How is age correlated with metastasis, TP53 expression, and overall survival in colorectal cancer?

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Introduction

Estimated New Cases

Males

Prostate	164,690	19%
Lung & bronchus	121,680	14%
Colon & rectum	75,610	9%
Urinary bladder	62,380	7%
Melanoma of the skin	55,150	6%
Kidney & renal pelvis	42,680	5%
Non-Hodgkin lymphoma	41,730	5%
Oral cavity & pharynx	37,160	4%
Leukemia	35,030	4%
Liver & intrahepatic bile duct	30,610	4%
All Sites	**856,370**	**100%**

Estimated Deaths

Males

Lung & bronchus	83,550	26%
Prostate	29,430	9%
Colon & rectum	27,390	8%
Pancreas	23,020	7%
Liver & intrahepatic bile duct	20,540	6%
Leukemia	14,270	4%
Esophagus	12,850	4%
Urinary bladder	12,520	4%
Non-Hodgkin lymphoma	11,510	4%
Kidney & renal pelvis	10,010	3%
All Sites	**323,630**	**100%**

Cancer Statistics, 2018

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THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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Background


THE CANCER GENOME ATLAS
CPTAC
National Cancer Institute
at the National Institutes of Health

Background cont.

- Metastasis
  - Increasingly common among younger patients
  - Incidences remained relatively constant among old patients
- Age
  - Primary cancer risk factor
  - Duration of carcinogenesis, vulnerability of aging tissues to environmental carcinogens, and other bodily changes that favor the development and the growth of cancer
- TP53
  - Codes for p53, tumor suppressor protein
  - ~ 50% of CRC patients
  - Lower survival rates in patients receiving chemotherapy

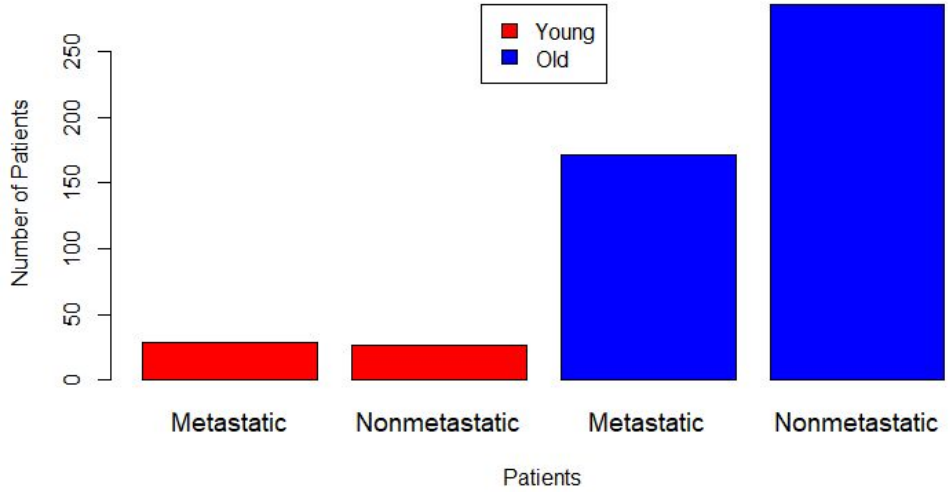
Methods

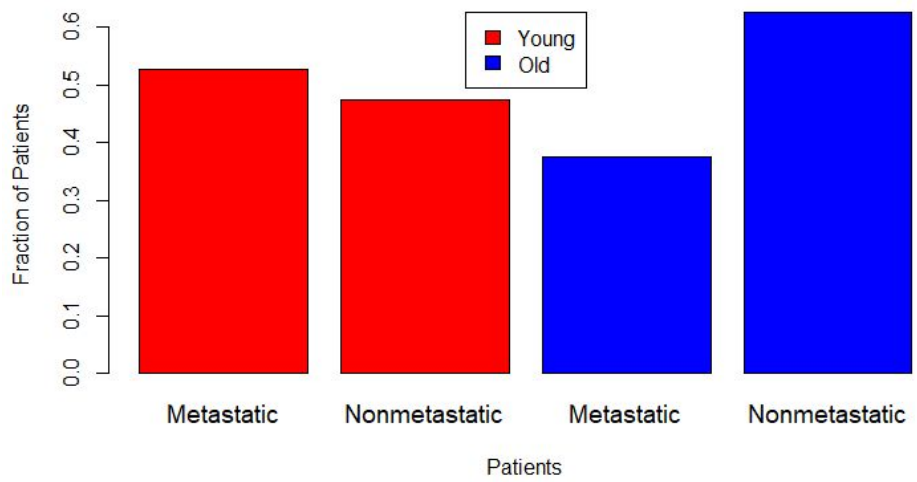
Variable	Metastatic status		Age	
	Non-metastatic	Metastatic	Young	Old
Categorization	Stages I, II	Stages III, IV	50 >	50 ≤
# of patients	312	200	49	348

Methods cont.

