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ORIGINAL ARTICLE

Retrospective Study

Impact of biliary stent-related events in patients diagnosed with advanced pancreatobiliary tumours receiving palliative chemotherapy

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Abstract

AIM: To determine the impact (morbidity/mortality) of biliary stent-related events (SRE) (cholangitis or stent obstruction) in chemotherapy-treated pancreatico-biliary patients.

METHODS: All consecutive patients with advanced pancreatobiliary cancer and a biliary stent *in-situ* prior to starting palliative chemotherapy were identified retrospectively from local electronic case-note records (Jan 13 to Jan 15). The primary end-point was SRE rate and the time-to-SRE (defined as time from first stenting before chemotherapy to date of SRE). Progression-free survival and overall survival were measured from the time of starting chemotherapy. Kaplan-Meier, Cox and Fine-Gray regression (univariate and multivariable) analyses were employed, as appropriate. For the analysis of time-to-SRE, death was considered as a competing event.

RESULTS: Ninety-six out of 693 screened patients were eligible; 89% had a metal stent (the remainder were plastic). The median time of follow-up was 9.6 mo (range 2.2 to 26.4). Forty-one patients (43%)

developed a SRE during follow-up [cholangitis (39%), stent obstruction (29%), both (32%)]. There were no significant differences in baseline characteristics between the SRE group and no-SRE groups. Recorded SRE-consequences were: none (37%), chemotherapy delay (24%), discontinuation (17%) and death (22%). The median time-to-SRE was 4.4 mo (95%CI: 3.6-5.5). Patients with severe comorbidities ($P < 0.001$) and patients with $\geqslant 2$ baseline stents/biliary procedures [HR = 2.3 (95%CI: 1.2-4.44), $P = 0.010$] had a shorter time-to-SRE on multivariable analysis. Stage was an independent prognostic factor for overall survival ($P = 0.029$) in the multivariable analysis adjusted for primary tumour site, performance status and development of SRE (SRE group *vs* no-SRE group).

CONCLUSION: SREs are common and impact on patient's morbidity. Our results highlight the need for prospective studies exploring the role of prophylactic strategies to prevent/delay SREs.

Key words: Advanced biliary tract cancer; Pancreatic cancer; Biliary obstruction; Biliary stent; Stent-related event

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Core tip: Most patients diagnosed with advanced malignancies of the pancreas or bile ducts present with biliary obstruction; this requires biliary stenting before starting treatment with palliative chemotherapy. The impact of developing stent-related events (SRE) such as cholangitis or stent obstruction (and the potential role of prophylactic treatment in order to reduce the risk of developing SREs) has not been explored in this patient population. Our results have identified that SREs are common and adversely impact on patient's morbidity (and possibly mortality) and support the need for prospective studies investigating the role of prophylaxis in this population.

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INTRODUCTION

Both pancreatic and biliary tract malignancies are known to have a poor prognosis, mainly due to late presentation of patients who experience non-specific symptoms for some time. Because of this delay, the majority of patients (around 80%) are diagnosed with advanced-stage cancer, which is not amenable to curative resection[1,2]. In the context of advanced pancreatobiliary malignancies, chemotherapy is considered the standard of care treatment and cornerstone of patients management; while the role of radiotherapy is not clearly stablished (even for locally advanced disease), at least in the first-line setting. Chemotherapy is given with palliative intent, its aim being to increase survival and reduce cancer-related symptoms thereby improving quality of life. Systemic treatment for patients with advanced biliary tract cancer includes gemcitabine alone or given in combination with cisplatin[3]. In patients with advanced pancreatic adenocarcinoma, chemotherapy may consist of monotherapy (gemcitabine) or combination therapy [gemcitabine-nab-paclitaxel doublet or FOLFIRINOX (5-fluorouracil, oxaliplatin and irinotecan)][4,5]. However, even with the newer chemotherapy combinations, the prognosis remains poor, with a median overall survival of less than 12 mo[5].

For patients presenting with biliary obstruction, re-establishment of biliary drainage prior to starting palliative chemotherapy is mandatory [*via* endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC)][6]. Two main types of biliary stents are usually employed: (1) plastic stents which have a small diameter and are used for potentially-resectable tumours which are then removed when the curative surgery is performed; and (2) metallic stents that are usually chosen for patients with unresectable cancers because of their larger diameter[7-9] and therefore, longer patency[10].

Unfortunately, despite successful first biliary stenting, some patients will develop a stent-related event (SRE) such as recurrence of biliary obstruction (with development of new obstructive jaundice) or infection (cholangitis)[11,12]. The median patency time of metallic biliary stents is estimated to be around 3.5 to 4.0 mo, although it varies depending on the diameter and type of the stent inserted (stent patency drops to 1.6 mo with plastic biliary stents)[10,13,14]. The development of a SRE has been postulated to be detrimental in many ways for the patient population with pancreatobiliary cancer receiving palliative chemotherapy, leading to shorter survival (due to SRE-related life-threatening complications) and negative impact on patients' quality of life (due to repeat hospitalisation). Moreover, chemotherapy dose intensity may be compromised as a result of admission-related treatment delays or discontinuations (for example, in patients with permanent deterioration of their performance status after hospitalisation).

