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Exploring the Cancer-Associated Role of PITRM1: A Pan-Cancer Bioinformatics Analysis

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ABSTRACT

PITRM1 is a mitochondrial protein that plays a role in protein quality control and normal mitochondrial function. Previous studies have shown that PITRM1 plays a role in mitochondrial homeostasis, neurodegeneration, and a number of other established functions, but recent evidence has emerged for a role in cancer biology. By leveraging publicly available cancer genomics datasets, the genomic alterations, expression patterns, mutation distribution, and survival associations of PITRM1 in cancer were examined. A pan-cancer analysis was performed on 12 studies, representing 156,010 samples and 148,790 patients, followed by brain-, lung-, and thyroid-focused analyses. The frequency of PITRM1 alteration differed by cancer type and included missense mutations, deep deletions, and amplifications. The pan-cancer survival analysis did not reveal any significant difference in overall survival with PITRM1 alteration status ($p=0.662$). In contrast, PITRM1 alterations were significantly associated with poorer survival in brain cancer ($p = 1.462 \times 10^{-4}$; HR = 2.641) and thyroid cancer ($p = 7.119 \times 10^{-4}$; HR = 2.150). There was no significant association with survival in lung cancer ($p = 0.435$). The different types of PITRM1 mutations were found throughout the protein domains by mutation analysis. These results indicate that the cancer association of PITRM1 could be dependent on tumor type and biological context. Additional clinical and experimental research is needed to evaluate the potential prognostic or functional role of PITRM1 in particular cancers.

KEYWORDS: *PITRM1, pan-cancer, cancer genomics, mitochondrial proteostasis, bioinformatics, brain cancer, thyroid cancer, lung cancer*

1. INTRODUCTION

Cancer is a highly heterogeneous disease that develops through the accumulation of genetic and epigenetic changes that affect cell growth, differentiation, survival, and tissue organization. Although cancers arise from different tissues, they share several biological features, including uncontrolled proliferation, resistance to cell death, genomic instability, and altered cellular metabolism. The combination of genetic alterations differs between cancer types and contributes to differences in tumor behavior, treatment response, and patient survival (Brown et al., 2023).

Oncogenes, tumor suppressor genes, kinases, cell-surface receptors and transcription factors are examples of genes associated with cancer. Mutations in genes like MYC, RAS, BRAF, TP53, BRCA1, and PTEN can affect cells' growth, DNA repair, and survival mechanisms (Chillón-Pino et al., 2024; Sinkala, 2023).

These genetic changes have helped in creating targeted drugs for cancer treatment. For instance, mutations in the epidermal growth factor receptor (EGFR) in lung cancer can help direct the use of EGFR-targeted medications, and mutations in BRAF have been used to help identify patients who may benefit from BRAF-targeted therapy. The examples illustrate how the discovery of molecular alterations in cancer can help to better understand the biology of tumour and develop new therapies.

Mitochondria are membrane-bound organelles which produce cellular energy and help regulate a number of processes that are important for cell survival, metabolism and stress responses. The mitochondrial electron transport chain (ETC) is a system of electron carriers in the inner mitochondrial membrane that carry electrons to respiratory complexes and create a proton gradient to generate adenosine triphosphate (ATP) via oxidative phosphorylation. Reactive oxygen species (ROS) are also formed by electron transfer and typically act as signaling molecules, but can lead to oxidative damage if present in excess. Cancer cells often experience metabolic and redox transformation wherein they are able to continue generating energy, withstand oxidative stress, and adapt to hypoxia and nutrient deprivation (Wang et al., 2025) . Thus, mitochondrial dysfunction may affect the progression of tumour by altering tumour energy metabolism, ROS signalling, tumour cell apoptosis, and cellular stress responses.

PITRM1 is a mitochondrial matrix protease that can degrade mitochondrial targeting sequences and other short peptides. Its activity helps in the control of mitochondrial protein quality and the prevention of accumulation of peptides that could otherwise interfere with mitochondrial function (Ståhl et al., 2002; Brunetti et al., 2021; Heller et al., 2026). PITRM1 has also been studied about neurodegeneration. Abnormal PITRM1 function has been implicated in the deposition of mitochondrial amyloid-β peptide and the development of Alzheimer's disease-like features, and mutations in PITRM1 have been correlated with neurological features including progressive ataxia, cognitive impairment, and psychiatric symptoms (Brunetti et al., 2015; Pérez et al., 2020). These results suggest that PITRM1 plays a role in preserving mitochondrial proteostasis, especially in mitochondria-sensitive cells.

PITRM1 has been studied extensively in the context of mitochondrial proteostasis and neurodegeneration, but it is unclear whether it has any relevance to cancer. Studies related to cancer have mostly focused on breast cancer and on experimental models, such as associations with mitochondrial dysfunction, ferroptosis, and therapeutic response. These results suggest that PITRM1 might play a role in tumor biology via mitochondrial and cellular stress responses, but this may not occur in all cancers.

However, the evidence supporting a cancer-associated role of PITRM1 is sparse and has been mostly in relation to breast cancer and experimental models. Whether the PITRM1 alterations, the changes in expression, and clinical associations are limited to specific tumor types or are more prevalent in cancer is thus not known. This is an important question because there may be significant functional differences in mitochondrial metabolism, oxidative stress, and proteostasis between tumor lineages. A gene that associates with tumor behavior in one cancer type may thus have a different or no measurable association in another cancer type.

In the current analysis, the authors will therefore explore whether PITRM1 displays distinct alterations at the genomic level and in expression, mutation distribution, and overall survival across cancer types, using

publicly available cancer datasets. Patterns of PITRM1 alteration were found in several cancer types, including brain, lung, and thyroid cancer, which were studied in more detail. The analysis is exploratory, and it does not imply a universal role for PITRM1 as an oncogene or tumor suppressor.

2. MATERIALS AND METHODS

2.1 Data Access:

The Cancer Genome Atlas (TCGA) data was obtained from cBioPortal for Cancer Genomics (https://www.cbioportal.org/) and Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia2.cancer-pku.cn/#index). The platforms were used to examine gene expression (OncoPrint) and genetic alteration and survival analysis of PITRM1 in different types of cancers (Tang et al., 2019; The Cancer Genome Atlas Network, 2012).

2.2 Data selection:

Cancer genomics datasets that were publicly available were downloaded from the cBioPortal for Cancer Genomics platform (https://www.cbioportal.org/) to examine the contribution of PITRM1 in various cancer types. The following criteria were used for the selection of datasets: (i) comprehensive genomic alteration data, such as mutations and copy number alterations, were available, (ii) clinical and survival data were available, (iii) the datasets were large-scale pan-cancer studies, and (iv) the datasets were publicly accessible with standardized annotation and quality control. Studies lacking full genomic and/or clinical information are not included in the analysis.

A total of 12 pan-cancer analyses (148,790 patients and 156,010 samples) were included for the pan-cancer analysis. The datasets selected were: Cancer Therapy and Clonal Hematopoiesis (MSK, Nat Genet 2020); China Pan-cancer (OrigiMed, Nature 2022); Metastasis Solid Cancers (UMich, Nature 2017); MSK MetTropism (MSK, Cell 2021); MSK-CHORD (MSK, Nature 2024); MSK-IMPACT 50K Clinical Sequencing Cohort (MSK, Cancer Cell 2026); MSK-IMPACT Clinical Sequencing Cohort (MSK, Nat Med 2017); MSS Mixed Solid Tumors (Broad/Dana-Farber, Nat Genet 2018); Pan-cancer Analysis of Whole Genomes (ICGC/TCGA, Nature 2020); SUMMIT-Neratinib Basket Study (Multi-Institute, Nature 2018); TMB and Immunotherapy (MSK, Nat Genet 2019); and Tumors with TRK Fusions (MSK, Clin Cancer Res 2020). These data sets were chosen as being representative of a variety of different types of cancers and for their high level of genomic profiling data for pan-cancer analysis of PITRM1.

2.3 Gene Expression Analysis

The Gene Expression Profiling Interactive Analysis 2 (GEPIA2) web server (http://gepia2.cancer-pku.cn/) was used for gene expression analysis for PITRM1, which uses the RNA sequencing data from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) projects. The gene symbol “PITRM1” was subjected to a GEPIA2 search, and its expression levels were analysed between tumor and normal tissues.

2.4 Oncoprint Analysis

The genomic alteration profile of PITRM1 was investigated and visualized in selected cancer types on the cBioPortal platform. The Symbol for the gene 'PITRM1' was entered into the 'Query by Gene' function of cBioPortal, and the resulting genomic alteration information was retrieved from the selected cancer studies.

A visualisation of the genomic alteration profile was done with the aid of an OncoPrint, with individual columns representing tumour samples and the row representing PITRM1. The platform-generated annotation and color coding were used to represent different classes of genomic alterations such as missense mutations, truncating mutations, splice-site alterations, amplifications, deep deletions, and multiple alterations. Samples with at least one detectable PITRM1 genomic alteration were categorized as 'altered', and those without detectable genomic alterations as 'unaltered'.

2.5 Analysis of Somatic Mutation Distribution

Somatic mutations in the PITRM1 protein sequence were visualized in terms of their distribution across the gene sequence in cBioPortal. PITRM1 mutation information was obtained from the tumor datasets selected by searching for PITRM1 gene mutations (Cerami et al. 2012).

The mutations were displayed using a mutation distribution or lollipop plot of the position and abundance of mutations throughout the PITRM1 protein sequence. Mutational alterations identified were classified based on the type of mutation, as annotated by the cBioPortal platform, such as missense mutations, truncating mutations, splice-site mutations, and in-frame mutations. Mutations were analyzed to see if there were any hot spots or recurring mutation locations within the protein PITRM1.

2.6 Analysis of Survival Prognosis

The "Comparison/Survival" module of cBioPortal was used for survival analysis. Genomic changes like mutations and copy number changes were analysed in the patients' genomes and classified into 'altered' and 'unaltered' groups.

The difference in overall survival was evaluated by the Kaplan–Meier survival curve analysis between the two groups. The log-rank test was used to check the statistical significance in the cBioPortal platform. Statistical significance was defined as a p-value < 0.05.

2.7 Genetic Alteration Analysis

The Cancer Types Summary module of the cBioPortal was used to quantify and profile genomic alterations in PITRM1 in cancer types. Mutations, gene amplifications, and deep deletions were identified.

Alteration frequencies were obtained from the cBioPortal platform and represent the percentage of samples with detectable PITRM1 alterations. Copy number alteration (CNA) data were analysed based on the CNA categories provided by cBioPortal. The patterns and frequencies of PITRM1 alterations were

compared between different cohorts of tumors using the resulting statistical summaries and graphical representations.

