Expression of serine/glycine metabolism-related proteins is different according to the thyroid cancer subtype

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Abstract

Background: The aim of this study was to investigate the expression and clinical implications of proteins related to serine/glycine metabolism in different subtypes of thyroid cancer.

Methods: Tissue microarray (TMA) was constructed with tissues from 557 thyroid cancers, consisting of 244 papillary thyroid carcinomas (PTC), 112 follicular carcinomas (FC), 70 medullary carcinomas (MC), 23 poorly differentiated carcinomas (PDC), and 8 anaplastic carcinomas (AC). Immunohistochemical staining of the serine/glycine metabolism-related molecules phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT), phosphoserine phosphatase (PSPH), serine hydromethyl transferase (SHMT), and glycine decarboxylase (GLDC) was performed with the TMA blocks and the results were analyzed together with clinicopathologic parameters.

Results: The expression of serine/glycine metabolism-related proteins differed among thyroid cancer subtypes. The expression rate of PHGDH (p < 0.001), PSAT1 (p = 0.001), PSPH (p = 0.008), and tumoral SHMT1 (p < 0.001) was higher in PDC and PTC (78.3, 21.7, 21.7, 30.4 and 63.4, 18.6, 12.8, 31.4 %, respectively), and lowest in MC (15.7, 1.4, 0.0, 10.0 %). Stromal SHMT1 expression was highest in AC (62.5 %) and absent in all FC (p < 0.001). In PTC, positivity for PSPH (p = 0.041), tumoral SHMT1 (p = 0.018), and stromal SHMT1 (p < 0.001) expression was higher in the conventional type compared to follicular type (14.1 versus 2.5 %, 33.6 versus 15.0 %, 42.1 versus 10.0 %, respectively). BRAF V600E mutation was associated with a higher rate of PHGDH (p < 0.001), PSAT1 (p = 0.001), PSPH (p < 0.001), tumoral SHMT1 (p = 0.001), stromal SHMT1 (p < 0.001), and GLDC (p < 0.001) expression compared to non-mutant cases (73.5 versus 40.6 %, 23.1 versus 8.5 %, 17.6 versus 1.9 %, 37.0 versus 18.9 %, 45.8 versus 21.7 %, 21.8 versus 6.6 %, respectively). In univariate analysis, stromal SHMT1 expression was associated with shorter disease-free survival (p = 0.015) in follicular variant PTC, and GLDC positivity was associated with shorter overall survival (OS) in sclerotic stromal type (p = 0.002). In FC, minimally invasive type, PSPH positivity correlated with shorter OS (p = 0.045) and in MC, PHGDH positivity correlated with shorter OS (p = 0.034).

Conclusion: The expression of serine/glycine metabolism-related proteins differs among different thyroid cancer types, with a higher rate of expression in PDC and PTC, and lower rate of expression in MC. In PTC, the rate of expression is lower in the follicular variant and higher in cases with BRAF V600E mutation.

Keywords: Glycine, Serine, Metabolism, Thyroid cancer
Background
In malignant neoplasms a metabolic shift from oxidative phosphorylation in mitochondria to glycolysis occurs, a phenomenon known as the Warburg effect [1]. Neoplastic cells exhibiting increased glycolysis show increased levels of glycolytic intermediates. Recent studies reported that the metabolism of glycolytic intermediates is involved in tumorigenesis, for example through the glycerine and serine metabolic pathways [2–5]. In the serine biosynthesis pathway, the 3-phosphoglycerate (3PG) that is generated in the glycolysis process is oxidized to 3-phosphohydroxypyruvate (pPYR) by phosphoglycerate dehydrogenase (PHGDH) [6]. pPYR is transaminated into phosphoserine (pSER) by phosphoserine aminotransferase (PSAT) [7], and pSER is dephosphorylated by phosphoserine phosphatase (PSPH) to produce serine [8]. In glycine metabolism, methylene-tetrahydrofolate is generated by glycine decarboxylase (GLDC), using glycine and tetrahydrofolate as substrates [9]. Serine metabolism and glycine metabolism are linked by serine hydromethyl transferase (SHMT), which catalyzes the reversible conversion of serine and glycine [10]. In previous studies, expression of PHGDH was reported to be increased in breast cancer and melanoma [3, 4], and expression of GLDC was reported to be increased in lung cancer [5], revealing a role of proteins related to serine/glycine metabolism in tumorigenesis.

