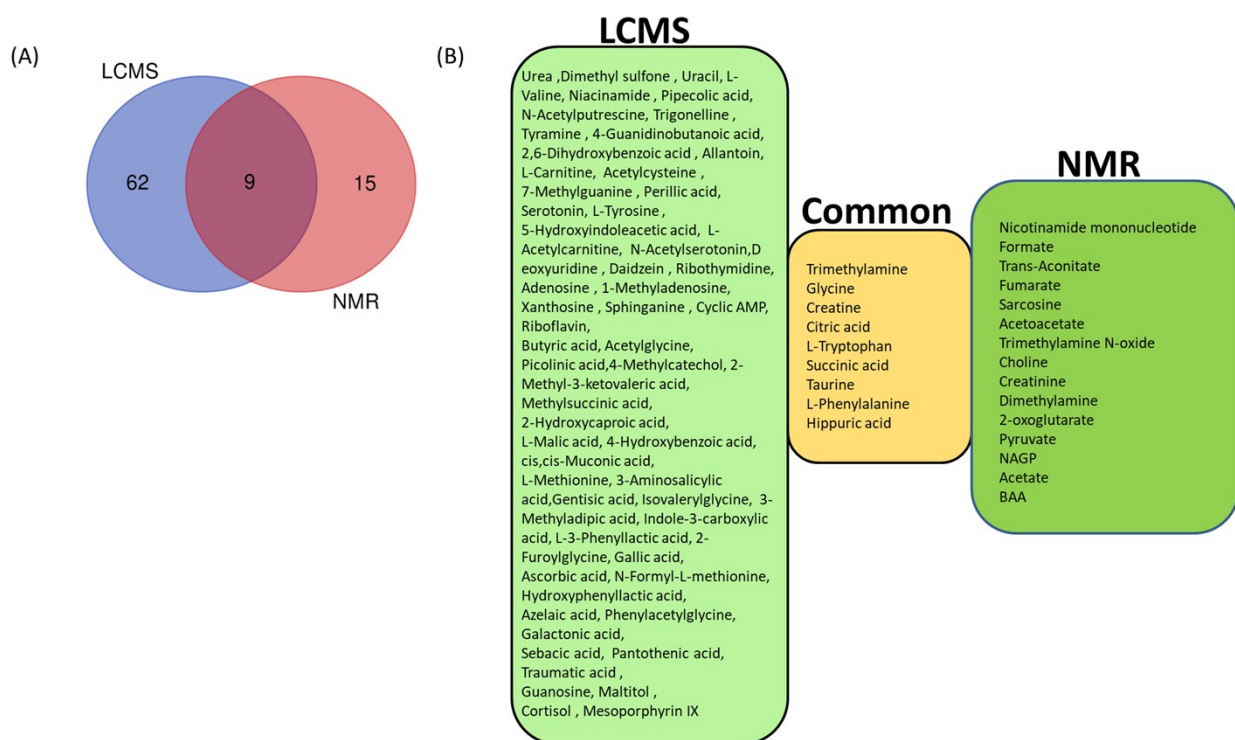


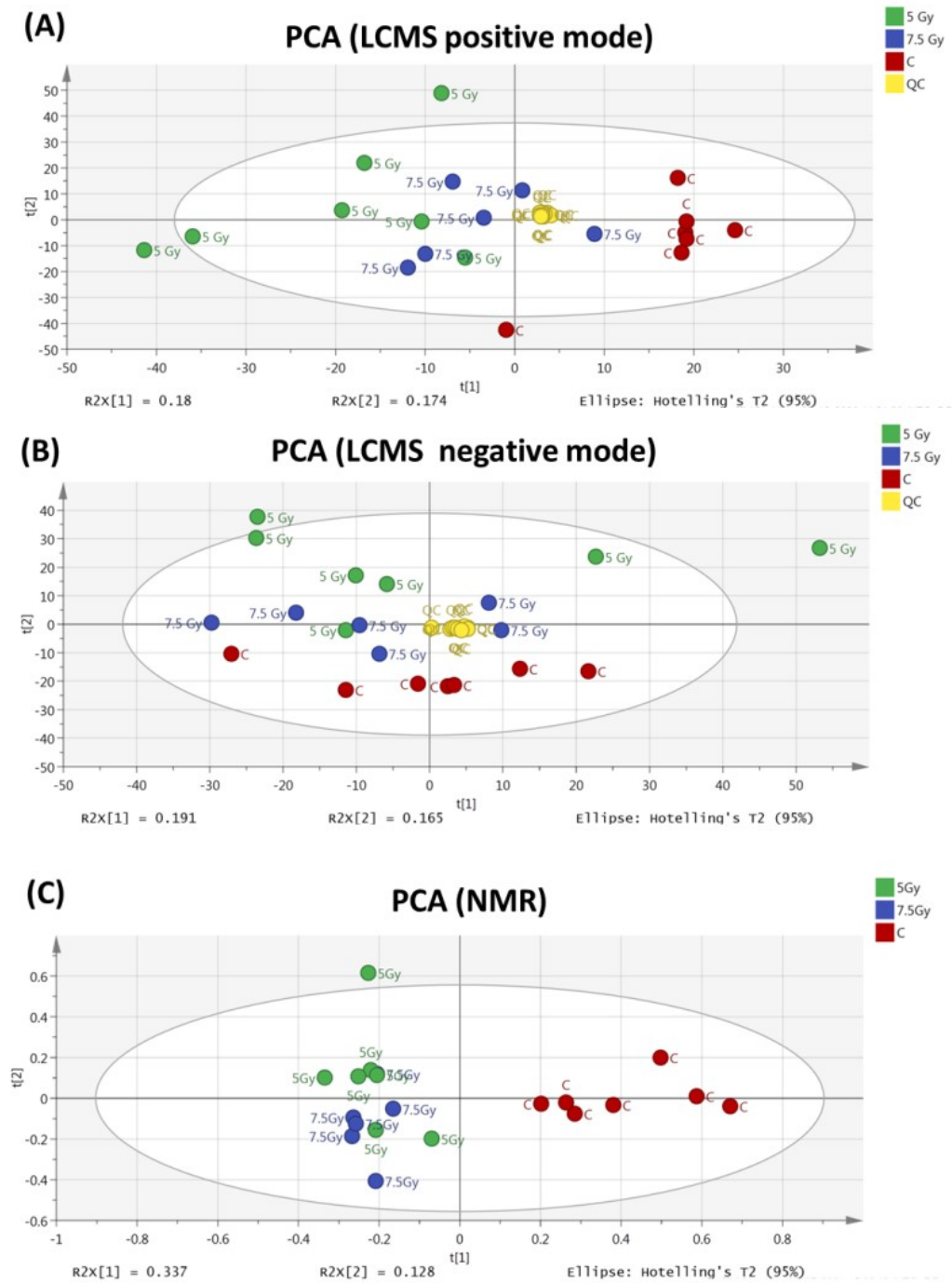
## Supplementary Figures

### Figure S1



**Figure S1:** Venn diagram showing (A) metabolite numbers and (B) metabolite names identified using LC-MS and NMR techniques.

