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Molecular Profiling and Prognostic Value of KRAS Gene Mutations in Tumor Samples and Liquid Biopsies from Patients with Pancreatic Ductal Adenocarcinoma: A Review

Marco Bellini^{1*}, Sophie Laurent² and Rajesh Menon³¹Department of Gastroenterology, University of Bologna, Bologna, Italy²Department of Medical Oncology, Sorbonne University, Paris, France³Department of Molecular Pathology, All India Institute of Medical Sciences, New Delhi, India

*Correspondence to: Marco Bellini, Department of Gastroenterology, University of Bologna, Bologna, Italy

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Abstract

KRAS is mutated in the large majority of pancreatic ductal adenocarcinomas, and the same mutation can now be read either from a tumour block or from a tube of blood. The two readings are not interchangeable. Tissue reports which variant a tumour carries; plasma reports whether the tumour is shedding enough DNA to be seen at all, and that fact carries prognostic weight of its own.

Objectives: To summarise published evidence on the frequency and subtype distribution of KRAS mutations in PDAC tissue, on the rate at which mutant KRAS is detected in plasma across disease settings, on concordance between the two compartments, and on the prognostic value attached to each.

Material and Methods: Narrative review of primary cohort studies, trial reports and meta-analyses indexed in PubMed and in the major oncology journals. Studies were eligible if they reported KRAS variant distribution in PDAC tissue, plasma detection rates for mutant KRAS or circulating tumour DNA, tissue-plasma concordance, or survival stratified by KRAS status in either compartment. No new patient data were generated for this review. Every frequency, survival estimate and effect size quoted is one published by the original investigators, and the figures and tables reproduce reported values only.

Results: KRAS is mutated in approximately 82 to 92 per cent of PDAC tumours. Among mutant cases the distribution is dominated by G12D (about 39 per cent), G12V (31 per cent), G12R (14 per cent) and Q61 (6 per cent), with G12C accounting for only 1 to 2 per cent. In the largest single-centre series reporting subtype-level survival ($n = 803$), median overall survival was 38 months for wild-type tumours, 34 months for G12R, 22 months for G12D (HR 1.7) and 20 months for Q61 (HR 1.9). Plasma detection is strongly stage-dependent, reported at 64.7 per cent in metastatic disease, 16.6 per cent in locally advanced disease and 19 per cent after resection. Detection of mutant KRAS in plasma before treatment was associated with a median overall survival of 10.5 months against 22.6 months when it was undetectable (HR 4.70, $p = 0.002$).

Conclusion: Tissue and plasma answer different questions. Tissue establishes the variant, which produces modest but reproducible prognostic separation. Plasma establishes tumour DNA shedding, which behaves as a stronger and more dynamic prognostic signal but is insensitive in localised disease. The two are complementary rather than substitutable, and the evidence base remains dominated by retrospective single-centre series.

Abbreviations: PDAC – Pancreatic Ductal Adenocarcinoma, ctDNA – Circulating Tumour DNA, cfDNA – Cell-Free DNA, ddPCR – Droplet Digital Polymerase Chain Reaction, NGS – Next-Generation Sequencing, OS – Overall Survival, HR – Hazard Ratio, MAF – Mutant Allele Fraction, WT – Wild Type.

Keywords: KRAS; Pancreatic Ductal Adenocarcinoma; Liquid Biopsy; Circulating Tumour DNA; Prognostic Biomarkers

Introduction

Pancreatic ductal adenocarcinoma remains one of the least forgiving solid tumours in oncology. Most patients present with disease that is already locally advanced or metastatic, cytotoxic chemotherapy remains the backbone of treatment, and long-term survival is confined to a small minority [1]. Against that background, any marker that separates patients by expected outcome, or that can be measured repeatedly without a needle in the pancreas, attracts

sustained interest.

KRAS occupies a peculiar place in this landscape. It is the defining oncogenic driver of the disease, present in the great majority of tumours, and for that very reason it is a poor discriminator: a marker carried by nine patients in ten cannot by itself stratify a population. What has changed over the past decade is that the question has become more granular. Investigators no longer ask only whether KRAS is mutated, but which variant is present, at what allele fraction, and in which compartment it can be detected

[2,3].

