Tumor profiling of 431 pancreatic tumors from elderly patients

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Abstract

Background: Pancreatic cancer (PC) is frequently a disease of the elderly and controversy exists as to whether these patients benefit from aggressive treatments. We aimed to investigate biomarker features from tumors taken from elderly PC patients to identify therapeutic implications. We also compared the results to those from younger patients to assess differences.

Methods: PC tumors were tested at Caris Life Sciences between 2009 and 2015 by immunohistochemistry, fluorescent/chromogenic in-situ hybridization and sequencing. De-identified biomarker data were analyzed.

Results: A total of 431 tumors from PC patients aged > = 75 years were analyzed: 50% were samples from pancreas, 50% were from metastatic sites. 26 of 47 genes sequenced carried mutations with frequencies ranging from 0.6% to 84%. The highest mutation rates were seen in KRAS (84%), TP53 (55%), BRCA2 (21%), SMAD4 (12%), ATM (4.4%), BRCA1 (4.2%) and PIK3CA (3.8%). Overexpression of TOPO1 and low expression of ERCC1, RRM1 and TS were seen in 45%, 73%, 86% and 79%, respectively, indicating potential benefit from irinotecan, platinums, gemcitabine and fluoropyrimidine, respectively. Tumor expression of PD-L1 was seen in 14% and tumor-infiltrating lymphocyte expression of PD-1 was seen in 45%. Overexpression of EGFR and cMET were seen in 91% and in 62%, respectively. When compared to 470 tumors from PC patients aged < = 50, KRAS mutations were significantly more common in the elderly than in younger patients (84% vs. 74%, p = 0.0018), while MLH1 mutations were seen exclusively in younger patients (0% vs. 4%, p = 0.0241). Moreover, expression of TOP2A (53%vs. 45%), ERCC1 (36% vs. 27%), RRM1 (20% vs. 14%), SPARC (20% vs. 14%) and PR (5% vs. 1%) were significantly more prevalent in the younger group (all p < 0.05).

Conclusions: Tumor profiling of 431 tumors from elderly PC patients suggests therapeutic opportunities including cytotoxic, biological as well as targeted agents for this patient group. A comparison with younger patients indicated that irinotecan, fluoropyrimidine and taxanes may provide equal benefit to elderly and younger patients, while platinums and gemcitabine may be more likely to benefit elderly patients.

Results:

Figure 1: Patient age distribution: A total of 3483 pancreatic tumors were identified in the Caris database profiled from 2009 to 2015. The age distribution is shown as below. 431 (12.4%) of tumors were from patients older than 75 yrs old and were investigated for biomarker features. Comparative studies were done with 470 tumors taken from patients younger than 50 yrs old.

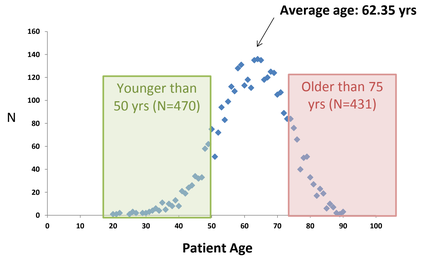
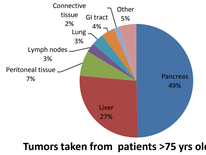
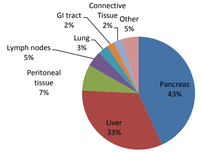


Figure 2: Tumor characteristics: The table shows the specimen sites, patient gender and age distribution for the older and younger populations. The pie charts depict the percentages of specimen sites within the two populations. 49% of tumors from the older population were taken from the primary tumor site while 43% of younger tumors were from the primary.

