

# Prognostic factors for bile leak and long term survival in 23 patients with Klatskin Tumors Type III exclusively

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## Research

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# Abstract

**Objective** A retrospective study, handling the prognostic factors for bile leak and long term survival in 23 patients, with Hilar Cholangiocarcinoma, Bismuth Type III exclusively.

**Methods** Between 2010 and 2017, 23 patients underwent major hepatectomy for Type III Klatskin Tumor at our institution. 11 patients underwent hepatectomy for Type IIIB tumors, 10 patients underwent right hepatectomy for Type IIIA and 2 were omitted for loss of follow-up.

**Results** In 20 patients an R0 resection was achieved. Survival at 1, 3 and 5 years was respectively 78.3%, 61.9% and 38.1%. A BMI > 24 kg/m<sup>2</sup> at presentation, was associated with a worse prognosis, at 1, 3 and 5 years, with statistical significance (p<0.05). A Creatinine > 0.74 at presentation, was associated with a decreased 5-year survival, with statistical significance (p<0.05).

**Conclusion** A BMI > 24 kg/m<sup>2</sup>, a Creatinine > 0.74, are factors of worse prognosis when present in a Type III Klatskin tumor patient. Age, sex, hemoglobin level, tumor size, cusa use, and the correlation of Type IIIB tumors with bile leakage, are all variables that showed borderline significance, and thus warrant further investigations in larger studies, using multicentric data.

## Introduction

Hilar Cholangiocarcinomas (CCA) were first reported by Altemeir in 1957, described by Gerald Klatskin in a series of 13 patients in 1965 and classified by Bismuth and Corlette in 1975 [1, 2, 3, 4].

Divided into 4 categories according to Bismuth-Corelette classification, Klatskin tumors constitute the most common type of CCAs (40–60%) [5], and second most common primary cancer of the liver (10–15%) after Hepatocellular carcinoma (HCC) [6].

Bismuth Type III Klatskin tumors have always been of greatest interest when dealing with CCAs. These constitute around 60–80% of CCAs and involve the hepatic duct bifurcation, either extending into the right hepatic duct (Type IIIa) or left hepatic duct (Type IIIb) [2].

Surgical resection remains the only curative intervention in Type III Klatskin tumors [7]. These tumors exhibit a high degree of lymphovascular invasion and lymphangiosis carcinomatosa extending up to 2 cm away from the tumor towards the liver and into the hepatoduodenal ligament [8, 9]. Moreover, direct infiltration into the liver is frequent owing to the location of these tumors at the hepatic hilar plate [10].

Therefore, Type IIIa Klatskin tumors are treated with a right hepatectomy involving En-bloc resection of segments VI, VII and VIII, right hepatic artery and portal vein, right extrahepatic bile ducts and portal lymphadenectomy. Right extended hepatectomy, involving resection of additional segments IV a&b is also possible when needed, in the context of a good left hepatic remnant [7]. Type IIIb Klatskin tumors are treated with a left hepatectomy involving En-bloc resection of segments II, III and IV a&b, left hepatic artery and portal vein, left extrahepatic bile ducts and portal lymphadenectomy. Left extended

hepatectomy, involving resection of additional segments V and VIII is also possible when needed, in the context of a good right hepatic remnant [11]. Segment I, aka Caudate Lobe, is to be resected if invaded or to close proximity to the tumor, but systemic resection was dropped out of the usual practice nowadays [7].

Many studies attempted to find prognostic factors for long term survival and predisposing factors for postoperative bile leak in order to optimize the approach towards this kind of tumors.

Bile leakage after hepatic resection predicts a bad prognosis [12]. It is associated with high-risk surgical interventions, in which, the cut surface exposed the major Glisson Sheath and included the hepatic hilum, a wide surface hepatectomy, advanced age, high postoperative white blood cell count, prolonged surgery time and left sided hepatectomy [12, 13, 14]. Very few studies handled bile leakage after liver resection for Klatskin tumors exclusively.

As for long term survival in Klatskin tumors, it remains a major subject of interest. Due to the aggressive nature of these cholangiocarcinomas, many factors have been studied in order to optimize the approach towards it, and try to achieve the maximal long term survival: R0 resection, lymph nodes harvesting, appropriate perioperative patient preparation... [15].

