatment offered to older patients [28]. In this series we excluded patients deemed unfit for surgical and chemotherapeutic treatment, following MDT discussion, from analysis (Fig. 3). Age retained significance in the multivariate model despite this exclusion criteria. Older people may potentially be presenting to MDT with later-stage or more aggressive disease precluding surgical treatment.

Hilar cholangiocarcinoma is a rare cancer with the majority of patients presenting with locally advanced or metastatic disease precluding surgical treatment. Many of the reported cohorts are small and historical with even relatively high volume centres rarely operating on more than 1 patient per month with hilar cholangiocarcinoma [29]. DeOliveira and colleagues have established a European multinational registry in an attempt to develop a significant international cohort and to standardise prospective reporting of hilar cholangiocarcinoma management and outcomes [30]. Provisional analysis of the data collated since inception indicates that increased co-operation and concordance is required to validate the utility of the registry [31].

Conclusion

This study has externally validated the utility of both the MSKCC and BC scoring systems for pre-operatively stratifying patients for potential resection. It has also provided a potential novel anatomical co-variate which could be used to augment scoring systems to increase predictive accuracy. However, acknowledgement of both systems limitations is required, particularly regarding the limitations of radiological imaging sensitivity which affect its utility by potentially pre-operatively under-staging disease.

Author statement

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