Figure S2

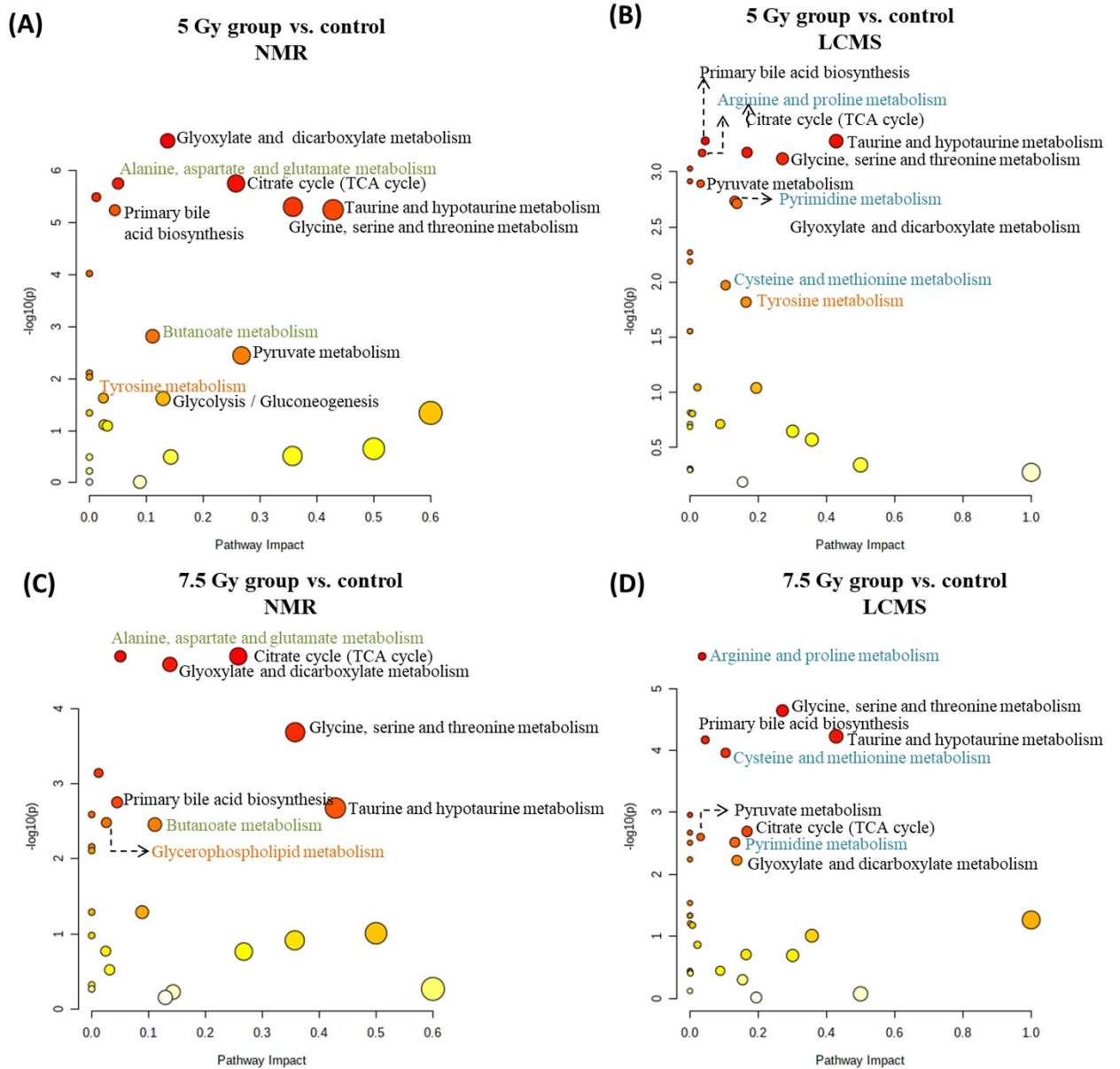


**Figure S2:** PCA score plot of m/z peaks in: (A) Positive mode, (B) Negative mode generated from LC-MS and (C) bins generated from NMR analysis in urine sample of control vs. irradiated.

(Quality control samples (QC): Yellow color; Control (C): Red; 5 Gy group: Green and 7.5 Gy group: Blue).



