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Comparison of thyroid transcription factor-1 expression by two monoclonal antibodies in pulmonary and non-pulmonary primary tumors

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Abstract

Thyroid transcription factor-1 (TTF-1) is a transcription factor that plays a role in the development and physiology of the thyroid and lungs. Expression of TTF-1 is used as a marker of lung and thyroid clinically. Commercially available clones of TTF-1 monoclonal antibodies, 8G7G3/1 and SPT24, have been reported to have different sensitivities for the detection of neoplasms of different origins. Although they are used extensively in daily practice, a comprehensive comparative study of these antibodies in a wide variety of neoplasms is lacking. We examined TTF-1 expression in primary tumors of the lung, prostate, pancreas, stomach, salivary glands, breast, bladder, colon and squamous cell carcinoma of the head and neck and compared the results obtained with both TTF-1 clones. The SPT24 clone detected more primary lung tumors of all histologic subtypes. Importantly, the SPT24 clone detected a significantly higher number of squamous cell carcinomas and carcinoid tumors of the lung. Among non-pulmonary primary tumors, a significant number of invasive urothelial carcinoma of the bladder (5.1%) was TTF-1 positive. Additionally, a small proportion of prostate (1.2%), stomach (0.9%), salivary gland (1.8%), and colon (2.5%) carcinomas were positive with both clones. Notably, both clones stained the same non-pulmonary tumors with similar intensity and distribution. Carcinomas of the pancreas, breast and squamous cell carcinomas of the head and neck were negative with both clones. In summary, the SPT24 clone detected a higher number of pulmonary non-small cell tumors of all histologic subtypes while both clones stained a similar proportion of non-pulmonary tumors.

Keywords

Thyroid transcription factor-1; SPT24 clone; 8G7G3/1 clone; tissue microarrays

Introduction

Thyroid transcription factor-1, also known as Nkx2.1 or thyroid-specific enhancer binding-protein, is a 38 kDa DNA-binding protein containing 371 amino acids. It is encoded by a gene located on chromosome 14q13 and is preferentially expressed in the thyroid and lung. In the thyroid, TTF-1 is expressed in follicular cells and C-cells in developing and adult thyroid gland where it activates thyroglobulin and thyroperoxidase gene transcription (1-4). In the lung, the

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The authors state no conflict of interest.

human TTF-1 protein has been detected during development as early as 11 weeks of gestation and is thought to play a role in the regulation of surfactant B production (5).

TTF-1 expression is employed widely as a marker of lung and thyroid tumors (6-8). In carcinomas of the lung, TTF-1 expression has been reported to be positive in nearly all small cell carcinomas, in the majority of adenocarcinomas and non-mucinous bronchio-alveolar carcinomas; however, TTF-1 is negative in squamous cell carcinomas and mucinous bronchio-alveolar carcinomas (6). As the lung is one of the most common sites of metastasis, TTF-1 is used as a reliable marker to distinguish between primary and secondary lung tumors, especially when dealing with an adenocarcinoma or a large-cell carcinoma (8-10).

Although, TTF-1 expression is thought to be quite specific for thyroid and lung, TTF-1 immunostaining has been reported to be positive in cases of colonic adenocarcinoma (11), ovarian epithelial neoplasms (12), and uterine tumors (13,14).

Recently, new clones of TTF-1 antibodies have become commercially available and their sensitivity and specificity in the detection of different types of lung and non-lung tumors has been partially reported. The most widely used in diagnostic laboratories is the clone 8G7G3/1 by Dako (15). Subsequently, SPT24 was introduced to the market and reported to be less specific for lung tissue since it was positive in occasional cases of metastatic colonic adenocarcinoma (11). Here, we performed a comprehensive comparative study of TTF-1 expression utilizing both clones in a series of primary tumors of the lung, as well as tumors of the prostate, pancreas, stomach, salivary glands, breast and squamous cell carcinoma of the head and neck.

