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Analysis of Endoscopic Radiofrequency Ablation of Biliary Malignant Strictures in Pancreatic Cancer Suggests Potential Survival Benefit --Manuscript Draft--

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Abstract:	<p>Background: Pancreatic carcinoma is often inoperable, carries a poor prognosis and is commonly complicated by malignant biliary obstruction. Phase I/II studies have demonstrated good safety and early stent patency using endoscopic biliary radiofrequency ablation (RFA) as an adjunct to self-expanding metal stent (SEMS) insertion for biliary decompression.</p> <p>Aim: To analyse the clinical efficacy of endobiliary RFA.</p> <p>Methods: Retrospective case-control analysis of 23 patients with surgically unresectable pancreatic carcinoma and malignant biliary obstruction undergoing endoscopic RFA and SEMS insertion, and 46 controls (SEMS insertion alone) in a single tertiary care centre. Controls were stringently matched for age, sex, metastases, ASA/co-morbidities. Survival, morbidity, and stent patency rates were assessed.</p> <p>Results: RFA and control groups were closely matched- ASA 2.35+/-0.65 vs. 2.54+/-0.50, p=0.086; metastases 9/23 (39.1%) vs. 18/46 (39.1%), p=0.800; chemotherapy 16/23 (69.6%) vs. 24/46 (52.2%), p=0.203. Median survival in RFA group was 226d (IQR 140-526d) vs. 123.5d (IQR 44-328d) in controls (p=0.010). RFA was independently predictive of survival at 90d (OR 21.07, 95% CI 1.45-306.64, p=0.026) and 180d (OR 4.48, 95% CI 1.04-19.30, p=0.044) in multivariate analysis. SEMS patency rates were equivalent in both groups. RFA was well tolerated with minimal side effects.</p> <p>Conclusions: Endoscopic RFA is a safe and efficacious adjunctive treatment in patients with advanced pancreatic malignancy and biliary obstruction and may confer early survival benefit. Randomised prospective clinical trials of this new modality are mandated.</p>
Author Comments:	<p>6 May 2015</p> <p>The Editor, Digestive Diseases and Sciences</p> <p>Re manuscript: Analysis of Endoscopic Radiofrequency Ablation of Biliary Malignant</p>

Strictures in Pancreatic Cancer Suggests Potential Survival Benefit

Dear Sir,

Thank you for considering our manuscript and for the helpful reviews.

Please find enclosed a revised version of the manuscript for reconsideration, together with a detailed point by point response to the reviewer comments.

We have taken independent statistical advice on the manuscript as suggested.

Yours sincerely,

Dr D Westaby MA FRCP
Lead Clinician for Pancreatobiliary Services
Department of Gastroenterology

RESPONSES TO REVIEWER COMMENTS

Reviewer #1: The authors present a retrospective series of 23 pts with unresectable panc ca treated with RFA and uncovered SEMS vs. 46 with uncovered alone and matched for chemo, mets, ASA, etc. It is novel data but the main premise for RFA is that it induces a coagulative necrosis - how it improves survival if it doesn't improve stent patency is not hypothesized. Stent patency was similar between the two groups. Are the authors suggesting that RFA may be able to reduce tumor burden? Several comments to help the authors improve the submission. I do feel that the manuscript would benefit from more clarity and defined goals for its work. What are the primary and secondary endpoints for the study. These should be clearly stated in the Methods.

The primary and secondary endpoints of the study are survival and stent patency/procedure safety, respectively. This has been highlighted in the methods section (cf point 13, below). Please see the response to point 14 below, re putative beneficial effects of RFA on patients with pancreatic cancer.

Other comments:

1) Those patients who underwent chemo was higher in the RFA group (70% vs. 52%) but not statistically sig't. This may be a Type 2 error given the small sample size and this limitation should be clearly highlighted in the discussion. In fact, this seems to be the most plausible explanation as to the survival benefit in the RFA group unless the authors can provide other possible hypothesis.

The possibility of a type 2 error is now mentioned in the relevant discussion section.

2) The improved median survival of 226D vs. 124D has a CI that goes through 1. Please explain the limitations of this analysis and include in the discussion.

The upper limit of the 95% CI is 1.06. This is represented in the fact that the two survival curves on Kaplan-Meier analysis cross at late time points, when the number of surviving patients is small. Our statistical analysis in this paper points to a difference in survival between RFA and control groups only at early time points. This is expanded on further in the discussion section.

3) Introduction: The following should be incorporated into the Discussion. 'Our retrospective analysis reveals a potential early survival benefit in patients treated with endobiliary RFA and forms the basis on which future large-scale prospective studies can be designed and justified in this disease'

Thank you. This change has been made.

4) Methods: Provide a specific estimate of expected survival that would have excluded

patients from the study 'who would have been expected to have only very limited survival'.

Patients were considered for RFA, or were included in the control group for the purposes of our study, if they were of sufficient fitness to have been considered for palliative chemotherapy by the cancer MDT. In general, patients whose predicted survival is less than six weeks were not referred for palliative chemotherapy. Of course, estimation of predicted survival patients with advanced cancer is not an exact science.