Thyroid cancer is a common malignant neoplasm that occurs in 1 % of the population [11]. The most common subtype is papillary thyroid carcinoma (PTC), although there are several other subtypes, including follicular carcinoma (FC), medullary carcinoma (MC), poorly differentiated carcinoma (PDC), and anaplastic carcinoma (AC). These subtypes differ in cell origin, clinical manifestation, metastatic pattern, and clinical prognosis [12].

A representative mutation gene in thyroid cancer is the BRAF mutation gene. BRAF is a 75–100 kDa protein in the Raf kinase family that is the most potent activator of MEK kinase in the Ras-Raf-MEK-ERK pathway [2, 5]. The Ras-Raf-MEK-ERK pathway is abnormally activated in tumors and this aberrant ERK signaling is due to the BRAF mutation [4]. The BRAF mutation first reported in 2002 is a mutation in nucleotide 1796 in about 90 % that converts valine to glutamic acid in codon 599 (V599E; After NOMENCLATURE CHANGE, it was renamed to V600E) [13]. The BRAF V600E mutation appears in a variety of tumors found in cancers including thyroid papillary carcinoma (36–53 %), malignant melanoma (40–70 %), colorectal carcinoma (5–22 %), glioma (11 %), and ovary serous carcinoma (30 %) [3]. The BRAF mutation in PTC is associated with extra-thyroidal extension, advanced TNM stage, lymph node metastasis, multifocality, and recurrence [14].

It is thought that tumor metabolism, including serine and glycine metabolism, may differ among these subtypes, however there are few reports on this subject. The aim of this study was to investigate the expression and clinical implications of proteins related to serine/glycine metabolism according to thyroid cancer subtype.

Methods
Patient selection
Patients who were diagnosed with PTC and had surgical resection from January 2012 to December 2013 were enrolled in this study. Patients who were diagnosed with other subtypes of thyroid cancer from January 2000 to December 2014 were also enrolled. Patients who received preoperative chemotherapy were excluded. A thyroid pathologist (Koo JS) reviewed hematoxylin/eosin (H&E)-stained slides for all cases. Clinicopathologic data were obtained from the patients’ medical records and included age at diagnosis, disease recurrence, metastasis, current status, and length of follow-up. Tumor size, location (right or left lobe), extent (confined to the thyroid parenchyma or with extrathyroidal spread), and number of metastatic lymph nodes were also noted from review of the slides and the surgical pathology reports.

Tissue microarray (TMA)
Representative areas were selected on H&E-stained slides and corresponding spots were marked on the surface of the matching paraffin blocks. Five-mm core biopsies were taken from selected areas and placed into a 5 × 4 recipient block. More than two tissue cores were extracted from each case to minimize extraction bias. Each tissue core was assigned a unique tissue microarray location number that was linked to a database containing other clinicopathologic data.

Immunohistochemistry
Antibodies used for immunohistochemistry are listed in Additional file 1: Table S1. All immunohistochemistry was performed with formalin-fixed paraffin-embedded tissue sections using an automatic immunohistochemistry staining device (Benchmark XT, Ventana Medical System, Tucson, AZ, USA). Briefly, 5-μm thick formaldehyde-fixed paraffin-embedded tissue sections were transferred onto adhesive slides and dried at 62 °C for 30 min. Standard heat epitope retrieval was performed for 30 min in ethylene diaminetetraacetic acid, pH 8.0, in the autostainer. The samples were then incubated sequentially with primary antibodies, biotinylated antimouse immunoglobulin, peroxidase-labeled streptavidin (LSAB kit, DakoCytomation), and 3,30-diaminobenzidine. Negative control samples were processed without the primary antibody. Slides were counterstained with
Harris hematoxylin. Positive control tissue was used as recommended by the manufacturer.

