European Journal of Cancer 111 (2019) 94–106

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Prediction of survival with second-line therapy in biliary tract cancer: Actualisation of the AGEO CT2BIL cohort and European multicentre validations

Cindy Neuzillet [a,b,*], Andrea Casadei Gardini [c], Bertrand Brieau [d], Caterina Vivaldi [e], Cristina Smolenschi [f], Giovanni Brandi [g], David Tougeron [h], Roberto Filippi [i,j], Angélique Vienot [k], Nicola Silvestris [l], Anne-Laure Pointet [m], Sara Lonardi [n], Benoît Rousseau [b], Mario Scartozzi [o], Laetitia Dahan [p], Giuseppe Aprile [q,r], Tarek Boussaha [s], David Malka [f], Shantini M. Crusz [t], Samuel Le Sourd [u], Aurélia Meurisse [v,w], Astrid Lièvre [x,y], Dewi Vernerey [v,w,**], the AGEO (Association des Gastro-Entérologues Oncologues)[1], GICO (Italian Group of Cholangiocarcinoma) Investigators[1], Gustave Roussy Institute Cohort[1], Barts Cancer Institute Cohort[1]

[a] *Medical Oncology, Curie Institute, Versailles Saint-Quentin University, Saint-Cloud, France*
[b] *Medical Oncology, Henri Mondor University Hospital, AP-HP, Créteil, France*
[c] *Division of Medical Oncology, Department of Medical and Surgical Sciences for Children and Adults, University Hospital of Modena, Italy*
[d] *Gastroenterology, Cochin University Hospital, AP-HP, Paris, France*
[e] *Oncology, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*
[f] *GI Oncology, Gustave Roussy Institute, Villejuif, France*
[g] *Oncology, Policlinico S. Orsola-Malpighi, Bologna, Italy*
[h] *Hepato-Gastroenterology, Poitiers University Hospital, Jean Bernard Hôpital, Poitiers, France*
[i] *Medical Oncology, Candiolo Cancer Institute, FPO, IRCCS, Candiolo, Italy*
[j] *Department of Oncology, University of Turin, Italy*

Abbreviations: 95% CI, 95% confidence interval; BSC, best supportive care; BTC, biliary tract cancer; CCA, cholangiocarcinoma; CA19-9, carbohydrate antigen 19-9; CR, complete response; ECOG, Eastern Cooperative Oncology Group; GEMCIS, gemcitabine plus cisplatin; GEMOX, gemcitabine plus oxaliplatin; HR, hazard ratio; IQR, interquartile range; L1, first-line (treatment); L2, second-line (treatment); OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; UK, United Kingdom.

* *Corresponding author*: Department of Medical Oncology, Curie Institute, Versailles Saint-Quentin University (UVSQ), 35 rue Dailly, 92210 Saint-Cloud, France.
** *Corresponding author*: Methodology and Quality of Life in Oncology Unit (INSERM UMR1098), Besançon University Hospital, 3 Boulevard Fleming, 25000 Besançon, France.
E-mail addresses: cindy.neuzillet@curie.fr (C. Neuzillet), dvernerey@chu-besancon.fr (D. Vernerey).

[1] The AGEO (Association des Gastro-Entérologues Oncologues), GICO (Italian Group of Cholangiocarcinoma), Gustave Roussy Institute Cohort, and Barts Cancer Institute Cohort investigators are listed in Appendix section.

https://doi.org/10.1016/j.ejca.2019.01.019

[k] Oncology, Besançon University Hospital, Besançon, France
[l] Medical Oncology Unit and Scientific Directorate, Cancer Institute "Giovanni Paolo II", Bari, Italy
[m] Gastroenterology and GI Oncology, George Pompidou European University Hospital, AP-HP, Paris, France
[n] Medical Oncology 1 Unit, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy
[o] Medical Oncology Unit, University of Cagliari, Cagliari, Italy
[p] Pôle "DACCORD" (Digestif, Anatomie Pathologique, Chirurgie, CISIH, Oncologie, Radiothérapie, Dermatologie), Service d'Oncologie Digestive, CHU Timone, Marseille, France
[q] Department of Oncology, Ospedale San Bortolo, Azienda ULSS8 Berica, Distretto Est, Vicenza, Italy
[r] Department of Oncology, University Hospital of Udine, Udine, Italy
[s] Oncology, Centre Multidisciplinaire d'Oncologie-CePo, Lausanne, Switzerland
[t] Oncology, Barts Cancer Institute-Queen Mary University of London, London, United Kingdom
[u] Gastroenterology and Hepatology, Centre Eugène Marquis, Rennes, France
[v] Methodology and Quality of Life in Oncology Unit, Besançon University Hospital, Besançon, France
[w] Univ. Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire et Génique, F-25000, Besançon, France
[x] Gastroenterology, Pontchaillou University Hospital, Rennes, France
[y] Rennes 1 University, Rennes, France

Received 23 October 2018; received in revised form 2 January 2019; accepted 13 January 2019

KEYWORDS
Cholangiocarcinoma;
Palliative chemotherapy;
Prognosis;
Prognostic biomarker;
Stratification

Abstract ***Background:*** The benefit of second-line chemotherapy (L2) over standard first-line (L1) gemcitabine plus cisplatin (GEMCIS) or oxaliplatin (GEMOX) chemotherapy in advanced biliary tract cancer (aBTC) is unclear. Our aim was to identify and validate prognostic factors for overall survival (OS) with L2 in aBTC to guide clinical decisions in this setting.

Methods: We performed a retrospective analysis of four prospective patient cohorts: a development cohort (28 French centres) and three validation cohorts from Italy, UK and France. All consecutive patients with aBTC receiving L2 after GEMCIS/GEMOX L1 between 2003 and 2016 were included. The association of clinicobiological data with OS was investigated in univariate and multivariate Cox analyses. A simple score was derived from the multivariate model.

Results: The development cohort included 405 patients treated with L1 GEMOX (91%) or GEMCIS. Of them, 55.3% were men, and median age was 64.8 years. Prior surgical resection was observed in 26.7%, and 94.8% had metastatic disease. Performance status (PS) was 0, 1 and 2 in 17.8%, 52.4% and 29.7%, respectively. Among 22 clinical parameters, eight were associated with OS in univariate analysis. In multivariate analysis, four were independent prognostic factors ($p < 0.05$): PS, reason for L1 discontinuation, prior resection of primary tumour and peritoneal carcinomatosis. The model had the Harrell's concordance index of 0.655, a good calibration and was validated in the three external cohorts (N = 392).

Conclusion: We validated previously reported predictive factors of OS with L2 and identified peritoneal carcinomatosis as a new pejorative factor in nearly 800 patients. Our model and score may be useful in daily practice and for future clinical trial design.