5) Expand on patients included that underwent ERCP (were these index ERCP?) and how was tissue diagnosis made (EUS-FNA or other?)?

In a proportion of patients in this study, in both RFA and control groups, this was an index ERCP. Many in both groups, however, had undergone a prior ERCP for urgent biliary decompression with plastic stenting at their local hospital before referral to our tertiary centre. The proportion of patients undergoing ERCP and prior plastic stenting was included in the original manuscript (Table 1 Patient Demographics), and this variable had been included in the multivariate analysis (Figure 2). This had been discussed in the Results section (paragraph 2) and has now has been expanded upon.

A tissue diagnosis was made either with biliary brush cytology at a prior ERCP, or with EUS-FNA. This detail has been included in the methods section.

6) What was wattage of RFA and duration?

10W were applied over 2 mins for each application. The total number of applications performed per ERCP procedure was dependent on the stricture length. This detail has been added to the methods section.

7) What % of patients were deemed surgically unresectable vs. medically inoperable?

All patients were surgically unresectable. This has been clarified in the manuscript.

8) Results: Remove "extremely" from "wall matched"

This has been changed

9) Give specific numbers re: those with liver mets and locally advanced disease. 'In the vast majority of cases spread was confined to the liver alone. The remainder of patients in both RFA and control cohorts had evidence of advanced local spread, often with significant vascular invasion that precluded surgery.'

9/23 had metastatic spread in the RFA group, 18/46 had metastatic spread in the control group. 14/23 had advanced local spread in the RFA group, 28/46 had advanced local spread in the control group. This is mentioned in the Results section (paragraph 2) and in table 1, and has been amended to read more clearly.

10) Authors state: 'protocol based necessity to obtain a definitive tissue diagnosis prior to RFA treatment' - isn't tissue diagnosis confirmed prior to uncovered SEMS in patients who were in the control arm?

Tissue diagnosis was confirmed in patients in the control arm prior to referral from the MDT for chemotherapy (an inclusion criteria for entry into this study). In some patients with clear evidence of metastatic disease or advanced local vascular invasion, tissue diagnosis was only confirmed subsequent to biliary stenting (or at time of stenting from brush cytology).

Paragraph 2 in the Results section has been amended to read less ambiguously.

11) What are specific percentages for : 'A vast majority of patients in both groups died of progressive malignant disease or carcinomatosis, rather than from cholangitis or stent obstruction, with a high proportion dying at early time-points particularly in the control group'

22/23 patients in the RFA group and 43/46 patients in the control group died of progressive malignant disease or carcinomatosis. This has been clarified in the manuscript.

12) More appropriate to incorporate in Discussion rather than Results and is slightly redundant with 1st sentence in the Discussion: Our initial pilot study of endobiliary RFA, which had included patients with cholangiocarcinoma as well as pancreatic carcinoma, had shown good early SEMS patency rates post procedure, with 21/22 and 17/22 patients maintaining stent patency at 30d and 90d, respectively. [8] In the study presented here spanning a longer followup period, a median patency rate of 472d was observed.

Thank you. This section has been considerably shortened.

13) Authors description of stent occlusion endpoint and censorship is confusing. Would focus the results on survival (primary endpoint - state this is primary endpoint) and then secondary endpoint of stent occlusion. This would help to make the manuscript easier to read.

Thank you. The manuscript has been edited to lend clarity to defining primary and secondary end-points. The analysis of a composite endpoint of stent occlusion and survival has been removed.

14) Discussion: Again, if RFA does not increase stent patency, why do authors think that survival is higher in the RFA group?

It is possible that endobiliary RFA may still have some effect on maintaining stent patency. Our analysis does not bear this out, but this may in part reflect the confounding effect of a high early mortality rate. This is already mentioned in the discussion section.

Furthermore, it is possible that endobiliary RFA could have beneficial effects on the immune regulation of tumour via the release of antigen as a result of tumour lysis and via the induction

of a local anti-inflammatory response. This is of course pure conjecture, and it is not possible to address this within the limits of this study, but similar effects are starting to be described in other tumours treated with RFA. A paragraph on this is now included in the discussion section.

15) References: Be sure journal guidelines with respect to number of authors.

The reference section has been verified for compliance with the journal's guidelines.

16) Table 2: Add "days" as title under 1st column

This has been amended

17) Figure 3: % "stent" patency should be added

This has been amended

Reviewer #2:

This is a well-done review of a small number of cases. The writing is technically good, and it was very nice that you did a case-control rather than just a descriptive retrospective case series. The numbers are quite small, and even with 2:1 matching not adequate to make any conclusions. You did build on the safety of the device and potentially pave the way for a RCT.

Thank you for your comments.

Reviewer 3: please have a statistician recheck the survival comparison statistics and comment on the lack of difference in Kaplan-Meier analysis

Thank you. Independent external statistical appraisal of the manuscript was obtained.