**Analysis of immunohistochemical staining**

This study used the semi-quantitative ordinal scoring system based on visual inspection by pathologists. Immunohistochemical markers were assessed by light microscopy. The expression of serine/glycine metabolism-related proteins was evaluated semi-quantitatively as previously reported [15]. Tumor and stromal cell staining was scored as follows: 0, negative or weak immunostaining in <1 % of the tumor/stroma; 1, focal expression in 1–10 % of tumor/stroma; 2, positive in 11–50 % of tumor/stroma; 3, positive in 51–100 % of tumor/stroma. The evaluation was performed throughout the whole area of the tumor, and a score of 2 or higher was defined as positive. For the evaluation of BRAF V600E, tissue samples that had scores of 20 % or higher were regarded as positive [16]. Two pathologists (KJS and KHM) independently evaluated the expression according the scoring system and any mismatched result was further evaluated by a third pathologist (JW).

**Statistical analysis**

Data were analyzed using SPSS for Windows, Version 12.0 (SPSS Inc., Chicago, IL, USA). For determination of statistical significance, Student’s t and Fisher’s exact tests were used for continuous and categorical variables, respectively. In the case of multiple comparisons, a corrected p value with the application of the Bonferroni multiple comparison procedure was used. Statistical significance was set to p < 0.05. Kaplan–Meier survival curves and log-rank statistics were employed to evaluate time to tumor recurrence and overall survival. Multivariate regression analysis was performed using the Cox proportional hazards model.

**Results**

**Basal characteristics of thyroid cancer**

Among 557 thyroid cancers, 344 (61.8 %) were PTC, 112 (20.1 %) were FC, 70 (12.6 %) were MC, 23 (4.1 %) were PDC, and 8 (1.4 %) were AC. Basal characteristics of MC, PDC, and AC are summarized in Additional file 1: Table S3. Basal characteristics of PTC are summarized in Additional file 1: Table S2.

**Expression of serine/glycine metabolism-related proteins in thyroid cancer subtypes**

The expression of serine/glycine metabolism-related proteins was investigated in all thyroid cancers. For the serine/glycine metabolism-related proteins, PHGDH had the highest expression rate (54.8 %) compared to lower expression rates of stromal SHMT1 (25.9 %), tumoral SHMT1 (25.5 %), GLDC (15.6 %), PSAT1 (14.4 %), and PSPH (10.8 %). Therefore, serine/glycine metabolism-related protein expression rate was low in most cases except for PHGDH (Table 1). The expression of PHGDH (p < 0.001), PSAT1 (p = 0.001), PSPH (p = 0.008), tumoral SHMT1 (p < 0.001), and stromal SHMT1 (p < 0.001) was different according to cancer subtype (Fig. 1a). The expression of PHGDH, PSAT1, PSPH, and tumoral SHMT1 was higher in PDC and PTC (78.3, 21.7, 21.7, 30.4 and 63.4, 18.6, 12.8, 31.4 %, respectively), and lowest in MC (15.7, 1.4, 0.0, 10.0 %). The expression of stromal SHMT1 was highest in AC (62.5 %) and lowest in FC (0.0 %) (Table 1; Fig. 2).

Among PTCs, the expression of PSPH (p = 0.041), tumoral SHMT1 (p = 0.018), and stromal SHMT1 (p < 0.001) differed according to histologic subtypes, with a higher rate of expression in the conventional type compared to follicular type (14.1 versus 2.5 %, 33.6 versus 15.0 %, 42.1 versus 10.0 %, respectively) (Table 2; Fig. 1b). BRAF V600E mutation status was associated with the expression of PHGDH (p < 0.001), PSAT1 (p = 0.001), PSPH (p < 0.001), tumoral SHMT1 (p = 0.001), and GLDC (p < 0.001), with higher expression of serine/glycine metabolism-related proteins in BRAF V600E mutation-positive cases compared to non-mutant cases (73.5 versus 40.6 %, 23.1 versus 8.5 %, 17.6 versus 1.9 %, 37.0 versus 18.9 %, 45.8 versus 21.7 %, 21.8 versus 6.6 %, respectively) (Table 2; Fig. 3).