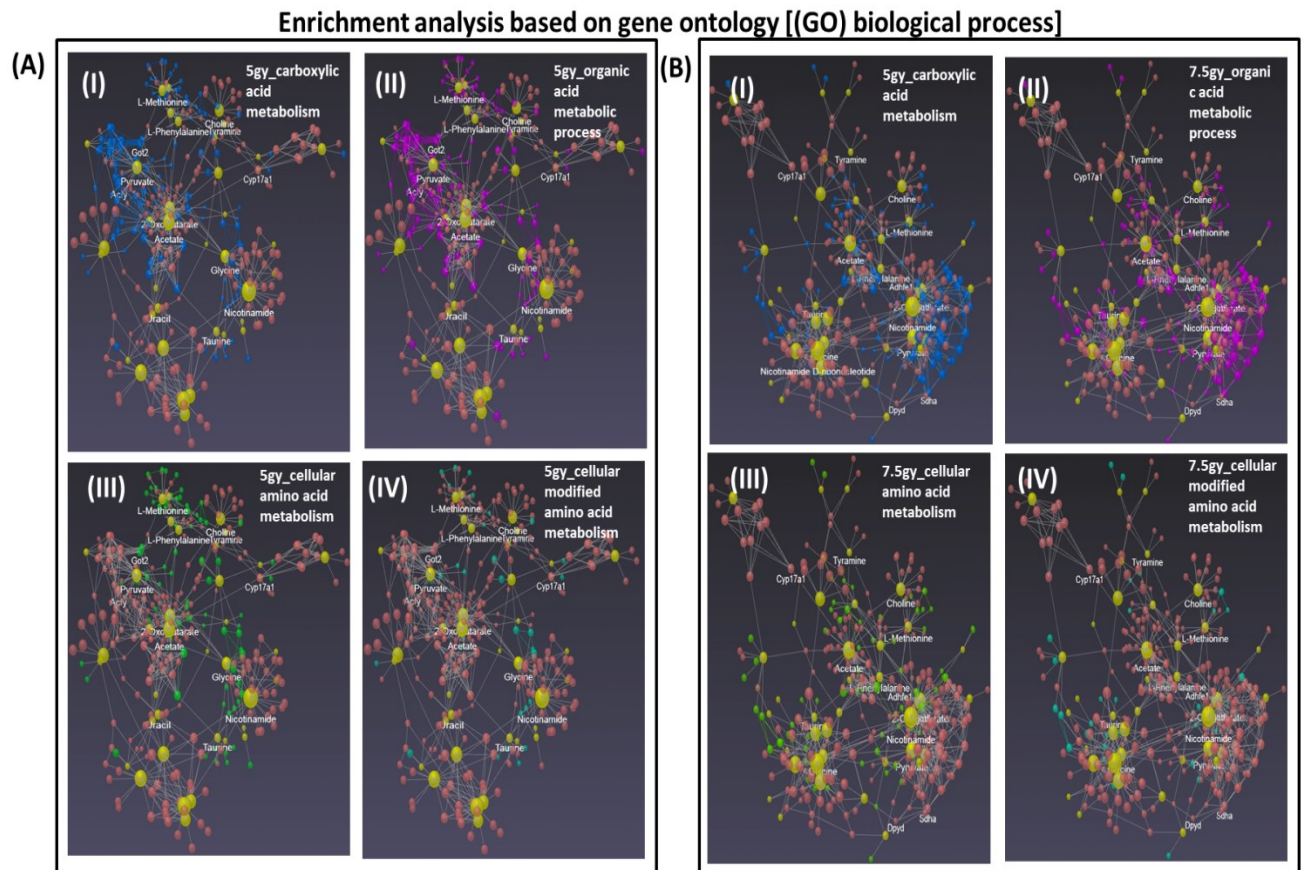
**Figure S4**



**Figure S4:** Dysregulated metabolic pathways based on individual pathway analysis of NMR and LC-MS data post radiation exposure.

(Pathways font color; Black: present in both NMR and LC-MS; Green: present only in NMR; Blue: present in LC-MS alone; Orange; unique to 5 Gy and 7.5 Gy dose group).

