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Comprehensive Landscape of STEAP Family Members Expression in Human Cancers: Unraveling the Potential Usefulness in Clinical Practice Using Integrated Bioinformatics Analysis

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Abstract: The human Six-Transmembrane Epithelial Antigen of the Prostate (STEAP) family comprises STEAP1-4. Several studies have pointed out STEAP proteins as putative biomarkers, as well as therapeutic targets in several types of human cancers, particularly in prostate cancer. However, the relationships and significance of the expression pattern of STEAP1-4 in cancer cases are barely known. Herein, the Oncomine database and cBioPortal platform were selected to predict the differential expression levels of STEAP members and clinical prognosis. The most common expression pattern observed was the combination of the over- and underexpression of distinct STEAP genes, but cervical and gastric cancer and lymphoma showed overexpression of all STEAP genes. It was also found that STEAP genes' expression levels were already deregulated in benign lesions. Regarding the prognostic value, it was found that STEAP1 (prostate), STEAP2 (brain and central nervous system), STEAP3 (kidney, leukemia and testicular) and STEAP4 (bladder, cervical, gastric) overexpression correlate with lower patient survival rate. However, in prostate cancer, overexpression of the STEAP4 gene was correlated with a higher survival rate. Overall, this study first showed that the expression levels of STEAP genes are highly variable in human cancers, which may be related to different patients' outcomes.

Keywords: STEAP members; human cancers; Oncomine; prognosis; cBioPortal

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1. Introduction

The Six-Transmembrane Epithelial Antigen of the Prostate (STEAP) family has been implicated in several types of cancer due to their over or underexpression in malignant cells compared to normal cells [1,2]. This protein family contains four members, named STEAP1, STEAP2, STEAP3 and STEAP4, which are encoded by genes located on chromosome 2 (STEAP 3) and chromosome 7 (STEAP 1, STEAP2 and STEAP4) [3].

STEAP1 was the first member to be discovered in 1999 as a prostate-specific cell-surface antigen highly expressed in prostate and many other cancers [1]. This finding nurtured further research that rapidly expanded and three more STEAP1-related proteins were identified: STEAP2 [4,5], STEAP3 [6,7] and STEAP4 [8]. The four STEAP proteins share similar six-transmembrane domains connected by intra and extracellular loops, suggesting their potential function as channels and/or transporter proteins [1,2,9]. Due to significant sequence homology with various metalloreductases, it has been suggested that STEAP

family members may play a role in iron and copper reduction [10,11]. In addition to the metalloreductase activity and their importance in metal metabolism, several studies have been indicating the involvement of the STEAP proteins in other biological processes, such as cell proliferation and invasion [12–16], apoptosis [17–19], oxidative stress [20–22], and inflammation [23–25].

Despite sharing a similar structure, the different STEAP proteins seem to have distinct expression patterns. STEAP1 is expressed in prostate epithelium and at very low levels in a variety of other organs, such as fetal and adult liver, kidney, pancreas and skeletal muscle [1,9]. However, STEAP1 is highly overexpressed in several cancers, including prostate cancer, pancreatic carcinoma, head and neck cancer, and lung carcinoma [1,2,26–28]. Furthermore, there are studies showing that high levels of STEAP1 are related to poor prognosis and biochemical recurrence survival of colorectal and prostate cancers [26,28–30]. STEAP2 is predominantly expressed in the prostatic tissue, but also has a significant expression in the brain, pancreas and ovary [4,5,9]. In contrast to other STEAPs, STEAP2 also shows a broad expression in neuronal tissue [9]. STEAP2 expression in prostate cancer and benign prostatic hyperplasia (BPH) was described by Porkka et al., which showed to be significantly higher in carcinoma than in hyperplasia [4], and significantly correlated with Gleason score [31]. In opposition, STEAP2 expression is low in breast cancer tissue, and associated with malignant phenotype and poor prognosis [32]. STEAP3 is expressed at very low levels in a great variety of tissues [6], whereas displaying higher expression in bone marrow, liver and in dorsal root ganglia [9]. The overexpression of STEAP3 in the human Burkitt's lymphoma cell line showed that STEAP3 maintains iron storage in human malignant cells and tumor proliferation under the hypoferric condition [33]. Recently, it was demonstrated that STEAP3 is highly expressed in malignant gliomas and renal cell carcinoma, and this upregulation was inversely correlated with patient overall survival [19,34]. STEAP3 has been shown to contain a p53-response element within the promoter region and to be transcriptionally activated by p53 in response to stress, suggesting its role as a tumor suppressor, in contrast with the other STEAP proteins [35,36]. STEAP4 is highly expressed in the adipose tissue, bone marrow, heart, lung, placenta and prostate [8,9]. In prostate cancer cells, STEAP4 increased the levels of reactive oxygen species through its iron reductase activity, and the knockdown of STEAP4 resulted in increased apoptosis and inhibition of cell proliferation [37]. Recent studies also showed that STEAP4 is increased in human colorectal cancer and predicted poor prognosis [38]. Moreover, STEAP4 overexpression increased the available levels of copper, which correlated with enhanced metastatic potential [39].

Overall, the available data indicate that the expression of STEAP members is highly specific of each type of cancer. However, the significance of the expression pattern of the different STEAP proteins in cancer cases is highly unknown. This study aims to clarify the expression levels of STEAPs in different types of cancer, and their possible use as biomarkers and/or therapeutic targets. The expression levels of STEAP1, STEAP2, STEAP3 and STEAP4 transcripts in the bladder, brain/central nervous system (CNS), breast, cervical, colorectal, esophageal, gastric, head and neck, kidney, leukemia, liver, lung, lymphoma, melanoma, ovarian, pancreatic, prostate, sarcoma and testicular cancers were analyzed using the Oncomine database and the cBioPortal platform. The correlation between STEAP genes expression and overall patient survival also was evaluated.

2. Materials and Methods

2.1. Oncomine Analysis

The expression levels of STEAP genes (STEAP1, STEAP2, STEAP3 and STEAP4) in bladder, brain/CNS, breast, cervical, colorectal, esophageal, gastric, head and neck, kidney, leukemia, liver, lung, lymphoma, melanoma, ovarian, pancreatic, prostate, sarcoma and testicular cancers were obtained from different human datasets available in the Oncomine Cancer Microarray database [40] (https://www.oncomine.org/ (accessed on

6 November 2020)). This database contains different datasets, each providing information from a single publication. The STEAP messenger RNA (mRNA) expression was compared between cancer cases and normal patients' samples for each cancer type. Oncomine uses Students' t-test statistics to compare the mean gene expression between cancer cases and normal tissue. To determine whether a gene is significantly over or underexpressed in cancer cases compared to normal tissue, a ± 2 fold-change threshold was defined and a p-value < 0.05, which is a standard value to consider results with statistical significance. The results retrieved from platform provided the p-value, fold-change variation, and rank (when each gene is ranked by its p-value). The datasets obtained for each cancer type were compiled in separate tables, which indicate the total number of samples in the datasets (cancer/normal samples), and the reference of the original publication of the data. Tables showed all the dataset found indicating statistically significant STEAPs' over and underexpression. The search date was November 2020.

2.2. cBioPortal Analysis

Alteration of STEAPs mRNA expression in all types of cancers across the multiple cancer genetic datasets, and patient overall survival was carried out using the cBioPortal web resource [41] (https://www.cbioportal.org/ (accessed on 27 April 2022)). The mRNA expression z-scores relative to the expression distribution of each gene in tumors that are diploid for this gene (log RNA Seq V2 RSEM) were assessed using the cBioPortal website tool, with a z-score threshold $\pm$ 1.8. All the samples not profiled were excluded. The prognostic value of STEAPs transcripts' expression in all the different human cancers was performed and analyzed using the GraphPad Prism 8.0.1. software, using the results extracted from the cBioPortal for Cancer Genomics database. Log-rank test to determine p-value was calculated. The analysis of association between STEAP expression levels and prognostic value was performed considering the existence of a minimum of 5 patients in each group. The search date was April 2022.

3. Results and Discussion

The different cancer types studied are organized alphabetically as defined in the Oncomine database, and the obtained results are presented in Sections 3.1–3.19. For each cancer type, the expression levels of STEAPs transcripts were analyzed and correlated with patients' overall survival.

3.1. Bladder Cancer

Bladder cancer is a common urologic cancer with the highest recurrence rate of any malignancy [42]. Usually, it originates from the epithelium that covers the inner surface of the bladder (urothelium), and urothelial carcinomas represent the most common type of bladder cancer. Less common bladder cancer types include squamous cell carcinoma, small-cell carcinoma and adenocarcinoma [43]. There is no standard or routine screening test for bladder cancer, and the treatment includes surgery, radiation therapy and chemotherapy [43].

Oncomine analysis revealed a significant underexpression of STEAP1 transcript in one of three datasets of infiltrating bladder urothelial and superficial bladder cancer compared to normal tissue (Table 1). Contrary findings were described considering the detection of STEAP1 protein. Azumi et al. [44] showed using immunohistochemistry that STEAP1 is overexpressed in 17 out of 20 urothelial carcinoma specimens. Challita et al. [45] detected STEAP1 immunoreactivity in 14 primary bladder transitional cancer specimens, of which 60% showed strong staining. Moreover, the authors of this study showed that blocking STEAP1 using a monoclonal antibody inhibited the in vivo growth of bladder tumor xenografts [45]. This discrepancy in results may be due to the origin of human samples, which are obtained from patients with different genetic background. In addition, the difference may also be due to tumor heterogeneity and/or the methodology used to evaluate the gene expression. Regarding STEAP2 and STEAP4 expression, Oncomine

analysis showed a significant underexpression of these transcripts in both infiltrating bladder urothelial and superficial bladder cancer, in opposite to STEAP3 that is clearly overexpressed in the same type of tumors (Table 1). Recently, microarrays and PCR analysis demonstrated that STEAP3 is overexpressed in bladder cancer T24 cell line resistant to cisplatin [46]. Overall, the results obtained suggest that targeting STEAP3 can be a good strategy in the treatment of bladder cancer, but more preclinical and clinical studies must be addressed to identify which patients may benefit from the knockdown of STEAP3.

In order to better clarify the relevance of STEAPs expression in bladder cancer and to evaluate if each transcript is associated with prognosis, the Bladder Cancer (MSK/TCGA, 2020) [47] dataset was extracted from the cBioPortal. The results showed that STEAP1 is overexpressed in 6% (19 out 296), STEAP2 is overexpressed in 8% (24 out 296 patients) and STEAP3 is overexpressed in 5% (16 out 296) of patients. Survival analysis revealed that the expression of these three STEAP family members is not associated with overall survival rate (Supplementary Figure S1). Data obtained from Bladder Cancer (MSK/TCGA, 2020) dataset [47] showed that only 2.4% (7 out 296) of patients overexpress STEAP4. Interestingly, survival analysis showed that STEAP4 overexpression is associated with lesser survival rate (Figure 1, $p = 0.0284$). From seven patients with STEAP4 overexpression, five have died in less than 5 years, the mean survival being 10.65 months, whereas in patients with normal levels of STEAP4 this value was 46.78 months. Although the number of patients with STEAP4 overexpression is low, it justifies exploring the clinical significance of STEAP4 overexpression in bladder cancer because it seems to be associated with poor prognosis.

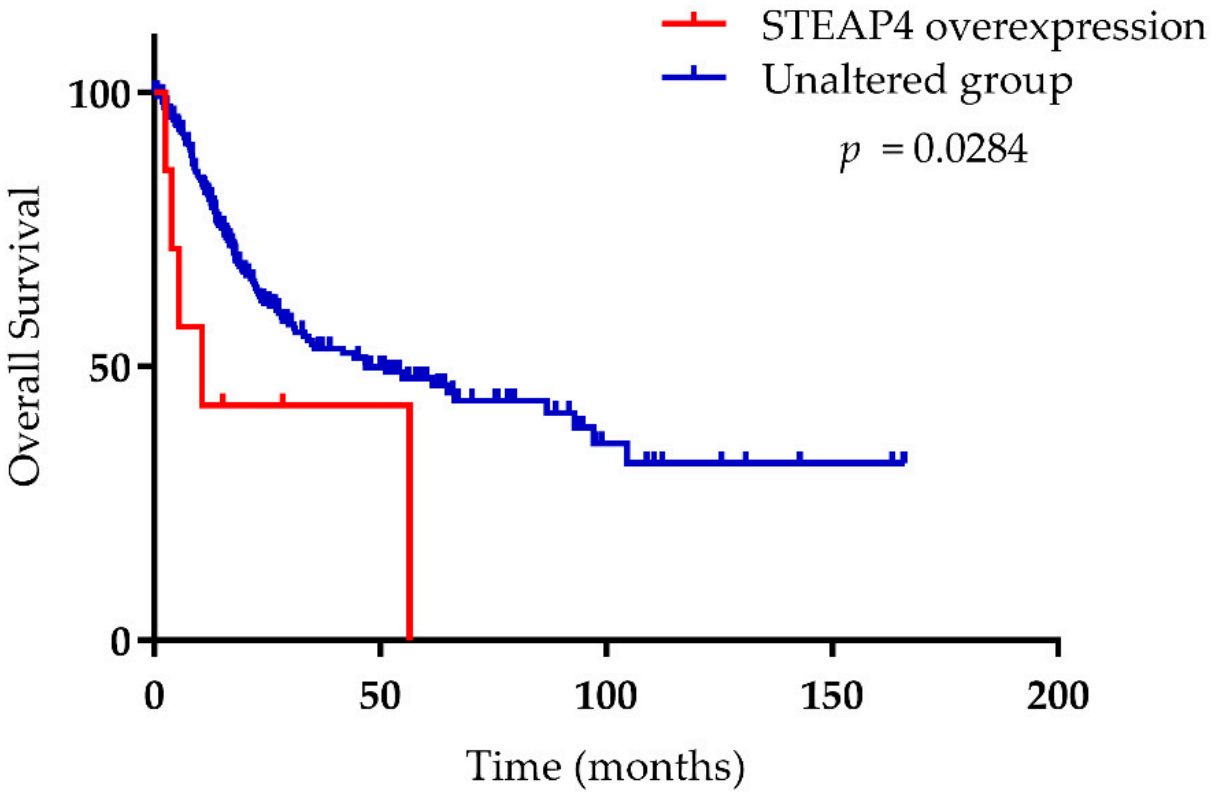

Figure 1. Correlation between STEAP4 gene expression and patients' overall survival in bladder cancer. Patients were stratified in two groups: STEAP4 overexpression (red line) and unaltered expression levels (blue line). Survival analysis showed that high levels of STEAP4 transcript are correlated with lower survival.

Table 1. Analysis of STEAP family members expression in human bladder cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Infiltrating Bladder Urothelial Carcinoma vs. Normal							
STEAP1	No difference	1.162	41	Sanchez-Carbayo Bladder 2	129 (81/48)	0.123	[48]
	No difference	1.074	56	Dyrskjot Bladder 3	27 (13/14)	0.379	[49]
	Underexpressed	−1.649	14	Lee Bladder	130 (62/68)	3.90×10^{-4}	[50]
STEAP2	Underexpressed	−1.614	17	Lee Bladder	130 (62/68)	0.001	[50]
STEAP3	Overexpressed	1.729	4	Dyrskjot Bladder 3	27 (13/14)	5.45×10^{-6}	[49]
	Overexpressed	1.667	3	Sanchez-Carbayo Bladder 2	129 (81/48)	1.11×10^{-11}	[48]
	Overexpressed	1.443	18	Lee Bladder	130 (62/68)	0.018	[50]
STEAP4	No difference	1.007	57	Dyrskjot Bladder 3	27 (13/14)	0.441	[49]
	No difference	−1.288	40	Sanchez-Carbayo Bladder 2	129 (81/48)	0.124	[48]
	Underexpressed	−1.29	31	Lee Bladder	130 (62/68)	0.035	[50]
Superficial Bladder Cancer vs. Normal							
STEAP1	No difference	−1.019	50	Sanchez-Carbayo Bladder 2	76 (28/48)	0.462	[48]
	No difference	−1.065	52	Dyrskjot Bladder 3	42 (28/14)	0.378	[49]
	Underexpressed	−2.131	5	Lee Bladder	256 (126/68)	3.58×10^{-10}	[50]
STEAP2	Underexpressed	−1.448	25	Lee Bladder	194 (126/68)	0.004	[50]
STEAP3	Overexpressed	2.084	1	Dyrskjot Bladder 3	42 (28/14)	1.26×10^{-9}	[49]
	Overexpressed	3.125	3	Sanchez-Carbayo Bladder 2	76 (28/48)	3.06×10^{-17}	[48]
	Overexpressed	1.741	7	Lee Bladder	194 (126/68)	1.39×10^{-4}	[50]
STEAP4	Underexpressed	−1.101	37	Dyrskjot Bladder 3	42 (28/14)	0.031	[49]
	Underexpressed	−1.942	26	Sanchez-Carbayo Bladder 2	76 (28/48)	0.01	[48]
	No difference	−1.217	37	Lee Bladder	194 (126/68)	0.071	[50]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.2. Brain/CNS Cancer

Several different types of tumors, benign and malignant, have been identified in the CNS—brain and spinal cord [51]. The prognosis for these tumors is associated to various factors, such as the patient's age and the location and histology of the tumor. About half of all CNS tumors in adults patients are cancerous, whereas in pediatric patients, more than 75% are cancerous. Gliomas are the most prevalent type of adult brain tumors accounting for 36% of malignant tumors [52]. They arise from the supporting cells of the brain—so-called glia—which are subdivided into astrocytes, ependymal cells and oligodendroglial cells. Currently, there is no screening test for CNS cancers, and standard treatment involves surgery, stereotaxic radiotherapy, systemic therapy and whole-brain radiation therapy [51].

Oncomine analysis revealed that STEAP1 is overexpressed in three out of seven datasets of glioblastoma (Table 2). On the other hand, STEAP1 is underexpressed in one out of five datasets of astrocytoma and in two out of four datasets of oligodendroglioma. In agreement with our data, it was recently shown that STEAP1 mRNA expression was increased in glioblastoma versus solid normal tissue from the TCGA cohort [53,54]. Regarding STEAP2, Oncomine analysis showed its over (one out of five) and underexpression (two out five) in datasets of glioblastoma. In oligodendroglioma, Oncomine analysis showed that STEAP2 is mostly underexpressed, but no significant differences were observed in astrocytoma. However, it should be highlighted that French Brain dataset showed a strong trend for the underexpression of STEAP2 (Table 2). Recent studies also showed that STEAP2 levels were downregulated in glioblastoma, and this low expression was associated with a better overall survival rate [53–55]. Concerning STEAP3, a strong overexpression of this transcript was observed in all types of CNS cancers analyzed (Table 2). In agreement with these datasets, other publications also showed the overexpression of STEAP3 in glioma [34,53,54]. For example, Han et al. [34] and Zhao et al. [54] described through the analysis of public available databases that STEAP3 is highly expressed in malignant gliomas, and this higher STEAP3 expression levels exhibit a significantly shorter overall patients' survival. Chen et al. [53] also showed that STEAP3 was overexpressed in glioblastoma, which was inversely correlated with patients' overall survival. Regarding

STEAP4, Oncomine analysis showed isolated datasets with significant underexpression (glioblastoma and oligodendroglioma) and overexpression (astrocytoma) of this family member (Table 2).

Using data from cBioPortal, the Glioblastoma dataset (TCGA, Cell 2013) [56] was selected to evaluate if STEAPs expression is associated with prognosis. The results obtained showed that STEAP1, STEAP2, STEAP3 and STEAP4 were overexpressed in 6% (9 in 152), 6% (9 in 152), 5% (8 in 152) and 4% (6 in 152) of patients, respectively. Survival analysis revealed that high expression of STEAP2 was directly associated with lower overall survival in glioblastoma (Figure 2, $p = 0.0173$). This result is in accordance with Chen et al. [53] and Prasad et al. [55], which, as referred previously, showed that the underexpression of STEAP2 is correlated with a better prognosis in glioblastoma patients. Overall, this result suggests that quantifying STEAP2 expression levels can be a good strategy to stratify glioblastoma patients and identify prognosis. Curiously, from the dataset selected from cBioPortal, STEAP3 did not correlate with overall survival (Supplementary Figure S2), though Chen et al. [53] and Han et al. [34] showed that high expression of STEAP3 was inversely correlated with patients' overall survival. Some studies indicate that glioblastoma with isocitrate dehydrogenase 1 (IDH1) mutations have improved outcome when compared to IDH1 wild-type [57,58]. Additionally, a study carried out by Pappula et al. [59] found that no significant differences were observed between STEAP3 levels and IDH1-status, supporting our analysis showing that STEAP3 levels are not associated with prognosis. Considering that an association between STEAP2 overexpression and patient overall survival was found, we also evaluated the association between STEAP2 overexpression and IDH1-status, but no differences were perceived. In fact, the glioblastoma dataset has 8 samples with IDH1 mutations and all of them have unaltered levels of STEAP2 (data not shown). However, more studies are needed to clarify the inconsistency of some results.

