Assessment of the effect of interval from presentation to surgery on outcome in patients with peri-ampullary malignancy

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Abstract

Background

Delay between diagnosis of peri-ampullary cancer (PC) and surgery may allow tumour progression and affect outcome. This study aims to explore associations of interval to surgery (IS) with pathological outcomes and survival in patients with PC.

Method

A database review of all patients undergoing surgery between 2006 and 2014 was undertaken. IS was measured from diagnosis by imaging. Potential association between IS and survival was measured using Cox regression analysis, and between IS and pathological outcome with multivariate logistic analysis.

Results

388 patients underwent surgery. The median IS was 49 days (1-551 days), and was not associated with any of the evaluated outcomes in patients with pancreatic (149) or distal bile duct (46) cancer. For patients with ampullary cancer (71) longer IS was associated with improved survival, with median survival of 1.3, 3.1 and 4.3 years for patients waiting <1 (9), 1-2 (37) and >2 (25) months for surgery (p=0.036). A higher rate of margin positivity (31.4%) was also noted among patients who waited less than the median IS compared to those waiting longer than this interval (11.4%) (p=0.032).

Conclusion

For patients with ampullary cancer there is a paradoxical improvement in outcome among those with a longer IS, which may be explained by progression to inoperability of more aggressive lesions.

Introduction

Peri-ampullary cancer (PC) most commonly originates within the pancreas, the distal common bile duct, or the duodenal ampulla. The organ of origin of PC is usually determined by pathological examination after resection and has important implications for prognosis. Five-year survival after surgical resection varies from 6.5%-20% for pancreatic cancer [1-7], 19.2%-30% for bile duct cancer [1, 3, 5, 6, 8, 9] and 33%-45% for ampullary cancer [1, 3, 5, 6]. The majority of tumours are however inoperable at the time of presentation due to local invasion or the presence of distant metastases. For operable tumours there will usually be an interval between radiological diagnosis and surgery, to allow referral, assessment and operative planning. In England, the National Cancer Plan stipulates a maximum interval of 62 days from primary referral to treatment for most solid cancers [10], although this figure is not based on evidence of safety for each tumour type. Tumour progression may take place during this interval, rendering tumours inoperable due either to local invasion or the development of metastases, and long-term survival may be affected.

Within any patient cohort there is likely to be a range of intervals between diagnosis and surgery, with some patients undergoing surgery very quickly, and some waiting many months. As PC is an aggressive malignancy, this period may constitute a significant part of the natural history of the disease. Analysis of the potential association of interval to surgery with pathological and surgical outcomes may reveal aspects of the behaviour of these tumours, and determine if the 62 day target to surgery disadvantages patients by allowing tumour progression.

This study aimed to investigate the interval to surgery in a consecutive series of patients undergoing surgery with the intention to resect PC and to explore associations with resectability, tumour stage and overall survival.

Material and methods

Review of a prospectively maintained database of consecutive patients undergoing surgical exploration for suspected PC between January 2006 and May 2014 was undertaken. Referrals came from five hospitals in a cancer network with a population of 1.7 million. The study cohort included patients with a histological diagnosis of pancreatic, bile duct or ampullary cancer, or those where the tumour was unresectable and biopsy confirmed the presence of adenocarcinoma. Patients receiving neoadjuvant chemotherapy were excluded. No patients were excluded from surgery due to disease progression in the interval between referral and surgery. Demographic and clinical data were retrieved. Pre-operative biliary obstruction was defined as any abnormality in liver function tests sufficient to prompt investigation by cross sectional imaging. As the time of receipt of the initial referral is variable and subject to administrative delays, the interval to surgery (IS) was measured from the date of the first imaging modality undertaken which raised the possible diagnosis of pancreatic head malignancy to the time of the surgical intervention, by review of individual radiology records. Surgical resection was performed by a classic Whipple resection with reconstruction by pancreatico-gastrostomy. Pathological reporting was undertaken according to Royal College of Pathologists guidelines[11] with axial slicing of the resection specimen. Tumours were classified according to histological origin (pancreatic, bile duct or ampullary) and nodal status and margin involvement status were retrieved from histology reports.