Figure S5



**Figure S5:** Functional pathway enrichment analysis based on gene ontology (GO) biological process of (A) 5 Gy and (B) 7.5 Gy radiation dose groups by OmicsNet.

(Query molecules:-yellow, edges:-grey color, nodes:-Peach and Query pathway network; (I) nodes-blue; (II) nodes-pink; (III) nodes-green; (IV) nodes-Turquoise).

**Figure S6**

S.No.	Metabolites	Multivariate [VIP scores (OPLSDA)]						Univariate				Multi-omics based pathway results
		LCMS		NMR		Multi-Block		LCMS		NMR		
		7.5gy	5Gy	7.5gy	5gy	7.5gy	5gy	7.5Gy	5Gy	7.5Gy	5Gy	
1	Creatine											
2	Taurine											
3	Citrate											
4	Trimethylamine											
5	2-oxoglutarate											
6	Branched chain amino acid											
7	Ascorbic acid											
8	Phenylacetylglycine											
9	Trigonelline											
10	Urea											
11	Galactonic acid											
12	L-Acetylcarnitine											
13	2-Methyl-3-ketovaleric acid											
14	Hippuric acid											
15	L-Carnitine											
16	Isovalerylglycine											
17	Sebacic acid											
18	L-Malic acid											
19	4-Guanidinobutanoic acid											
20	Adenosine											
21	Ribothymidine											
22	Succinate											
23	Trimethylamine N-oxide											
24	Choline											
25	Creatinine											
26	Phenylalanine											
27	Acetate											
28	Deoxyuridine											
29	Butyric acid											
30	Dimethyl amine											
31	Fumarate											
32	L-Methionine											
33	N-acetyl glycoprotein											

**Figure S6:** Overlapping significant metabolites with multi-omics based EGFR tyrosine kinase inhibitor (TKI) resistance pathway.

(Orange: Metabolites overlapping with EGFR tyrosine kinase inhibitor resistance pathway; Green: metabolites having VIP score >1; Purple: FDR corrected (p-values <0.05) metabolites in univariate analysis).

**Table S1:** Tabular representation of perturbed pathways post irradiation.

<b>5 Gy vs. control</b>							
<b>Pathways</b>	<b>Total Cmpd</b>	<b>Hits</b>	<b>Raw p</b>	<b>-log10(p)</b>	<b>Holm adjust</b>	<b>FDR</b>	<b>Impact</b>
Glyoxylate and dicarboxylate metabolism	32	6	3.33E-08	7.4772	1.17E-06	1.17E-06	0.138
Citrate cycle (TCA cycle)	20	6	4.41E-07	6.3559	1.50E-05	7.71E-06	0.302
Alanine, aspartate and glutamate metabolism	28	5	1.71E-06	5.7676	5.63E-05	1.99E-05	0.05
Taurine and hypotaurine metabolism	8	1	0.0005253	3.2796	0.01681	0.003006	0.429
Primary bile acid biosynthesis	46	2	0.00055053	3.2592	0.017066	0.003006	0.045
Arginine and proline metabolism	38	4	0.00068219	3.1661	0.020466	0.003006	0.036
Glycine, serine and threonine metabolism	34	5	0.00068526	3.1641	0.020466	0.003006	0.358
Pyruvate metabolism	22	4	0.00068701	3.163	0.020466	0.003006	0.299
Pyrimidine metabolism	39	2	0.0018419	2.7347	0.049731	0.007163	0.132
Tyrosine metabolism	42	6	0.0021814	2.6613	0.056716	0.007629	0.189
Butanoate metabolism	15	4	0.0023978	2.6202	0.059944	0.007629	0.111