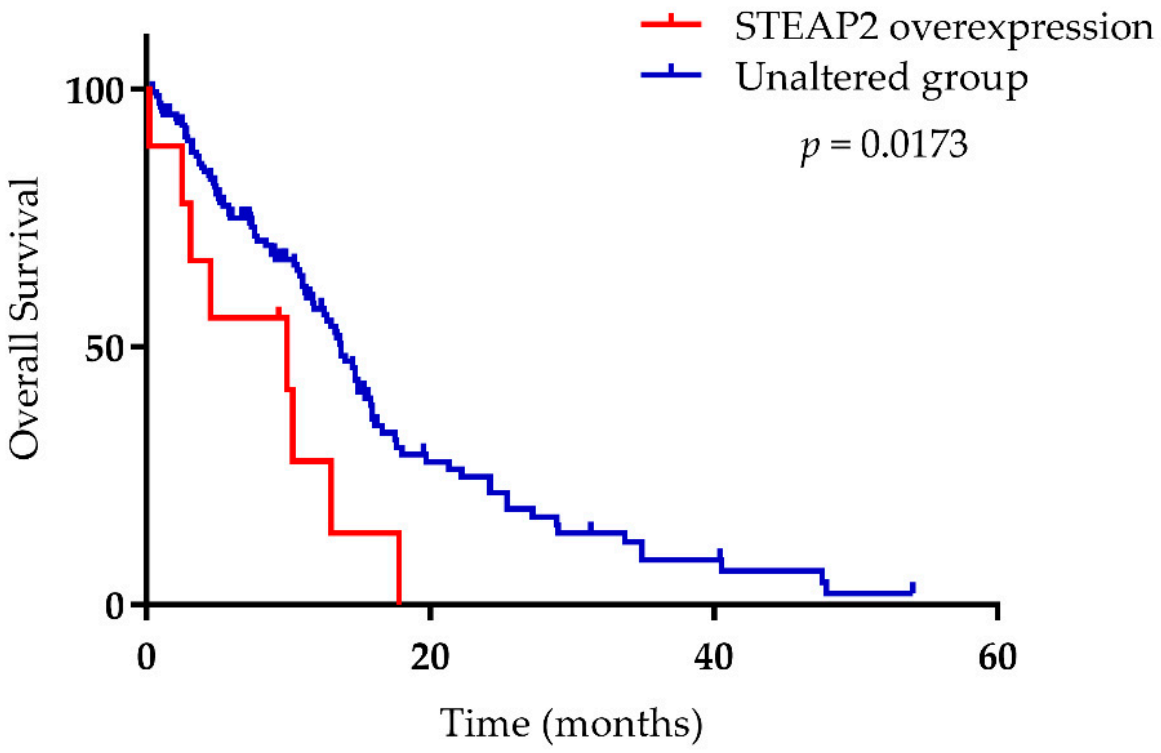

Figure 2. Correlation between STEAP2 gene expression and patients' overall survival in brain/CNS cancer. Patients were stratified in two groups: STEAP2 overexpression (red line) and unaltered expression levels (blue line). Survival analysis showed that high levels of STEAP2 transcript are correlated with lower survival.

Table 2. Analysis of STEAP family members expression in human brain/CNS cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Glioblastoma vs. Normal							
STEAP1	Overexpressed	2.965	4	Lee Brain	25 (22/3)	4.54×10^{-5}	[60]
	No difference	1.594	31	Liang Brain	32 (29/3)	0.148	[61]
	Overexpressed	1.355	17	Murat Brain	84 (80/4)	0.002	[62]
	No difference	−1.308	48	TCGA Brain	15 (5/10)	0.102	[63]
	No difference	1.124	40	Shai Brain	34 (27/7)	0.164	[64]
	Overexpressed	1.332	19	Sun Brain	104 (81/23)	2.06×10^{-5}	[65]
	Underexpressed	−1.68	23	Bredel Brain 2	31 (27/4)	0.005	[66]
STEAP2	Overexpressed	4.854	14	Lee Brain	25 (22/3)	0.021	[60]
	No difference	−1.428	28	Liang Brain	31 (28/3)	0.138	[61]
	No difference	−1.079	45	Bredel Brain 2	31 (27/4)	0.138	[66]
	Underexpressed	−3.622	11	Sun Brain	104 (81/23)	7.58×10^{-12}	[65]
	Underexpressed	−3.766	2	Murat Brain	84 (8/40)	2.78×10^{-8}	[62]
STEAP3	Overexpressed	3.427	1	Sun Brain	104 (81/23)	1.65×10^{-22}	[65]
	Overexpressed	4.968	2	TCGA Brain	552 (542/10)	2.93×10^{-12}	[63]
	Overexpressed	5.978	6	Bredel Brain 2	31 (27/4)	1.11×10^{-5}	[66]
	Overexpressed	2.349	9	Liang Brain	33 (30/3)	0.014	[61]
	Overexpressed	4.311	7	Lee Brain	25 (22/3)	8.89×10^{-4}	[60]
	Overexpressed	1.627	8	Murat Brain	84 (80/4)	3.29×10^{-5}	[62]
STEAP4	No difference	1.381	26	Liang Brain	33 (30/3)	0.109	[61]
	No difference	1.898	29	Lee Brain	25 (22/3)	0.208	[60]
	No difference	1.12	49	Sun Brain	104 (81/23)	0.169	[65]
	No difference	−1.754	38	Bredel Brain 2	28 (24/4)	0.062	[66]
	Underexpressed	−1.184	37	TCGA Brain	15 (5/10)	0.041	[63]
	No difference	1.117	46	Murat Brain	84 (80/4)	0.127	[62]
Astrocytoma vs. Normal							
STEAP1	No difference	1.709	24	Liang Brain	6 (3/3)	0.124	[61]
	No difference	−1.207	54	Shai Brain	10 (3/7)	0.188	[64]
	No difference	1.121	41	Sun Brain	42 (19/23)	0.147	[65]
	Underexpressed	−1.289	14	Bredel Brain 2	10 (6/4)	0.004	[66]
STEAP2	No difference	−1.341	38	Liang Brain	6 (3/3)	0.208	[61]
	No difference	1.041	45	Bredel Brain 2	10 (6/4)	0.311	[66]
STEAP3	Overexpressed	2.299	7	Sun Brain	42 (19/23)	2.12×10^{-5}	[65]
	No difference	−1.58	21	Liang Brain	6 (3/3)	0.073	[61]
STEAP4	Overexpressed	1.662	12	Liang Brain	6 (3/3)	0.048	[61]
	No difference	−1.1	53	Sun Brain	42 (19/23)	0.242	[65]
	No difference	−1.34	47	Bredel Brain 2	9 (5/4)	0.179	[66]
Oligodendroglioma vs. Normal							
STEAP1	No difference	−1.111	54	Shai Brain	10 (3/7)	0.188	[64]
	Underexpressed	−1.134	40	Sun Brain	73 (50/23)	0.035	[65]
	No difference	−1.084	47	French Brain	29 (23/6)	0.206	[67]
	Underexpressed	−1.136	5	Bredel Brain 2	9 (5/4)	0.001	[66]
STEAP2	No difference	1.022	50	Bredel Brain 2	9 (5/4)	0.424	[66]
	Underexpressed	−1.877	28	French Brain	29 (23/6)	0.043	[67]
	Underexpressed	−1.885	17	Sun Brain	73 (50/23)	5.13×10^{-6}	[65]
STEAP3	Overexpressed	1.364	21	French Brain	29 (23/6)	0.004	[67]
STEAP4	No difference	1.242	45	Sun Brain	73 (50/23)	0.193	[65]
	Underexpressed	−1.966	29	Bredel Brain 2	9 (5/4)	0.042	[66]
	No difference	1.029	46	French Brain	29 (23/6)	0.177	[67]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.3. Breast Cancer

Breast cancer is the most frequently diagnosed life-threatening cancer in women [68]. There are many different types of breast cancer, though invasive ductal carcinoma and invasive lobular carcinoma are the most common [68]. In addition to histological grade, the expression of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor-2 (HER2) are determined in breast cancer cells in order to predict the prognosis and decide the best treatment option. Standard treatments for breast cancer patients include surgery, molecular treatments targeting ER and/or HER2, radiation therapy and chemotherapy [68].

Oncomine analysis revealed that STEAP1 is underexpressed in five out of ten invasive ductal breast carcinoma datasets analyzed (Table 3). In lobular breast carcinoma, STEAP1 is underexpressed in two out of eight datasets, and in fibroadenoma it is also underexpressed with significant results obtained in all datasets analyzed (Table 3). It should be noted that in invasive ductal breast carcinoma, there is 1 dataset where STEAP1 is overexpressed. This result is in accordance with Maia et al. [69] that analyzed the levels of this protein in 42 samples of infiltrating ductal carcinoma and verified that STEAP1 is overexpressed in human breast cancer cases. Another study also showed that STEAP1 mRNA is overexpressed in 77% of all the tumors analyzed (28/36) when compared with the corresponding normal tissue [70]. On the other hand, a study demonstrated an underexpression of STEAP1 protein in 211 primary breast cancer samples compared to normal breast tissue (n = 40) [71]. Moreover, the low expression of STEAP1 was associated with the emergence of the malignant phenotype and poor prognosis [70]. This discrepancy of results may be due to the clinicopathological characteristics of samples, as well as a consequence of differences in the methodological approaches used to evaluate STEAP1 expression. Relative to STEAP2, Oncomine analysis showed that this transcript is underexpressed in 4 out of 10 invasive ductal breast carcinoma datasets analyzed (Table 3). In lobular breast carcinoma, it was found 1 dataset showing the overexpression of STEAP2 and other its underexpression (Table 3). A recently published article showed that low expression levels of STEAP2 are detected in breast cancer tissue, and that it is associated with malignant phenotype and poor prognosis [32]. Concerning STEAP3, Oncomine analysis indicated its overexpression in invasive ductal breast carcinoma (2 out 7 datasets), whereas the underexpression was found in the same proportion, 2 out 7 datasets analyzed (Table 3). For lobular breast carcinoma, STEAP3 was overexpressed in 2 out of 5 datasets available (Table 3). Relative to STEAP4, Oncomine analysis revealed significant underexpression of this transcript in both invasive ductal (3 out of 7 datasets) and lobular breast carcinoma (2 out of 5 datasets). However, in lobular breast carcinoma there is a dataset showing a significant overexpression of STEAP4 (Table 3). A recent study also showed that STEAP4 upregulation was linked to malignant breast tissues, suggesting that this STEAP family member may represent a novel breast cancer related biomarker [72].

From cBioPortal, using Breast Invasive Carcinoma dataset (TCGA, Cell 2015) [73], it was verified an overexpression of STEAP1, STEAP2, STEAP3, and STEAP4 in 6% (49/817), 6% (48/817), 6% (53/817) and in 6% (52/817) of patients, respectively. In this same platform, survival analysis indicated that overexpression of STEAPs did not correlate with patients' overall survival (Supplementary Figure S3). Contrarily, a recent study showed that breast cancer patients with high levels of STEAP1, STEAP2, or STEAP4 had a good prognosis, whereas those with low expression displayed high overall mortality [74]. This difference may be due to the source of the data since our work used data from cBioPortal [73] and this study used data from online Kaplan-Meier plotter tool (https://kmplot.com/analysis/ (accessed on 28 February 2021)) to analyze the prognostic value of STEAPs in breast cancer patients.

Table 3. Analysis of STEAP family members expression in human breast cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Invasive Ductal Breast Carcinoma vs. Normal							
STEAP1	No difference	−2.025	22	Ma Breast 4	23 (9/14)	0.066	[75]
	Overexpressed	1.549	32	Zhao Breast	41 (38/3)	0.025	[76]
	Underexpressed	−2.151	15	Sorlie Breast 2	82 (78/4)	0.024	[77]
	Underexpressed	−2.296	12	Sorlie Breast	66 (62/4)	0.013	[78]
	No difference	−2.301	17	Perou Breast	38 (35/3)	0.054	[79]
	No difference	−1.26	32	Radvanyi Breast	36 (28/8)	0.199	[80]
	Underexpressed	−1.923	7	Curtis Breast	1700 (1556/144)	8.32×10^{-40}	[81]
	No difference	1.115	55	Turashvili Breast	25 (5/20)	0.413	[82]
	Underexpressed	−3.133	5	TCGA Breast	450 (389/61)	4.07×10^{-27}	[63]
	Underexpressed	−2.602	14	Richardson Breast 2	47 (40/7)	0.001	[83]
STEAP2	No difference	1.966	19	Radvanyi Breast	33 (28/5)	0.068	[80]
	Underexpressed	−2.132	8	TCGA Breast	450 (389/61)	4.73×10^{-22}	[63]
	No difference	−3.814	23	Sorlie Breast 2	92 (89/3)	0.067	[77]
	No difference	−2.738	23	Perou Breast	39 (36/3)	0.115	[79]
	Underexpressed	−3.395	16	Sorlie Breast	68 (64/4)	0.031	[78]
	No difference	−1.343	32	Zhao Breast	41 (38/3)	0.139	[76]
	No difference	−1.057	63	Turashvili Breast	25 (5/20)	0.46	[82]
	Underexpressed	−1.859	4	Curtis Breast	1700 (1556/144)	7.32×10^{-60}	[81]
	No difference	−1.529	40	Ma Breast 4	23 (9/14)	0.22	[75]
	Underexpressed	−5.471	3	Richardson Breast 2	47 (40/7)	1.53×10^{-8}	[83]
STEAP3	No difference	1.038	62	Radvanyi Breast	39 (30/9)	0.435	[80]
	Overexpressed	1.15	41	Curtis Breast	1700 (1556/144)	8.55×10^{-6}	[81]
	Overexpressed	1.309	31	TCGA Breast	450 (389/61)	3.19×10^{-6}	[63]
	No difference	1.158	52	Zhao Breast	38 (35/3)	0.167	[76]
	Underexpressed	−1.452	13	Ma Breast 4	23 (9/14)	0.019	[75]
	No difference	1.36	50	Richardson Breast 2	47 (40/7)	0.058	[83]
	Underexpressed	−3.647	3	Turashvili Breast	25 (5/20)	0.006	[82]
STEAP4	No difference	2.276	24	Radvanyi Breast	27 (21/6)	0.098	[80]
	No difference	1.218	27	Ma Breast 4	23 (9/14)	0.044	[75]
	Underexpressed	−1.198	22	Curtis Breast	1700 (1556/144)	1.2×10^{-10}	[81]
	Underexpressed	−2.537	19	Zhao Breast	40 (37/3)	0.034	[76]
	Underexpressed	−2.845	13	TCGA Breast	450 (389/61)	1.7×10^{-16}	[63]
	No difference	−2.553	17	Turashvili Breast	25 (5/20)	0.077	[82]
	No difference	−1.527	89	Richardson Breast 2	47 (40/7)	0.948	[83]
Lobular Breast Carcinoma vs. Normal							
STEAP1	No difference	1.261	41	Zhao Breast	24 (21/3)	0.078	[76]
	No difference	−1.352	31	Sorlie Breast 2	9 (5/4)	0.203	[77]
	No difference	−1.534	19	Sorlie Breast	8 (4/4)	0.129	[78]
	No difference	−1.604	23	Perou Breast	7 (4/3)	0.133	[79]
	No difference	1.57	52	Radvanyi Breast	8 (5/3)	0.336	[80]
	Underexpressed	−1.8	9	Curtis Breast	292 (148/144)	9.83×10^{-20}	[81]
	No difference	1.086	61	Turashvili Breast	25 (5/20)	0.413	[82]
	Underexpressed	−2.211	91	TCGA Breast	97 (36/61	7.89×10^{-6}	[63]
STEAP2	No difference	1.423	44	Radvanyi Breast	12 (7/5)	0.263	[80]
	Overexpressed	1.325	41	TCGA Breast	97 (36/61)	0.031	[63]
	No difference	−2.276	24	Sorlie Breast 2	9 (6/3)	0.141	[77]
	No difference	−1.966	28	Perou Breast	7 (4/3)	0.187	[79]
	No difference	−2.768	11	Sorlie Breast	8 (4/4)	0.062	[78]
	No difference	1.02	69	Zhao Breast	24 (21/3)	0.481	[76]
	No difference	1.446	49	Turashvili Breast	25 (5/20)	0.307	[82]
	Underexpressed	−1.469	15	Curtis Breast	292 (148/144)	4.25×10^{-11}	[81]
STEAP3	No difference	−1.391	25	Radvanyi Breast	16 (7/9)	0.204	[80]
	Overexpressed	1.11	45	Curtis Breast	292 (148/144)	0.020	[81]
	Overexpressed	1.225	37	TCGA Breast	97 (36/61)	0.013	[63]
	No difference	1.066	63	Zhao Breast	24 (21/3)	0.338	[76]
	No difference	1.053	65	Turashvili Breast	25 (5/20)	0.452	[82]
STEAP4	Overexpressed	3.969	7	Radvanyi Breast	11 (5/6)	0.024	[80]
	Underexpressed	−1.108	35	Curtis Breast	292 (148/144)	0.006	[81]
	No difference	1.035	68	Zhao Breast	23 (20/3)	0.463	[76]
	Underexpressed	−2.024	22	TCGA Breast	97 (36/61)	1.29×10^{-4}	[63]
	No difference	−3.8	16	Turashvili Breast	25 (5/20)	0.103	[82]

Table 3. *Cont.*

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Fibroadenoma vs. Normal							
STEAP1	Underexpressed	−2.412	5	Sorlie Breast 2	6 (2/4)	0.02	[77]
	Underexpressed	−2.95	3	Sorlie Breast	7 (3/4)	0.006	[78]
STEAP2	No difference	−2.031	25	Sorlie Breast 2	5 (2/3)	0.168	[77]
	No difference	−2.581	17	Sorlie Breast	7 (3/4)	0.081	[78]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.4. Cervical Cancer

Cervical cancer is the third most common malignancy in women worldwide and remains a leading cause of cancer-related death for women in developing countries [84]. This type of cancer is commonly caused by human papillomavirus (HPV) infection, and vaccination against HPV provides the most effective method of primary prevention against cervical cancer. Controlling the incidence of cervical cancer can be realized in two ways: preventing the appearance of precancer lesions in first place; and detecting precancers before they become true cancer [85]. Cervical squamous cell carcinoma is the most common pathohistological form and represents over 90% of all cervical cancers [85]. Standard treatment involves surgery, radiation therapy and chemotherapy [84].

Oncomine analysis revealed a significant overexpression of STEAP1 and STEAP3 in cervical squamous cell carcinoma (Table 4). Regarding STEAP2 and STEAP4, no significant expression difference could be found in the databases available (Table 4).

In the cBioPortal and selecting the Cervical Squamous Cell Carcinoma (TCGA, Pan-Cancer Atlas) [86], STEAP1, STEAP2, STEAP3, and STEAP4 mRNA expression was high in 7% (21/294), 6% (18/294), 5% (16/294) and 4% (12/294) of cervical cancer patients, respectively. Survival analysis showed that the high expression of the STEAP4 gene was directly correlated with a lower survival rate, suggesting its prognostic value in cervical cancer (Figure 3, $p = 0.0004$, Supplementary Figure S4).

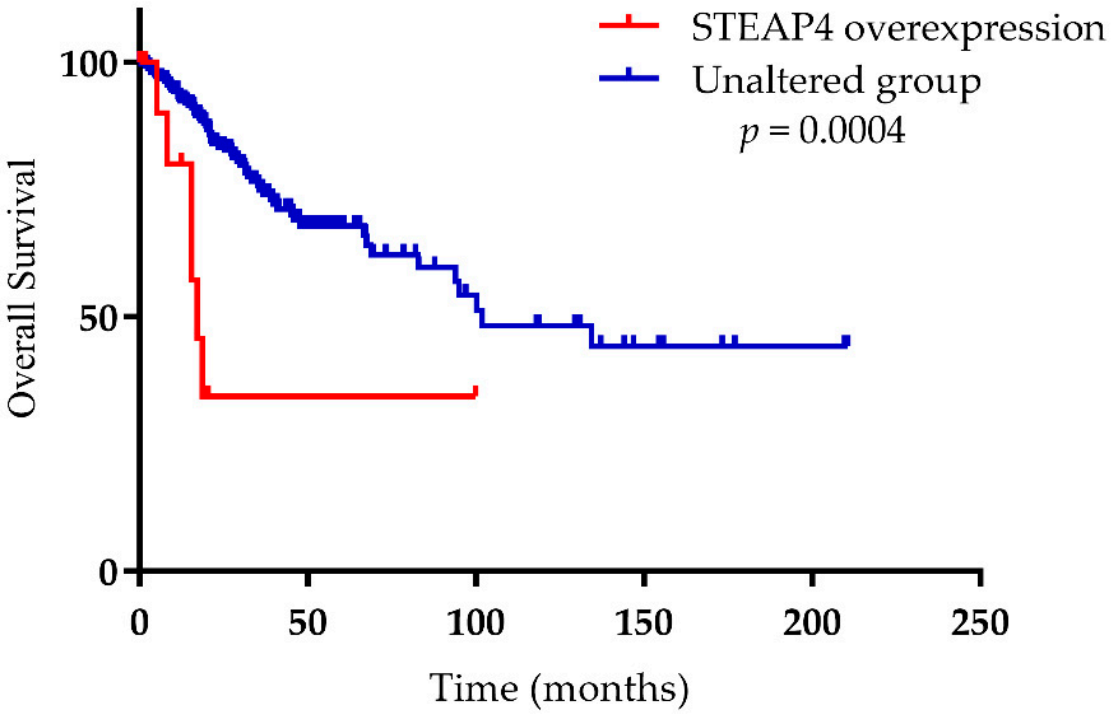

Figure 3. Correlation between STEAP4 gene expression and patients' overall survival in cervical cancer. Patients were stratified in two groups: STEAP4 overexpression (red line) and unaltered expression levels (blue line). Survival analysis showed that high levels of STEAP4 transcript are correlated with lower survival.