Continuous variables were compared with Kruskal-Wallis test and categorical variables by Chi square test. The mean and variance of tumour size across different tumour types were compared using Bayesian double generalised linear models.

Dates of death were determined by access to General Practice records and survival times calculated from the time of diagnosis. Kaplan-Meier survival analysis and Cox Proportional Hazard models were used to assess the effect of potential influence of monthly time intervals to surgery on post-operative survival. Multivariate logistic models were then used to explore potential associations between pre-operative variables including IS as a binary variable (< or ≥ median) with histological tumour stage.

Results

388 patients (223 males) of median age 67 years fulfilling the study criteria underwent surgical exploration during the study period and resection was completed in 266 cases (68.6%). In 122 patients the tumour was found to be inoperable due to local invasion of vascular structures (70) or the development of distant metastases (47). Operative details could not be retrieved in three patients, tumour mass could not be identified in one patient and one patient did not tolerate surgery. Lateral resections of a small venous patch were undertaken in 32 patients. The median IS for 388 patients was 49 (1-551) days, and was similar in groups undergoing resection (49 days, range 1-551) or surgical exploration only (50 days, range 11-512) (P=0.940). The IS in 331 patients (85.3%) with biliary obstruction at the time of initial presentation was 47 days (1-512) compared to 69 (14-551) in those without this complication (p=0.001). Pancreatic tumours were noted to be larger than both ampullary and bile duct tumours (Table 1). In regression analysis the variance in size of ampullary tumours was noted to be greater than both pancreatic tumours (coefficient = -1.075; credible interval -1.441 to -0.704) and bile duct tumours (coefficient = -0.63; credible interval -1.096 to -0.165).

After minimum follow-up of 12 months the median survival (range) from diagnosis of the whole cohort was 17.2 months (1.4-114.6) and was significantly longer in patients

undergoing surgical resection (23.7 months, range 1.5-114.6) compared to those having surgical exploration only (11.2 months, range 1.4-75.7) The median survival (range) of patients undergoing resection of pancreatic, bile duct and ampullary cancer was 17.3 (1.5-114.6), 28.1 (5.8-104) and 33.3 (2.1-107.1) months respectively. No patients were lost to follow-up. Pre-operative IS was not associated with survival for patients undergoing resection of pancreatic or bile duct cancer, but a positive association was noted for patients with ampullary cancer (Figure 1). Cox regression analysis of survival data confirmed the reduced hazard of death at any time after surgery associated with a longer IS in patients with ampullary cancer only (Table 2). Multivariable analysis of potential associations between pre-operative factors and histological outcomes and survival confirms the reduced risk of positive resection margin in patients with a longer interval to surgery (Table 3). The proportion of ampullary cancer specimens removed within less than the median IS (49 days) with involved margins was 31%, compared to 11.4% among those removed after this interval from diagnosis (p=0.032). An association between tumour size with age and female gender is also noted (Table 3).

Discussion

Patients with PC may suffer significant delays between presentation and surgery. This may be contributed to by the vague nature of symptoms at the time of presentation [12, 13], the need for biliary drainage [14], delays incurred during referral to regional centres and capacity issues restricting access to operating time. Because of perceived delays in the treatment of cancer cases NHS guidelines introduced a target of 62 days from referral to treatment for most solid tumours in 2000 [10]. Concerns may be raised that this delay will reduce the operability of the pancreatic head lesion, allow tumour progression and impair long-term survival. The main finding of this study is that no association is noted between delay to surgery and any outcome in patients with pancreatic or distal bile duct cancer, but that a longer interval to surgery is

paradoxically associated with improved outcome in patients with ampullary cancer. A proportional increase in survival is noted with each extra months delay prior to surgery associated with a hazard ratio of death of 0.55 after surgical resection. In corroboration of this finding the chance of an involved resection margin is also reduced for patients with ampullary cancer who wait longer for surgery.