Hence, we decided to isolate 23 patients with exclusively Type III a&b Klatskin Tumors, operated at our institution, and investigate the association between clinicopathological features and postoperative morbidity, bile leak in particular, and long-term survival.

## **Methods**

### **Patients**

We retrospectively reviewed Saint George Hospital University Medical Centre records between 2006 and 2016. After excluding patients with unresectable tumors discovered during laparotomy or laparoscopy, 23 patients operated for Type III Klatskin Tumors were identified. Medical records were retrieved since the first patients' admission till the time of death (IRB-REC/O/O17-191519, Protocol No: 005-2019, study No. 05/19). All the surgeries were performed by a single surgeon.

### **Classification and resectability**

Bismuth-Corlette classification was used to define the tumors, based on the preoperative imaging and investigations, and in order to plan the surgical intervention. All patients underwent CT scan, with or without MRCP and/or ERCP to help define the Type of tumor, the locoregional extent of the disease and rule out distant metastasis. Patients were considered resectable if they had Type III a or b Klatskin tumor with: no distant metastasis, no invasion of the main portal vein or both its branches, and no contralateral involvement of the hepatic artery or portal vein [16, 17].

### **Surgery and Postoperative care**

All surgical interventions were executed by a single surgeon, following the exact same surgical techniques described above. Two Blake drains were systematically placed at the end of the surgery anterior and posterior to the anastomosis. Patients were transferred to the Intensive Care Unit for 48 hours monitoring. Our postoperative protocol is illustrated in Fig. 1.

## Statistical analysis

We first reported the demographic characteristics of our patients. Categorical variables were summarized by proportions and percentages. Second, we searched for associations between the variables we collected (age, sex, jaundice, creatinine, tumour size, resection margins, BMI... and 3 main outcomes: mortality at 1, 3 and 5 years, and postoperative bile. For independent categorical variables chi-square was used, and for independent continuous variables student's t-test or its non-parametric equivalent were used. Survival analysis was done using Kaplan-Meier methods. P-value less than 0.05 were considered statistically significant. Spearman's rho test was also used to determine correlation between Survival and: age, preoperative hemoglobin level and BMI. All statistical analysis was done using SPSS V24.0.

## Results

The mean age for operated patients was 60.65 years, 87% presenting with obstructive jaundice.

11 underwent left hepatectomy and 10 underwent right hepatectomy. 2 of the 23 patients were lost to follow-up, so they were omitted from the statistical analysis performed.

R0 resection was achieved in 21 out of the 23 patients (91.3%) and they were all subject to lymph nodes dissection involving the porta hepatis. The average tumor size was 3.43 cm with the smallest 1 cm and the largest 9 cm. Most of those were Moderately differentiated cholangiocarcinomas. 78% had perineural invasion and 40% had positive regional lymph nodes involvement (Fig. 2).

## Survival

The long term survival mean was 40.48 months and the disease free survival mean was 38.85 months (Fig. 3). Survival at 1, 3 and 5 years was respectively 78.3%, 61.9% and 38.1%, slightly higher than the literature [15].

A BMI > 24 kg/m<sup>2</sup> at presentation, was associated with a worse prognosis, at 1, 3 and 5 years, with statistical significance p = 0.02, 0.02 and 0.016 respectively (Fig. 3).

A Creatinine > 0.74 at presentation, was associated with a decreased 5-year survival, with statistical significance p = 0.043 (Fig. 3).

Many variables revealed a strong correlation with overall survival, and were classified as borderline statistically significant such as Age & Sex, on 1-year survival (p = 0.07 & 0.089).

The use of Cusa & the Preoperative Hemoglobin level affected the overall survival ( $p = 0.073$  &  $0.088$ ).

The Tumor Size (Fig. 3), affected disease free survival ( $p = 0.081$ ).

## Bile leak

10 (43.5%) of our patients developed postoperative bile leak, none exhibiting hemodynamic instability due to the leak, and none requiring surgical intervention. 6 of those patients developed bile hue in their drains, that resolved spontaneously between day 5 and 7 postoperatively, 3 were discharged with the drain, which was removed 3 weeks later once a mature fistulous tract was formed, and 1 patient required CT-guided drainage of a biloma and drain removal 3 weeks thereafter.