1. Introduction

Although of low incidence (~12,000 new cases/year in Europe), biliary tract cancers (BTCs) are the second primary liver tumour after hepatocellular carcinoma [1]. They are classified into three subtypes based on anatomic location: (1) intrahepatic cholangiocarcinoma (CCA); (2) extrahepatic CCA and (3) gallbladder carcinoma [2,3]. Their prognosis is poor, mainly because of late diagnosis, frequently at an advanced stage (~65%) [2,3]. The 5-year overall survival (OS) rate is only 18% [4].

Therapeutic options for advanced BTC (aBTC) are limited [2,3]. In 2010, the gemcitabine plus cisplatin (GEMCIS) doublet became the first-line (L1) reference chemotherapy based on the ABC-02 phase III trial, which showed the superiority of GEMCIS over gemcitabine in patients with aBTC and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 [5]. Similar results were found in a Japanese randomised phase II trial [6] and in a meta-analysis pooling the results from these two studies [7]. Owing to better tolerance and simpler outpatient administration, many

European centres use the GEMOX (gemcitabine plus oxaliplatin) doublet as an equivalent to GEMCIS [8]. Overall, gemcitabine plus platinum chemotherapy is well-established L1 standard in patients with aBTC and a PS $\leq$ 2 [2,3].

Beyond failure of L1, up to 30%–40% of patients remain in a good clinical condition and are able to receive subsequent line(s) of therapy [10]. There is no recommended treatment in this setting [2,3]. In a systematic review of the literature, Lamarca *et al.* [11] reported a median OS of 7.2 months with second-line chemotherapy (L2) in patients with aBTC. The ABC-07 phase III trial (NCT01926236) is ongoing to assess the clinical benefit of L2 administration *vs.* best supportive care (BSC).

Not all patients seem to benefit from L2, and it has to be discussed in terms of risk/benefit ratio on an individual basis. Thus, identification of reliable prognostic factors for risk stratification of patients with aBTC in L2 setting is warranted to improve therapeutic decisions. However, there is no well-validated and widely accepted prognostic model for application in routine practice or in clinical trials.

We performed a multicenter European study to develop and validate a prognostic model and score for OS in patients with aBTC treated with L2. The model and score may be useful tools to guide clinicians' decision for L2 administration and to optimise future clinical trial design.

2. Materials and methods

2.1. Patients

All consecutive patients with histologically proven aBTC who were treated between January 2003 and January 2016 in 28 French centres were included in the development cohort. Patients were considered eligible if they (i) were $\geq$18 years old, (ii) had aBTC (metastatic, locally advanced or recurrent after surgery) not amenable to curative treatment and (iii) had progressed or were intolerant to L1 with gemcitabine plus platinum (GEMCIS or GEMOX). Patients were excluded if they (i) had been treated with gemcitabine plus platinum doublet in the adjuvant setting, (ii) received L1 gemcitabine single agent or (iii) had an ampullary carcinoma. The external validation cohorts included consecutive patients with aBTC who received L2 between January 2003 and January 2016 with the same inclusion criteria in three other cohorts: (i) an Italian multicenter cohort (nine centres), (ii) a United Kingdom (UK) single-institutional cohort (Barts Cancer Institute, London) and (iii) a French single-institutional cohort (Gustave Roussy Institute, Villejuif).

The database was registered and declared to the National French Commission for bioinformatics data and patient liberty and approved by the Advisory Committee on Information Processing in the field of health research (declaration number: 14–115). In accordance with French regulation, an information letter was given to all patients and non-opposition was verified.

Demographics; cancer history and treatment and pathological, clinical, biological and radiological (tumour response as per Response Evaluation Criteria in Solid Tumours, v1.1, criteria) data were retrospectively collected from medical records.

2.2. Statistical analysis

Median value (interquartile range) and frequency (percentage) were provided for the description of continuous and categorical variables, respectively. Medians and proportions were compared using Student's t-test and chi-squared test (or Fisher's exact test, if appropriate), respectively.

OS with L2 was calculated from the date of first administration of L2 to the date of death from any cause. Survival data were censored at the last follow-up. OS with L2 was estimated using the Kaplan–Meier method and described using median or rate at specific time points with 95% confidence intervals (95% CIs). Follow-up duration was calculated using a reverse Kaplan–Meier estimation [12].

Cox proportional hazard models were performed to estimate hazard ratio (HR) and 95% CI for factors associated with OS in L2. The association of 22 baseline parameters with OS in L2 was first assessed using univariate Cox analyses, and then parameters with p values < 0.05 were entered into a final multivariable Cox regression model, after considering collinearity among variables with a correlation matrix. When used continuously in the Cox model, a potential non-linear relationship between predictors and OS was first investigated using the fractional polynomials method to determine the best transformation for continuous variables [13] and validated by the restricted cubic splines method with graphical evaluation. The assumption of proportionality was checked by plotting log-minus-log survival curves and by cumulative martingale process plots.

Accuracy of the final model was verified regarding two parameters: discrimination and calibration. The predictive value and the discrimination ability of the final model were assessed with the Harrell's concordance index (C-index) [14]. Random samples of the population were used to derive 95% CI bootstrap percentile for the C-statistic. Calibration was assessed by visual examination of the calibration plot. Internal validation of the final model was performed with a bootstrap sample procedure.

The final model was used to establish a nomogram, allowing the estimation of median and individual L2 OS probabilities at 3, 6, 12 and 24 months. At a population

Table 1
Patient characteristics in the development and external validation cohorts.

