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Adjuvant therapy confers no survival benefit following curative surgery for peri-ampullary adenocarcinoma: a Meta-Analysis

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ABSTRACT

Objective

The aim of this meta-analysis was to determine the survival **benefit** from adjuvant therapy for peri-ampullary cancers.

Background

Peri-ampullary cancers are uncommon malignancies, often amenable to surgery. Several studies have suggested a role of adjuvant chemo- and chemo-radiotherapy in improving survival for peri-ampullary cancers with variable results.

Methods

A systematic review of the literature **was undertaken** between the 1st January 2000 and 31st December 2015 to elicit and analyse the pooled overall survival associated with the use of either adjuvant chemo- and chemo-radiotherapy, as **opposed** to observation in the treatment of surgically resected peri-ampullary cancers. Included articles were also screened for information regarding stage, prognostic factors and toxicity-related events.

Results

Seven hundred and four titles were screened, of which ninety-three full text articles retrieved. Fourteen full text articles were included in the study, **six of which were randomized control trials**. A total of 1671 patients (904 in the control and 767 whom underwent adjuvant therapy) were included. The median

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5-year overall survival was 37.5% compared 40% in the control and adjuvant groups, respectively (HR 1.08, p=0.067). In 31.4% of adjuvant patients, one or more WHO grade 3 or 4 toxicity-related events was noted. High T-stage was associated worse survival (**regression** coefficient -0.14, P=0.04), whilst nodal status and grade of differentiation were not.

Discussion

This review has **found** no associated survival benefit of adjuvant therapy in the treatment of peri-ampullary cancers. Further studies should aim to critically investigate if patients with advanced disease specifically, would benefit from specific adjuvant treatment strategies, to prevent exposing patients to significant toxic side effects.

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INTRODUCTION

Peri-ampullary cancers are uncommon malignancies with an age-standardised incidence of 0.6 per 100,000 in the UK[1]. Surgical resection is the treatment modality of choice, with ampullary cancer accounting for 10% to 20% of **pancreatoduodenectomies** performed for peri-ampullary carcinomas[2]. Despite its relative higher resectability rates compared to pancreatic adenocarcinoma however, the 5-year survival has been estimated at only 20% to 50%[3,4]. **Adjuvant therapy, including chemo- and chemoradiotherapy,** has thus been proposed as a treatment modality to enhance long-term survival.

In 1985, the Gastrointestinal Stromal Group (GISTG) suggested a potential survival benefit to the use of **adjuvant therapy** for pancreatic adenocarcinoma[5]. Since then the results of this, and similar studies, **there has been a suggestion** to include this for all peri-ampullary cancers. The latter however, **defined as malignancies arising in the ampulla of Vater, but extending into the distal common bile duct or adjacent duodenum,** are a pathologically distinct group of malignancies. **Whilst not classified as such,** histologically these cancers can be of two-types: intestinal and pancreatobiliary depending on the type of epithelium they arise from. Clinically they often present earlier due to local obstruction which leads to jaundice and pain. As such there is **not strong evidence to suggest these tumours would respond comparably to pancreatic cancer**[6]. Chemotherapy may be beneficial in the context of advanced or metastatic ampullary cancers, **where studies have shown a median overall survival of 12.5 months with certain regimen**[7]. However, in resectable

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cancers, using adjuvant therapy potentially exposes patients to high levels of toxicity with little benefit.

As there is no clear consensus on the most efficacious chemotherapy regimen and there is limited evidence available, practical guidelines regarding adjuvant therapy have not been produced. Many regimes utilize 5-fluorouracil or a derivative in combination with gemcitabine, mitomycin or a platinum-based drug[8]. Toxicity is an often cited complication of chemotherapy and these commonly used regimes can be associated with side effects such as pancytopenia, cardiovascular disease and dermatological manifestations. Whilst it has been suggested that prognostic factors such as lymph node invasion and resection margin status could better stratify those of whom would benefit most from chemotherapy, few of these scores are widely validated or utilized clinically[9]. **As such there is a clear need to better understand the role for adjuvant therapy in peri-ampullary cancer, and moreover define that role with respect to prognostic factors, to avoid excess morbidity. In order to appreciate the true impact of incorporating adjuvant therapy, an analysis of the various regimen that have already been tested in the literature is required.**

The aim of this meta-analysis was to determine from the published literature the survival benefit, if any, of adjuvant chemotherapy for peri-ampullary cancers.