Among follicular neoplasms, the expression of PSAT1 was higher in follicular adenoma compared to FC (24.2 versus 8.0 %, p = 0.001, Table 3). There was no difference in serine/glycine metabolism-related protein expression between the minimally invasive and widely invasive type of FC (Table 4).
Correlation between the expression of serine/glycine metabolism-related proteins and clinicopathologic factors

Correlations between the expression of serine/glycine metabolism-related proteins and clinicopathologic factors of thyroid cancers were analyzed. In PTC, PHGDH expression was associated with tumor size ($p = 0.003$), with an increased tumor size in PHGDH-positive cases. In addition, stromal histologic type of PTC was associated with PHGDH ($p = 0.006$), tumoral SHMT1 ($p = 0.005$), and stromal SHMT1 ($p < 0.001$) expression. Inflammatory type showed a lower rate of PHGDH expression compared to other subtypes, and desmoplastic type and inflammatory type had a higher rate of tumoral and stromal SHMT1 expression compared to pauci type and sclerotic type (Fig. 4).
Impact of the expression of serine/glycine metabolism-related proteins on patient prognosis

In analysis of the impact of the expression of serine/glycine metabolism-related proteins on patient prognosis, the expression of serine/glycine metabolism-related proteins did not have an association with prognosis for overall PTC (Table 5). However, for follicular variant PTC the expression of stromal SHMT1 was associated with shorter disease-free survival (DFS; \( p = 0.015 \)), and in the sclerotic stromal type, GLDC positivity was associated with shorter overall survival (OS; \( p = 0.002 \)). PSPH positivity was associated with shorter OS in minimally invasive type FC (\( p = 0.045 \)) and PHGDH positivity correlated with shorter OS in MC (\( p = 0.034 \), and Fig. 5).
Discussion

In this study, we investigated the expression of proteins related to serine/glycine metabolism in thyroid cancers and found differences in expression according to the different types of thyroid cancer. In general, the rate of serine/glycine metabolism-related protein expression was higher in PDC and PTC, and lower in MC. As there are no previous studies regarding serine/glycine metabolism in thyroid cancer a direct comparison cannot be made, however MC is a tumor that originates from C-cells whereas other thyroid neoplasms originate from follicular cells, so they might be expected to have different metabolic features. The results of our study suggest that C-cell origin MC may have lower serine/glycine metabolic activity, although further study is required to examine this finding.

Table 2 Expression of glutamine metabolism-related proteins according to the histologic subtype of PTC

| Parameters          | Total n = 344 (%) | Histologic subtype |  |  |  |  |
|---------------------|------------------|--------------------|---|---|---|---|
|                     |                  | Conventional type n = 304 (%) |  |  |  |  |
|                     |                  | Follicular variant n = 40 (%) |  |  |  |  |
| PHGDH in tumor      |                  |  |  |  |  |  |
| Negative            | 126 (36.6)       | 113 (37.2)         | 13 (32.5) | 63 (59.4) | 63 (26.5) | 0.564 | 0.001 |
| Positive            | 218 (63.4)       | 191 (62.8)         | 27 (67.5) | 43 (40.6) | 175 (73.5) | 0.501 | 0.001 |
| PHGDH in tumor      |                  |  |  |  |  |  |
| Negative            | 280 (81.4)       | 249 (81.9)         | 31 (77.5) | 97 (91.5) | 183 (76.9) | 0.041 | 0.001 |
| Positive            | 64 (18.6)        | 55 (18.1)          | 9 (22.5)  | 9 (8.5)   | 55 (23.1)  | 0.116 | 0.001 |
| PSAT1 in tumor      |                  |  |  |  |  |  |
| Negative            | 300 (87.2)       | 261 (85.9)         | 39 (97.5) | 104 (98.1) | 196 (82.4) | 0.018 | 0.001 |
| Positive            | 44 (12.8)        | 43 (14.1)          | 1 (2.5)   | 2 (1.9)   | 42 (17.6)  | 0.018 | 0.001 |
| PSAT1 in tumor      |                  |  |  |  |  |  |
| Negative            | 236 (68.6)       | 202 (64.4)         | 34 (85.0) | 86 (81.1) | 150 (63.0) | 0.018 | 0.001 |
| Positive            | 108 (31.4)       | 102 (33.6)         | 6 (15.0)  | 20 (18.9) | 88 (37.0)  | 0.018 | 0.001 |
| SHMT1 in tumor      |                  |  |  |  |  |  |
| Negative            | 212 (61.6)       | 176 (57.9)         | 36 (90.0) | 83 (78.3) | 129 (54.2) | 0.016 | 0.001 |
| Positive            | 132 (38.4)       | 128 (42.1)         | 4 (10.0)  | 23 (21.7) | 109 (45.8) | 0.016 | 0.001 |
| SHMT1 in stroma     |                  |  |  |  |  |  |
| Negative            | 285 (82.8)       | 248 (81.6)         | 37 (92.5) | 99 (93.4) | 186 (78.2) | 0.016 | 0.001 |
| Positive            | 59 (17.2)        | 56 (18.4)          | 3 (7.5)   | 7 (6.6)   | 52 (21.8)  | 0.016 | 0.001 |