Material and Methods

Tissue samples

Tissue microarrays were constructed from archival paraffin embedded tissue samples from patients with pulmonary and non-pulmonary primary tumors. Metastatic tumors of the lung were studied by whole-block tissue sections. Cases were retrieved by diagnosis search from the surgical pathology files of Rhode Island Hospital and The Miriam Hospital/Lifespan Academic Medical Center, Providence, RI. The study was performed in accordance with the guidelines and approval from the Institutional Review Committee for Research on Human Subjects. Primary lung tumor microarrays were composed of 374 cases, including 185 adenocarcinomas, 97 squamous cell carcinomas, 47 large cell carcinomas, 23 carcinoid tumors and 22 unclassified tumors. Non-lung primary tumors included 160 prostate, 120 colon, 110 gastric and 110 pancreatic ductal adenocarcinomas, 98 invasive urothelial carcinomas of the bladder, 56 salivary gland tumors, 38 squamous cell carcinomas of head and neck and 34 invasive ductal carcinomas of the breast. None of the patients with non-lung tumors had a history of lung cancer, based on chart review.

Immunohistochemistry

Tissue microarrays and tissue sections were immunostained using monoclonal antibodies to TTF-1, clones 8G7G3/1 (dilution 1:100, Dako North America, Inc. Carpinteria, CA) and SPT24 (dilution 1:25, Novocastra Laboratories Ltd., Newcastle Upon Tyne, NE12 8EW, United Kingdom). Both antibodies are IgG₁ kappa isotype. Staining was performed using the Ventana Discovery System (Ventana, Tucson, AZ). Antigen retrieval was performed using the Cell Conditioning Solution (CC1) kit from Ventana following the manufacturer protocol. Reduction of endogenous peroxidase activity, background blocking and chromogen system was performed by using the Discovery DAB Map kit (RUO) from Ventana following the manufacturer protocol. Counter-stain was done with hematoxylin. Thyroid microarrays

constructed with tumor and normal tissue were used as positive controls. The immunohistochemical stains were scored using a two-tiered scoring system: positive or negative. A positive score was based on moderate to strong nuclear staining. AM and LJW independently scored each of the sections without knowledge of the histologic diagnosis or staining pattern with the other marker. There was a high correlation between the two scores and in the few discrepant cases; a consensus was reached after joint review.

Statistical Analysis

Statistical analysis was performed using the GraphPad Prism Software. P values were calculated using Fisher's exact test.

Results

Pulmonary primary tumors

A total of 374 cases of non-small cell carcinoma of the lung was evaluated (Table 1). Staining was limited to the nuclei where it was present as a finely granular diffuse pattern in the majority of the cells. Notably, SPT24 detected a higher number of positive cases through all histologic subtypes of lung tumors. Expression of TTF-1 in adenocarcinomas was similar using both antibody clones, with a trend towards higher staining with the SPT24 clone ($P=0.08$) (Figure 1a). The differential staining was highest in squamous cell carcinoma and carcinoid tumors. In squamous cell carcinomas, the SPT24 clone detected 14 of 97 (16.8%) cases as opposed to the 8G7G3/1 clone which detected 1 of 97 (1%) cases ($P=0.003$) (Figure 1b). Staining of carcinoid tumors was also significantly higher with SPT24 clone, which detected 14 of 23 (60.8%) cases as opposed to the 8G7G3/1 clone which detected 4 of 23 (17.4%) cases ($P=0.003$) (Figure 1c). The proportion of large cell carcinomas and poorly differentiated carcinomas stained similar with both antibody clones.

In addition to primary tumors of the lung, we conducted a small pilot study of metastatic lung carcinomas to other organs which was heavily weighted towards poorly differentiated tumors (17 poorly differentiated carcinomas unclassified, 5 adenocarcinomas and 1 squamous carcinoma). The metastatic tumors studied included 9 metastases to lymph nodes, 4 brain, 4 adrenal, 4 liver and 2 bone. There was no statistically significance in the difference of staining between the two clones (results not shown).

Non-pulmonary primary tumors

TTF-1 expression was present in a small subset of non-lung primary tumors of the urinary bladder, colon, stomach and salivary gland, but not in squamous cell carcinomas of the head and neck, pancreatic adenocarcinomas or invasive mammary carcinomas (Table 1). The non-lung primary tumor type that showed the highest number of positive cases was invasive urothelial carcinoma of the urinary bladder (5 of 98 cases, 5.1%; Figure 2). Three of these cases contained more than 70% positive cells (Figure 2a), while 2 cases were focally positive staining 20% of the cells (Figure 2b). The intensity and distribution of positive cells was similar with both antibodies. Three cases of colon cancer were positive using both antibody clones. As illustrated in figure 3, the intensity and extent of stain was also similar when using either SPT24 or 8G7G3/1 clones (Figure 3). Single cases of salivary gland adenoid cystic carcinoma and gastric adenocarcinoma were positive. While the salivary gland tumor stained homogeneously (Figure 4a), the staining in the gastric adenocarcinoma case was focally positive (30%; Figure 4b).