METHODS

Literature Search Strategy

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A literature search of PubMed, OvidMedline, Embase and Google Scholar electronic databases was conducted from January 2000 up to and including December 2015 for studies regarding the use of adjuvant chemotherapy in the treatment of peri-ampullary cancer in patients whom had undergone surgery with curative intent (**Fig. 1)**. Search MeSH terms used included: *ampullary cancer, ampulla of Vater, peri-ampullary neoplasm, peri ampullary, adjuvant chemotherapy and chemoradiotherapy* in various combinations and with the names of specific surgical procedures. Research titles were then screened for suitability and full-text copies were retrieved. **A study was considered suitable if it provided survival data for more than 3 years for both an adjuvant therapy group (either chemo- or chemoradiotherapy), with surgery-alone (so-called control group) in the treatment of peri-ampullary cancer, as defined previously**. Further potentially appropriate papers were highlighted by assessing the reference lists and citations of the articles being screened. The **literature search was completed independently by two authors [AA and SRM] and discrepancies discussed until a consensus regarding relevance was reached. The data was extracted directly from the published Kaplan-Meier curves and verified for each study by each author independently. This was collated into an anonymised database for analysis.**

All studies that investigated the use of any chemotherapy-based adjuvant regimen, **including chemo- and chemoradiotherapy,** for patients whom had undergone any surgical procedure with curative intent for either ampullary or peri-ampullary cancer (as defined as malignancy located in the distal common bile duct, ampulla of Vater or adjacent duodenum). Exclusion criteria involved

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studies with no available English translation, no full text edition available, those in which no Kaplan-Meier was available and those involving palliative surgery or adjuvant regimen involving radiotherapy alone. Of those studies meeting inclusion criteria the year of publication, population demographics, the number of patients enrolled, the overall survival **and any adverse outcomes reported** were extracted. Kaplan-Meier curves of survival were assessed and survival independently calculated and verified by two independent authors (AA and SRM).

Literature Standard

A composite score combining the Jadad and the Cochrane Risk-of-Bias tool, was used to appraise the standard of the literature (Appendix 1). They were implemented individually and independently, as has been previously described with both, to assess the quality and risk of bias of the included studies[10,11]. The scores from each were combined to give a composite summary score. Prompting questions are used to allow the reviewer to assess whether there is a risk of bias with respect each of the domains. A total score above 3 denotes a level of rigor in each. **Whilst these scores are utilized primarily in randomized trials, for consistency they were incorporated into the appraisal of the non-randomized studies. The limitation of this is discussed later.**

Statistical Analysis

The logarithm of the hazard ratio (HR) with 95 % confidence intervals (CI) was used as the primary summary statistic. To estimate HR and its variance, this was extracted from the study directly or required additional calculation depending

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on the method of data being presented: annual mortality rates, survival curves, number of deaths or percentage freedom from death[12].

Meta-analysis of data was conducted using a random effects model. Publication bias was explored graphically with funnel plots to detect asymmetry and any outliers. Inter-study heterogeneity was assessed using the Chi square statistic and the I^2 value to measure the degree of variation not attributable to chance alone. This was graded as low (I^2<25 %), moderate (I^2 = 25–75 %) or high (I^2 >75 %). The significance level was set at P<0.05.

A further sub-group analysis of the included randomized controls trials was conducted, to further appraise the validity of the conclusions drawn.

We performed meta-regression to quantitatively assess the impact of the: 1.) T-stage of the tumour, 2.) N-Stage of the disease; and 3.) the grade of differentiation on the overall effect. Three covariates of interest were created; T-stage; continuous variable with the ratio of T 3+4 V. T1+2 in each study; N- stage; continuous variable with the ratio of N+ V. N0 in each study; and Grade of differentiation; continuous variable with the ratio of Poor Grade V. Well Grade in each study. The significance level was set at P<0.05.

Calculations were performed by GM and verified by TA. This study was performed in line with journal recommendations, following the MOOSE guidelines, using appropriate statistical software (STATA/SE12)[13].

RESULTS

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Included Studies

Fourteen full text articles met the inclusion criteria and were appraised following the literature search[3, 6, 14-25] (Fig 1). A total of 1671 patients were enrolled in the studies, 904 of whom underwent surgery alone (so-called control group) and 767 who had adjuvant chemotherapy. **Six studies were randomized control trials, two were prospective cohort studies and the remaining six studies were retrospective**. The full demographics of these studies can be seen in Table 1.

A classical Whipple's procedure was the most commonly undertaken procedure (754 cases), whilst a pylorus-preserving pancreatoduodenectomy was completed in 423 cases. In five studies (Takado et al, Smeenk et al, Neoptolemos et al, Schiergens et al and Narang et al) all or some of the study patients underwent an unspecified resection.

Survival Outcomes

The **pooled 5-year overall survival across the fourteen studies for** the control group was 37.5%, compared with 40% in the adjuvant chemotherapy group (HR 1.08, I^2 39.1%, p=0.067) (Fig 2).

Randomised Control Trial Analysis

Six studies were randomized control trials. There was no difference in the 5-year overall survival between control and adjuvant therapy groups (HR 1.01 (95% CI 0.80-1.26), I^2 45.5%, p=0.102) (Appendix 2).

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Adverse Outcomes

In nine studies details of adverse effects from adjuvant therapy were provided (Table 2). No treatment related mortality was noted. Severe haematological complications (WHO Grade 3 or 4) such as neutropenia or thrombocytopenia were the most commonly stated side effects of adjuvant therapy **(16.3%). Severe diarrhoea occurred in 4.4% of patients, stomatitis in 3.3%, nausea in 3.3%, severe sepsis in 0.26% and obstruction or alopecia in 0.13%.**

Meta-regression

In three studies (Bhatia et al, Lazaryan et al and Neoptolemos et al) stage data for subjects was not explicitly stated. Of the remaining studies, 407 patients in the surgery-alone group were T stage 1 or 2, whilst there were 239 in the adjuvant group (p=0.086). There were 270 patients with T stage 3 or 4 in the surgery-alone group and 329 in the adjuvant group (P=0.309).