PTC papillary thyroid carcinoma; PHGDH phosphoglycerate dehydrogenase; PSAT phosphoserine aminotransferase; PSPH phosphoserine phosphatase; SHMT serine hydromethyl transferase; GLDC glycine decarboxylase

Italic values represent p < 0.05
present study showed that stromal SHMT1 expression was highest in AC. In previous studies of breast cancer, it was reported that serine/glycine metabolism-related proteins were expressed not only in tumor cells but also in stromal cells [17, 18]. Moreover, glycolysis [19–21] and glutamine metabolism were reported to mediate metabolic interactions between cancer cells and stromal cells such as cancer-associated fibroblasts (CAFs) [20, 22–25]. Metabolic interactions between cancer cells and CAFs promote tumor cell proliferation and growth, suggesting that serine/glycine metabolic activity in both tumor and stroma contributes to tumor aggressiveness in AC.

We observed a higher rate of serine/glycine metabolism-related protein expression in cases of PTC with the BRAF V600E mutation. In meta-analysis studies, the BRAF V600E mutation is reported to be associated with extra-thyroidal extension, advanced TNM stage, lymph node metastasis, multifocality, and recurrence [14], suggesting that PTC with a BRAF V600E mutation has more aggressive tumor biology. In general, higher metabolic activity is related to increased tumor aggressiveness [26–28], and higher expression levels of proteins related to serine/glycine metabolism might be expected in BRAF V600E-positive cases. In addition, PTC with the BRAF V600E mutation is reported to have enhanced glucose metabolism [29]. Since serine metabolism initiates from 3PG, which is generated in the glycolysis pathway, increased serine metabolism might be expected when glycolysis is increased.

A clinical implication of this study is the potential application of targeted therapy against the serine/glycine metabolism pathway. Preclinical studies are ongoing to identify drugs that target multiple sites of one-carbon metabolism, such as GLDC, PSAT, PSPH, and PHGDH, as a novel therapeutic approach [30, 31].

**Conclusion**

The expression of serine/glycine metabolism-related proteins differs among different thyroid cancer types, with a higher rate of expression in PDC and PTC, and a lower rate of expression in MC. In PTC, the rate of serine/glycine metabolism-related protein expression is lower in the follicular variant, and higher in cases with the BRAF V600E mutation.
Table 3 Expression of serine/glycine metabolism-related proteins in follicular neoplasm