Discussion

The expression of TTF-1 by immunohistochemistry was first shown by Lazzaro *et al.* in fetal rat lung, thyroid gland and neuro-hypophysis. The antibody used in that study was developed against peptides E1, A2 and F1, spanning amino acid residues 2-14, 92-104 and 110-122 from the *TTF-1* coding region, respectively (16). Subsequently, Holzinger *et al.* produced and characterized the 8G7G3/1 monoclonal antibody to TTF-1 and reported positive nuclear staining in pulmonary adenocarcinomas and small cell carcinomas of the lung, but negative staining in breast and colon carcinomas (15). Thereafter, TTF-1 was considered a very specific marker for adenocarcinoma and small cell carcinoma of lung in histological as well as cytological specimens and gained popularity among pathologists as a useful marker of lung and thyroid (8,10). Concomitantly, several studies began to challenge the specificity of TTF-1. For example, the expression of TTF-1 in extrapulmonary small cell carcinomas raised initial concern (9,17). More recently, Alkushi *et al.* reported a TTF-1 positive case of uterine papillary serous carcinoma in their study of cervical and uterine adenocarcinoma (18). TTF-1 staining has also been observed in ependymoma (19), glioblastoma multiforme (20), mixed mullerian tumor of ovary (21), serous, mixed serous and endometrioid carcinoma of ovary (12), clear cell carcinoma of the ovary (22), endocervical adenocarcinoma (13), mucinous carcinoma of the ovary (14), primary and metastatic colonic adenocarcinoma (11,23), atrophic gastritis and ciliated metaplasia (24), prostate adenocarcinoma (25), melanoma (26), and in nephroblastoma (27).

Penman *et al.* studied primary and metastatic colonic adenocarcinomas with 8G7G3/1 or SPT24 TTF-1 clones and described different detection capability, with SPT24 being more sensitive for lung adenocarcinomas. However, only the SPT24 clone detected a few adenocarcinomas of colonic origin (11). Recently, Wong *et al.* reported two cases of TTF-1 positive colonic adenocarcinoma using the 8G7G3/1 clone (23). In our study, 3/120 (2.5%) primary colonic adenocarcinoma were positive for TTF-1 with SPT24 or 8G3G7/1 clones. Interestingly, both antibodies stained the tumors with similar extents and intensities.

We noted positive staining in 5 of 98 (5.1%) cases of invasive urothelial carcinoma and in one of 56 (1.8%) cases of salivary gland carcinoma with both TTF-1 clones. This is the first report of TTF-1 expression in urothelial carcinoma and salivary gland carcinoma in the English literature. Two cases (2.1%) of prostatic ductal adenocarcinoma were positive for TTF-1 with both antibody clones. Lim *et al.* described a TTF-1 positive prostate adenocarcinoma with predominant ductal differentiation (25).

Differences in the results of immunohistochemical TTF-1 expression by different TTF-1 clones have been emphasized in few other studies. For instance, 14 of 28 glioblastoma multiforme tumors stained with TTF-1 clone SPT24, while all of these cases were negative using the 8G7G3-1 TTF-1 clone (20). Recently, Zhang *et al.* concluded that the SPT24 clone was the most sensitive primary antibody for TTF-1 using the Refine/Bond Max Autostainer. In their study, TTF-1 reactivity could be detected in all major histologic subtypes of gynecologic tumors, in up to 26% of all cases tested on routine surgical specimens, and in 6.4% of cases on tissue microarray. In addition to malignant tumors, this study also reports positive TTF-1 staining in benign tumors and in benign tubal and endometrial epithelia (14).