Table 4. Analysis of STEAP family members expression in human cervical cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over are highlighted by red filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Cervical Squamous Cell Carcinoma vs. Normal							
STEAP1	Overexpressed	1.935	13	Biewenga Cervix	45 (40/5)	5.89×10^{-5}	[87]
	No difference	1.08	48	Zhai Cervix	31 (21/10)	0.299	[88]
	No difference	1.101	47	Scotto Cervix 2	56 (32/24)	0.298	[89]
	Overexpressed	1.697	41	Pyeon Multi-cancer	42 (20/22)	0.018	[90]
STEAP2	No difference	1.014	63	Pyeon Multi-cancer	42 (20/22)	0.464	[90]
	No difference	1.017	64	Biewenga Cervix	45 (40/5)	0.452	[87]
STEAP3	Overexpressed	1.438	6	Scotto Cervix 2	56 (32/24)	1.05×10^{-5}	[89]
	Overexpressed	2.07	13	Biewenga Cervix	45 (40/5)	7.39×10^{-5}	[87]
	Overexpressed	1.466	31	Pyeon Multi-cancer	42 (20/22)	0.002	[90]
STEAP4	No difference	−1.074	52	Zhai Cervix	31 (21/10)	0.342	[88]
	No difference	1.162	56	Biewenga Cervix	45 (40/5)	0.170	[87]
	No difference	−2.22	92	Scotto Cervix 2	56 (32/24)	0.998	[89]
	No difference	1.048	61	Pyeon Multi-cancer	42 (20/22)	0.369	[90]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.5. Colorectal Cancer

Colorectal cancer is the most common type of gastrointestinal cancer. The incidence of this type of cancer is strongly influenced by diet, but genetic factors and inflammatory conditions of the digestive tract are part of the etiology of this disease [91]. It is the second leading cause of cancer death in women and the third in men. Adenocarcinomas of the colon and rectum represent approximately 90% of all colorectal cancer cases. Treatment options include chemotherapy, radiotherapy and surgery [91].

Of the datasets analyzed on the Oncomine, STEAP1 seems to be overexpressed in colorectal carcinoma, and rectal and colon adenocarcinoma (Table 5). Some previous studies are in accordance with this analysis. Lee et al. [29] demonstrated the strong staining of STEAP1 in a tissue array of 165 cancer specimens from primary colorectal cancer patients, and Nakamura et al. [20] showed that STEAP1 expression was significantly higher in colorectal cancer tissues compared with normal colonic tissues. Both studies also indicated that the expression of STEAP1 is negatively correlated with overall survival [20,29]. Dataset of Colorectal Adenocarcinoma (TCGA, PanCancer Atlas) [86] was extracted from cBioPortal and indicated that STEAP1 is overexpressed in 5% of cases (28 out 592), but higher expression of STEAP1 did not significantly correlate with the overall survival of colorectal cancer patients.

Regarding STEAP2, the Oncomine analysis revealed a dataset indicating its significant overexpression in colorectal carcinoma and other the underexpression (Table 5). No previous studies were found reporting the underexpression of STEAP2, but a study showed the overexpression of STEAP2 in colorectal cancer cases [92]. Data from the Colorectal Adenocarcinoma (TCGA, PanCancer Atlas) [86] also indicated that STEAP2 is overexpressed in 7% (39 out 592) of patients.

Oncomine analysis showed that STEAP3 is overexpressed in colorectal carcinoma, and in rectal and colon adenocarcinoma (Table 5). Accordingly, Barresi et al. [93] showed that the metalloreductase STEAP3 was increased in primary invasive colorectal cancer samples. The analysis of Colorectal Adenocarcinoma (TCGA, PanCancer Atlas) [86] indicated that STEAP3 is overexpressed in 4% of patients (24 out 592).

STEAP4 is underexpressed in colorectal carcinoma and colon adenocarcinoma, whereas being overexpressed in rectal carcinoma (Table 5). Available literature has conflicting reports for the expression of STEAP4. Barresi et al. [93] showed the underexpression of STEAP4 mRNA in colorectal carcinoma samples from twenty-seven patients and three human colorectal adenocarcinoma cell lines. However, another study in human STEAP4-expressing transgenic mice demonstrated that the overexpression of STEAP4 led to more severe colitis through increased oxidative stress, and consequently increased the develop-

ment of colorectal tumors compared with control mice [38]. A difference in the models used may explain the discrepancy in the results. In Colorectal Adenocarcinoma (TCGA, PanCancer Atlas) [86] dataset, STEAP4 overexpression was observed in 5% of patients (28 out 592).

Concerning the survival analysis, the results of dataset selected from the cBioPortal did not reveal significant differences between STEAPs overexpression and overall survival (Supplementary Figure S5).

Table 5. Analysis of STEAP family members expression in human colorectal cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Colorectal Carcinoma vs. Normal							
STEAP1	No difference	1.257	26	Zou Colon	17 (9/8)	0.100	[94]
	Overexpressed	1.629	13	Skrzypczak Colorectal	60 (36/24)	4.41×10^{-5}	[95]
	No difference	1.003	62	Skrzypczak Colorectal 2	15 (5/10)	0.497	[95]
	No difference	−1.372	89	Hong Colorectal	82 (70/12)	0.989	[96]
STEAP2	No difference	1.117	43	Zou Colon	17 (9/8)	0.333	[94]
	Overexpressed	1.596	28	Skrzypczak Colorectal 2	15 (5/10)	0.002	[95]
	No difference	−1.203	31	Skrzypczak Colorectal	60 (36/24)	0.044	[95]
	Underexpressed	−1.466	14	Hong Colorectal	82 (70/12)	1.74×10^{-4}	[96]
STEAP3	Overexpressed	1.394	7	Skrzypczak Colorectal 2	15 (5/10)	3.37×10^{-7}	[95]
	Overexpressed	1.195	33	Skrzypczak Colorectal	60 (36/24)	0.022	[95]
	No difference	−1.018	68	Hong Colorectal	82 (70/12)	0.558	[96]
STEAP4	No difference	1.119	41	Skrzypczak Colorectal 2	15 (5/10)	0.058	[95]
	No difference	1.153	54	Skrzypczak Colorectal	60 (36/24)	0.242	[95]
	Underexpressed	−2.091	20	Hong Colorectal	82 (70/12)	0.005	[96]
Rectal Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	1.729	18	Gaedcke Colorectal	130 (65/65)	2.07×10^{-9}	[97]
	Overexpressed	1.947	28	Sabates-Bellver Colon	39 (7/32)	0.005	[98]
	No difference	1.053	59	Kaiser Colon	13 (8/5)	0.390	[99]
	No difference	1.019	60	TCGA Colorectal	82 (60/22)	0.436	[63]
STEAP2	Overexpressed	1.326	29	Gaedcke Colorectal	130 (65/65)	1.23×10^{-5}	[97]
	No difference	1.08	53	Kaiser Colon	13 (8/5)	0.266	[99]
	No difference	−1.106	69	TCGA Colorectal	123 (101/22)	0.809	[63]
	No difference	1.036	68	Sabates-Bellver Colon	39 (7/32)	0.416	[98]
STEAP3	Overexpressed	1.939	9	Sabates-Bellver Colon	39 (7/32)	3.66×10^{-5}	[98]
	Overexpressed	1.707	11	Gaedcke Colorectal	130 (65/65)	2.36×10^{-14}	[97]
	No difference	−1.148	71	TCGA Colorectal	82 (60/22)	0.876	[63]
	No difference	1.04	60	Kaiser Colon	13 (8/5)	0.423	[99]
STEAP4	No difference	1.131	52	TCGA Colorectal	82 (60/22)	0.165	[63]
	No difference	1.094	37	Kaiser Colon	13 (8/5)	0.059	[99]
	Overexpressed	1.556	32	Gaedcke Colorectal	130 (65/65)	8.75×10^{-5}	[97]
	No difference	1.061	68	Sabates-Bellver Colon	39 (7/32)	0.429	[98]
Colon Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	1.771	22	Sabates-Bellver Colon	57 (25/32)	1.49×10^{-5}	[98]
	No difference	−1.134	43	Kaiser Colon	46 (41/5)	0.069	[99]
	No difference	1.09	54	TCGA Colorectal	123 (101/22)	0.218	[63]
	No difference	1.628	41	Skrzypczak Colorectal 2	15 (5/10)	0.073	[95]
STEAP2	Overexpressed	1.215	22	Ki Colon	91 (50/41)	7.99×10^{-4}	[100]
	Overexpressed	1.658	16	Skrzypczak Colorectal 2	15 (5/10)	0.001	[95]
	No difference	1.024	61	Kaiser Colon	46 (41/5)	0.379	[99]
	No difference	−1.031	64	TCGA Colorectal	123 (101/22)	0.624	[63]
	No difference	1.006	71	Sabates-Bellver Colon	39 (7/32)	0.476	[98]
STEAP3	Overexpressed	1.472	8	Skrzypczak Colorectal 2	15 (5/10)	3.12×10^{-5}	[95]
	Overexpressed	1.572	18	Sabates-Bellver Colon	57 (25/32)	2.37×10^{-6}	[98]
	No difference	−1.02	63	TCGA Colorectal	123 (101/22)	0.570	[63]
	No difference	1.237	52	Kaiser Colon	46 (41/5)	0.141	[99]
STEAP4	No difference	1.082	49	Skrzypczak Colorectal 2	15 (5/10)	0.148	[95]
	No difference	1.191	49	TCGA Colorectal	123 (101/22)	0.088	[63]
	No difference	1.037	52	Kaiser Colon	46 (41/5)	0.140	[99]
	Underexpressed	−2.042	2	Sabates-Bellver Colon	39 (7/32)	7.88×10^{-5}	[98]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.6. Esophageal Cancer

Esophageal cancer is the sixth leading cause of cancer death and the eighth most common cancer worldwide [101]. There is a significant gender distribution, with the incidence of disease being about 2–4-fold higher among males compared to females [102]. The two most common types of esophageal cancer are adenocarcinoma (predominantly in USA) and squamous cell carcinoma (most common worldwide) [102]. Smoking and alcohol consumption are the main risk factors for squamous cell carcinoma. The risk for esophageal adenocarcinoma has been shown to be increased in Barrett's esophagus, a condition characterized by replacement of the esophageal tissue by tissue such as that of the intestinal lining that occurs in individuals with long-term gastroesophageal reflux disease [101,102]. Endoscopy is the gold standard for diagnosis and surgical techniques are the main option to achieve the eradication of the disease [101].

Oncomine analysis showed a clear overexpression of STEAP1 and STEAP2 in Barrett's esophagus, esophageal squamous cell carcinoma and esophageal adenocarcinoma (Table 6). STEAP3 is also overexpressed in esophageal squamous cell carcinoma and esophageal adenocarcinoma, but no differences were found in Barrett's esophagus (Table 6). In the case of STEAP4, Oncomine analysis showed its underexpression in Barrett's esophagus, esophageal squamous cell carcinoma and esophageal adenocarcinoma (Table 6).

Using the dataset of Esophageal Adenocarcinoma (TCGA, PanCancer Atlas) [86] retrieved from the cBioPortal, its was found that the STEAP1, STEAP2, STEAP3 and STEAP4 mRNA is overexpressed in 20% (37 of 181), 22% (39 of 181), 12% (21 of 181) and 5% (9 of 181) of patients, respectively. However, no significant differences were observed between STEAPs overexpression and the overall survival of esophageal cancer patients (Supplementary Figure S6).

Table 6. Analysis of STEAP family members expression in human esophageal cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Barrett's Esophagus vs. Normal							
STEAP1	Overexpressed	2.922	8	Hao Esophagus	39 (14/25)	0.001	[103]
	Overexpressed	2.019	4	Kimchi Esophagus	16 (8/8)	0.005	[104]
	No difference	−1.049	51	Kim Esophagus	43 (15/28)	0.610	[105]
STEAP2	Overexpressed	2.178	6	Hao Esophagus	41 (13/28)	3.98×10^{-4}	[103]
	Overexpressed	1.985	7	Kim Esophagus	43 (15/28)	8.10×10^{-6}	[105]
STEAP3	No difference	1.369	28	Hao Esophagus	42 (14/28)	0.066	[103]
	No difference	1.056	39	Kimchi Esophagus	16 (8/8)	0.367	[104]
	No difference	1.019	37	Kim Esophagus	43 (15/28)	0.198	[105]
STEAP4	No difference	1.129	40	Kimchi Esophagus	16 (8/8)	0.377	[104]
	No difference	1.296	40	Hao Esophagus	41 (13/28)	0.160	[103]
	Underexpressed	−1.791	12	Kim Esophagus	43 (15/28)	2.36×10^{-7}	[105]
Esophageal Squamous Cell Carcinoma vs. Normal							
STEAP1	Overexpressed	1.798	7	Su Esophagus 2	106 (53/53)	1.40×10^{-10}	[106]
	Overexpressed	1.577	18	Hu Esophagus	34 (17/17)	0.002	[107]
STEAP2	Overexpressed	1.118	38	Su Esophagus 2	102 (51/51)	0.040	[106]
STEAP3	Overexpressed	1.278	30	Hu Esophagus	34 (17/17)	0.031	[107]
	Overexpressed	1.165	28	Su Esophagus 2	106 (53/53)	0.002	[106]
STEAP4	Underexpressed	−1.39	25	Hu Esophagus	34 (17/17)	0.012	[107]
	Underexpressed	−1.744	7	Su Esophagus 2	102 (51/51)	7.01×10^{-9}	[106]
Esophageal Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	14.326	1	Hao Esophagus	30 (5/25)	7.24×10^{-9}	[103]
	Overexpressed	2.102	12	Kimchi Esophagus	16 (8/8)	0.013	[104]
	No difference	1.034	46	Kim Esophagus	93 (75/28)	0.409	[105]
STEAP2	Overexpressed	2.448	6	Hao Esophagus	31 (5/26)	1.66×10^{-4}	[103]
	Overexpressed	1.672	10	Kim Esophagus	93 (75/28)	4.10×10^{-7}	[105]
STEAP3	Overexpressed	1.743	35	Hao Esophagus	33 (5/28)	0.046	[103]
	No difference	−1.122	48	Kimchi Esophagus	16 (8/8)	0.247	[104]
	No difference	1.028	30	Kim Esophagus	93 (75/28)	0.057	[105]
STEAP4	No difference	−1.895	33	Kimchi Esophagus	16 (8/8)	0.086	[104]
	No difference	1.325	61	Hao Esophagus	33 (5/28)	0.314	[103]
	Underexpressed	−1.396	29	Kim Esophagus	93 (75/28)	0.001	[105]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.7. Gastric Cancer

Gastric carcinoma, also called stomach carcinoma, is the fourth most common malignancy and remains the second cause of death by malignancies worldwide [108]. More than 90% of gastric cancers are adenocarcinomas and develop from the cells of the innermost lining of the stomach (the mucosa) [108]. The cause of gastric cancer is multifactorial, but the Helicobacter pylori infection is considered to be the primary cause, as well as the family history, smoking habits, alcohol, high-salt diet or smoked foods, and low intake of fruits and vegetables [108]. Diagnosis of gastric cancer is made by endoscopy, by the direct visualization of a mass, and histological confirmation, analyzing the mass and adjacent tissue. Treatment includes surgery resection, immunotherapy, chemotherapy and radiotherapy [108].

Oncomine analysis revealed strong overexpression of STEAP1 and STEAP2 in all types of gastric cancer (Table 7). Corroborating this data, Wu et al. [109] and Zhang et al. [110] showed that STEAP1 is an up-regulated gene in gastric cancer and that its expression promotes cell proliferation, migration, invasiveness and tumorigenicity. Furthermore, it was also shown that RNAi-mediated silencing of STEAP1 potentiated the chemosensitivity of the human MKN45 gastric cancer cells to docetaxel [109], highlighting the importance of STEAP1 as a putative predictor of treatment response in gastric cancer patients. No previous studies have indicated the overexpression of STEAP2 in gastric cancer, but the consistency of the Oncomine analysis' results across different cancer types and databases supports its biological relevance. Regarding STEAP3, no differences in its expression levels were observed after the Oncomine analysis in all gastric cancer types, but STEAP4 was found to be overexpressed in one dataset for diffuse gastric adenocarcinoma (Table 7).

Analysis of the Stomach Adenocarcinoma (TCGA, PanCancer Atlas) [86] dataset selected from the cBioPortal, showed that 9% (39/412), 11% (44/412), 6% (26/412) and 6% (24/412) of patients display overexpression of STEAP1, STEAP2, STEAP3 and STEAP4, respectively. Survival analysis only indicated a significant correlation between STEAP4 overexpression and the overall survival of gastric cancer patients (Figure 4, $p = 0.0457$, Supplementary Figure S7). Of 24 patients with STEAP4 overexpression, 14 have died, being the mean survival 19,96 months. Dataset selected from the cBioPortal showed no significant differences between STEAP1 overexpression and patients' survival. However, a recent study showed that higher STEAP1 gene expression levels were associated with poor prognosis [110], which supports the investigation of STEAP1 as a putative prognostic marker in gastric carcinoma.

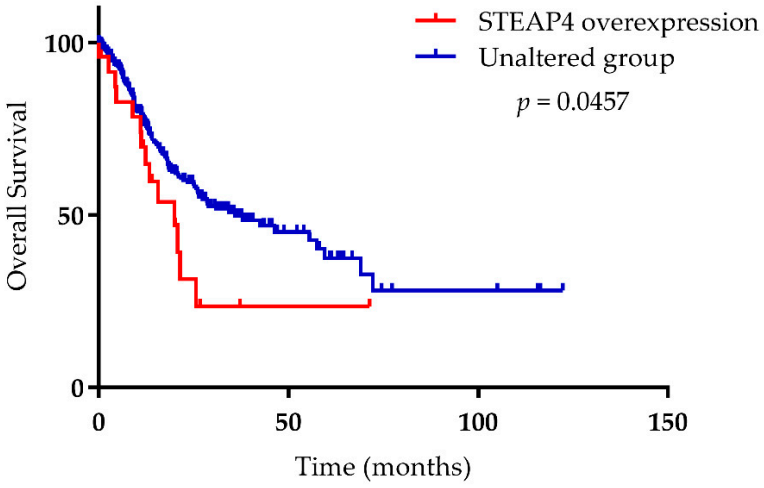

Figure 4. Correlation between STEAP4 gene expression and patients' overall survival in gastric cancer. Patients were stratified in two groups: STEAP4 overexpression (red line) and unaltered expression levels (blue line). Survival analysis showed that high levels of STEAP4 transcript are correlated with lower survival.

Table 7. Analysis of STEAP family members expression in human gastric cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over are highlighted by red filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Gastric Cancer vs. Normal							
STEAP1	Overexpressed	2.544	5	Cui Gastric	160 (80/80)	2.04×10^{-4}	[111]
	Overexpressed	2.193	23	Wang Gastric	27 (12/15)	0.020	[112]
STEAP2	Overexpressed	1.478	3	Cui Gastric	160 (80/80)	1.95×10^{-5}	[111]
	No difference	1.116	60	Wang Gastric	27 (12/15)	0.327	[112]
STEAP3	No difference	−1.057	46	Cui Gastric	160 (80/80)	0.335	[111]
	No difference	1.078	62	Wang Gastric	27 (12/15)	0.371	[112]
STEAP4	No difference	−1.073	43	Cui Gastric	160 (80/80)	0.273	[111]
	No difference	−1.94	20	Wang Gastric	27 (12/15)	0.059	[112]
Gastric Intestinal Type Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	1.928	8	Cho Gastric	39 (20/19)	0.002	[113]
	Overexpressed	1.862	8	Chen Gastric	93 (66/27)	1.75×10^{-8}	[114]
	Overexpressed	2.309	13	DErrico Gastric	57 (26/31)	2.76×10^{-6}	[115]
STEAP2	Overexpressed	1.689	8	Cho Gastric	39 (20/19)	0.002	[113]
	Overexpressed	1.252	34	Chen Gastric	75 (56/19)	0.013	[114]
	Overexpressed	1.35	30	DErrico Gastric	57 (26/31)	0.002	[115]
STEAP3	No difference	1.315	48	DErrico Gastric	57 (26/31)	0.061	[115]
	No difference	1.014	52	Cho Gastric	39 (29/19)	0.305	[113]
STEAP4	No difference	1.028	71	DErrico Gastric	57 (26/31)	0.459	[115]
	No difference	1.029	41	Cho Gastric	39 (29/19)	0.151	[113]
Diffuse Gastric Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	2.13	2	Cho Gastric	50 (31/19)	8.30×10^{-7}	[113]
	Overexpressed	1.689	5	Chen Gastric	39 (12/27)	1.05×10^{-4}	[114]
	Overexpressed	1.987	18	DErrico Gastric	37 (6/31)	0.015	[115]
STEAP2	Overexpressed	1.565	10	Cho Gastric	50 (31/19)	7.38×10^{-4}	[113]
	Overexpressed	1.262	15	Chen Gastric	28 (9/19)	0.004	[114]
	No difference	1.341	33	DErrico Gastric	37 (6/31)	0.064	[115]
STEAP3	No difference	−1.052	45	DErrico Gastric	37 (6/31)	0.368	[115]
	No difference	1.004	59	Cho Gastric	23 (4/19)	0.431	[113]
STEAP4	Overexpressed	1.501	27	DErrico Gastric	37 (6/31)	0.037	[115]
	No difference	1.027	44	Cho Gastric	50 (31/19)	0.15	[113]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.8. Head and Neck Cancer

Head and neck cancers are categorized by the structure affected (e.g., oral cavity, pharynx, larynx and sinonasal tract). Squamous cell carcinomas account for more than 90% of head and neck cancers [116]. Tobacco consumption, alcohol consumption, exposure to environmental pollutants and HPV infection increase the risk of head and neck cancers. Treatments vary dependently on cancer location but generally, include surgery and/or radiation therapy and chemotherapy [116].