The Kaplan-Meier analysis was deemed valid to assess survival and stent patency differences between the two groups. The lack of a statistically significant difference (log rank analysis) was confirmed and is in keeping with the survival curves. Given that all subjects were uncensored (ie all subjects reached an end point of death) it was considered appropriate to compare survival directly between RFA and control groups using a Mann-Whitney test (non parametrically distribution).

Review of the survival curves suggests that differences are most marked at early time points. Indeed, when using the Gehan-Breslow-Wilcoxon test to compare survival curves, a statistically significant difference is seen ($p=0.014$). This test does not require a consistent hazard ratio and will often lend more weight to differences in survival at early time points. It was not used in the analysis of our study, however, as it is more conventional to use the log rank method.

It was recommended that survival differences at early time points could be tested by capping the KM analysis at various time points (ie 90d, 180d, 270d, 360d). This has been performed and has demonstrated significantly greater survival in the RFA groups at 90d and 180d only. This data is now presented in tabular form in a revised table 2.

It was advised that the use of fisher's exact test to examine for differences in the composite end point of survival and stent patency was invalid. Alternative statistical methods were suggested. However, in the light of comments made by other reviewers it was decided to omit this aspect of the data analysis altogether from the revised manuscript. It was accepted that the inclusion of this data and its analysis would likely cause confusion and detract from the message conveyed by analysis of the primary and secondary end points (survival and stent patency). As result, the previous version of table 2 and figure 4 have been removed.

Managing Editor: Please also make sure the revised title, abstract, and keywords meet the following requirements, which have been recently added to DDS author instructions at <http://www.springer.com/medicine/internal/journal/10620?detailsPage=contentItemPage&CIPageCounter=142504>:

Thank you. This has been verified.

**Analysis of Endoscopic Radiofrequency Ablation of Biliary
Malignant Strictures in Pancreatic Cancer Suggests Potential
Survival Benefit**

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7 **Disclosures**
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9 NH, stockholder & director of EMcision Ltd, UK.
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11 YK, NP, AS, CK, PV & DW have no potential conflicts to disclose.
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ABSTRACT

Background: Pancreatic carcinoma is often inoperable, carries a poor prognosis and is commonly complicated by malignant biliary obstruction. Phase I/II studies have demonstrated good safety and early stent patency using endoscopic biliary radiofrequency ablation (RFA) as an adjunct to self-expanding metal stent (SEMS) insertion for biliary decompression.

Aim: To analyse the clinical efficacy of endobiliary RFA.

Methods: Retrospective case-control analysis of 23 patients with surgically unresectable pancreatic carcinoma and malignant biliary obstruction undergoing endoscopic RFA and SEMS insertion, and 46 controls (SEMS insertion alone) in a single tertiary care centre. Controls were stringently matched for age, sex, metastases, ASA/co-morbidities. Survival, morbidity, and stent patency rates were assessed.

Results: RFA and control groups were closely matched- ASA 2.35 $\pm$ 0.65 vs. 2.54 $\pm$ 0.50, $p=0.086$; metastases 9/23 (39.1%) vs. 18/46 (39.1%), $p=0.800$; chemotherapy 16/23 (69.6%) vs. 24/46 (52.2%), $p=0.203$. Median survival in RFA group was 226d (IQR 140-526d) vs. 123.5d (IQR 44-328d) in controls ($p=0.010$). RFA was independently predictive of survival at 90d (OR 21.07, 95% CI 1.45-306.64, $p=0.026$) and 180d (OR 4.48, 95% CI 1.04-19.30, $p=0.044$) in multivariate analysis. SEMS patency rates were equivalent in both groups. RFA was well tolerated with minimal side effects.

Conclusions: Endoscopic RFA is a safe and efficacious adjunctive treatment in patients with advanced pancreatic malignancy and biliary obstruction and may confer

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4 early survival benefit. Randomised prospective clinical trials of this new modality are
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6 mandated.
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16 **Keywords**
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19 Biliary metal stent, malignant biliary stricture, therapeutic endoscopy, obstructive
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INTRODUCTION

Pancreatic carcinoma is one of the most common cancers of the gastrointestinal tract and has a relatively poor prognosis. Only 10-20% of pancreatic carcinoma is amenable to definitive curative surgery on presentation. [1] Radiotherapy and palliative chemotherapy are the mainstays of treatment in patients with unresectable disease due to local or distant metastatic spread. Survival is limited even with current advances in chemotherapy, with median survival rates of five to seven months reported for pancreatic carcinoma. [2,3] Distal biliary duct obstruction is a common problem and many patients with inoperable pancreatic cancer will require self-expanding metal stent (SEMS) insertion for definitive biliary decompression. [4] SEMS occlusion is a considerable clinical problem in this palliative patient population with significant associated morbidity and mortality. [4,5]