Characteristics	Development cohort	External validation cohorts		
	AGEO CT2BIL (n = 405)	Italy (n = 297)	France (n = 71)	UK (n = 24)
Sex[a]				
Male	224 (55.3%)	150 (50.5%)	34 (47.9%)	12 (50.0%)
Age (years), median (IQR)	64.8 (58.2–71.3)	64.7 (57.2–69.9)	62.6 (56.3–68.9)	66.7 (59.7–72.5)
Missing	0	1	1	0
Primary tumour site				
Intrahepatic	214 (53.1%)	171 (57.6%)	43 (60.6%)	10 (41.7%)
Extrahepatic/hilar	109 (27.1%)	72 (24.2%)	14 (19.7%)	4 (16.6%)
Gallbladder	80 (19.8%)	54 (18.2%)	14 (19.7%)	10 (41.7%)
Missing	2	0	0	0
Prior resection of primary tumour[a,b]				
Yes	108 (26.7%)	92 (31.0%)	9 (12.7%)	7 (29.2%)
Radiotherapy				
Yes	25 (6.2%)	23 (7.7%)	5 (7.0%)	3 (13.0%)
Missing	3	0	0	1
Biliary drainage				
Yes	129 (32.3%)	65 (22.1%)	22 (31.0%)	7 (30.4%)
Missing	6	3	0	1
Type of L1 regimen				
Gemcitabine + oxaliplatin	368 (90.9%)	176 (59.3%)	66 (94.3%)	0 (0%)
Gemcitabine + cisplatin	37 (9.1%)	121 (40.7%)	4 (5.7%)	24 (100.0%)
Missing	0	0	1	0
Best response to L1				
CR	14 (3.5%)	3 (1.0%)	2 (2.9%)	0 (0%)
PR/SD	251 (62.8%)	178 (59.9%)	49 (70.0%)	19 (79.2%)
PD	135 (33.8%)	116 (39.1%)	19 (27.1%)	5 (20.8%)
Missing	5	0	1	0
Duration of L1 (months)[c]	6.4 (3.2–11.0)	6.5 (3.7–9.7)	5.9 (2.9–9.4)	11.0 (7.2–18.3)
Missing	0	2	0	0
Reason for L1 discontinuation				
Toxicity	42 (10.4%)	25 (8.5%)	7 (9.9%)	2 (8.3%)
Other	51 (12.6%)	76 (25.9%)	7 (9.9%)	13 (54.2%)
PD	312 (77.0%)	193 (65.7%)	57 (80.3%)	9 (37.5%)
Missing	0	3	0	0
PS at the beginning of L2				
0	69 (17.8%)	88 (30.4%)	24 (33.8%)	7 (29.2%)
1	203 (52.4%)	152 (52.6%)	32 (45.1%)	10 (41.7%)
2	115 (29.7%)	49 (17.0%)	15 (21.1%)	7 (29.1%)
Missing	18	8	0	2
Disease stage at the beginning of L2				
Metastatic	384 (94.8%)	281 (94.9%)	68 (95.8%)	24 (100.0%)
Locally advanced	21 (5.2%)	15 (5.1%)	3 (4.2%)	0 (0%)
Missing	0	1	0	0
Metastatic sites				
Liver[a] (yes)	251 (62.0%)	185 (62.3%)	47 (66.2%)	15 (62.5%)
Lung (yes)	116 (28.6%)	79 (26.9%)	20 (28.2%)	4 (16.7%)
Missing	0	3	0	0
Bone (yes)	39 (9.6%)	32 (10.9%)	9 (12.7%)	4 (16.7%)
Missing	0	4	0	0
Lymph node (yes)	139 (34.3%)	156 (53.1%)	39 (54.9%)	13 (54.2%)
Missing	0	3	3	0
Peritoneum (yes)	151 (37.3%)	81 (27.5%)	24 (33.8%)	6 (25.0%)
Missing	0	3	0	0
Total bilirubin (μmol/L), median (IQR)	12.0 (7.0–17.0)	10.3 (7.2–15.4)	9.0 (7.0–19.0)	7.5 (5.5–9.5)
Missing	109	58	28	0
Albumin (g/L), median (IQR)	34.5 (30.0–38.5)	36.0 (31.0–39.0)	34.5 (29.0–39.0)	40.0 (36.0–42.5)
Missing	238	123	37	0
Serum CA19-9 (UI/mL), median (IQR)	166.0 (38.0–1139.0)	161.0 (40.1–1099.0)	470.0 (73.0–5212.0)	335.0 (62.0–847.0)
Missing	154	60	28	10
Type of L2 regimen				
Fluoropyrimidine monotherapy	63 (15.6%)	98 (33.0%)	12 (17.4%)	15 (62.5%)
Fluoropyrimidine + irinotecan	194 (47.9%)	60 (20.2%)	16 (23.2%)	0 (0.0%)
Fluoropyrimidine + platinum	94 (23.2%)	16 (5.4%)	4 (5.8%)	7 (29.2%)

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Development cohort	External validation cohorts		
	AGEO CT2BIL (n = 405)	Italy (n = 297)	France (n = 71)	UK (n = 24)
Gemcitabine-based combination	28 (6.9%)	91 (30.6%)	15 (21.7%)	2 (8.3%)
Taxane	5 (1.2%)	5 (1.7%)	2 (2.9%)	0 (0.0%)
Others	21 (5.2%)	27 (9.1%)	20 (29.0%)	0 (0.0%)

CA19-9: carbohydrate antigen 19-9, CR: complete response, IQR: interquartile range, L1: first-line treatment, L2: second-line treatment, PD: progressive disease, PR: partial response, PS: performance status, SD: stable disease.

[a] No missing data.

[b] Prior resection of the primary tumour was defined as surgery with R0/R1 resection and no evidence of disease within 1 month after surgery.

[c] Duration of L1 was calculated from the date of first administration of L1 to the date of first administration of L2.

level, to define risk groups with distinct survival profiles, we constructed a simple score based on the prognostic factors identified and considering their relative weight on OS. The prognostic score discrimination ability (C-index) was assessed in each cohort.

A clinical benefit–centred accuracy of the final model was evaluated by a decision curve analysis [15] in each cohort.

Another multivariate analysis was performed by including carbohydrate antigen 19-9 (CA19-9) but not initially selected in the multivariate model because of the high rate of missing data.

All analyses were performed using SAS, version 9.4, and R software, version 2.15.2. *P* values of less than 0.05 were considered statistically significant, and all tests were two-sided. More details are provided in the Supplementary Material.

3. Results

3.1. Population-based prospective cohort

The development cohort included 405 patients treated with L1 GEMOX (91%) or GEMCIS (9%) [Table 1]. Median follow-up was 34.6 months (95% CI = 28.9–51.4).

In the external validation cohorts, 297, 71 and 24 patients were included in the Italian, French and UK cohort, respectively. The cohorts displayed similar patient characteristics [Table 1], except for (i) primary tumour location, (ii) prior surgical resection of the primary tumour, (iii) L1 regimen and (iv) ECOG PS at the beginning of L2.

3.2. Determinants of OS in patients receiving second-line therapy

In univariate Cox analysis, we identified nine parameters as prognostic factors for OS with p values < 0.05: (i) prior resection of primary tumour, (ii) biliary drainage, (iii) best tumour response with L1, (iv) duration of L1, (v) reason for L1 discontinuation, (vi) ECOG PS at the beginning of L2, (vii) number of metastatic sites, (viii) bone metastases and (ix) peritoneal carcinomatosis [Table 2A and Supplementary Figure 1]. Primary tumour site and type of L2 regimen were not significantly associated with OS.

A correlation matrix was used to detect relevant interactions between investigated parameters and select variables for multivariate analysis [Supplementary Figure 2].

The multivariable Cox analysis showed four independent risk factors for OS: (i) ECOG PS ($p < 0.0001$), (ii) reason for L1 discontinuation ($p = 0.0020$), (iii) prior resection of primary tumour ($p = 0.0314$), and (iv) peritoneal carcinomatosis ($p = 0.0181$) [Table 2B]. The type of L2 regimen was not associated with OS ($p = 0.8129$).