In this series a high percentage of resected patients were shown to have ampullary cancer (26%). This is consistent with the adoption of a standardised pathological reporting protocol, which has led to higher rates of diagnoses other than pancreatic cancer in peri-ampullary malignancy [15, 16]. PC usually presents with biliary obstruction caused by mass effect and operability is determined by the sequence of invasion, as vascular invasion is a major cause of irresectability [17-19]. Lesions of the ampulla lie furthest from the vascular structures and may be less likely to be inoperable than lesions of the pancreatic parenchyma, which encases the junction between superior mesenteric and portal vein. Surgery is offered to patients who do not have invasion of vascular structures or distant metastases detected on pre-operative imaging, though these findings are often encountered at the time of surgery. This may be caused by understaging by CT scan [20] or by tumour progression in the interval to surgery, which is more likely in aggressive tumours. These results suggest that for pancreatic and bile duct tumours the timing of surgery in relation to pre-operative imaging within the range measured in the study has no effect on resectability, tumour stage or survival after resection. This implies that the operative findings and surgical outcome are determined before imaging takes place and these tumours change little in the interval to surgery. For ampullary tumours however it appears that a longer wait for surgery results in selection of a subset of patients whose tumours remain resectable, with better prognostic characteristics, as shown by the reduced risk of an involved resection margin and improved long-term survival. This may be explained by the progression of a more aggressive subset of ampullary tumours in the interval

to surgery leading to inoperability. This more aggressive subset probably includes older patients, in whom resected ampullary tumours are shown to be larger. In support of this concept we have noted a greater variance in size of ampullary tumours than pancreatic and bile duct tumours. Less aggressive ampullary tumours remain confined to the region of the ampulla while others progress to invade vascular structures. As ampullary tumours are located a greater distance from the vascular structures than pancreatic and bile duct tumours they are likely to cause vascular obstruction as a relatively delayed event compared to biliary obstruction. Results for the whole cohort however do not show an association between interval to surgery and resectability. It is probable that the small proportion of patients with ampullary cancer who progress to inoperability is masked in the larger group of patients with pancreatic and bile duct cancer, where IS is shown to have no effect on resectability and outcome.

In the event of inoperability usually a biopsy is taken and the presence of malignancy confirmed. Determining the organ of origin in this situation is difficult however, as this requires examination of the spatial relationship of periampullary lesions [11]. Histological tissue stains have low specificity in determining precise tumour phenotype [21]. Usually in this situation a diagnosis of adenocarcinoma is made and patients often referred for palliative treatment with chemotherapy targeted at pancreatic cancer. Our results provide indirect evidence that among this patient group there will also be patients with ampullary cancer which has progressed to involve vascular structures.

A potential weakness of this study is the variable timing of the initial imaging. Often this was performed after the development of progressive jaundice, so there was an uninterrupted time line from presentation to surgery. In some patients however an initial presentation with spontaneously resolving biliary obstruction was investigated which revealed potential PC, but the issue was not taken forward due to clinical improvement. This presentation accounts for

the very long IS in some patients. Although spontaneously resolving biliary obstruction has been reported previously in ampullary cancer [22], we have noted a similar phenomenon in pancreatic and bile duct cancer in this study. Another potential weakness is the lack of discrimination of ampullary tumours into intestinal or pancreatico-biliary phenotype. These two tumours have different anatomical and morphological characteristics, in addition to different prognosis. It is possible that the phenomenon we have observed occurs differentially in these two subsets. Distinguishing between these two phenotypes however does not form part of the Royal College of Pathologists' dataset [11].

Previous evidence has shown that delayed diagnosis and a prolonged interval to surgery has an adverse outcome in other tumour types including breast cancer [23], non-small cell lung cancer [24], and urological cancer [25]. There is little data available however on what constitutes a safe interval to surgery after diagnosis. The 62 day interval adopted as a target for treatment of most solid tumours in England was selected as a pragmatic figure without evidence of beneficial effect for each tumour type. Although there is evidence that late diagnosis has a negative effect on outcome in pancreatic cancer, as shown by the low resection rate [26], the study shows that following symptomatic presentation delay of up to two months prior to resection has no further effect on outcome in pancreatic and bile duct cancer. For ampullary cancer however a delay to surgery within the 62 day target period has a measurable effect, with some lesions progressing to inoperability and improved outcome of the selected cases which remain resectable. This finding has significant implications for planning surgery in patients with PC, as the final histological tumour type is not known until surgery is completed, and early surgery for these patients is therefore preferable. Also these findings suggest that in some patients with inoperable PC the tumour may originate within the ampulla, rather than the pancreas. This may have implications for the selection of palliative chemotherapy in this patient group.