No statistically significant variable was found to affect bile leakage, but borderline statistical significance was noted with Left-sided, (Fig. 2) or Type IIIb cholangiocarcinomas ( $p = 0.074$ ).

## Discussion

Klatskin tumors remain ones of the most challenging cancers to deal with. The difficulty of the surgical intervention per se, combined to the aggressive behavior of these tumors, makes the optimization of the approach towards it of crucial importance. In a time R0 resection remains the cornerstone of an appropriate oncologic intervention [15], we tried to study many variables, some of which can be altered and some not, and narrow the study criteria to Type III tumors only, in order to see whether a pre or post-operative preparation can be further made to ameliorate the outcomes in terms of bile leakage and long term survival.

A BMI  $> 24 \text{ kg/m}^2$  and a Creatinine  $> 0.74$ , are factors of worse prognosis when present in a Type III Klatskin tumor patient, with statistical significance. Older age, female sex, lower hemoglobin level, larger tumor size and the no-use of Cusa device, showed borderline significance in predicting a worse prognosis and decreased long term survival. Type IIIb tumors showed borderline significance for postoperative bile leakage. All borderline significant variables warrant further investigations in larger studies, using multicentric data.

In a time, BMI, age, sex, tumor size and side are variables that cannot be altered or modified, one can work on optimizing the other variables. Altering the preoperative Creatinine and Hemoglobin levels, and using Cusa for liver resection, might be small steps in enhancing the survival of patients undergoing hepatectomy for Type III Klatskin tumors. In a time, we know that the prognosis of the latter is dismal, any additional interference offering even a minimal advantage for a better outcome should in our opinion be embraced and dwelled upon.

## Conclusion

A BMI > 24 kg/m<sup>2</sup>, a Creatinine > 0.74, are factors of worse prognosis when present in a Type III Klatskin tumor patient. Age, sex, hemoglobin level, tumor size, cusa use, and the correlation of Type IIIB tumors with bile leakage, are all variables that showed borderline significance, and thus warrant further investigations in larger studies, using multicentric data.

## Abbreviations

CCA: Cholangiocarcinomas	FFP: Fresh Frozen Plasma
HCC: Hepatocellular carcinoma	PRBC: Packed Red Blood Cells
CT: Computed Tomography	CBC: Complete Blood Count
MRCP: Magnetic resonance cholangiopancreatography	PT: Prothrombin Time
BMI: Body Mass Index	PTT: Partial thromboplastin time

## Declarations

### Ethics approval and consent to participate

Ethical approval was obtained from our institutional ethical committee board: IRB/REC of University of Balamand/ Saint George Hospital University Medical Center (IRB-REC/O/017-19/519 / Protocol No: 005-2019).

### Consent for publication

Not applicable.

### Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Competing interests

The authors declare that they have no competing interests.

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The authors have no funding source to disclose for this work.

### Authors' contributions

The authors contributed equally to this manuscript.