Our results demonstrate that the extent of TTF-1 expression depends on the type of TTF-1 clone used only when testing primary lung tumors. Although not statistically significant, we found a trend towards higher TTF-1 positivity in pulmonary adenocarcinomas with the SPT24 clone. Furthermore, a significantly higher number of carcinoids and squamous cell carcinoma was positive for TTF-1 with the SPT24 clone. This is important as previous studies performed with the 8G7G3/1 clone reported inconsistent expression of TTF-1 in carcinoids and minimal

to absent expression in squamous cell carcinomas. Oliveira *et al.* reported 95% (19 of 20) of lung carcinoids were variably positive for TTF-1 using 8G7G3/1 clone (28). Pelosi *et al.* reported 5.0% TTF-1 positive squamous cell carcinomas with the 8G3G7/1 clone while Kaufman *et al.* reported all of the squamous cell carcinomas were negative with the same TTF-1 clone (9,29).

The relatively high positivity on squamous cell carcinomas of the lung (14 of 97) with the SPT24 clone is interesting. Currently, there is no clinically useful marker to separate primary from metastatic squamous cell carcinoma involving the lung. Although further testing of additional non-pulmonary squamous cell carcinoma cases is mandated, negativity of all our squamous cell carcinomas of the head and neck (0 of 38) suggests a relative specificity of the TTF-1 SPT24 clone towards squamous neoplasms originating in the lungs.

Immunohistochemistry for TTF-1 is also frequently used to establish the pulmonary origin of a metastatic carcinoma to an extrapulmonary site. We studied a relatively small set of metastatic lung carcinomas to other organs and saw no statistically significant difference in staining between the two antibody clones. It is possible that a larger number of metastatic tumors, including more squamous cell carcinomas and carcinoid tumors, are needed in order to detect sensitivity differences between the two clones as seen in the primary lung tumors.

Although certain previous reports suggest that the SPT24 clone is more sensitive than the 8G3G7/1 clone in detecting non-pulmonary tumors, the discrepancies with our results could be explained due to technical differences such as antibody dilutions, antigen retrieval, detection systems, etc. For example, Penman *et al.* reported three out of six TTF-1 positive colon cancer cases with the SPT24 clone and none with the 8G3G7/1 clone, yet they used a different staining system, antigen retrieval and antibody dilution (11). Furthermore, Zhang *et al.* show that detection of TTF-1 expression in gynecologic tumors can vary as a result of different antigen retrieval and detection system used (14). Importantly, by applying the technical conditions presented here we detect exactly the same number of TTF-1 positive extrapulmonary tumors with both antibody clones while showing a different sensitivity limited to the lung. One could speculate that the higher detection rate of SPT24 clone in primary lung tumors is due to its higher lung specificity. However, this assumption could prove to be wrong if comparable numbers of TTF-1 expressing tumors of non-pulmonary origins are tested. Unfortunately, the low prevalence of extrapulmonary TTF-1 positive tumors prevented us from proving or refuting that hypothesis.

In summary, we report a comprehensive comparative study of TTF-1 expression by two monoclonal antibodies in pulmonary and extrapulmonary tumors. Our results show that the TTF-1 SPT24 clone has a higher detection rate of all histologic subtypes of non-small cell pulmonary primary tumors with a clear advantage over 8G7G3/1 in squamous cell carcinomas and carcinoid tumors. Consistent with previous results, our study suggests that caution should be used when interpreting TTF-1 immunostain results, since a small proportion of non-pulmonary primary tumors are positive with both SPT24 or 8G7G3/1 antibody clones. Importantly, this study adds bladder urothelial carcinoma and salivary gland tumors to the already extensive list of non-pulmonary and non-thyroid primary tumors that express TTF-1.