Meta-regression analysis elicited that only advanced T-stage (T3 or T4) was independently associated with significantly worse 5- year overall survival (P=0.04) as seen in Table 3. Due to the lack of demographic data no further sub-group analysis could be completed.

Literature Standard

Results from the quality analysis are shown in Figure 3. Only 36% of studies had a Jadad or Risk-of-bias score greater than or equal to 3, denoting a low level of quality of included studies, and high potential level of bias. However, the median

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composite score was 3.5 (range 1 to 6), would suggest a level of skew caused by a few high quality studies included in the evaluation.

DISCUSSION

This review has demonstrated that there was no associated survival benefit conferred by the use of adjuvant therapy in peri-ampullary cancer when compared with post-surgical observation (5-year overall survival rates 0.40 v. 0.38 respectively, p=0.06). Peri-ampullary cancers represent a group of malignancies distinct from those arising from other hepato-biliary structures. These cancers are pathologically adenocarcinomas, and in an estimated 80% of cases are amenable to surgical resection[24, 26]. However this treatment regimen is often augmented by the use of adjuvant chemo- and chemo-radiotherapy, especially amongst those with advanced disease. The pooled overall survival rates demonstrated in this study, are congruent with current estimates, which suggest the 5 year survival for peri-ampullary cancers is between 30 to 50%[23,27].

In addition to not revealing an apparent survival benefit, we also demonstrated that there were a number of side effects reported as a result of the use of adjuvant therapy. Whilst no treatment associated mortality was recorded, of the 767 patients whom had adjuvant therapy, there were 247 WHO grade 3 or 4 toxic effects, indicating a high number of potential life-threatening consequences[28]. The evaluation of overall survival in this study, is therefore more appropriate than simply appraising loco-regional control, as it acknowledges a holistic approach, and the detriment to survival of treatment-

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related complications. Furthermore, this effect is likely to represent an underestimate as five studies did not report toxicity. These side effects were most commonly systemic in nature including haematological disturbances, nausea and diarrhea and are frequently associated with the use of 5-fluorouracil[29], which was the principle agent employed in the majority of the chemotherapeutic regimes.

The utilization of any adjunctive (neoadjuvant or adjuvant) therapy in the treatment of any malignancy is a cost-benefit balance. The benefit is typically evaluated in terms of survival, and in this case no survival benefit was gained through adjuvant therapy. The cost is most commonly considered in terms of complications as a result of adjunctive therapy and consequent impact upon quality of life. This study again showed approximately one-third of patients experience serious complications resulting from the adjuvant therapy. Therefore in terms of cost-benefit assessment, adjuvant therapy provides no benefit but confers significant cost to the patient.

The use of adjuvant chemotherapy has been established in the treatment of pancreatic cancers, where numerous studies have shown a survival benefit[30, 31]. Peri-ampullary cancers however, present earlier due to their tendency to obstruct the distal common bile duct, and thus will often have not yet invaded local vascular, lymphatic or neural structures[6, 30]. As such the outcomes of surgical resection are better than those associated with pancreatic cancers. In this way, peri-ampullary cancers represent a distinct group of malignancies, and

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the likelihood of adjuvant therapy to bestow a survival benefit is an assumption by-proxy.

In 2008, Krishnan et al published a series of 114 patients, which suggested a survival benefit for the use of adjuvant chemo-radiotherapy in ampullary cancers. They propose the role for adjuvant therapy should be in advanced or 'high-risk' patients, defining the latter as those with stage T3 or T4 disease, but fail to demonstrate any survival benefit over an observation based strategy[13, 32]. Contrary to these findings however, we have shown through meta-regression analyses that high T stage (T3 or T4) unlike lymph node status or high tumor grade, was associated with a worse 5-year overall survival, these patients with advanced stage only should therefore be considered for a trial of adjuvant therapy following surgery. However due to the limitations of the numbers of patients in each group within the included studies, we have not been able to further analyse the potential survival benefit conferred by adjuvant chemotherapy in these advanced cases alone. For this reason we cannot discount a potential role for adjuvant therapy in advanced disease (T3 or T4), where the risk-benefit of chemotherapy may lie in favour of a trial of treatment.

The ambiguity with respect the term 'high-risk' has led several studies, all be them often small and retrospective, to investigate alternative means by which to better inform patient selection for trials of adjuvant therapy[33]. Colussi et al proposed a composite score whereby having an age at diagnosis greater than 75, WHO performance status of 2, poorly differentiated tumour and TIIb or III reduced 5-year disease free survival by 75%[34]. Patients in this group may be

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more appropriately given a trial of adjuvant chemotherapy, were the potential benefits would outweigh the risks. Other factors including high telomerase activity, pre-operative CA 19-9 level, perineural invasion and high UICC stage which have all been associated with reduced survival in peri-ampullary cancers[35,36].

