Modern Pathology (2020) 33:657–664
https://doi.org/10.1038/s41379-019-0373-y

ARTICLE

RET gene rearrangements occur in a subset of pancreatic acinar cell carcinomas

Angela Chou[1,2,3,4] · Ian S. Brown[5,6] · M. Priyanthi Kumarasinghe[7] · Aurel Perren[8] · Denise Riley[9] · Yoomee Kim[9] · Marina Pajic[3,10] · Angela Steinmann[3] · Vivek Rathi[11,12] · Nigel B. Jamieson[13] · Joanne Verheij[14] · Stijn van Roessel[15] · Chris B. Nahm[2,16] · Anubhav Mittal[2,16] · Jaswinder Samra[2,16] · Anthony J. Gill[1,2,3,4]

Received: 21 May 2019 / Accepted: 7 September 2019 / Published online: 26 September 2019

Abstract

Pancreatic acinar cell carcinoma is relatively rare (1 to 2% of pancreatic malignancies) but may be under-recognized. In contrast to pancreatic ductal adenocarcinoma, most acinar cell carcinomas lack mutations in *KRAS*, *DPC*, *CDKN2A* or *TP53*, but appear to have a high incidence of gene rearrangements, with up to 20% reported to be driven by *BRAF* fusions. With the development of a new class of RET-specific tyrosine kinase inhibitors, which appear to have particularly strong activity against *RET* gene rearranged tumours, there is now considerable interest in identifying *RET* gene rearrangements across a wide range of cancers. *RET* rearrangements have been reported to occur at a very low incidence (<1%) in all pancreatic carcinomas. We postulated that given its unique molecular profile, *RET* gene rearrangements may be common in acinar cell carcinomas. We performed fluorescent in-situ hybridization (FISH) studies on a cohort of 40 acinar cell spectrum tumours comprising 36 pure acinar cell carcinomas, three pancreatoblastomas and one mixed acinar-pancreatic neuroendocrine tumour. *RET* gene rearrangements were identified in 3 (7.5%) cases and *BRAF* gene rearrangements in 5 (12.5%). All gene rearranged tumours were pure acinar cell carcinomas. Our findings indicate that amongst all pancreatic carcinomas, acinar carcinomas are highly enriched for potentially actionable gene rearrangements in *RET* or *BRAF*. FISH testing is inexpensive and readily available in the routine clinical setting and may have a role in the assessment of all acinar cell carcinomas—at this stage to recruit patients for clinical trials of new targeted therapies, but perhaps in the near future as part of routine care.

✉ Anthony J. Gill
affgill@med.usyd.edu.au

1 Cancer Diagnosis and Pathology Group, Kolling Institute of Medical Research, Royal North Shore Hospital, St Leonards, NSW, Australia

2 University of Sydney, Sydney, NSW, Australia

3 The Kinghorn Cancer Centre and Garvan Institute of Medical Research, Darlinghurst, NSW, Australia

4 NSW Health Pathology, Department of Anatomical Pathology, Royal North Shore Hospital, St Leonards, NSW, Australia

5 Envoi Specialist Pathologists, Kevin Grove, QLD, Australia

6 Department of Anatomical Pathology, Central Laboratory, Pathology Queensland, Herston, QLD, Australia

7 Pathwest Laboratory Medicine, QE2 Medical Centre, Perth, WA, Australia

8 Institute of Pathology, University of Bern, Bern, Switzerland

9 Department of Anatomical Pathology, SYDPATH, St Vincent's Hospital, Darlinghurst, NSW, Australia

10 St Vincent's Clinical School, Faculty of Medicine, University of NSW, Sydney, NSW, Australia

11 Department of Anatomical Pathology, St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia

12 The University of Melbourne, Fitzroy, VIC 3065, Australia

13 Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Garscube Estate, Glasgow, Scotland, UK