Cancer-specific analyses were conducted using histological subtypes or disease subtypes reported by cBioPortal, provided sufficient data was available for these types. Broad cancer-level results are the aggregate cancer-level results from the selected cBioPortal study, while the subtype-level results are reported separately if available. This distinction is significant as there are different histological and molecular subtypes of an organ system that may have different genomic profiles and clinical outcomes.

3. RESULTS

3.1 Pan-Cancer Expression of PITRM1

PITRM1 expression profile was first analysed in various tumour and corresponding normal tissue types. The expression pattern showed large differences among tumor types, suggesting that PITRM1 is not generally expressed in all cancers. In several tumor categories, PITRM1 expression was down-regulated compared to the normal tissues, while others had relatively similar or up-regulated tumor expression.

The expression profile thus suggested that the expression of PITRM1 is tissue-specific and might reflect tissue-specific metabolic needs and mitochondrial activity between the different tumor lineages.

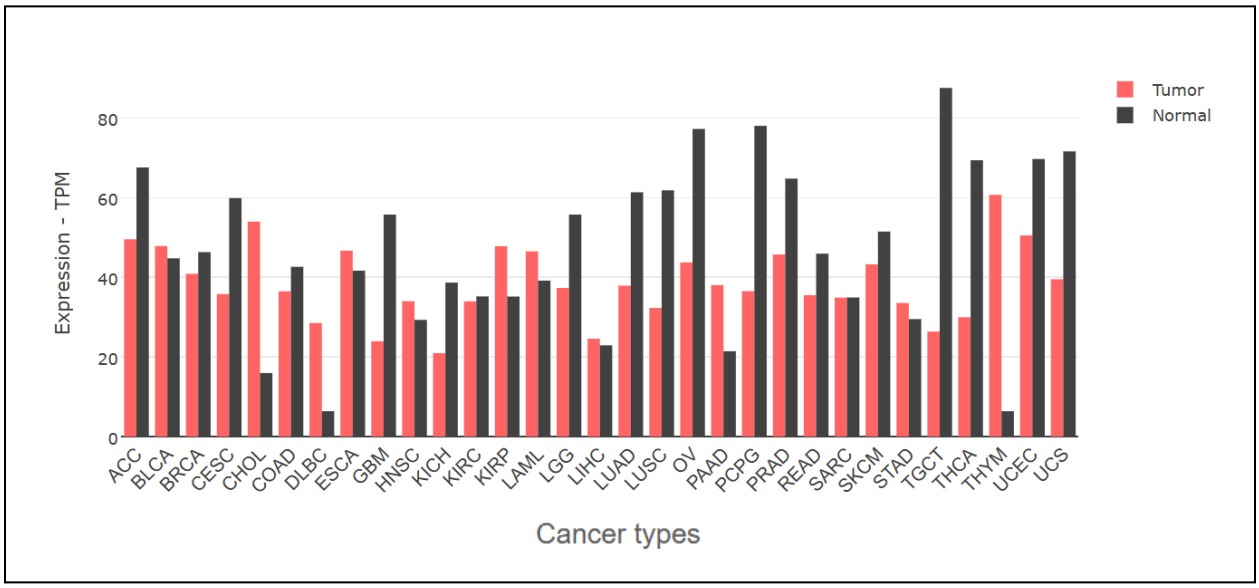


Figure 1. Gene expression profile in tumour and normal tissues. The bar plot shows the median expression of PITRM1 in tumor and normal tissues. Higher or lower expression represents differences in the median transcript abundance of PITRM1 between tumor and normal tissues.

The profile of genomic alterations of PITRM1 was then explored in a large pan-cancer cohort of 156,010 samples from 148,790 patients, across 12 studies. The changes in PITRM1 included amplification, deep deletion, and missense events. The overall OncoPrint showed that there was no detectable alteration in the majority of samples, and only a small number of samples had alterations in PITRM1.

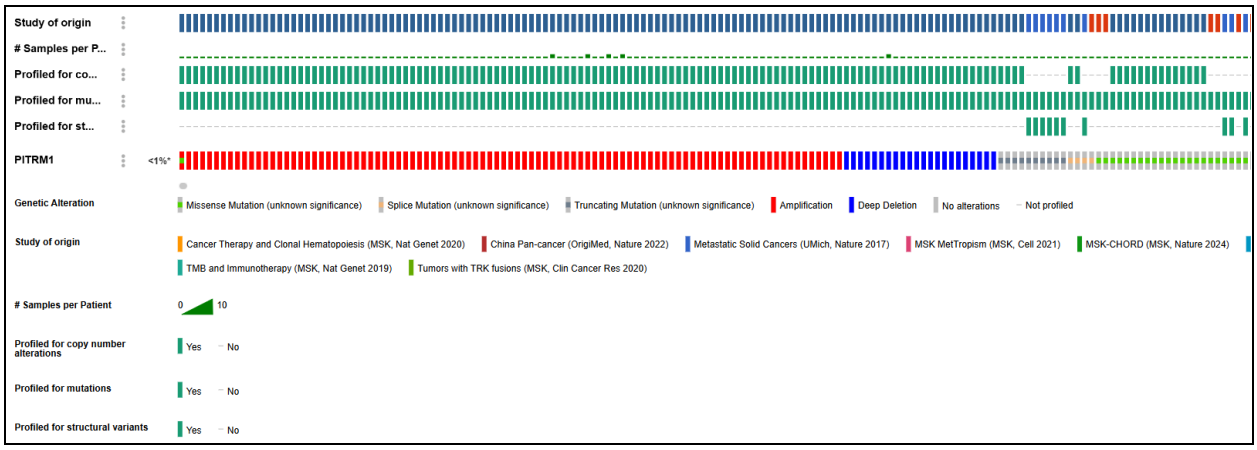


Figure 2. Pan-cancer PITRM1 OncoPrint analysis. The OncoPrint summarizes PITRM1 genomic alterations across the selected cancer datasets. Each column represents a tumor sample, and the PITRM1 row represents the presence and type of genomic alteration. Alterations include missense mutations, truncating mutations, splice-site alterations, amplifications, deep deletions, and multiple alterations, as annotated by cBioPortal.

The analysis of Cancer Types Summary showed significant differences in the frequency of PITRM1 alterations for each of the tumor categories. Alteration frequencies were higher in some tumor types (exceeding ~10%) than in several common adult cancers (significantly lower frequencies). The most significant changes were noted in specific tumor types and not throughout the pan-cancer set.

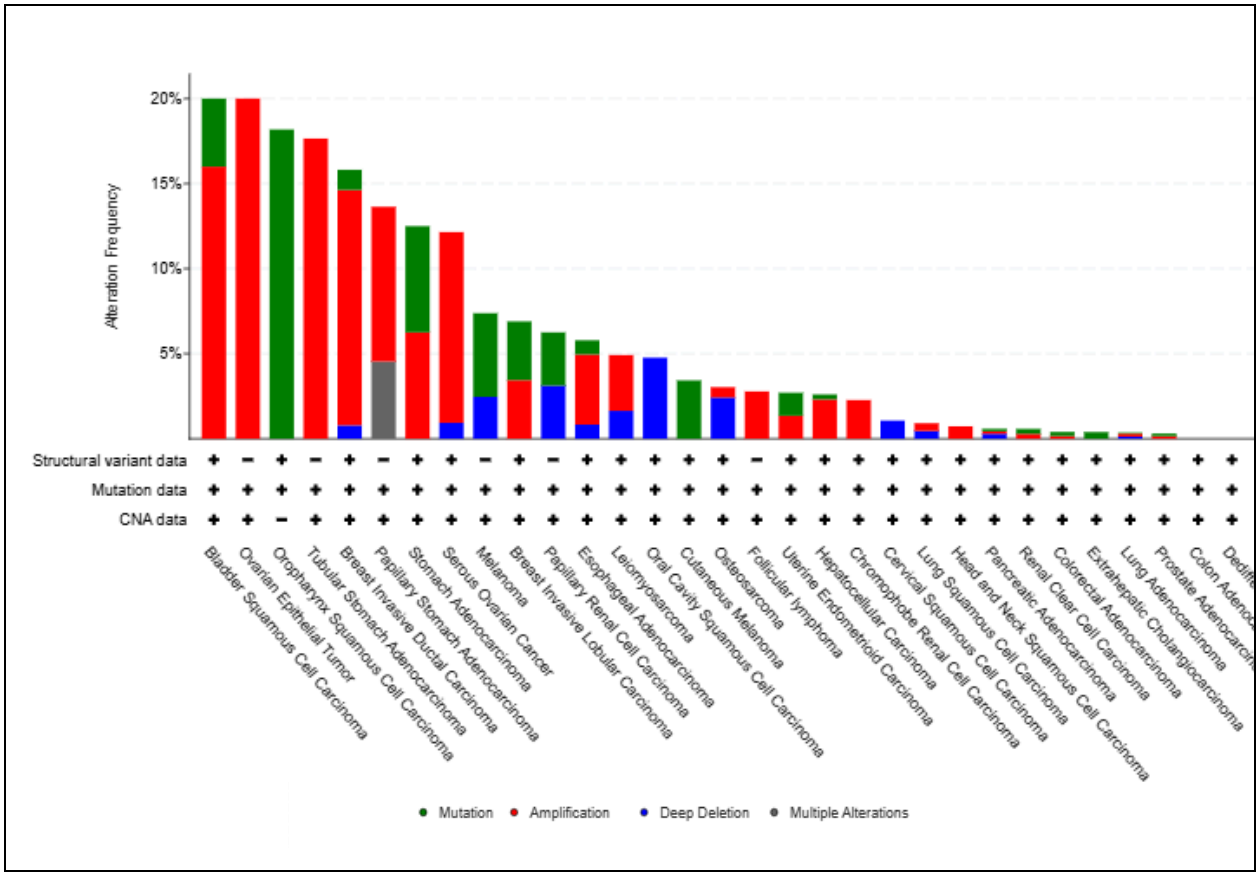


Figure 3. Analysis of PITRM1 by genetic alteration in cancer types. The bar graph shows the percentage of samples with detectable PITRM1 genomic alterations in the analyzed cancer categories. Alteration frequencies include mutations and copy-number alterations as reported by cBioPortal.

The protein-level mutation analysis revealed that PITRM1 mutations were not concentrated in one hotspot. The protein has a number of structural regions that are related to peptidases, and the variants identified occurred at different positions within the protein, which has a length of about 1,038 amino acids.