Radiofrequency ablation (RFA) has been used to deliver heat energy to instigate local tumor necrosis in primary and secondary liver cancer via percutaneous and intra-operative routes. [6] Endoscopically applied RFA can induce the coagulative necrosis of tissue within biliary strictures at sites of deployment. [7] Moreover, a pilot study conducted in our tertiary referral hepato-pancreato-biliary (HPB) centre demonstrated good safety and 90d patency rates of endoscopically-applied RFA in patients with inoperable pancreatic carcinoma and bile duct obstruction. [8] RFA, used as an adjunct to SEMS insertion, was shown to be technically feasible with highly acceptable patient tolerance. Following on from this, the safety and technical success of endoscopic RFA

has been replicated across a number of centres. [9] More recent studies are starting to describe their experience of the efficacy of endoscopic RFA in the treatment of malignant biliary strictures [10-14]. Many studies have included heterogeneous groups of patients with a range of underlying malignancies (pancreatic carcinoma, cholangiocarcinoma, hepatic metastases), hindering the applicability of such findings to specific patient populations. [11-14]

Here we set out to investigate the efficacy and safety of endobiliary RFA in the treatment of malignant bile duct obstruction in patients with inoperable pancreatic carcinoma alone, and compare outcomes to historical controls.

PATIENTS AND METHODS

Patient Selection and Matching

A retrospective analysis was performed on patients presenting to our tertiary care HPB centre with bile duct obstruction secondary to inoperable pancreatic carcinoma. Patients who had undergone endoscopic insertion of uncovered biliary SEMS, with or without adjunctive endobiliary RFA, were included in the analysis. Each patient included in the study had their treatment plan decided by the HPB cancer multi-disciplinary team comprising HPB-dedicated gastroenterologists, surgeons, radiologists and oncologists. To be eligible for RFA, patients had to have surgically unresectable pancreatic cancer with associated biliary obstruction that was amenable to endoscopic drainage assessed by cross-sectional imaging. Only patients deemed to be of sufficient health for palliative chemotherapy at time of disease presentation were included in the retrospective analysis. This criterion was chosen to exclude patients of extreme frailty and those with extensive, advanced disease, who would have been expected to have only very limited survival (i.e. less than six weeks).

All patients with surgically unresectable pancreatic cancer treated with endobiliary RFA in our tertiary care centre between January 2009 and November 2011 were included in the analysis (23 in total). All had a tissue diagnosis of malignancy confirmed at prior ERCP with brush cytology, or with EUS-guided fine needle aspiration. The control group

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4 comprised patients with surgically unresectable pancreatic cancer, chosen from the
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6 same patient population, treated with an uncovered SEMS alone between September
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8 2005 and August 2010 (46 in total). Patients in both groups were treated by the same
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10 operators, using the same endoscopic practice and equipment. Management decisions
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12 about patient care had been made by the same cancer MDT, the members of which had
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14 remained unchanged over the study period. Key factors in the management of
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16 malignant biliary strictures had also remained the same, namely the determination of
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18 surgical resectability, techniques for the establishment of biliary drainage, indications for
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20 palliative chemotherapy, and type of chemotherapeutic agent used. The type of
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22 uncovered biliary SEMS used remained unchanged (Wallflex, Boston Scientific, Natick,
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24 Mass). The inclusion criteria for the control group were exactly the same as those for
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26 the RFA-treated cohort. The control group comprised patients that met suitability criteria
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28 for endobiliary RFA, but were not treated. This was either because they had presented
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30 prior to the introduction of such therapy in our centre, or because they had presented
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32 during periods when the RFA catheter was not available.
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43 To facilitate a robust comparison of outcomes, patients in the RFA treatment and control
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45 groups were strictly matched according to the following five criteria: age (within a ten-
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47 year range), sex, co-morbidity, ASA category, and the presence or absence of
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49 metastases at time of treatment. Two control patients were selected for each RFA
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51 treated case, on a best-fit basis, to form the control group. Matching was performed
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53 strictly blinded to outcome data, with only demographic data relevant to case matching
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55 available at time of selection.
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Endoscopic Intervention

All endoscopic biliary interventions were performed under standard operating conditions within the HPB unit at Imperial College Healthcare NHS Trust by two highly experienced endoscopists (DW, PV) using Olympus TJF-260 duodenoscopes (Olympus, Tokyo, Japan). As a treatment modality, endobiliary RFA was approved by the local institutional research ethics and new devices committees (08/H0718/46). Full details of the RFA treatment protocol, including the safety and feasibility of the technique, are previously described. [8] RF energy was applied to the malignant biliary stricture using the Habib™ EndoHPB RFA catheter (EMcision UK, London, UK), which has US Food and Drug Administration 510(k) marketing clearance and EU European Conformity approval. This 8F catheter was passed over a standard 0.035-inch guidewire and was coupled to a radiofrequency generator (RF 1500X, RITA Medical Systems Inc, Fremont, CA; or ERBE VIO200D, ERBE Medical UK Ltd, Leeds, UK), to deliver 10W over a 2min period for each application. Sequential ablative energy was applied to the stricture under fluoroscopic guidance to induce coagulative tissue necrosis over its entire length, the total number of applications dependent on stricture length. This was immediately followed by the insertion of an uncovered biliary SEMS (Wallstent, Boston Scientific, Natick, MA) to preserve bile duct patency and integrity.