14 Department of Pathology, Cancer Centre Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

15 Department of Surgery, Cancer Centre Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

16 Upper GI Surgical Unit, Royal North Shore Hospital, St Leonards, NSW, Australia

Introduction

Pancreatic acinar cell carcinoma is a relatively rare neoplasm which accounts for less than 1–2% of pancreatic malignancies in adults and ~15% of pancreatic malignancies in children where there is some morphological and clinical overlap with pancreatoblastoma (differentiated from acinar cell carcinoma by the presence of squamous morules) [1–3]. Early reports suggested a 3-year survival as low as 26% and a mean survival of 18 months with ~50% of patients presenting with metastatic disease [1, 4, 5]. More recent data have indicated an improved 5-year survival of 43% (up to 72% if undergoing resection; 22% for those who are inoperable) – summarized by Klimstra et al. and La Rosa et al. [3, 6]. That is, although the prognosis is better than pancreatic ductal adenocarcinoma, the majority of patients with acinar cell carcinoma will still succumb to disease. Currently, the only effective treatment is surgery for early stage resectable tumours, with the addition of platinum-based chemotherapy for the up to 20% of acinar cell carcinomas, which may be associated with somatic or germline *BRCA* mutations [7]. Therefore new therapies for patients with metastatic disease are required.

Recently large scale genomic projects have demonstrated that the molecular characteristics of acinar carcinoma are very different to pancreatic ductal adenocarcinoma [8–10]. In contrast to pancreatic ductal adenocarcinoma which very frequently harbours mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*, somatic mutations in acinar carcinomas are very heterogeneous with recurrent mutation of individual genes being rare. However pathogenic gene rearrangements, rare in pancreatic ductal adenocarcinoma, appear to be relatively common in acinar cell carcinoma. For example, several studies have demonstrated gene rearrangements in *BRAF* in ~20% of acinar carcinomas [11–14]. Importantly these fusions, which cause downstream activation of the MAPK signalling pathway, are potentially targetable with currently available MEK inhibitors and therapeutic MEK inhibition (an established approach in melanoma) is under active investigation in *BRAF* gene rearranged acinar carcinomas [15].

The *RET* proto-oncogene located at chromosome 10q11.21 encodes for a ligand dependent receptor tyrosine kinase. Activating *RET* gene abnormalities are well recognized drivers of certain malignancies, with germline or somatic mutations being associated with up to 65% of medullary thyroid carcinomas and somatic fusions being found in 10–20% of papillary thyroid carcinomas [16, 17]. Apart from these tumours with a high incidence of *RET* gene abnormalities, *RET* mutations and fusions have been reported at a low incidence in a range of malignancies including 1–3% of non-small cell lung carcinomas and less than 1% of pancreatic carcinomas [16].

For some time mulitkinase inhibitors originally designed to target other tyrosine kinases but with non-selective action against *RET* including vandetinib, cabozantinib, lenvatinib, ponantinib, sunitinib, regorafenib and sorafenib have been available [16–18]. Results have been less impressive than with some other targeted therapies and tempered by side effects due to inhibition of other 'off-target' tyrosine kinases, however unequivocal responses have been reported particularly for cases associated with *RET* fusions [17, 19, 20].

Recently a new generation of highly specific small molecule *RET* tyrosine kinase inhibitors have been developed. These compounds which include LOXO-292 and BLU-667 have shown potential in early phase clinical trials [17, 21, 22]. For example in a recent and ongoing early phase basket trial for any malignancy harbouring *RET* fusions or mutations, LOXO-292 demonstrated an overall response rate of 77% in *RET* fusion positive malignancies of any lineage, with 92% of responses being ongoing and minimal toxicity [22, 23]. Of note two of the fusion positive patients in this trial were described as having 'pancreatic cancer' although the precise histology was not specified.

RET fusions are known to be rare in pancreatic malignancies. In one study, 1 of 160 (0.6%) of pancreatic cancers were shown to harbour a pathogenic *RET* fusion [16]. In the Australian Pancreatic Genome Initiative (APGI) and International Cancer Genome Consortium (ICGC) cohort of 456 pancreatic carcinomas only 1 (0.2%) *RET* fusion positive cancer was identified [24–26]. Of note we have reviewed the histology of this tumour and confirmed that this was an acinar cell carcinoma harbouring a *CCDC6-RET* fusion rather than a conventional pancreatic adenocarcinoma. Given the relatively low incidence of acinar carcinomas, the fact that it is molecularly distinct from pancreatic ductal adenocarcinomas and the finding that acinar cell carcinomas are known to be associated with a high incidence of *BRAF* fusions, we therefore postulated that pathogenic *RET* fusions would be relatively common in acinar cell carcinomas.

