



Comparative molecular analyses of pancreatic cancer (PC): KRAS wild type vs. KRAS mutant tumors and primary tumors vs. distant metastases

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Abstract (No. 4121)

Background: Targeted therapies have a minimal role in PC partly because of the molecular characterization is not well understood. Little is known about the molecular characteristics of subset of PC that doesn't carry KRAS mutations. Better knowledge would enhance our ability to develop targeted therapies.

Methods: PC tumors submitted to Caris Life Sciences for IHC (protein expression), ISH (gene amplification), and NGS sequencing between 2009 and 2015 were studied. Chi-square tests determined differences.

Results: A total of 2426 PC tumors were examined. KRAS mutations (85%) were the most frequent genetic alteration. Other commonly mutated genes were TP53 (63%), SMAD4 (13%), BRCA2 (12%), ATM/APC/NTRK1 (5% each), BRCA1 (4%) and cMET/PIK3CA (3% each). BRAF mutations were seen in 6% of the RAS-WT tumors. When compared to RAS MT, KRAS WT tumors had a greater frequency of BRCA1 (9% vs. 3%, p = 0.05), CTNNB1 (5% vs. 0.2%; p < 0.01), and GNAS (4% vs. 1.5%, p = 0.02), and FGFR2 (1.2% vs. 0.1%, p < 0.01) mutations, whereas SMAD4 and TP53 mutations were higher in KRAS MT (15% vs. 5%, p = 0.02; 68% vs. 28%, p < 0.01, respectively). KRAS MT had higher expression and amplification of cMET (66% vs. 49%, p < 0.01; 2.5% vs. 0%, p = 0.04), and higher expression of EGFR (90% vs. 82%, p = 0.04), whereas, KRAS WT tumors had higher HER2 expression and amplification (2% vs. 0.4%, 6% vs. 0.7%; both p-values < 0.01). Comparing 1o (n = 1099) with Met (n = 1327) PC, 1o tumors had a higher frequency of "low" ERCC1 (81% vs. 63%, p < 0.01) and "low" RRM1 (87% vs. 77%, p < 0.01), and higher PD1+ TILs (45% vs. 34%, p < 0.01). Conversely, cMET (62% vs. 51%, p = 0.006), PDL1 (10% vs. 5%, p = 0.01), and TOPO1 (65 vs. 33, p < 0.01) were overexpressed at higher rates in Met PC. Lung Mets, had a higher expression of HER2 (2.3% vs. 0.5%; < 0.01), and PD1 TILs (50% vs. 33%; p = 0.03) than liver Mets, whereas, the PIK3CA mutation rate was higher in liver Mets (4% vs. 0%; p = 0.03).

Conclusion: Genomic differences between KRAS WT vs. MT suggest different carcinogenic pathways and tumor biology. Primary tumors may carry genetic alterations that are distinct from distant metastases. Mutations in druggable genes (e.g., HER-2, PIK3CA, BRCA2) may provide therapeutic opportunities.

Background

- Activation of the RAS signaling pathway is common in human cancers, and PC exhibits the highest frequency of KRAS gene mutations, at a rate of ~90%¹
- The molecular characteristics of PC lacking RAS activation is not well understood
- Erlotinib is the only targeted therapy used in PC and lacks predictive markers. Further, targeting approaches against RAS oncoproteins have not yielded success; therefore, this disease is still lacking viable targeted therapy approaches, for both RAS-mutated and RAS-wildtype PC.
- In addition to a disease lacking targeted therapy approaches, approximately half of all PC are metastatic at diagnosis, typically to the liver or peritoneal cavity, and patients are usually treated with systemic chemotherapy.

Comparison of RAS-mutated and -wildtype PC, as well as primary verses metastatic disease were investigated to identify targetable alterations in different subsets of patients.

Methods

PC tumors submitted to Caris Life Sciences for IHC (protein expression), ISH (gene amplification), and NGS sequencing (Illumina MiSeq and NextSeq platforms) between 2009 and 2015 were studied. For comparisons, RAS MT subgroup includes KRAS, HRAS, NRAS and BRAF mutated-PC. Chi-square tests determined differences between subgroups. Antibodies and cutoffs for IHC and ISH can be provided upon request.

