UNIVERSITE DE NANTES

_____

FACULTE DE MEDECINE

_____

Année : 2019 N° 2019-150

THESE

pour le

DIPLOME D'ETAT DE DOCTEUR EN MEDECINE

HEPATO-GASTRO-ENTEROLOGIE

par

Miloud AZARFANE

Né le 15 Novembre 1989 à AGEN (47)

_____

Présentée et soutenue publiquement le 01 Octobre 2019

_____

FACTEURS PREDICTIFS DE FAISABILITE D'UNE CHIMIOTHERAPIE APRES DRAINAGE BILIAIRE POUR TUMEURS DES VOIES BILIAIRES NON RESECABLES AVEC ICTERE

_____

Président : Monsieur le Professeur Tamara MATYSIAK BUDNIK

Directeur de thèse : Monsieur le Docteur Yann TOUCHEFEU

REMERCIEMENTS

Je remercie le Professeur Tamara Matysiak-Budnik de m'avoir fait l'honneur de présider mon jury de thèse. Merci pour votre aide dans la rédaction de mon article, pour votre expertise, et également pour votre volonté à nous enseigner en anglais.

Je remercie le Dr Yann Touchefeu d'avoir dirigé ce travail de thèse. Merci pour m'avoir confié ce sujet très intéressant. Merci pour ta disponibilité, ta patience, ton aide précieuse, tes connaissances. J'ai réellement apprécié travailler et apprendre à tes cotés. J'espère que nous pourrons continuer à collaborer ensemble à l'avenir.

Je remercie le Dr Gournay d'avoir accepté de faire partie de mon jury, mais également de m'avoir montré l'étendue et la richesse de l'hépatologie et de m'y avoir donné gout. Merci également de m'avoir mis le sur la piste de ce sujet de thèse très intéressant.

Je remercie le Professeur Bruley Des Varannes de faire partie de mon jury de thèse. Merci pour votre investissement au sein de notre formation.

Je remercie le Professeur Jaafar Bennouna d'avoir accepté de faire partie de mon jury de thèse. Obtenir l'évaluation d'un oncologue expérimenté est un honneur.

Je remercie ma famille, mes parents, mes frères, qui ont toujours cru en moi, toujours soutenu, et sans qui je ne serais pas là aujourd'hui. Merci pour votre fierté.

Je remercie tous les médecins actuels et passés du service d'hépato-gastro-entérologie : Dr Trang, Dr Bourreille, Pr Coron, Dr Le Rhun, Dr Musquer, Dr Cauchin, Dr Archambeaud, Dr Jirka, qui m'ont également fait confiance, et appris énormément. De même que les chefs de clinique et assistants sans qui le quotidien à l'hôpital aurait été très différent : Annie, Nicolas C., Sarah, Lucille, Marie, Pauline, Nicolas E., Matthieu.

Je remercie mes amis proches : Clément, Elise, Eric, Hugo, Jeremy, Mariette, Matthieu, Maxime, Noham, Pierre, Rim… Merci pour votre présence, votre soutien, nos voyages, et surtout votre humour.

Je remercie l'équipe d'Hépatologie du CHU de Rennes : Pauline, Caroline J., Caroline L., Edouard, Pr Moirand, Pr Guyader, Ludivine, Grégoire. Merci pour votre accueil chaleureux, de m'avoir fait progressé, et votre confiance. Merci également aux internes Rennais, j'ai apprécié le semestre avec vous.

Je remercie l'équipe de La Roche sur Yon : Matthieu, Lucille, Vincent, Paul, Carelle, Cécile, Margot, Dr Faroux, Morgane. Une super équipe avec qui j'ai hâte de continuer à travailler.

Je remercie mes co-internes, qui ont été d'un grand soutient durant cet internat : Maëva, Marion, Catherine, Alix, Marine, Astrid D., Orianne, Lucie, Laure, Astrid I., Geoffrey, Pierrine, Quentin, Victor, Juliette.

Je remercie Mme Dessomme Brigitte, statisticienne au CHU de Nantes, qui m'a généreusement aidé dans ce travail.

SOMMAIRE :

Predictive factors of chemotherapy initiation after biliary drainage for advanced biliary tract cancer : a retrospective multicenter study.

Azarfane M[(1)], Lièvre A[(2,8)], Senellart H[(3)], Dessomme B[(4)], Guillouche P[(5)], Meyer J[(6)], Bennouna J [(1)], Wallenhorst T[(2)], Salimon M[(1)], Gournay J[(1)], Matysiak-Budnik T[(1)], Lim A[(7)], Edeline J[(2, 8)], Touchefeu Y[(1)]

Affiliations

[1] IMAD, Department of Gastroenterology and Digestive Oncology, University Hospital, Nantes, France

[2] Department of Gastroenterology, CHU Pontchaillou, Rennes 1 University, Rennes, France.