For these reasons we sought to investigate the incidence of *RET* gene rearrangements in a large cohort of acinar cell carcinomas and also took the opportunity to screen the same cohort for *BRAF* gene rearrangements.

Methods

We searched the institutional databases of multiple centres from Australia, one centre from Amsterdam, Netherlands and one centre from Bern, Switzerland for all cases recorded as pancreatic acinar cell carcinoma, pancreatoblastoma or mixed pancreatic acinar cell carcinoma-neurondocrine tumour. All cases were independently reviewed centrally by

two surgical pathologists with expertize in pancreatic pathology to confirm the diagnosis (AJG and AC). Inclusion criteria included the expression of trypsin and BCL10 by immunohistochemistry and sufficient tumour in formalin-fixed paraffin-embedded tissue blocks for further testing. All tumours also underwent beta-catenin immunohistochemistry to highlight the squamous morule component of pancreatoblastomas.

Clinicopathological data collected included tumour size, age, sex, date of surgery, type of operation, type of sample, size of tumour, metastasis at presentation, lymph node involvement, AJCC pathological stage, and mitotic rate per 10 high power fields (2 mm^2).

Fluorescent in-situ hybridization (FISH) was performed on formalin-fixed paraffin-embedded sections of tumours using Zytolight SPEC *RET* and *BRAF* dual colour break-apart probes (ZytoVision, Bremerhaven, Germany) according to the manufacturer's instructions. Both probes include green and orange labelled probes that directly hybridize to the genes. The orange probe hybridizes to the proximal end and the green probe hybridizes to the distal end of the 10q11.21 and 7q34 chromosomal regions harbouring the *RET* and *BRAF* genes respectively. A rearrangement negative tumour cell was defined by the detection of fused green and orange signals. A rearrangement positive tumour cell was defined as the presence of a split green and orange signal, which was at least two signals diameter apart (Fig. 1b, f). At least 50 tumour nuclei were counted, and for a case to be considered as positive, at least 15% of the tumour nuclei were required to demonstrate split signals. The *BRAF* FISH status of 11 cases has previously been presented in a technical report [14].

RNA from formalin-fixed paraffin-embedded tumour samples was extracted using the Qiagen MiRNeasy FFPE kit using the manufacturer's instructions. RNA library was prepared using a custom designed Ion AmpliSeq RNA panel (Thermo Fisher Scientific, Waltham, MA, USA) which covers transcripts for fusion partners with *RET, CCDC6, PRKARIA, NCOA4, GOLGA5, TRIM24* and *TRIM33*, before sequencing on the Ion GeneStudio S5 sequencer (Thermofisher Scientific). Sequence data were then analysed using the Ion report software (Thermofisher Scientific). RNA library was also prepared using a hybridization capture-based Trusight® RNA fusion panel (Illumina, San Diego, CA, USA) before sequencing on the Illumina Miseq sequencer, and sequencing data were analysed using the Illumina Basespace RNA-Seq alignment App.

Statistical analysis was performed using IBM SPSS Statistics software v23. Continuous variables were compared using the Student's *t* test and categorical variables were compared using the Fisher's exact test. A *p* value of <0.05 was considered statistically significant.

Results

Of 40 cases of confirmed pancreatic acinar cell spectrum lesions with material available for FISH studies identified, 36 were pure acinar cell carcinomas, 3 were pancreatoblastomas and one case was a mixed acinar cell carcinoma-neuroendocrine tumour. Beta-catenin immunohistochemistry demonstrated aberrant positive nuclear staining only in the squamous morular component of the three pancreatoblastomas. No other cases demonstrated nuclear staining for beta-catenin. Thirty-six cases demonstrated diffuse positive staining for trypsin and BCL10, whilst four cases showed focal staining for both markers. The clinicopathological characteristics of the cohort are summarized in Table 1. Briefly, there were 30 males and ten females. The median age was 66 years (mean 61 years, range 17–86 years). The median tumour size was 37 mm (mean 45 mm, range 13–140 mm). Nine patients presented with stage I disease, 14 with stage II disease and 12 with stage IV disease. The median mitotic rate was 5 per 10 high power fields (2 mm^2) (mean 11/hpf; range 1–44/10 hpf).