<b>7.5 Gy vs. control</b>							
<b>Pathways</b>	<b>Total Cmpd</b>	<b>Hits</b>	<b>Raw p</b>	<b>-log10(p)</b>	<b>Holm adjust</b>	<b>FDR</b>	<b>Impact</b>
Arginine and proline metabolism	38	4	3.12E-06	5.5054	0.000109	6.08E-05	0.036
Glyoxylate and dicarboxylate metabolism	32	6	4.22E-06	5.3752	0.000143	6.08E-05	0.138
Citrate cycle (TCA cycle)	20	6	5.21E-06	5.2834	0.000172	6.08E-05	0.302
Glycine, serine and threonine metabolism	34	5	9.99E-06	5.0003	0.00032	8.74E-05	0.358
Alanine, aspartate and glutamate metabolism	28	5	2.01E-05	4.6977	0.000622	0.00014	0.05
Primary bile acid biosynthesis	46	2	4.30E-05	4.367	0.001289	0.000251	0.045
Taurine and hypotaurine metabolism	8	1	5.93E-05	4.2272	0.001719	0.000296	0.429
Pyruvate metabolism	22	4	0.0023897	2.6217	0.064523	0.009293	0.299
Pyrimidine metabolism	39	2	0.0030379	2.5174	0.078987	0.010473	0.132
Glycerophospholipid metabolism	36	1	0.0032915	2.4826	0.082287	0.010473	0.026
Butanoate metabolism	15	4	0.0036733	2.4349	0.08816	0.010714	0.111

**Table S2:** Tabular representation of functional pathway enrichment analysis based on gene ontology (GO) biological process by OmicsNet in 5 Gy and 7.5 Gy radiation dose groups.

**5 Gy vs. control**

Pathway	Total	Expected	Hits	P.Value	FDR
EGFR tyrosine kinase inhibitor resistance	1540	50.2	251	4.57E-158	1.52E-155
Cysteine and methionine metabolism	52	1.69	37	2.29E-44	3.80E-42
Endocrine resistance	120	3.9	50	1.21E-43	1.34E-41
Citrate cycle (TCA cycle)	32	1.04	28	1.78E-38	1.47E-36
Tyrosine metabolism	40	1.3	30	3.03E-37	2.01E-35
Pyruvate metabolism	38	1.23	29	2.05E-36	1.13E-34
Nicotinate and nicotinamide metabolism	43	1.4	30	1.20E-35	5.68E-34
Glycine, serine and threonine metabolism	40	1.3	29	2.74E-35	1.14E-33
Tryptophan metabolism	48	1.56	31	3.62E-35	1.33E-33
ABC transporters	77	2.5	35	2.93E-32	9.72E-31
Phenylalanine metabolism	23	0.747	21	6.34E-30	1.91E-28
Antifolate resistance	19	0.617	18	1.75E-26	4.85E-25
Glycolysis / Gluconeogenesis	66	2.14	27	1.50E-23	3.82E-22
Alanine, aspartate and glutamate metabolism	38	1.23	20	1.74E-20	4.13E-19
Valine, leucine and isoleucine degradation	56	1.82	23	2.91E-20	6.45E-19
Pyrimidine metabolism	58	1.88	22	1.58E-18	3.27E-17
beta-Alanine metabolism	32	1.04	17	1.13E-17	2.21E-16
Glyoxylate and dicarboxylate metabolism	31	1.01	16	1.96E-16	3.61E-15
Arginine and proline metabolism	50	1.62	19	3.55E-16	6.20E-15
Histidine metabolism	24	0.78	13	6.19E-14	1.03E-12
Phenylalanine, tyrosine and tryptophan biosynthesis	8	0.26	8	1.13E-12	1.78E-11
Taurine and hypotaurine metabolism	11	0.357	9	1.85E-12	2.79E-11
Lysine degradation	61	1.98	16	5.48E-11	7.91E-10
Riboflavin metabolism	8	0.26	7	2.76E-10	3.82E-09
Propanoate metabolism	33	1.07	11	3.59E-09	4.77E-08
Drug metabolism - cytochrome P450	69	2.24	15	3.83E-09	4.88E-08
Butanoate metabolism	27	0.877	10	5.78E-09	7.11E-08
Purine metabolism	136	4.42	20	1.30E-08	1.54E-07
Selenocompound metabolism	17	0.552	7	5.22E-07	5.97E-06
Valine, leucine and isoleucine biosynthesis	4	0.13	4	1.09E-06	1.20E-05
Aminoacyl-tRNA biosynthesis	66	2.14	12	1.12E-06	1.20E-05
Arginine biosynthesis	19	0.617	7	1.28E-06	1.29E-05
One carbon pool by folate	19	0.617	7	1.28E-06	1.29E-05
Vitamin B6 metabolism	9	0.292	5	3.96E-06	3.86E-05
Drug metabolism - other enzymes	88	2.86	13	4.61E-06	4.37E-05
Steroid hormone biosynthesis	89	2.89	13	5.24E-06	4.83E-05
Synthesis and degradation of ketone bodies	11	0.357	5	1.37E-05	0.000123



