



Original Research Article

IHC–The need of the hour in classifying lung tumours effectively on guided biopsies!

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ARTICLE INFO

Article history:

Received 30-03-2019

Accepted 17-05-2019

Available online 22-11-2019

Keywords:

NSCLC

Lung carcinoma

P63

TTF1

IHC

ABSTRACT

Introduction: IHC forms an effective supplement to the morphological diagnosis in the emphatic categorisation of the lung carcinomas, especially the undifferentiated NSCLC i.e NOS types, which is very essential for an effective therapy. In this regard P63 and TTF-1 are considered the most important markers in subclassifying the NSCLC. P63 is a sensitive marker for squamous cell carcinoma, and TTF-1 for adenocarcinoma.

Objectives: 1) Immunohistochemical study of guided biopsies of the lung using TTF-1 and p63 markers. 2) To improve diagnostic clarity in poorly differentiated tumours.

Materials and Methods: Forty guided biopsies which were proved malignant on histopathology were taken from August 2012 to August 2014, at a tertiary health care centre, Bangalore.

Results: Of the total 40 cases, 13 cases (32.5%) were diagnosed as NSCLC NOS because of their inconclusive morphology on H&E for any particular subtype. Following immunohistochemistry, their number reduced to 4 (10%), from a massive 13 (32.5%) cases. One case of NSCLC favor SCC was rediagnosed as NSCLC favor adenocarcinoma, because it was positive for TTF-1 and negative for p63, and one case of LCNEC being rediagnosed as NSCLC favor adenocarcinoma as it was negative for both synaptophysin and p63, but positive for TTF-1.

Conclusion: In this study p63 stained 87% of the cases that were suspected to be squamous cell carcinoma and TTF-1 stained all the 7 cases suspected to be adenocarcinoma on a preliminary H&E report. Further these two stains were able to categorise the 9 out of the 13 cases of NSCLC NOS effectively into specific types.

Abbreviations: SCLC - small cell lung carcinoma NSCLC- Non-small cell lung carcinoma; NOS, not otherwise specified; LCNEC-Large cell neuroendocrine carcinoma IHC: Immunohistochemistry.

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1. Introduction

Recently there has been a lot of emphasis on differentiating SCC from adenocarcinoma due to the difference in the way they are managed with SCC having a higher resectability. P63 has been shown to be a sensitive marker for squamous cell carcinoma,¹ and TTF-1 to be a sensitive marker for adenocarcinoma.

According to WHO, In the case of the lung tumours showing ambiguous morphology a preliminary diagnosis

as NSCLC-NOS can be issued but needs to be confirmed with a panel of IHC markers.. It is suggested that only one squamous cell marker and one adenocarcinoma marker be used to diagnose the cases, as this leaves more tissue for molecular studies. TTF-1 is considered the marker to be used to identify adenocarcinomas and p63 is considered a reliable marker for squamous cell carcinoma along with p40. Cases positive for an adenocarcinoma marker with a negative squamous cell marker should be classified as NSCLC favor adenocarcinoma, and those that are positive for a squamous marker and negative for an adenocarcinoma marker should be classified as NSCLC favor squamous

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cell carcinoma. And most importantly, If a case is positive for TTF-1, it should be classified as NSCLC favor adenocarcinoma despite any expression of squamous cell markers.

2. Materials and Methods

A total of Forty (bronchoscopic and CT)-guided biopsies were taken from August 2012 to August 2014, at a tertiary health care centre, Bangalore

A positive result was defined as an unequivocal nuclear staining of at least 10% of the targeted tumor cells for both TTF-1 and p63, and cytoplasmic staining for the synaptophysin stain when used. The control used for TTF-1 was a follicular carcinoma of the thyroid. The control used for p63 was a skin biopsy

3. Results

The 2011 IASLC/ATS/ERS (International Association for the Study of Lung Cancers/ American Thoracic Society/ European Respiratory Society) for lung biopsy specimens was used to classify and diagnose the biopsies in both the H&E and IHC sections.²

Of the forty lung biopsies studied, the following was the distribution of cases following a preliminary diagnosis on H& E