| Parameters          | Total n = 264 (%) | Follicular adenoma n = 152 (%) | Follicular carcinoma n = 112 (%) | p value |
|---------------------|-------------------|--------------------------------|---------------------------------|---------|
| PHGDH in tumor      |                   |                                |                                 |         |
| Negative            | 147 (55.7)        | 89 (58.6)                      | 58 (51.8)                       | 0.274   |
| Positive            | 117 (44.3)        | 63 (41.4)                      | 54 (48.2)                       |         |
| PSAT1 in tumor      |                   |                                |                                 |         |
| Negative            | 219 (82.6)        | 116 (75.8)                     | 103 (92.0)                      | 0.001   |
| Positive            | 46 (17.4)         | 37 (24.2)                      | 9 (8.0)                         |         |
| PSPH in tumor       |                   |                                |                                 |         |
| Negative            | 244 (92.1)        | 143 (93.5)                     | 101 (90.2)                      | 0.328   |
| Positive            | 21 (7.9)          | 10 (6.5)                       | 11 (9.8)                        |         |
| SHMT1 in tumor      |                   |                                |                                 |         |
| Negative            | 211 (79.6)        | 117 (76.5)                     | 94 (83.9)                       | 0.137   |
| Positive            | 54 (20.4)         | 36 (23.5)                      | 18 (16.1)                       |         |
| GLDC in tumor       |                   |                                |                                 |         |
| Negative            | 234 (88.3)        | 138 (90.2)                     | 96 (85.7)                       | 0.262   |
| Positive            | 31 (11.7)         | 15 (9.8)                       | 16 (14.3)                       |         |

*PHGDH* phosphoglycerate dehydrogenase; *PSAT* phosphoserine aminotransferase; *PSPH* phosphoserine phosphatase; *SHMT* serine hydromethyl transferase; *GLDC* glycine decarboxylase

Italic value represents p < 0.05

Table 4 Expression of serine/glycine metabolism-related proteins according to the histologic subtype of follicular carcinoma

| Parameters          | Total n = 112 (%) | FC, minimally invasive type n = 99 (%) | FC, widely invasive type n = 13 (%) | p value |
|---------------------|-------------------|---------------------------------------|-------------------------------------|---------|
| PHGDH in tumor      |                   |                                       |                                     |         |
| Negative            | 58 (51.8)         | 50 (50.5)                             | 8 (61.5)                            | 0.454   |
| Positive            | 54 (48.2)         | 49 (49.5)                             | 5 (38.5)                            |         |
| PSAT1 in tumor      |                   |                                       |                                     |         |
| Negative            | 103 (92.0)        | 91 (91.9)                             | 12 (92.3)                           | 1.000   |
| Positive            | 9 (8.0)           | 8 (8.1)                               | 1 (7.7)                             |         |
| PSPH in tumor       |                   |                                       |                                     |         |
| Negative            | 101 (90.2)        | 88 (88.9)                             | 13 (100.0)                          | 0.357   |
| Positive            | 11 (9.8)          | 11 (11.1)                             | 0 (0.0)                             |         |
| SHMT1 in tumor      |                   |                                       |                                     |         |
| Negative            | 94 (83.9)         | 82 (82.8)                             | 12 (92.3)                           | 0.689   |
| Positive            | 18 (16.1)         | 17 (17.2)                             | 1 (7.7)                             |         |
| GLDC in tumor       |                   |                                       |                                     |         |
| Negative            | 96 (85.7)         | 85 (85.9)                             | 11 (84.6)                           | 1.000   |
| Positive            | 16 (14.3)         | 14 (14.1)                             | 2 (15.4)                            |         |

*PHGDH* phosphoglycerate dehydrogenase; *PSAT* phosphoserine aminotransferase; *PSPH* phosphoserine phosphatase; *SHMT* serine hydromethyl transferase; *GLDC* glycine decarboxylase
Fig. 4 Correlation between the expression of serine/glycine metabolism-related proteins and clinicopathologic factors in papillary carcinoma. 