FISH testing for *RET* was successful in all 40 cases. *BRAF* testing failed in only one case where the signal intensity was too weak for interpretation. Rearrangement of the *RET* gene was found in three cases (7.5%) and *BRAF* rearrangement found in five cases (12.5%) (Fig. 1). Of note one of the three *RET* fusion positive cases (PACC12) was later confirmed to be the APGI case known to harbour *a RET-CCDC6* fusion.

Gene rearrangements were only identified in pure acinar cell carcinomas and the presence of *BRAF* and *RET* rearrangements were mutually exclusive. Morphologically, cases with *RET* or *BRAF* rearrangement did not show any distinctive features compared to cases not harbouring gene rearrangements, and all rearranged cases demonstrated diffuse strong expression for BCL10 and trypsin. The clinicopathological characteristics of the eight rearranged cases are summarized in Table 2.

Since only pure acinar cell carcinomas were positive for *RET* or *BRAF* rearrangements, univariate analysis was performed comparing gene rearrangement positive and rearrangement negative cases in the 36 pure acinar cell carcinoma cases. There was no significant difference between the two groups based on sex ($p = 0.558$), age at presentation ($p = 0.542$), size ($p = 0.638$), metastasis at presentation ($p = 0.827$), nodal involvement at presentation ($p = 0.064$), pathological stage ($p = 0.171$) and mitotic rate ($p = 0.332$) (Table 3).

The three *RET*-rearranged acinar carcinomas detected by FISH were sequenced using a custom designed Ion AmpliSeq RNA panel (Thermo Fisher Scientific) which covers transcripts for fusion partners with *CCDC6*, *PRKARIA*, *NCOA4*, *GOLGA5*, *TRIM24*, *TRIM33*.