Furthermore, peri-ampullary cancers can be broadly divided into two subtypes: intestinal and pancreato-biliary. These can be differentiated utilising immunohistochemical staining for markers such as MUK2 and CD20, and may impact upon which treatments are suitable for an individual patient. The prognosis of these two sub-types has been shown to differ, with the latter having been associated with significantly worse progression-free and overall survival [37]. Moreover these sub-types exhibit contrasting responses to various chemotherapeutic regimes, with pancreato-biliary type showing greater response with gemcitabine based therapies, and intestinal type responding better with fluoropyrimidine treatments.[21, 38] This discrepancy may also explain the fact that with metastatic disease, studies advocate a 5-FU regime, whilst others suggest the use of a gemcitabine-cisplatin combination[39,40]. In order therefore, to appreciate the true survival benefit, if any, of adjuvant therapy, not only do prognostic factors that stratify patients require prospective identification, but so do the optimal chemotherapeutic regimes to be used in these high-risk pathological sub-groups.

There were a number of limitations to this review predominantly due to the studies included, which was highlighted by the study quality analysis. Peri-

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ampullary cancers represent a heterogeneous group of cancers, and the inclusion criteria for the studies differed accordingly. Whilst the exact inclusion criteria are shown in Table 1, the majority of studies defined peri-ampullary cancers as those emanating from the ampulla of Vater or peri-ampullary stuctures, with gross distortion of the ampulla. Despite being a limitation of this study, this echoes the clinical scenario, whereby such peri-ampullary cancers would be treated in similar fashion. **Furthermore, two studies incorporated in-situ carcinoma, however this would lead to an overestimation of overall survival, and the effect of adjuvant therapy.** In addition, the majority of the studies constituted retrospective evaluation of single-center practice, and as such the generalizability of the results is affected. **Sub-group assessment of the RCTs alone, echoed the findings of the primary analysis demonstrating no overall survival benefit. This enhances the reliability of the conclusions drawn.** Despite this few studies were designated with a Risk-of-Bias score or Jadad score greater than 3, as investigators would not have been blinded to the survival outcomes. **Whilst these scores are primarily designed for the assessment of randomized control trials, a low score indicates the potential biases within the non-randomized trials included.** Despite this, similar findings were found in the prospective and randomized control trials included. Furthermore, while there was no significant difference between the stage of the patients in the control and adjuvant therapy groups, other prognostic factors, including resection margin and histological sub-type of the peri-ampullary cancer were not often explicitly stated, precluding them from the analysis. As such there is potential for the adjuvant group to have a worse prognosis irrespective of treatment given skewing the results. Owing to the significant

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heterogeneity amongst the treatment regimen used in the studies any analysis as to which regime was superior could not be undertaken. The studies utilised different agents, **with 5-fluorouracil being the most common. This, in addition to the variation in the number of chemotherapy cycles and the use of radiotherapy, limits the generalizability of the results**. However, the differences in chemotherapy regimen are due to the lack of consensus as to which are the most efficacious, as such the results would parallel those noted in the clinical setting.

In spite of these limitations, the fact that only 14 studies met the inclusion criteria demonstrates the paucity of evidence regarding the use of adjuvant chemotherapy in peri-ampullary cancers. **Currently, clinicians will need to assess patients on an individual basis, in order to gauge whether they may benefit from adjuvant therapy, which may involve reserving its use to more advanced cases to avoid unnecessary treatment-related morbidity.** As peri-ampullary cancers vary according to their sub-classification, and treatment protocols are currently ill-defined, further work should prospectively examine the effect of certain adjuvant chemotherapy regimen with respect specific histological subtypes, to better highlight the effects of treatment. Furthermore, future work should focus upon critically assessing adjuvant therapies in select cases, in order to truly ascertain if there is a value in incorporating them in the treatment paradigm of peri-ampullary malignancy, to prevent exposing patients to the potentially avoidable toxic effects of chemo-radiotherapy and better tailoring treatment to the high-risk patients, with advanced disease, whom may benefit from it.