The last of these is the substantive shift. Mutant KRAS can be recovered from cell-free DNA in plasma, and the assays that do so are now routine in several centres. This creates two parallel readouts from the same underlying lesion. A tissue sample gives the variant with near-complete certainty but only at one point in time and only where a biopsy is obtainable. A plasma sample can be repeated indefinitely, but returns a result only when the tumour sheds enough DNA to cross the detection threshold [4,5].

That difference is not a technical nuisance. Shedding correlates with tumour burden, and a negative plasma result in a patient with radiologically evident disease is itself informative. The consequence is that the two compartments carry prognostic information of different kinds, and the literature has not always kept them apart. The aim of this review is to set out, side by side, what has actually been reported for each: how often KRAS is mutated and in what distribution, how often it is detectable in plasma and under what conditions, how well the two agree, and what each predicts.

Material and Methods

Search strategy: PubMed and the archives of the major oncology and gastroenterology journals were searched for primary cohort studies, clinical trial reports, systematic reviews and meta-analyses addressing KRAS mutation profiling in pancreatic ductal adenocarcinoma. Search terms combined KRAS with pancreatic ductal adenocarcinoma, liquid biopsy, circulating tumour DNA, cell-free DNA, variant allele fraction and overall survival. Reference lists of retrieved reviews were screened by hand for further primary sources.

Eligibility: Studies were included if they reported at least one of the following in patients with histologically or cytologically confirmed PDAC: the frequency or subtype distribution of KRAS mutations in tumour tissue; the detection rate of mutant KRAS or ctDNA in plasma, stratified by disease setting where available; concordance between tissue and plasma genotyping; or survival outcomes stratified by KRAS status in either compartment. Case reports, studies confined to non-ductal pancreatic neoplasms and studies without extractable numerical outcomes were excluded.

Data extraction and handling: For each included study the design, sample size, compartment sampled, assay platform, reported frequencies and reported survival estimates with their measures of uncertainty were extracted as published. No pooling, re-analysis or recalculation was performed, and no patient-level data were obtained. Where different studies report the same quantity with different denominators, both are reported rather than reconciled. Figures 1 to 4 and Tables 1 and 2 reproduce published values only; they contain no derived or modelled estimates. This is a narrative synthesis and was not registered as a systematic review.

Results

KRAS mutation frequency in tumour tissue: Reported prevalence varies with cohort composition and assay sensitivity rather than with any real biological disagreement. In a retrospective series of 803 patients profiled at a single tertiary centre, KRAS was mutated in 82 per cent of tumours [2]. Reviews of larger sequencing databases place the figure closer to 90 per cent, and comprehensive genomic profiling of tissue from commercial platforms has reported oncogenic RAS alterations in approximately 92 per cent of cases. Cohorts with a higher proportion of resected, well-differentiated tumours consistently report more wild-type cases than metastatic cohorts do, and East Asian series report a higher wild-type fraction

than European or North American ones [2,3].

Within the mutant group the distribution is stable across cohorts. Codon 12 substitutions dominate, with G12D the most frequent, followed by G12V and G12R; codon 61 substitutions account for a small minority (Figure 1). G12C, the variant for which covalent inhibitors were first developed, is present in only 1 to 2 per cent of PDAC, which is the central obstacle to transferring the lung cancer experience to this disease [2,3].

KRAS VARIANT DISTRIBUTION IN PDAC TUMOUR TISSUE (n = 803)

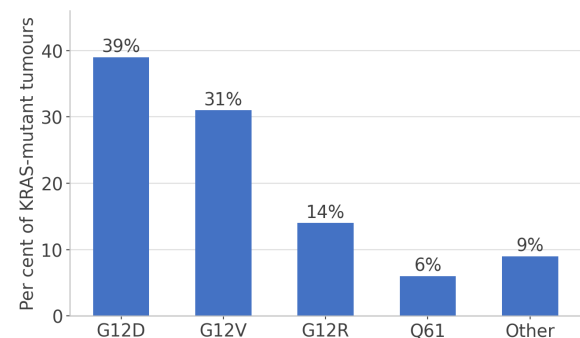


Figure 1: Distribution of KRAS variant subtypes among KRAS-mutant PDAC tumours, as reported in a single-centre cohort of 803 patients [2]