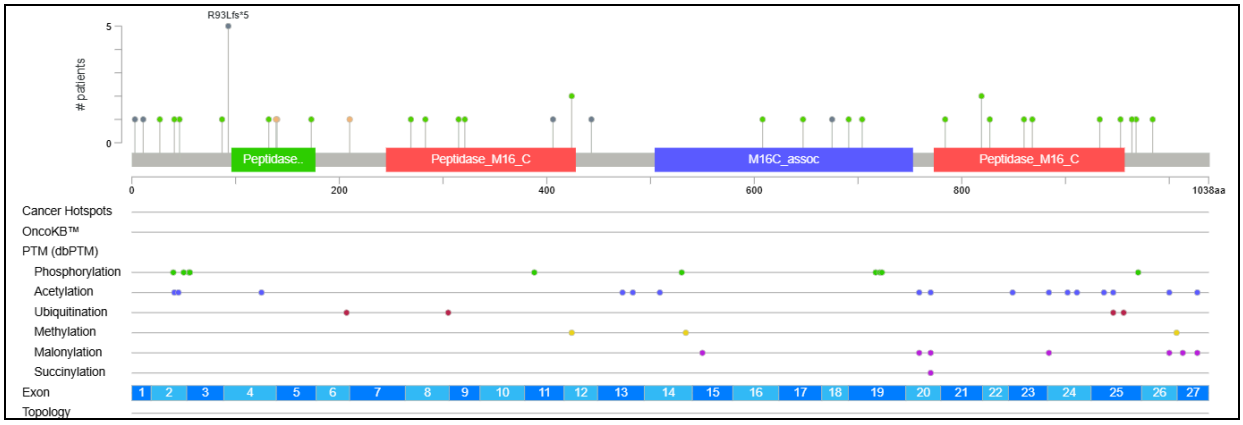


Figure 4. Distribution of somatic mutations in PITRM1.The lollipop plot shows the positions and relative frequency of reported PITRM1 somatic mutations across the 1,038-amino-acid protein. Mutation classes and protein domains are indicated in the figure.

Overall survival was then analyzed based on the presence or absence of PITRM1 alteration. There were 18 patients in the altered group and 612 patients in the unaltered group. The unaltered group had 217 events, and the altered group had 10 events. The median overall survival was ~ 37.73 months in the altered group and ~37.04 months in the unaltered group. The log-rank p-value was 0.662, which showed that the overall survival of PITRM1-altered patients and unaltered patients was not statistically different.

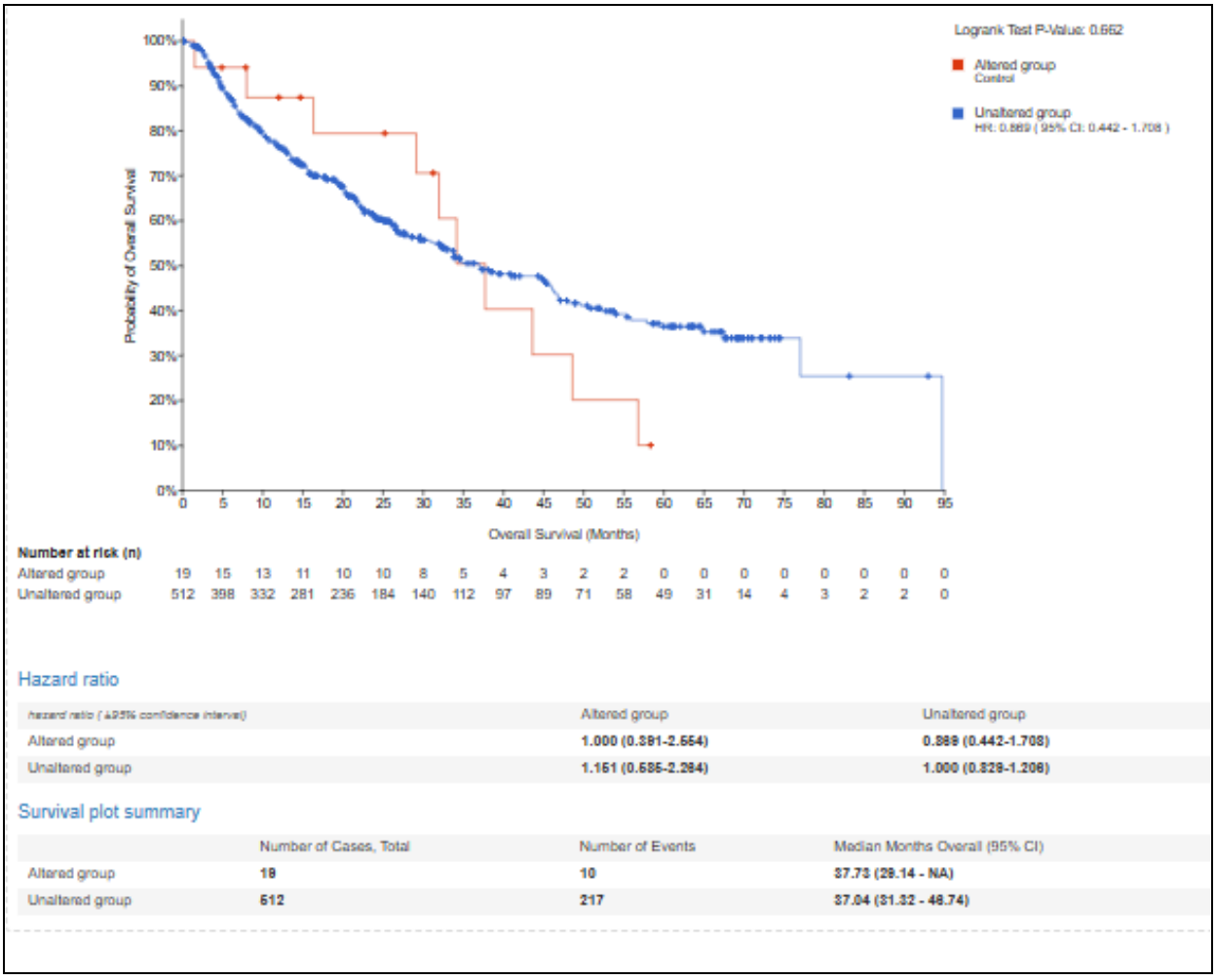


Figure 5. Overall survival in pan-cancer analysis of PITRM1. Kaplan–Meier curves compare overall survival between patients with detectable PITRM1 genomic alterations and patients without detectable PITRM1 alterations. Statistical significance was assessed using the log-rank test.

3.2 Role of PITRM1 in Brain Cancer

A targeted study of PITRM1 was conducted in 1,044 samples from 1,030 patients in two studies with brain cancer. The OncoPrint indicated that the frequency of PITRM1 alterations in a subset of brain tumor samples was high, with amplification and deep deletion being major categories of alterations and with a few missense mutation events.

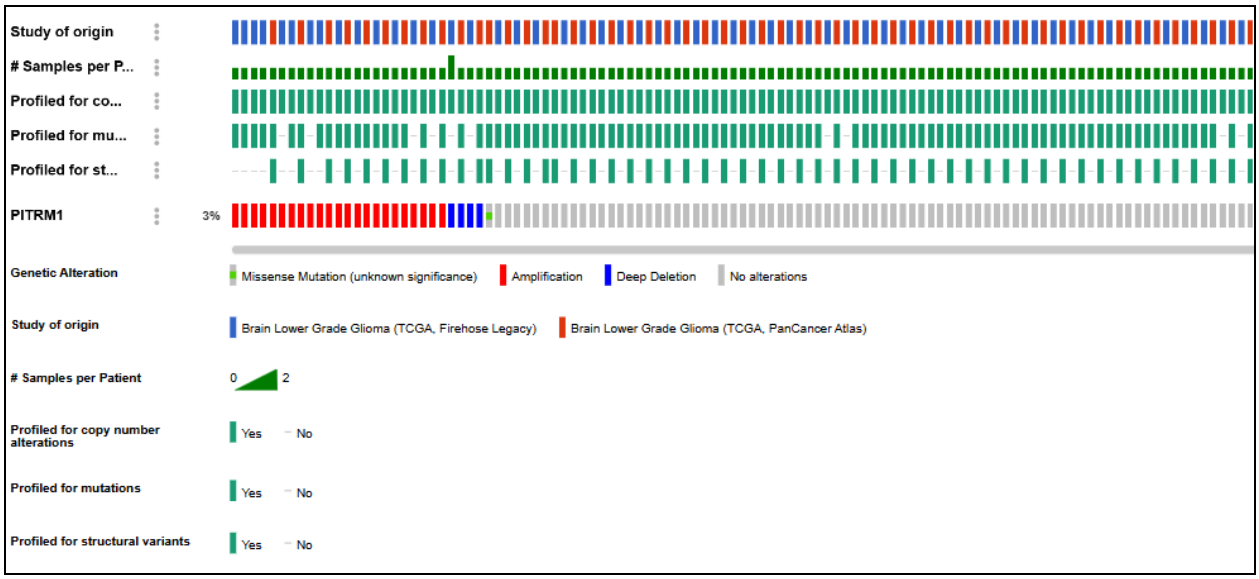


Figure 6. Analysis of PITRM1 in brain cancer datasets using OncoPrint. The OncoPrint summarizes PITRM1 genomic alterations across the analyzed brain cancer datasets. Individual columns represent tumor samples, and colors indicate the type of PITRM1 alteration.

The Cancer Types Summary showed significant variation between the different types of brain tumors. There was an approximately 6.2% alteration frequency in anaplastic astrocytoma, and further alterations were found in anaplastic oligodendroglioma, astrocytoma, and oligodendroglioma categories. These results identified changes in the PITRM1 gene in specific types of neural tumors and not across all brain cancers.