Oncomine analysis showed that STEAP1 was significantly overexpressed in almost all the oral cavity squamous cell and tongue carcinoma datasets analyzed (Table 8). No significant differences were found for STEAP2 expression in oral cavity squamous cell and tongue carcinoma (Table 8). Regarding the expression of STEAP3, a strong overexpression was found in all head and neck cancers analyzed. In what concerns STEAP4, Oncomine analysis showed its underexpression in oral cavity squamous cell carcinoma (Table 8).

In Head and Neck Squamous Cell Carcinoma (TCGA, Nature 2015) [117] dataset retrieved from the cBioPortal, STEAP1, STEAP2, STEAP3 and STEAP4 overexpression was detected in 11% (30 of 279), 11% (32 of 279), 8% (23 of 279) and 5% (15 of 279) of patients, respectively. However, no association was found between the overexpression of STEAPs and the overall survival of head and neck cancer patients (Supplementary Figure S8).

Table 8. Analysis of STEAP family members expression in human head and neck cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Oral Cavity Squamous Cell Carcinoma vs. Normal							
STEAP1	Overexpressed	2.879	2	Toruner Head-Neck	20 (16/4)	8.74×10^{-5}	[118]
	Overexpressed	3.657	18	Pyeon Multi-cancer	26 (4/22)	0.037	[90]
	Overexpressed	1.639	7	Peng Head-Neck	79 (57/22)	1.84×10^{-8}	[119]
STEAP2	No difference	1.406	36	Pyeon Multi-cancer	26 (4/22)	0.153	[90]
	No difference	1.047	40	Peng Head-Neck	79 (57/22)	0.310	[119]
STEAP3	Overexpressed	1.457	5	Peng Head-Neck	79 (57/22)	1.53×10^{-9}	[119]
	Overexpressed	1.525	17	Toruner Head-Neck	20 (16/4)	0.021	[118]
	No difference	1.58	35	Pyeon Multi-cancer	26 (4/22)	0.139	[90]
STEAP4	Underexpressed	−1.14	22	Pyeon Multi-cancer	26 (4/22)	0.024	[90]
	No difference	−1.087	31	Toruner Head-Neck	20 (16/4)	0.103	[118]
	Underexpressed	−1.555	23	Peng Head-Neck	79 (57/22)	0.003	[119]
Tongue Carcinoma vs. Normal							
STEAP1	Overexpressed	2.32	16	Pyeon Multi-cancer	37 (15/22)	0.001	[90]
	Overexpressed	2.122	13	Estilo Head-Neck	57 (31/26)	2.59×10^{-5}	[120]
	Overexpressed	1.535	16	Talbot Lung	59 (31/28)	9.08×10^{-5}	[121]
	Overexpressed	2.483	8	Ye Head-Neck	38 (26/12)	0.001	[122]
	No difference	−1.08	47	Kuriakose Head-Neck	25 (3/22)	0.42	[123]
STEAP2	No difference	−1.038	59	Pyeon Multi-cancer	37 (15/22)	0.384	[90]
	No difference	1.019	68	Ye Head-Neck	38 (26/12)	0.457	[122]
STEAP3	Overexpressed	1.347	18	Pyeon Multi-cancer	37 (15/22)	0.002	[90]
	Overexpressed	1.115	29	Ye Head-Neck	38 (26/12)	0.044	[122]
STEAP4	No difference	1.248	33	Ye Head-Neck	38 (26/12)	0.063	[122]
	No difference	1.07	53	Pyeon Multi-cancer	37 (15/22)	0.294	[90]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.9. Kidney Cancer

Approximately 90% of kidney cancers are renal cell carcinomas, also known as renal cell cancer or renal cell adenocarcinoma, subdivided into clear cell (7 out of 10 people with renal cell carcinoma are this kind of cancer), papillary (second most common subtype), and chromophobe. Other types of kidney cancer include Wilms tumors (nephroblastoma), which usually occur in children under 5 years old, and renal oncocytoma, a benign renal tumor [124]. The incidence of kidney cancer is higher in men than in women, and the factors that contribute to kidney cancer include smoking, obesity, hypertension and particular inherited conditions [125]. Currently, there is no standard screening test for kidney cancer. However, individuals with increased risk due to inherited conditions can be screened for kidney cancer using computed tomography and magnetic resonance imaging. Treatment includes surgery, radiation therapy and chemotherapy [125].

Data from Oncomine analysis revealed that STEAP1 is underexpressed in renal oncocytoma and chromophobe renal cell carcinoma, whereas being overexpressed in papillary renal cell carcinoma as detailed in Table 9. In clear cell renal cell carcinoma, Oncomine analysis showed both a significant over and underexpression of STEAP1 dependently on the database (Table 9). These inconsistent results are probably due to the heterogeneity of the samples used in the two studies [126,127]. However, in the biomedical literature there is a study that showed that STEAP1 immunohistochemical staining was detected in 18 of the 20 (90%) renal cell carcinoma specimens [44]. This led the authors of this study to suggest the use of STEAP1 as a potential target for anticancer T-cell based immunotherapy for renal cell carcinoma. High STEAP1 mRNA expression was found in 5% (28 of 510) of patients within the Kidney Renal Clear Cell Carcinoma (TCGA, PanCancer Atlas) [86] dataset retrieved from the cBioPortal. However, no significant differences were observed concerning the overall survival of kidney cancer patients (Supplementary Figure S9).

Datasets from Oncomine revealed a significant underexpression of STEAP2 in clear cell renal cell carcinoma and renal Wilms tumor (Table 9). On the other hand, the kid-

ney renal clear cell carcinoma (TCGA, PanCancer Atlas) [86] dataset extracted from the cBioPortal presented high STEAP2 mRNA expression in 8% (42 of 510) of patients, but no statistical significance was observed between STEAP2 overexpression and patients' survival (Supplementary Figure S9).

Relative to STEAP3, Oncomine analysis indicated that it is significantly overexpressed in clear cell renal cell carcinoma, papillary renal cell carcinoma and renal Wilms tumor (Table 9). This result is in accordance with what was previously described by Borys et al. [128], showing the upregulation of STEAP3 expression in clear cell renal cell carcinoma tumor samples (T3 vs. T1 stages). In the Kidney Renal Clear Cell Carcinoma (TCGA, PanCancer Atlas) [86] from the cBioPortal, it was found that STEAP3 mRNA is overexpressed in 5% (24 of 510) of patients. Survival analysis also revealed a negative association between STEAP3 overexpression and patients' survival (Figure 5, $p = 0.0016$). This result is supported by two recent works showing that renal cell carcinoma patients with high expression of STEAP3 had shorter overall survival [129,130].

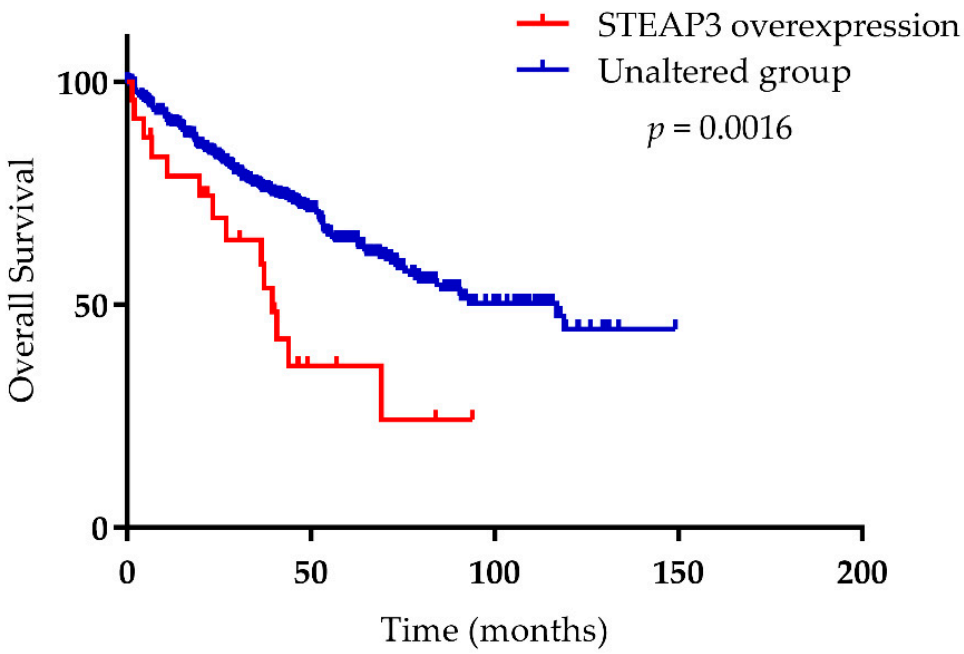

Figure 5. Correlation between STEAP3 gene expression and patients' overall survival in kidney cancer. Patients were stratified in two groups: STEAP3 overexpression (red line) and unaltered expression levels (blue line). Survival analysis showed that high levels of STEAP3 transcript are correlated with lower survival.

Concerning STEAP4, Oncomine analysis indicated a significant underexpression in papillary renal cell carcinoma, and an overexpression in renal oncocytoma and chromophobe renal cell carcinoma (Table 9). In clear cell renal carcinoma, one of the datasets indicated a significant underexpression of STEAP4, and two datasets showed its significant overexpression (Table 9). Study performed by Jones et al. [131] used microarrays approach in samples of patients from Germany. Lenburg et al. [132] and Yusenko et al. [127] used an RNA hybridization and SNP-based oligoarrays approach, respectively, from samples of patients provided of different demographic regions (Lenburg et al.: USA and Yusenko et al.: Germany, Hungary and Sweden). These differences may justify the differences in results. Data extracted from the Kidney Renal Clear Cell Carcinoma (TCGA, PanCancer Atlas) [86] indicated the high STEAP4 mRNA expression in 5% (23 of 510) of patients, but this higher expression was not associated with patients' survival (Supplementary Figure S9).

Table 9. Analysis of STEAP family members expression in human kidney cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Clear Cell Renal Cell Carcinoma vs. Normal							
STEAP1	Underexpressed	−1.304	13	Higgins Renal	29 (26/3)	0.013	[126]
	Overexpressed	1.764	21	Yusenko Renal	31 (26/5)	0.014	[127]
	No difference	−1.008	52	Jones Renal	46 (23/23)	0.456	[131]
	No difference	1.055	47	Gumz Renal	20 (10/10)	0.330	[133]
	No difference	−1.17	26	Lenburg Renal	18 (9/9)	0.052	[132]
STEAP2	No difference	−1.27	27	Yusenko Renal	31 (26/5)	0.132	[127]
	Underexpressed	−1.322	21	Lenburg Renal	18 (9/9)	0.027	[132]
STEAP3	Overexpressed	1.629	18	Lenburg Renal	18 (9/9)	0.019	[132]
	Overexpressed	1.921	31	Jones Renal	46 (23/23)	0.001	[131]
	No difference	1.833	32	Yusenko Renal	31 (26/5)	0.055	[127]
	No difference	−1.005	60	Gumz Renal	20 (10/10)	0.491	[133]
STEAP4	Underexpressed	−1.629	11	Jones Renal	46 (23/23)	4.7×10^{-7}	[131]
	Overexpressed	1.899	17	Lenburg Renal	18 (9/9)	0.017	[132]
	Overexpressed	4.584	25	Yusenko Renal	31 (26/5)	0.027	[127]
	No difference	−1.942	35	Cutcliffe Renal	17 (14/3)	0.259	[134]
	No difference	−2.059	33	Gumz Renal	20 (10/10)	0.056	[133]
Papillary Renal Cell Carcinoma vs. Normal							
STEAP1	No difference	−1.179	20	Higgins Renal	7 (4/3)	0.067	[126]
	Overexpressed	1.649	22	Yusenko Renal	31 (26/5)	0.033	[127]
	No difference	−1.044	47	Jones Renal	34(11/23)	0.359	[131]
STEAP2	No difference	1.196	44	Yusenko Renal	24 (19/5)	0.172	[127]
STEAP3	No difference	−1.011	49	Jones Renal	34 (11/23)	0.46	[131]
	Overexpressed	1.957	24	Yusenko Renal	24 (19/5)	0.040	[127]
STEAP4	Underexpressed	−1.19	33	Jones Renal	34 (11/23)	0.043	[131]
	No difference	1.238	61	Yusenko Renal	24 (19/5)	0.368	[127]
Chromophobe Renal Cell Carcinoma vs. Normal							
STEAP1	No difference	−1.162	26	Higgins Renal	6 (3/3)	0.19	[126]
	Underexpressed	−3.393	8	Yusenko Renal	9 (4/5)	0.01	[127]
	No difference	−1.173	26	Jones Renal	29 (6/23)	0.051	[131]
STEAP2	No difference	−4.435	27	Yusenko Renal	9 (4/5)	0.117	[127]
STEAP3	No difference	1.055	51	Jones Renal	29 (6/23)	0.175	[131]
	No difference	2.02	47	Yusenko Renal	9 (4/5)	0.176	[127]
STEAP4	Overexpressed	2.672	3	Jones Renal	29 (6/23)	4.23×10^{-9}	[131]
	No difference	1.151	65	Yusenko Renal	9 (4/5)	0.426	[127]
Renal Wilms Tumor vs. Normal							
STEAP1	No difference	−1.281	46	Yusenko Renal	9 (4/5)	0.361	[127]
	No difference	−1.113	35	Cutcliffe Renal	21 (18/3)	0.318	[134]
STEAP2	Underexpressed	−1.919	6	Yusenko Renal	9 (4/5)	0.01	[127]
STEAP3	Overexpressed	1.488	6	Cutcliffe Renal	21 (18/3)	0.003	[134]
	No difference	1.182	59	Yusenko Renal	9 (4/5)	0.347	[127]
STEAP4	No difference	1.472	57	Yusenko Renal	9 (4/5)	0.316	[127]
	No difference	−1.395	38	Cutcliffe Renal	21 (18/3)	0.369	[134]
Renal Oncocytoma vs. Normal							
STEAP1	No difference	−1.526	40	Yusenko Renal	9 (4/5)	0.256	[127]
	Underexpressed	−1.237	26	Jones Renal	35 (12/23)	0.008	[131]
STEAP2	No difference	−1.374	44	Yusenko Renal	9 (4/5)	0.317	[127]
STEAP3	No difference	1.108	53	Jones Renal	35 (12/23)	0.163	[131]
	No difference	2.305	41	Yusenko Renal	9 (4/5)	0.104	[127]
STEAP4	Overexpressed	3.041	2	Jones Renal	35 (12/23)	2.83×10^{-18}	[127]
	No difference	1.477	60	Yusenko Renal	9 (4/5)	0.311	[127]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.10. Leukemia

Leukemia is a cancer of the body's blood-forming tissues, including the bone marrow and the lymphatic system, and is one of the most common cancers in childhood [135]. This cancer is characterized by a bone marrow that produces abnormal white blood cells, known as leukemia cells. These cells are resistant to apoptosis, and their expansion can hamper the proper function of normal white blood cells, red blood cells, and platelets. The major types of leukemia are acute lymphoblastic leukemia (ALL, this is the most common type of leukemia in young children), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML) and other rarer types including hairy cell leukemia, myelodysplastic syndromes and myeloproliferative disorders [135]. The main risk factors to develop some types of leukemia include previous cancer treatment, genetic disorders, exposure to certain chemicals (such as benzene), smoking, radiation exposure and family history of leukemia. The treatment approaches comprise active surveillance, chemotherapy, radiation therapy, surgery, and stem cell transplantation [135].

Oncomine analysis revealed significant overexpression of STEAP1 in T- and B-cell ALL and its underexpression in CLL. In AML, there were conflicting results for STEAP1 expression (Table 10). Andersson et al. [136] showed significant overexpression of STEAP1, whereas the studies of Stegmaier et al. [137] and Valk et al. [138] reported a significant underexpression. The Andersson et al. study used samples collected from children, contrarily to Stegmaier et al. and Valk et al., which used samples from adults. Innate differences in immunity between the adults and pediatric population could potentially have confounded the results of STEAP1 expression on this type of leukemia. Moreaux et al. [26] carried out a study similar to ours using published databases, and also found the overexpression of STEAP1 in various types of leukemia compared to normal bone marrow, namely in T-cell ALL ($p = 5.6 \times 10^{-9}$), AML ($p = 3.3 \times 10^{-9}$) and B-cell ALL ($p = 8.3 \times 10^{-12}$) [136]. The same study also showed that high expression of STEAP1 was significantly associated with the reduced overall survival of AML patients ($n = 79$; $p = 0.0005$) [26].

Oncomine analysis showed contradictory results concerning the expression of STEAP2 and STEAP4 in T- and B-cell ALL. Haferlach et al. [139] indicated a significant overexpression of STEAP2 transcript in all types of leukemia analyzed. In contrast, Andersson et al. [136] data showed its significant underexpression in T-cell ALL, B-cell ALL and AML (Table 10). The same trend was found regarding STEAP4. A study performed by Coustan-Smith et al. [140] showed the significant overexpression of STEAP4, whereas the Haferlach et al. [139] and Andersson et al. [136] showed its significant underexpression (Table 10). Important methodological differences exist among studies, which altogether may explain the inconsistency of results. The Haferlach et al. study [139] comprises data from a multicenter study conducted across seven countries in eleven different centers, whereas Andersson et al. [136] and Coustan-Smith et al. [140] studies are single studies conducted in the Sweden and Finland, respectively. Another drawback for the analysis in different data sets is the age of participants and selected controls. The Andersson et al. study [136] used leukemia samples collected from children not specifying the children's age range, whereas the Coustan-Smith et al. study [140] used leukemia samples from children aged 1–18 years. In the control group, Haferlach et al. [139] used bone marrow samples from healthy individuals or without leukemia (such individuals may have a preexisting blood disorder such as hemophilia), Andersson et al. [136] used healthy adult controls and Coustan-Smith et al. [140] used healthy age-matched donors (2–25 years).

Relative to STEAP3, a significant underexpression was observed in all types of leukemia analyzed from Oncomine.

The Acute Myeloid Leukemia (TCGA, PanCancer Atlas) [86] dataset was selected from the cBioPortal to analyze the prognosis value of STEAPs gene in this cancer type. It showed the overexpression of STEAP1, STEAP2, STEAP3 and STEAP4 in 3% (6/173), 1.2% (2/173), 5% (8/173) and 3% (6/173) of patients, respectively. Survival analysis revealed that the higher expression of STEAP1and STEAP4 did not correlate with the overall survival of leukemia patients (Supplementary Figure S10). However, STEAP3 overexpression was

correlated with the lower survival rate of leukemia patients (Figure 6, $p = 0.0010$). Of the 8 patients with high STEAP3 levels, 7 died within 0.99 months, whereas in patients with unaltered STEAP3 levels, the mean overall survival was 17 months. This result suggests that the higher expression of STEAP3 can be associated with very poor prognosis.