3.3. Performance assessment and internal validation of the final model

The multivariate model had a C-index of 0.655 (95% CI = 0.621–0.688). The calibration plots showed an optimal agreement between model prediction and actual observation for predicting OS probability at 3, 6, 12 and 24 months [Supplementary Figure 3]. In the internal validation, uncertainties around HR measured with a bootstrapping procedure reflected the robustness of the final model [Table 2B].

3.4. Prognostic nomogram and score for OS

A nomogram integrating all statistically significant independent factors for OS was built [Supplementary Figure 4].

The nomogram highlighted that ECOG PS had a heavily predominant weight on OS [Fig. 1A and Supplementary Figure 4], whereas the prognostic significance of other factors was much lower and of similar magnitude of association with OS. Nevertheless, the addition of the three other identified risk factors to the PS in the model significantly improved its discrimination capacity because the C-statistics increased from 0.624 to 0.655 (delta: 0.03, 95% CI = 0.01–0.05).

Therefore, we decided to consider reason for L1 discontinuation, prior primary tumour surgery and peritoneal carcinomatosis as risk factors of equivalent

Table 2A
Prognostic factors associated with overall survival in univariate analysis in the development cohort.

Parameters	Number of patients	Number of events	HR	95% CI	*p*
Sex[a]					
Female	181	152	1	–	–
Male	224	194	1.114	[0.900; 1.378]	0.3214
Age (years[a])					
Continuous	405	346	1.006	[0.994; 1.017]	0.3336
Age (years[a])					
<70	286	240	1	–	–
≥70	119	106	1.073	[0.852; 1.350]	0.5498
Primary tumour site					
Intrahepatic	214	190	1	–	
Extrahepatic/hilar	109	89	0.965	[0.750; 1.242]	
Gallbladder	80	66	1.042	[0.787; 1.379]	0.8950
Missing	2				
Prior resection of primary tumour[a,b]					
Yes	108	84	1		
No	297	262	1.615	[1.259; 2.073]	0.0002
R0 resection of primary tumour					
Yes	73	56	1		
No	33	26	1.251	[0.780; 2.007]	0.3535
Missing	2				
Radiotherapy					
Yes	25	22	1		
No	377	321	1.043	[0.676; 1.609]	0.8487
Missing	3				
Biliary drainage					
Yes	129	108	1		
No	270	232	0.735	[0.583; 0.925]	0.0087
Missing	6				
Delay between diagnosis of advanced BTC and beginning of L1[a]					
< 1 month	169	144			
1–3 months	206	178	1.167	[0.934; 1.457]	
> 3 months	30	24	0.787	[0.510; 1.215]	0.1220
Type of L1 regimen[a]					
Gemcitabine + oxaliplatin	368	316	1		
Gemcitabine + cisplatin	37	30	0.843	[0.580; 1.227]	0.3734
Best response to L1					
CR	14	10	1		
PR/SD	251	219	2.270	[1.199; 4.298]	
PD	135	114	2.924	[1.518; 5.631]	0.0022
Missing	5				
Duration of L1[c] **(months[a])**					
Continuous	405	346	0.980	[0.964; 0.997]	0.0194
Duration of L1[c] **(months[a])**					
< 3	82	73	1		
3–6	111	89	0.939	[0.689; 1.280]	
> 6	212	184	0.747	[0.569; 0.982]	0.0573
Reason for L1 discontinuation[a]					
Toxicity/Other	93	80	1		
PD	312	266	1.691	[1.311; 2.182]	<0.0001
PS at the beginning of L2					
0	69	53	1		
1	203	175	1.817	[1.327; 2.489]	
2	115	103	3.647	[2.582; 5.152]	<0.0001
Missing	18				
Disease stage at the beginning of L2[a]					
Metastatic	384	330	1		
Locally advanced	21	16	0.758	[0.458; 1.253]	0.2793
Number of metastatic sites at the beginning of L2[a]					
Continuous	405	346	1.158	[1.049; 1.279]	0.0037
Number of metastatic sites at the beginning of L2[a]					
< 2	153	127	1		
≥ 2	252	219	1.289	[1.034; 1.606]	0.0238
Liver metastasis[a]					

(*continued on next page*)

Table 2A (*continued*)

Parameters	Number of patients	Number of events	HR	95% CI	*p*
No	154	132	1		
Yes	251	214	1.117	[0.899; 1.388]	0.319
Lung metastasis					
No	289	242	1		
Yes	115	103	1.103	[0.875; 1.392]	0.4069
Missing	1				
Bone metastasis					
No	365	310	1		
Yes	39	35	1.563	[1.099; 2.222]	0.0129
Missing	1				
Lymph node metastasis					
No	265	229	1		
Yes	139	116	1.092	[0.873; 1.366]	0.4396
Missing	1				
Peritoneal carcinomatosis					
No	254	206	1		
Yes	150	139	1.449	[1.167; 1.798]	0.0008
Missing	1				
Total bilirubin (μmol/L)					
Continuous	296	254	1.010	[1.004; 1.016]	<0.0001
Missing	109				
Total bilirubin (μmol/L)					
≤17	244	204	1		
>17	52	50	1.666	[1.220; 2.275]	0.0013
Missing	109				
Albumin (g/L)					
Continuous	167	143	0.947	[0.923; 0.971]	<0.0001
Missing	238				
Albumin (g/L)					
<35 g/L	88	84	1		
≥35 g/L	79	59	0.500	[0.355; 0.704]	<0.0001
Missing	238				
Serum CA 19-9 (UI/mL)					
Continuous (log value)	251	207	1.359	[1.188; 1.556]	<0.0001
Missing	154				
Serum CA 19-9 (UI/mL)					
<400	162	130	1		
≥400	89	77	1.878	[1.411; 2.500]	<0.0001
Missing	154				
Type of L2 regimen[a]					
Fluoropyrimidine monotherapy	63	57	1		
Fluoropyrimidine + irinotecan	194	154	0.969	[0.714; 1.314]	
Fluoropyrimidine + platinum	94	88	0.871	[0.624; 1.217]	
Gemcitabine-based combination	28	26	0.785	[0.493; 1.249]	
Taxane	5	3	0.764	[0.239; 2.443]	
Others	21	18	0.787	[0.463; 1.339]	0.8129
Fluoropyrimidine-based regimen[a]					
No	50	44	1		
Yes	355	302	1.058	[0.771; 1.453]	0.7274
Targeted therapy[a]					
No	377	319	1		
Anti-EGFR: cetuximab or erlotinib	8	8	0.804	[0.397; 1.629]	
Antiangiogenic: bevacizumab or sunitinib or sorafenib	20	19	0.981	[0.617; 1.560]	0.8316
Center location[a]					
Paris area	172	137	1		
Other French centres	233	209	1.141	[0.919; 1.417]	0.2316

95% CI: 95% confidence interval, EGFR: epidermal growth factor receptor, CA 19-9: carbohydrate antigen 19-9, HR: hazard ratio, L1: first-line treatment, L2: second-line treatment, PD: progressive disease, PR: partial response, PS: performance status, SD: stable disease, BTC: biliary tract cancer, CR: complete response.