The aim of this study was to analyse the incidence (measured as SRE rate and time-to-SRE) and impact of SREs in patients with advanced biliary tract and pancreatic malignancies receiving palliative chemotherapy and, in doing so, to provide reference data in order to design an adequately-powered clinical trial to investigate the role of prophylaxis for the

prevention or delay of SREs in patients with biliary stents who are due to commence chemotherapy.

MATERIALS AND METHODS

Patients were identified retrospectively from local electronic case-note records at a single institution (The Christie NHS Foundation Trust, Manchester, United Kingdom). All consecutive patients diagnosed with hepato-pancreato-biliary (HPB) malignancies referred between January 2013 and January 2015 were screened. The local audit committee approved this study (CE15/1400).

Eligible patients were those meeting the following inclusion criteria: advanced (unresectable or metastatic) biliary tract malignancy [gallbladder, bile duct (cholangiocarcinoma) or ampullary] or pancreatic cancer (adenocarcinoma); had an *in-situ* biliary stent for biliary obstruction at the time of starting palliative chemotherapy; and went on to receive standard first-line palliative chemotherapy. Patients with hepatocellular carcinoma were excluded.

Demographic data [including fitness at baseline assessed by Eastern Cooperative Oncology Group Performance Status score (ECOG-PS)], characteristics of the primary tumour (tumour site and stage (AJCC 7th Edition[15]) and details of the treatment administered were collected from the local records. Radiological response to treatment was assessed 3-monthly as per Response Evaluation Criteria In Solid Tumours (RECIST v.1.1)[16]. Comorbidities in addition to the index cancer were classified according to the Adult Comorbidity Evaluation (ACE)-27 index which is systematically used in our institution[17]. Characteristics of the biliary stent fitted at baseline and details of any SRE (if any) were collected. Patients who developed at least one SRE during the follow-up were included in the SRE group, while those who did not were included in the no-SRE group.

The primary objective of this study was to assess the SRE rate and the time-to-SRE in a population of patients with a diagnosis of biliary or pancreatic cancer receiving palliative chemotherapy. Secondary objectives included analysis of the impact of the development of a SRE on the patient's planned chemotherapy schedule, progression-free survival (PFS) and overall survival (OS).

A stent-related event (SRE) was defined as any one or more of the following: (1) any episode of jaundice which was considered significant enough for new stenting or medical treatment and was confirmed by radiological imaging to be associated with biliary dilatation; (2) any episode of infection which was clinically in keeping with cholangitis (bile duct infection) requiring antibiotic therapy; (3) bacteraemia with isolation in blood cultures of bacteria suspected to have originated in the biliary tract; and (4) any episode of cholecystitis or gallbladder perforation.

The following were not considered SREs: (1) jaundice related to high tumour burden liver disease with no significant change in biliary dilatation compared with previous imaging; (2) episodes of neutropenic or non-neutropenic fever with no identified biliary focus; and (3) patients with non-clinically significant biliary occlusion or biliary dilatation (*i.e.,* radiological evidence only with no jaundice, increasing bilirubin, increasing liver function tests (LFTs), fever or evidence of infection) who required no action (no new stenting or no new antibiotic therapy).

Time on follow-up was defined as the time from first biliary stent insertion to date of last follow-up available. Time-to-SRE was defined as the period between the date of the first biliary stenting and the date of the first evidence (clinical or radiological) of SRE. The median time-to-SRE was calculated in patients developing a SRE during follow-up. The risk of developing a SRE at different time-points was estimated for all patients, using the Kaplan-Meier method. For the analysis of time-to-SRE, death was considered a competing event; thus, Fine-Gray regression was employed for identification of factors related to longer/shorter time-to-SRE. For multivariable analysis of factors impacting time-to-SRE, those variables which showed statistically significant *P*-value in the univariate analysis ($P < 0.05$) were included.

In order to provide data regarding the impact of chemotherapy in PFS and OS, PFS and OS were defined as the time from starting chemotherapy to the time of progression (radiological or clinical) and the date of death/last follow-up, respectively. Median PFS and OS were estimated by the Kaplan-Meier method. The log-rank test and univariate/multivariable Cox regression models were used to identify potential prognostic factors for both PFS and OS. For assessment of factors with an impact on OS, variables considered of interest [such as site of primary tumour, stage, ECOG-PS and development of SRE (SRE group *vs* no-SRE group)] and those variables which showed statistically significant *P* in the univariate analysis ($P < 0.05$) were included in multivariable analysis.

Statistical *t*-test, χ^2 test and the Mann-Whitney test (in case of non-normal distribution as per Shapiro-Wilk test) were applied as appropriate. Two-sided significance test with a *P* of < 0.05 was considered significant. Stata version 12.0 software was employed for the statistical analysis.

RESULTS

A total of 693 patients diagnosed with HPB malignancies were screened; 96 met the criteria for inclusion (Figure 1). The median time of follow-up was 9.6 mo (range 2.2 to 26.4). By the end of the follow-up period, 45% and 69% of the patients had progressed and died, respectively. There were no significant differences ($P = 0.1308$) in median follow-up between the SRE group [10.5 mo (range: 2.1-26.4)] and the no-SRE group [8.5 mo (range 3.2-18.9)].