Table 1: Distribution of cases following preliminary diagnosis on H&E

Cases	Number	Percentage
Small cell carcinoma	4	10%
Squamous cell carcinoma	3	7.5%
Adenocarcinoma	5	12.5%
NSCLC favor Squamous cell carcinoma	12	30%
NSCLC favor adenocarcinoma	2	5%
NSCLC NOS	13	32.5%
LCNEC	1	2.5%
Total	40	100%

The most common interpretation was NSCLC, NOS type. There were thirteen cases with this diagnosis which made a 32.5% of the cases. The second most common diagnosis was NSCLC favor squamous cell carcinoma with 12 cases amounting to 30% of the total. 5 cases were adenocarcinoma with a share of 12.5%, followed by small cell carcinomas with 4 cases (10%). Next was the diagnosis of squamous cell carcinoma with 3 cases (7.5%). There were 2 cases diagnosed as NSCLC favor adenocarcinoma this was 5% of the cases and last was a case of large cell neuroendocrine carcinoma which was 2.5% of the cases studied. Small cell carcinoma accounted for 4 (10%) of the cases and NSCLC (including all the groups that included non-small cell carcinomas) accounted for 33 (82.5%) cases and one case of LCNEC accounted for the remaining 2.5%.

Overall, a definitive diagnosis was offered for 13 cases out of 40 that is for 32.5% of the cases, a probable diagnosis(NSCLC favour SCC or Adeno) was offered for 14 out of the 40 cases that is 35% of the cases. But the remaining 13 cases that is 32.5% were diagnosed only as NSCLC NOS type because their morphology on H&E was not conclusive for a diagnosis for any particular subtype of NSCLC.

3.1. Results of the immunohistochemical study

Table 2: Distribution of cases diagnosed after IHC

Diagnosis	No of Cases	Percentage %
Small cell carcinoma (SCLC)	4	10%
Squamouscell carcinoma (SCC)	3	7.5%
Adenocarcinoma (ADC)	5	12.5%
NSCLC favor SCC	15	37.5%
NSCLC favor ADC	9	22.5%
NSCLC NOS	4	10%
Total	40	100%

There was a significant variation with the diagnosis following immunohistochemistry, specifically in the diagnosis of NSCLC NOS, which is the diagnosis that requires more clarity to start treatment. The number of cases of NSCLC NOS reduced to 4 (10%), from a massive 13 (32.5%) cases. The 9 cases from this group that got probable diagnosis following staining with TTF-1 and p63 were— 5 were diagnosed as NSCLC favor adenocarcinoma, 4 were diagnosed as NSCLC favor squamous cell carcinoma. Other changes in diagnosis was one case of NSCLC favor SCC was rediagnosed as NSCLC favor adenocarcinoma, because it was positive for TTF-1 and negative for p63, and the one case of LCNEC being rediagnosed as NSCLC favor adenocarcinoma as it was negative for both synaptophysin and p63, but positive for TTF-1.

To summarize the most important result from the IHC was the diagnoses that were derived from the previously grouped NSCLC NOS. There was a 22.5% reduction of cases from this group with 9 cases getting a more clear diagnosis. The remaining 4 cases in the NSLCL NOS group remained negative for both TTF-1 and p63 and could not be subclassified.

IHC staining of the histologically straightforward cases was: In the cases diagnosed as SCLC (4bcases), 2 expressed only TTF-1 the other two were negative for both TTF-1 and p63. All 4 cases were confirmed to be positive for synaptophysin. (Figure 3) Out of the 3 cases diagnosed as squamous cell carcinoma, all three stained only p63, they were all negative for TTF-1. Out of 5 cases diagnosed as adenocarcinoma, all 5 expressed only TTF-1 and were negative for p63.

There were 12 cases diagnosed as NSCLC favor SCC on H&E, in this group, 10 cases out of 12 (83.33%) expressed only p63, one case (8.33%) expressed only TTF-1, hence reclassified as adenocarcinoma, and the last one was negative for both p63 and TTF-1.

In the group diagnosed as NSCLC favor adenocarcinoma, there were two cases on H&E, both of which were positive only for TTF-1.

If we were to combine the groups of adenocarcinoma and NSCLC favor adenocarcinoma as diagnosed on H&E, we see that all 7 of them are positive exclusively for TTF-1.