Data Collection and Analysis

Data included in the analysis were collected and analysed retrospectively until patient death. The primary end-point of the study was patient survival. Secondary end-points were stent patency and procedure related safety and tolerability. Patient survival and stent patency were characterised by Kaplan-Meier analysis, using the Log Rank method to compare differences between the two cohorts. As all patients in both groups were followed up until death, a two-tailed Mann Whitney test was also performed (non-parametric data) to compare overall survival times. Factors known to govern survival in pancreatic carcinoma, as well as variables found to be significantly different between RFA and control groups, were entered into a multivariate logistic regression analysis to determine parameters associated with survival in this study.

Stent occlusion was defined as radiological evidence of stent malfunction (evidence of increase in upstream bile duct dilatation, absence of aerobilia, presence of occlusive material within stent) in conjunction with a rise in serum bilirubin to greater than 50 μ mol/L.

The t test and chi-squared analysis were used to interrogate differences between RFA and control cohorts as indicated. Statistical analysis was performed using GraphPad Prism v6.0 (GraphPad Software, SD) and MedCalc v11.6 (MedCalc Software, Mariakerke, Belgium). Significance was taken at a p value <0.05.

RESULTS

In total, 23 patients with biliary obstruction due to inoperable pancreatic carcinoma received endoscopic RFA to common bile duct stricture followed by contemporaneous SEMS insertion. Endobiliary RFA was well tolerated, with a median post endoscopy in-patient stay of 1 day (IQR 1-4; range, 1-8). Procedure-related adverse events were rare and comparable to those of endoscopic biliary stenting alone. [15] Clinically insignificant hyperamylasaemia and antibiotic-responsive cholangitis developed in one patient each. There was no procedure-related mortality in the first 30d.

The control cohort consisted of 46 patients undergoing SEMS insertion alone for precisely the same indication, carefully matched for age, sex, presence of metastases, ASA category and co-morbidity. Details of patient demographics are supplied in table 1. RFA treated and control groups were well matched according to these parameters. Importantly, patients were strictly matched for tumour burden, with just over one third having metastatic spread at time of treatment in both groups (39.1% RFA, 39.1% control). In the vast majority of cases metastatic spread was confined to the liver alone. The remainder of patients in both RFA and control cohorts had evidence of advanced local spread precluding curative surgery (60.1% RFA, 60.1% control). RFA and control groups were well matched by degree of hyperbilirubinaemia at time of disease presentation and underwent definitive biliary intervention after a similar time interval. However a significantly greater number of patients had undergone a prior index ERCP with temporary plastic stenting of the biliary tree in the RFA-treated group compared to

controls (82.6% vs. 39.1%, respectively, $p=0.0008$). This difference reflected the fact that many patients treated with RFA had been referred into our tertiary centre from other local or regional hospitals, where plastic stenting had already been performed, often as a temporizing measure before a definitive tissue diagnosis was obtained. There was no significant difference in the proportion of patients subsequently going on to receive palliative chemotherapy after RFA/SEMS insertion across the two groups (69.6% vs. 52.2%, respectively, $p=0.203$). The chemotherapeutic regimens used were the same in RFA and control groups and were unchanged over the study period. Single agent cisplatin, or combination cisplatin/gemcitabine, was used dependent on patient co-morbidity.

Kaplan-Meier analysis revealed differences in survival in those patients treated with RFA, though statistical significance was not achieved ($p=0.094$, hazard ratio 0.660, 95% CI 0.410 – 1.063, see figure 1). All patients in the RFA and control groups had died over the follow-up period. Thus, as there were no censored data, a direct comparison of survival was performed. This showed a statistically significant survival advantage in those treated with RFA (median 226d IQR 140-526d vs. median 123.5d IQR 44-328d, $p=0.010$). A vast majority of patients in both groups died of progressive malignant disease or carcinomatosis (22/23 RFA, 43/46 control), rather than from cholangitis or stent obstruction, with a high proportion dying at early time-points particularly in the control group. Review of the survival curves shows a separation at early time points (figure 1). This was interrogated further with Kaplan-Meier analysis capped at varying time points (90d, 180d, 270d, 360d post treatment). Analysis shows that RFA was