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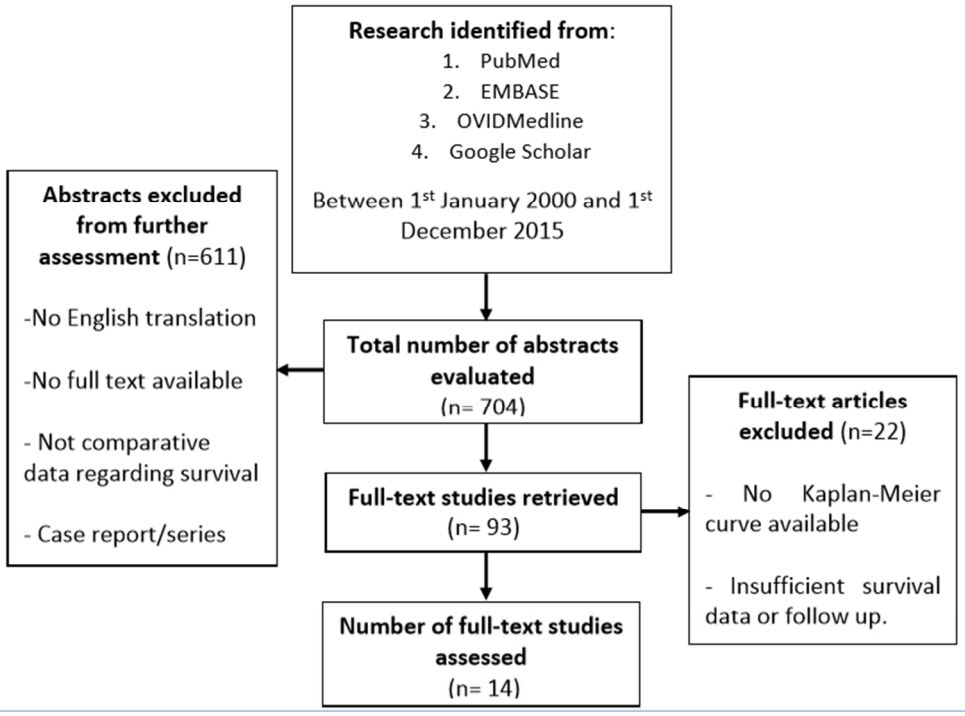

Figure 1: Diagram demonstrating the literature search strategy
(Fig 1)
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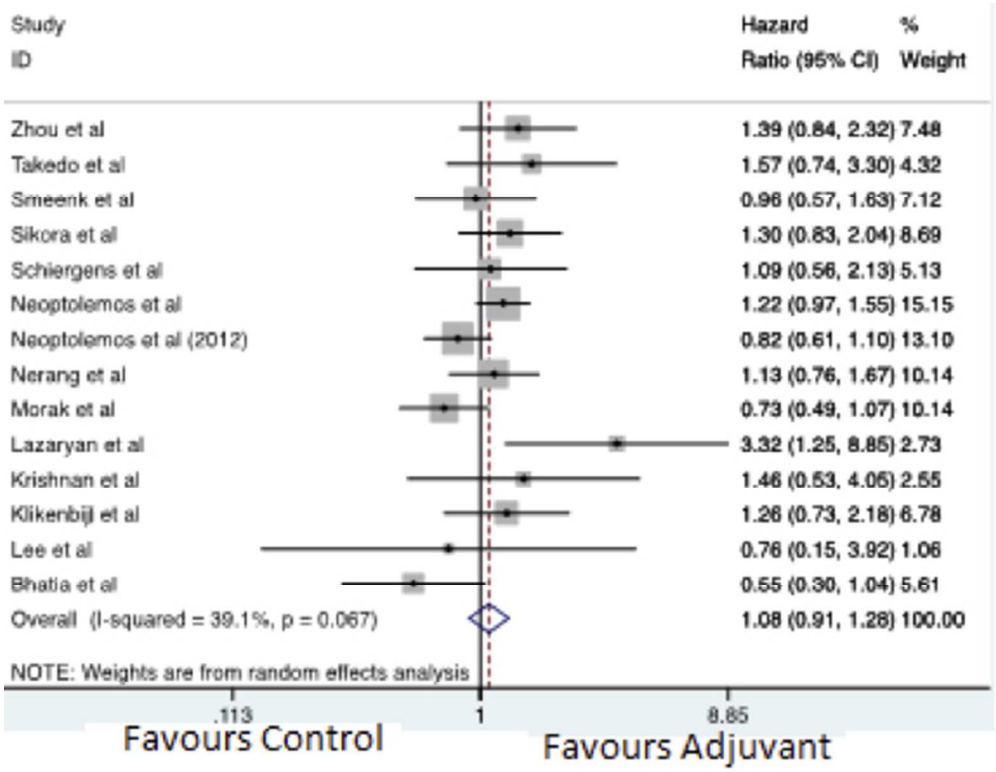

Figure 2a: Forest plot showing the hazard ratios associated with each of the fourteen studies and the pooled overall hazard ratio. The weight contributed by each study is shown as a percentage.
(Fig 2)
97x75mm (150 x 150 DPI)