Acknowledgments

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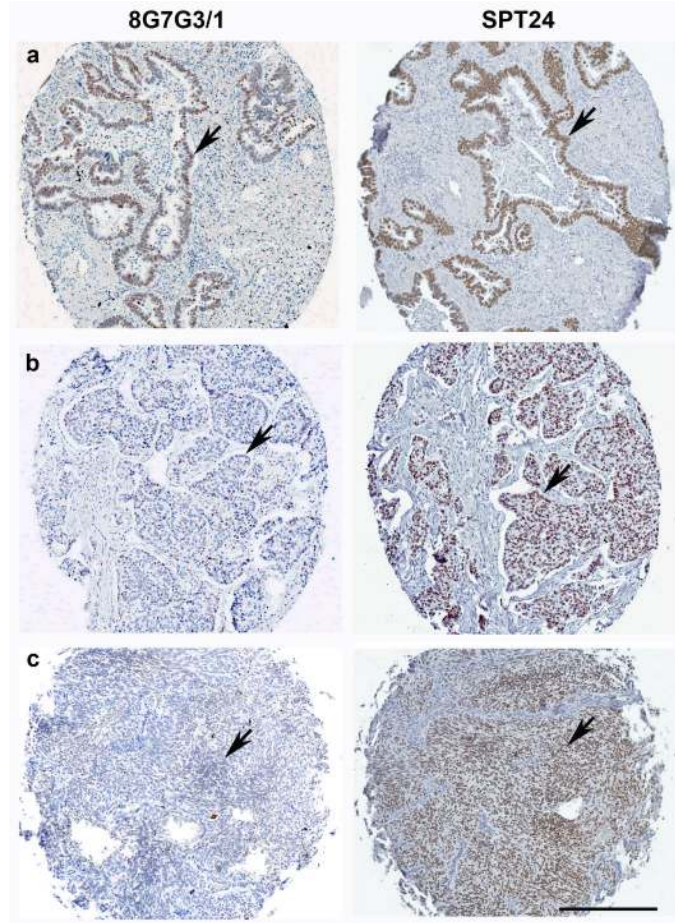


Figure 1. TTF-1 expression in lung primary tumors. (a) Neoplastic epithelial cells of adenocarcinomas are positive for TTF-1 with either 8G7G3/1 or SPT24 clones (arrows). (b) Nuclear staining of tumor cells in squamous cell carcinoma was noted using SPT24 clone (arrow, right), while the same case was negative with the 8G7G3/1 clone (arrow, left). (c) Diffusely positive TTF-1 expression in a case of carcinoid tumor was detected by SPT24 clone (arrow, right); the same case was negative with the 8G7G3/1 clone (arrow, left). Bar 200 μ .

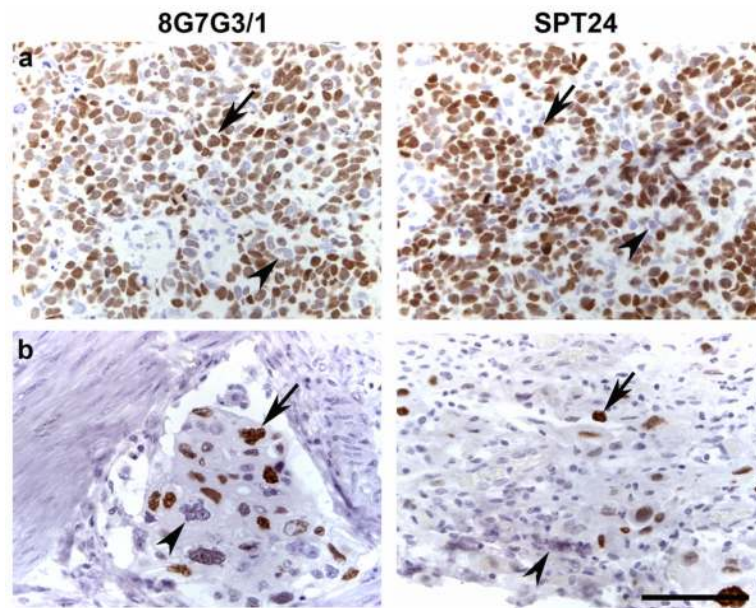


Figure 2. TTF-1 expression in invasive urothelial carcinoma of the bladder. (a) Three of 98 bladder cancer cases showed diffuse positive staining of the majority of the tumor cells (arrows) while some tumor cells remained negative (arrowheads). (b) Two of 98 cases of bladder cancer showed focal positive staining (arrows), while the majority of tumor cells were negative (arrowheads). Note that the intensity and number of positive cells is similar with either antibody clone (a and b). Bar 50 μ .