Table 10. Analysis of STEAP family members expression in human leukemia. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
T-Cell Acute Lymphoblastic Leukemia vs. Normal							
STEAP1	Overexpressed	3.812	2	Andersson Leukemia	17 (11/6)	5.62×10^{-9}	[136]
	No difference	−1.014	49	Haferlach Leukemia	248 (174/74)	0.175	[139]
	No difference	−1.315	42	Coustan-Smith Leukemia	50 (46/4)	0.239	[140]
STEAP2	Overexpressed	1.027	36	Haferlach Leukemia	248 (174/74)	0.001	[139]
	Underexpressed	−2.202	15	Andersson Leukemia	17 (11/6)	8.18×10^{-5}	[136]
STEAP3	Underexpressed	−3.525	2	Haferlach Leukemia	248 (174/74)	5.53×10^{-44}	[139]
	No difference	1.441	45	Coustan-Smith Leukemia	50 (46/4)	0.233	[140]
STEAP4	Overexpressed	3.472	5	Coustan-Smith Leukemia	50 (46/4)	9.05×10^{-5}	[140]
	Underexpressed	−2.268	10	Haferlach Leukemia	248 (174/74)	4.08×10^{-19}	[139]
	Underexpressed	−26.262	2	Andersson Leukemia	15 (9/6)	6.45×10^{-9}	[136]
B-Cell Acute Lymphoblastic Leukemia vs. Normal							
STEAP1	Overexpressed	3.533	4	Andersson Leukemia	92 (86/6)	8.25×10^{-12}	[136]
	No difference	−1.021	46	Haferlach Leukemia	248 (174/74)	0.081	[139]
	No difference	−1.189	50	Coustan-Smith Leukemia	242 (238/4)	0.317	[140]
STEAP2	Overexpressed	1.019	41	Haferlach Leukemia	248 (174/74)	0.018	[139]
	Underexpressed	−2.006	16	Andersson Leukemia	93 (87/6)	2.94×10^{-5}	[136]
STEAP3	Underexpressed	−3.483	3	Haferlach Leukemia	248 (174/74)	1.78×10^{-42}	[139]
	No difference	1.337	43	Coustan-Smith Leukemia	242 (238/4)	0.275	[140]
STEAP4	Overexpressed	3.687	4	Coustan-Smith Leukemia	242 (238/4)	6.93×10^{-4}	[140]
	Underexpressed	−2.385	9	Haferlach Leukemia	248 (174/74)	1.65×10^{-20}	[139]
	Underexpressed	−24.399	9	Andersson Leukemia	88 (82/6)	1.47×10^{-7}	[136]
Acute Myeloid Leukemia vs. Normal							
STEAP1	Overexpressed	2.323	3	Andersson Leukemia	29 (23/6)	3.28×10^{-9}	[136]
	No difference	−1	51	Haferlach Leukemia	616 (542/74)	0.496	[139]
	Underexpressed	−2.196	13	Stegmaier Leukemia	15 (9/6)	0.007	[137]
	Underexpressed	−1.179	11	Valk Leukemia	293 (285/8)	0.035	[138]
STEAP2	Overexpressed	1.013	49	Haferlach Leukemia	616 (542/74)	0.042	[139]
	Underexpressed	−2.077	9	Andersson Leukemia	29 (23/6)	5.86×10^{-6}	[136]
STEAP3	Underexpressed	−1.483	9	Haferlach Leukemia	616 (542/74)	5.07×10^{-11}	[139]
	No difference	−1.122	52	Stegmaier Leukemia	15 (9/6)	0.355	[137]
	No difference	1.017	69	Valk Leukemia	293 (285/8)	0.450	[138]
STEAP4	Underexpressed	−2.068	5	Haferlach Leukemia	616 (542/74)	1.44×10^{-16}	[139]
	No difference	−2.02	42	Stegmaier Leukemia	15 (9/6)	0.213	[137]
	Underexpressed	−16.371	2	Andersson Leukemia	29 (23/6)	6.93×10^{-10}	[136]
	No difference	−1.567	24	Valk Leukemia	293 (285/8)	0.194	[138]
Chronic Lymphocytic Leukemia vs. Normal							
STEAP1	Underexpressed	−1.943	20	Basso Lymphoma	59 (34/25)	0.007	[141]
	No difference	−1.019	46	Haferlach Leukemia	522 (448/74)	0.105	[139]
	Underexpressed	−2.151	24	Haslinger Leukemia	111 (100/11)	0.01	[142]
STEAP2	Overexpressed	1.014	51	Haferlach Leukemia	522 (448/74)	0.043	[139]
STEAP3	Underexpressed	−3.937	4	Haferlach Leukemia	522 (448/74)	1.62×10^{-41}	[139]
STEAP4	Underexpressed	−2.149	15	Haferlach Leukemia	522 (448/74)	1.23×10^{-17}	[139]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

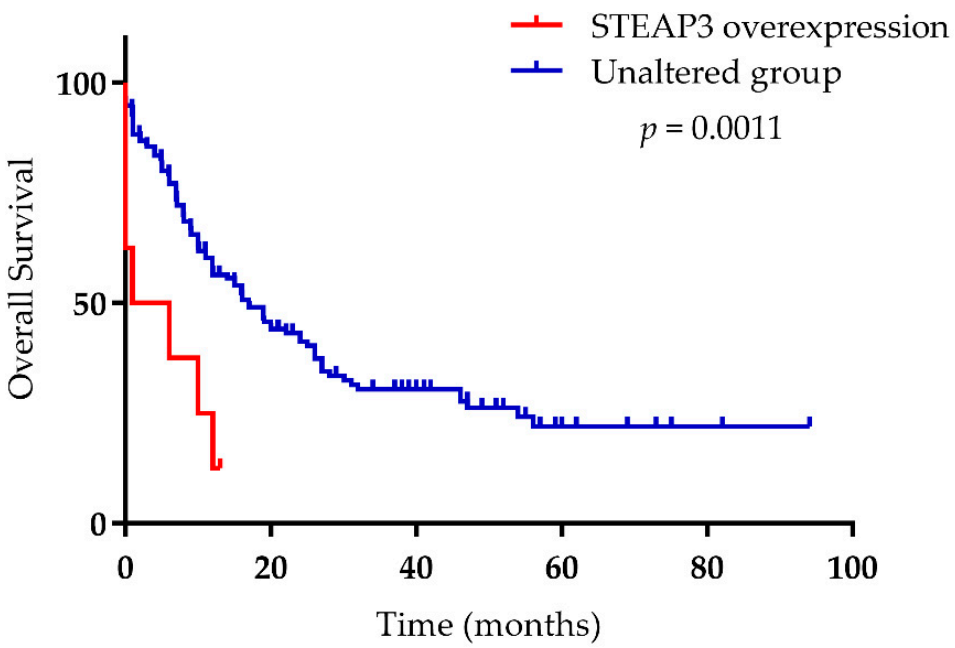

Figure 6. Correlation between STEAP3 gene expression and patients' overall survival in leukemia. Patients were stratified in two groups: STEAP3 overexpression (red line) and unaltered expression levels (blue line). Survival analysis showed that high levels of STEAP3 transcript are correlated with lower survival.

3.11. Liver Cancer

Hepatocellular carcinoma (HCC), also known as hepatoma, is the seventh most common type of liver cancer, accounting for 75% of all liver malignancies [143]. Other types of liver cancer, such as intrahepatic cholangiocarcinoma and hepatoblastoma, are much less common. HCC is commonly caused by cirrhosis of the liver due to alcohol abuse, hepatitis B and C, hemochromatosis, steatohepatitis, obesity and diabetes. The treatment options for liver cancer include surgery, liver transplant, chemotherapy, radiation therapy, ablation, embolization and chemoembolization [143].

Oncomine analysis showed significant over (Roessler et al. [144]) and underexpression (Mas et al. [145]) of STEAP1 in HCC (Table 11). One possible explanation for these opposite results can be the different characteristics of patients. Roessler et al. [144] used patients' samples diagnosed with HCC where most patients had a history of hepatitis B virus (HBV) infection or HBV-related liver cirrhosis. On the other hand, the Mas et al. [145] used liver tissue samples from patients with or without HCC (hepatitis C virus (HCV)-cirrhotic). According to this last study, a work recently published showed that STEAP1 is up-regulated in the liver cancer tissue compared to non-cancerous hepatic tissue, and significantly associated with poor overall survival and recurrence-free survival in liver cancer [12].

Regarding STEAP2, Oncomine analysis revealed its significant overexpression in HCC (Table 11). A previous study performed by Zeballos et al. [146] also found that STEAP2 is specifically overexpressed in HCC of Hispanics in comparison to HCC tumors in non-Hispanic whites, and it appears to play a malignant-promoting role. Using Liver HCC (TCGA, PanCancer Atlas) [86] dataset retrieved from cBioPortal, it was observed the overexpression of STEAP1 and STEAP2 in 8% (29 of 366) and 5% (17 of 366) of patients, respectively.

Regarding STEAP3 and STEAP4, Oncomine analysis showed their strong underexpression in HCC (Table 11). In agreement with our analysis, Coulouarn et al. [147] showed that the levels of the STEAP3 protein in HCC patients were lower in the tumor mass compared to the surrounding non-tumor tissue; Caillot et al. [148] showed a strong and significant decrease of STEAP3 expression in liver tumors according to its level of differentiation, with the lowest expression values observed in moderately or poorly differentiated tumors; and

Wang et al. [14] also showed that non-cancerous adjacent liver tissues and well-developed HCC tissues exhibited strong cytoplasm expression of STEAP3, while poor-differentiated HCC tissues showed low STEAP3 expression in the cytoplasm. These studies suggest that this protein may provide a prognostic marker for HCC. For STEAP4, there are studies supporting our analysis. Sonohara et al. [149] and Yamada et al. [150] revealed the reduced STEAP4 expression levels in HCC when compared to non-tumor liver tissues. Both studies still report that 32 of 48 (66.7%) of tumors had hypermethylation in the STEAP4 gene promoter, and the levels of methylation of own gene were significantly higher in 25 (93%) of the 27 HCC tumors, compared to non-tumor tissue counterparts [149,150]. In accordance with the Liver HCC (TCGA, PanCancer Atlas) [86] dataset, STEAP3 and STEAP4 were overexpressed in 6% (23 of 366) and 1.9% (7 of 366) of patients, respectively.

No significant association was observed concerning the relationship between STEAPs overexpression and patient's survival (Supplementary Figure S11).

Table 11. Analysis of STEAP family members expression in human liver cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Hepatocellular Carcinoma vs. Normal							
STEAP1	No difference	−1.051	37	Chen Liver	179 (103/76)	0.124	[151]
	Overexpressed	2.309	21	Roessler Liver	43 (22/21)	0.003	[144]
	Overexpressed	1.87	26	Roessler Liver 2	445 (225/220)	4.34×10^{-12}	[144]
	Underexpressed	−2.348	18	Mas Liver	57 (38/19)	1.45×10^{-4}	[145]
	No difference	−1.924	40	Wurmbach Liver	45 (35/10)	0.073	[152]
STEAP2	Overexpressed	1.463	21	Chen Liver	173 (98/75)	3.15×10^{-4}	[151]
	No difference	1.155	49	Wurmbach Liver	45 (35/10)	0.329	[152]
STEAP3	Underexpressed	−3.051	1	Chen Liver	180 (104/76)	3.55×10^{-24}	[151]
	Underexpressed	−6.944	1	Wurmbach Liver	45 (35/10)	7.99×10^{-12}	[152]
	Underexpressed	−3.863	1	Roessler Liver 2	445 (225/220)	3.25×10^{-74}	[144]
	Underexpressed	−4.137	2	Roessler Liver	43 (22/21)	4.91×10^{-9}	[144]
	Underexpressed	−2.295	2	Mas Liver	57 (38/19)	5.56×10^{-10}	[145]
STEAP4	Underexpressed	−5.633	4	Wurmbach Liver	45 (35/10)	5.0×10^{-5}	[152]
	Underexpressed	−1.671	34	Mas Liver	57 (38/19)	0.01	[145]
	Underexpressed	−2.845	7	Chen Liver	159 (88/71)	1.12×10^{-10}	[151]
	Underexpressed	−1.097	24	Roessler Liver	43 (22/21)	0.006	[144]
	Underexpressed	−1.141	21	Roessler Liver 2	445 (225/220)	8.27×10^{-9}	[144]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.12. Lung Cancer

Lung cancer encompasses different types of cancer starting in the lung or related structures. There are two main types of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [153]. NSCLC is the most common type and constitutes about 80 to 85% of all cases. There are three main cancer subtypes within NSCLC: adenocarcinoma (the most common), squamous cell carcinoma and large cell carcinoma [153]. The biggest risk factor for lung cancer is smoking. Other risk factors include a family history of lung cancer, breathing in secondhand smoke and previous radiation therapy to the chest. The main treatment option includes surgery, radiation therapy, chemotherapy, and targeted therapy [153].

Oncomine analysis showed strong overexpression of STEAP1, STEAP2 and STEAP3 and an underexpression of STEAP4 in squamous cell lung carcinoma and lung adenocarcinoma (Table 12). Several published studies support these results. Guo et al. [154], Huo et al. [155] and Liu et al. [156] showed the upregulation of STEAP1 expression in patients with lung adenocarcinoma and several human lung adenocarcinoma cell lines. Furthermore, STEAP1 overexpression correlates with the clinical prognosis of lung adenocarcinoma showing a poor prognosis [154,156]. Other study revealed the higher levels of STEAP2 in non-small cell lung cancer patients, which were significantly associated with patient shorter survival [157]. Regarding STEAP3, the results are contradictory. Our

analysis showed an overexpression of STEAP3 in squamous cell lung carcinoma, whereas a study carried out by Boelens et al. [158] showed its downregulation compared with normal bronchial epithelial cells of current smokers. No definitive explanation exists for the differences among studies, but they could likely be due to the characteristics of samples collected.

In a lung adenocarcinoma (TCGA, Nature 2014) [159] dataset retrieved from cBioPortal, STEAP1, STEAP2, STEAP3 and STEAP4 were overexpressed in 11% (25 of 230), 11% (25 of 230), 4% (10 of 230) and 7% (15 of 230) of patients, but no association was observed with patient's survival (Supplementary Figure S12).

Table 12. Analysis of STEAP family members expression in human lung cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Squamous Cell Lung Carcinoma vs. Normal							
STEAP1	Overexpressed	4.633	2	Hou Lung	82 (27/65)	5.06×10^{-16}	[160]
	Overexpressed	3.287	4	Garber Lung	19 (13/6)	2.31×10^{-4}	[161]
	Overexpressed	2.358	8	Wachi Lung	10 (5/5)	0.005	[162]
	Overexpressed	1.796	11	Talbot Lung	62 (34/28)	2.46×10^{-6}	[121]
	Overexpressed	2.744	12	Bhattacharjee Lung	38 (21/17)	0.019	[163]
STEAP2	No difference	1.600	29	Garber Lung	18 (13/5)	0.071	[161]
	Overexpressed	1.289	49	Hou Lung	82 (27/65)	0.041	[160]
STEAP3	No difference	1.155	48	Garber Lung	19 (13/6)	0.292	[161]
	Overexpressed	1.538	13	Wachi Lung	10 (5/5)	0.013	[162]
	Overexpressed	1.242	33	Hou Lung	82 (27/65)	0.003	[160]
STEAP4	Underexpressed	−12.225	1	Garber Lung	19 (13/6)	2.79×10^{-09}	[161]
	Underexpressed	−1.465	7	Wachi Lung	10 (5/5)	0.002	[162]
	Underexpressed	−5.802	1	Hou Lung	82 (27/65)	7.36×10^{-24}	[160]
Lung Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	2.451	12	Hou Lung	110 (45/65)	1.57×10^{-6}	[160]
	Overexpressed	3.033	3	Landi Lung	107 (58/49)	8.78×10^{-16}	[164]
	Overexpressed	2.888	7	Stearman Lung	39 (20/19)	4.53×10^{-5}	[165]
	Overexpressed	2.612	6	Su Lung	57 (27/30)	7.78×10^{-5}	[166]
	Overexpressed	2.970	5	Garber Lung	46 (40/6)	3.89×10^{-4}	[161]
	No difference	1.099	27	Bhattacharjee Lung	149 (123/17)	0.404	[163]
	Overexpressed	2.703	13	Okayama Lung	246 (226/20)	1.39×10^{-7}	[167]
	No difference	1.135	39	Selamat Lung	116 (58/58)	0.075	[168]
STEAP2	No difference	1.555	39	Garber Lung	44 (39/5)	0.080	[161]
	Overexpressed	1.498	33	Okayama Lung	246 (226/20)	0.002	[167]
	No difference	1.075	46	Selamat Lung	116 (58/58)	0.177	[168]
	No difference	1.163	60	Hou Lung	110 (45/65)	0.140	[160]
STEAP3	Overexpressed	2.512	5	Okayama Lung	246 (226/20)	2.39×10^{-11}	[167]
	Overexpressed	1.734	3	Su Lung	57 (27/30)	9.17×10^{-7}	[166]
	Overexpressed	1.823	23	Garber Lung	46 (40/6)	0.017	[161]
	Overexpressed	1.500	6	Landi Lung	107 (58/49)	3.89×10^{-11}	[164]
	Overexpressed	1.826	5	Selamat Lung	116 (58/58)	5.83×10^{-13}	[168]
	Overexpressed	1.311	16	Hou Lung	110 (45/65)	1.82×10^{-5}	[160]
STEAP4	No difference	1.014	60	Landi Lung	107 (58/49)	0.424	[164]
	Underexpressed	−4.561	1	Garber Lung	46 (40/6)	3.33×10^{-07}	[161]
	Underexpressed	−1.716	25	Su Lung	57 (27/30)	0.031	[166]
	No difference	1.111	63	Okayama Lung	246 (226/20)	0.256	[167]
	Underexpressed	−1.212	24	Selamat Lung	116 (58/58)	0.002	[168]
	Underexpressed	−2.259	1	Hou Lung	84 (19/65)	3.26×10^{-26}	[160]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.13. Lymphoma

Lymphomas are cancers that occur in the lymphatic system. The two major lymphoma types are Hodgkin's lymphoma (10%) and non-Hodgkin's lymphoma (90%, NHL), and both can occur in either children or adults [169]. NHL can originate from B-cells (90%) but also from T-cells or natural killer cells. Types of B-cell NHLs include low-grade lymphomas (for example, follicular lymphoma) and high-grade lymphomas (for example, diffuse large B-cell lymphoma and Burkitt lymphoma) [169]. Factors that can increase the risk

of lymphoma include some infections (such as HIV, Epstein-Barr virus and Helicobacter pylori), a weak immune system and age. Lymphoma treatment may involve chemotherapy, immunotherapy, radiation therapy and a bone marrow transplant or some combination of these [169].

Oncomine analysis revealed a general overexpression of all STEAP genes in follicular, diffuse large B-Cell, Burkitt's and Hodgkin's lymphoma (Table 13). The data in Oncomine for Burkitt's lymphoma revealed no significant differences in the expression of STEAP2 and STEAP4 transcripts. In follicular lymphoma, there was contradictory information concerning STEAP1 expression. Basso et al. [141] showed its overexpression contrary with the reported by Compagno et al. [170]. Both studies were conducted in the United States, and there is not enough information to speculate about the reasons that may explain the different results.

Table 13. Analysis of STEAP family members expression in human lymphoma. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Follicular Lymphoma vs. Normal							
STEAP1	Overexpressed	2.225	4	Basso Lymphoma	31 (6/25)	0.004	[141]
	No difference	1.045	66	Brune Lymphoma	30 (5/25)	0.309	[171]
	Underexpressed	−1.23	50	Compagno Lymphoma	58 (38/20)	0.009	[170]
	No difference	−1.036	61	Storz Lymphoma	14 (8/6)	0.401	[172]
STEAP2	No difference	1.074	43	Storz Lymphoma	14 (8/6)	0.254	[172]
	No difference	1.075	40	Compagno Lymphoma	58 (38/20)	0.104	[170]
	Overexpressed	1.135	29	Brune Lymphoma	30 (5/25)	0.030	[171]
STEAP3	Overexpressed	1.302	15	Compagno Lymphoma	58 (38/20)	5.53×10^{-6}	[170]
	Overexpressed	1.086	16	Brune Lymphoma	30 (5/25)	0.007	[171]
	No difference	1.369	42	Storz Lymphoma	9 (3/6)	0.237	[172]
STEAP4	Overexpressed	2.634	3	Compagno Lymphoma	58 (38/20)	4.12×10^{-17}	[170]
	Overexpressed	1.148	17	Brune Lymphoma	30 (5/25)	0.007	[171]
	No difference	−1.393	27	Storz Lymphoma	14 (8/6)	0.057	[172]
Diffuse Large B-Cell Lymphoma vs. Normal							
STEAP1	Overexpressed	1.786	26	Basso Lymphoma	57 (32/25)	0.024	[141]
	Overexpressed	1.332	41	Brune Lymphoma	36 (11/25)	0.035	[171]
	Overexpressed	2.153	19	Compagno Lymphoma	64 (44/20)	1.23×10^{-6}	[170]
	No difference	−1.003	64	Storz Lymphoma	12 (6/6)	0.495	[172]
STEAP2	Overexpressed	1.199	17	Storz Lymphoma	12 (6/6)	0.044	[172]
	Overexpressed	1.71	17	Compagno Lymphoma	64 (44/20)	3.07×10^{-7}	[170]
	Overexpressed	1.097	34	Brune Lymphoma	36 (11/25)	0.016	[171]
STEAP3	Overexpressed	2.261	6	Compagno Lymphoma	64 (44/20)	2.73×10^{-13}	[170]
	Overexpressed	1.513	16	Brune Lymphoma	36 (11/25)	8.33×10^{-4}	[171]
	No difference	1.032	58	Storz Lymphoma	9 (3/6)	0.447	[172]
STEAP4	Overexpressed	3.226	11	Compagno Lymphoma	64 (44/20)	8.6×10^{-10}	[170]
	Overexpressed	1.129	30	Brune Lymphoma	36 (11/25)	0.009	[171]
	No difference	−1.236	38	Storz Lymphoma	12 (6/6)	0.144	[172]
Burkitt's Lymphoma vs. Normal							
STEAP1	Overexpressed	1.715	33	Basso Lymphoma	42 (17/25)	0.045	[141]
	No difference	−1.049	40	Brune Lymphoma	30 (5/25)	0.264	[171]
STEAP2	No difference	−1.003	49	Brune Lymphoma	30 (5/25)	0.47	[171]
STEAP3	Overexpressed	1.219	25	Brune Lymphoma	30 (5/25)	0.006	[171]
STEAP4	No difference	1.078	50	Brune Lymphoma	30 (5/25)	0.078	[171]
Hodgkin's Lymphoma vs. Normal							
STEAP1	Overexpressed	1.109	37	Brune Lymphoma	37 (12/25)	0.038	[171]
	No difference	1.524	35	Eckerle Lymphoma	45 (4/41)	0.055	[173]
STEAP2	Overexpressed	1.103	24	Brune Lymphoma	37 (12/25)	0.008	[171]
	No difference	1.277	40	Eckerle Lymphoma	45 (4/41)	0.070	[173]
STEAP3	Overexpressed	1.882	3	Brune Lymphoma	37 (12/25)	4.93×10^{-6}	[171]
	Overexpressed	1.506	5	Eckerle Lymphoma	45 (4/41)	9.87×10^{-4}	[173]
STEAP4	Overexpressed	1.202	20	Eckerle Lymphoma	45 (4/41)	0.018	[173]
	Overexpressed	1.066	39	Brune Lymphoma	37 (12/25)	0.045	[171]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

Using Diffuse Large B-Cell Lymphoma (TCGA, PanCancer Atlas) [86] dataset from the cBioPortal, STEAP1, STEAP2, STEAP3 and STEAP4 were found to be overexpressed in 6% (3 of 48), 15% (7 of 48), 4% (2 of 48) and 2.1% (1 of 48 of) of patients, respectively. Survival analysis performed only for STEAP2 (more than 5 cases) revealed no association with overall survival of patients with Diffuse Large B-Cell Lymphoma (Supplementary Figure S13).