The authors declare no conflict of interest

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Confirmation was obtained from the South West Health Research Authority that under the harmonised Guidance Approval for Research Ethics Committees (REC), REC review was not required because patient data was collected in the course of their normal hospital care and was anonymised for research purposes. No patient consent was required for this study.

N=266		Cancer Origin			p
		Pancreas (149)	Bile duct (46)	Ampulla (71)	
Median age (range)		67.9 (41.3- 82.1)	65.7 (43.7-84.1)	66.2 (411.2-86.4)	.312
Gender (% male)		55	69.6	53.5	.171
ASA	I	6	4	9	.056
	2	84	22	42	
	3	44	15	14	
	4	1	0	0	
	Missing	14	5	6	
Median IS (range) (days)		48 (1-551)	50 (5-294)	51 (14-477)	.881
Median tumour size (range) (mm)		30 (12-70)	22 (10-70)	25 (5-80)	.002
Involved lymph nodes (%)		127 (85.2)	26 (56.5)	40 (56.3)	.0001
Involved resection margin (%)		119 (79.9)	23 (50)	15 (21.1)	.0001
30 day post-operative mortality (%)		3 (2)	0	3 (4.2)	0.275

Table 1. Interval to surgery and pathological outcome among 266 patients undergoing resection of peri-ampullary cancer.

Tumour type	Exponent	95% confidence interval of exponent	p
Pancreas (149)	0.927	0.716-1.199	0.562
Bile duct (46)	0.769	0.397-1.489	0.435
Ampulla (71)	0.555	0.320-0.963	0.036*

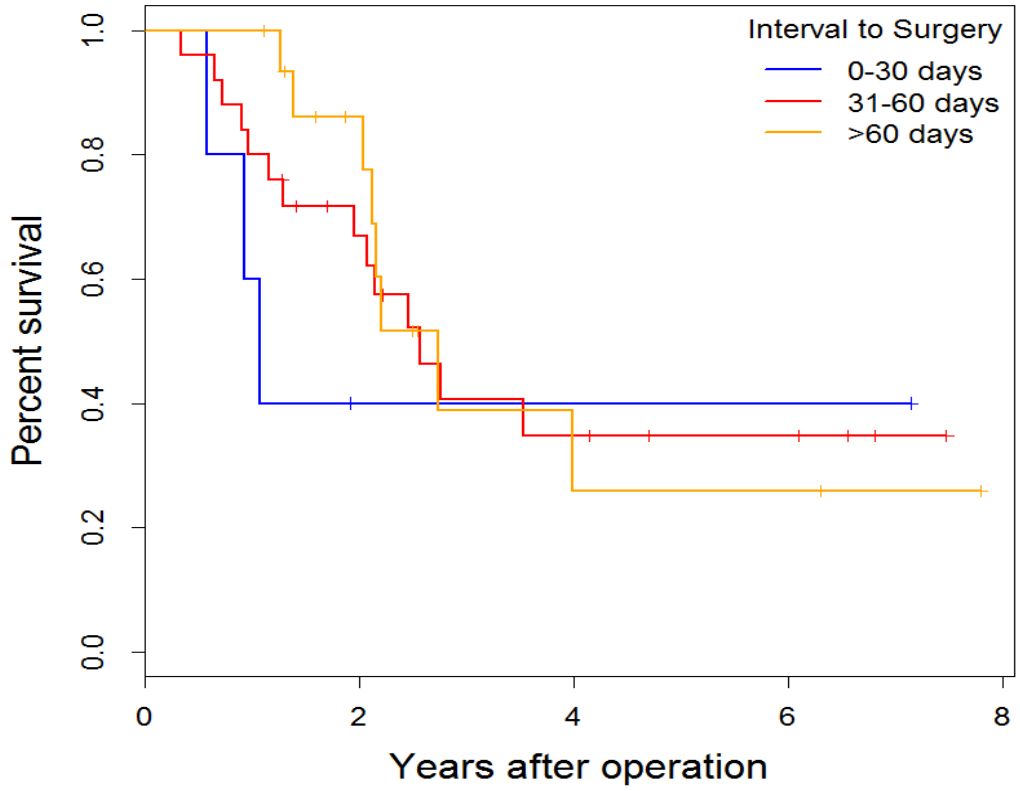
Table 2. Cox regression analysis of association of interval to surgery with survival of patient cohorts, determined by tumour origin.