Prognostic value of KRAS status and subtype in tissue: Mutation status alone separates outcomes, but not dramatically. In the 803-patient series, KRAS status and subtype were jointly prognostic ($p < 0.001$). Patients with wild-type tumours had a median overall survival of 38 months. G12R behaved almost identically at 34 months. G12D and Q61 both fared worse, at 22 months (HR 1.7, 95% CI 1.3-2.3, $p < 0.001$) and 20 months (HR 1.9, 95% CI 1.2-3.0, $p = 0.006$) respectively, taking wild-type as the reference (Figure 2) [2].

The same series reported that G12D was enriched in metastatic tumours relative to non-metastatic ones (34 versus 24 per cent, OR 1.7, $p = 0.001$), while G12R was enriched in well and moderately differentiated tumours (14 versus 9 per cent, OR 1.7, $p = 0.04$) [2]. Whether the survival difference reflects variant biology or the stage distribution that the variants keep company with is not resolved by these data. Independent work on co-occurring PI3K pathway alterations has reached broadly compatible conclusions, and has raised the same confounding difficulty: the cohorts in which G12R appears favourable are also cohorts enriched for other features associated with better outcome [3].

MEDIAN OVERALL SURVIVAL BY KRAS STATUS AND SUBTYPE

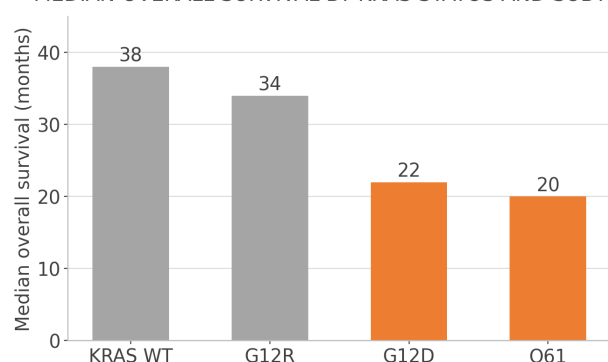


Figure 2: Median overall survival by KRAS status and variant subtype in the same cohort (n = 803); wild-type is the reference group [2]

Study	n	Compartment	Principal reported finding
Yousef et al. 2024 [2]	803	Tissue (NGS)	KRAS mutant in 82%; subtype prognostic for OS
Diehl et al. 2022 [3]	—	Tissue	Variant and co-occurring PI3K alterations affect survival
Bettegowda et al. 2014 [4]	Multi-tumour	Plasma	ctDNA burden roughly ten-fold lower in localised disease
Sausen et al. 2015 [6]	101	Tissue + plasma	Post-operative ctDNA anticipates radiological recurrence
Pietrasz et al. 2017 [5]	135	Plasma (NGS, dPCR)	ctDNA an independent prognostic factor in stage III-IV

Table 1: Principal studies reviewed, with the compartment sampled and the finding as reported by the original investigators

Detection of mutant KRAS in plasma: The single most consistent finding in the liquid biopsy literature is that detection tracks tumour burden. In a cohort of 135 patients sampled across disease settings, mutant ctDNA was found in 44 of 68 patients with metastatic disease (64.7 per cent) but in only 6 of 36 with locally advanced disease (16.6 per cent), a difference significant at $p < 0.001$. Among 31 patients sampled after curative resection, ctDNA was detected in 6 (19 per cent), with a median mutant allele fraction of 4.4 per cent (Figure 3) [5]. KRAS was the most frequently detected gene, present in 86 per cent of the patients in whom any ctDNA was found [5].

Earlier work quantifying the relationship between stage and ctDNA abundance found median ctDNA burden in localised pancreatic cancer to be roughly ten times lower than in metastatic samples, and reported detection in the region of 90 per cent of metastatic cases using high-depth assays [4]. The discrepancy between that figure and the 64.7 per cent above is a matter of assay depth and plasma input rather than of biology, and it is the main reason detection rates cannot be compared across studies without reference to method [4,5,9].