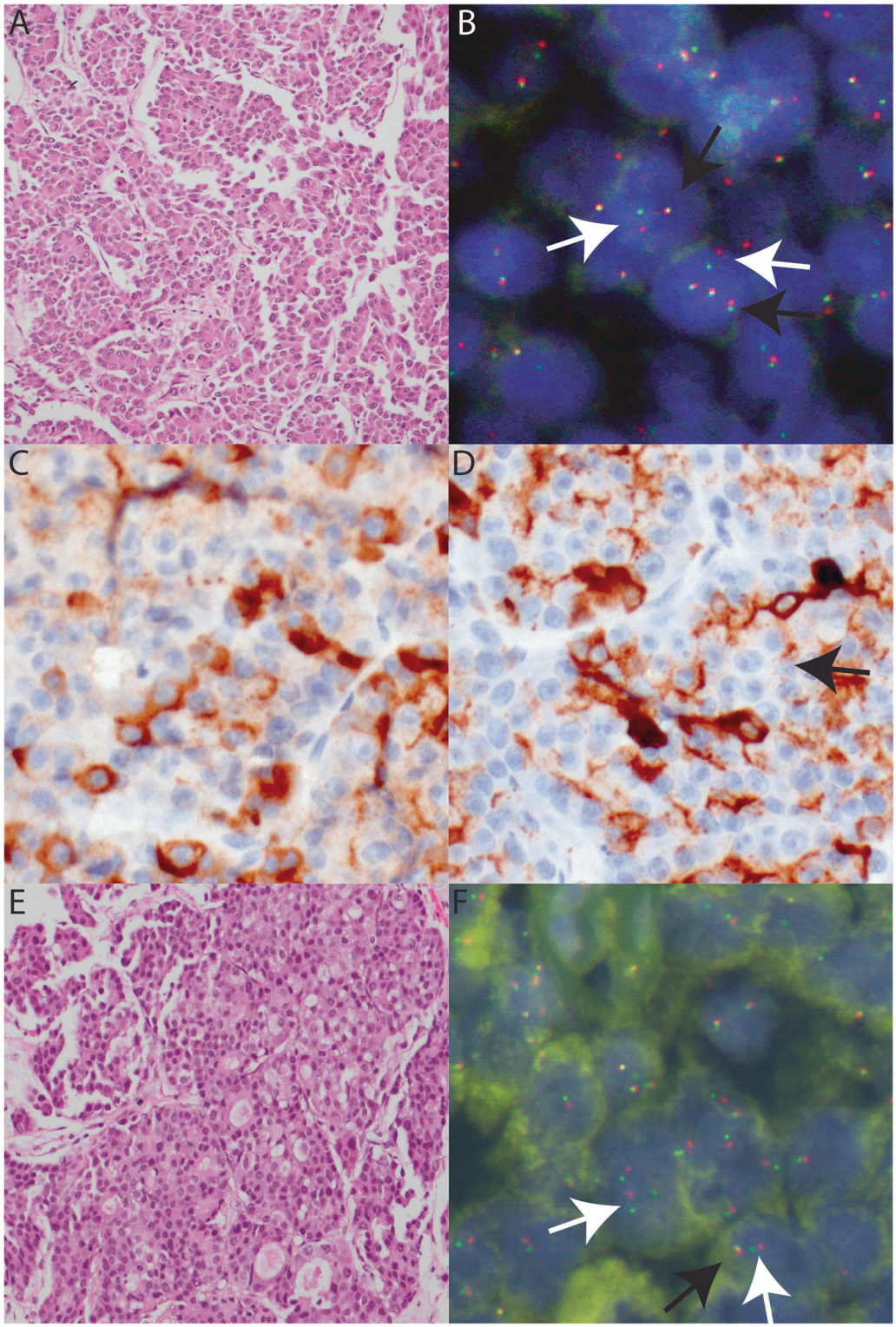

Fig. 1 **a** A RET-rearranged acinar cell carcinoma (H&E original magnification ×200). **b** *RET* FISH using break-apart probe shows the presence of one fused orange–green signal (black arrow) and one separated orange–green signal (white arrow) in the tumour cells, confirming *RET* rearrangement. This pattern was present in >15% of tumour cells. (original ×1000) **c** BCL10 IHC demonstrating positive cytoplasmic staining in acinar cell carcinoma (original magnification ×600). **d** Trypsin IHC demonstrating positive cytoplasmic staining in acinar cell carcinoma (original magnification ×600). **e** A BRAF-rearranged acinar cell carcinoma (H&E original ×200). **f** *BRAF* FISH using break-apart probe. The presence of a split signal (white arrow) confirms *BRAF* rearrangement in a tumour cell, which is usually accompanied by a fused signal (black arrow) (original ×1000)

Table 1 Clinicopathological characteristics of the entire cohort including pure acinar cell carcinomas ($n = 36$), pancreatoblastomas ($n = 3$) and one mixed acinar cell-neuroendocrine tumour

Characteristics	$n = 40$
Sex	
Male	30
Female	10
Age (years)	
Median	66
Mean	61
Range	17–86
Operation	
Whipples resection	18
Distal pancreatectomy	8
Biopsy	13
Autopsy	1
Size (mm)	
Median	37
Mean	45
Range	13–140
Metastasis at presentation	
Present	13
Absent	27
Node involvement at presentation	
Present	9
Absent	31
Stage (AJCC 2018)	
I	9
II	14
III	0
IV	12
Uncertain	5
Mitotic rate (per 10 hpf)	
Median	5
Mean	11
Range	1–44

Unfortunately PACC12 was inadequate for sequencing due to low RNA quantity and quality. The two other samples (PACC14 and PACC33) were negative for the *RET* fusion transcripts covered by the panel. As PACC12 was known to harbour *a RET-CCDC6* fusion by the APGI data, only PACC14 and PACC33 were further examined using the Trusight RNA fusion panel. However due to poor coverage of exons, the results were inconclusive.