Results

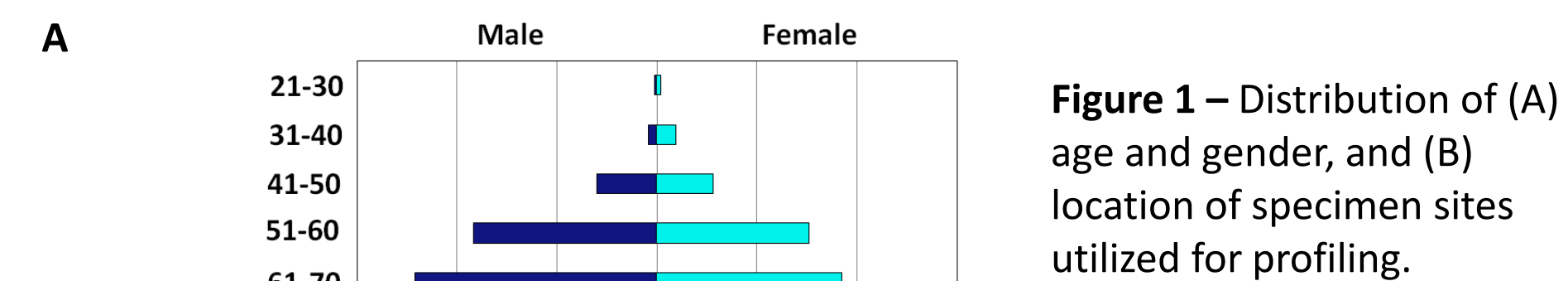
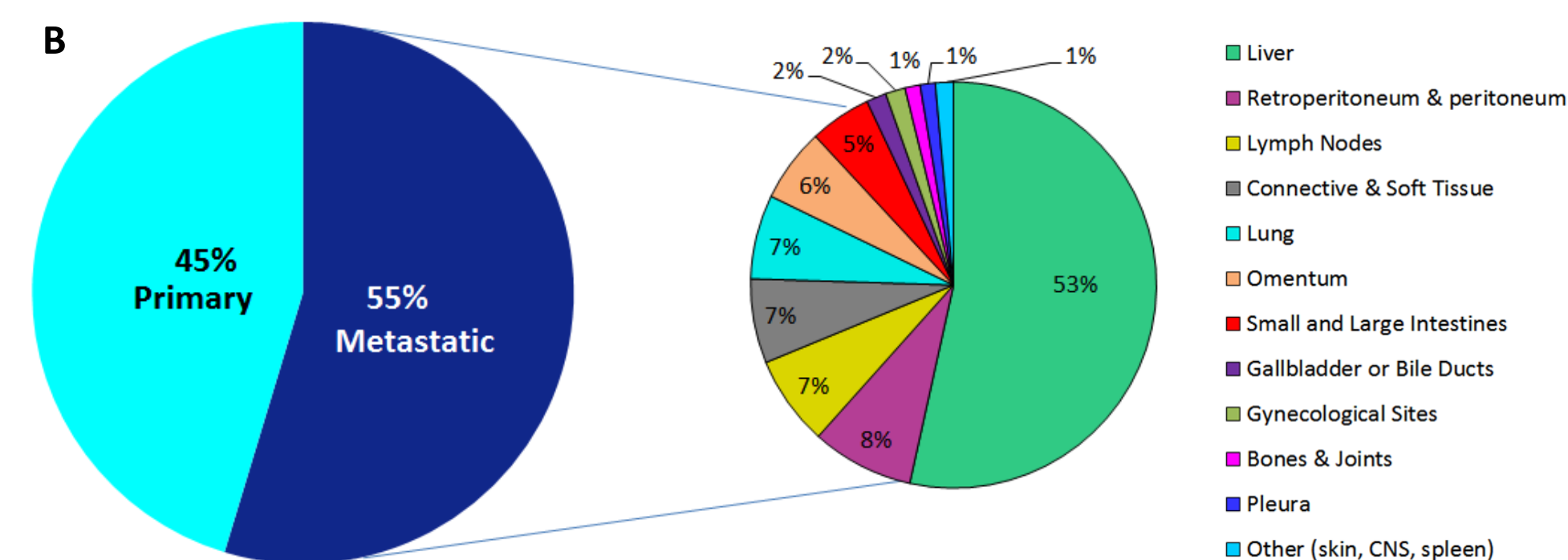