[a] No missing data.

[b] Prior resection of the primary tumour was defined as surgery with R0/R1 resection and no evidence of disease within 1 month post-surgery.

[c] Duration of L1 was calculated from the date of first administration of L1 to the date of first administration of L2.

prognostic weight and analysed them in each ECOG PS stratum [Supplementary Figure 5]. We observed that the survival curves of patients with one, two or three risk factors were quite similar, whereas patients with no risk factor had a more favourable survival. We then defined two groups of patients: (i) those with ≥ one risk factor(s) *vs.* (ii) those with no risk factor.

The CT2BIL prognostic score was based on the ECOG PS and the presence of risk factors [Fig. 1B–C]. Finally, owing to the low number of patients with score 0, we grouped scores 0 and 1 together [Supplementary Figure 6]. Hence, patients were categorised into three risk groups with median OS of 12.7 months (95% CI = 8.5–14.9, score 0–1), 6.9 months (95% CI = 6.5–8.5, score 2) and 3.5 months (95% CI = 3.0–4.2, score 3), respectively ($p < 0.0001$) [Fig. 1B–C]. The C-index of the final score was 0.633, 95% CI = 0.602–0.663.

3.5. External validation of the prognostic model and score

Information for the four baseline parameters that were required for the score calculation was available for 285 (95.9%), 71 (100%) and 24 (100%) patients from the Italian, French and UK cohorts, respectively. The multivariate model was replicated in all three cohorts [Table 3A–C].

The good discrimination ability of the final model was externally confirmed with C-index of 0.651 (95% CI = 0.615–0.687), 0.704 (95% CI = 0.590–0.818) and 0.867 (95% CI = 0.770–0.964) in the Italian, French and UK cohorts, respectively.

Then, we validated the discrimination ability of the score developed by identifying three risk groups with distinct OS outcomes ($p < 0.0001$ in each cohort) [Fig. 2–F].

3.6. Clinical benefit analysis

The clinical benefit–centred accuracy of the final model was confirmed by a decision curve analysis [Fig. 3A–D]. The net benefit for decisions based on the PS was better than considering patients on the same level of risk in each cohort. Our final multivariate model further improved the benefit for threshold values > 10%. Overall, the decision curve showed that the net benefit for decision based on our final multivariable model is of interest.

3.7. Clinicobiological model

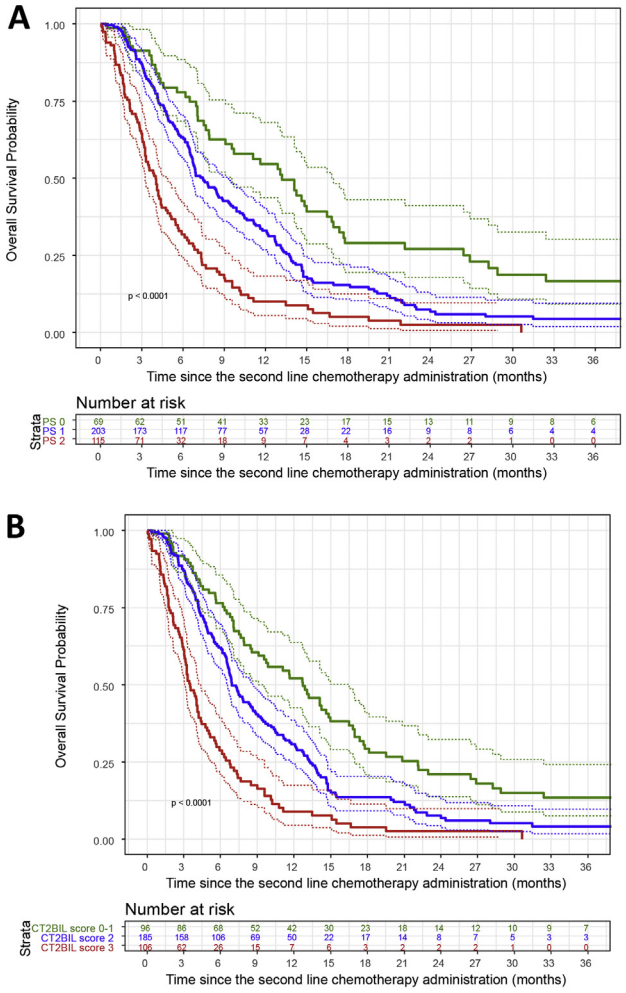
In an exploratory approach, CA19-9 serum level was added in the previously identified clinical model. Analysis of CA19-9 as a continuous (log) variable was more informative than the categorical model (<*vs.* ≥ 400 UI/mL).

Analysis of patients with complete data for the four clinical factors and CA19-9 identified CA19-9 as an independent marker significantly associated with OS ($p = 0.008$ in the development cohort and $p < 0.0001$

Table 2B
Prognostic factors associated with overall survival in multivariate analysis in the development cohort (n = 387).

Parameters	Number of patients	Number of events	HR	95% CI	*p*	Internal validation 95% BCA HR
Prior resection of primary tumour[a]						
Yes	103	79	1			
No	284	252	1.333	[1.026; 1.733]	0.0314	[0.990; 1.724]
Reason for discontinuation of L1						
Toxicity/ other	92	80	1			
PD	295	251	1.506	[1.162; 1.952]	0.0020	[1.176; 1.927]
PS at the beginning of L2						
0	69	53	1			
1	203	175	1.537	[1.114; 2.121]		[1.180; 2.133]
2	115	103	3.045	[2.139; 4.335]	<0.0001	[2.010; 4.577]
Peritoneal carcinomatosis						
No	241	196	1			
Yes	146	135	1.309	[1.047; 1.636]	0.0181	[1.008; 1.688]

Multivariate Cox final model.
95% CI: 95% confidence interval, BCA: accelerated bootstrap, HR: hazard ratio, L1: first-line treatment, L2: second-line treatment, PD: progressive disease, PS: performance status.
[a] Prior resection of the primary tumour was defined as surgery with R0/R1 resection and no evidence of disease within 1 month post-surgery.