Discussion

This is the first study to systematically screen a large cohort of acinar cell carcinomas specifically for *RET* gene

Table 2 Characteristics of eight *RET*/BRAF-rearranged pancreatic acinar cell carcinomas

Tumour ID	Histological type	Specimen type	Sex	Age (years)	Tumour size (mm)	pT	pN	pM	AJCC stage (8th ed)	*BRAF* rearrangement	*% BRAF* split signal	*RET* rearrangement	*% RET* split signal	Mitotic rate per 10 hpf	Trypsin IHC	BCL10 IHC
PACC12[a]	PACC	Whipples Resection	M	64	40	2	1	0	2B	Neg	4	Pos	90	2	Pos	Pos
PACC14	PACC	Whipples Resection	M	55	30	2	0	0	1B	Neg	0	Pos	29	1	Pos	Pos
PACC16	PACC	Whipples Resection	M	67	20	1	1	0	2B	Pos	75	Neg	0	5	Pos	Pos
PACC17	PACC	Whipples Resection	M	63	45	3	1	0	2B	Pos	85	Neg	0	12	Pos	Pos
PACC18	PACC	Whipples Resection	F	76	30	2	1	0	2B	Pos	90	Neg	4	2	Pos	Pos
PACC23	PACC	distal pancreateas	M	59	45	3	0	1	4	Pos	88	Neg	0	31	Pos	Pos
PACC24	PACC	liver biopsy	M	34	–	–	0	1	4	Pos	90	Neg	4	5	Pos	Pos
PACC33	PACC	liver biopsy	M	55	–	–	0	1	4	Neg	4	Pos	36	3	Pos	Pos

All 8 cases show diffuse trypsin and BCL10 staining

[a]PACC12 is the Australian Pancreatic Genome Initiative case with *RET-CCDC6* fusion

Table 3 Comparison of *RET*/*BRAF* gene rearrangement positive and negative cases in 36 pure acinar cell carcinomas

$n = 36$	Positive for *BRAF* or *RET* rearrangement	Negative for *BRAF* or *RET* rearrangement	p value
Sex			
Male	7	22	0.558
Female	1	6	
Age (years)			
Mean	59	63	0.542
Size (mm)			
Mean	35	40	0.638
Metastasis at presentation			
Present	3	9	0.827
Absent	5	18	
Node involvement at presentation			
Present	4	5	0.064
Absent	4	23	
Stage (AJCC 2018)			
I	0	7	
II	5	8	0.171
III	0	0	
IV	3	8	
Mitotic rate (per 10 hpf)			
Mean	7.6	12.6	0.332

rearrangements. Given that the reported incidence of *RET* gene rearrangements in all pancreatic cancers is as low as 0.2 to 0.6% [16, 24–26], our novel finding of a relatively high incidence (3 of 36, 8%) in pure acinar cell carcinomas strongly supports our central hypothesis—that *RET* gene rearrangements are highly over-represented in acinar cell carcinomas. Our concurrent confirmation of an even higher incidence of *BRAF* gene rearrangements in pure acinar cell carcinomas (5 of 36, 14%) is in keeping with other studies that have reported an incidence of up to 20% and supports the established finding that *BRAF* fusions are also highly over-represented in acinar cell carcinomass [11, 12, 14].

We note that in our cohort, *BRAF* and *RET* gene rearrangements were mutually exclusive and only occurred in pure acinar carcinomas. This exclusiveness was also found in a pan-cancer cohort of solid tumours ($n = 4871$) where *RET* aberrations were also mutually exclusive with gene aberrations that affect MAPK signalling pathway such as (*KRAS*, *NRAS*, *BRAF* and *NF1*) [16]. Given the high frequency of *KRAS* mutations in conventional pancreatic adenocarcinomas (more than 93% in our centre) [24–26], this further supports our contention that *RET* gene rearrangements are particularly over-represented in acinar carcinomas and very uncommon in conventional pancreatic ductal adenocarcinomas. Indeed we think it is likely that at least some if not the majority of 'pancreatic cancers' (reported without further specification of histology) in studies of carcinomas of multiple primary sites and the early basket clinical trials of the novel small molecule *RET* inhibitor LOXO-292 may represent acinar carcinomas [16, 22, 23]. Of course only specific histologic review of the fusion positive cases from these studies would definitively prove this hypothesis. In a similar vein we acknowledge the recent publication by Singhi et al., where $n = 4$ (0.1%) of 3738 pancreatic adenocarcinomas undergoing molecular testing were found to have a *RET* fusion (all were *KRAS* wild type) [27] and note that in this study, although there was secondary pathological review based on H&E stained sections and scanned images, the authors did not state if immunohistochemistry for BCL10 or trypsin was performed to exclude the possibility that these cases may represent acinar carcinomas. This is important because we suspect that acinar cell carcinomas may be under-recognized. For example we previously reviewed an APGI/ICGC pancreatic carcinoma originally classified as pancreatic ductal adenocarcinoma after it was found to be *KRAS* wild type and harbour an oncogenic *SDK1-BRAF* fusion [24–26]. Upon review we demonstrated that it was actually a misclassified acinar cell carcinoma based on both morphology and diffuse strong expression of BCL10 and trypsin (data not shown). We therefore recommend that pathologists should have a low threshold for considering the diagnosis of acinar cell carcinoma and performing BCL10 and trypsin immunohistochemistry.