		N (Age >75 yrs)	N (Age <50 yrs)
	Total	431	470
Specimen sites	Pancreas	212	203
	Liver	115	153
	Peritoneal tissue	31	35
	Lymph nodes	11	21
	Lung	15	14
	GI tract	16	10
	Connective tissue	7	11
	Other	21	23
Patient Gender	Female	201 (47%)	231 (49%)
	Male	230 (53%)	239 (51%)
Age	Average	79.1	44.6
	Interquartile Range	76-81	42-49
	Maximum	90	49.9
	Minimum	75.1	20



Tumors taken from patients >75 yrs old



Tumors taken from patients <50 yrs old

Results: continued

Figure 3: Biomarker frequencies observed in the elderly cohort tested by immunohistochemistry(IHC), ISH (in-situ hybridization, including chromogenic in-situ hybridization and fluorescent in-situ hybridization). Therapies associated with the corresponding biomarker aberrations are shown in the boxes. An asterisk indicates that low expression of the protein marker suggest responsiveness to the therapy.

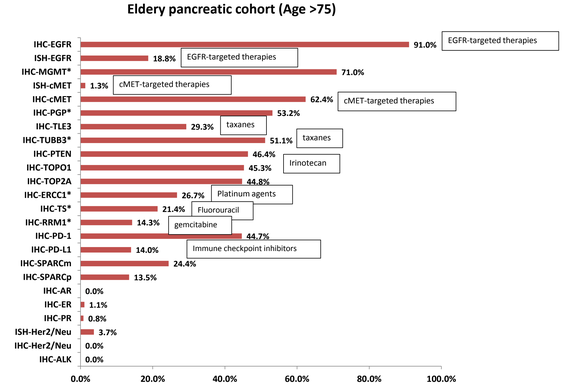
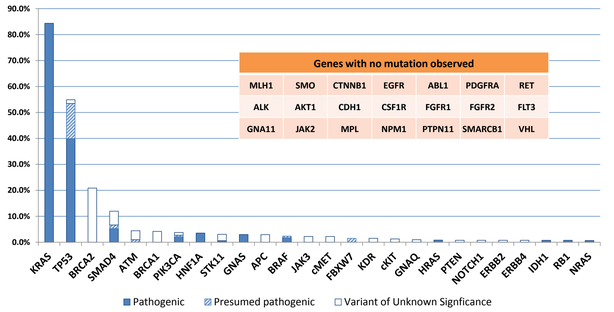
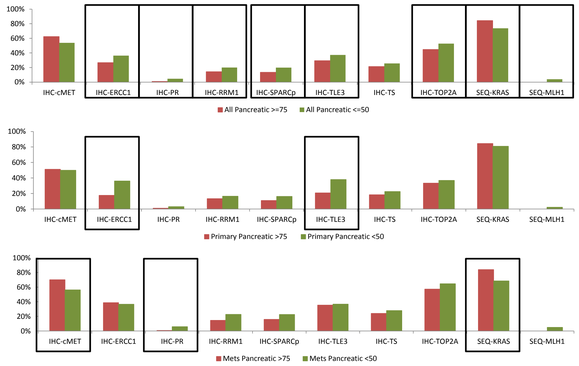


Figure 4: Gene mutation frequencies observed in the elderly cohort tested by NextGen sequencing.



Results: continued

Figure 5: Selected IHC, ISH and NGS markers in the complete cohort (upper), primary tumors (middle) and tumors taken from distant metastatic sites (bottom) were compared to the corresponding cohorts taken from the younger cohort (age <50). A black box indicates that the difference reaches statistical significance by two-tailed Fisher-Exact test.



Conclusions

- This study using IHC, ISH and NGS revealed differences in molecular aberrations between elderly pancreatic cancer patients and younger patients.
  1. ERCC1 protein expression is less prevalent in the elderly cohort, especially in the primary tumors.
  2. Expression of SPARC and TLE3 are decreased in the elderly patients.
  3. KRAS mutation is more prevalent in the elderly patient population, especially in tumors from the metastatic sites.
- These results suggest that platinum and gemcitabine may be more effective in the elderly pancreatic cancer patients. Further outcome studies will be helpful to confirm these findings.