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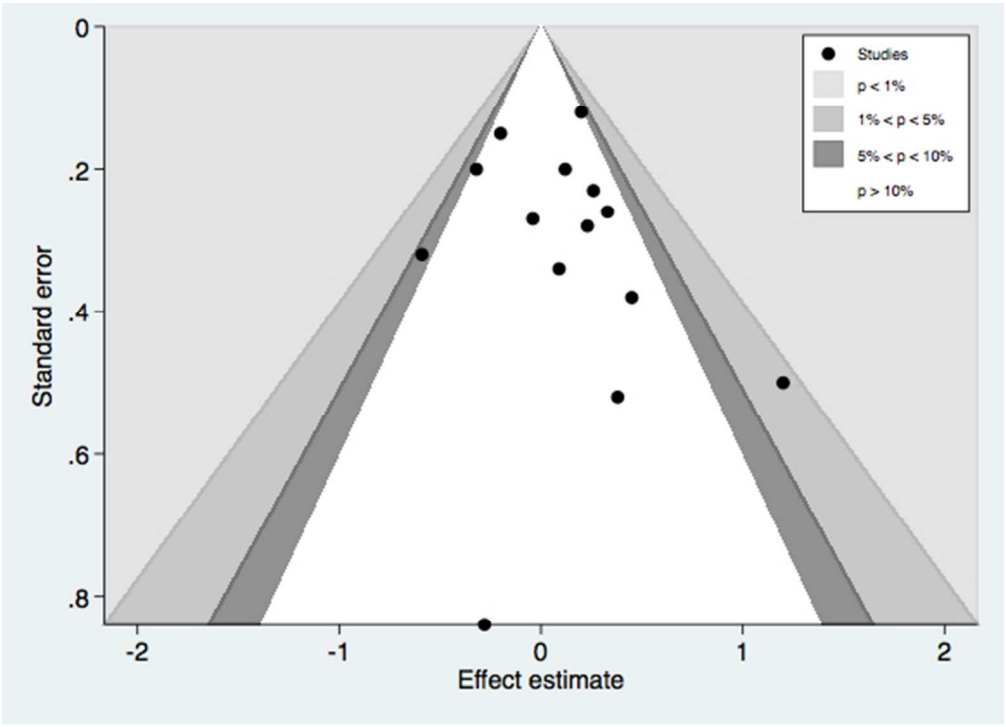

Figure 2b: Funnel plot showing the systematic heterogeneity of the studies included.
(Fig 2)
98x70mm (150 x 150 DPI)

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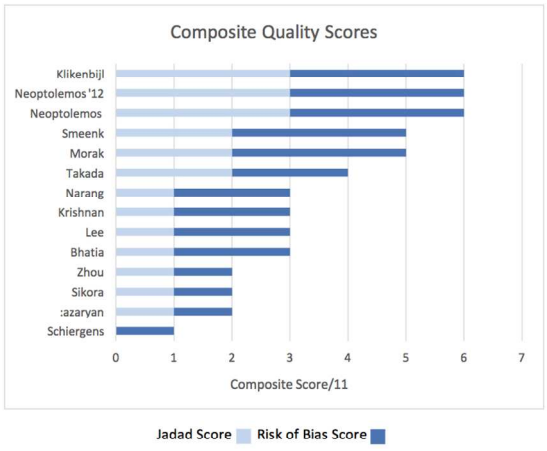

Figure 3: Chart showing the quality scores achieved by each of the included studies.
Figure 3
209x296mm (150 x 150 DPI)

Study	Year	Country	Type	Inclusion Definition	N	M:F	Age	Treatments	Timing of Adjuvant Therapy	Group	T Stage				5 year OS	P-value
											1	2	3	4		
Bhatia	2006	USA	Retro Cohort	Adenocarcinoma directly involving papilla, ampulla and peri-ampullary region if the ampulla was grossly involved	125	70:55	67 (29-89)	RT dose 50.4 Gy (45-59Gy) in 28f (29) 5-FU 400-500mg/m^2 bolus (25) 5-FU 225mg/m^2 infusion (4)	3 days at the beginning and end of radiotherapy regime 45 days after surgery	Control (96) Adjuvant (29) *Control (30) *Adjuvant (24)	48	39	36	2	11 48 13 50	0.01
Lee	2000	USA	Retro Cohort	In situ or dysplastic disease or carcinoma with bulk of disease in ampulla	39	29:10	65 (42- 78)	RT dose 48.6Gy (45- 60Gy) (13) 5-FU bolus (4) 5-FU 96 hr infusion (9)	NS	Control (26) Adjuvant (13)	11 1	7 6	8 6	0 0	47^ 81^	0.13
Klikenbijl	2000	Netherlands	RCT	Peri-ampullary-papilla, duodenal and distal ductal	76	NS	61 (24-80)	RT dose 40Gy 5-FU infusion 197mg/kg (99-275mg/kg) (31)	Day before RT then 0,3,5 days depending on toxicity	Control (41) Adjuvant (35)	2 3	22 13	16 19	0 0	36 38	0.74
Krishnan	2008	USA	Retro Cohort	Ampullary adenocarcinoma only	96	57:39	64 (28-87)	RT dose 50.4Gy (45-55.8Gy) (29) 5-FU 300mg/m^2 (29) Capecitabine 800-900mg/m^2 (24) Cisplatin (2)	Twice a day during RT for 36 days.	Control (41) Adjuvant (55)	17 12	18 16	4 26	2 2	69 60	0.53
Lazaryan	2011	USA	Retro Cohort	Ampullary adenocarcinoma only	72	42:30	72 (36-88)	RT (24) 5-FU (19) Gemcitabine (5)	NS	Control (47) Adjuvant (23)	25	37	7	0	78 61	0.04
Morak	2008	Netherlands	RCT	Peri-ampullary (distal ductal or papilla of Vater)	120	58:62	69 (33-75) 62 (36-79	5-FU 600mg/m^2 day 2(59) Cisplatin day 5 60mg/m^2 (59)	5 day regime, 6 cycles for 4 weeks	Control (61) Adjuvant (59)	0 0	11 11	40 41	10 7	13 25	0.25