3.14. Melanoma

Melanoma is a type of skin cancer that occurs when pigment-producing cells, the melanocytes, begin to lose control of proliferation. Melanoma is more deadly than non-melanoma skin cancers, which usually respond well to treatment and rarely metastasize [174]. A risk factor for melanoma is the presence of benign melanocytic skin nevus, more commonly known as moles and freckles. Other risk factors include fair skin, high exposure to natural (sun) or artificial UV light, a history of blistering sunburns, and family history (or personal) of melanoma or atypical moles [175]. Based on the stage of melanoma and other conditions, treatment options might include surgery, immunotherapy, targeted therapy drugs and chemotherapy [175].

Oncomine analysis revealed significant overexpression of STEAP1 and underexpression of STEAP2 and STEAP3 in melanoma (Table 14). Regarding STEAP4, significant over (Critchley-Thorne et al. [176]) and underexpression (Haqq et al. [177] and Riker et al. [178]) was found, as detailed in Table 14. Differences in the samples source may have contributed to the different findings obtained. Haqq et al. [177] and Riker et al. [178] studies used tissue samples that contain > 5% melanoma cells, whereas Critchley-Thorne et al. [176] used peripheral blood mononuclear cells from patients with stage IV melanoma.

From Skin Cutaneous Melanoma (TCGA, PanCancer Atlas) [86] dataset in the cBioPortal, we identified STEAP1, STEAP2, STEAP3 and STEAP4 mRNA overexpression in 2.5% (11 out 441), 2.3% (10 out 441), 4% (16 out 441) and 4% (18 out 441) of patients. However, no correlation was observed between STEAP genes expression and patients' overall survival (Supplementary Figure S14).

Table 14. Analysis of STEAP family members expression in human melanoma. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Melanoma vs. Normal							
STEAP1	Overexpressed	4.635	23	Haqq Melanoma	9 (6/3)	0.015	[177]
	Overexpressed	2.319	19	Riker Melanoma	18 (14/4)	0.042	[178]
	No difference	−1.317	37	Talantov Melanoma	52 (45/7)	0.082	[179]
	No difference	−1.1	14	Critchley-Thorne Melanoma	46 (23/23)	0.174	[176]
STEAP2	No difference	1.038	59	Haqq Melanoma	9 (6/3)	0.402	[177]
	No difference	1.05	23	Critchley-Thorne Melanoma	46 (23/23)	0.219	[176]
	Underexpressed	−2.195	11	Riker Melanoma	18 (14/4)	0.006	[178]
STEAP3	No difference	1.217	37	Haqq Melanoma	9 (6/3)	0.080	[177]
	Underexpressed	−2.669	4	Talantov Melanoma	52 (45/7)	1.88×10^{-7}	[179]
	No difference	1.003	54	Critchley-Thorne Melanoma	46 (23/23)	0.473	[176]
	No difference	−1.185	37	Riker Melanoma	18 (14/4)	0.152	[178]
STEAP4	Overexpressed	1.119	3	Critchley-Thorne Melanoma	46 (23/23)	0.036	[176]
	Underexpressed	−2.802	18	Haqq Melanoma	9 (6/3)	0.036	[177]
	No difference	1.131	58	Talantov Melanoma	52 (45/7)	0.414	[179]
	Underexpressed	−2.521	14	Riker Melanoma	18 (14/4)	0.01	[178]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.15. Ovarian Cancer

Ovarian cancer is one of the gynecological malignancies responsible for thousands of deaths in women worldwide. About 90% of ovary tumors are epithelial and histologically classified as serous (the most common), endometrioid, clear cell and mucinous adenocarcinoma [180]. Risk factors for ovarian cancer include age (over 50), a family history of ovarian or breast cancer, hormone replacement therapy, endometriosis, and other risks,

such as overweight, smoking and exposure to asbestos. The main treatments for this cancer are surgery and chemotherapy [181].

Oncomine analysis showed that STEAP1 is overexpressed in all types of ovarian adenocarcinomas, but no significant differences were observed in ovarian carcinoma (Table 15). In agreement with our data, a recent study using 594 samples indicated that STEAP1 was highly expressed in the human ovarian cancer tissues, whereas low expression levels were found in normal ovarian tissues and benign tumors [182]. High STEAP1 expression, mostly localized to the cell membrane and cytoplasm of cancer cells, was positively correlated with poor tissue differentiation, higher clinical stage, and lymph node metastasis, though not significantly correlated with histological types [182]. However, analysis of the Ovarian Serous Cystadenocarcinoma (TCGA, PanCancer Atlas) [86] dataset from the cBioPortal indicated overexpression of STEAP1 in 5% (14/300) of patients. No correlation was found with patients' overall survival (Supplementary Figure S15).

Relative to STEAP2, Oncomine analysis revealed its significant overexpression in ovarian serous and mucinous adenocarcinoma, and a significant underexpression in ovarian clear cell adenocarcinoma. In ovarian endometrioid adenocarcinoma no significant differences were observed, and there was no data for STEAP2 expression in ovarian carcinoma (Table 15). Considering Ovarian Serous Cystademocarcinoma (TCGA, PanCancer Atlas) [86] in the cBioPortal platform, STEAP2 was overexpressed in 6% (17/300) of patients, but no correlation was observed with patients' overall survival (Supplementary Figure S15).

Concerning STEAP3, Oncomine analysis indicated a strong significant overexpression in all types of adenocarcinomas, but no significant differences were found for ovarian carcinoma (Table 15). A previous studies showed that STEAP3 mRNA was overexpressed in ovarian serous cystadenocarcinoma compared with health ovaries [183,184]. The same studies also demonstrated that higher STEAP3 levels were associated with shorter overall survival [183,184]. However, in Ovarian Serous Cystademocarcinoma (TCGA, PanCancer Atlas) [86] dataset from the cBioPortal, STEAP3 was overexpressed in 4% (13/300) of queried patients, but no significant differences were found considering overall survival (Supplementary Figure S15). The clinicopathological characteristics of samples used in the studies referred to above [183,184] and those of cBioPortal platform database may be the reason for the differences verified.

In what concerns STEAP4, Oncomine analysis showed its underexpression in ovarian serous adenocarcinoma, and the overexpression in ovarian mucinous adenocarcinoma and ovarian carcinoma (Table 15). In the Ovarian Serous Cystademocarcinoma (TCGA, PanCancer Atlas) [86] database of the cBioPortal, it was observed STEAP4 overexpression in 4% (13/300) of patients, which did not correlate with patients' overall survival (Supplementary Figure S15).

Table 15. Analysis of STEAP family members expression in human ovarian cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Ovarian Serous Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	1.495	8	Lu Ovarian	25 (20/5)	0.001	[185]
	No difference	1.602	27	Adib Ovarian	10 (6/4)	0.088	[186]
	No difference	1.03	49	Hendrix Ovarian	45 (41/4)	0.185	[187]
	No difference	−1.249	48	Yoshihara Ovarian	53 (43/10)	0.206	[188]
STEAP2	Overexpressed	1.21	24	Lu Ovarian	25 (20/5)	0.040	[185]
	No difference	1.238	36	Yoshihara Ovarian	50 (40/10)	0.289	[188]
STEAP3	Overexpressed	2.876	4	Yoshihara Ovarian	53 (43/10)	5.16×10^{-7}	[188]
	Overexpressed	1.307	8	Hendrix Ovarian	45 (41/4)	1.27×10^{-5}	[187]
	Overexpressed	1.559	4	Lu Ovarian	25 (20/5)	1.18×10^{-4}	[185]
STEAP4	No difference	1.083	44	Lu Ovarian	25 (20/5)	0.184	[185]
	No difference	−1.009	53	Hendrix Ovarian	45 (41/4)	0.432	[187]
	Underexpressed	−25.706	4	Yoshihara Ovarian	33 (23/10)	1.58×10^{-10}	[188]

Table 15. *Cont.*

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Ovarian Endometrioid Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	1.542	3	Lu Ovarian	14 (9/5)	7.91×10^{-4}	[185]
	No difference	1.031	50	Hendrix Ovarian	41 (37/4)	0.207	[187]
STEAP2	No difference	1.033	59	Lu Ovarian	14 (9/5)	0.354	[185]
STEAP3	Overexpressed	1.368	6	Hendrix Ovarian	41 (37/4)	1.96×10^{-6}	[187]
	Overexpressed	1.399	2	Lu Ovarian	14 (9/5)	0.004	[185]
STEAP4	No difference	1.064	51	Lu Ovarian	14 (9/5)	0.247	[185]
	No difference	−1024	50	Hendrix Ovarian	41 (37/4)	0.326	[187]
Ovarian Clear Cell Adenocarcinoma vs. Normal							
STEAP1	No difference	1.074	50	Lu Ovarian	12 (7/5)	0.227	[185]
	Overexpressed	1.124	20	Hendrix Ovarian	17 (13/4)	0.004	[187]
STEAP2	Underexpressed	−1.195	3	Lu Ovarian	12 (7/5)	0.003	[185]
STEAP3	Overexpressed	1.467	2	Hendrix Ovarian	12 (8/4)	1.30×10^{-6}	[187]
	No difference	1.162	31	Lu Ovarian	12 (7/5)	0.084	[185]
STEAP4	No difference	2.347	60	Lu Ovarian	14 (9/5)	0.346	[185]
	No difference	−1.035	48	Hendrix Ovarian	12 (8/4)	0.286	[187]
Ovarian Mucinous Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	1.969	1	Lu Ovarian	14 (9/5)	1.13×10^{-4}	[185]
	Overexpressed	1.124	20	Hendrix Ovarian	17 (13/4)	0.004	[187]
STEAP2	Overexpressed	1.546	1	Lu Ovarian	14 (9/5)	1.14×10^{-4}	[185]
STEAP3	Overexpressed	1.429	3	Hendrix Ovarian	17 (13/4)	1.87×10^{-6}	[187]
	Overexpressed	1.272	2	Lu Ovarian	14 (9/5)	0.001	[185]
STEAP4	Overexpressed	2.347	10	Lu Ovarian	14 (9/5)	0.019	[185]
	No difference	−1.016	53	Hendrix Ovarian	17 (13/4)	0.397	[187]
Ovarian Carcinoma vs. Normal							
STEAP1	No difference	−1.301	40	Bonome Ovarian	195 (185/10)	0.136	[189]
STEAP3	No difference	1.081	56	Bonome Ovarian	195 (185/10)	0.094	[189]
STEAP4	Overexpressed	1.086	41	Bonome Ovarian	195 (185/10)	0.006	[189]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.16. Pancreatic Cancer

The most common type of pancreatic cancer is adenocarcinoma. About nine out of ten people with pancreatic cancer have this type of cancer [190]. Pancreatic adenocarcinoma is the seventh leading cause of cancer-related death in both genders and is associated with an extremely poor prognosis due to the lack of early symptoms and rapid tumor progression [190]. Risk factors for pancreatic cancer are cigarette smoking, chronic pancreatitis and family history. The treatment may involve surgery, chemotherapy, vaccination, pain management, immunotherapy and dietary changes [190].

Oncomine analysis showed significant overexpression of STEAP1, STEAP2 and STEAP3 in pancreatic ductal adenocarcinoma, as described in Table 16. In agreement with our analysis, other research group found that STEAP3 gene is upregulated in pancreatic adenocarcinoma compared to normal tissue [191], and that high levels of STEAP3 transcript possessed significative adverse effects on pancreatic adenocarcinoma prognosis. Oncomine analysis showed conflicting data for STEAP4 (Table 16), where Badea et al. (Romania) [192] showed the overexpression of STEAP4, whereas its underexpression was reported by Buchholz et al. (Germany) [193]. Beyond the geographic differences, Badea et al. [192] used samples of 36 pancreatic cancer patients, and Buchholz et al. [193] used samples of 51 patients with pancreatic ductal adenocarcinoma in the head of the pancreas. No more information is available to determine if other clinicopathological characteristics may explain the discrepancy in the results.

In pancreatic carcinoma, Oncomine analysis showed the significant overexpression of STEAP2 and STEAP3, and a significant underexpression of STEAP4. For STEAP1, it was also found contradictory results, once Segara et al. [194] and Pei et al. [195] showed its overexpression, and Buchholz et al. [193] indicated an underexpression (Table 16). In a study similar to ours considering three independent studies, Moreaux et al. [26] also showed the overexpression of STEAP1 in cancer cases compared to the normal pancreas, namely in pancreatic ductal adenocarcinoma ($p = 1.6 \times 10^{-13}$) [192], pancreatic carcinoma ($p = 6.1 \times 10^{-5}$) [194], and pancreatic adenocarcinoma ($p = 0.007$) [196].

From the Pancreatic Adenocarcinoma (TCGA, PanCancer Atlas) [86] dataset of the cBioPortal platform, 10% (17 of 177), 7% (13 of 177), 5% (9 of 177) and 5% (9 of 177) of samples presented STEAP1, STEAP2, STEAP3 and STEAP4 mRNA overexpression, respectively. However, no significant correlation was observed with patients' overall survival with this type of cancer (Supplementary Figure S16).

Table 16. Analysis of STEAP family members expression in human pancreatic cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Pancreatic Ductal Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	4.841	1	Badea Pancreas	78 (39/39)	1.63×10^{-13}	[192]
	Overexpressed	1.77	7	Grutzmann Pancreas	22 (11/11)	0.028	[197]
	Overexpressed	4.528	10	Iacobuzio-Donahue Pancreas 2	17 (12/5)	0.007	[196]
	No difference	1.278	22	Ishikawa Pancreas	49 (24/25)	0.137	[198]
	No difference	−1.036	54	Buchholz Pancreas	10 (5/5)	0.467	[193]
STEAP2	Overexpressed	4.826	1	Iacobuzio-Donahue Pancreas 2	17 (12/5)	2.58×10^{-5}	[196]
	Overexpressed	2.45	3	Badea Pancreas	78 (39/39)	1.72×10^{-11}	[192]
	No difference	1.084	23	Buchholz Pancreas	14 (8/6)	0.103	[193]
	No difference	1.186	40	Ishikawa Pancreas	49 (24/25)	0.282	[198]
	No difference	1.271	55	Grutzmann Pancreas	22 (11/11)	0.341	[197]
STEAP3	Overexpressed	1.726	5	Grutzmann Pancreas	22 (11/11)	0.020	[197]
	Overexpressed	1.832	6	Ishikawa Pancreas	49 (24/25)	0.029	[198]
	No difference	−1.128	33	Buchholz Pancreas	14 (8/6)	0.168	[193]
	No difference	1.143	51	Badea Pancreas	78 (39/39)	0.144	[192]
STEAP4	Overexpressed	1.72	38	Badea Pancreas	78 (39/39)	0.004	[192]
	No difference	1.147	47	Grutzmann Pancreas	22 (11/11)	0.270	[197]
	No difference	−1.246	39	Iacobuzio-Donahue Pancreas 2	16 (11/5)	0.269	[196]
	Underexpressed	−1.528	13	Buchholz Pancreas	14 (8/6)	0.017	[193]
	No difference	−1.159	49	Ishikawa Pancreas	49 (24/25)	0.302	[198]
Pancreatic Carcinoma vs. Normal							
STEAP1	Overexpressed	2.983	2	Segara Pancreas	17 (11/6)	6.05×10^{-5}	[194]
	Overexpressed	2.673	14	Pei Pancreas	52 (36/16)	7.00×10^{-4}	[195]
	Underexpressed	−1.476	15	Buchholz Pancreas	27 (23/5)	0.05	[193]
STEAP2	No difference	−1.045	38	Buchholz Pancreas	29 (23/6)	0.251	[193]
	Overexpressed	1.775	21	Pei Pancreas	52 (36/16)	0.004	[195]
STEAP3	Overexpressed	1.35	30	Pei Pancreas	52 (36/16)	0.025	[195]
	No difference	1.048	41	Buchholz Pancreas	30 (24/6)	0.362	[193]
	No difference	−1.165	29	Segara Pancreas	17 (11/6)	0.087	[194]
STEAP4	No difference	1.048	48	Segara Pancreas	17 (11/6)	0.189	[194]
	No difference	−1.115	27	Buchholz Pancreas	30 (24/6)	0.14	[193]
	Underexpressed	−1.435	24	Pei Pancreas	52 (36/16)	0.013	[195]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.17. Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer and the second most common cause of cancer-related death in men in the Western world [199]. There are three different stages involved in the development of this disease. Prostate cancer develops from precursor lesions, designated prostatic intraepithelial neoplasia (PIN) and proliferative inflammatory atrophy (PIA), which evolve to carcinoma. Around 70 to 80% of the diagnosed prostatic adenocarcinomas emerge in the peripheral zone, while BPH commonly evolves in the transition zone [200]. The risk factors for prostate cancer can be endogenous (age, family history, ethnicity, hormones and oxidative stress) or exogenous (dietary factors, physical inactivity, obesity, environmental factors, occupation and smoking). Of all these factors, family history and age are considered the strongest risk factors. Treatment options for men with prostate cancer might include surgery, radiation therapy, cryotherapy, hormone therapy, chemotherapy and immunotherapy [199].

Oncomine analysis showed overexpression of STEAP1, STEAP2 and STEAP4 in prostate carcinoma, prostate adenocarcinoma and PIN, as indicated in Table 17. In BPH,

only STEAP2 was found as overexpressed STEAP transcript (Table 17). In agreement with our data, several studies showed the higher STEAP1 expression in malignant prostate tissue and PIN, and its correlation with tumor aggressiveness [1,28,201,202]. In addition, it has also been shown that silencing STEAP1 expression can inhibit the proliferation of prostate cancer cells promoting apoptosis [16]. Several other studies have demonstrated high expression of STEAP2 in prostate cancer [5,13,31,201], and that the knockdown of STEAP2 decreased aggressiveness of prostate cancer cells by reducing proliferation, migration and invasion [31]. There is also a study that corroborates the higher expression found for STEAP4 in prostate cancer tissue associated to poor overall survival [8,15,25]. Knockdown of STEAP4 significantly attenuated inflammation in prostate cancer cells and consequently decreased cell proliferation of these cells [15,25].

Relative to STEAP3, Oncomine analysis indicated its significant over and underexpression in prostate carcinoma, and a significant underexpression in prostate adenocarcinoma (Table 17). Varambally et al. [203] reported the overexpression of STEAP3, whereas Grasso et al. [204] and Taylor et al. [205] studies indicated the underexpression. All three studies were conducted in the USA, and enough information exists about samples' clinicopathological data to justify these differences. It was only indicated that the Varambally et al. study [203] used benign prostate tissues of clinically localized prostate cancer, and hormone-refractory metastatic tissues; Grasso et al. [204] used 50 lethal samples (heavily pre-treated metastatic castration-resistant prostate cancer obtained at rapid autopsy) and 11 high-grade localized prostate cancers with treatment-naïve patients, and the Taylor et al. study [205] used 218 tumor samples from patients treated by radical prostatectomy. There is another study showing the significantly lower expression of STEAP3 in poorly differentiated adenocarcinoma compared to well and moderately differentiated stages showing that no differences were observed in the STEAP3 expression levels compared BPH [6]. Similar to our work, a study performed by Burnell et al. [201] showed the higher STEAP1, STEAP2 and STEAP4 expression in prostate cancer specimens relative to the normal prostate tissue. In opposition to our data, Burnell et al. also showed the high STEAP3 expression in 209 prostatectomy patients [201]. No information was found to justify this discrepancy in results.