C

PS	≥ 1 RF	CT2BIL score
0	No	0
	Yes	1
1	No	
	Yes	2
2	No	
	Yes	3

Fig. 1. **Kaplan–Meier curves of the overall survival estimation and its 95% confidence interval (95% CI) for three risk groups in the development cohort based** on performance status (PS) ($p < 0.0001$) (A) or on the CT2BIL score ($p < 0.0001$) (B), with user-friendly guide for CT2BIL score calculation (C). Log-rank tests. RF: risk factor (reason for L1 discontinuation, prior resection of primary tumour, and peritoneal carcinomatosis).

and $p = 0.01$ in the Italian and French validation cohorts, respectively) [Supplementary Table 1]. The multivariate model with CA19-9 was established based on patients for whom the five parameters were available. Overall, CA19-9 provided additional prognostic information, but the increase in the C-index value was modest [Supplementary Table 1].

4. Discussion and conclusions

Identification of prognostic factors for risk stratification of patients with aBTC in L2 setting is warranted to determine which patients are the most likely to benefit from the administration of chemotherapy. A pre-L2 estimation of OS may be useful to select patients for treatment, considering that patients who are at high risk of death within three months should not receive chemotherapy and should rather be managed with BSC only. In previously published studies, PS, response to L1, tumour stage, primary tumour location, prior surgical resection of the primary tumour and CA19-9 were independently associated with OS with L2 (mainly 5-fluorouracil–based chemotherapy) [Table 4] [10,16–18].

Our results validate, in nearly 800 patients from four independent cohorts treated with various types of L2 regimen, some of these previously reported prognostic factors (ECOG PS, L1 efficacy, primary tumour surgery, CA19-9) and identify peritoneal carcinomatosis as a new pejorative prognostic factor. This is the largest database available in aBTC in the L2 setting [10,16–18]. We performed our analysis in a rigorous methodological framework [19] and provided transparent reporting of the multivariate model as suggested in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement [13,20]. These prognostic models and derived tools could be useful to strengthen decision-making for clinicians and be applied to the stratification of patient randomisation and for pre-planned subgroup analyses in future clinical trials. However, we acknowledge that our study is limited by its retrospective nature for data collection and the high rate of missing data for biological data, requiring further prospective validation.

Moreover, our work highlights the prognostic burden of PS in aBTC and provides a word of caution when making statistical assumptions and interpreting results from single-arm phase II studies in the L2 setting. Indeed, the majority of trials enrol patients with PS 0–1 only, who display a clearly more favourable survival (median OS up to 13 months in PS 0) than the overall 6–7 months estimation that has been classically reported in 'real life' studies in the overall (PS 0–2) patient population. Consequently, although it may be challenging because of the low incidence of this disease, our results strongly support prospective evaluation of OS in BTC in L2 setting and the use of at least non-comparative randomised phase II design including a control arm to verify the calibration of the assumptions made in the experimental arm. This is even more crucial given the paucity of phase III studies in these patients.

Finally, the C-index remains <0.70, indicating that an important part of the patient heterogeneity in death

Table 3A
Prognostic factors associated with overall survival in multivariate analysis in the Italian validation cohort (n = 285).

Parameters	Number of patients	Number of events	HR	95% CI	*p*
Prior resection of primary tumour					
Yes	85	71	1		
No	201	174	1.454	[1.093; 1.933]	0.0100
Reason for discontinuation of L1					
Toxicity/ Other	99	80	1		
PD	187	165	1.839	[1.393; 2.427]	<0.0001
PS at the beginning of L2					
0	88	75	1		
1	149	125	1.231	[0.913; 1.658]	
2	49	45	2.198	[1.488; 3.247]	0.0003
Peritoneal carcinomatosis					
No	206	175	1		
Yes	80	70	1.399	[1.049; 1.865]	0.0223

Multivariate Cox final model.
95% CI: 95% confidence interval, HR: hazard ratio, L1: first-line treatment, L2: second-line treatment, PD: progressive disease, PS: performance status.

Table 3B
Prognostic factors associated with overall survival in multivariate analysis in the French validation cohort (n = 71).

	Number of patients	Number of events	HR	95% CI	*p*
Prior resection of primary tumour					
Yes	62	48	1		
No	9	7	1.851	[0.786; 4.362]	0.1591
Reason for discontinuation of L1					
Toxicity/ Other	14	8	1		
PD	57	47	3.078	[1.388; 6.823]	0.0063
PS at the beginning of L2					
0	24	15			
1	32	27	1	[1.015; 3.876]	
2	15	13	1.984 6.704	[2.909; 15.452]	<0.0001
Peritoneal carcinomatosis					
No	47	35	1		
Yes	24	20	1.003	[0.568; 1.769]	0.9928

Multivariate Cox final model.
95% CI: 95% confidence interval, HR: hazard ratio, L1: first-line treatment, L2: second-line treatment, PD: progressive disease, PS: performance status.

Table 3C
Prognostic factors associated with overall survival in multivariate analysis in the UK validation cohort (n = 24).

	Number of patients	Number of events	HR	95% CI	*p*
Prior resection of primary tumour					
Yes	7	6	1		
No	17	15	4.788	[1.032; 22.209]	0.0454
Reason for discontinuation of L1					
Toxicity/ Other	15	12	1		
PD	9	9	31.893	[5.151; 197.464]	0.0002
PS at the beginning of L2					
0	7	5	1		
1	10	9	7.441	[1.287; 43.025]	
2	7	7	20.421	[2.843; 146.701]	0.0110
Peritoneal carcinomatosis					
No	18	15	1		
Yes	6	6	15.327	[2.977; 78.900]	0.0011

Multivariate Cox final model.
95% CI: 95% confidence interval, HR: hazard ratio, L1: first-line treatment, L2: second-line treatment, PD: progressive disease, PS: performance status.