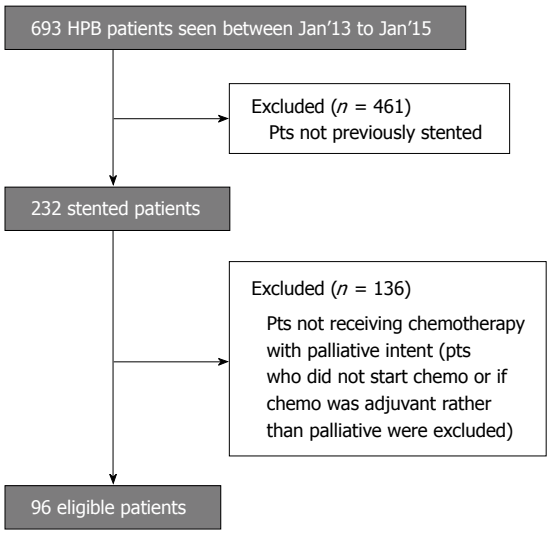

Figure 1 Patient flow. Ninety-six out of the 693 patients screened were found to be eligible. HPB: Hepato-pancreato-biliary cancer; Jan: January; Pts: Patients.

The rate of patients who died and progressed was also similar between both groups [rate of death: 71% (SRE group) *vs* 67% (no-SRE group); $P = 0.825$] [rate of progression: 54% (SRE group) *vs* 38% (no-SRE group); $P = 0.151$].

Patient demographics

The median age at the time of commencing palliative chemotherapy was 66.6 years (range 26-83.8) with a similar proportion of males (56%) and females (44%). The primary tumour site was as follows: 78% pancreas, 18% bile duct (cholangiocarcinoma), 3% ampulla and 1% gallbladder cancer. Most patients (60%) had locally advanced disease. All patients were fit for chemotherapy and started first-line systemic treatment as per clinician discretion. The median time between first stenting and start of chemotherapy was 1.8 mo (range: 0.1-12.6). The most frequently used chemotherapy schedules were single agent gemcitabine (39%) followed by gemcitabine and capecitabine combination (26%). The median time of chemotherapy duration was 3.2 mo (range 0.1-7.6); there were no differences in baseline characteristics between the SRE group and the no-SRE group (see detail in Table 1). None of the patients included were on long-term antibiotics or ursodeoxycholic acid.

Biliary stenting characteristics at baseline

Most of patients had one (73%) or two (22%) biliary stents fitted at the time of starting systemic chemotherapy; only 3 patients and 1 patient had three and four stents *in-situ*, respectively. In 85 patients (89%), stents were metallic. A higher proportion of patients in the SRE group when compared to the no-SRE group had $\geqslant$ 2 biliary stents or biliary procedures [41% (SRE group) *vs* 15% (no-SRE group); $P = 0.004$]. See Table 2.

Stent-related events rate and its consequences

During follow-up, 41 (43%) patients developed a SRE; the type of SRE was as follows: cholangitis (16 patients; 39%), stent obstruction (12; 29%) and combination of both (13; 32%). Moreover, in 14 out of the 41 patients with a first SRE (34%), further SREs were documented. Development of at least one SRE during the follow-up led to the following consequences: a delay in chemotherapy (10 patients; 24%), interruption of chemotherapy (7; 17%) and death (9; 22%). In 15 of the patients (37%), there was no significant SRE-related repercussion. No relationship was found between type of stent and type of SRE ($P = 0.815$; full data not show); nor between the type of SRE and its consequence ($P = 0.166$; full data not shown). See Table 2.

Time to stent-related event

The median time-to-SRE was 4.4 mo (95%CI: 3.6-5.5) when calculated for the SRE group only. Table 3 summarises the estimated risk of SRE for all patients (SRE group and no-SRE group) at different time-points during the follow up, showing a cumulative risk of developing SRE during the time on follow-up. Figure 2 represents each of the patients included in this study, showing the time to SRE in the context of other clinically significant events.

Patients with severe comorbidities (*vs* patients with no comorbidities) ($P < 0.001$) and patients with $\geqslant$ 2 stent/biliary procedure before starting chemotherapy (*vs* 1) had shorter time-to-SRE on multivariable analysis (HR = 2.3, 95%CI: 1.2-4.44, $P = 0.010$). See Table 4.

Progression-free survival

Only nine patients (9%) were still receiving first-line chemotherapy at the time of the analysis: eight in the no-SRE group and one in the SRE group. The most frequent reason for stopping chemotherapy was toxicity (46%), followed by completion of planned treatment (27%), progressive disease (17%) or death (1%). Estimated median PFS was 6.7 mo (95%CI: 4.4-7.8), with similar results in both SRE group and no-SRE group [6.7 (95%CI: 4.3-8.7) and 6.8 (95%CI: 3.9-7.8), respectively] [HR = 0.9 (95%CI: 0.6-1.5), $P = 0.7666$]. There were no statistically significant differences with respect to the reason for chemotherapy discontinuation between the SRE group and the no-SRE group ($P = 0.058$; full data not shown).