As described by our research group [30], Prostate Adenocarcinoma (MSKCC, Cancer Cell 2010) [205] dataset from the cBioPortal indicated that 17.3% (26 of 150) of patients have high STEAP1 mRNA expression levels, 16% (24 of 150) overexpress STEAP2, 18% (27 of 150) have low levels of STEAP3 mRNA, and 37.3% (56 of 150) showed STEAP4 overexpression. Furthermore, the same dataset also indicated high expression of STEAP3 in 4% (6 of 150) and low expression of STEAP4 in 4.7% (7 of 150) of patients. All associations with no significant differences in prostate cancer patient's survival were represented in Supplementary Figure S17. Survival analysis indicated that the higher expression of STEAP1 is directly correlated with lower survival of prostate cancer patients (Figure 7a, $p = 0.0087$). Inversely, higher expression of STEAP4 is directly correlated with higher overall survival when compared to the group with unaltered STEAP4 expression (Figure 7b, $p = 0.0394$). These findings suggest that STEAP1 and STEAP4 could be indicators of bad and good prognosis to prostate cancer patients, respectively. However, a study previously referred showed opposite results, indicating that patients with high STEAP4 expression relapsed more quickly than those with medium or low STEAP4 gene expression [201]. Both studies have relatively a small number of samples (Prostate Adenocarcinoma (MSKCC, Cancer Cell 2010) dataset = 43; Burnell study = 36), and this may be the reason for the difference obtained.

Table 17. Analysis of STEAP family members expression in human prostate cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Prostate Carcinoma vs. Normal							
STEAP1	Overexpressed	2.092	1	Singh Prostate	102 (52 / 50)	1.88×10^{-6}	[206]
	Overexpressed	2.995	8	Welsh Prostate	34 (25/9)	2.42×10^{-4}	[207]
	Overexpressed	1.829	9	Yu Prostate	112 (65/23)	8.08×10^{-4}	[208]
	No difference	1.346	12	Holzbeierlein Prostate	54 (40/4)	0.264	[209]
	Ove-expressed	1.551	9	Liu Prostate	57 (44/13)	0.006	[210]
	Overexpressed	2.292	11	Tomlins Prostate	52 (30/22)	0.002	[211]
	Overexpressed	1.391	7	Taylor Prostate 3	185 (131/29)	4.79×10^{-4}	[205]
	Overexpressed	2.073	10	Grasso Prostate	122 (59/28)	4.50×10^{-4}	[204]
	No difference	1.419	15	Luo Prostate 2	30 (15/15)	0.061	[212]
	No difference	1.842	32	LaTulippe Prostate	35 (23/3)	0.206	[213]
	No difference	1.057	36	Lapointe Prostate	112 (60/40)	0.069	[214]
	No difference	1.212	49	Arredouani Prostate	21 (13/8)	0.172	[215]
	No difference	1.089	51	Varambally Prostate	19 (7/6)	0.376	[203]
STEAP2	No difference	1.471	32	Tomlins Prostate	53 (30/23)	0.09	[211]
	Overexpressed	1.099	7	Taylor Prostate 3	160 (131/29)	5.91×10^{-4}	[205]
	Overexpressed	1.256	24	Lapointe Prostate	103 (62/41)	0.009	[214]
	No difference	1.347	22	Luo Prostate 2	30 (15/15)	0.098	[212]
	Overexpressed	1.368	24	Grasso Prostate	122 (59/28)	0.027	[204]
	No difference	1.116	57	Arredouani Prostate	21 (13/8)	0.267	[215]
	No difference	−1.036	61	Varambally Prostate	13 (7/6)	0.403	[203]
STEAP3	Overexpressed	1.419	2	Varambally Prostate	13 (7/6)	0.001	[203]
	No difference	−1.141	39	Tomlins Prostate	48 (28/20)	0.198	[211]
	No difference	−1.075	20	Liu Prostate	57 (44/13)	0.087	[210]
	No difference	−1.179	27	Luo Prostate 2	30 (15/15)	0.135	[212]
	Underexpressed	−1.378	15	Grasso Prostate	121 (59/27)	7.28×10^{-4}	[204]
	No difference	−1.316	20	Arredouani Prostate	21 (13/8)	0.059	[215]
	Underexpressed	−1.112	9	Taylor Prostate 3	160 (131/29)	2.24×10^{-4}	[205]
STEAP4	Overexpressed	2.039	7	Grasso Prostate	122 (59/28)	8.96×10^{-5}	[204]
	Overexpressed	1.504	2	Taylor Prostate 3	160 (131/29)	1.49×10^{-7}	[205]
	Overexpressed	1.802	6	Lapointe Prostate	95 (58/37)	1.59×10^{-6}	[214]
	Overexpressed	1.24	7	Liu Prostate	57 (44/13)	0.004	[210]
	No difference	1.426	36	Tomlins Prostate	52 (29/23)	0.127	[211]
	Overexpressed	1.872	11	Luo Prostate 2	30 (15/15)	0.040	[212]
	No difference	1.663	19	Varambally Prostate	13 (7/6)	0.069	[203]
	Overexpressed	1.522	19	Arredouani Prostate	21 (13/8)	0.024	[215]
Prostate Adenocarcinoma vs. Normal							
STEAP1	Overexpressed	2.221	9	Vanaja Prostate	40 (27/8)	9.61×10^{-4}	[216]
	No difference	−1.128	63	Wallace Prostate	89 (69/20)	0.261	[217]
STEAP2	Overexpressed	1.574	27	Vanaja Prostate	40 (27/8)	0.032	[216]
STEAP3	No difference	−1.084	52	Wallace Prostate	89 (69/20)	0.111	[217]
	Underexpressed	−1.247	9	Vanaja Prostate	40 (27/8)	0.015	[216]
STEAP4	Overexpressed	1.717	8	Vanaja Prostate	40 (27/8)	7.36×10^{-4}	[216]
	Overexpressed	1.564	15	Wallace Prostate	89 (69/20)	0.016	[217]
Prostatic Intraepithelial Neoplasia vs. Normal							
STEAP1	Overexpressed	2.661	12	Tomlins Prostate	34 (13/22)	0.005	[211]
STEAP2	Overexpressed	2.275	8	Tomlins Prostate	36 (13/23)	0.002	[211]
STEAP3	No difference	−1.3	28	Tomlins Prostate	33 (13/20)	0.095	[211]
STEAP4	Overexpressed	2.887	12	Tomlins Prostate	36 (13/23)	0.005	[211]
Benign Prostatic Hyperplasia Epithelial vs. Normal							
STEAP1	No difference	2.020	30	Tomlins Prostate	26 (4/22)	0.212	[211]
STEAP2	Overexpressed	4.054	1	Tomlins Prostate	27 (4/23)	6.02×10^{-6}	[211]
STEAP3	No difference	−1.037	40	Tomlins Prostate	42 (2/20)	0.388	[211]
STEAP4	No difference	1.017	54	Tomlins Prostate	27 (4/23)	0.488	[211]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

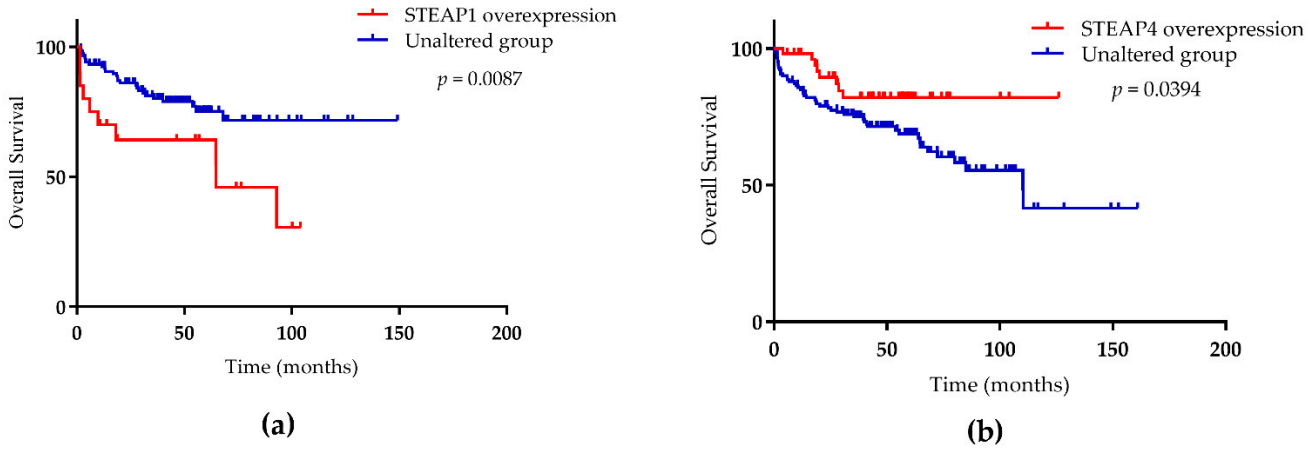

Figure 7. Correlation between STEAP1 (**a**) and STEAP4 (**b**) gene expression and patients' overall in prostate cancer. (**a**) patients were stratified in two groups: STEAP1 overexpressed (red line) and unaltered expression levels (blue line); (**b**) patients were stratified in two groups: STEAP4 overexpressed (red line) and unaltered expression levels (blue line). Survival analysis showed that high levels of STEAP1 transcript are correlated with lower survival (**a**), and high levels of STEAP4 transcript are correlated with higher survival (**b**).

3.18. Sarcoma

A sarcoma is a rare cancer that develops from abnormal mesenchymal cells. These tumors are most common in the bones, muscles, tendons, cartilage, nerves, fat and/or vascular tissues [218]. There are more than 50 types of sarcoma, but they can be grouped into two main types: soft tissue sarcoma (angiosarcoma, gastrointestinal stromal tumor, liposarcoma, leiomyosarcoma, synovial sarcoma, neurofibrosarcoma, rhabdomyosarcoma, fibrosarcomas, myxofibrosarcoma, mesenchymomas, vascular sarcoma, schwannoma, Kaposi's sarcoma) and bone sarcoma (osteosarcoma, Ewing sarcoma, chondrosarcoma, fibrosarcoma) [218,219]. Risk factors for sarcoma include inherited conditions such as retinoblastoma, Li–Faumeni syndrome, familial adenomatous polyposis, neurofibromatosis, Werner syndrome and tuberous sclerosis and also chemical and/or radiation exposure. Usually, sarcoma is diagnosed using imaging techniques such as X-ray, magnetic resonance imaging, computerized tomography and/or PET scan. Additionally, a biopsy is needed to confirm the diagnosis. Treatment options include surgery, radiation therapy and/or chemotherapy [219].

Oncomine analysis revealed a significant overexpression of STEAP1 in fibrosarcoma and synovial sarcoma, and a significant underexpression of STEAP1 and STEAP4 in pleomorphic liposarcoma, dedifferentiated liposarcoma, leiomyosarcoma, myxofibrosarcoma and myxoid/round cell liposarcoma (Table 18). Relative to STEAP3, Oncomine analysis showed a significant underexpression in synovial sarcoma, malignant fibrous histiocytoma and leiomyosarcoma (Table 18). There was no data for STEAP2 in all types of sarcomas listed in Table 18. Grunewald et al. [21] analyzed 114 Ewing's sarcoma and found STEAP1 protein expression in 62.3% of the Ewing's sarcoma samples (predominant localization at the plasma membrane), and also detected high membranous STEAP1 immunoreactivity in 53.5% of samples, which was correlated with better overall survival (p = 0.021). Schirmer et al. [220] also showed that STEAP1130-specific T cells inhibited Ewing's sarcoma growth more effectively than unspecific T cells, suggesting that STEAP1-specific T cell receptors could be potentially useful for immunotherapy of the STEAP1-expressing tumors.

To understand if some of the STEAPs transcripts have prognostic value in sarcoma patients, Sarcoma (TCGA, PanCancer Atlas) [86] dataset from cBioPortal was used. STEAP1, STEAP2, STEAP3 and STEAP4 were overexpressed in 5% (13 of 253), 4% (9 of 253), 6% (15 of 253) and 4% (10 of 253) of the patients, respectively. However, the overexpression of STEAPs' mRNA did not correlate with patients' overall survival (Supplementary Figure S18).

Table 18. Analysis of STEAP family members expression in human sarcoma. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Pleomorphic Liposarcoma vs. Normal							
STEAP1	No difference	2.209	21	Detwiller Sarcoma	18 (3/15)	0.067	[221]
	Underexpression	−2.015	12	Barretina Sarcoma	32 (23/9)	8.20×10^{-4}	[222]
STEAP3	No difference	1.019	56	Barretina Sarcoma	32 (23/9)	0.421	[222]
	No difference	−1.069	52	Detwiller Sarcoma	18 (3/15)	0.427	[221]
STEAP4	No difference	2.227	41	Detwiller Sarcoma	18 (3/15)	0.275	[221]
	Underexpression	−1.561	5	Barretina Sarcoma	32 (23/9)	2.58×10^{-5}	[222]
Fibrosarcoma vs. Normal							
STEAP1	Overexpressed	2.108	22	Detwiller Sarcoma	22 (7/15)	0.036	[221]
STEAP3	No difference	−1.488	31	Detwiller Sarcoma	22 (7/15)	0.096	[221]
STEAP4	No difference	−1.73	39	Detwiller Sarcoma	22 (7/15)	0.168	[221]
Synovial Sarcoma vs. Normal							
STEAP1	Overexpressed	2.377	24	Detwiller Sarcoma	19 (4/15)	0.031	[221]
STEAP3	Underexpression	−2.04	7	Detwiller Sarcoma	19 (4/15)	0.002	[221]
STEAP4	No difference	−1.44	51	Detwiller Sarcoma	19 (4/15)	0.296	[221]
Dedifferentiated Liposarcoma vs. Normal							
STEAP1	No difference	1.281	34	Detwiller Sarcoma	19 (4/15)	0.206	[221]
	Underexpression	−2.595	4	Barretina Sarcoma	55 (46/9)	1.56×10^{-6}	[222]
STEAP3	No difference	1.025	54	Barretina Sarcoma	55 (46/9)	0.377	[222]
	No difference	−1.577	24	Detwiller Sarcoma	19 (4/15)	0.098	[221]
STEAP4	No difference	1.426	45	Detwiller Sarcoma	19 (4/15)	0.351	[221]
	Underexpression	−1.525	8	Barretina Sarcoma	55 (46/9)	4.38×10^{-5}	[222]
Malignant Fibrous Histiocytoma vs. Normal							
STEAP1	No difference	1.179	49	Detwiller Sarcoma	24 (9/15)	0.354	[221]
STEAP3	Underexpression	−1.559	18	Detwiller Sarcoma	24 (9/15)	0.020	[221]
STEAP4	No difference	1.812	34	Detwiller Sarcoma	24 (9/15)	0.097	[221]
Leiomyosarcoma vs. Normal							
STEAP1	No difference	1.116	49	Detwiller Sarcoma	21 (6/15)	0.376	[221]
	Underexpression	−3.613	5	Barretina Sarcoma	35 (26/9)	1.52×10^{-6}	[222]
STEAP3	Underexpression	−1.911	7	Detwiller Sarcoma	21 (6/15)	0.003	[221]
STEAP4	No difference	1.164	51	Detwiller Sarcoma	21 (6/15)	0.419	[221]
	Underexpression	−1.616	7	Barretina Sarcoma	35 (26/9)	1.21×10^{-5}	[222]
Myxofibrosarcoma vs. Normal							
STEAP1	Underexpression	−2.438	11	Barretina Sarcoma	40 (31/9)	1.21×10^{-4}	[222]
STEAP3	No difference	1.118	48	Barretina Sarcoma	40 (31/9)	0.148	[222]
STEAP4	Underexpression	−1.529	9	Barretina Sarcoma	40 (31/9)	3.93×10^{-5}	[222]
Myxoid/Round Cell Liposarcoma vs. Normal							
STEAP1	No difference	−1.003	55	Detwiller Sarcoma	19 (4/15)	0.495	[221]
	Underexpression	−2.811	4	Barretina Sarcoma	29 (20/9)	2.86×10^{-7}	[222]
STEAP3	No difference	1.055	50	Barretina Sarcoma	29 (20/9)	0.216	[222]
	No difference	−1.033	51	Detwiller Sarcoma	19 (4/15)	0.430	[221]
STEAP4	Underexpression	−2.181	19	Detwiller Sarcoma	19 (4/15)	0.05	[221]
	Underexpression	−1.579	10	Barretina Sarcoma	29 (20/9)	4.37×10^{-5}	[222]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

3.19. Testicular Cancer

Testicular cancer is a relatively rare type of cancer, accounting for just 1% of all cancers in men. It mostly affects men between 15 and 45 years of age [223]. The most common type of testicular cancer is germ cell testicular cancer, which accounts for around 95% of all cases [223]. Germ cell testicular cancer can be divided in two subtypes, seminoma and non-seminoma [224]. Seminomas, in general, are not as aggressive as non-seminomas. Non-seminoma tumors tend to develop earlier in life and grow and spread rapidly. Several different types of non-seminoma tumors exist, including teratomas, embryonal carcinoma, mixed germ cell tumor and yolk sac tumor [224]. There are many risk factors for testicular cancer, including cryptorchidism (an undescended testicle), family history, age, race and HIV infection. Chemotherapy, radiotherapy and surgery are the three main treatments for testicular cancer [223].

Oncomine analysis revealed a significant underexpression of STEAP1 in both seminoma, not otherwise specified (NOS) and non-seminoma (testicular embryonal carcinoma, NOS and testicular intratubular germ cell neoplasia) (Table 19). However, Testicular Germ Cell Tumors (TCGA, PanCancer Atlas) [86] dataset, retrieved from the cBioPortal, indicated high expression of STEAP1 in 25% (37 of 149) of patients, although it did not correlate with patients' survival (Supplementary Figure S19).

Relative to STEAP2, Oncomine analysis showed its overexpression in all types of non-seminoma and NOS, and an underexpression in the seminoma dataset (Table 19). From the cBioPortal, Testicular Germ Cell Tumors (TCGA, PanCancer Atlas) [86] indicated that STEAP2 is overexpressed in 9% (13 of 149) of queried patients, but no correlation was observed with patients' survival (Supplementary Figure S19).

Concerning STEAP3, Oncomine analysis showed its significant underexpression in seminoma and non-seminoma, and a significant overexpression in seminoma, NOS and non-seminoma, NOS (Table 19). Skotheim et al. [225] showed underexpression of STEAP3, whereas the Korkola et al. [226] showed an overexpression. Both studies used microarray technology, but Skotheim et al. study was conducted in Norway, and the Korkola et al. study was conducted in New York. However, this difference cannot explain the discrepancy in the results obtained for two studies. To our knowledge, there is no data on the STEAP3 mRNA levels in testicular cancer. In Testicular Germ Cell Tumors (TCGA, PanCancer Atlas) [86] dataset from the cBioPortal, it was also found the overexpression of STEAP3 in 5% (7 of 149) of patients, showing that higher expression of STEAP3 is directly correlated with lower survival of testicular cancer patients (Figure 8, $p = 0.0281$).

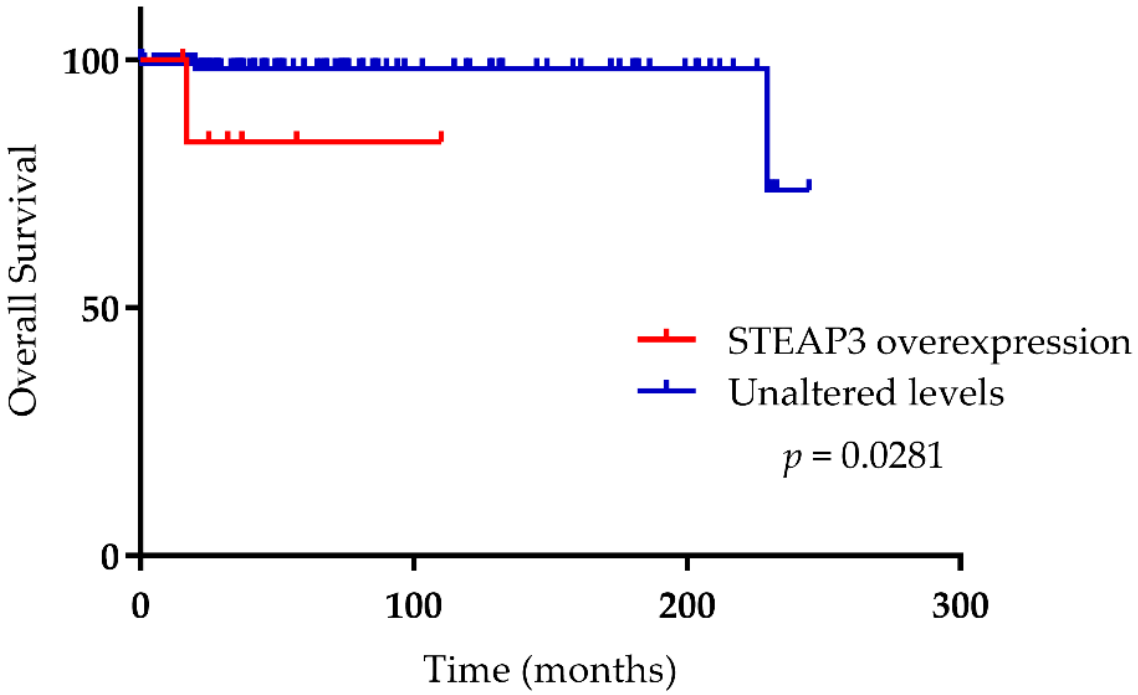

Figure 8. Correlation between STEAP3 gene expression and patients' overall survival in testicular cancer. Patients were stratified in two groups: STEAP3 overexpression (red line) and unaltered expression levels (blue line). Survival analysis showed that high levels of STEAP3 transcript are correlated with lower survival.