[3] Integrated Center for Oncology, Centre René Gauducheau, Saint Herblain, France

[4] Department of Epidemiology and Biostatistics, University Hospital, Nantes, France

[5] Department of Gastroenterology, Clinique Jules Vernes, Nantes, France

[6] Department of Radiology, University Hospital, Nantes, France

[7]Department of Gastroenterology, Santé Atlantique, Saint Herblain, France

[8] Centre Eugène Marquis, Oncology Department, Rennes, France

Corresponding author : Yann Touchefeu

Yann Touchefeu, MD, PhD

IMAD, Hépato-Gastroentérologie & Oncologie Digestive

Hôtel Dieu, CHU de Nantes

1, Place Alexis Ricordeau

44000 Nantes, France

Tel: +33240083152

Fax: +3324008154

Email: yann.touchefeu@chu-nantes.fr

Keywords : Biliary tract cancer ; predictives factors ; prognostics factors ; chemotherapy ; jaundice.

Abstract

Introduction : In unresectable biliary tract cancers, management of biliary obstruction is often the first step before introduction of chemotherapy. Our aim was to study the predictive factors of initiation of chemotherapy after biliary drainage in a series of patients presenting with advanced biliary tract cancer and obstructive jaundice.

Methods : Data of all patients treated for unresectable biliary tract cancer in seven institutions from January 2009 to January 2019, were retrospectively collected. Mann-Whitney, Chi2, Fisher tests, and Cox proportional hazards regression models were used to compute p values, Odd ratios (ORs), and 95% confidence intervals (CIs).

Results : Among 82 patients included in this study (median age 68 years, range 35-91 years, men 61%), 48 (59%) received chemotherapy. In univariate analysis, younger age, male gender, ECOG score ≤2, high albumin level, low C-reactive protein level, and endoscopic drainage were significantly associated with introduction of chemotherapy. In multivariate analysis, only ECOG score ≤ 2 at diagnosis (OR 70.4 ; 95% CI [4.6-1097.6] ; p=0.002) and male gender (OR 5.0 ; 95 % CI [1.5-16.5] ; p=0.009), were significant independent predictive factors of introduction of chemotherapy.

Conclusion : In our series of patients, ECOG score ≤ 2 and male gender were the only independent predictive factors of introduction of chemotherapy. These results may help defining the initial therapeutic strategy.

Abbreviations

ALAT : alanine-aminotransferases, ASAT : aspartate-aminotransferases, BTC: biliary tract cancer, CAR : CRP/Albumin ratio, CRP : C-Reactive protein, GGT : gamma-glutamyl-transpeptidase, PAL : alkaline phosphatase, OS : Overall Survival, PNN : polynuclear neutrophils , ULN : upper limit normal.

Introduction

Biliary tract cancers (BTC) account for about 3% of all gastrointestinal tumors and they represent the second most common primary hepatic tumors. BTC include intrahepatic, peri-hilar, distal and gallblader carcinomas. Most patients present with advanced and unresectable disease at diagnosis. In patients eligible for chemotherapy, doublet with cisplatin and gemcitabine became the standard first line treatment based on the results of the ABC-02 study that showed an overall survival benefit over gemcitabine alone(1). Jaundice is acommon symptom at the diagnosis of BTC (70-84%)(2,3), mostly due to biliary tract obstruction. It is a poor prognostic factor(4). Biliary drainage can be achieved by percutaneous transhepatic or endoscopic methods. The drainage of the bile ducts aims to improve symptoms related to cholestasis, such as jaundice, pruritus and pain, to reduce the risk of cholangitis, but also to improve the nutritional and general status of the patient. These benefits can make the patients eligible for chemotherapy after biliary drainage. To guide the therapeutic strategy (biliary drainage alone or followed by chemotherapy), it is important to identify prognostic factors and predictive factors for initiation of chemotherapy after biliary drainage.

The optimal management of BTC must be defined at multidisciplinary team meetings involving different specialists among whom gastro-enterologists, interventional radiologists, surgeons and oncologists. In advanced BTC with obstructive jaundice, biliary drainage is the first step of management before initiation of chemotherapy. However, some patients cannot receive chemotherapy after initial drainage. The aim of this study was to analyse the predictive factors of initiation of chemotherapy in a series of patients presenting with advanced BTC and obstructive jaundice requiring biliary drainage.

Patients and methods

Patients.

From January 2009 to January 2019, all patients with histologically documented unresectable cholangiocarcinoma complicated by biliary obstruction requiring percutaneous or endoscopic drainage in seven participating centers, were identified. Clinical, biological and histological characteristics were collected using electronic medical records.