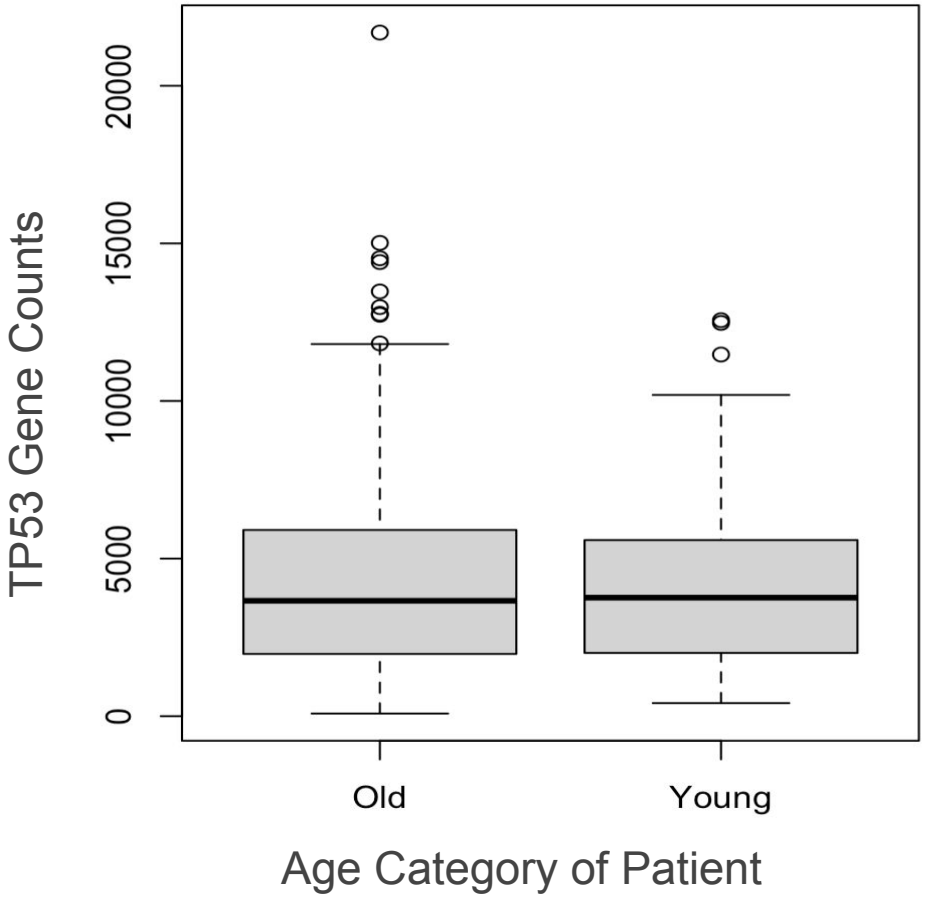
Language	Plot type	Variables	Data source
R	Bar graphs	Age groups, metastatic status	TCGA clinical
	Kaplan-Meier	Age groups	TCGA clinical
	coOncoplot	Top 5 mutated genes, age groups	TCGA MAF
	Box plot	Age groups, TP53 counts	TCGA SumExp
	Lollipop plot	TP53 mutations, age groups	TCGA MAF
Python	Spearman correlation	Transcriptomics, proteomics of coOncoplot genes	CPTAC

Comparing the percentage and direct counts, respectively, among age category and metastatic status