Overall survival

The estimated median OS was 8.6 mo (95%CI: 6.8-9.8). Even though there seemed to be a trend for longer survival in the SRE group [median OS 9.8 mo (95%CI: 7.4-11.6)] than in the no-SRE group [median OS 7.6 mo (95%CI: 5.7-9.6)] differences were not statistically significant (Log-rank test $P =$

Table 1 Demographic characteristics of patients included in the study

Variables		All patients (n = 96)	SRE group (n = 41; 43%)	no-SRE group (n = 55; 57%)	P-value for distribution within baseline parameter (χ^2 test), SRE *vs* no-SRE groups
Gender	Female	42 (44)	20 (49)	22 (40)	0.391
	Male	54 (56)	21 (51)	33 (60)	
Age[1]	Median (range)	66.6 (26-83.8)	64.9 (26-84)	67.6 (42.4-83.2)	0.8833[2]
Primary tumour site	Ampulla	3 (3)	1 (2)	2 (4)	0.380[3]
	Bile duct (cholangiocarcinoma)	17 (18)	10 (24)	7 (13)	
	Intrahepatic	5 (31)	3 (33)	2 (29)	1.000[4]
	Extrahepatic	11 (69)	6 (67)	5 (71)	
	Gallbladder	1 (1)	0 (0)	1 (2)	
	Pancreas	75 (78)	30 (73)	45 (82)	
	Head	66 (89)	26 (90)	40 (89)	1.000[5]
	Body	8 (11)	3 (10)	5 (11)	
Stage	Locally advanced	58 (60)	22 (54)	36 (65)	0.294
	Metastatic	38 (40)	19 (46)	19 (35)	
ECOG-PS	0	17 (18)	9 (22)	8 (15)	0.547
	1	51 (53)	22 (54)	29 (53)	
	⩾ 2	28 (29)	10 (24)	18 (33)	
Diabetic	No	68 (71)	29 (71)	39 (71)	1.000
	Yes	28 (29)	12 (29)	16 (29)	
Comorbidities	None	31 (32)	14 (34)	17 (31)	0.428
	Mild	41 (43)	18 (44)	23 (42)	
	Moderate	20 (21)	9 (22)	11 (20)	
	Severe	4 (4)	0 (0)	4 (7)	
Line of palliative chemotherapy	First	96 (100)	41 (100)	55 (100)	1.000
Type of chemotherapy	FOLFIRINOX	11 (11)	4 (10)	7 (13)	0.605
	Cisplatin Gemcitabine	13 (14)	8 (20)	5 (9)	
	Gemcitabine Nab-paclitaxel	7 (7)	2 (5)	5 (9)	
	Gemcitabine +/- TH302	2 (2)	0 (0)	2 (4)	
	Gemcitabine Capecitabine	25 (26)	12 (29)	13 (24)	
	Gemcitabine single agent	37 (39)	15 (37)	22 (40)	
	FOLFOX	1 (1)	0 (0)	1 (2)	
Time from first stent to starting chemotherapy[1]	Median (range)	1.8 (0.1-12.6)	1.6 (0.6-5.8)	1.9 (0.1-12.6)	0.1824[2]
Time of chemotherapy duration[1]	Median (range)	3.2 (0.1-7.6)	3.8 (0.1-7.2)	3.1 (0.1-7.6)	0.4520[2]

No differences were identified between SRE group and the no-SRE group. [1]Variables do not meet a normal distribution (as per Shapiro-Wilks test); [2]Mann-Whitney P-value has been provided for variables not meeting normal distribution criteria; [3]the P for χ^2 test for comparison of distribution of primary tumour [ampulla *vs* bile duct (cholangiocarcinoma) *vs* gallbladder *vs* pancreas] between SRE group and no-SRE group; [4]the P for χ^2 test for comparison of distribution of primary tumour [type of bile duct tumour (cholangiocarcinoma): intrahepatic *vs* extrahepatic] between SRE group and no-SRE group; [5]The P for χ^2 test for comparison of distribution of primary tumour (site of pancreatic cancer: head *vs* body) between SRE group and no-SRE group. SRE: Stent-related event; ECOG-PS: ECOG performance status; FOLFIRINOX: 5-fluorouracil, oxaliplatin and irinotecan combination; FOLFOX: 5-fluorouracil and oxaliplatin combination.

0.0947). When the impact on OS of the SRE-related consequence was analysed, we identified a longer OS in the group of patients with mild consequences [none/chemotherapy delay; median OS 11.6 mo (95%CI: 9.8-20)] compared to those with severe consequences [interruption of chemotherapy or death; median OS 4.4 mo (95%CI: 2.6-8.7)]; [HR = 3.8 (95%CI: 1.7-8.2), P = 0.001] (Figure 3). Stage was an independent prognostic factor for OS [HR = 1.8 (95%CI: 1.06-2.9), P = 0.029)] in multivariable analysis adjusted for primary tumour, ECOG-PS and development of SRE (SRE group *vs* no-SRE group) (Table 5).