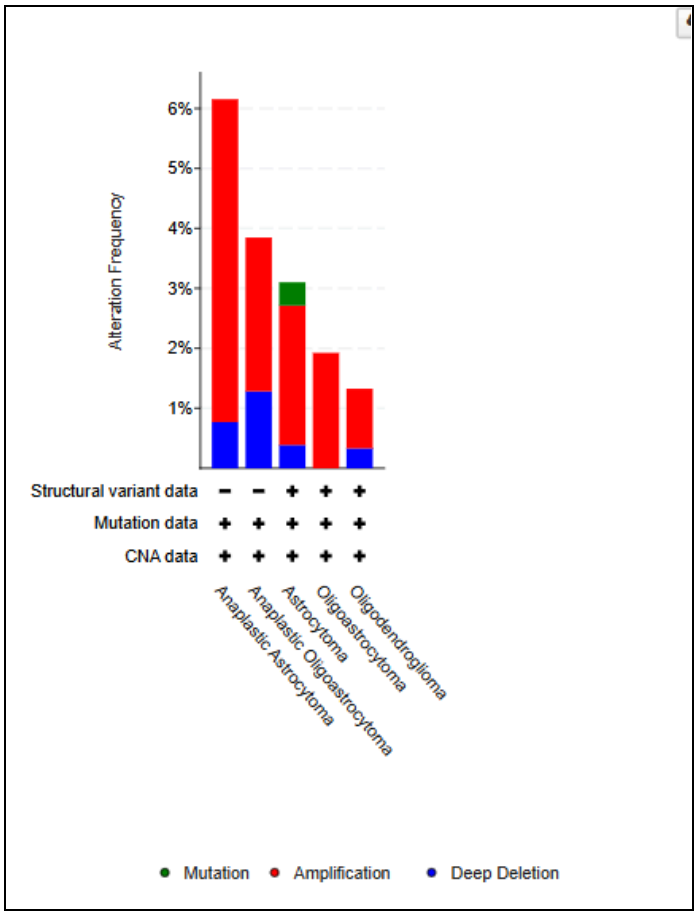


Figure 7. Analysis of PITRM1 gene alteration in brain cancer of different types. The bar graph shows the percentage of samples with PITRM1 genomic alterations across the brain tumor categories represented in the selected datasets.

The mutation distribution analysis showed some protein-level variants in PITRM1. The variants were spread throughout the protein and were not associated with any single mutation hotspot.

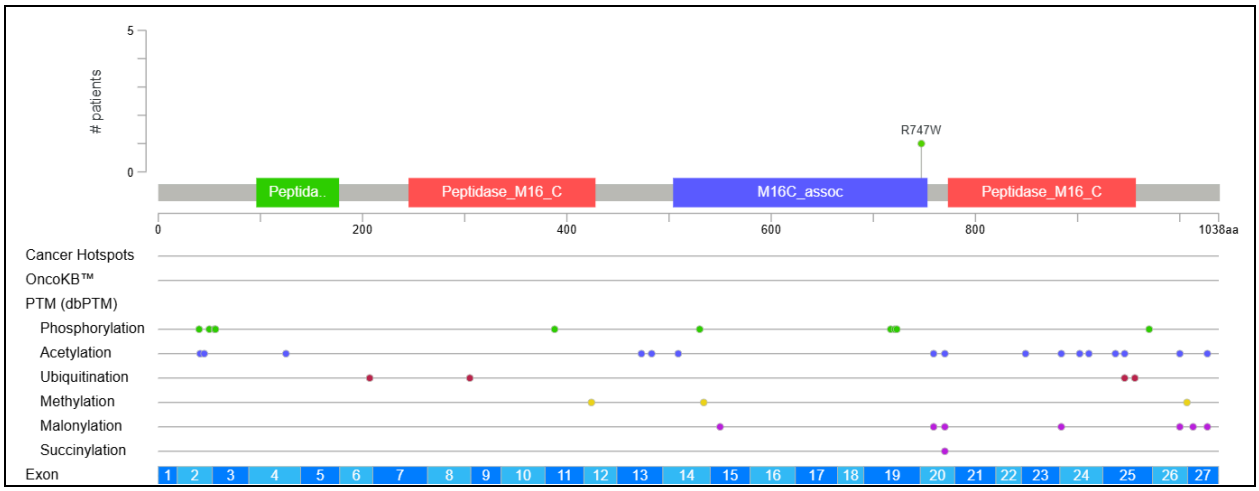
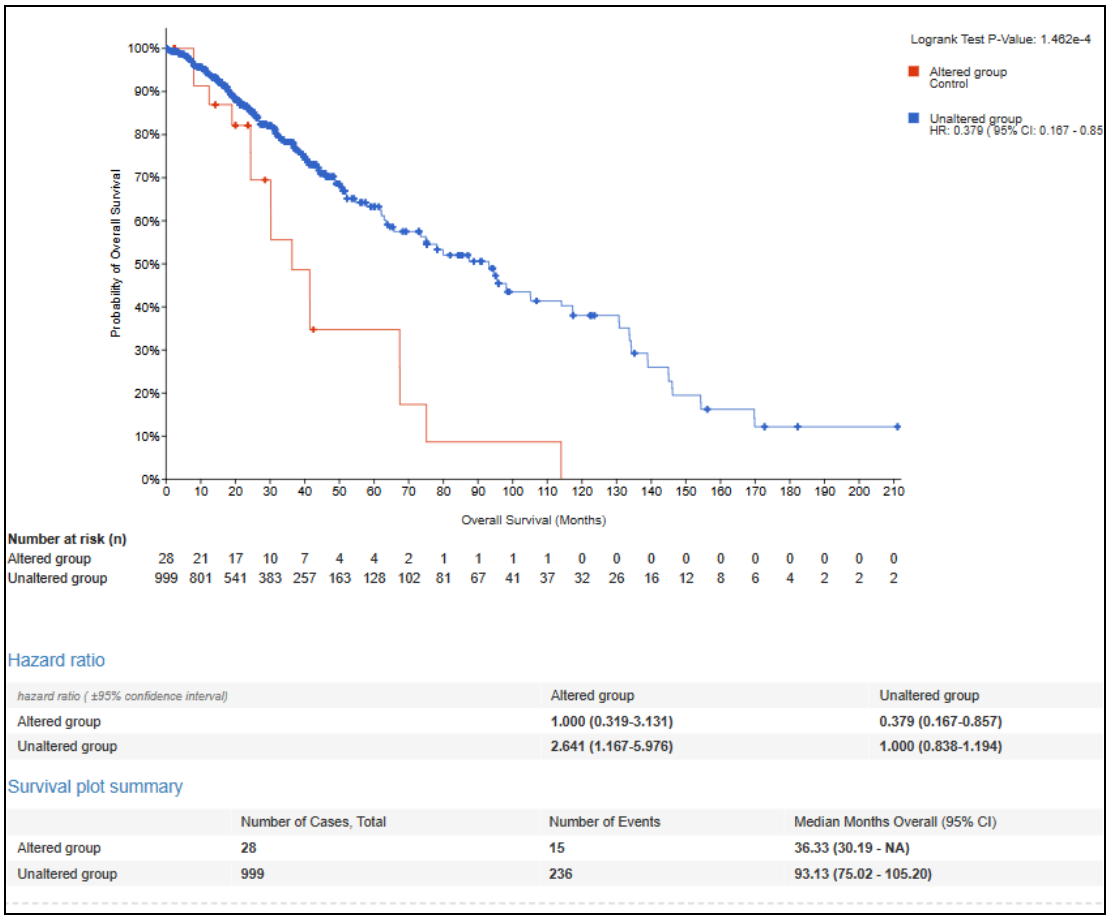


Figure 8. Distribution of somatic mutations in PITRM1 in brain cancer. The lollipop plot shows the positions of PITRM1 protein-level mutations identified in the analyzed brain cancer datasets.

The brain-cancer survival analysis revealed a significant difference between the PITRM1-altered and unaltered groups. The number of patients and events in the altered group is 28 patients and 15 events, while in the unaltered group there are 999 patients and 236 events. The median overall survival was 36.33 months and 93.13 months, respectively, in the altered and unaltered groups. The difference in survival between the two groups was statistically significant, with a p-value of 1.462×10^{-4} (log-rank test). In this group, the hazard ratio of the altered group to the unaltered group was around 2.64, indicating an association between PITRM1 alteration status and shorter overall survival in this cohort.



Hazard ratio

hazard ratio (±95% confidence interval)	Altered group	Unaltered group
Altered group	**1.000 (0.319-3.131)**	**0.379 (0.167-0.857)**
Unaltered group	**2.641 (1.167-5.976)**	**1.000 (0.838-1.194)**

Survival plot summary

	Number of Cases, Total	Number of Events	Median Months Overall (95% CI)
Altered group	**28**	**15**	**36.33 (30.19 - NA)**
Unaltered group	**999**	**236**	**93.13 (75.02 - 105.20)**

Figure 9. Overall survival analysis of PITRM1 in brain cancer. Kaplan–Meier survival curves compare patients with PITRM1 alterations and patients without detectable PITRM1 alterations. The log-rank test was used to assess the difference between groups.

3.3 Role of PITRM1 in Lung Cancer

The lung-cancer study included 41 studies and 13,241 patients with lung cancer and 15,910 samples. The OncoPrint showed that in a comparatively small number of samples of lung cancer, there were alterations PITRM1 genomic alterations. The main categories of genomic alterations detectable were amplification and deep deletion, with some missense events.

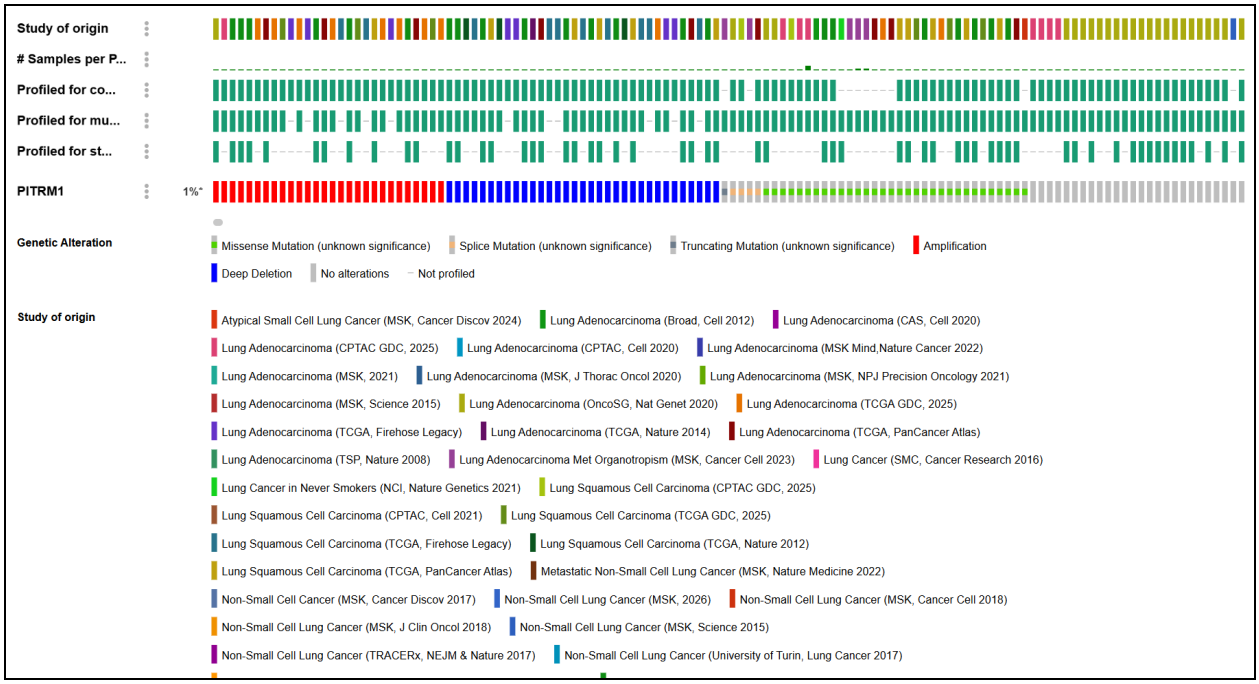


Figure 10. Analyses of PITRM1 in lung cancer datasets using OncoPrint. The OncoPrint summarizes PITRM1 genomic alterations across the analyzed lung cancer datasets. Individual columns represent tumor samples, and colors indicate alteration types.