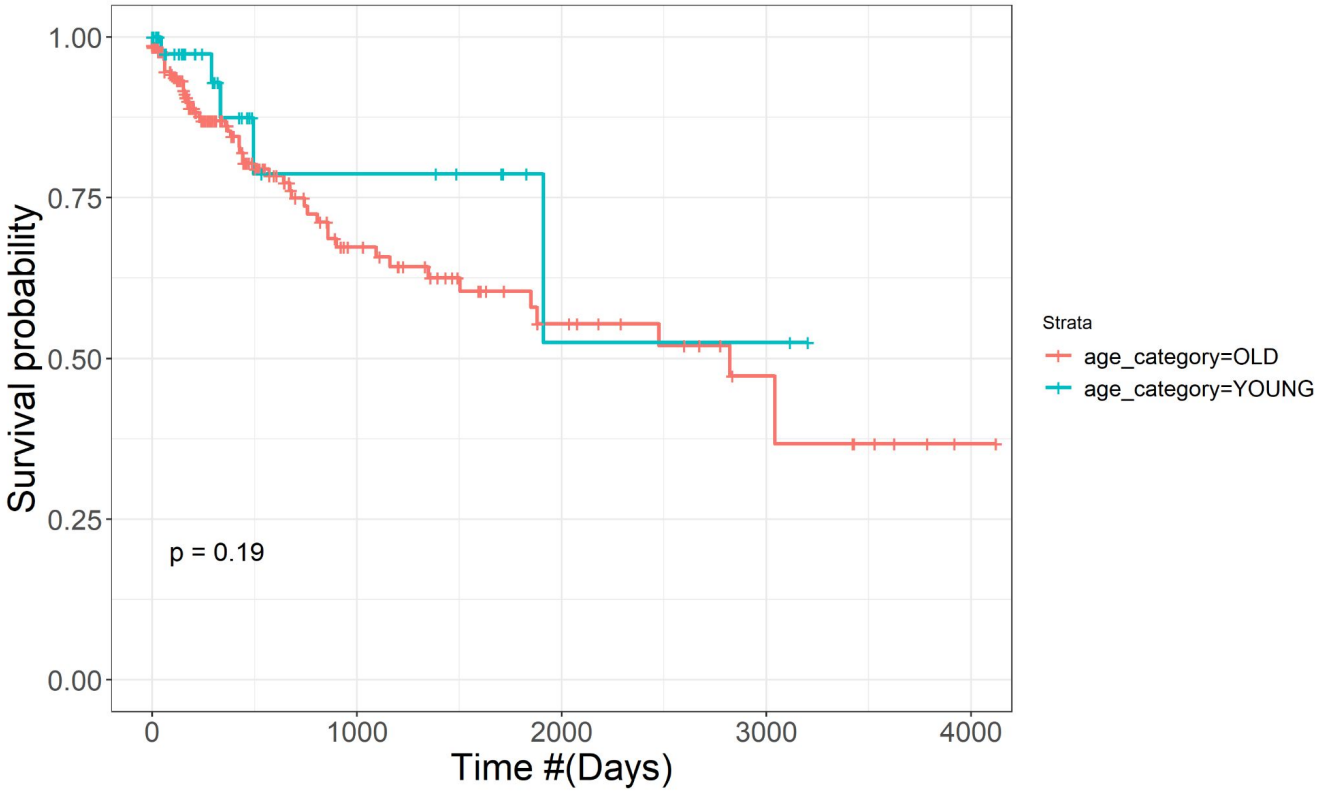




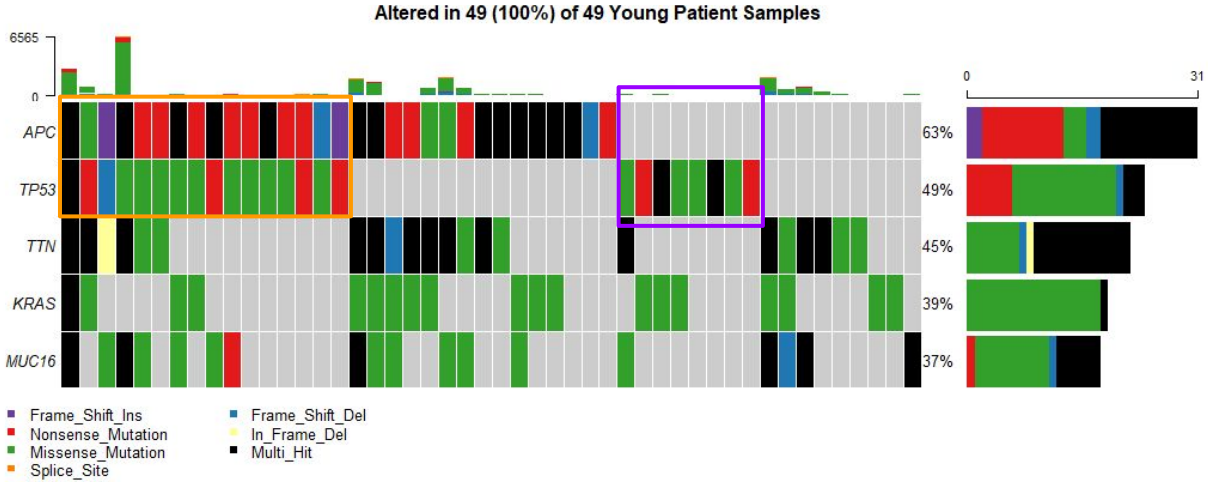
Comparing TP53 counts between age

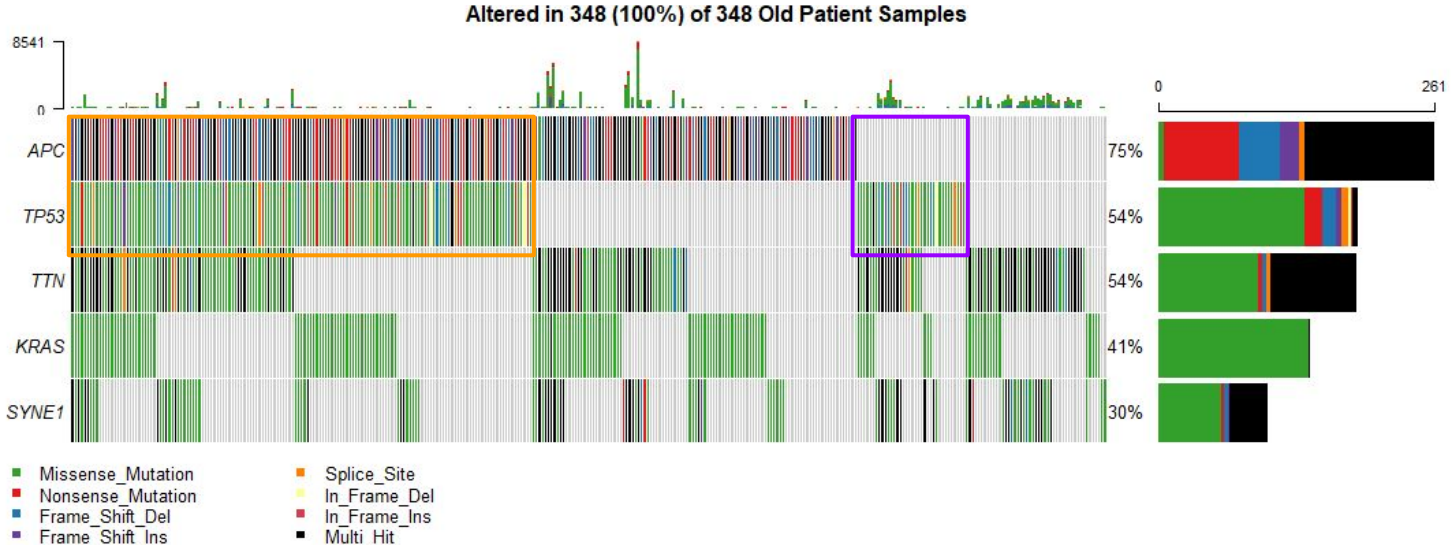