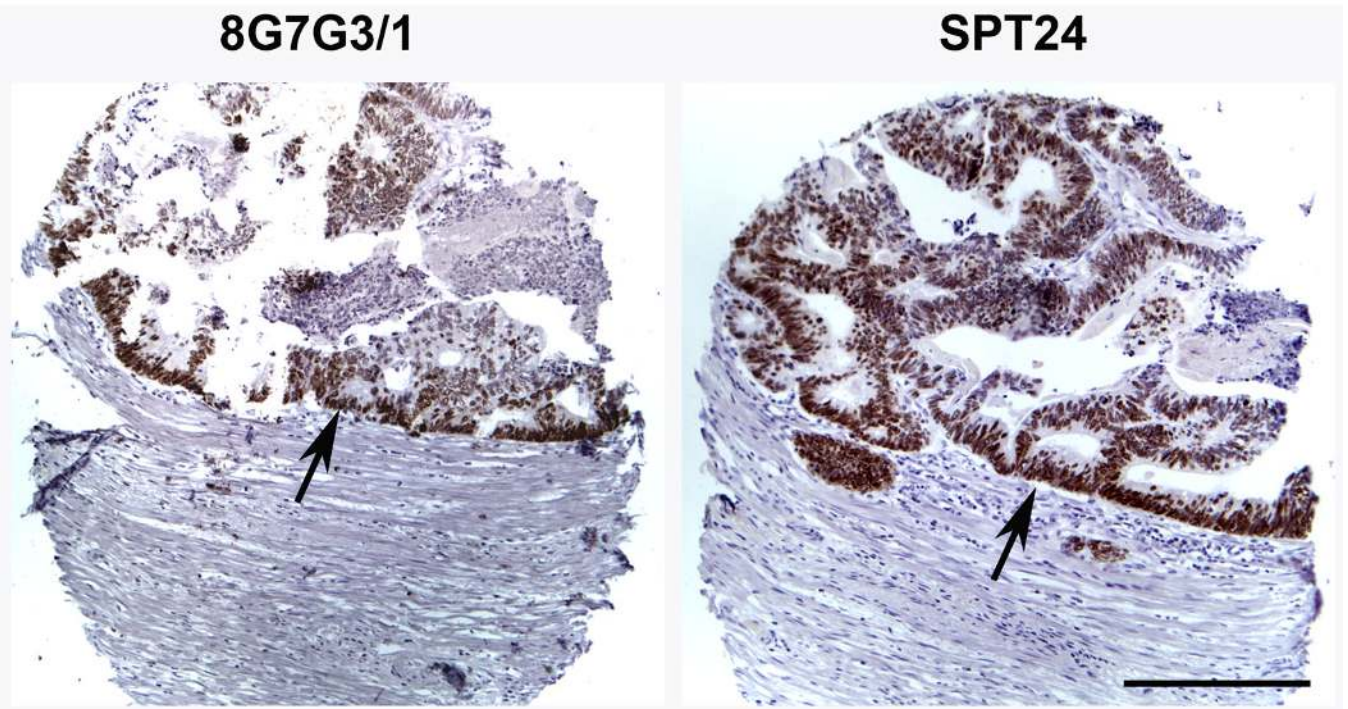


Figure 3. TTF-1 expression in colon adenocarcinoma. Epithelial cells stained positive for TTF-1 with both antibody clones (arrows). Bar 200 μ .