Pantothenate and CoA biosynthesis	18	0.585	6	1.49E-05	0.00013
Fatty acid degradation	50	1.62	9	2.76E-05	0.000235
Metabolism of xenobiotics by cytochrome P450	67	2.18	10	5.38E-05	0.000436
Pancreatic cancer	95	3.09	12	5.38E-05	0.000436
Ether lipid metabolism	47	1.53	8	0.000117	0.000927
Folate biosynthesis	26	0.845	6	0.000148	0.00114
Glutathione metabolism	65	2.11	9	0.00023	0.00173
Inflammatory bowel disease (IBD)	67	2.18	9	0.00029	0.00214
Non-alcoholic fatty liver disease (NAFLD)	69	2.24	9	0.000364	0.0026
Longevity regulating pathway	84	2.73	10	0.000368	0.0026
Thyroid hormone synthesis	57	1.85	8	0.000465	0.00322
Glycerophospholipid metabolism	97	3.15	10	0.00116	0.00785
Ascorbate and aldarate metabolism	27	0.877	5	0.00157	0.0104
Fanconi anemia pathway	34	1.1	5	0.00449	0.0292
Retinol metabolism	91	2.96	8	0.00928	0.0593
Type II diabetes mellitus	101	3.28	8	0.0167	0.105
Cortisol synthesis and secretion	104	3.38	8	0.0197	0.121
Protein processing in endoplasmic reticulum	8	0.26	2	0.0259	0.156
D-Arginine and D-ornithine metabolism	1	0.0325	1	0.0325	0.193
Endocrine and other factor-regulated calcium reabsorption	159	5.17	10	0.0343	0.2
Glycerolipid metabolism	61	1.98	5	0.0475	0.268
Sulfur metabolism	11	0.357	2	0.0477	0.268

### 7.5 Gy vs. control

Pathway	Total	Expected	Hits	P.Value	FDR
EGFR tyrosine kinase inhibitor resistance	1540	50.7	254	2.36E-160	7.84E-158
Cysteine and methionine metabolism	52	1.71	37	3.47E-44	5.76E-42
Endocrine resistance	120	3.94	50	2.12E-43	2.34E-41
Citrate cycle (TCA cycle)	32	1.05	28	2.42E-38	2.01E-36
Tyrosine metabolism	40	1.31	30	4.22E-37	2.80E-35
Pyruvate metabolism	38	1.25	29	2.82E-36	1.56E-34
Nicotinate and nicotinamide metabolism	43	1.41	30	1.67E-35	7.92E-34
Glycine, serine and threonine metabolism	40	1.31	29	3.78E-35	1.57E-33
Tryptophan metabolism	48	1.58	31	5.09E-35	1.88E-33
ABC transporters	77	2.53	35	4.29E-32	1.42E-30
Phenylalanine metabolism	23	0.755	21	7.99E-30	2.41E-28
Antifolate resistance	19	0.624	18	2.13E-26	5.90E-25
Glycolysis / Gluconeogenesis	66	2.17	27	1.99E-23	5.09E-22
Valine, leucine and isoleucine degradation	56	1.84	24	1.59E-21	3.78E-20
Alanine, aspartate and glutamate metabolism	38	1.25	20	2.16E-20	4.78E-19
Pyrimidine metabolism	58	1.9	22	1.98E-18	4.12E-17
beta-Alanine metabolism	32	1.05	17	1.36E-17	2.65E-16