DISCUSSION

In patients with advanced/inoperable cancers of the pancreas or biliary tract receiving chemotherapy and with an indwelling biliary stent at the start of treatment, we observed a high rate of SREs; moreover two-thirds of patients had some kind of consequence from the SRE (chemotherapy delay, discontinuation or early death). In addition, one-third of patients with a first SRE developed further events, highlighting the importance of close follow-up for early detection and management of such events. Although we observed

Table 2 Characteristics of the baseline biliary stenting and stent-related event

Variables		All patients (n = 96)	SRE group (n = 41; 43%)	no-SRE group (n = 55; 57%)	P-value for distribution within baseline parameter (χ^2 test), SRE *vs* no-SRE groups
Stents at baseline	1	70 (73)	24 (59)	46 (84)	0.008
	2	21 (22)	13 (32)	8 (14)	
	3	3 (3)	3 (7)	0 (0)	
	4	1 (1)	1 (2)	0 (0)	
	Not specified	1 (1)	0 (0)	1 (2)	
Number of stents/biliary interventions at baseline	1 previous stent/intervention	70 (73)	24 (59)	46 (84)	0.004
	⩾ 2 previous stent/intervention	25 (26)	17 (41)	8 (15)	
	Not specified	1 (1)	0 (0)	1 (1)	
Type of stent (baseline)	Metal	85 (89)	37 (90)	48 (87)	0.170
	Plastic	7 (7)	4 (10)	3 (5)	
	Not specified	4 (4)	0 (0)	4 (7)	
Type of SRE (SRE group only)	Cholangitis	16 (17)	16 (39)	-	-
	Stent obstruction	12 (13)	12 (29)	-	
	Both	13 (14)	13 (32)	-	
Consequence of SRE (SRE group only)	None	15 (16)	15 (37)	-	-
	Chemotherapy delayed	10 (10)	10 (24)	-	
	Chemotherapy stopped	7 (7)	7 (17)	-	
	Death	9 (9)	9 (22)	-	
Further SRE (SRE group only)	No	27 (28)	27 (66)	-	-
	Yes	14 (15)	14 (34)	-	

Forty-three percent of patients developed a SRE during the follow-up. SRE: Stent-related event.

Table 3 Risk of development of stent-related event increased with longer follow-up period in the absence of competing event (death)

Time-point of follow-up since first biliary stenting	Estimated risk of development of SRE rate for all patients
3 mo	11.5% (95%CI: 6.5-19.7)
6 mo	32.0% (95%CI: 23.5-42.7)
12 mo	48.6% (95%CI: 37.5-61)
18 mo	59.9% (95%CI: 44-76.5)
24 mo	79.9% (95%CI: 48.03-98.1)

SRE: Stent-related event.

no significant relationship between the type of stent and type of SRE, this may be explained by the small proportion of patients (11%) with plastic stents. Finally, there were no differences between the type of SRE developed (obstruction, infection or both) and its consequences; be it mortality, chemotherapy delay or discontinuation rate. Therefore all SREs should be considered as a medical emergency and early management is essential, due to the potentially life-threatening consequences.

Stent-related events occurred early with a median time-to-SRE of only 4.4 mo. Moreover, the risk increases with time rising 3-fold between month 3 and month 6 and up to 80% in patients alive at 24 mo. This highlights the importance of clinician (including primary and secondary care) and patient (and their cares) awareness of early detection and treatment of a SRE. Although some guidelines suggest replacement of plastic stents every six months[18] there are no such recommendations for metallic stents.

The only factor associated with a higher rate of SRE was the number of biliary stents or procedures at baseline (1 *vs* ⩾ 2); none of the other baseline characteristics had this impact, including disease stage or site of primary tumour, highlighting the challenge that clinicians face in identifying patients at increased risk of a SRE. In addition to the number of stents at baseline, the presence of severe comorbidity was associated with earlier development of a SRE (*i.e.*, earlier time-to-SRE). The fact that stage had no impact on time-to-SRE is likely to reflect the fact that stent occlusion arises from the primary (stented) disease rather than metastases, in the vast majority of patients.

The development of a SRE may be expected to be more frequent in patients receiving chemotherapy due to its known myelosuppressive effect[13] and particularly in patients receiving highly myelosuppressive treatment, such as FOLFIRINOX[5]. This was not confirmed in this study although this may again be due to the small number of patients receiving this regimen, and the fact that prophylactic granulocyte-colony stimulating factor (G-CSF) was routinely prescribed for these patients to reduce duration of neutropenia. The median time-to-SRE in our study was similar to previously published data in a non-chemotherapy population[13], suggesting that chemotherapy may not have as much as an impact on SREs as might be expected. Neither did we observe a higher rate of SREs if chemotherapy was delayed at baseline (due to potentially greater risk of tumour in-growth).

The development of a SRE did not impact on PFS; however there was a non-significant trend towards longer OS in the SRE group, compared with the no-SRE group. This cannot be interpreted as a causality effect