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4 associated with statistically significant improved survival at 90d and 180d only (see
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6 table 2).
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11 Multivariate logistic regression analysis was then performed to ascertain whether RFA
12 was independently associated with survival at these clinically relevant time-points (90d,
13 180d, 270d, 360d, see figure 2). The association of other parameters known to be
14 pertinent to survival in patients with advanced pancreatic carcinoma (i.e. presence of
15 metastases, chemotherapy, ASA score), as well as factors shown to be appreciably
16 different between RFA and control groups (i.e. prior plastic stenting), were also
17 analysed. As expected chemotherapy was strongly predictive of survival at multiple
18 time-points, with ASA score and the presence of metastases associated with worse
19 early survival rates. Importantly, RFA was independently predictive of survival at 90d
20 and 180d, but not at later time-points (OR 21.07, 95% CI 1.45-306.64, p=0.026 at 90d;
21 OR 4.48, 95% CI 1.04-19.30, p=0.044 at 180d).
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41 In this study, where all patients were followed up until death, a median stent patency
42 rate of 472d was observed in the RFA treated group. Kaplan-Meier analysis, however,
43 demonstrated that there was no difference in SEMS patency rates between RFA-treated
44 groups and controls (median 472d vs.324d, respectively, HR 1.186, 95% CI 0.536 to
45 2.656, p=0.669; see figure 3). Moreover, only 9/23 in RFA treated group and 14/46
46 controls reached the end-point of stent occlusion. High rates of censorship (14/23 and
47 32/46, respectively) resulted from high death rates particularly at early time points. In
48 practice, patients presenting to our centre with biliary obstruction due to stent occlusion
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4 were usually treated with further SEMS insertion. SEMS occlusion per se was very
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6 rarely a direct cause of mortality. Differences in survival between RFA and control
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8 groups may confound observed differences in stent occlusion due to a disproportionate
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10 number of patients dying with a patent stent in the two groups.
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DISCUSSION

We have previously shown that endobiliary RFA can be safely performed to palliate patients with unresectable malignant bile duct obstruction due to both pancreatic carcinoma and cholangiocarcinoma. [8] Indeed, recently other centres are beginning to report on their experience with this endoscopic modality in the same diseases. [10,11,13,14,16] Endobiliary RFA via a percutaneous approach and for benign indications has also been described. [12,17]. In our analysis of efficacy, we have demonstrated that endobiliary RFA is a factor associated with early survival benefit in patients with metastatic or locally advanced inoperable pancreatic carcinoma. Given the limitations inherent in retrospective studies, we have sought to conduct as robust and meaningful an analysis as possible by defining a control group stringently matched according to five separate key criteria likely to impact on patient survival. We demonstrate significantly higher median survival rates in patients receiving RFA of approximately 7.5 months, a 3.5-month increase over closely matched controls, and show that RFA treatment is independently predictive of survival in the first 180d by multivariate analysis. It appears that this survival advantage is lost at later time points, when RFA is no longer predictive of survival, with survival curves crossing and the confidence interval exceeds 1.0. By comparison, published median survival rates after palliative chemotherapy in metastatic pancreatic cancer range between five and seven months. [3,18] In recent trials, only FOLFIRINOX has been shown to significantly increase median survival up to eleven months, though it is only suitable in patients with

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4 high performance status, is harder to tolerate, and has largely been studied in patients
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6 without malignant biliary obstruction requiring stenting. [19] The impact of any therapy
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8 that prolongs survival in advanced or metastatic pancreatic carcinoma is likely to be
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10 most pronounced at early time-points given the high early mortality rate of this condition
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12 and the poor medium-term prognosis. In our study, survival differences were most
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14 pronounced at early time-points in patients receiving RFA. Our practice involved
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16 administering only one session of endobiliary RFA. Whether further benefit could be
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18 derived from repeated applications of RFA has not been fully investigated.
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26 When endobiliary RFA was first proposed as a treatment modality, it was developed as
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28 a tool to improve and maintain stent luminal integrity. [8] Interestingly, in the
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30 retrospective analysis presented here, RFA did not appear to alter absolute stent
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32 patency rates, and this has also been reported previously in other studies. [13] It is thus
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34 possible that the observed improvements in patient survival were not linked to better
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36 maintenance of biliary drainage. Indeed, a substantial majority of patients in both RFA
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38 and control groups died of carcinomatosis rather than direct clinical consequences of
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40 stent occlusion. The successful institution of chemotherapy can often be disrupted by
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42 failure to resolve biliary obstruction in clinical practice. However, there was no
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44 statistically significant difference in the proportion of patients receiving palliative
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46 chemotherapy in the two groups, albeit the possibility of a type 2 error exists given the
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48 sample sizes involved. In effect, true stent patency rates may be difficult to ascertain, in
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50 the face of a high early mortality rates, as many patients will have died with a patent
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52 stent before exposure to the risk of occlusion. This is exemplified in our study where
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4 median stent patency rates are paradoxically higher than median survival rates in both
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6 RFA and control groups using Kaplan Meier analysis.
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11 Research in solid organ malignancies such as breast, hepatocellular carcinoma and
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13 metastatic colorectal cancer, suggests that RFA may have beneficial effects beyond the
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15 simple local ablation of tumour tissue. Some evidence suggests that RFA may play a
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17 role by inducing indirect anti-tumoural effects. [20] Several potential mechanisms are
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19 postulated, including the induction of anti-tumoural T-cell responses via the release of
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21 tumour antigen secondary to RFA-induced tissue necrosis or via the stimulation of local
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23 inflammatory responses. [21] Endobiliary RFA induces the coagulative necrosis of
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25 tissue within the biliary stricture where it is deployed. [7] It is possible that similar
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27 mediators and pathways may account for the differences in survival noted in our
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29 analysis, though this is pure speculation as our retrospective study was not intended or
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31 designed to address this.
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41 Treatment options for patients with advanced pancreatic carcinoma are limited, with
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43 palliative chemotherapy providing only modest survival advantage and radiotherapy
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45 having limited effect. There are limited data on other endoscopic therapeutic biliary
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47 interventions. Prospective studies on the use of photodynamic therapy (PDT) in
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49 unresectable hilar cholangiocarcinoma suggest both improvements in biliary drainage
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51 and in patient survival. [22] However, debate continues to surround efficacy, and
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53 significant concerns remain about its side effect profile. To date, PDT has only been
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4 trialled in one small phase I study in patients with pancreatic carcinoma, and its role in
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6 the management of this condition remains undefined. [23]
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11 Other strategies are required, and the study presented here provides further evidence
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13 that endobiliary RFA could potentially play such a role. Till now, the largest such study
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15 reported the experience and outcomes of endobiliary RFA across many centres with
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17 good median survival rates (10.6 months), but in a cohort of 58 patients of mixed
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19 disease aetiology and without a uniform post-RFA biliary stenting approach, making
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21 results harder to interpret. [14] A recently published retrospective study suggested a
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23 survival advantage in patients treated with RFA compared to matched controls, though
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25 again extrapolation of this data is difficult as both groups were of mixed disease
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27 aetiology- cholangiocarcinoma and pancreatic carcinoma (n=8). [13]
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36 Here, we confirm that endoscopic RFA is a safe and well-tolerated adjunctive treatment
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38 for malignant biliary obstruction in a controlled study of patients with pancreatic
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40 carcinoma alone, and show that it may have the potential to confer an early survival
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42 benefit. Though conclusions on the clinical effectiveness of this treatment modality
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44 should be reserved, this study presents further data that provide the foundation upon
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46 which prospective randomised controlled trials can be mandated and designed.
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REFERENCES