Figure 1 – Distribution of (A) age and gender, and (B) location of specimen sites utilized for profiling.



Results

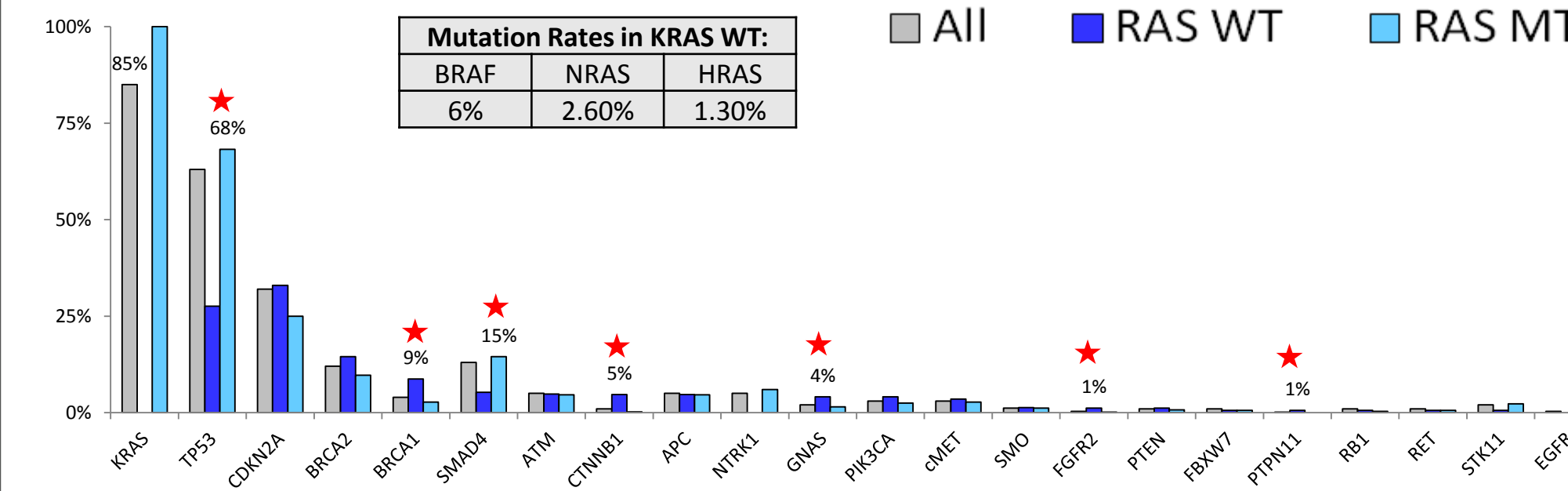


Figure 2 – Differences in mutation rates in KRAS WT and KRAS MT PC. Rates of mutation frequency in all PC are shown in grey bars. Statistically significant differences between KRAS WT and KRAS MT subgroups*.