The Cancer Types Summary revealed that PITRM1 alterations were found in the following lung cancer types: lung adenocarcinoma, lung squamous cell carcinoma, non-small-cell lung cancer, and small-cell lung cancer. The frequency of alterations was the lowest in the low single-digit range, indicating PITRM1 is a relatively infrequently altered genomic driver in lung cancer.

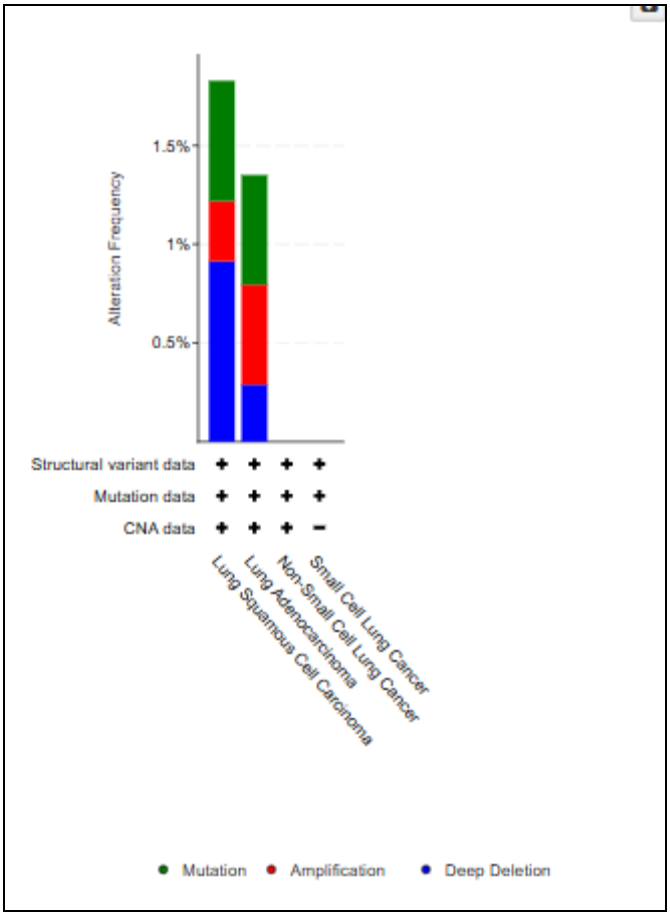


Figure 11. Genetic alteration analysis of PITRM1 across lung cancer types. The bar graph shows the percentage of samples with PITRM1 genomic alterations in the indicated lung cancer categories.

The lollipop plot also shows that mutations of PITRM1 in lung cancer are not clustered in one hotspot, but rather spread throughout the protein. Changes are seen in several functional and structural domains such as Peptidase_M16, Peptidase_M16_C, and M16C_assoc. There are several mutation sites throughout the coding sequence, including H511Y. These variants are distributed across regions known to be modified by post-translational events such as phosphorylation, acetylation, ubiquitination, methylation, and others, as shown by the accompanying functional tracks.

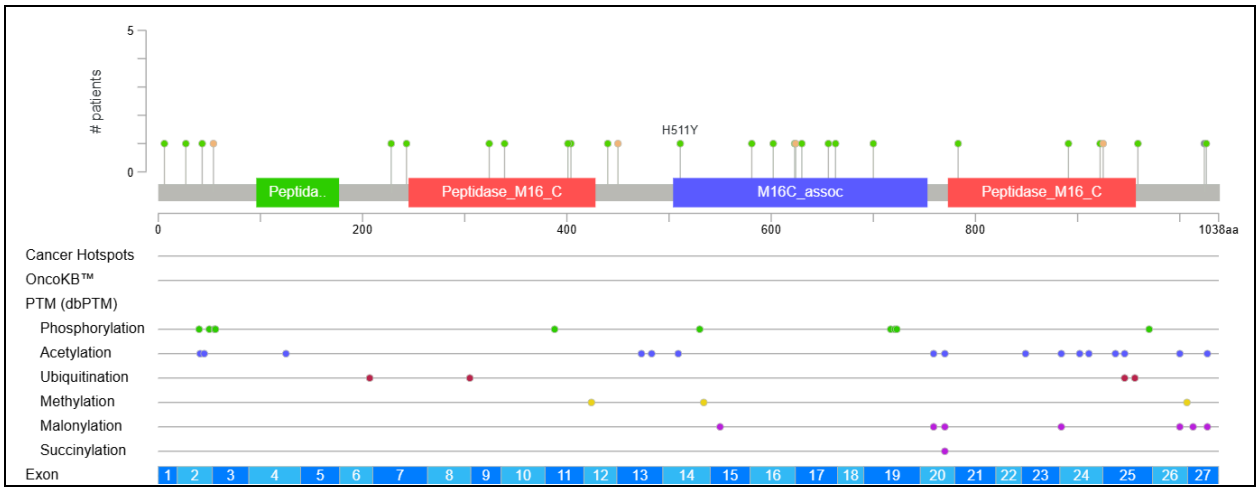


Figure 12. Distribution of somatic mutations in PITRM1 in lung cancer. The lollipop plot shows the positions of PITRM1 protein-level mutations identified in the analyzed lung cancer datasets. Protein domains and annotated functional regions are indicated where available.

There were 73 altered and 4,950 unaltered patients in the overall survival analysis. There were 28 events in the altered group, and 1,848 events in the unaltered group. The overall survival was 31.74 months for the altered group and 53.29 months for the unaltered group. The median survival time was shorter in the altered group, but the difference was not statistically significant (p = 0.435 on the log-rank test).

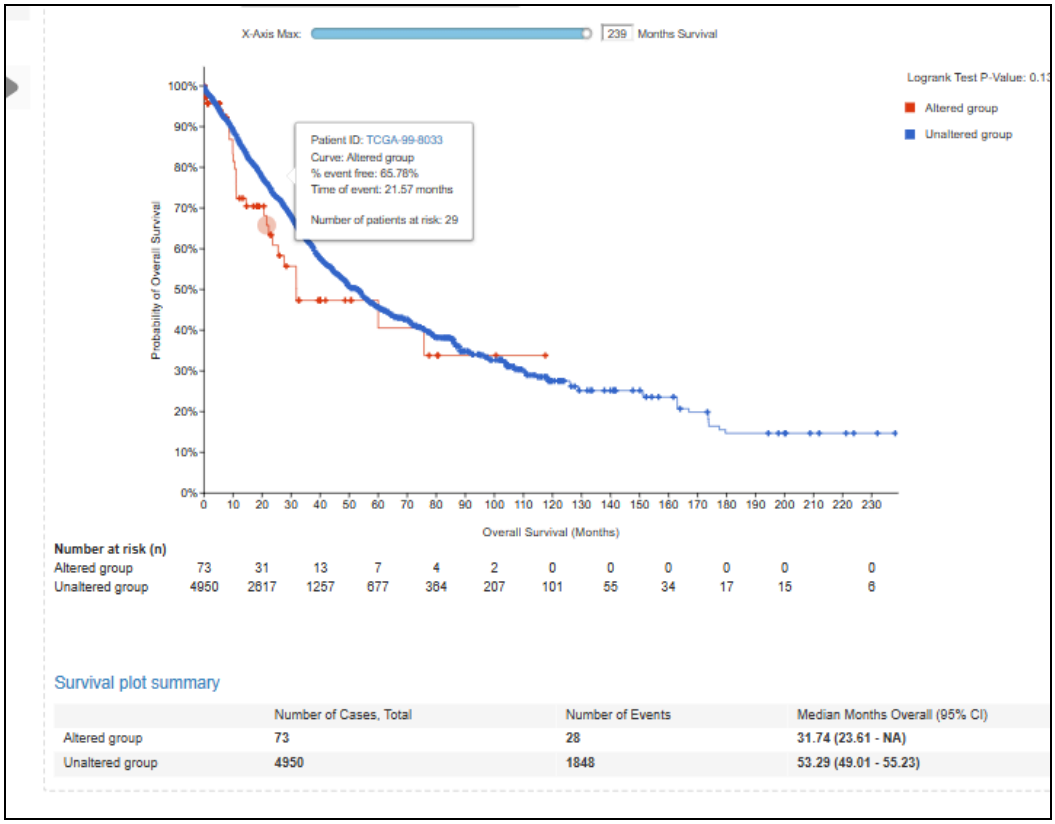


Figure 13. Lung cancer overall survival analysis of PITRM1. Kaplan–Meier survival curves compare overall survival between PITRM1-altered and unaltered patients. The difference was evaluated using the log-rank test.

3.4 Role of PITRM1 in Thyroid cancer

The thyroid-cancer study included 307 samples from 275 patients in two studies. A significant proportion (34 patients, 12%, and 43 samples, 14%) of patients had alterations in PITRM1, compared with several other cancer-specific analyses.