- 1 Ghaneh P, Costello E, Neoptolemos JP. Biology and management of pancreatic cancer *Gut*. 2007;56:1134-1152.
- 2 Herrmann R, Bodoky G, Ruhstaller Tet al. . Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group *J Clin Oncol*. 2007;25:2212-2217.
- 3 Verslype C, Prenen H, Van Cutsem E. The role of chemotherapy in biliary tract carcinoma *HPB (Oxford)*. 2008;10:164-167.
- 4 Davids PH, Groen AK, Rauws EA, Tytgat GN, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction *Lancet*. 1992;340:1488-1492.
- 5 O'Brien S, Hatfield AR, Craig PI, Williams SP. A three year follow up of self expanding metal stents in the endoscopic palliation of longterm survivors with malignant biliary obstruction *Gut*. 1995;36:618-621.
- 6 Sutherland LM, Williams JA, Padbury RT, Gotley DC, Stokes B, Maddern GJ. Radiofrequency ablation of liver tumors: a systematic review *Arch Surg*. 2006;141:181-190.
- 7 Itoi T, Isayama H, Sofuni Aet al. . Evaluation of effects of a novel endoscopically applied radiofrequency ablation biliary catheter using an ex-vivo pig liver *J Hepatobiliary Pancreat Sci*. 2012;19:543-547.