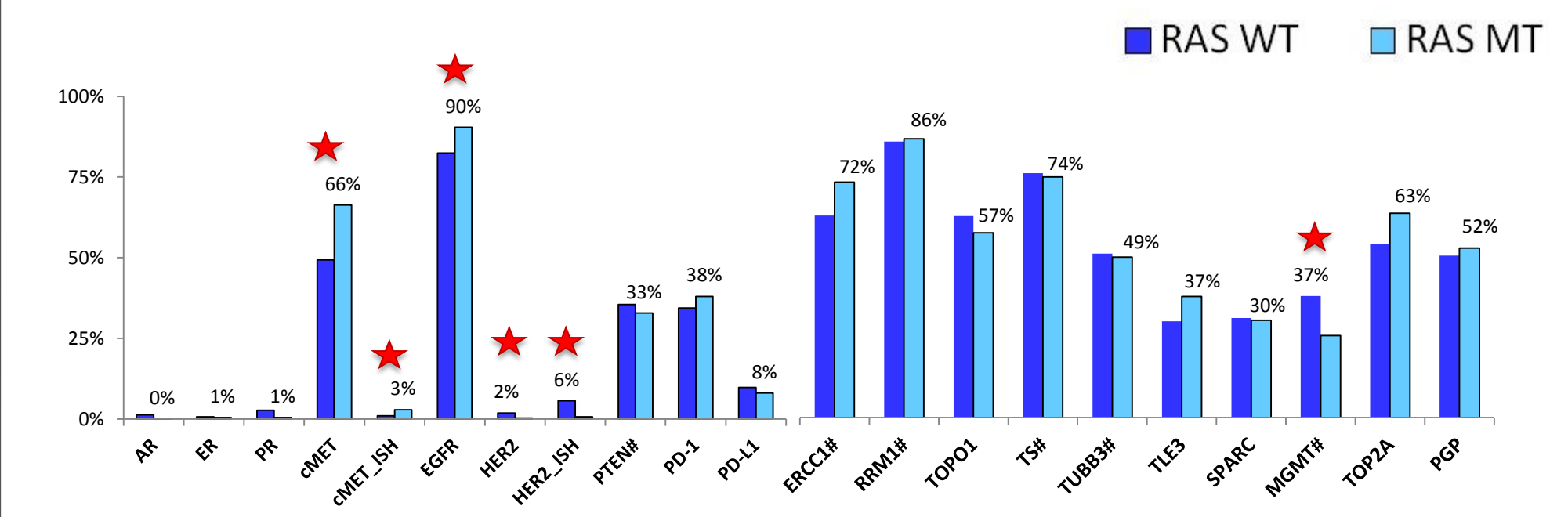


Figure 3 – Biomarker (IHC and ISH) differences between KRAS WT and MT PC. All frequencies shown are positivity or amplification rates, except where indicated by # which shows rate of low or negative expression. Statistically significant differences between KRAS WT and KRAS MT subgroups*.

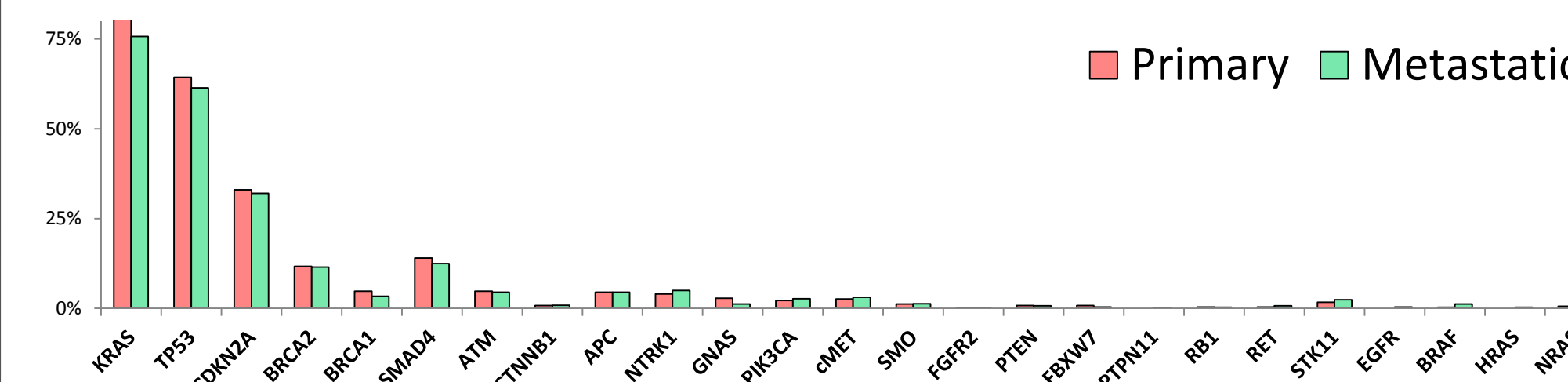


Figure 4 – Differences in mutation rates in primary and metastatic PC. There were no statistically significant differences identified between these two subgroups.