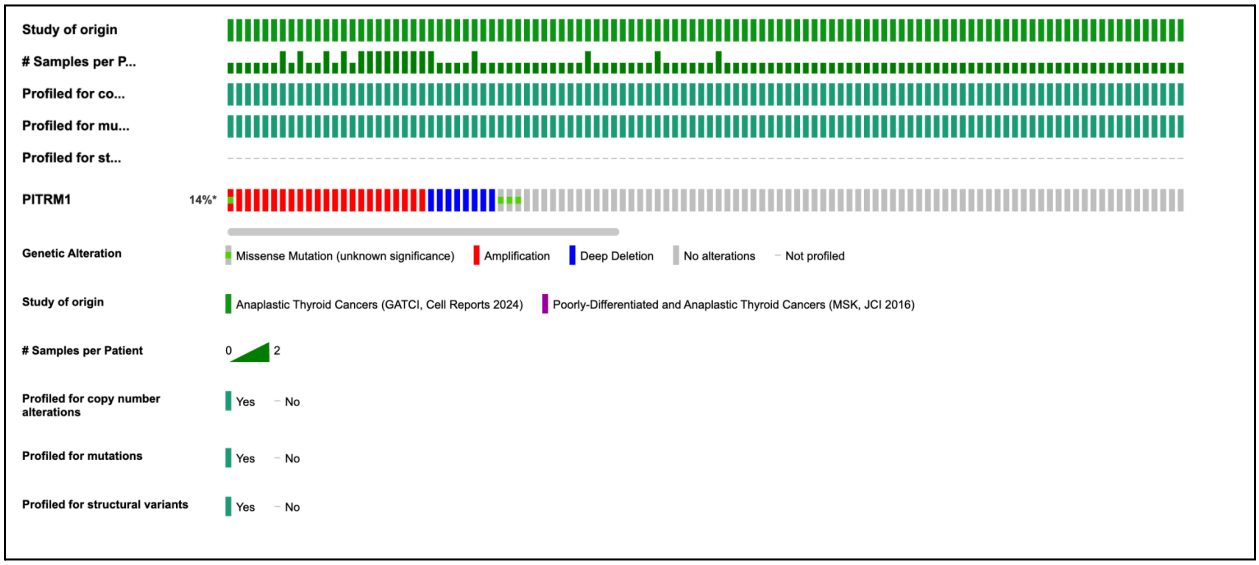


Figure 14. Analysis of PITRM1 on thyroid cancer datasets using OncoPrint. The OncoPrint summarizes PITRM1 genomic alterations across the analyzed thyroid cancer datasets. Individual columns represent samples, and colors indicate the type of PITRM1 alteration.

The Cancer Types Summary showed variation in PITRM1 alteration frequency among the thyroid cancer subtypes represented in the selected datasets. The highest alteration frequency was observed in Anaplastic Thyroid Cancer with 22%. The most common alteration type was amplification, followed by deep deletion and lesser amounts of mutation events.

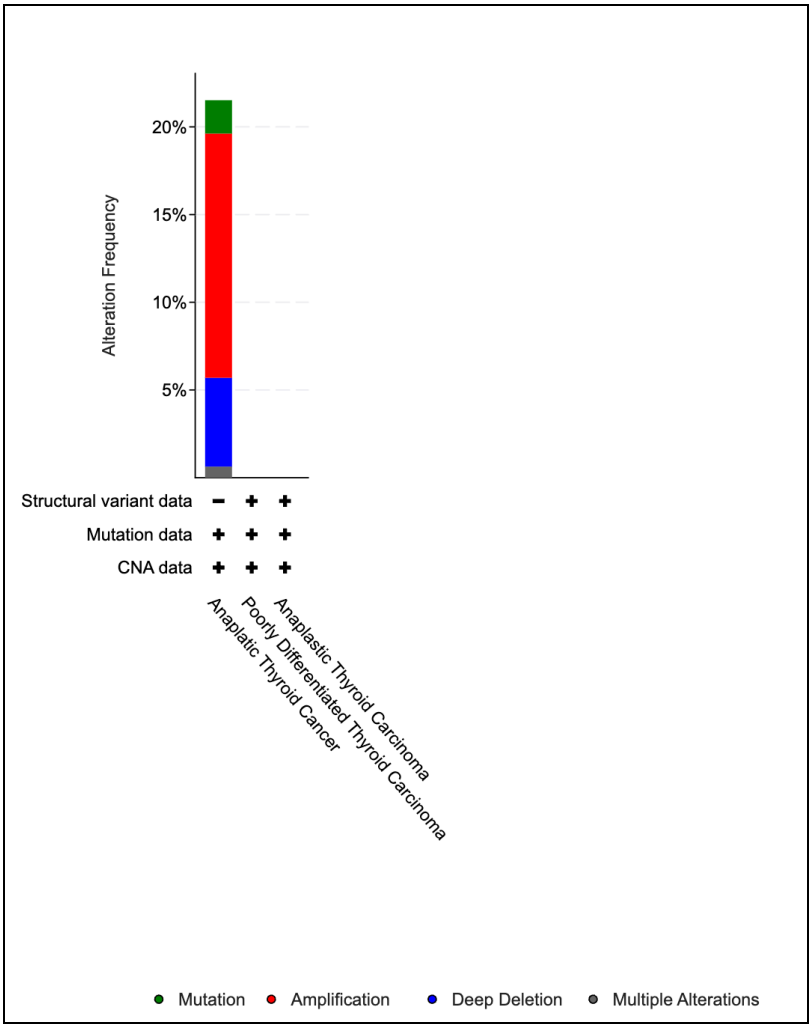


Figure 15. Analysis of PITRM1 by genetic alteration in different types of thyroid cancer. The bar graph shows the percentage of samples with PITRM1 genomic alterations in the thyroid cancer categories represented in the selected datasets. Individual alteration types are indicated according to the cBioPortal classification.

Protein-level mutation analysis revealed several mutations in PITRM1. An example of the representative changes seen in the mutation distribution plot is the T876M change, which occurs in the latter part of the PITRM1 protein. This variant is present, suggesting that these changes are also present at the protein level in addition to the prominent copy-number changes seen in the thyroid cancer cohort.

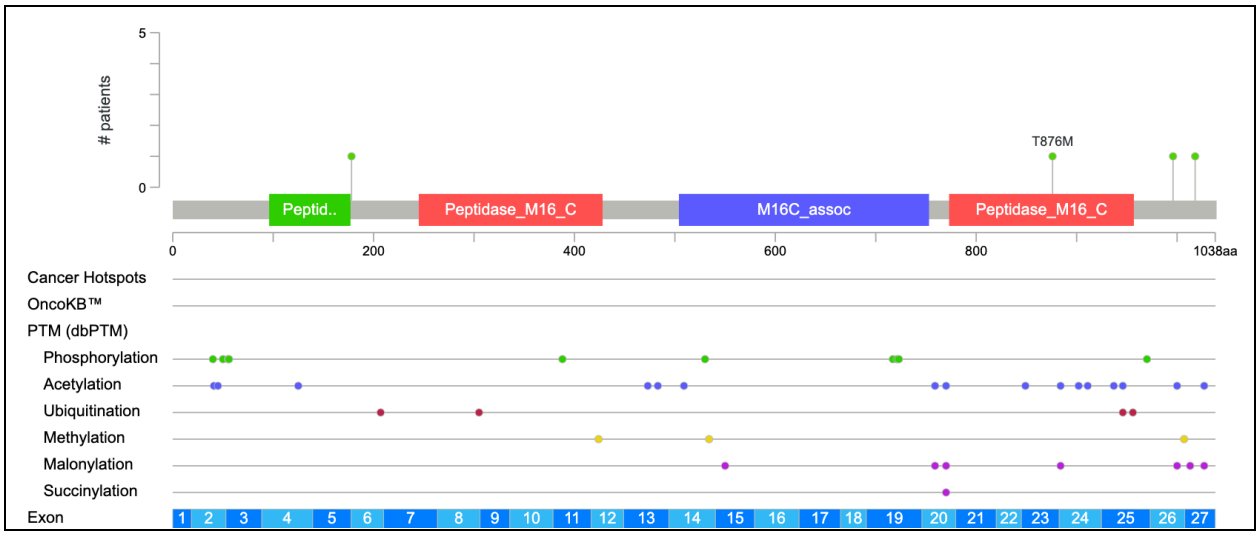


Figure 16. Thyroid cancer distribution of somatic mutations of PITRM1. The lollipop plot shows the positions of PITRM1 protein-level mutations identified in the analyzed thyroid cancer datasets, including the T876M substitution.

The results of overall survival analysis of the thyroid cancer cohort revealed that there was a statistically significant difference between PITRM1-altered and unaltered groups (log-rank test, $p = 7.119 \times 10^{-4}$). The PITRM1-altered group consisted of 27 patients, and 21 patients had an occurrence, while the unaltered group consisted of 190 patients, and 130 had an occurrence. The median overall survival was 5.13 months (95% CI: 3.32–9.33) in the PITRM1-altered group compared with 11.96 months (95% CI: 9.24–24.44) in the unaltered group. The hazard ratio for the unaltered group compared to the altered group was 0.465 (95% CI: 0.249 – 0.870), which is the reciprocal of 2.15 for the altered group. In this cohort of thyroid cancer patients, therefore, the alteration status of PITRM1 was highly associated with overall survival in the studied thyroid cancer patient cohort.