Regarding STEAP4, Oncomine analysis showed a significant overexpression in teratoma, NOS and mixed germ cell tumor, NOS, and a significant underexpression in testicular yolk sac tumor, NOS (Table 19). From the cBioPortal, in Testicular Germ Cell Tumors (TCGA, PanCancer Atlas) [86], STEAP4 overexpression was found in 9% (13 of 149) of patients.

Table 19. Analysis of STEAP family members expression in human testicular cancer. mRNA expression was compared between tumors and normal tissues using the Oncomine database. Expression level of STEAPs, fold-change variation, rank and datasets used are indicated. Statistically significant over or underexpression are highlighted by red or green filling, respectively.

Gene	Expression Level	Fold-Change	Rank (Top %)	Dataset	#Samples	*p*-Value	Reference
Testicular Seminoma vs. Normal							
STEAP1	No difference	1.260	23	Skotheim Testis	6 (3/3)	0.078	[225]
	No difference	1.067	43	Sperger Others	41 (22/19)	0.199	[227]
STEAP2	No difference	−1.125	53	Skotheim Testis	6 (3/3)	0.684	[225]
	Underexpressed	−1.329	35	Sperger Others	31 (14/17)	0.042	[227]
STEAP3	Underexpressed	−1.612	26	Skotheim Testis	6 (3/3)	0.034	[225]
STEAP4	No difference	−1.200	63	Skotheim Testis	6 (3/3)	0.867	[225]
Seminoma, Not Otherwise Specified vs. Normal							
STEAP1	Underexpressed	−1.222	37	Korkola Seminoma	18 (12/6)	0.033	[226]
STEAP2	Overexpressed	1.111	36	Korkola Seminoma	18 (12/6)	0.006	[226]
STEAP3	Overexpressed	1.532	34	Korkola Seminoma	18 (12/6)	0.0073	[226]
STEAP4	No difference	1.008	64	Korkola Seminoma	18 (12/6)	0.374	[226]
Testicular Teratoma vs. Normal							
STEAP1	No difference	1.254	24	Skotheim Testis	7 (4/3)	0.133	[225]
STEAP2	No difference	1.200	26	Skotheim Testis	7 (4/3)	0.157	[225]
STEAP3	Underexpressed	−2.067	10	Skotheim Testis	7 (4/3)	0.012	[225]
STEAP4	No difference	1.060	44	Skotheim Testis	7 (4/3)	0.45	[225]
Teratoma, Not Otherwise Specified vs. Normal							
STEAP1	No difference	1.194	64	Korkola Seminoma	20 (14/6)	0.851	[226]
STEAP2	Overexpressed	2.443	4	Korkola Seminoma	20 (14/6)	2.79×10^{-8}	[226]
STEAP3	Overexpressed	1.751	9	Korkola Seminoma	20 (14/6)	2.48×10^{-6}	[226]
STEAP4	Overexpressed	2.770	28	Korkola Seminoma	20 (14/6)	0.002	[226]
Testicular Yolk Sac Tumor vs. Normal							
STEAP1	No difference	1.302	22	Skotheim Testis	7 (4/3)	0.101	[225]
STEAP2	No difference	−1.051	56	Skotheim Testis	7 (4/3)	0.682	[225]
STEAP3	Underexpressed	−1.935	16	Skotheim Testis	7 (4/3)	0.013	[225]
STEAP4	No difference	−1.043	52	Skotheim Testis	7 (4/3)	0.630	[225]
Yolk Sac Tumor, Not Otherwise Specified vs. Normal							
STEAP1	No difference	1.225	61	Korkola Seminoma	15 (9/6)	0.755	[226]
STEAP2	Overexpressed	1.283	33	Korkola Seminoma	15 (9/6)	0.019	[226]
STEAP3	Overexpressed	1.461	15	Korkola Seminoma	15 (9/6)	8.90×10^{-4}	[226]
STEAP4	Underexpressed	−1.784	32	Korkola Seminoma	15 (9/6)	0.023	[226]
Testicular Embryonal Carcinoma vs. Normal							
STEAP1	No difference	1.288	22	Skotheim Testis	8 (5/3)	0.106	[225]
STEAP2	No difference	1.037	41	Skotheim Testis	8 (5/3)	0.380	[225]
STEAP3	Underexpressed	−1.516	25	Skotheim Testis	8 (5/3)	0.048	[225]
STEAP4	No difference	−1.185	62	Skotheim Testis	8 (5/3)	0.792	[225]
Embryonal Carcinoma, Not Otherwise Specified vs. Normal							
STEAP1	Underexpressed	−1.282	35	Korkola Seminoma	21 (15/6)	0.016	[226]
STEAP2	Overexpressed	1.220	35	Korkola Seminoma	21 (15/6)	0.005	[226]
STEAP3	Overexpressed	1.539	16	Korkola Seminoma	21 (15/6)	5.66×10^{-5}	[226]
STEAP4	No difference	1.062	52	Korkola Seminoma	21 (15/6)	0.076	[226]
Testicular Intratubular Germ Cell Neoplasia vs. Normal							
STEAP1	Underexpressed	−1.214	9	Skotheim Testis	6 (3/3)	0.045	[225]
STEAP2	No difference	−1.053	53	Skotheim Testis	6 (3/3)	0.636	[225]
STEAP3	Underexpressed	−1.669	7	Skotheim Testis	6 (3/3)	0.032	[225]
STEAP4	No difference	1.169	21	Skotheim Testis	6 (3/3)	0.190	[225]
Mixed Germ Cell Tumor, Not Otherwise Specified vs. Normal							
STEAP1	No difference	−1.020	48	Korkola Seminoma	47 (41/6)	0.408	[226]
STEAP2	Overexpressed	1.356	15	Korkola Seminoma	47 (41/6)	1.87×10^{-6}	[226]
STEAP3	Overexpressed	1.484	20	Korkola Seminoma	47 (41/6)	2.29×10^{-5}	[226]
STEAP4	Overexpressed	1.141	41	Korkola Seminoma	47 (41/6)	0.003	[226]

#Samples—Total number of samples. Numbers in () mean the number of cancer cases vs. normal tissue.

4. Conclusions

The development of "omics" and bioinformatics tools allowed us to analyze how the STEAP genes are differentially expressed in human cancers and their transcripts expression levels correlate with patients' overall survival rate. This approach is of paramount relevance considering the use of these proteins as therapeutic targets and/or biomarkers of prognosis.

Our results showed that there is a deregulation of STEAPs' expression in several human cancers and that their expression levels might be helpful for predicting the clinical outcome of cancer patients. Table 20 summarizes the analysis obtained from the Oncomine database considering different types of human cancers. Overall, the results obtained are robust as independent studies show the same trend concerning the expression of distinct STEAP transcripts. Based on the highest overexpression levels, it is clear that targeting STEAP1 may be advantageous in cervical, colorectal, esophageal, gastric, lung, ovarian and prostate cancer; STEAP2 in esophageal, gastric, liver, lung and pancreatic cancer; STEAP3 in bladder, glioblastoma, cervical, colorectal, esophageal, head and neck, kidney, lung, lymphoma, ovarian and pancreatic cancer; and STEAP4 in lymphoma and prostate cancers. In colorectal, head and neck, kidney, leukemia, lymphoma, melanoma, pancreatic, sarcoma and testicular cancer, different studies indicated the over or underexpression of STEAP transcripts (Table 20). Thus, further investigation is required to determine the STEAPs' biology in these cancer types; for example, to evaluate whether the STEAP proteins levels are also altered and how they contribute to cancer development.

Table 20. Expression of STEAP1, STEAP2, STEAP3 and STEAP4 genes in human cancers. Summary of the Oncomine analysis results indicating the overexpression (red arrow, ▲) or underexpression (green arrow, ▼) of STEAPs' mRNA. Multiple arrows indicate the number of independent studies with significant data.

	Cancer Type	STEAP1	STEAP2	STEAP3	STEAP4
Bladder	Infiltrating Bladder Urothelial Carcinoma	▼	▼	▲▲▲	▼
	Superficial Bladder Cancer	▼	▼	▲▲▲	▼▼
Brain/CNS	Glioblastoma	▲▲▲▼	▲▼▼	▲▲▲▲▲▲	▼
	Astrocytoma	▼	n.s.	▲▲	▲
	Oligodendroglioma	▼▼	▼▼	▲	▼
Breast	Invasive Ductal Breast Carcinoma	▲▼▼▼▼▼	▼▼▼▼	▲▲▼▼	▼▼▼
	Lobular Breast Carcinoma	▼▼	▲▼	▲▲	▲▼▼
	Fibroadenoma	▼▼	n.s.	n.s.	n.s.
Cervical	Cervical Squamous Cell Carcinoma	▲▲	n.s.	▲▲▲	n.s.
Colorectal	Carcinoma	▲	▲▼	▲▲	▼
	Rectal Adenocarcinoma	▲▲	▲	▲▲	▲
	Colon Adenocarcinoma	▲	▲▲	▲▲	▼
Esophageal	Barrett's Esophagus	▲▲	▲▲	n.s.	▼
	Esophageal Squamous Cell Carcinoma	▲▲	▲	▲▲	▼▼
	Esophageal Adenocarcinoma	▲▲	▲▲	▲	▼
Gastric	Gastric Cancer	▲▲	▲	n.s.	n.s.
	Gastric Intestinal Type Adenocarcinoma	▲▲▲	▲▲▲	n.s.	n.s.
	Diffuse Gastric Adenocarcinoma	▲▲▲	▲▲	n.s.	▲
Head and Neck	Oral Cavity Carcinoma	▲▲▲	n.s.	▲▲	▼▼
	Tongue Carcinoma	▲▲▲▲	n.s.	▲▲	n.s.
	Thyroid Gland Papillary Carcinoma	▼	▼▼	▲▲	▲
Kidney	Clear Cell Renal Cell Carcinoma	▼▲	▼	▲▲	▼▲▲
	Papillary Renal Cell Carcinoma	▲	n.s.	▲	▼
	Chromophobe Renal Cell Carcinoma	▼	n.s.	n.s.	▲
	Renal Wilms Tumor	n.s.	▼	▲	n.s.
	Renal Oncocytoma	▼	n.s.	n.s.	▲
Leukemia	T-Cell Acute Lymphoblastic Leukemia	▲	▲▼	▼	▲▼▼
	B-Cell Acute Lymphoblastic Leukemia	▲	▲▼	▼	▲▼▼
	Acute Myeloid Leukemia	▲▼▼	▲▼	▼	▼▼
	Chronic Lymphocytic Leukemia	▼▼	▲	▼	▼
Liver	Hepatocellular Carcinoma	▲▲▼	▲	▼▼▼▼	▼▼▼▼▼

Table 20. *Cont.*

	Cancer Type	STEAP1	STEAP2	STEAP3	STEAP4
Lung	Squamous Cell Lung Carcinoma	▲▲▲▲▲	▲	▲▲	▼▼▼
	Lung Adenocarcinoma	▲▲▲▲▲▲	▲	▲▲▲▲▲▲	▼▼▼▼
Lymphoma	Follicular Lymphoma	▲	▲	▲▲	▲▲
	Diffuse Large B-Cell Lymphoma	▲▲▲	▲▲▲	▲▲	▲▲
	Burkitt's Lymphoma	▲	n.s.	▲	n.s.
	Hodgkin's Lymphoma	▲	▲	▲▲	▲▲
Melanoma	Melanoma	▲▲	▼	▼	▲▼▼
Ovarian	Ovarian Serous Adenocarcinoma	▲	▲	▲▲▲	▼
	Ovarian Endometrioid Adenocarcinoma	▲	n.s.	▲▲	n.s.
	Ovarian Clear Cell Adenocarcinoma	▲	▼	▲	n.s.
	Ovarian Mucinous Adenocarcinoma	▲▲	▲	▲▲	▲
	Ovarian Carcinoma	n.s.	-	n.s.	▲
Pancreatic	Pancreatic Ductal Adenocarcinoma	▲▲▲	▲▲	▲▲	▲▼
	Pancreatic Carcinoma	▲▲▼	▲	▲	▼
Prostate	Prostate Carcinoma	▲▲▲▲▲▲▲	▲▲▲	▲	▲▲▲▲▲▲
	Prostate Adenocarcinoma	▲	▲	▼	▲▲
	Prostatic Intraepithelial Neoplasia	▲	▲	n.s.	▲
	Benign Prostatic Hyperplasia Epithelial	n.s.	▲	n.s.	n.s.
Sarcoma	Pleomorphic Liposarcoma	▼	-	n.s.	▼
	Fibrosarcoma	n.s.	-	n.s.	n.s.
	Synovial Sarcoma	n.s.	-	▼	n.s.
	Dedifferentiated Liposarcoma	▼	-	n.s.	▼
	Malignant Fibrous Histiocytoma	n.s.	-	▼	n.s.
	Leiomyosarcoma	▼	-	▼	▼
	Myxofibrosarcoma	▼	-	n.s.	▼
	Myxoid/Round Cell Liposarcoma	▼	-	n.s.	▼▼
Testicular	Testicular Seminoma	n.s.	▼	▼	n.s.
	Seminoma, Not Otherwise Specified	▼	▲	▲	n.s.
	Testicular Teratoma	n.s.	n.s.	▼	n.s.
	Teratoma, Not Otherwise Specified	n.s.	▲	▲	▲
	Testicular Yolk Sac Tumor	n.s.	n.s.	▼	n.s.
	Yolk Sac Tumor, Not Otherwise Specified	n.s.	▲	▲	▼
	Testicular Embryonal Carcinoma	n.s.	n.s.	▼	n.s.
	Embryonal Carcinoma, Not Otherwise Specified	▼	▲	▲	n.s.
	Testicular Intratubular Germ Cell Neoplasia	▼	n.s.	▼	n.s.
	Mixed Germ Cell Tumor, Not Otherwise Specified	n.s.	▲	▲	▲

(n.s.), not significant; (-), no data available.

Interestingly, the expression of STEAP genes is already changed in benign lesions (e.g., breast fibroadenoma, Barrett's esophagus, prostatic intraepithelial neoplasia, and begin prostatic hyperplasia epithelial) (Table 20). For example, STEAP1 was found to be underexpressed in fibroadenomas, anticipating the prevalent pattern of downregulation described in breast carcinoma. Similarly, STEAP1, STEAP2 and STEAP4 presented an overexpression in prostatic intraepithelial neoplasia, which is the typical pattern in prostate carcinogenesis. Curiously, in the benign prostatic hyperplasia epithelial, only STEAP2 appeared to be significantly overexpressed, which is maintained throughout the carcinogenic process. In esophageal disease, STEAP1 and STEAP2 presented overexpression, whereas STEAP4 was underexpressed, a pattern that is kept in esophageal cancer. NHL, follicular lymphoma (low-grade lymphoma, slow growing), displayed overexpression of all four STEAP transcripts, which becomes more pronounced in diffuse large B-cell and Burkitt's lymphoma (high grade NHL, more aggressive). Overall, these results suggest that the

deregulation of STEAPs expression levels may be involved in malignant transformation, increasing the risk of cancer onset and development.

Figure 9 depicts the results obtained for the value of STEAP genes as prognostic markers based on the relationship between expression levels and patients' survival rate. In general, data extracted from the cBioPortal platform indicated that STEAP genes' overexpression is significantly correlated to lower patients' survival in bladder, brain/CNS, cervical, gastric, kidney, leukemia, prostate and testicular cancer (Figure 9). On the other hand, the overexpression of STEAP4 was associated with a better prognosis in prostate cancer patients. This was the only condition where the overexpression of a STEAP gene was correlated with a good disease prognosis, as indicated by the higher survival rates. Overall, STEAP4 gene expression displayed the most significant differences presented from the datasets extracted by the cBioPortal platform, supporting the notion that abnormal levels of STEAP4 can be used as a prognostic marker for some cancers.

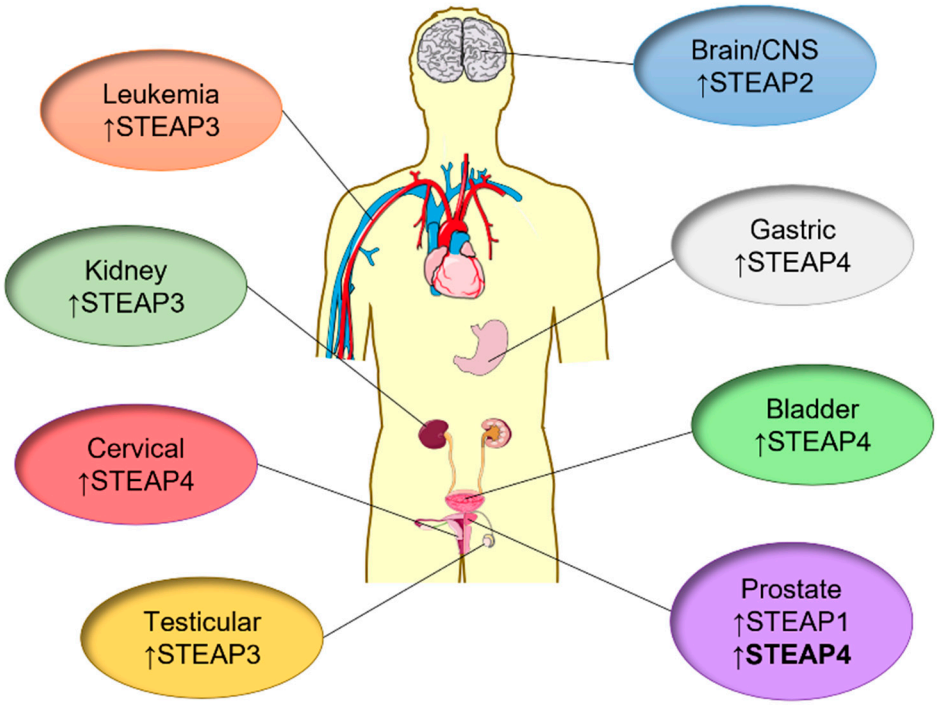

Figure 9. Prognostic value of STEAP genes expression in human cancers. High expression (↑) of STEAP1, STEAP2, STEAP3 and STEAP4 transcripts correlates with lower patients' survival for all cancer types indicated in figure, whereas high expression of STEAP4 (bold) is correlated with better survival.

This study further expanded the existing knowledge concerning the expression of STEAP family members in several types of human cancers, revealing their potential as therapeutic targets and prognosis biomarkers.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/data7050064/s1, Figure S1: Correlation between STEAP1, STEAP2 and STEAP3 genes expression and patients' overall survival in bladder cancer. Figure S2: Correlation between STEAP1, STEAP3 and STEAP4 genes expression and patients' overall survival in brain/CNS cancer. Figure S3: Correlation between all STEAPs genes expression and patients' overall survival in breast cancer. Figure S4: Correlation between STEAP1, STEAP2 and STEAP3 genes expression and patients' overall survival in cervical cancer. Figures S5 and S6: Correlation between all STEAPs genes expression and patients' overall survival in colorectal and esophageal cancers, respectively. Figure S7: Correlation between STEAP1, STEAP2 and STEAP3 genes expression and patients' overall survival in gastric cancer. Figure S8: Correlation between all STEAPs genes expression and patients' overall

survival in head and neck cancer. Figure S9: Correlation between STEAP1, STEAP2 and STEAP4 genes expression and patients' overall survival in Kidney cancer. Figure S10: Correlation between STEAP1 and STEAP4 genes expression and patients' overall survival in leukemia cancer. Figures S11 and S12: Correlation between all STEAPs genes expression and patients' overall survival in liver and lung cancers, respectively. Figure S13: Correlation between STEAP2 gene expression and patients' overall survival in lymphoma cancer. Figures S14–S16: Correlation between all STEAPs genes expression and patients' overall survival in melanoma, ovarian and pancreatic cancers, respectively. Figure S17: Correlation between STEAP2, STEAP3 and STEAP4 genes expression and patients' overall survival in prostate cancer. Figure S18: Correlation between all STEAPs genes expression and patients' overall survival in sarcoma cancer. Figure S19: Correlation between STEAP1, STEAP2 and STEAP4 genes expression and patients' overall survival in testicular cancer.

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