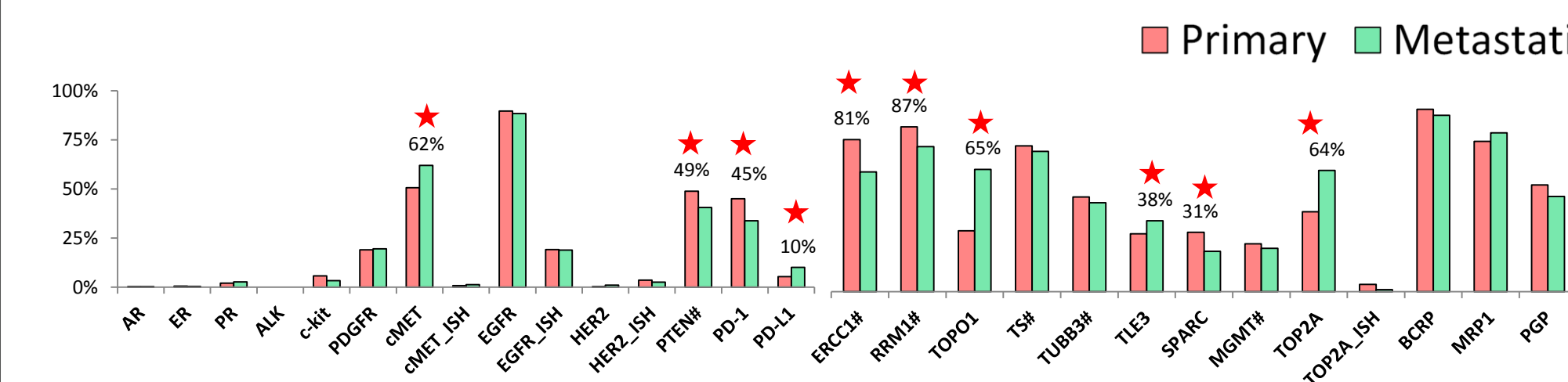


Figure 5 – Biomarker (IHC and ISH) differences between primary and metastatic PC. All frequencies shown are positivity or amplification rates, except where indicated by # which shows rate of low or negative expression. Statistically significant differences between subgroups*.