Outcome assessment.

Date of diagnosis was defined as the date of the first imaging confirming dilatation of the biliary ducts. Chemotherapy was considered as performed if patients received at least one complete cycle of the chemotherapy regimen. Overall survival (OS) was defined as the time between the diagnosis and death (from all causes). Data were last updated in June 2019.

*Statistics***.**

The group of patients who received chemotherapy and the group of patients who did not received chemotherapy after the drainage were compared. Clinical and demographic data, as well as laboratory tests values, were analyzed in univariate analysis. Comparisons were performed using the non-parametric Mann-Whitney test for continuous data and the Chi2 and Fisher test for categorial data. Variables with a P-value <0.05 or clinically relevant with a P<0.20 in univariate analysis were included in the multivariate analysis, performed with the Cox proportional hazard model, with a significance level of P<0.05. Kaplan–Meier survival curves for overall survival (OS) were generated, and these curves were compared using log-rank tests. Progression free survival was analysed with the log-rank test. Analyses were performed using the software Graph Pad Prism 6 and XLStat 2017. Results are expressed as median (Min-Max). P<0,05 was considered statistically significant.

Consent and ethics statement.

It was a retrospective study including patients managed with standard care only. The majority of patient was dead or lost to follow-up at the time of data collection. A consent form was not required for this study. The study has been performed according to the Declaration of Helsinki and its latter amendments. According to the French law, since all

the patients are dead, the analysis of their data is possible in strict respect of anonymization and medical confidentiality.

Results

Study population

Among 550 patients with BTC who were screened, 82 patients met all the inclusion criteria and were included in the study (*Figure 1)*. The main characteristics of these patients are described in *Table 1*. Most of the patients were males (61%), with ECOG score less or equal to 2 (83%). The median age was 68 years (35-91.5). Tumors were peri-hilar, intra-hepatic, distal and gallbladder tumors in respectively 52, 21, 15 and 12% of patients. Concerning perihilar tumors (n=43), there were Bismuth I, II, III and IV in respectively 4, 14, 14, and 11 patients. The median level of bilirubin at diagnosis was 189.5 (26-589) μmol/L, and 292 (62-711) μmol/L at the time of drainage.

Biliary drainage procedures and chemotherapy

Fifty four patients (66%) had an endoscopic biliary stenting and twenty eight (44%) a percutaneous one. Twelve patients had a failure of one procedure of drainage, requiring to use the alternative way of drainage. Median time between diagnosis and biliary drainage was 12 (0-63) days.

Forty-eight patients (59%) received chemotherapy. Median time between biliary drainage and first chemotherapy cycle was 42 days (6-380). The median bilirubin level for patients at the time of chemotherapy introduction was 27.80 (10-444) μmol/L. Median duration of chemotherapy was 122 (±88.47) days. Twenty-five patients (52%) received gemcitabine plus oxaliplatine as first line chemotherapy, 11 (23%) gemcitabine plus cisplatin, 4 (8.3%) Folfox, 3 (6.3%) Gemcitabine alone, 2 (4.1%) LV5FU2 plus cisplatin and 3 (6.3%) a combination of gemcitabine, oxaliplatin and regorafenib in a therapeutic trial. Seventeen percent of patients who received chemotherapy were ≥ 75 years old.

The main reason for not administrating chemotherapy was notified in the medical records in 27 patients: persistent poor general condition (n=16), patient's refusal (n=5), inadequate persistent jaundice (n=2), recurrent cholangitis (n=2), and 2 patients died early.

Predictive factors for chemotherapy introduction

We compared the group of patients who received chemotherapy and the group of patients who

did not receive chemotherapy *(Table 2)*. In univariate analysis, young age (p=0.0014), male gender (p=0.03), ECOG score ≤2 at diagnosis (p=0.00003), albumin level at diagnosis (p=0.023), C-Reactive Protein (CRP) level at diagnosis (p=0.046), endoscopic drainage (p=0.029) were significantly associated with chemotherapy introduction. The CAR (C-Reactive Protein /Albumin Ratio) was calculated, with a significant difference between the two groups (p=0.017).

In the multivariate analysis, ECOG score ≤ 2 at diagnosis (OR 70.5 ; 95% CI [4.5-1097.6] ; p=0.002) and male gender (OR 5.0 ; 95 % CI [1.5-16.5] ; p=0.009) were the only significant independent predictive factors of chemotherapy introduction.