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Narang	2011	USA	Retro/ Pros Cohort	Ampullary adenocarcinoma centered on or associated with in situ carcinoma of papilla or ampulla	186	109:77	68 (29-90)	RT dose 50.4Gy (37.8-50.4Gy) 5-FU (63) Gemcitabine (3)	4 weeks with 2 week rest	Control (120) Adjuvant (66)	37 8	46 20	33 34	4 4	37.2 42.1	0.84
Neoptolemos	2004	UK	RCT	Pancreatic and peri-ampullary	289	170:119	62 (52- 68) 61 (55-66)	RT dose 20Gy 5-FU 425mg/m^2 (145) Leucovorin 20mg/m^2 (145)	5 out of 28 days, 6 cycles	Control (144) Adjuvant (145)	-	-	-	-	10 20	0.05
Neoptolemos	2012	UK	RCT	Ampullary, intra-pancreatic ductal, non-descript or peri-ampullary duodenal	287	177:110	62 (55-69)	5-FU bolus 425mg/m^2 (143)	5 out of 28 days, 6 cycles	Control (144) Adjuvant (143)	34 24	41 36	56 69	11 7	36 40	NS
Schiergens	2015	Germany	Pros Cohort	In situ carcinoma and involvement of ampulla of Vater	95	52:43	65 (32-84)	Gemcitabine (34)	NS	Control (61) Adjuvant (34)	-	45	-	50	45 35	0.83
Sikora	2004	India	Retro series	Ampullary- no further definition	104	76:28	50 (40-60)	RT dose 50.4Gy 5-FU 325-500mg/m^2 (49)	5 days repeated at 4 week interval for 6 months Or bolus weekly for 12 cycles	Control (55) Adjuvant (49)	-	73	31	0	28 38	0.3
Smeenk	2007	Netherlands	RCT	Peri-ampullary (ampulla of Vater, peri-ampullary duodenal and distal ductal)	97	NS	60 (23-79)	RT dose 40Gy 5-FU 197mg/kg (99-275mg/kg)	Day before RT then 0,3,5 days depending on toxicity	Control (50) Adjuvant (47)	5 5	23 16	19 25	1 1	42 40	0.92
Takada	2002	Japan	RCT	Ampullary- no further definition	48	24:24	61 (37-74)	MMC 6mg/m^2 (24) 5-FU 300mg/m^2 (24)	5 days on week 1 and 3 postop tem daily oral 5FU	Control (24) Adjuvant (24)	0 0	9 11	15 9	4 0	34 28	>0.05

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									until recurrence							
Zhou	2009	USA	Retro Cohort	Ampullary adenocarcinoma directly from papilla or ampulla	111	67:44	66 (29-90)	RT 50.4Gy (38.7-54Gy) 5-FU (37) Capecitabine (10) Gemcitabine (3)	NS	Control (61) Adjuvant (50)	16 2	27 17	16 27	2 4	38 35	0.22

OS Overall Survival *NS* Not stated

Retro. Retrospective, *Pros.* Prospective, *RCT* Randomised Control Trial. *Control* group represents those whom had a surgery-alone treatment paradigm.

RT Radiotherapy, *5-FU* 5-Fluorouracil, *MMC* Mitomycin C, *Gy* Gray, *Whipple's* Classic pancreaticoduodenectomy, *PPPD* Pylorus Sparing pancreaticoduodenectomy

**54 Node positive patients with Kaplan Meier data available*

^ 3-year survival

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Study	Year	WHO Toxicity Grade				Other stated adverse events
		1	2	3	4	
Bhatia	2006	NS				
Lee	2000	NS				
Klikenbijl	2000	Haematological	NS	Nausea (7)	Sepsis (1)	
Krishnan	2008	NS				
Lazaryan	2011	NS				
Morak	2008	NS		Haematological (11)	Haematological (2)	Catheter related (5) Discontinuations (13)
Narang	2011	NS	Nausea (17) Diarrhoea (11) -Weight loss (6) Fatigue (6) Pain (5)	Haematological (1) Sepsis (1)	NS	Discontinuations (8)
Neoptolemos	2004	NS		Haematological (7) Stomatitis (9) Diarrhoea (6) Other (7)		-
Neoptolemos	2012	NS		Haematological (101) Diarrhoea (25) Stomatitis (16) Fatigue (26) Alopecia (1) Nausea (11)		-
Schiergens	2015	NS				
Sikora	2004	Haematological (30) Non-haematological (34)		Haematological (3) Diarrhoea (2) Obstruction (1)		Late diarrhoea/colic (20)
Smeenk	2007	Unspecified (35)		Nausea (7) Diarrhoea (1) Constipation (1)	NS	Duodenal Ulcer (1)
Takada	2002	NS	Haematological (3) Anorexia (5) Nausea (3)	NS		
Zhou	2009	NS				Nausea (14) Diarrhoea (6) Pain (5) Fatigue (4) Weight loss (4) Mucositis (3) Haematological (3) Dermatological (2)