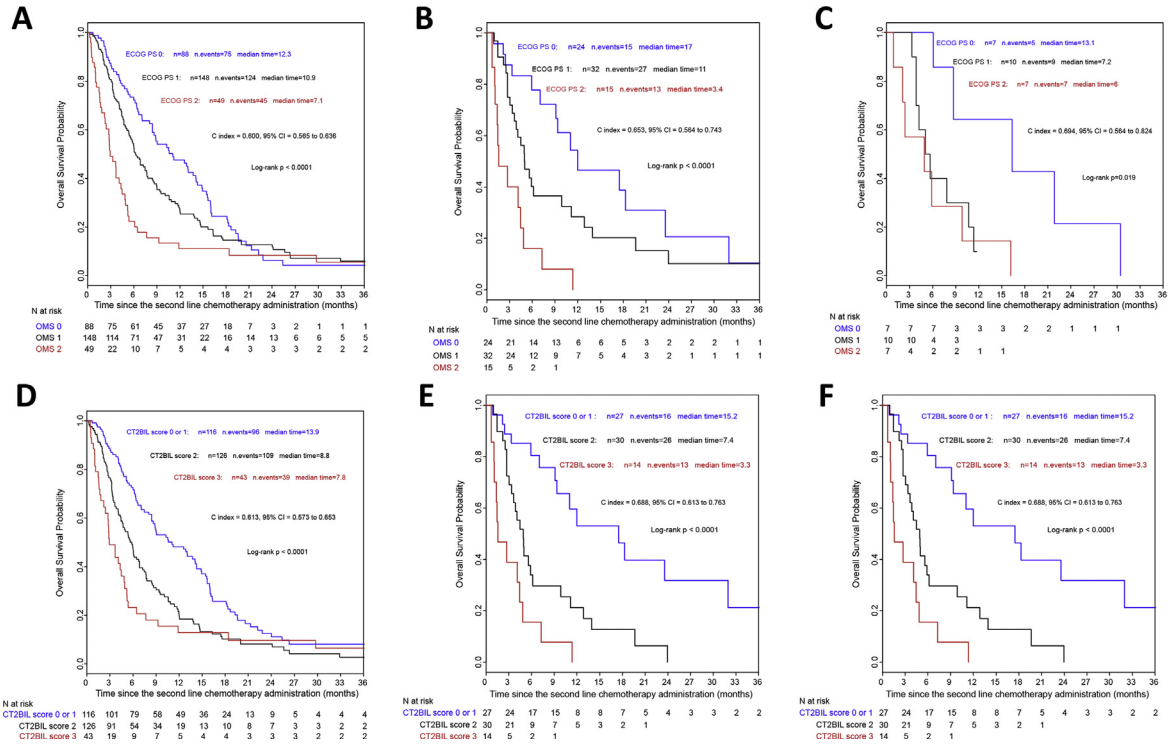


Fig. 2. **Kaplan–Meier curves of overall survival for three risk groups in the external validation cohorts** based on performance status (PS) (A, $p < 0.0001$; B, $p < 0.0001$; C, $p < 0.0001$) or on the CT2BIL score (D, $p < 0.0001$; E, $p = 0.019$; F, $p < 0.0001$), in the Italian (A, D), French (B, E) and UK (C, F), respectively. Log-rank tests. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

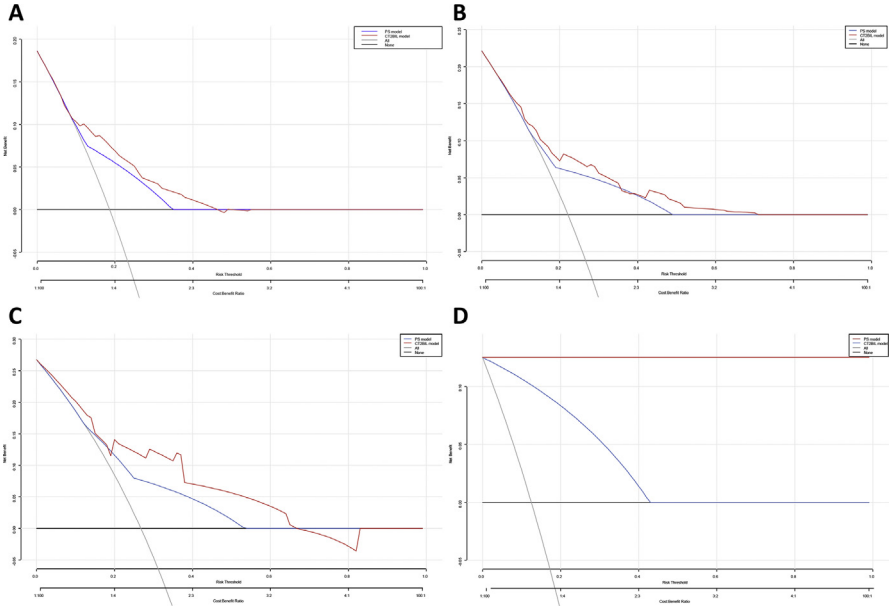


Fig. 3. **Decision curves to plot the net benefit achieved by making clinical decisions** based on the performance status (PS) (blue) or on the final multivariate model (red) for risk of death predictions at three months in the development cohort (A) and the external validation cohorts (Italy–B, French–C and UK–D). Net benefit = true positive rate − (false positive rate × weighting factor). Weighting factor = W = Threshold probability/(1-threshold probability) = ratio of harm to benefit. The decision curve analysis shows a threshold of risk of death at 3 months at which decisions will cause greater benefit for true positives and false positives will be reduced. Here, the decision is defined by the possibility of not treating a patient with second-line chemotherapy (L2). In this context, the clinician must ensure that the patient is at high risk of death at three months and minimise false positives, that is, patients who are still alive at three months who must be treated. The grey curve represents the benefit achieved by making clinical decisions in all assuming that all patients would be dead at three months. The black curve represents the benefit achieved by making clinical decisions in none assuming that all patients would be alive at three months. Overall, the decision curve shows that the net benefit for decision based on our final multivariable model is of interest. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Summary of previously published retrospective studies of second-line chemotherapy in patients with advanced biliary tract carcinoma.

Author, Year (ref)	Number of patients	mPFS (months)	mOS (months)	Prognostic factors (multivariate analysis)
Brieau *et al.*, 2015 [10]	196	3.2	6.7	• PS 0-1 • PR/SD with L1 • CA19-9 $\leq$ 400 UI/ml
Fornaro *et al.*, 2014 [16]	300	3.2	7.2	• PS 0 • CA19-9 $\leq$ 152 UI/ml • PFS with L1 $\geq$ 6 months • Surgery on primary tumour
Fornaro *et al.*, 2015 [17]	174 Pooled analysis with published data: 499	3.0 3.1	6.6 6.3	• PS 0 • CA19-9 < 157 UI/ml • Locally advanced stage
Kim *et al.*, 2017 [18]	321	1.9	6.5	• Intra-hepatic CCA • TTP with L1 > 4 months • CA19-9 at diagnosis • Metastatic stage at diagnosis

CA19-9: carbohydrate antigen 19-9, CCA: cholangiocarcinoma; L1: first-line chemotherapy, SD: stable disease, mPFS: median progression-free survival, mOS: median overall survival, PFS: progression-free survival, PS: performance status, PR: partial response, TTP: time to tumour progression.

risk remains unexplained by classical clinical factors even in this large, well-documented, European database. Better understanding of BTC prognosis may emerge from molecular studies [21] and also from the development of more informative databases including easily available clinicobiological parameters that were not available in our study, such as smoking status or neutrophil-to-lymphocyte ratio [22,23].

Overall, our results highlight a considerable heterogeneity in survival in patients with aBTC receiving L2, with median OS ranging from 3 to 13 months. A better and adequate discrimination of these patient subgroups is essential to improve therapeutic strategies at the patient level and reduce confusion in clinical research by optimising the design of future clinical trials.

Conflict of interest statement

None declared.