Overall survival

Median OS was 4.9 months (0.2-38.66) in the group of patients who did not receive chemotherapy and 12.2 months (1.87-60.98) in the group of patients who received chemotherapy (HR = 2.93 ; IC 95% [1.604-5.351] ; p<0,0001) *(Figure 2).* Median OS was 12.7 months (1.87-60.98) for patients with bilirubin level <1.5xULN at the introduction of chemotherapy, and 10.8 months (2.14-50.20) for patients with bilirubin level >1.5xULN at the introduction of chemotherapy (HR = 0.80 ; IC 95% [0.51-1.53] ; p=0.57).

Prognostics factors for OS

In univariate analysis chemotherapy (p< 0.0001), ECOG score ≤2 at diagnosis (p=0.0003), younger age (p=0.041) and male gender (p=0.025) were significant factors associated with better OS, while gallbladder cancers were associated with a poor OS (p=0.034). In multivariate analysis, chemotherapy (HR=0.332 ; IC 95% [0.000-0.623] ; p=0.001) was associated with better OS while gallbladder tumors was a poor prognostic factor (HR=2.503 ; 95%CI [1.086-5.766] ; p=0.031) *(Table 3)*.

Progression Free survival

Median PFS was 8.98 months (1.65-32.61) in the group of patients who received chemotherapy. Median PFS was 8.82 months (3.97-32.61) for patients with bilirubin level <1.5xULN at the introduction of chemotherapy, and 8.98 months (1.65-20.85) for patients with bilirubin level >1.5xULN at the introduction of chemotherapy (HR = 0.64 ; IC 95% [0.31-1.35] ; p=0.38).

Chemotherapy toxicity

Twenty four patients had a toxicity of chemotherapy, grade 3 or less (haematological and neurological only). There was no difference of chemotherapy toxicity between patients with bilirubin level <1.5xULN at the introduction of chemotherapy (toxicities were grade 1, 2 or 3, for respectively 2, 9 and 1 patients) and those with bilirubin level >1.5xULN (toxicities were grade 1, 2 or 3, for respectively 1, 4 and 3 patients) at the introduction of chemotherapy (CI95% [0.35-7.37] ; p=0.74).

Discussion

In our study, 59% of patients received chemotherapy after biliary drainage. ECOG score ≤ 2 and male gender were the only independent predictive factors of initiation of chemotherapy.

ECOG score is an independent prognostic factor for OS and PFS in advanced biliary tract cancer, in first or second line of chemotherapy(1,5–7). ECOG score was also prognostic in univariate analysis in our study but not in multivariate analysis. To our knowledge, in this setting, this is the first study investigating the initiation of chemotherapy rate after biliary drainage. Moreover ECOG was an independent predictive factor for chemotherapy introduction. It is also important to highlight the factors that were not predictive. In particular, age was not a significant factor in multivariate analysis. Older age should not be considered as a negative predictive factor, or even as a contraindication of chemotherapy. The G8 questionnaire may be proposed to these patients, and if necessary, management should be multidisciplinary and based on appropriate geriatric assessment to avoid undertreatment(8).

The current analysis support also previous evidence that chemotherapy was a prognostic factor for OS(1,7). Median OS of patients treated with chemotherapy was 12.16 months, in range of results from the literature (11 months in the Gemcitabine and Cisplatin combination arm of the ABC-02 trial) (1).

In our study, male gender was a significant factor for chemotherapy introduction, both in univariate and multivariate analysis. In the ABC-02 study and in a large study from the Surveillance, Epidemiology, and End Results Program, male gender was associated with increased mortality(1,9). In our study, we could not identify any explanation to these data.

In univariate analysis, albumin level < 35 g/L was a predictive factor. Due to few data available in the medical records, this factor could not be included in multivariate analysis. Low albumin level can be multi-factorial (denutrition, inflammation). In advanced BTC, low serum albumin is a prognostic factor in pre-operative treatment, but also in palliative treatment. The serum level of CRP was also a significant predictive factor in univariate analysis, but cholangitis and leukocyte counts at diagnosis were not. In a meta-analysis(10) of 10 studies including 4592 patients with solids cancers, the C-reactive protein/Albumin Ratio (CAR) was significantly associated with poor overall survival. In our study, the CAR was a significant predictive factor in univariate analysis. However, due to few albumin and CRP

levels available in the medical records, this factor could not be included in multivariate analysis.