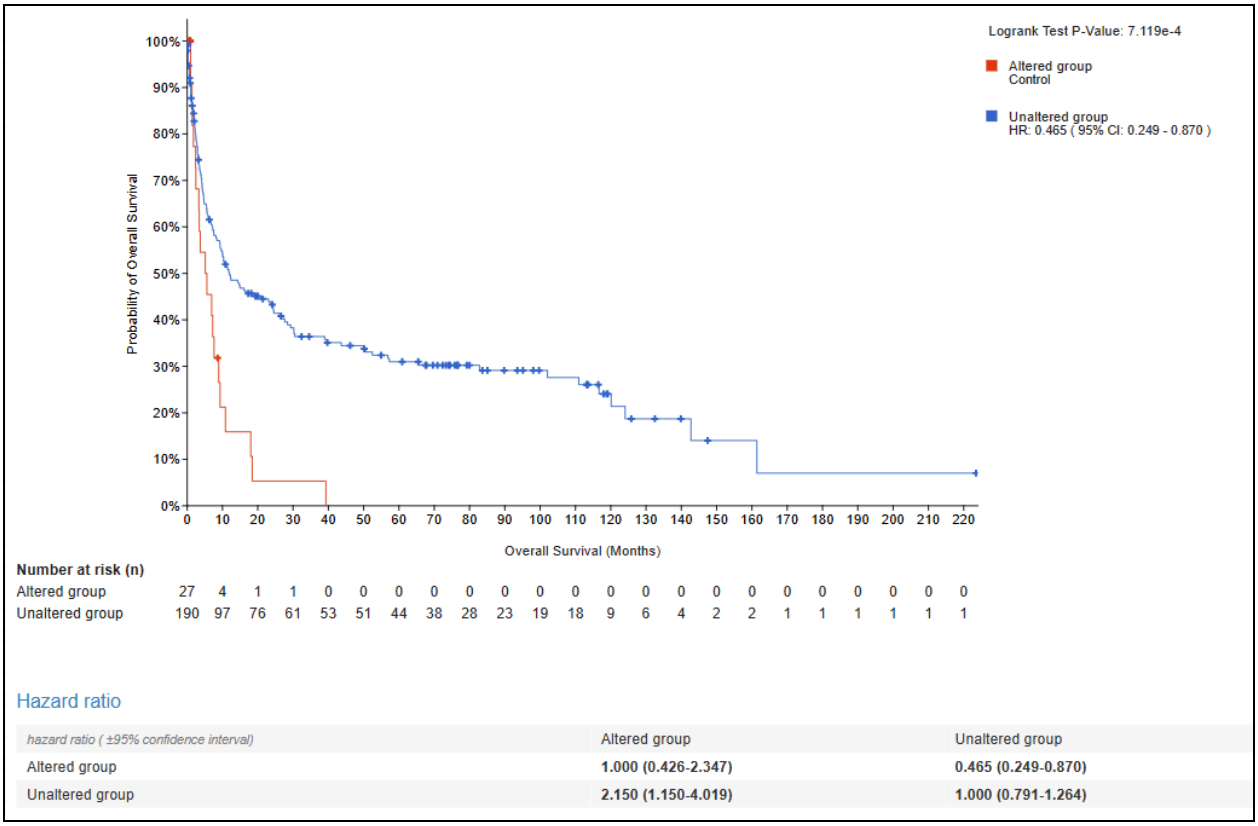


Figure 17. Overall survival analysis of PITRM1 in thyroid cancer. Kaplan–Meier survival curves compare overall survival between patients with PITRM1 alterations and patients without detectable PITRM1 alterations. The difference was evaluated using the log-rank test.

4. DISCUSSION

PITRM1 is a mitochondrial matrix protease that plays a role in mitochondrial protein quality control and the degradation of mitochondrial targeting sequences and other peptides. The biological functions it is known to regulate are therefore distinct from those of classic cancer-related genes that directly control the cell cycle, growth factor signaling or apoptosis. The current analysis indicates rather that the association of PITRM1 and cancer could be more context- and tumor-specific. The expression differences, the frequency of genomic alterations, and the association with survival found in the analysed cancers suggest that PITRM1 may play a context-dependent, rather than universal, role (Anne-lie Ståhl et al., 2002; Brunetti et al., 2021).

The differential expression of PITRM1 in tumor and normal tissues is an important first step in understanding the potential role of PITRM1 in cancer. Extensive alterations in mitochondria involve energy production, redox regulation, metabolite synthesis, and cellular stress responses, all of which are central to their role. Therefore, variations in the expression of PITRM1 in various cancers could be due to a variation in the requirement of mitochondrial proteostasis among them and not necessarily an indication

of its role in cancer as an oncogene. In particular, the ability of PITRM1 to transport mitochondrial presequences is of relevance, since the accumulation of these peptides could affect the proteostasis or membrane function of mitochondria (Brunetti et al., 2021; Heller et al., 2026).

The genomic analysis also shows that PITRM1 is not a typical highly recurrent cancer driver for all types of cancer. This was observed throughout the pan-cancer cohort with markedly different frequencies in cancer lineages. This is consistent with the general rule that the genomic importance of the genes associated with cancer can vary depending on tissue type, molecular background, and selective pressure. Genomes of cancers consist of a mix of frequent drivers and sporadic mutations, with biological significance not always being correlated with high mutation frequency (Sinkala, 2023; Chillón-Pino et al., 2024).

For PITRM1, Copy number changes, changes in transcription, changes in metabolism, or interaction with mitochondrial stress-response pathways may then be more biologically relevant than mutations. Defects in PITRM1-dependent presequence processing have been shown to have consequences other than just peptide degradation, as mitochondrial stress signaling was found to be responsive to such defects (Fessler et al., 2022).

The brain-cancer results are particularly remarkable since the strongest survival association for the present dataset was found in this cancer type. This is a very large survival difference, which is biologically plausible, because of the known role of PITRM1 in neuronal mitochondrial proteostasis. Neurodegenerative phenotypes such as progressive neurological disease and amyloid deposition have been previously linked to PITRM1 dysfunction, suggesting that neural cells are especially susceptible to disturbances in mitochondrial peptide clearance (Brunetti et al., 2015; María José Pérez et al., 2020). As a result, the association between the alteration status of the PITRM1 gene and overall survival in the brain cancer cohort opens the door to discussing the possibility of the contribution of mitochondrial proteostatic vulnerability to the differences between subgroups of brain cancer.

The connection between PITRM1-related mitochondrial damage and neurodegeneration could also be useful in explaining its possible function in cancer. Mitochondrial stress, proteostasis defects, oxidative imbalance, and changes in the pathways involved in cell survival, processes of both cancer and neurodegenerative disease can involve very different biological outcomes. Chronic mitochondrial and proteotoxic stress can lead to ongoing neuronal dysfunction and loss in neurodegenerative diseases. Cancer cells, on the other hand, might become accustomed to metabolic and oxidative stress by turning on mechanisms that help the cells survive and grow. Therefore, PITRM1 may be one place where, depending on the context, mitochondrial protein quality control affects cell fate. These responses to proteostatic stress in mitochondria are induced by PITRM1 deficiency in neuronal models, and can be activated in cancer cells in an attempt to cope with adverse metabolic conditions (Brunetti et al., 2021).

The finding in brain cancer, however, should not be viewed as proof that alteration of PITRM1 directly results in poor survival. The altered cohort was much smaller than the unaltered cohort, and genomic alterations might help to define tumors with wider molecular differences. This association may thus signal a tumor state, instead of being a direct consequence of the action of PITRM1. Experimental work to

investigate the role of PITRM1 loss or gain in models of brain tumour would be required to assess the ability of altered PITRM1 activity to impact the tumour's proliferation, mitochondrial stress, metabolic adaptation or therapeutic sensitivity.

The lung-cancer analysis was somewhat different. The median survival of the altered group was numerically shorter than that of the unaltered group, but there was no significant difference in survival. This is significant as it shows that the survival association seen in PITRM1 is not found in all tumour types. There is considerable molecular and histological variation in lung tumors, and the effects of a mitochondrial gene may vary among adenocarcinoma, squamous carcinoma, and small-cell disease. Tumor heterogeneity can also lead to the lack of association between the particular genomic alteration and prognosis of the disease when several molecular subtypes are linked together (Mroz & Rocco, 2017).

In thyroid cancer, PITRM1 alteration was relatively common and was linked to a marked survival difference. The high alteration frequency may indicate that PITRM1 has a greater genomic relevance in the thyroid cohorts analyzed than in many other types of tumors. The biological interpretation is different from the one that is mainly based on loss-of-function mutations, as amplification was the most frequent of the alterations observed in the thyroid cancer cohort. The analysis does not indicate whether increasing the dosage of PITRM1 would affect the expression or the enzyme activity of PITRM1 in the mitochondria, but it may lead to changes in mitochondrial peptide degradation and adaptation to stress.

The T876M substitution was also detected by the thyroid mutation distribution. Protein-level mutation mapping is helpful for the identification of candidate mutations for further study, as the position of a substitution in a functional domain may have an impact on the structure or function of the protein. However, the diagnosis of pathogenicity from a cancer dataset containing T876M is not conclusive. Structural analysis, enzymatic assays, and cellular studies will be needed to determine whether or not this substitution will affect the stability of PITRM1, recognition of its substrate(s), or its proteolytic activity. It has become more widely appreciated that the context of protein structure plays a crucial role in deciphering cancer-causing mutations (Chillón-Pino et al., 2024).

Another potential explanation of the relevance of PITRM1 to cancer is its relationship to mitochondrial stress. With the growing recognition of the role of mitochondrial dysfunction in cancer biology, tumor cells require adaptation of their metabolism and proteostatic systems for rapid proliferation, oxidative stress, hypoxia, and nutrient limitation. It has been reported that PITRM1 is involved in the mitochondrial processing environment, and the study showed that the expression of PITRM1 is regulated in response to hypoxia and glucose deprivation of glioma cells (Minchenko et al., 2020). This observation may help to explain a link between PITRM1 and the metabolic stresses encountered by tumors.

Experimental studies of triple-negative breast cancer have also been recently reported, giving another mechanism for the role of PITRM1 in cancer. Xu et al. (2026) reported that PITRM1 was significantly upregulated in breast cancer, especially TNBC, and that the depletion of PITRM1 correlated with mitochondrial dysfunction, decreased expression of SLC7A11, and ferroptosis. Based on these results, PITRM1 could play a role in the maintenance of mitochondrial and redox homeostasis by cancer cells during therapeutic stress. This is especially relevant for the present findings as it provides support for the

concept that PITRM1 might affect cancer by "cellular stress adaptation" rather than a regular oncogenic pathway.

The results of these studies together suggest a context-dependent interpretation of the role of PITRM1, not a universal cancer role. The three focused cancer groups exhibited varying patterns of genomic alteration and the association with survival, but the pan-cancer analysis was unable to reveal any significant difference in overall survival by PITRM1 alteration status. The lack of a pan-cancer association does not preclude the possibility of lineage-specific relationships; pooling biologically different cancer types might mask lineage-specific associations. Pan-cancer analysis can thus yield a general picture and pinpoint those cancer types that need a more targeted approach (Weinstein et al., 2013).

Overall, it presents the analysis of PITRM1, a well-known factor for mitochondrial proteostasis, in the context of the cancer genome. The results reveal cancer-type-specific differences in PITRM1 expression, genomic alteration, mutation distribution, and survival association, with the largest survival association found in the brain-tumor cohort, and an additional association found in the thyroid-cancer cohort. These results are correlative and cannot be considered as proof of PITRM1 being an oncogene, tumor suppressor, prognostic or therapeutic target. Direct effects of PITRM1 or general molecular features of the tumors with PITRM1 alterations should be confirmed in independent clinical cohorts and in functional experiments.

5. LIMITATIONS

The present study has a number of limitations. First, it was a retrospective analysis of publicly available data, and the variation in sequencing platforms, patient cohorts, data processing, and tumor composition could affect the patterns observed. Second, the number of patients with altered PITRM1 was small in several of the survival cohorts. This decreases the level of statistical power and can lead to unstable survival estimates. The cancer-specific survival analyses were therefore included as exploratory analyses and not definitive prognostic evaluations. Thirdly, the survival analyses did not account for potentially important clinical variables, including age, tumor stage, treatment, histological subtype, and molecular subtype. Fourth, there are biologically distinct histological and molecular subtypes that are included in broad cancer categories, and grouping these categories together may mask relationships among subtypes. Fifth, protein-level variants, such as the thyroid analysis T876M, were identified in this study, but the effect of these variants on the structure and/or enzymatic activity of PITRM1 has not been experimentally determined. Lastly, the analyses are associations, and not causal relationships. Thus, independent patient cohorts and functional experiments are needed before using PITRM1 as a prognostic biomarker or therapeutic target.