Table 2: Table showing the toxicity related events presented in the fourteen studies. *NS* Not stated

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Table 3. The influence of the T-stage, nodal status and the grade of differentiation on overall survival as assessed by meta-regression. *Std Err.* Standard Error. *Coefficient*. Regression Coefficient

Meta-regression analysis					
T- Stage of the Tumor		**Nodal Status**		**Grade of Differentiation**	
Coefficient (Std Err.)	P-Value	Coefficient (Std Err.)	P-Value	Coefficient (Std Err.)	P-Value
-0.14 (0.06)	0.04	-0.38 (0.23)	0.12	-0.11 (0.18)	0.57

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Appendix 1a: Jadad appraisal of the fourteen included studies. *0*-not stated, *-1*- stated but inappropriate, *+1*- stated and appropriate.

Study	Year	Randomised? (0/1)	Method of Randomisation? (-1/0/1)	Double blinded? (0/1)	Method of Blinding? (-1/0/1)	Withdrawals described? (0/1)	Total (5)
Schiergens	2015	0	0	0	0	0	0
Lazaryan	2011	0	0	0	0	1	1
Sikora	2004	0	0	0	0	1	1
Zhou	2009	0	0	0	0	1	1
Bhatia	2006	0	0	0	0	1	1
Lee	2000	0	0	0	0	1	1
Krishnan	2008	0	0	0	0	1	1
Narang	2011	0	0	0	0	1	1
Takada	2002	1	0	0	0	1	2
Morak	2008	1	0	0	0	1	2
Smeenk	2007	1	0	0	0	1	2
Neoptolemos	2004	1	1	0	0	1	3
Neoptolemos	2012	1	1	0	0	1	3
Klikenbijl	2000	1	1	0	0	1	3

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Appendix 1b: Risk-of-Bias score of the fourteen included studies. *0*-not stated, *-1*- stated but inappropriate, *+1*- stated and appropriate.

Study	Year	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcomes	Freedom from Selective Reporting	Freedom from other Bias	Risk-of-bias/6
Schiergens	2015	1	0	0	1	0	-1	1
Lazaryan	2011	1	0	0	0	1	-1	1
Sikora	2004	1	0	0	0	1	-1	1
Zhou	2009	1	0	0	1	0	-1	1
Bhatia	2006	1	0	0	1	1	-1	2
Lee	2000	1	0	0	1	1	-1	2
Krishnan	2008	1	0	0	1	1	-1	2
Narang	2011	1	0	0	1	1	-1	2
Takada	2002	1	0	0	1	1	-1	2
Morak	2008	1	-1	0	1	1	1	3
Smeenk	2007	1	0	0	1	1	0	3
Neoptolemos	2004	1	0	0	1	1	0	3
Neoptolemos	2012	1	1	0	1	1	-1	3
Klikenbijl	2000	1	0	0	1	0	1	3

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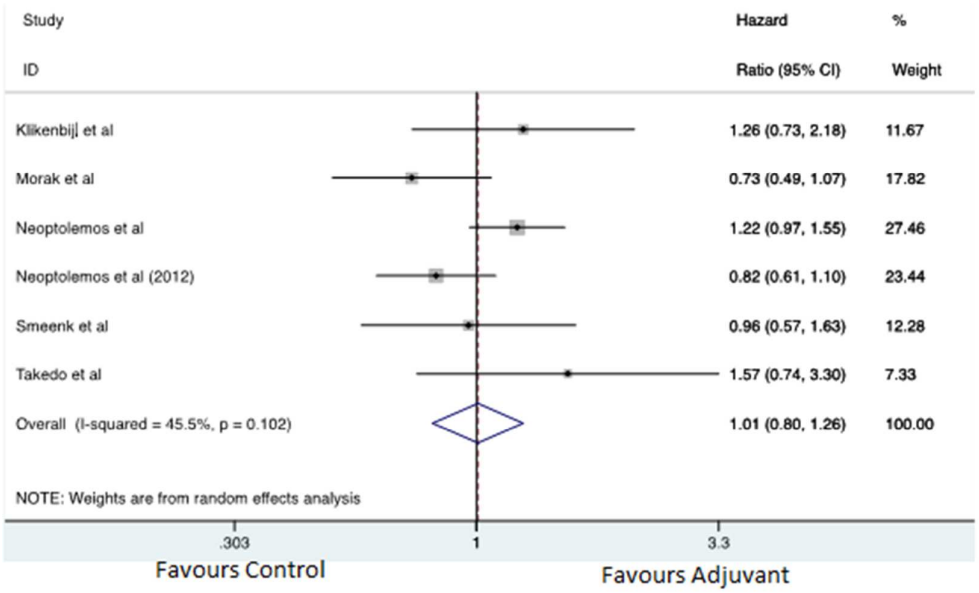
Appendix 2a: Forest plot showing the hazard ratios associated with each of the six RCT studies and the pooled overall hazard ratio. The weight contributed by each study is shown as a percentage.



Appendix 2b: Funnel plot showing the systematic heterogeneity of the six RCT studies included.