	Tumour Size			Nodal status			Resection margin status		
	Co-efficient	SD	p	Co-efficient	SD	p	Co-efficient	SD	p
Interval to surgery (< or > median)	-0.140	0.134	0.232	-0.504	0.514	0.326	-1.486	0.691	0.032*
Gender	-0.510	0.119	0.000*	-0.670	0.525	0.202	-0.230	0.646	0.722
Age	-0.017	0.006	0.005*	-0.004	0.026	0.878	-0.004	0.033	0.912
Biliary obstruction at presentation	-0.161	0.165	0.312	0.846	0.702	0.228	-0.884	0.834	0.289

Table 3. Multivariate analysis of potential associations with tumour size, nodal status and resection margin status among 71 patients undergoing resection of ampullary cancer

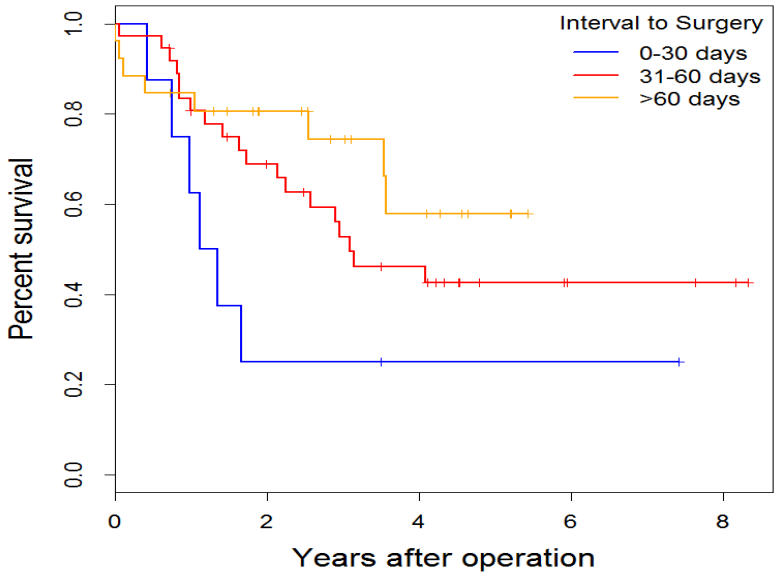
Number at risk (Pancreatic cancer)

Years	0	2	4	6	8
0-30 days	33	11	5	3	2
30-60 days	69	21	5	2	1
>60 days	47	12	5	0	



Number at risk (Bile duct cancer)

Years	0	2	4	6	8
0-30 days	5	2	1	1	0
30-60 days	25	14	5	4	0
>60 days	16	10	2	2	1



Number at risk (Ampullary cancer)

Interval to surgery/Years	0	2	4	6	8
0-30 days	8	2	1	1	0
30-60 days	37	22	12	5	2
>60 days	26	18	7	0	

Figure 1. Survival curves of patients undergoing pancreatic head resection for a) pancreatic (149), b) bile duct (46) and c) ampullary cancer (71), divided into subsets determined by the interval to surgery from initial investigation.

References

1. Chen SC, Shyr YM, Wang SE. Longterm survival after pancreaticoduodenectomy for periampullary adenocarcinomas. *HPB* : the official journal of the International Hepato Pancreato Biliary Association. 2013;15(12):951-957.

2. Cleary SP, Gryfe R, Guindi M, Greig P, Smith L, Mackenzie R, et al. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. *JACS*. 2004;198(5):722-731.

3. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periampullary adenocarcinoma: analysis of 5-year survivors. *Annals of surgery*. 1998;227(6):821-831.

4. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *JOCS* : official journal of the Society for Surgery of the Alimentary Tract. 2000;4(6):567-579.

5. Riall TS, Cameron JL, Lillemoe KD, Winter JM, Campbell KA, Hruban RH, et al. Resected periampullary adenocarcinoma: 5-year survivors and their 6- to 10-year follow-up. *Surgery*. 2006;140(5):764-772.