In the phase III ABC-02 trial investigating gemcitabine plus cisplatin compared to gemcitabine alone, bilirubin level>1,5ULN was an exclusion criteria. In a phase I study, elevated bilirubin level was associated with increased toxicity of gemcitabine(11). However, another study did not demonstrated increased toxicity of Gemcitabine-Cisplatin combination in patients treated for advanced BTC(12). In our study, the median bilirubin level for patients at time of chemotherapy was 30 (10-444) µmol/L. Almost 50% patients received chemotherapy while the bilirubin level was >1,5ULN. OS of patients receiving chemotherapy was similar between patients with bilirubin superior or inferior to 1,5xULN. It highlights that biological and clinical criteria in daily clinical practice can differ from those in clinical trials, and that normal or subnormal bilirubin level is not mandatory to initiate chemotherapy(12). Importantly, biliary drainage does not only aim at making the patient eligible for chemotherapy but also at improving the nutritional status and the general condition.

This study has some limitations. First, this is retrospective study, leading to biases and missing data. Some factors could not be evaluated, such as percentage of drained liver or other biological values including Carbohydrate antigen 19-9 and lactate dehydrogenase. However, this is a homogeneous series of patients with advanced BTC and jaundice, excluding other cancers. In this setting, this is the first study not only focusing on the bilirubin level after biliary drainage, but also investigating the initiation of chemotherapy rate which may be a more clinically relevant endpoint in daily practice.

In conclusion, ECOG score ≤ 2 and male gender were the only independent predictive factors of introduction of chemotherapy. Further prospective studies should better define predictive factors that will help defining and optimizing the therapeutic strategy in patients with advanced BTC and obstructive jaundice.

Annexes

Figure 1. Flow chart

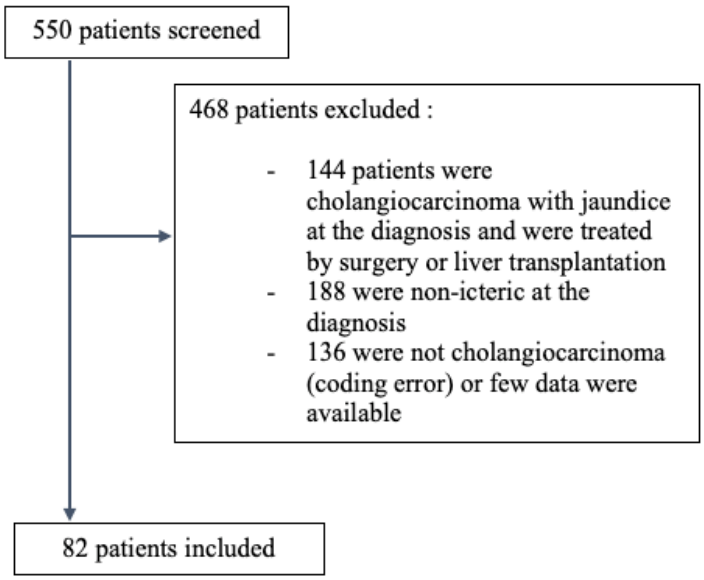


Figure 2. Survival curves.

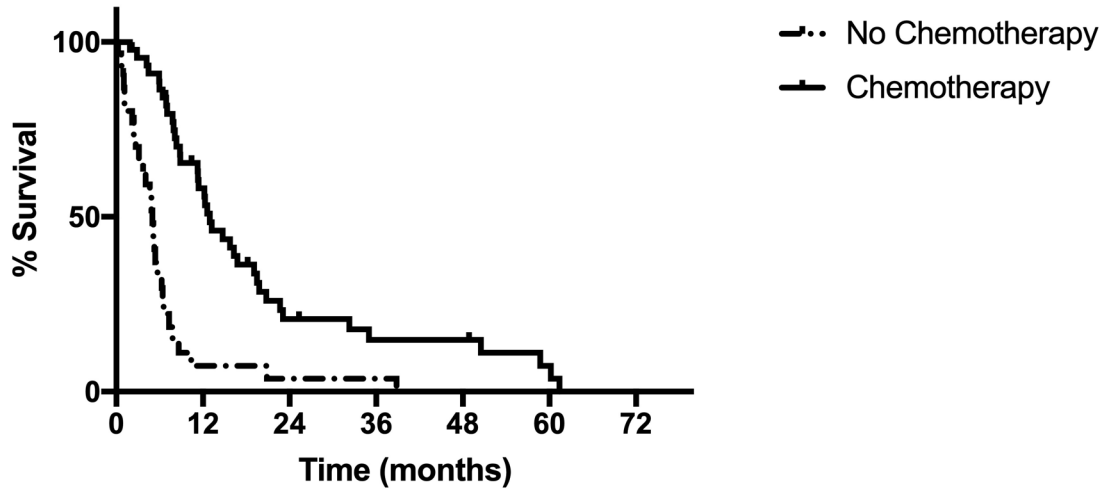


Table 1. Patient characteristics (82 patients)

