Multimodal molecular comparison of primary versus metastatic pancreatic tumors

Metastatic pancreatic adenocarcinoma is the third leading cause of cancer-associated mortality with a median overall survival of <12 months. Despite improved outcomes with multimodality therapy in early stage pancreatic cancer, >70% of patients with recurrent disease ultimately die. It is likely that then circulating metastases are already present at initial diagnosis. Advances in the understanding and multimodal characterization of solid tumors have allowed for the development of molecularly targeted therapeutic agents in a number of solid tumors, and we have demonstrated up to 25% of pancreatic adenocarcinomas harbor “actionable” molecular alterations.

In an effort to assess the multimodal changes that may occur as a pancreatic cancer metastasizes, we compared the frequency of genetic, protein, and phosphoprotein alterations from primary vs. metastatic pancreatic tumors and from metastases of different sites. By focusing on potential actionable genetic, proteinic, and phosphoprotein information, we sought to explore whether targeted therapies could be tailored to patients at metastatic progression based on primary surgical material.

RESULTS

Comprehensive multi-omic (genomic, proteomic, and phosphoprotein alterations) testing was performed by Pancreta through Pancreta Precision Medicine for 505 patients with pancreatic adenocarcinoma as part of the Know Your Tumor Initiative, in conjunction with the Pancreatic Cancer Action Network. We compared proteomic results between metastatic lesions and primary tumors and found significant differences (FDR-adjusted q-value < 0.10, Fisher’s exact test).

- Within distant metastases, we observed possible tissue-specific patterns of protein expression with increased TUBB3 and decreased PTEN in the liver compared to the lung (FDR-adjusted q-value < 0.10).
- The four most common mutations (Fig. 5A) seen in pancreatic adenocarcinoma were detected at similar frequencies across primary pancreatic tumors (182), liver lesions (234), lung lesions (34), and metastases at other sites (52, excluded from analysis).
- Highly actionable alterations were detected in 40 primary tumors (22%) which was significantly different (q-value = 0.3, Fisher’s exact test) than the 85 metastatic lesions with highly actionable findings (26%).
- No statistically significant differences in specific genes were observed between primary vs. metastatic lesions, nor across the site of metastasis after correcting for multiple hypotheses.
- The proportion of actionable alterations (including mutations in the homologous recombination DNA repair pathway) was similar across subgroups.

Fig. 2 – Geographic distribution of patients who received Pancreta Reports for pancreatic adenocarcinoma based on biopsies of the primary tumor (182 blue dots) or of a distant metastasis (323 orange dots). We have provided Pancreta Reports to 505 of the 505 patients in the analysis cohort and their oncologists from 41 different states across the United States (Fig. 2).

Table 1 – Baseline characteristics of analysis cohort.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary (n = 182)</th>
<th>Metastatic (n = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male (96) (53%)</td>
<td>Female (86) (50%)</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;65 years old (101) (55%)</td>
<td>&gt;65 years old (84) (43%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>African American (2%)</td>
<td>Asian (6%)</td>
</tr>
<tr>
<td>Smoking History</td>
<td>Current or Former (66) (36%)</td>
<td>Current or Former (41) (23%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes (10) (6%)</td>
<td>Yes (11) (6%)</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;25 (90) (50%)</td>
<td>&lt;25 (91) (53%)</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Yes (103) (60%)</td>
<td>Yes (189) (58%)</td>
</tr>
<tr>
<td>Metastasis Type</td>
<td>Liver (71) (42%)</td>
<td>Liver (192) (60%)</td>
</tr>
<tr>
<td>Primary Tissue</td>
<td>Metastatic (55) (30%)</td>
<td>Metastatic (182) (56%)</td>
</tr>
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</table>

Fig. 3 – Comparative frequencies of protein or phosphoprotein positivity between primary and metastatic tumors. Each point represents an individual protein biomarker with size corresponding to the inverse log-transformed FDR-adjusted q-value and red indicating trends toward significant differences (q-value < 0.1).

Fig. 4 – Comparative frequencies of protein or phosphoprotein positivity between liver and lung metastatic lesions in patients with pancreatic adenocarcinoma. Each point represents an individual protein or phosphoprotein biomarker with size corresponding to the inverse log-transformed FDR-adjusted q-value and red indicating trends toward significant differences (q-value < 0.1).

Fig. 5 – Comparative frequencies of genomic alterations between metastatic lesions and primary pancreatic tumors. Each point represents an individual gene with size corresponding to the inverse log-transformed unadjusted q-value. Labels are shown for genes with a modest trend toward significance (unadjusted p-value < 0.05).

Fig. 6 – Frequency heatmap of less common genomic alterations seen across primary pancreatic tumors and metastatic lesions in the lung, liver, or other areas of the abdomen. Hierarchical clustering was based on euclidian distance with single linkage for the percentages shown.

CONCLUSIONS

- The comparison of the molecular characteristics of primary vs metastatic pancreatic adenocarcinoma in patients who have received Pancreta Reports reveals that the molecular characteristics are very similar and that actionable alterations are identified at the same frequency.
- Our findings support the belief that primary pancreatic cancers metastasize very early and thus:
  - o The role of biomarker-directed therapy for early-stage pancreatic cancers in lieu of, or in addition to standard therapy could be further evaluated in prospective clinical trials.
  - o In addition, re-biopsy at recurrence may not be necessary which can decrease patient discomfort and anxiety, cost, and delay to next treatment.
- This is consistent with previously published reports, where the driver mutations were similar (although acknowledging differences in methods).1 3
- This is unlike the data observed from other solid tumors (e.g., colon, lung, breast cancer) in which substantial molecular discordance heterogeneity exists between primary tumors and metastases.6 7

REFERENCES