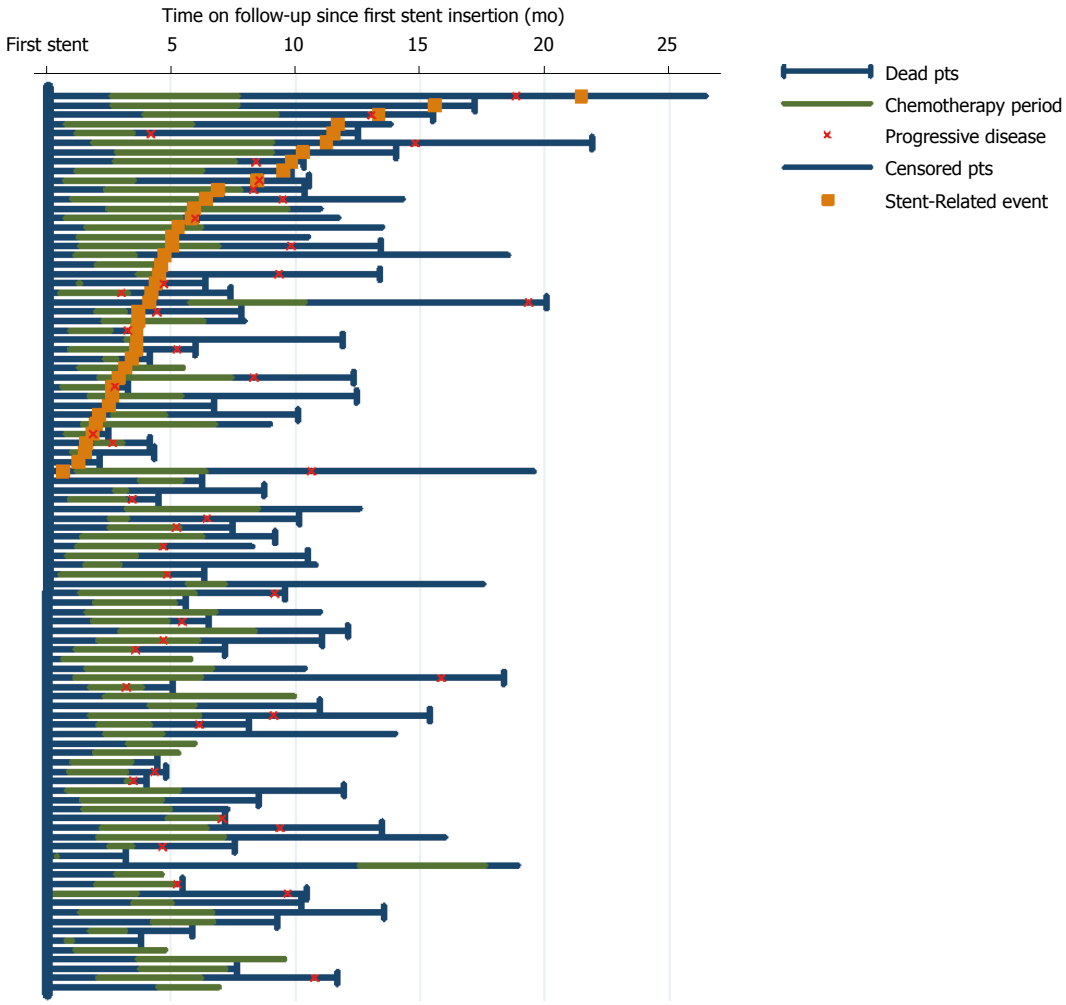

Figure 2 Graphical representation of each of the patient's follow-up included in this study, time on chemotherapy, and time of radiological progression and development of a stent-related event.

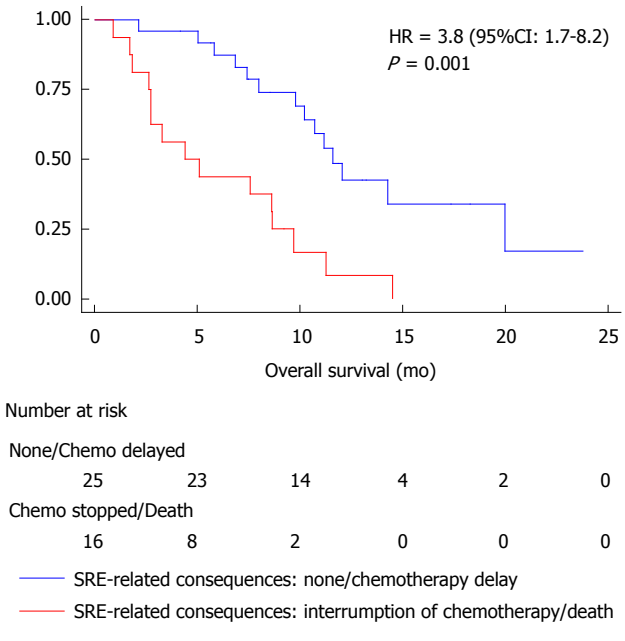

Figure 3 Kaplan Meier graphic. Overall survival and type of stent-related event (SRE)-related consequence [mild (none/chemotherapy delayed) *vs* severe (chemotherapy interrupted/death)].

(patients with SRE live longer) but rather a "time-at-risk" effect (patients who live longer have more time to develop a SRE). This was the main reason for including death as a "competing event" in the statistical analysis for time-to-SRE. In fact, the development of a SRE did not impact on survival in the multivariable analysis for OS, confirming this approach. Importance of "time-at-risk" in the development of a SRE is also supported by the following: a higher number of patients still receiving chemotherapy at the data cut-off point in the no-SRE group (8 patients *vs* 1 patient in the SRE group); and longer (though statistically non-significant) follow-up in the SRE group.