	Chemotherapy group	No Chemotherapy group
Characteristics	48	34
Age (years)	65.78 (35-81.5)	73.87 (35.2-91.5)
Male gender (n=50)	68 %	32 %
ECOG score ≤2 (n=65)	71 %	29
Weight loss at diagnosis (%)	7.8 (0-26.7)	6.8 (0-22.7)
Localization (n=82):		
Intra-hépatic	11 %	10 %
Peri-hilar	27 %	26 %
Distal	13 %	1 %
Gallblader	7 %	5 %
Cholangitis at diagnosis (n=8)	50 %	50 %
Pruritus at the diagnosis (n=45)	51 %	49 %
Serum Bilirubin level at diagnosis (µmol/L)	186.5 (61-538)	192 (26-589)
Albumin level (n=45)		
≤ 35 g/L	33 %	31 %
>35 g/L	31 %	5 %
CRP level (mg/L)	17.90 (0-130)	33.90 (3-157)
C-Reactive Protein/Albumin Ratio	0.57 (0.05-2.75)	1.54 (0.30-7.85)
Leucocytes counts at diagnostic (G/L)	8.21 (3.6-14.8)	9.20 (4.58-17.22)
PNN counts at diagnostic (/mm3)	5800 (1070-9580)	6730 (1049-14140)
Time between diagnosis and drainage (days)	12 (0-63)	11.50 (0-35)
Serum Bilirubin level at drainage (µmol/L)	292 (98-711)	298.5 (62-637)
Drainage technique (n=82) :		
Percutaneous	33 %	33 %
Endoscopic	26 %	8 %
Early complication of drainage (n=45)	64 %	36 %
Failure of a previous technique of drainage (n=12)	50 %	50 %

Table 2. Univariate and multivariate analysis of factors associated with chemotherapy introduction.

	Univariate analysis			Multivariate analysis		
Variables	HR	CI 95%	P-value	HR	CI 95%	P-value
Age < 70 years	3.667	[1.455-9.243]	0.0014			
Male gender	2.732	[1.092-6.835]	0.030	5.0	[1.494-16.540]	0.009
ECOG score ≤2	29.053	[3.526-239.36]	0.00003	70.465	[4.524-1097.55]	0.002
Percentage of weigth loss at diagnosis	0.978	[0.889-1.077]	0.44			
Localization :			0.07			0.096
Intra-hépatic	1.074	[0.349-3.306]		0.966	[0.237-3.934]	
Péri-hilar	10.500	[1.244-88.591]		1	-	
Distal	1.432	[0.353-5.802]		9.326	[0.908-95.750]	
Gallblader	1	-		7.590	[0.800-71.992]	
Cholangitis at diagnosis	1.433	[0.332-6.186]	0.71			
Pruritus at the diagnosis	1.833	[0.738-4.556]	0.19			
Serum Bilirubin level at diagnosis (µmol/L)	1	[0.997-1.004]	0.95			
Albumin level			0.023			
≤ 35 g/L	1	-				
>35 g/L	6.533	[1.254-34.051]				
CRP level (mg/L)	2.708	[0.708-10.36]	0.046			
C-Reactive Protein/Albumin Ratio	3.249	[1.109-9.521]	0.017			
Leucocytes counts at diagnostic (G/L)	1.092	[0.885-1.346]	0.459			
PNN counts at diagnostic (/mm3)	1	[1-1]	0.147			

Table 2. Univariate and multivariate analysis of factors associated with chemotherapy introduction.

	Univariate analysis			Multivariate analysis		
Variables	HR	CI 95%	P-value	HR	CI 95%	P-value
Time between diagnosis and drainage (days)	0.977	[0.951-1.003]	0.93			
Serum Bilirubin level at drainage (µmol/L)	1	[0.997-1.003]	1			
Drainage technique : Percutaneous Endoscopic	 0.851 3.630	 [0.743-3.297] [1.270-10.373]	 0.57 0.029			
Early complication of drainage	1.622	[0.663-3.968]	0.288			
Failure of a previous technique of drainage	1.615	[0.471-5.542]	0.65			