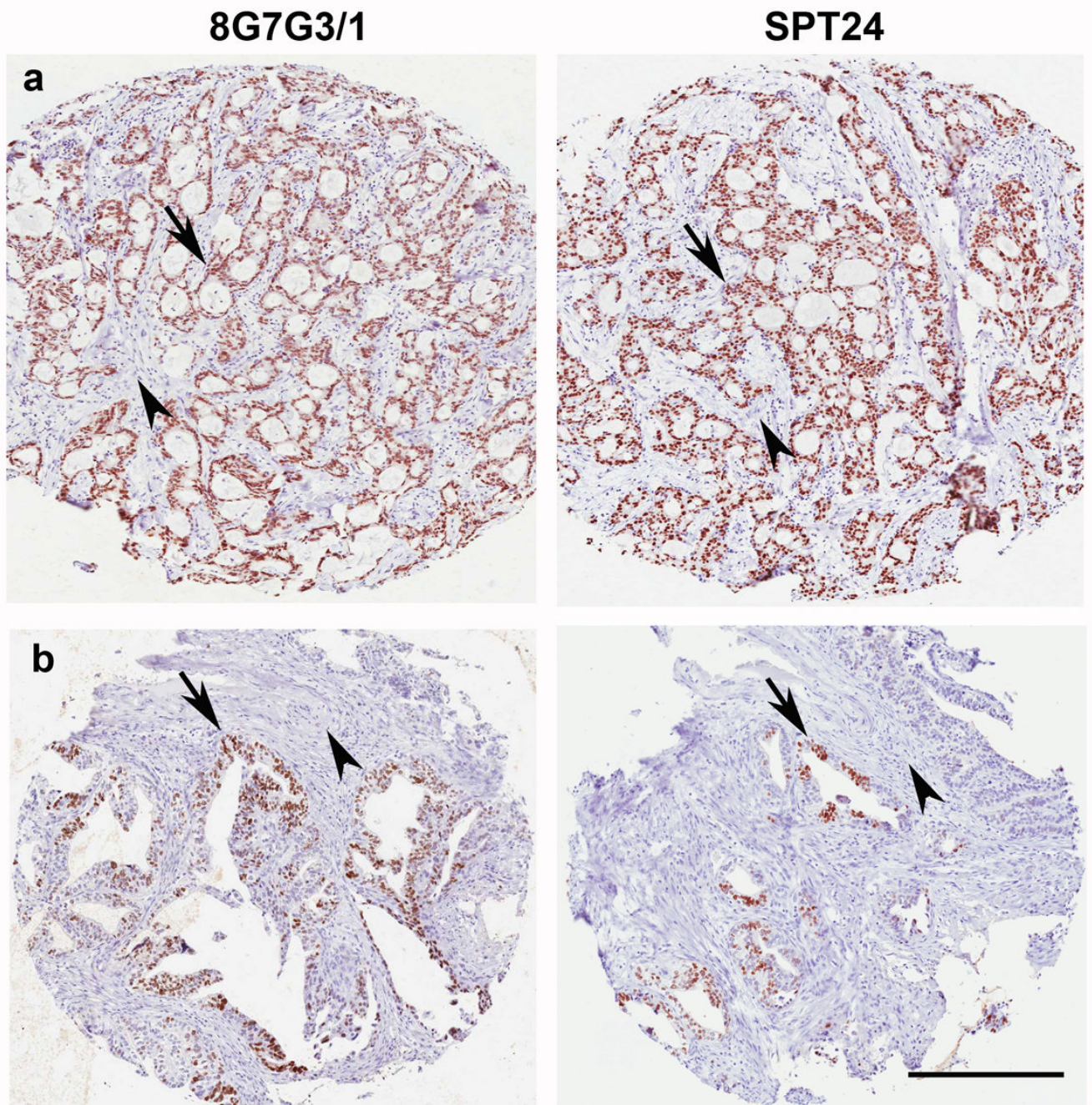


Figure 4.

TTF-1 expression in a case of salivary gland tumor and gastric adenocarcinoma. (a) Epithelial cells of a case of adenoid cystic carcinoma of the salivary gland stained diffusely positive with either antibody clone (arrows). Stromal cells were negative (arrowheads). (b) Focal nuclear staining of epithelial cells (arrows) was seen in a single case of gastric adenocarcinoma. Stromal cells were negative (arrowheads). Note similar intensity and number of positive cells with either antibody clone (a and b). Bar 200 μ .

Table 1

Summary of immunohistochemistry results.

	Total cases	SPT24	8G7G3/1	P
Lung	374			
<i>Adenocarcinoma</i>	185	134 (72.4%)	121 (65.4%)	0.08
<i>Large Cell</i>	47	22(46.8%)	17(36.2%)	0.201
<i>Carcinoid</i>	23	14(60.8%)	4(17.4%)	0.003
<i>Squamous Cell</i>	97	14(16.8%)	1(1.0%)	0.003
<i>Unclassified</i>	22	10(45.5%)	7(31.8%)	0.26
Bladder	98	5 (5.1%)	5 (5.1%)	NS
Colon	120	3 (2.5%)	3 (2.5%)	NS
Prostate	160	2(1.2%)	2(1.2%)	NS
Stomach	110	1(0.9%)	1(0.9%)	NS
Salivary Gland	56	1(1.8%)	1(1.8%)	NS
Squamous cell carcinoma of head and neck	38	0(0%)	0(0%)	NS
Pancreatic adenocarcinomas	110	0(0%)	0(0%)	NS
Breast	34	0(0%)	0(0%)	NS

NS: not significant