Table 2
Positive rate of immunohistochemical markers according to histology of primary mediastinal tumors.

Histology (n = 21)	Glut1	Glut3	Hexo I	HIF-1α	VEGF	CD34	EGFR	p-Akt	p-mTOR	p-S6K	p53
Schwannoma (n = 6)	50% (3/6)	33% (2/6)	83% (5/6)	100% (6/6)	50% (3/6)	17% (1/6)	17% (1/6)	17% (1/6)	0% (0/6)	50% (3/6)	33% (2/6)
Teratoma (n = 3)	67% (2/3)	0% (0/3)	33% (1/3)	0% (0/3)	0% (0/3)	67% (2/3)	67% (2/3)	33% (1/3)	33% (1/3)	33% (1/3)	0% (0/3)
Cyst (n = 4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)	0% (0/4)
Sarcoma (n = 3)	33% (1/3)	50% (2/4)	67% (2/3)	33% (1/3)	67% (2/3)	100% (3/3)	67% (2/3)	67% (2/3)	0% (0/3)	100% (3/3)	0% (0/3)
Undifferential carcinoma (n = 1)	100% (1/1)	0% (0/1)	100% (1/1)	100% (1/1)	100% (1/1)	0% (0/1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)
Seminoma (n = 1)	0% (0/1)	0% (0/1)	100% (1/1)	100% (1/1)	100% (1/1)	0% (0/1)	0% (0/1)	100% (1/1)	0% (0/1)	100% (1/1)	0% (0/1)
Mediastinal goiter (n = 1)	0% (0/1)	0% (0/1)	100% (1/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	100% (1/1)	0% (0/1)
Ganglioneuroma (n = 1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)	0% (0/1)
Hodgkin lymphoma (n = 1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	100% (1/1)	0% (0/1)
Total positive rate (%)	38%	23%	43%	48%	38%	33%	29%	33%	14%	52%	14%

Abbreviations: Glut1, glucose transporter 1; Glut3, glucose transporter 3; Hexo I, hexokinase I; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin.

Table 3
Relationship between ^{18}F-FDG uptake and biomarkers.

Biomarkers	Spearman γ	95% confidence interval	p-Value
Glut1	0.5965	0.1471–0.8471	0.0115
Glut3	0.0362	−0.4647 to 0.5195	0.8903
Hexokinase I	0.4047	−0.1097 to 0.7481	0.1071
HIF-1α	0.5400	0.0646–0.8156	0.0253
VEGF	0.3559	−0.1657 to 0.7219	0.1609
CD34	0.3408	−0.1824 to 0.7136	0.1808
EFGR	0.5973	0.1484–0.8421	0.0013
p-Akt	0.6170	0.1788–0.8510	0.0083
p-mTOR	0.2728	−0.2539 to 0.6747	0.2895
p-S6K	0.5580	0.0902–0.8241	0.0199

Abbreviations: Glut1, glucose transporter 1; Glut3, glucose transporter 3; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin.

A previous *in vivo* study demonstrated that changes in ^{18}F-FDG uptake during mTOR inhibitor correlated with p-Akt activation and Glut1 expression [18]. This report suggests that ^{18}F-FDG PET correlates with Akt pathway activity in neoplasm. EGFR is an upstream component of the PI3K/AKT pathway, and our data suggests that not only p-Akt but also EGFR activity is closely associated with the mechanism of ^{18}F-FDG uptake within tumor cells. As this association may be different according to the histological type of primary mediastinal tumors, further study is warranted.

The present study has several limitations. Firstly, our population was a small sample size, including a heterogeneous group of tumors. Non-thymic mediastinal neoplasms were rare tumors, thus, the present study warrants a larger multicenter study. Another limitation is that our study includes various histological types, therefore, the biological correlation of ^{18}F-FDG uptake in one histological type seems to be unclear. Moreover, it is unclear whether ^{18}F-FDG uptake is associated with outcome in primary mediastinal neoplasms. In thymic epithelial tumors, we reported that a high uptake of ^{18}F-FDG is significantly related to poor outcome [13].

In conclusion, glucose metabolism (Glut1), hypoxia (HIF-1α), EGFR and p-Akt play an important role on ^{18}F-FDG uptake in primary mediastinal non-thymic neoplasms. These biomarkers were highly expressed in schwannoma, teratoma and high grade malignancies, whereas all patients with cyst and ganglioneuroma had no positive expression of these biomarkers. Our results suggest that ^{18}F-FDG uptake was useful for predicting the grade of malignancy.

Table 4
Relationship between T/M ratio of ^{18}F-FDG uptake and different variables.

Different variables	T/M ratio of ^{18}F-FDG uptake		
	High (n = 9)	Low (n = 12)	p-Value
Age (≤65/>65 years)	6/3	10/2	0.6108
Gender (male/female)	3/6	5/7	1.0000
Smoking history (yes/no)	4/5	4/8	0.6731
Maximal size of tumor (≤43/>43 mm)	6/3	2/10	0.0318
Glut 1 (positive/negative)	6/3	2/10	0.0318
Glut 3 (positive/negative)	3/6	2/10	0.6018
Hexokinase I (positive/negative)	6/3	3/9	0.0872
HIF-1α (positive/negative)	6/3	4/8	0.1984
VEGF (positive/negative)	6/3	2/10	0.0318
CD34 (positive/negative)	5/4	2/10	0.1588
EGFR (positive/negative)	6/3	0/12	0.0015
p-Akt (positive/negative)	6/3	1/11	0.0158
p-mTOR (positive/negative)	3/6	0/12	0.0632
p-S6K (positive/negative)	8/1	3/9	0.0075
p53 (positive/negative)	2/7	1/11	0.5534

Abbreviations: Glut1, glucose transporter 1; Glut3, glucose transporter 3; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin.

But, a large scale study is necessary for the confirmation of our results.

Conflict of interest statement

We, all authors, have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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