Glyoxylate and dicarboxylate metabolism	31	1.02	16	2.32E-16	4.28E-15
Arginine and proline metabolism	50	1.64	19	4.33E-16	7.56E-15
Histidine metabolism	24	0.788	13	7.10E-14	1.18E-12
Butanoate metabolism	27	0.887	13	5.22E-13	8.26E-12
Phenylalanine, tyrosine and tryptophan biosynthesis	8	0.263	8	1.23E-12	1.85E-11
Taurine and hypotaurine metabolism	11	0.361	9	2.03E-12	2.94E-11
Lysine degradation	61	2	16	6.43E-11	8.90E-10
Riboflavin metabolism	8	0.263	7	2.98E-10	3.95E-09
Propanoate metabolism	33	1.08	11	4.01E-09	5.13E-08
Drug metabolism - cytochrome P450	69	2.27	15	4.42E-09	5.44E-08
Synthesis and degradation of ketone bodies	11	0.361	7	1.13E-08	1.34E-07
Purine metabolism	136	4.47	20	1.56E-08	1.79E-07
Selenocompound metabolism	17	0.558	7	5.61E-07	6.20E-06
Valine, leucine and isoleucine biosynthesis	4	0.131	4	1.14E-06	1.22E-05
Aminoacyl-tRNA biosynthesis	66	2.17	12	1.26E-06	1.30E-05
Arginine biosynthesis	19	0.624	7	1.37E-06	1.34E-05
One carbon pool by folate	19	0.624	7	1.37E-06	1.34E-05
Vitamin B6 metabolism	9	0.296	5	4.17E-06	3.95E-05
Drug metabolism - other enzymes	88	2.89	13	5.17E-06	4.77E-05
Steroid hormone biosynthesis	89	2.92	13	5.88E-06	5.28E-05
Pantothenate and CoA biosynthesis	18	0.591	6	1.58E-05	0.000138
Fatty acid degradation	50	1.64	9	3.00E-05	0.000255
Metabolism of xenobiotics by cytochrome P450	67	2.2	10	5.89E-05	0.000483
Pancreatic cancer	95	3.12	12	5.96E-05	0.000483
Ether lipid metabolism	47	1.54	8	0.000126	0.000998
Folate biosynthesis	26	0.854	6	0.000157	0.00121
Glutathione metabolism	65	2.13	9	0.000249	0.00188
Inflammatory bowel disease (IBD)	67	2.2	9	0.000314	0.00232
Non-alcoholic fatty liver disease (NAFLD)	69	2.27	9	0.000393	0.00283
Longevity regulating pathway	84	2.76	10	0.000401	0.00283
Thyroid hormone synthesis	57	1.87	8	5.00E-04	0.00346
Glycerophospholipid metabolism	97	3.19	10	0.00126	0.00851
Ascorbate and aldarate metabolism	27	0.887	5	0.00164	0.0109
Fanconi anemia pathway	34	1.12	5	0.00469	0.0306
Retinol metabolism	91	2.99	8	0.00986	0.063
Type II diabetes mellitus	101	3.32	8	0.0177	0.111
Cortisol synthesis and secretion	104	3.41	8	0.0208	0.128
Protein processing in endoplasmic reticulum	8	0.263	2	0.0264	0.159
D-Arginine and D-ornithine metabolism	1	0.0328	1	0.0328	0.195
Endocrine and other factor-regulated calcium reabsorption	159	5.22	10	0.0364	0.212
Sulfur metabolism	11	0.361	2	0.0486	0.277
Glycerolipid metabolism	61	2	5	0.0493	0.277