6. He J, Ahuja N, Makary MA, Cameron JL, Eckhauser FE, Choti MA, et al. 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. *HPB* : the official journal of the International Hepato Pancreato Biliary Association. 2014;16(1):83-90.

7. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Buchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg*. 2004;91(5):586-594.

8. DeOliveira ML, Cunningham SC, Cameron JL, Kamangar F, Winter JM, Lillemoe KD, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Annals of surgery*. 2007;245(5):755-762.

9. Jang JY, Kim SW, Park DJ, Ahn YJ, Yoon YS, Choi MG, et al. Actual Long-term Outcome of Extrahepatic Bile Duct Cancer After Surgical Resection. *Annals of surgery*. 2005;241(1):77-84.

10. Department of Health. Referral guidelines for suspected cancer 2000. Available from: http://www.doh.gov.uk/pub/docs/doh/guidelines.pdf.

11. The Royal College of Pathologists | Publications | Datasets and Tissue pathways for gastrointestinal and pancreatobiliary pathology 2009 [cited 2015 18.05.2015]. Available from: http://www.rcpath.org/publications-media/publications/datasets.

12. Chauhan A, Pai C, Binu V. Clinical Profile of Patients With Periampullary Carcinoma. *GCR*. 2010(Suppl 1):S28.

13. DiMagno EP. Pancreatic cancer: clinical presentation, pitfalls and early clues. *Annals of oncology*. 1999;10 Suppl 4:140-142.

14. Roque J, Ho SH, Goh KL. Preoperative drainage for malignant biliary strictures: is it time for self-expanding metallic stents? *Clinical endoscopy*. 2015;48(1):8-14.

15. Pomianowska E, Grzyb K, Westgaard A, Clausen OP, Gladhaug IP. Reclassification of tumour origin in resected periampullary adenocarcinomas reveals underestimation of distal bile duct cancer. *EJSO*. 2012;38(11):1043-1050.

16. Katz MH, Bouvet M, Al-Refaie W, Gilpin EA, Moossa AR. Non-pancreatic periampullary adenocarcinomas: an explanation for favorable prognosis. *Hepato-gastroenterology*. 2004;51(57):842-846.

17. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. *Gut*. 2005;54 Suppl 5:v1-16.

18. Beger HG, Rau B, Gansauge F, Poch B, Link KH. Treatment of pancreatic cancer: challenge of the facts. *WJS*. 2003;27(10):1075-84.

19. Lu DS, Reber HA, Krasny RM, Kadell BM, Sayre J. Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *AJR*. 1997;168(6):1439-1443.

20. Bluemke DA, Cameron JL, Hruban RH, Pitt HA, Siegelman SS, Soyer P, et al. Potentially resectable pancreatic adenocarcinoma: spiral CT assessment with surgical and pathologic correlation. *Radiology*. 1995;197(2):381-385.

21. Duval JV, Savas L, Banner BF. Expression of cytokeratins 7 and 20 in carcinomas of the extrahepatic biliary tract, pancreas, and gallbladder. *Arch Pathol Lab Med.* 2000;124(8):1196-1200.

22. Everett MT. Intermittent jaundice in ampullary carcinoma. *Br J Surg*. 1968;55(7):557-558.

23. Richards MA, Smith P, Ramirez AJ, Fentiman IS, Rubens RD. The influence on survival of delay in the presentation and treatment of symptomatic breast cancer. *BJC*. 1999;79(5-6):858-64.

24. Myrdal G LM, Hillerdal G, Lamberg K, Agustsson T, Ståhle E. Effect of delays on prognosis in patients with non-small cell lung cancer. *Thorax*. 2004;59(1):45-49.

25. Bourgade V, Drouin SJ, Yates DR, Parra J, Bitker MO, Cussenot O, et al. Impact of the length of time between diagnosis and surgical removal of urologic neoplasms on survival. *World J Urol*. 2014;32(2):475-479.

26. Picozzi VJ, Delgado EC, Neil NJ, Malpass TW. Delay in diagnosis and treatment of pancreas cancer: The experience of a tertiary referral center. Gastrointestinal Cancers Symposium; San Francisco, California 2009.