Our study population is representative of the population of interest when comparing characteristics such as rate of locally advanced patients; higher rate of biliary obstruction in patients with locally advanced disease[18]; predominance of pancreatic cancer compared to biliary malignancies[19]; median PFS and median OS (in keeping with a non-trial population). Moreover, the fact that tumour stage was identified as a prognostic factor in the multivariable analysis for OS was reassuring. The majority of patients with metallic

Table 4 Univariate and multivariable analysis looking for factors related with time-to-stent-related event

Time-to-SRE		Univariate analysis (Fine-Gray regression)		Multivariable analysis (Fine-Gray regression)	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Primary	BTC	Ref		X	
	Pancreas	0.8 (0.4-1.5)	0.407		
Stage	Locally advanced	Ref		X	
	Metastatic	1.4 (0.8-2.6)	0.251		
ECOG-PS	0/1	Ref		X	
	⩾ 2	0.8 (0.4-1.5)	0.435		
Comorbidities	None	Ref		Ref	
	Mild	0.8 (0.4-1.7)	0.605	1.1 (0.5-2.2)	0.844
	Moderate	0.9 (0.4-1.9)	0.734	1.1 (0.5-2.2)	0.986
	Severe	3.6×10^{-8} (1.2×10^{-8}-1.1×10^{-7})	< 0.001	9.4×10^{-7} (2.9×10^{-7}-3.1×10^{-6})	< 0.001
Number of stents/biliary interventions at baseline	1	Ref		Ref	
	⩾ 2	2.5 (1.4-4.6)	0.003	2.3 (1.2-4.44)	0.010
Type of the most recent stent	Metal	Ref		X	
	Plastic	2.1 (0.7-6.5)	0.182		

Fine-Gray Regression; competing event: Death. BTC: Biliary tract cancer; ECOG-PS: ECOG performance status.

Table 5 Univariate and multivariable analysis looking for factors related with overall survival (Cox Regression)

Overall survival		Univariate analysis (Cox regression)		Multivariable analysis (Cox regression)	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Primary site	BTC	Ref		Ref	
	Pancreas	1.6 (0.8-2.9)	0.153	1.5 (0.8-2.8)	0.205
Stage	Locally advanced	Ref		Ref	
	Metastatic	1.6 (0.99-2.9)	0.067	1.8 (1.06-2.9)	0.029
ECOG-PS	0/1	Ref		Ref	
	⩾ 2	0.9 (0.5-1.6)	0.748	0.9 (0.5-1.6)	0.716
Stent-related event	No-SRE group	Ref		Ref	
	SRE group	0.7 (0.4-1.1)	0.098	0.6 (0.4-1.01)	0.205

For assessment of factors with an impact on OS, variables considered of interest [such as site of primary tumour, stage, ECOG-PS and development of SRE (yes/no)] and those variables which showed statistically significant *P*-value in the univariate analysis were included in multivariable analysis. BTC: Biliary tract cancer; ECOG-PS: ECOG performance status.

stents at baseline is in keeping with international standards for palliative patients who are expected to be treated with chemotherapy (*i.e.,* have an estimated survival of > 3 mo) in whom a plastic stent should not be considered as a standard[20]. The small number of patients with ECOG ⩾ 2 is the likely reason why ECOG-PS did not impact on OS as chemotherapy is usually considered only for patients of good performance status (PS 0-1 and selected PS 2 patients).

There are limitations associated with our retrospective series; although all consecutive patients with a diagnosis of advanced pancreatobiliary malignancy were included, the patients were already preselected by fitness and comorbidities for referral for consideration for chemotherapy. Moreover, retrospective collection of data may be subject to reporting bias. In addition, patients with different primary tumour sites were included who were in receipt of differing chemotherapeutic agents; however completeness of data and inclusion of patients from a recent era makes our findings credible. Our series did not include any non-stented patients and therefore comparisons of SRE rate between stented and not-stented populations, which could be useful for assessing whether the combination of chemotherapy and biliary stent increased the risk of SRE, are not possible. Finally, most of our patients had a metal stent *in situ*; making our data not representative of population with plastic biliary stents.

To date, there is no evidence supporting the use of prophylactic therapy, such as antibiotics or ursodeoxycholic acid, aimed at reducing or delaying SREs in these patients; thus clinicians currently treat rather than prevent SREs[33]. One purpose of our study was to generate data to inform the design of future clinical trials exploring the role of prophylaxis for the prevention or delay of SREs in this specific population. This rationale has already been investigated by some studies (summarised in Table 6): overall, these trials are under-powered and involved patients with both benign and malignant biliary strictures who had plastic stents *in-situ*. No adequately-powered studies have been performed; neither has this question been addressed in patients with metal stents (now considered the standard of care in the palliative setting) or in a population receiving chemotherapy

Table 6 Summary of the available literature exploring the role of prophylactic treatment for stent-related event