There are different methods for detecting gene rearrangements in malignancies including whole-genome and transcriptome sequencing, RNA sequencing, real-time polymerase chain reaction (RT-PCR) and FISH. Each of these techniques have their advantages and disadvantages in clinical practice. FISH is appealing in the diagnostic surgical pathology laboratory as it can be readily performed on formalin-fixed paraffin-embedded tissue (including archived specimens) and has the advantage of low cost, minimal tissue requirement, rapid turnaround and, importantly, a low failure rate. Indeed, we were able to detect the presence or absence of *BRAF* or *RET* gene rearrangement using FISH break-apart probes in all cases except one due to poor signal quality (1/80), yet had significant difficulties in achieving results for fusion testing using the RNA fusion panels. However one very significant disadvantage of FISH is that it detects only the presence of a gene rearrangement. Whilst it is assumed that this usually reflects an oncogenic fusion gene, FISH studies do not definitively prove a fusion or identify the partner gene. At the time of writing 12 different *RET* fusions partners have been identified (*TRIM33, NCOA4, KIF5B, CCDC6, PRKARIA, GOLGA5, TRIM24, KTN1, RAB61P2, MBD1, RFP, SQSTM1*) but there are also reports of gene rearrangements without identified partners [16, 28]. Our amplicon-based gene panel included only six

of these genes (*CCDC6*, *PRKARIA*, *NCOA4*, *GOLGA5*, *TRIM24*, *TRIM33*), therefore it is likely that the *RET* fusions in our samples were not covered by this panel and hence not detected. Unfortunately using a comprehensive 507 gene hybridization capture-based panel we could not obtain adequate regional coverage of *RET* to adequately interpret the result. Therefore whilst we were confident with the identification of a fusion partner for one case (*RET-CCDC6* in case PACC12), we could not identify a fusion partner for the other *RET* gene rearranged cases. This is important because it is possible that these FISH aberrations may reflect genomic instability at the chromosomal locus rather than a true driving fusion gene. Furthermore current entry criteria for many clinical trials (including the LOXO trial) requires identification of a gene fusion, with FISH studies alone being considered insufficient. Therefore, whilst FISH testing has some advantages, this approach is not without its limitations compared to *RET* fusion analysis.

In conclusion, *RET* and *BRAF* rearrangements are found in ~20% of acinar cell carcinomas and can be readily identified in the routine clinical setting using FISH. The identification of *RET* gene aberrations is clinically highly significant, as they are already targetable using FDA-approved multikinase inhibitors and the subject of ongoing but promising clinical trials of more specific inhibitors. In the era of personalized medicine pathologists are often encouraged to perform pan-cancer panel testing for numerous molecular abnormalities regardless of morphology or histogenesis. We propose that basic morphology, with simple confirmatory immunohistochemistry for BCL10 and trypsin, can be used to diagnose acinar cell carcinoma and serve as a cost effective method to triage molecular testing for *RET* and *BRAF* gene rearrangements in pancreatic malignancies. We therefore recommend a low threshold for considering the diagnosis of acinar cell carcinoma and, in confirmed cases of acinar cell carcinoma, for testing for these gene rearrangements. At this stage this would be primarily to recruit patients for clinical trials of new targeted therapies. However given the provisional results of these clinical trials, probably in the near future *RET* and *BRAF* fusion testing and targeting will be part of routine clinical care for all acinar cell carcinomas.

Acknowledgements AC is supported by the CINSW ECF (AC0430). This study was supported by the Avner Australian Pancreatic Cancer Genome Initiative (APGI) BioResource partially funded by the Avner Pancreatic Cancer Foundation Grant, www.avnersfoundation.org.au.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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