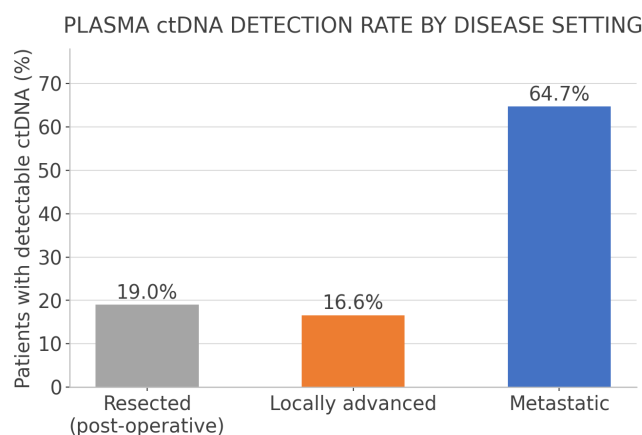


Figure 3: Reported plasma ctDNA detection rate by disease setting in a cohort of 135 patients [5]

Concordance between tissue and plasma: Where both compartments have been genotyped in the same patients, specificity has been high and sensitivity moderate. Discordant cases are overwhelmingly of one type: KRAS mutant in tissue, undetected in plasma. The explanation offered consistently is low shedding in a tumour with a dense stromal compartment and, in localised disease, low tumour volume; sensitivity improves when the analysis is restricted to metastatic patients [5,9]. Studies that have examined

intratumoural heterogeneity report that this is not the source of the problem, since KRAS point mutations are largely stable between tumour centre and invasion front and between primary and metastasis [12].

Prognostic value of plasma KRAS: Detection of mutant KRAS in plasma before treatment has been associated with materially shorter survival. In patients with metastatic disease carrying a KRAS mutation in tissue and treated with first-line chemotherapy, median overall survival was 10.5 months where KRAS was detected in plasma against 22.6 months where it was not, with a hazard ratio for death of 4.70 (95% CI 1.70-12.98, $p = 0.002$) (Figure 4) [19]. Comparable direction and magnitude have been reported across independent cohorts and confirmed in pooled analyses [11,18].

Median overall survival by baseline plasma KRAS status

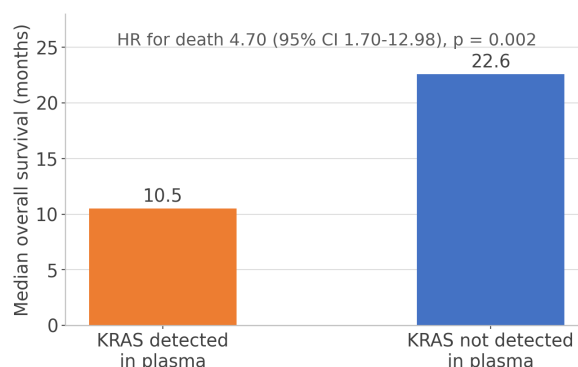


Figure 4: Median overall survival by baseline plasma KRAS status in patients with metastatic PDAC carrying a tissue KRAS mutation [19]

Study	Setting	n	Detection	Reported association
Pietrasz 2017 [5]	Metastatic	68	64.7%	Independent prognostic factor
Pietrasz 2017 [5]	Locally advanced	36	16.6%	Improves prognostic staging
Pietrasz 2017 [5]	Post-resection	31	19%	Prognostic for recurrence
Fabregat-Franco 2022 [19]	Metastatic	—	—	OS 10.5 vs 22.6 mo, HR 4.70
Sausen 2015 [6]	Resected	101	—	Detection precedes imaging relapse

Table 2: Reported plasma detection rates and prognostic associations. Detection rates are as published and are not comparable across differing assay platforms

Dynamic measurement during treatment: The prognostic signal is not confined to the baseline sample. Serial measurement of mutant KRAS during chemotherapy has been reported to predict radiological response earlier than conventional markers, with the magnitude of early fall in ctDNA corresponding to both progression-free and overall survival [12,14]. Quantitative monitoring studies have reached the same conclusion in advanced disease [14], and mutant allele fraction has been shown to track clinical stage [17]. This is the property that most clearly distinguishes plasma from tissue: a tumour block cannot be resampled weekly.