**a** In PTC, PHGDH expression is associated with tumor size, with an increased tumor size in PHGDH-positive cases. 

**b** Inflammatory type shows a lower rate of PHGDH expression compared to other subtypes, and desmoplastic type and inflammatory type have a higher rate of tumoral (**c**) and stromal (**d**) SHMT1 expression compared to pauci type and sclerotic type.
Table 5 Univariate analysis of the impact of serine/glycine-related protein expression in papillary thyroid carcinoma on disease-free and overall survival by the log-rank test

| Parameter           | Number of patients* | Disease-free survival | Overall survival |
|---------------------|---------------------|-----------------------|------------------|
|                     |         | Mean survival (95% CI) months | p value | Mean survival (95% CI) months | p value |
| PHGDH in tumor      | 0.790   | 105 (101–108) | 0.806 | 106 (103–109)   |
| Negative            | 126/6/6 | 105 (101–108) | 0.806 | 106 (103–109)   |
| Positive            | 218/12/12| 106 (104–109) | 0.806 | 107 (105–110)   |
| PSAT1 in tumor      | 0.159   | 106 (103–109) | 0.231 | 108 (106–110)   |
| Negative            | 280/17/13| 106 (103–109) | 0.231 | 108 (106–110)   |
| Positive            | 64/1/5  | 108 (105–111) | 0.231 | 103 (97–108)    |
| PSPH in tumor       | 0.606   | 108 (105–110) | 0.221 | 109 (106–110)   |
| Negative            | 300/15/14| 107 (105–109) | 0.221 | 108 (106–110)   |
| Positive            | 44/3/4  | 103 (96–110)  | 0.221 | 103 (96–109)    |
| SHMT1 in tumor      | 0.498   | 107 (105–110) | 0.248 | 108 (106–110)   |
| Negative            | 236/11/10| 107 (105–110) | 0.248 | 108 (106–110)   |
| Positive            | 108/7/8 | 104 (100–109) | 0.248 | 105 (101–109)   |
| SHMT1 in stroma     | 0.655   | 106 (103–109) | 0.684 | 108 (106–110)   |
| Negative            | 212/12/10| 106 (103–109) | 0.684 | 108 (106–110)   |
| Positive            | 132/6/8 | 107 (104–111) | 0.684 | 107 (103–110)   |
| GLDC in tumor       | 0.516   | 107 (105–109) | 0.059 | 108 (106–110)   |
| Negative            | 285/14/12| 107 (105–109) | 0.059 | 108 (106–110)   |
| Positive            | 59/4/6  | 104 (97–110)  | 0.059 | 103 (97–109)    |

CI: confidence interval; PHGDH: phosphoglycerate dehydrogenase; PSAT: phosphoserine aminotransferase; PSPH: phosphoserine phosphatase; SHMT: serine hydromethyltransferase; GLDC: glycine decarboxylase

* Cases of anaplastic carcinoma were excluded
Fig. 5  Impact of the expression of serine/glycine metabolism-related proteins on patient prognosis. **a** For follicular variant PTC, the expression of stromal SHMT1 is associated with shorter disease-free survival. **b** In the sclerotic stromal type, GLDC positivity is associated with shorter overall survival. **c** PSPH positivity is associated with shorter OS in minimally invasive type FC. **d** PHGDH positivity correlated with shorter OS in MC.

Additional file

**Additional file 1:** Table S1. Source, clone, and dilution of antibodies used in this study. **Table S2.** Basal characteristics of thyroid papillary carcinoma. **Table S3.** Basal characteristics of thyroid follicular carcinoma. **Table S4.** Basal characteristics of thyroid medullary carcinoma, poorly differentiated carcinoma, and anaplastic carcinoma.

**Abbreviations**

3PG: 3-phosphoglycerate; pPYR: phosphohydroxypyruvate; PHGDH: phosphoglycerate dehydrogenase; pSER: phosphoserine; PSAT: phosphoserine aminotransferase; PSPH: phosphoserine phosphatase; GLDC: glycine decarboxylase; SHMT: serine hydromethyl transferase; PTC: papillary thyroid carcinoma; FC: follicular carcinoma; MC: medullary carcinoma; PDC: poorly differentiated carcinoma; AC: anaplastic carcinoma; H&E: hematoxylin and eosin; CAF: cancer-associated fibroblast.
Authors' contributions
WYS participated in the design of the study and performed the statistical analysis. HMK did immunoassays. WHJ participated in the study design. JSK conceived the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB) of Yonsei University Severance Hospital. Informed consent from patients was exempted by IRB.

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