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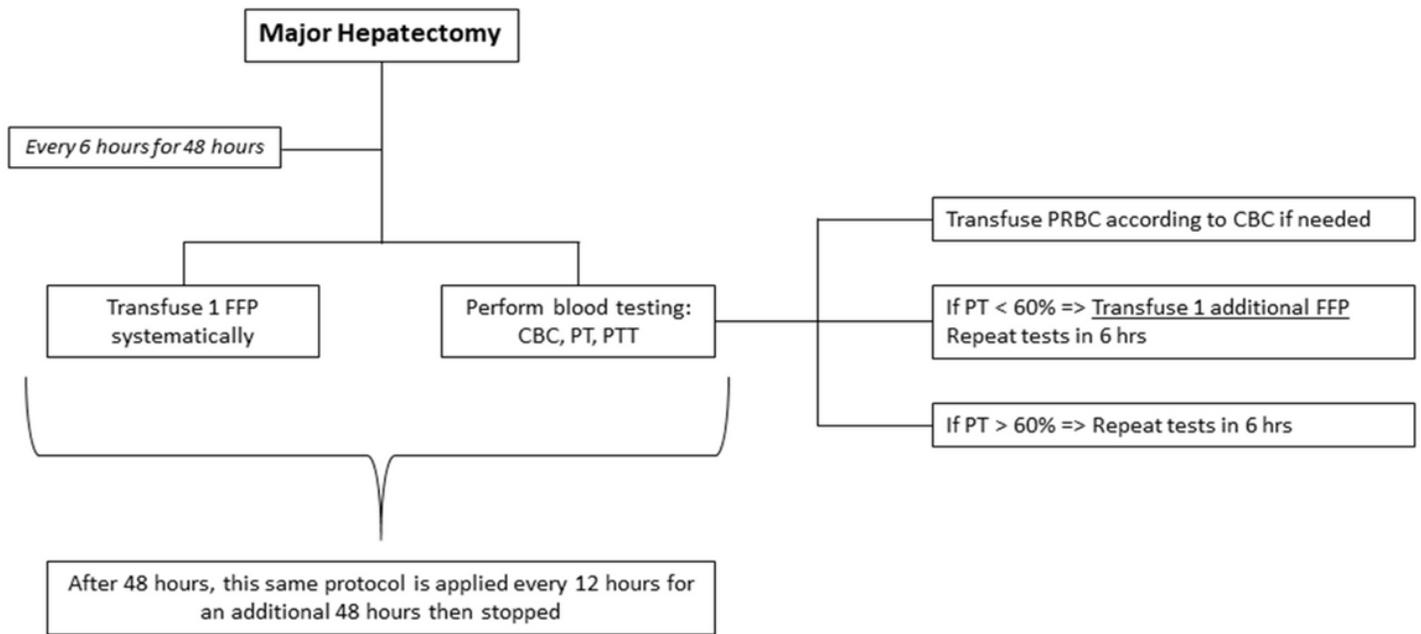
None.