Discussion

Taken together the published data support a fairly simple reading. The two compartments are not competing sources of the same information. Tissue genotyping answers the question of which variant is present, and does so reliably. That answer carries prognostic weight, but the separation is modest: roughly 16 to 18

months of median survival between the best and worst subtype groups in the largest series [2], within a disease where stage moves survival by considerably more.

Plasma genotyping answers a different question. A positive result establishes that the tumour is shedding detectable DNA, and shedding is a function of burden, vascularity and biological aggressiveness. The prognostic separation attached to plasma positivity is correspondingly larger, with hazard ratios in the region of four or five reported for baseline detection in metastatic disease [19]. The corollary is that the same property makes plasma an unreliable ruling-out test in early disease. A detection rate below 20 per cent in locally advanced and post-resection settings [5] is not adequate for a screening or surveillance role on its own, whatever its prognostic value when positive.

Therapeutic implications

The clinical value of subtype-level genotyping is currently limited by the variant distribution itself. Direct inhibition has been demonstrated for G12C, and in the pancreatic cohort of a phase 1/2 trial sotorasib produced a confirmed objective response rate of 21 per cent and a disease control rate of 84 per cent in heavily pretreated patients, with a median progression-free survival of 4.0 months [21]. That is a meaningful result for a population with no established third-line standard. It applies, however, to the 1 to 2 per cent of patients who carry G12C [2,21]. The variants that account for the great majority of the disease, G12D and G12V, remained without an approved targeted option at the time of the studies reviewed here.

This is the practical asymmetry worth stating plainly: genotyping is currently more valuable for prognosis and for trial allocation than for treatment selection in unselected patients. Where liquid biopsy has the clearest present utility is in patients from whom adequate tissue cannot be obtained, a substantial group given that only a minority of patients present with resectable disease [1,20].

Study limitations

The limitations here are those of the underlying literature rather than of the synthesis. The evidence base is dominated by retrospective, single-centre cohorts, with the attendant selection effects; the cohorts that report subtype-level survival are largely drawn from tertiary referral centres. Detection rates are not comparable across studies, because assay depth, plasma volume and cfDNA input differ substantially and are frequently under-reported. Survival comparisons between variant subtypes are confounded by stage and by differentiation, both of which are unevenly distributed across the subtypes [2]. Few studies apply a prespecified analysis plan for the subtype comparisons, so the risk of multiplicity is real.

Two gaps are worth naming. First, prospective studies that fix the assay and the sampling schedule in advance remain scarce, so the reported prognostic hazard ratios should be read as consistent in direction rather than as precise. Second, almost no study reported here separates the prognostic contribution of tumour burden from that of the variant itself, which is exactly the separation a clinician would want before acting on a plasma result.

Conclusion

Across the published evidence, KRAS mutation is near-ubiquitous in pancreatic ductal adenocarcinoma, and its variant distribution is stable enough across cohorts to be treated as settled. Subtype carries reproducible but modest prognostic information in tissue. Detection of mutant KRAS in plasma carries stronger prognostic information but is sharply limited by stage-dependent sensitivity, and is best

understood as a measure of tumour DNA shedding rather than as a substitute for tissue genotyping. The two compartments should be reported and interpreted separately. Prospective studies with prespecified assays and sampling schedules are the obvious next requirement, and until they exist the hazard ratios summarised here should be read as directionally consistent rather than as precise estimates.

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We are grateful to the investigators behind the primary cohorts drawn on in this article. Their published datasets and reported outcomes constitute the whole of the evidence discussed here.

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Conflict of Interest

None of the authors has any competing interest to declare.

Ethics Statement

This work synthesises studies already in the published record. No fresh patient data were gathered and no human or animal participants took part, so ethical approval was not sought.

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