Author' contribution

C.N., A.L. and D.V. contributed in design of the work, analysis/interpretation of data and manuscript writing. Acquisition of data was carried out by C.N., A.C.G., B.B., C.V., C.S., G.B., D.T., R.F., A.V., N.S., A.-L.P., S.L., B.R., M.S., L.D., G.A., T.B., D.M., S.M.C., S.L.S. and A.L. C.N. and A.M. contributed in data management. All authors revised and approved the final manuscript.

Financial support

No specific funding.

Appendix

Additional investigators

AGEO investigators:

- Ludovic Evesque, Gastroenterology and Hepatology, Centre Antoine-Lacassagne, Nice, France
- Alexandra Heurgué, Hepatology and Digestive Oncology, Reims University Hospital, Reims, France
- Jérôme Desramé, Gastroenterology and Hepatology, Jean Mermoz Private Hospital, Lyon, France
- Thierry Lecomte, Hepato-Gastroenterology and GI Oncology, Tours University Hospital, Tours, France
- Wulfran Cacheux, Medical Oncology, Curie Institute, Saint-Cloud, France
- Jean-Baptiste Bachet, Hepato-Gastroenterology and GI Oncology, AP-HP, Pitié-Salpétrière University Hospital, Paris, France
- Jean-Marc Phelip, Hepato-Gastroenterology and GI Oncology, Saint Etienne University Hospital, Saint Etienne, France
- Vincent Hautefeuille, Hepato-Gastroenterology and GI Oncology, Amiens Picardie University Hospital, Amiens, France
- Nassim Hammoudi, Saint Louis University Hospital, AP-HP, Paris, France
- Florence Mary, Gastroenterology, Avicenne University Hospital, AP-HP, Bobigny, France
- Christophe Locher, Hepato-Gastroenterology, Meaux Hospital, Meaux, France
- Anne Bidault-Thirot, Anthony Private Hospital, Anthony, France
- Lysiane Marthey, Béclère University Hospital, AP-HP, Clamart, France
- Yann Touchefeu, Hepato-Gastroenterology and GI Oncology, Nantes University Hospital, Nantes, France
- Valérie Moulin, Hepato-Gastroenterology, La Rochelle Hospital, La Rochelle, France

- Aziz Zaanan, Gastroenterology and GI Oncology, George Pompidou European University Hospital, AP-HP, Paris, France
- Julien Taïeb, Gastroenterology and GI Oncology, George Pompidou European University Hospital, AP-HP, Paris, France

GICO investigators:

- Mariaelena Casagrande, Department of Oncology, Azienda ospedaliera-Universitaria Santa Maria della Misericordia, Pisa, Italy
- Sabina Murgioni, Medical Oncology 1 Unit, Istituto Oncologico Veneto, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Padua, Italy
- Daniele Santini, Department of Medical Oncology, Università 'Campus Bio-Medico di Roma', Rome, Italy
- Lorenzo Fornaro, Unit of Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
- Francesco Montagnani, Department of Oncology, Azienda Sanitaria locale di Biella, Ponderano, Italy
- Francesco Leone: Medical Oncology, Candiolo Cancer Institute, FPO, IRCCS, Candiolo, Italy, end Department of Oncology, University of Turin, Italy
- Luca Faloppi, Oncology, University Hospital and University of Cagliari, Cagliari, Italy
- Elisa Giommoni, Azienda ospedaliero-Universitaria Careggi, Florence, Italy
- Stefania Eufemia Lutrino, Department of Medical Oncology, Antonio Perrino Hospital, Brindisi, Italy
- Andrea Palloni, Oncology, Policlinico S. Orsola-Malpighi, Bologna, Italy
- Oronzo Brunetti, Medical Oncology Unit , Hospital of Barletta , Barletta , Italy
- Francesca Bergamo, Unit of Oncology 2, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
- Enrico Vasile, Oncology, Università degli Studi di Torino, Torino, Italy

Gustave Roussy Institute Cohort: David Malka, GI Oncology, Gustave Roussy Institute, Villejuif, France.

Barts Cancer Institute Cohort: David Propper, Oncology, Barts Cancer Institute-Queen Mary University of London, London, United Kingdom.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.01.019.

References

[1] Lepage C, Capocaccia R, Hackl M, et al. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999-2007: results of EUROCARE-5. Eur J Cancer 2015;51:2169–78.
[2] Valle JW, Borbath I, Khan SA, et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v28–37.
[3] Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma - evolving concepts and therapeutic strategies. Nat Rev Clin Oncol 2018;15:95–111.
[4] Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271–89.
[5] Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–81.
[6] Okusaka T, Nakachi K, Fukutomi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer 2010;103:469–74.
[7] Valle JW, Furuse J, Jitlal M, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann Oncol 2014;25:391–8.
[8] Fiteni F, Nguyen T, Vernerey D, et al. Cisplatin/gemcitabine or oxaliplatin/gemcitabine in the treatment of advanced biliary tract cancer: a systematic review. Cancer Med 2014;3:1502–11.
[10] Brieau B, Dahan L, De Rycke Y, et al. Second-line chemotherapy for advanced biliary tract cancer after failure of the gemcitabine-platinum combination: a large multicenter study by the Association des Gastro-Enterologues Oncologues. Cancer 2015;121:3290–7.
[11] Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. Ann Oncol 2014;25:2328–38.
[12] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Contr Clin Trials 1996;17:343–6.
[13] Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med 2015;162:W1–73.
[14] Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
[15] Fitzgerald M, Saville BR, Lewis RJ. Decision curve analysis. JAMA 2015;313:409–10.
[16] Fornaro L, Cereda S, Aprile G, et al. Multivariate prognostic factors analysis for second-line chemotherapy in advanced biliary tract cancer. Br J Cancer 2014;110:2165–9.
[17] Fornaro L, Vivaldi C, Cereda S, et al. Second-line chemotherapy in advanced biliary cancer progressed to first-line platinum-gemcitabine combination: a multicenter survey and pooled analysis with published data. J Exp Clin Cancer Res 2015;34:156.
[18] Kim BJ, Yoo C, Kim KP, et al. Efficacy of fluoropyrimidine-based chemotherapy in patients with advanced biliary tract cancer after failure of gemcitabine plus cisplatin: retrospective analysis of 321 patients. Br J Cancer 2017;116:561–7.
[19] Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015;16:e173–80.
[20] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. Br J Cancer 2015;112:251–9.
[21] Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. Nat Genet 2015;47:1003–10.
[22] Wardell CP, Fujita M, Yamada T, et al. Genomic characterization of biliary tract cancers identifies driver genes and predisposing mutations. J Hepatol 2018;68:959–69.
[23] Vienot A, Beinse G, Louvet C, et al. Overall survival prediction and usefulness of second-line chemotherapy in advanced pancreatic adenocarcinoma. J Natl Cancer Inst 2017;109.