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## Figures



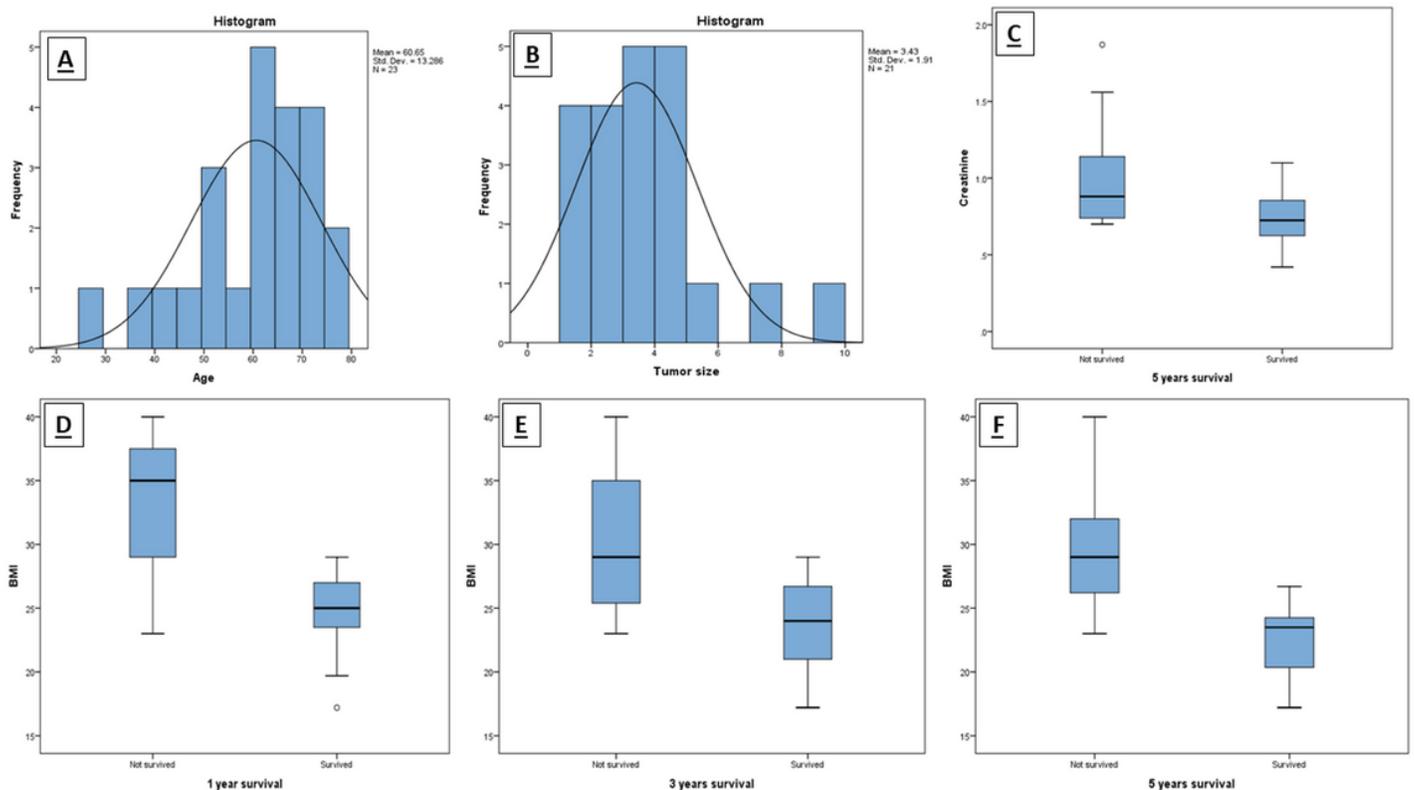
**Figure 1**

Transfusions and Laboratory work-up protocol, adopted at Saint Georges Hospital University Medical Center after Major Hepatectomy (Anatomical Right/ Right Extended or Left/ Left Extended hepatectomy)  
 FFP: Fresh Frozen Plasma; PRBC: Packed Red Blood Cells; CBC: Complete Blood Count; PT: Prothrombin Time; PTT: Partial thromboplastin time

Continuous Variables			Discrete Variables			
	Bile leak P-value	Survival P-value		N (%)	Survival (M ± SD)	Bile leak (%)
Age	0.613	0.167	Sex			
Tumor size	0.277	0.139	Male	11 (52.4)	47 ± 44.9	40
WBC count	0.549	0.921	Female	10 (47.6)	33.3 ± 36.3	46.2
Total Bilirubin	0.627	0.609			<i>P=0.450</i>	<i>P=0.552</i>
Albumin	0.116	0.696	Tumor side			
PT	0.279	0.966	Right	10 (47.6)	34.3 ± 33.9	25
Preoperative hemoglobin	0.357	0.186	Left	11 (52.4)	46.1 ± 46.8	63.6
PRBCs units used	0.161	0.788			<i>P=0.514</i>	<i>P=0.074</i>
FFPs units used	0.520	0.389	Tumor differentiation			
CRP day1	0.783	0.961	Poor & Moderate	14 (70)	32.1 ± 28.8	37.5
CRP day2	0.693	0.963	Well	6 (30)	64.8 ± 58	50
CRP day3	0.140	0.994			<i>P=0.236</i>	<i>P=0.477</i>
CRP day4	0.216	0.736	Positive margins			
			Negative	20 (95.2)	41.3 ± 41.5	42.9
			Positive	1 (4.8)	25	50
					<i>P=0.707</i>	<i>P=0.692</i>
			Perineural invasion			
			Present	17 (80.9)	38.3 ± 40.3	44.4
			Absent	4 (19.1)	49.8 ± 46.9	40
					<i>P=0.675</i>	<i>P=0.633</i>
			Surgery type			
			Normal	16 (76.2)	44.9 ± 44.7	41.2
			Extended	5 (23.8)	26.4 ± 20.4	50
					<i>P=0.219</i>	<i>P=0.537</i>
			CUSA			
			Used	17 (80.9)	45 ± 43.8	47.4
			Not used	4 (19.1)	21.3 ± 13	25
					<i>P=0.073</i>	<i>P=0.404</i>

Figure 2

Analyzed variables (continuous and discrete), and their effect on Survival and Bile leakage



### Figure 3

Histograms showing the repartition of Age (A) and Survival in months (B), and the effect of Creatinine on 5 years' survival (C), and BMI on 1, 3 and 5 years' survival (D, E, F)