Results

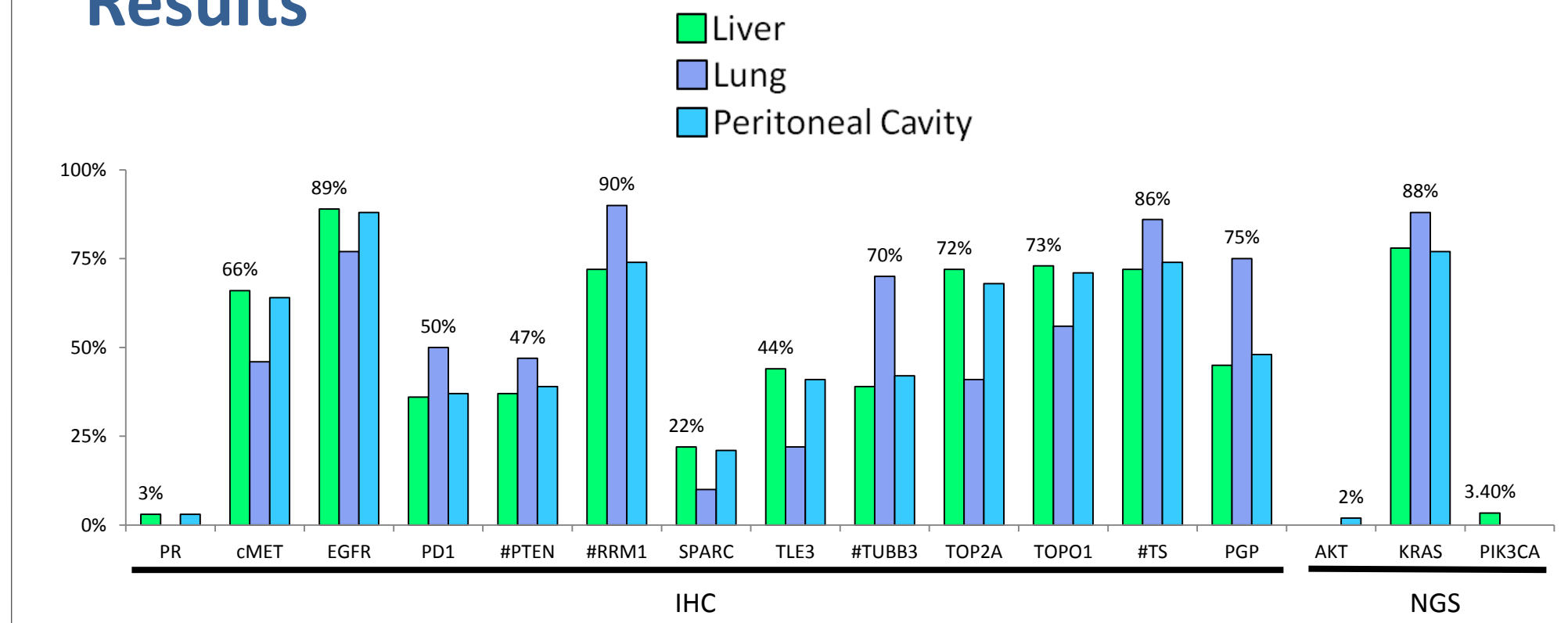


Figure 6 – Biomarker (IHC and NGS) differences between site-specific metastases. All frequencies shown are positivity or mutation rates, except where indicated by # which shows rate of low or negative expression. Only differences showing statistical significance are shown.

Conclusions

- Slight differences in mutation frequencies were observed, with higher frequencies in TP53 and SMAD4 in RAS MT PC and BRCA1 (and BRCA2, not significant), CTNNB1, GNAS and FGFR2 in RAS WT PC. Targeting of BRCA with DNA-damaging agents or PARP inhibitors, and Wnt pathway and FGFR2 inhibitors all deserve further investigation for subsets of RAS WT PC.
- Based on IHC data, HER2 positivity and low expression of MGMT occur with higher frequency in RAS WT PC, suggesting HER2-targeted therapies and alkylating agents as additional potential therapy options in RAS WT PC. cMET positivity was significantly higher in RAS MT PC, suggesting a potential role for cMET-targeted therapies in RAS MT PC.
- Comparisons between primary (localized) and metastatic PC showed no differences in mutation rates, however many differences were found for protein and gene copy number assays. Specifically, TOPO1, TOP2A, TLE3, PDL1 and cMET were all detected at higher frequencies in metastatic disease. In contrast, PC confined to the pancreas exhibited higher rates of PD-1 TILs, SPARC, and low expression of PTEN, ERCC1 and RRM1. These differences indicate potential differences in treatment of primary and metastatic disease.
- When site-specific metastases were compared for differences in biomarker expression, high PD1+ TILs and PGP, along with high rates of low PTEN, RRM1, TUBB3 and TS were correlated with lung metastases, whereas liver and peritoneal metastases exhibited similar patterns, with higher rates of cMET, EGFR, SPARC, TLE3, TOP2A and TOPO1. Higher rates mutations in KRAS were associated with lung metastases; AKT was associated with peritoneal metastases and PIK3CA with liver metastases. These site-specific differences indicate potential differences in treatment, according to the site of metastasis.

References

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