Table 3. Prognostic factors for overall survival : hazard-ratio (HR), CI 95%, and P-value in univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
Variables	HR	CI 95%	P-value	HR	CI 95%	P-value
Chemotherapy performed	0.275	[0.000-0.464]	< 0.0001	0.332	[0.000-0.623]	0.001
Age < 70 years	0.595	[0.000-0.979]	0.041	0.902	[0.493-1.650]	0.902
Male gender	0.554	[0.000-0.927]	0.025	0.721	[0.403-1.291]	0.271
ECOG score ≤2	0.49	[0.000-0.980]	0.046	0.528	[0.205-1.357]	0.185
Percentage of weigth loss at diagnosis	1.377	[0.694-2.731]	0.360			
Localization :						
Intra-hépatic	0.764	[0.415-1.408]	0.388			
Péri-hilar	0.786	[0.479-1.292]	0.343			
Distal	1.364	[0.685-2.716]	0.377			
Gallblader	2.180	[1.063-4.471]	0.034	2.503	[1.086-5.766]	0.031
Cholangitis at diagnosis	1.615	[0.689-3.790]	0.270			
Pruritus at the diagnosis	1.615	[0.689-3.790]	0.270			
Serum Bilirubin level at diagnosis (µmol/L)	0.999	[0.997-1.002]	0.570			
Albumin level						
≤ 35 g/L	1.158	[0.539-2.489]	0.706			
>35 g/L	0.921	[0.420-2.019]	0.836			
CRP level (mg/L)	1.014	[1.005-1.023]	0.003			
C-Reactive Protein/Albumin Ratio	1.476	[1.163-1.874]	0.001			
Leucocytes counts at diagnostic (G/L)	1.075	[0.960-1.203]	0.213			

Table 3. Prognostic factors for overall survival : hazard-ratio (HR), CI 95%, and P-value in univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
Variables	HR	CI 95%	P-value	HR	CI 95%	P-value
PNN counts at diagnostic (/mm3)	1.000	[1.000-1.000]	0.090			
Time between diagnosis and drainage (days)	0.987	[0.968-1.007]	0.203			
Serum Bilirubin level at drainage (µmol/L)	1.000	[0.998-1.002]	0.735			
Drainage technique : Percutaneous Endoscopic	0.915 1.093	[0.542-1.543] [0.648-1.844]	0.738 0.738			
Early complication of drainage	1.231	[0.755-2.007]	0.404			
Failure of a previous technique of drainage	1.743	[0.843-3.605]	0.134			

Références :

1. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer. N Engl J Med. 2010 Apr 8;362(14):1273–81.

2. Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg. 1996 Oct;224(4):463–73; discussion 473-475.

3. Monson JR, Donohue JH, McEntee GP, McIlrath DC, van Heerden JA, Shorter RG, et al. Radical resection for carcinoma of the ampulla of Vater. Arch Surg Chic Ill 1960. 1991 Mar;126(3):353–7.

4. Regimbeau JM, Fuks D, Bachellier P, Le Treut YP, Pruvot FR, Navarro F, et al. Prognostic value of jaundice in patients with gallbladder cancer by the AFC-GBC-2009 study group. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2011 Jun;37(6):505–12.

5. Brieau B, Dahan L, De Rycke Y, Boussaha T, Vasseur P, Tougeron D, 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-Entérologues Oncologues. Cancer. 2015 Sep 15;121(18):3290–7.

6. Neuzillet C, Casadei Gardini A, Brieau B, Vivaldi C, Smolenschi C, Brandi G, et al. Prediction of survival with second-line therapy in biliary tract cancer: Actualisation of the AGEO CT2BIL cohort and European multicentre validations. Eur J Cancer Oxf Engl 1990. 2019 Apr;111:94–106.

7. Kim BJ, Hyung J, Yoo C, Kim K, Park S-J, Lee SS, et al. Prognostic factors in patients with advanced biliary tract cancer treated with first-line gemcitabine plus cisplatin: retrospective analysis of 740 patients. Cancer Chemother Pharmacol. 2017 Jul;80(1):209–15.

8. Soubeyran P, Bellera C, Goyard J, Heitz D, Curé H, Rousselot H, et al. Screening for Vulnerability in Older Cancer Patients: The ONCODAGE Prospective Multicenter Cohort Study. PLoS ONE [Internet]. 2014 Dec 11 [cited 2019 Aug 24];9(12).

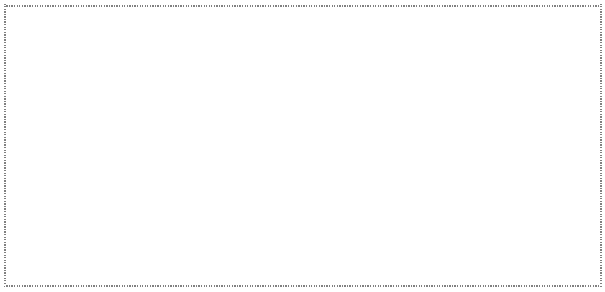
9. Bridgewater J, Lopes A, Wasan H, Malka D, Jensen L, Okusaka T, et al. Prognostic factors for progression-free and overall survival in advanced biliary tract cancer. Ann Oncol Off J Eur Soc Med Oncol. 2016 Jan;27(1):134–40.