Determining differences in survival probability based on age

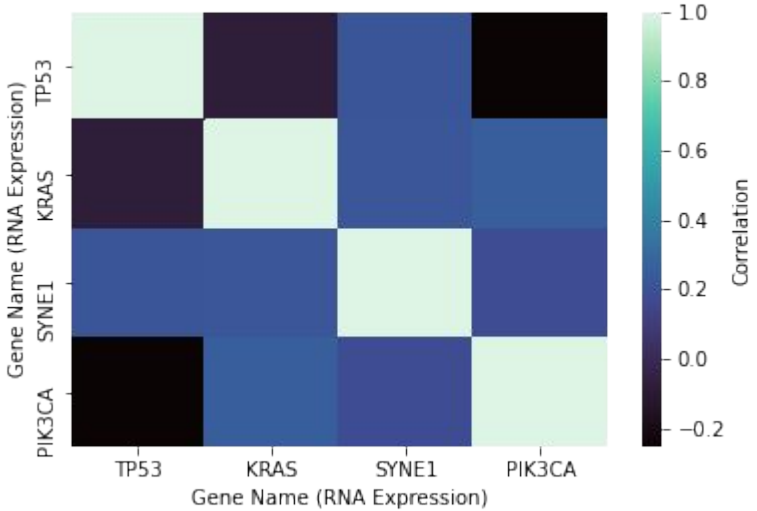


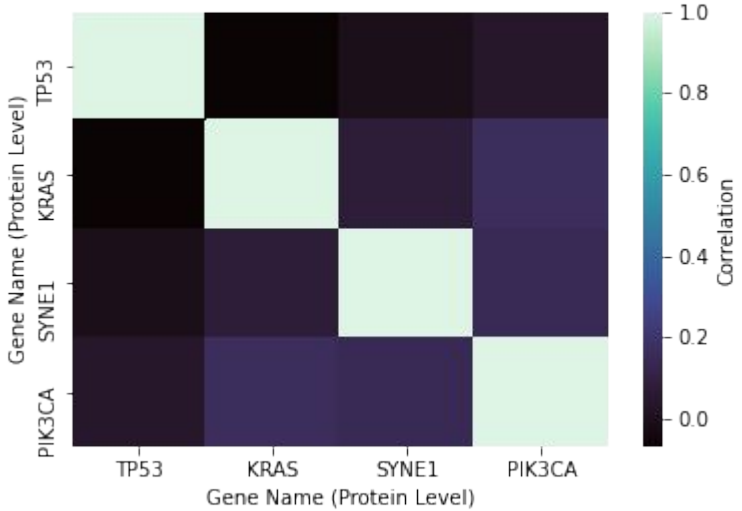
Top 5 mutated genes among patients in the Young category