- 1
2
3
4 8 Steel AW, Postgate AJ, Khorsandi Set al. . Endoscopically applied
5
6 radiofrequency ablation appears to be safe in the treatment of malignant biliary
7
8 obstruction *Gastrointest Endosc.* 2011;73:149-153.
9
10
11 9 Wadsworth CA, Westaby D, Khan SA. Endoscopic radiofrequency ablation for
12
13 cholangiocarcinoma *Current opinion in gastroenterology.* 2013;29:305-311.
14
15
16 10 Tal AO, Vermehren J, Friedrich-Rust Met al. . Intraductal endoscopic
17
18 radiofrequency ablation for the treatment of hilar non-resectable malignant bile
19
20 duct obstruction *World J Gastrointest Endosc.* 2014;6:13-19.
21
22
23 11 Figueroa-Barojas P, Bakhru MR, Habib NAet al. . Safety and efficacy of
24
25 radiofrequency ablation in the management of unresectable bile duct and
26
27 pancreatic cancer: a novel palliation technique *Journal of oncology.*
28
29 2013;2013:910897.
30
31
32
33 12 Mizandari M, Pai M, Xi Fet al. . Percutaneous intraductal radiofrequency ablation
34
35 is a safe treatment for malignant biliary obstruction: feasibility and early results
36
37 *Cardiovascular and interventional radiology.* 2013;36:814-819.
38
39
40 13 Sharaiha RZ, Natov N, Glockenberg KS, Widmer J, Gaidhane M, Kahaleh M.
41
42 Comparison of Metal Stenting with Radiofrequency Ablation Versus Stenting
43
44 Alone for Treating Malignant Biliary Strictures: Is There an Added Benefit? *Dig*
45
46 *Dis Sci.* 2014.
47
48
49
50 14 Dolak W, Schreiber F, Schwaighofer Het al. . Endoscopic radiofrequency ablation
51
52 for malignant biliary obstruction: a nationwide retrospective study of 84
53
54 consecutive applications *Surg Endosc.* 2014;28:854-860.
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 15 Cote GA, Kumar N, Ansstas Met al. . Risk of post-ERCP pancreatitis with
5
6 placement of self-expandable metallic stents *Gastrointest Endosc.* 2010;72:748-
7
8 754.
9
10
11 16 Alis H, Sengoz C, Gonenc M, Kalayci MU, Kocatas A. Endobiliary radiofrequency
12
13 ablation for malignant biliary obstruction *Hepatobiliary & pancreatic diseases*
14
15 *international : HBPD INT.* 2013;12:423-427.
16
17
18 17 Hu B, Gao DJ, Wu J, Wang TT, Yang XM, Ye X. Intraductal radiofrequency
19
20 ablation for refractory benign biliary stricture: pilot feasibility study *Digestive*
21
22 *endoscopy : official journal of the Japan Gastroenterological Endoscopy Society.*
23
24 2014;26:581-585.
25
26
27
28 18 Cunningham D, Chau I, Stocken DDet al. . Phase III randomized comparison of
29
30 gemcitabine versus gemcitabine plus capecitabine in patients with advanced
31
32 pancreatic cancer *J Clin Oncol.* 2009;27:5513-5518.
33
34
35 19 Conroy T, Desseigne F, Ychou Met al. . FOLFIRINOX versus gemcitabine for
36
37 metastatic pancreatic cancer *N Engl J Med.* 2011;364:1817-1825.
38
39
40 20 Hansler J, Wissniowski TT, Schuppan Det al. . Activation and dramatically
41
42 increased cytolytic activity of tumor specific T lymphocytes after radio-frequency
43
44 ablation in patients with hepatocellular carcinoma and colorectal liver metastases
45
46 *World J Gastroenterol.* 2006;12:3716-3721.
47
48
49
50 21 den Brok MH, Suttmuller RP, van der Voort Ret al. . In situ tumor ablation creates
51
52 an antigen source for the generation of antitumor immunity *Cancer Res.*
53
54 2004;64:4024-4029.
55
56
57
58
59
60
61
62
63
64
65

- 1
2
3
4 22 Ortner ME, Caca K, Berr Fet al. . Successful photodynamic therapy for
5
6 nonresectable cholangiocarcinoma: a randomized prospective study
7
8
9 *Gastroenterology*. 2003;125:1355-1363.
10
11 23 Bown SG, Rogowska AZ, Whitelaw DEet al. . Photodynamic therapy for cancer
12
13 of the pancreas *Gut*. 2002;50:549-557.
14
15
16
17
18
19
20
21
22
23
24
25
26
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Table 1. Patient Demographics

	RFA (n=23)	Control (n=46)	p value
Male	12	24	n/a
Age (yrs)*	68.9 +/- 9.0	69.8 +/- 9.9	0.791
ASA grade *	2.35 +/- 0.65	2.54 +/- 0.50	0.086
Metastases	9 (39.1%)	18 (39.1%)	0.800
Chemotherapy	16 (69.6%)	24 (52.2%)	0.203
Bilirubin (μmol/L) at diagnosis	244.1 +/- 48.4	203.9 +/- 149.9	0.420
Time (d) diagnosis to RFA/SEMS*	44.4 +/- 33.3	39.0 +/- 76.5	0.765
Plastic Stenting prior to RFA/SEMS	19/23 (82.6%)	18/46 (39.1%)	0.0008

(*mean +/- standard deviation)

(*mean +/- standard deviation)

Table 2. Kaplan Meier survival analysis at defined time points

Survival	90d	180d	270d	360d
Hazard Ratio	0.10	0.31	0.69	0.54
95% CI	0.09-0.65	0.19-0.75	0.38-1.29	0.32-0.99
*P value	0.004	0.005	0.25	0.06

* Log Rank

FIGURE LEGENDS

Figure 1. Early survival benefit of radiofrequency ablation (RFA). Kaplan-Meier analysis showing endobiliary RFA is associated with increased survival rates in patients with inoperable pancreatic carcinoma and biliary obstruction compared to controls (median 226d vs. 123.5d; p value as shown).

Figure 2. Multivariate analysis of predictors of survival. Radiofrequency ablation (RFA) is independently associated with survival at 90d and 180d in patients with inoperable pancreatic carcinoma and malignant biliary obstruction. Odds Ratio (95% confidence interval) and p value as shown. Analysis performed at 90d, 180d, 270d & 360d after endoscopic management of biliary obstruction.

Figure 3. Radiofrequency ablation (RFA) has no discernable effect on stent patency. Kaplan-Meier analysis showing no difference in overall stent patency rates after endobiliary RFA in patients with inoperable pancreatic carcinoma and biliary obstruction compared to controls (median 472d vs. 324d; p value as shown).

Figure 1
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