10. Li N, Tian G-W, Wang Y, Zhang H, Wang Z, Li G. Prognostic Role of the Pretreatment C-Reactive Protein/Albumin Ratio in Solid Cancers: A Meta-Analysis. Sci Rep [Internet]. 2017 Jan 27 [cited 2019 Apr 24];7.

11. Venook AP, Egorin MJ, Rosner GL, Hollis D, Mani S, Hawkins M, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. J Clin Oncol Off J Am Soc Clin Oncol. 2000 Jul;18(14):2780–7.

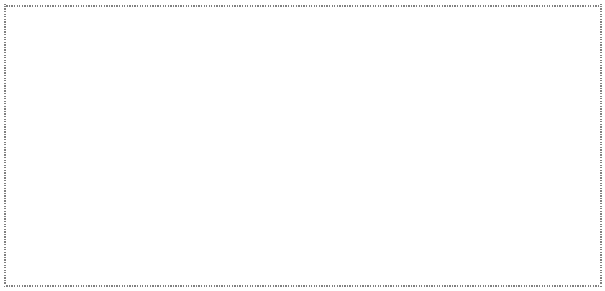
12. Lamarca A, Benafif S, Ross P, Bridgewater J, Valle JW. Cisplatin and gemcitabine in patients with advanced biliary tract cancer (ABC) and persistent jaundice despite optimal stenting: Effective intervention in patients with luminal disease. Eur J Cancer. 2015 Sep;51(13):1694–703.

Vu, le Président du Jury,
(tampon et signature)



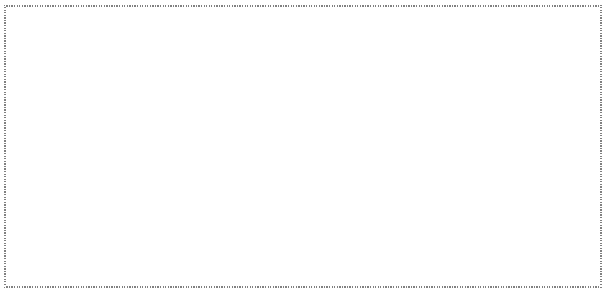
Titre Prénom NOM

Vu, le Directeur de Thèse,
(tampon et signature)



Titre Prénom NOM

Vu, le Doyen de la Faculté,



Professeur Pascale JOLLIET

NOM : AZARFANE PRENOM : MILOUD

Titre de Thèse : FACTEURS PREDICTIFS DE FAISABILITE D'UNE CHIMIOTHERAPIE APRES DRAINAGE BILIAIRE POUR TUMEURS DES VOIES BILIAIRES NON RESECABLES AVEC ICTERE

RESUME

Introduction : Pour les cancers des voies biliaires non opérables, la gestion de l'obstruction biliaire est souvent la première étape avant l'introduction de la chimiothérapie. L'objectif était d'étudier les facteurs prédictifs de l'introduction de la chimiothérapie dans une série de patients ayant une tumeur des voies biliaires avancée et compliquée d'obstruction biliaire.

Méthodes : Les données de tous les patients traités pour une tumeur des voies biliaires non opérable et ayant eu un drainage biliaire, dans 7 centres, de Janvier 2009 à Janvier 2019, ont été analysés rétrospectivement. Les tests de Mann-Whitney, Chi2, Fisher et modèle de Cox ont été utilisés pour obtenir la valeur p, l'intervalle de confiance 95% et le Odd ratio.

Résultats : Parmi les 82 patients inclus (de 35 à 91 ans, âge médian 68 ans, 61% d'hommes), 48 (59%) ont reçus de la chimiothérapie. En analyse univariée, l'âge jeune, le sexe masculin, le score ECOG ≤2, un taux élevé d'albumine, un taux bas de la C-Réactive protéine et le drainage endoscopique étaient significativement associés à l'introduction de la chimiothérapie. En analyse multivariée, seulement le score ECOG ≤2 au diagnostic (OR 70.4 ; 95% CI [4.6-1097.6] ; p=0.002) et le sexe masculin (OR 5.0 ; 95 % CI [1.5-16.5] ; p=0.009) étaient des facteurs prédictifs de l'introduction de la chimiothérapie de façon significative et indépendante.

Conclusion : Le score ECOG ≤2 et le sexe masculin étaient les seuls facteurs prédictifs de l'introduction de la chimiothérapie de façon significative et indépendante. Ces résultats pourront aider à mieux définir la stratégie thérapeutique des patients atteints d'une tumeur des voies biliaires non opérable et compliquée d'obstruction biliaire au diagnostic.

MOTS-CLES

Cholangiocarcinome ; Chimiothérapie ; Ictère ; Facteurs prédictifs ; Facteurs pronostics.