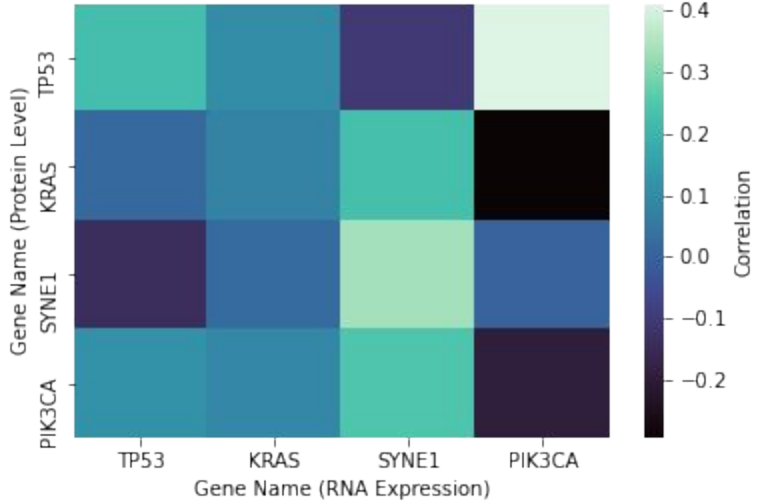


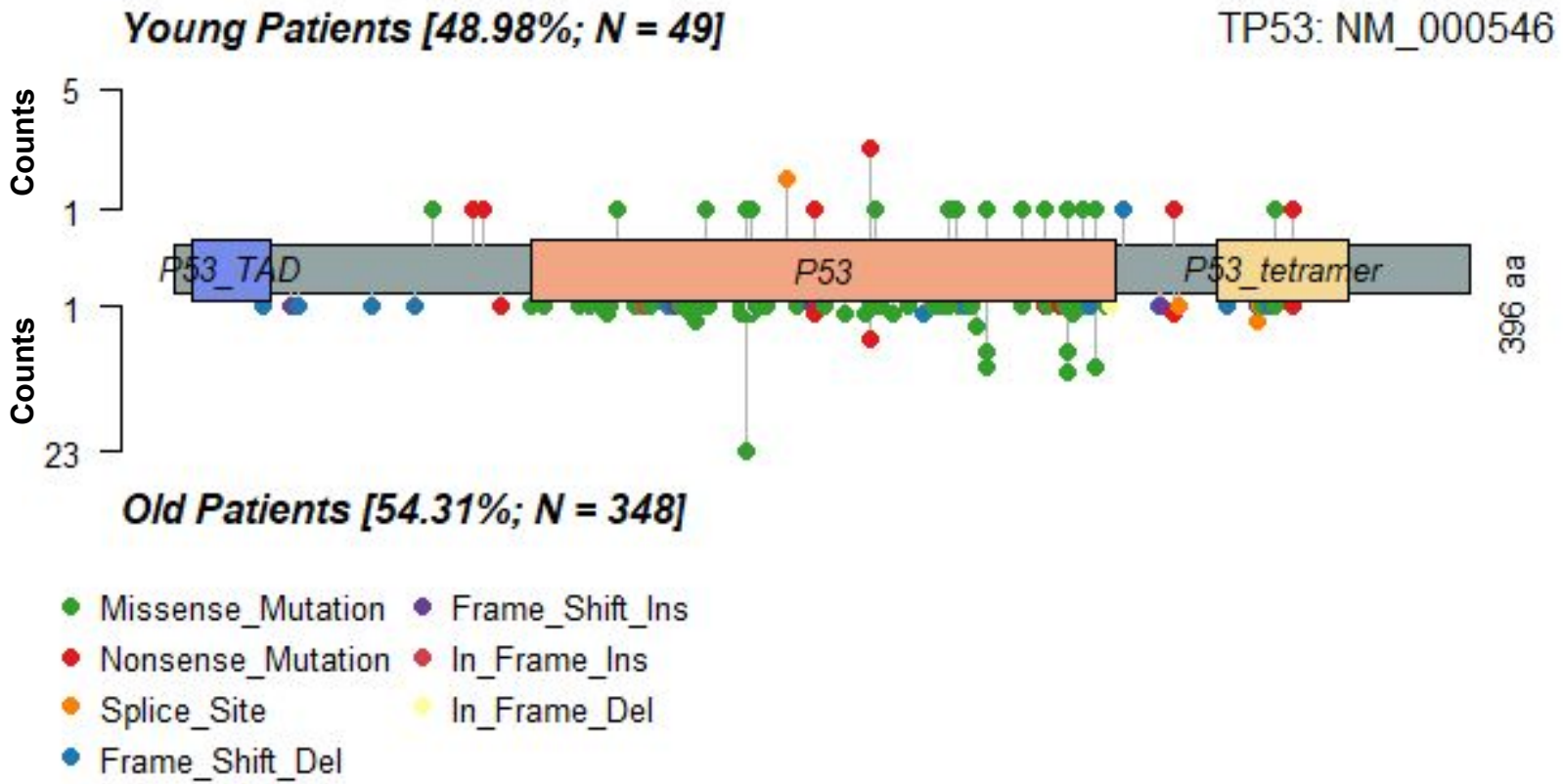


Top 5 mutated genes among patients in the Old category


Gene Name (RNA Expression)
TP53
KRAS
SYNE1
PIK3CA
Gene Name (RNA Expression)
Correlation
1.0
0.8
0.6
0.4
0.2
0.0
−0.2


Gene Name (Protein Level)
TP53
KRAS
SYNE1
PIK3CA
Gene Name (Protein Level)
Correlation
1.0
0.8
0.6
0.4
0.2
0.0


Gene Name (Protein Level)
TP53
KRAS
SYNE1
PIK3CA
Gene Name (RNA Expression)
Correlation
0.4
0.3
0.2
0.1
0.0
−0.1
−0.2


Young Patients [48.98%; N = 49]
TP53: NM_000546
Counts
5
1
P53_TAD
P53
P53_tetramer
396 aa
1
Counts
23
Old Patients [54.31%; N = 348]
Missense_Mutation
Frame_Shift_Ins
Nonsense_Mutation
In_Frame_Ins
Splice_Site
In_Frame_Del
Frame_Shift_Del

Discussion

- Limitations
  - Selection bias
- Metastasis percentage greater in younger patients
  - Increase in anti-inflammaging factors (Pretzsch)
  - Diagnostic classification differences based on age (Yang)
  - Mucinous adenocarcinoma in old, Right-sided location cancer in young
- No significant difference in TP53 expression between age
  - More mutations in older patients

Discussion cont.

- Correlation of PIK3CA RNA with TP53 protein presence
  - PIK3CA responsible for cell growth and division
  - Suggests role in co-activity of both genes in CRC
  - Consistent with study on lung cancer, indicates correlation beyond CRC

Future Directions

- Higher percentage of metastatic patients in younger category
- Role of TP53 and PIK3CA co-expression
- TP53 post translational modifications from RNA to protein
- APC gene
- Proposed study
  - In-depth analysis of age and metastasis
  - Multiple datasets to reduce selection bias

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