6. CONCLUSION

In this study, PITRM1 was bioinformatically characterized across various cancer types using public genomic, expression, and survival datasets. The expression of PITRM1 was found to be different in all types of tumors, while tumor lineage-specific alterations in the genome were detected in varying

proportions. The pan-cancer survival analysis did not show a significant correlation between alteration status of PITRM1 and overall survival.

More specific patterns emerged when analyses were broken down by cancer, however. A statistically significant association with poorer overall survival was observed for brain cancer for PITRM1 alteration, and for lung cancer, no association was found. Thyroid cancer showed a relatively high frequency of alterations in PITRM1, and a significantly worse survival rate for those with altered PITRM1 compared to those with unaltered. A variant of thyroid cancer, T876M, was also found in the protein-level mutation analysis.

Combined, these results suggest that PITRM1 may have cancer-type-specific genomic and clinical associations. It is well established to play a role in mitochondrial proteostasis, and emerging research connects it to tumor metabolism, ferroptosis and therapeutic resistance, making it a good candidate for further investigation into its biological function. Additional functional studies and integrated multi-omics analysis of larger independent cohorts of patients will be required to assess the potential of PITRM1 to be used in the diagnosis, prognosis or discovery of novel drugs for specific cancers.

7. FUTURE PERSPECTIVES

The PITRM1 variants identified in the present analysis, including T876M and other substitutions identified in the analyzed datasets, should be characterized experimentally in future studies. Structural modelling and enzymatic assays may allow assessment of whether these variants affect protein stability, the recognition of the substrate, and its proteolytic activity.

Functional studies should also explore whether the increased abundance of PITRM1 in the tumor cells is associated with amplification of this gene and whether the increased activity of PITRM1 gives a survival advantage to the tumor cells under metabolic or therapeutic stress. This would be especially applicable to the thyroid-cancer results, which showed a relatively high incidence of PITRM1 alterations.

Independent glioma cohorts and experimental models should be used to examine the association that is observed in brain cancer. As PITRM1 is closely related to mitochondrial proteostasis and neuronal biology, it is important to explore the potential of altered PITRM1 activity to impact mitochondrial unfolded-protein responses, oxidative stress, and the survival of tumor cells, as well as mitochondrial membrane potential.

Further studies are necessary to reveal the connection between PITRM1 and ferroptosis. Based on recent experimental studies, which link PITRM1 to SLC7A11 and ferroptotic responses in TNBC, it can be hypothesized that PITRM1 could be involved in redox adaptation and therapeutic resistance (Xu et al., 2026). It would be interesting to investigate whether PITRM1 status could be used to predict sensitivity to ferroptosis-inducing drugs or combinations of drugs in the future.

Future studies should combine genomic alterations of PITRM1 with RNA expression, DNA methylation, protein abundance, and metabolic profile and/or single-cell data. These analyses can differentiate whether

PITRM1 changes are found in the tumor cells, or if the changes are part of a larger process in the tumor microenvironment.

Lastly, independent clinical cohorts should be used to examine whether the survival associations found in brain and thyroid cancers are significant after controlling for stage, age, treatment, histological subtype, and other clinicopathological factors. Only following this validation and experimental validation can PITRM1 be considered a potential therapeutic vulnerability or a prognostic biomarker.

AUTHOR'S CONTRIBUTION:

Amaara Subramaniam conceptualised the study, did a literature survey, carried out bioinformatics analysis, analysed the data, wrote and corrected the manuscript.

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CONFLICT OF INTEREST:

There is no potential conflict of interest to disclose.

REFERENCES:

Anne-lie Ståhl, Moberg, P., Ytterberg, J., Oleg Panfilov, Brockenhuus, H., Nilsson, F., & Glaser, E. (2002). *Isolation and identification of a novel mitochondrial metalloprotease (PreP) that degrades targeting presequences in plants*. *277*(44), 41931–41939. https://doi.org/10.1074/jbc.m205500200

Brown, M., Leon, A., Katarzyna Kedzierska, Moore, C. E., Belnoue-Davis, H. L., Flach, S., … Church, D. N. (2023). Functional analysis reveals driver cooperativity and novel mechanisms in endometrial carcinogenesis. *Embo Molecular Medicine*. https://doi.org/10.15252/emmm.202217094

Brunetti, D., Catania, A., Viscomi, C., Deleidi, M., Bindoff, L. A., Ghezzi, D., & Zeviani, M. (2021). Role of PITRM1 in mitochondrial dysfunction and neurodegeneration. *Biomedicines*, *9*(7), 833. https://doi.org/10.3390/biomedicines9070833

Brunetti, D., Janniche Torsvik, Dallabona, C., Pedro Filipe Teixeira, Paweł Sztromwasser, Fernández-Vizarra, E., … Bindoff, L. A. (2015). Defective PITRM 1 mitochondrial peptidase is associated with AB amyloidotic neurodegeneration. *EMBO Molecular Medicine*, *8*(3), 176–190. https://doi.org/10.15252/emmm.201505894

Cerami, E., Gao, J., Dogrusoz, U., Gross, B. E., Sumer, S. O., Aksoy, B. A., … Schultz, N. (2012). The cBio cancer genomics portal: An open platform for exploring multidimensional cancer genomics data. *Cancer Discovery*, *2*(5), 401–404. https://doi.org/10.1158/2159-8290.cd-12-0095

Chillón-Pino, D., Badonyi, M., Semple, C. A., & Marsh, J. A. (2024). Protein structural context of cancer mutations reveals molecular mechanisms and candidate driver genes. *Cell Reports*, *43*(11), 114905. https://doi.org/10.1016/j.celrep.2024.114905

Fessler, E., Krumwiede, L., & Jae, L. T. (2022). DELE1 tracks perturbed protein import and processing in human mitochondria. *Nature Communications*, *13*(1). https://doi.org/10.1038/s41467-022-29479-y

Gao, J., Aksoy, B. A., Dogrusoz, U., Dresdner, G., Gross, B., Sumer, S. O., … Schultz, N. (2013). Integrative analysis of Complex Cancer Genomics and clinical profiles using the cBioPortal. *Science Signaling*, *6*(269), pl1–pl1. https://doi.org/10.1126/scisignal.2004088

Giercuszkiewicz-Haśnik, K., Morak-Młodawska, B., & Jeleń, M. (2026). Molecularly targeted therapies in oncology: Mechanisms, resistance, and combination strategies. *Molecules*, *31*(7), 1195. https://doi.org/10.3390/molecules31071195

Heller, E. M., Lenhard, S., Rapaport, D., & Herrmann, J. (2026). Mitochondrial presequences are more than just address labels. *Protein Science*, *35*(3). https://doi.org/10.1002/pro.70491

Hytönen, M. K., Sarviaho, R., Jackson, C. B., Syrjä, P., Jokinen, T., Matiasek, K., … Lohi, H. (2021). In-frame deletion in canine PITRM1 is associated with a severe early-onset epilepsy, mitochondrial dysfunction and neurodegeneration. *Human Genetics*, *140*(11), 1593–1609. https://doi.org/10.1007/s00439-021-02279-y

Kaplan, E. L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*, *53*(282), 457–481. https://doi.org/10.1080/01621459.1958.10501452

Kunová, N., Havalová, H., Ondrovičová, G., Stojkovičová, B., Bauer, J. A., Bauerová-Hlinková, V., … Kutejová, E. (2022). Mitochondrial processing peptidases—Structure, function and the role in human diseases. *International Journal of Molecular Sciences*, *23*(3), 1297. https://doi.org/10.3390/ijms23031297

María José Pérez, Ivanyuk, D., Panagiotakopoulou, V., Gabriele Di Napoli, Kalb, S., Brunetti, D., … Michela Deleidi. (2020). Loss of function of the mitochondrial peptidase PITRM1 induces proteotoxic stress and Alzheimer's disease-like pathology in human cerebral organoids. *Molecular Psychiatry*, *26*(10), 5733–5750. https://doi.org/10.1038/s41380-020-0807-4

Minchenko, D. O., Khita, O. O., Tsymbal, D. O., Danilovskyi, S. V., Rudnytska, O. V., Halkin, O. V., … Minchenko, O. H. (2020). Expression of IDE and PITRM1 genes in ERN1 knockdown U87 glioma cells: Effect of hypoxia and glucose deprivation. *Endocrine Regulations*, *54*(3), 183–195. https://doi.org/10.2478/enr-2020-0021

Mroz, E. A., & Rocco, J. W. (2017). The challenges of tumor genetic diversity. *Cancer*, *123*(6), 917–927. https://doi.org/10.1002/cncr.30430

Sinkala, M. (2023). Mutational landscape of cancer-driver genes across human cancers. *Scientific Reports*, *13*(1), 12742. https://doi.org/10.1038/s41598-023-39608-2

Tang, Z., Kang, B., Li, C., Chen, T., & Zhang, Z. (2019). GEPIA2: aN enhanced web server for large-scale expression profiling and interactive analysis. *Nucleic Acids Research*, *47*(W1), W556–W560. https://doi.org/10.1093/nar/gkz430

The Cancer Genome Atlas Network. (2012). Comprehensive molecular characterization of human colon and rectal cancer. *Nature*, *487*(7407), 330–337. https://doi.org/10.1038/nature11252

Wang, L., Zhou, X., & Lu, T. (2025). Role of mitochondria in physiological activities, diseases, and therapy. *Molecular Biomedicine*, *6*(1). https://doi.org/10.1186/s43556-025-00284-5

Weinstein, J. N., Collisson, E. A., Mills, G. B., Shaw, K. R. M., Ozenberger, B. A., Ellrott, K., … Stuart, J. M. (2013). The cancer genome atlas pan-cancer analysis project. *Nature Genetics*, *45*(10), 1113–1120. https://doi.org/10.1038/ng.2764

Xu, Y., Yang, K., Sheng, Y., Chen, J., & Zhao, Y. (2026). Ivermectin B1a sensitizes TNBC cells to cyclophosphamide therapy in vitro by targeting PITRM1/SLC7A11-mediated ferroptotic pathway. *Letters in Drug Design & Discovery*, *23*(4), 100437. https://doi.org/10.1016/j.lddd.2