Disease	Ref.	Randomised	Type of stent	Total number of patients	Number of patients per arm	Treatment arm(s): Stent insertion plus....	Investigation and result
Benign	Sciumè *et al*[21], 2004	Yes (not blinded)	Plastic	90	49/41	Ursodeoxycholic acid and levofloxacin *vs* Ursodeoxycholic acid alone	Longer stent patency with lower cholangitis and admission rate.
	Katsinelos *et al*[22], 2008	Yes (blinded)	Plastic	41	21/20	Ursodeoxycholic acid *vs* Placebo	Common bile duct stones. No reduction in the bile duct stone size.
	Han *et al*[23], 2009	No	Plastic	28	28	Ursodeoxycholic acid and terpene	Gallstones in elderly patients. Size of gallstones was reduced.
	Lee *et al*[24], 2011	No	Plastic	51	51	Ursodeoxycholic acid	Gallstones in elderly patients. No benefit of adding Ursodeoxycholic acid.
	Nishizawa *et al*[25], 2013	No	Plastic	36 patients, 63 procedures	Non-randomised, two arms: 20/43 procedures	Ursodeoxycholic acid *vs* Observation	Bile duct stones. Longer patency time and reduction in gallstone size in the intervention cohort.
Malignant	Ghosh *et al*[26], 1994[1]	Yes (not blinded)	Plastic	70	31/39	Ursodeoxycholic acid + antibiotic (ampicillin, metronidazole, ciprofloxacin) *vs* Observation	No differences in stent occlusion rate.
	Barrioz *et al*[27], 1994[1]	Yes (not blinded)	Plastic	20	Not specified	Ursodeoxycholic acid and norfloxacin *vs* Observation	Longer stent patency, prolonged median survival and shorter mean hospital stay.
	Luman *et al*[28], 1999[1]	Yes (not blinded)	Not specified	40	20/20	Ciprofloxacin and rowachol *vs* Observation	Similar rate of obstruction and time to event.
	Sung *et al*[29], 1999[1]	Yes (not blinded)	Plastic	58	Not specified	Ursodeoxycholic acid *vs* Observation	Similar rate of obstruction and time to event.
	De Lédinghen *et al*[30], 2000[1]	Yes (not blinded)	Plastic	62	33/29	Ursodeoxycholic acid and norfloxacin *vs* Observation	Stopped after the interim analysis. No differences in stent patency.
	Halm *et al*[31], 2001[2]	Yes (not blinded)	Plastic	52	26/26	Ursodeoxycholic acid and ofloxacin *vs* Ursodeoxycholic acid alone	Similar rate of obstruction and times to stent obstruction.
	Chan *et al*[32], 2005[2]	Yes (double blinded)	Plastic	94	50/44	Ciprofloxacin *vs* Placebo	No differences in stent patency. Lower rate of cholangitis, but there was improvement in quality of life.

Overall, studies are underpowered for reaching definitive conclusions. [1]These studies were included in The Cochrane review[33]; [2]These studies were not included in The Cochrane review[33].

for advanced pancreas/biliary cancer. In 2002 the Cochrane collaboration concluded that well-designed studies with sufficient statistical power were essential to address this issue[33]. Our results highlight the importance of performing adequately-powered prospective studies looking for prevention of these events.

Stent-related events can result in life-threatening complications in patients with advanced pancreatobiliary cancer who are receiving palliative chemotherapy; 43% of patients in our series developed a SRE and 63% of them had a SRE-related impact on delivery of chemotherapy or resulting in death. The risk of developing SREs increases with prolonged time on treatment and/or follow-up; moreover, risk is higher in patients with severe comorbidities and patients with $\geqslant$ 2 biliary stent or biliary procedures at baseline. Thus, close monitoring for early diagnosis and treatment is required. Our data will inform the design of future, prospective clinical trial(s) to evaluate how the risk of SREs and their sequelae can be reduced; as well as the clinical and socio-economic impact of doing so.

COMMENTS

Background

Despite successful first biliary stenting, some patients with biliary and pancreatic malignancies will develop a stent-related event (SRE) such as recurrence of biliary obstruction (with development of new obstructive jaundice) or infection (cholangitis). Development of these events is detrimental, especially

in a chemotherapy-treated population.

Research frontiers

The aim of this study was to analyse the incidence (measured as SRE rate and time-to-SRE) and impact of SREs in patients with advanced biliary tract and pancreatic malignancies receiving palliative chemotherapy and, in doing so, to provide reference data in order to design an adequately-powered clinical trial to investigate the role of prophylaxis for the prevention or delay of SREs in patients with biliary stents who are due to commence chemotherapy.

Innovations and breakthroughs

In patients with advanced/inoperable cancers of the pancreas or biliary tract receiving chemotherapy and with an indwelling biliary stent at the start of treatment, the authors observed a high rate of SREs; moreover, in two-thirds of these patients there was a direct consequence from the SRE (chemotherapy delay, discontinuation or early death). Therefore all SREs should be considered as a medical emergency and early management is essential, due to their potentially life-threatening consequences.

Applications

Although the authors have demonstrated that SREs are frequent and may be associated with adverse outcomes, there is, to date, no evidence supporting the use of prophylactic therapy, such as antibiotics or ursodeoxycholic acid, aimed at reducing or delaying SREs in these patients; thus clinicians currently treat rather than prevent SREs. One purpose of our study was to generate data to inform the design of future clinical trials exploring the role of prophylaxis for the prevention or delay of SREs in this specific population.

Terminology

Stent-related events: recurrence of biliary obstruction with stent obstruction (with development of new obstructive jaundice) or infection (cholangitis) following successful first biliary stenting.

Peer-review

The authors explored the occurrence and consequences of stent-related events in a retrospective cohort of patients with pancreatico-biliary cancer stented for biliary obstruction. They showed that 43% patients developed a stent-related during the follow-up, which could lead to chemotherapy delay or discontinuation, or death.

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