If we were to combine the groups of SCC and NSCLC favor SCC, we have 15 cases out of which, 13 were positive for only p63, out of the 13, all three cases from the group of SCC were positive for p63. In the group NSCLC favor SCC, there was one case that was negative for p63 and positive only for TTF-1, this was rediagnosed as NSCLC favor adenocarcinoma.

Despite the use of both TTF-1 and p63, four of the cases did not express either of the markers. These cases remained diagnosed in the group of NSCLC NOS. Other data has shown that poorly differentiated cases sometimes do not take up either stains, in these instances, molecular testing is required to give a diagnosis with greater clarity.

There were 4 cases in this study diagnosed as small cell lung cancer (SCLC), they all strongly expressed synaptophysin which was used to confirm the diagnosis (Figure 3). Two of the cases expressed TTF-1, but none of the four expressed p63.

3.2. Overall analysis of the markers TTF-1 and P63

One of the major results from this study is that both the markers TTF-1 and p63 are mutually exclusive in the data studied. When one has taken up the stain the other has not. It has happened that both have been negative but both being positive in the same case has not been found in the data that has been analyzed in the 40 cases studied.

4. Discussion

In this study all the NSCLC cases account for 35 out of the 40 cases, that forms a percentage of 87.5%, which is in accordance with the worldwide average of 80% of all the lung carcinoma cases.³

In this study p63 stained 87% of the cases that were suspected to be squamous cell carcinoma and TTF-1 stained all the 7 cases (100%) suspected to be adenocarcinoma on a preliminary H&E report. This 100% staining may be due to the few number of cases - there were only 7 cases that were suspected to be adenocarcinomas on H&E.

Further these two stains were able to give more clarity to 9 out of the 13 diagnoses of NSCLC NOS that were made on H&E screening. This is a reduction of 22.5% in the cases of NSCLC NOS group.

In this study there were 7 cases of adenocarcinoma diagnosed on H&E, if we add the 2 groups of adenocarcinoma and NSCLC favor adenocarcinoma. All 7 were stained positively by TTF-1 which was a result of 100% positive stain for adenocarcinoma.(Table 3)

There were 4 cases of small cell lung cancer (SCLC), diagnosed in this study of 40 cases, this amounted to 10% of the cases. All 4 SCLC cases were positive for synaptophysin hence their diagnosis was confirmed. 2 out of the 4 cases were positive for TTF-1 and 2 were negative (50% positive). The SCLC cases were all negative for p63. In the study conducted by Hecht JL, Pinkus JL and Weinstein LJ,¹¹ out of the 4 cases they had only one case positive for TTF-1. Other studies showed 83% and 92% positivity in 52 and 12 cases of SCLC studied respectively

4.1. Comparison with other studies done with TTF-1 in squamous cell carcinoma of the lung

01 case out of the 15 cases expressed TTF-1(6.7%). When compared to studies done by Pelosi G, Fraggetta F, Pasini F, *et al*,⁴ Sturm N, Lantuejoul S, Laverriere MH *et al*,⁵ Hecht JL, Pinkus JL, Weinstein LJ.¹¹ Tan D, Li Q, Deeb G, *et al*.¹³ Our study was close to the studies of Pelosi G, Fraggetta F, Pasini F, *et al*⁴

4.2. Comparison studies done with p63 in squamous cell carcinoma (Table 5)

This study had a total of 15 cases diagnosed as squamous cell carcinoma on H&E if we were to consider both SCC and NSCLC favor SCC as one group, out of the 15 cases one was positive for TTF-1 the same case was also negative for p63 this is 1/15 cases (7%), but as it was p63 negative its diagnosis was changed to NSCLC favor adenocarcinoma as per the guidelines of the 2011 IASLC/ATS/ERS classification for lung biopsy specimens.²

P63 is one of the most important markers for squamous cell carcinoma. In this study of 40 cases, 12 were diagnosed as NSCLC favor SCC and 3 were diagnosed outright as SCC on H&E. Out of the 15 cases of squamous cell carcinoma, 13 cases were positive for p63. This is a percentage of 87% of the cases. This is comparable to two studies, one done by Kargi A, Gurel D, Tuna B,¹⁷ other study was done by Loo PS, Thomas SC, Nicolson MC, Fyfe MN, Kerr KM.¹⁸

P63 is a very important marker to differentiate poorly differentiated SCC and small cell lung cancer (SCLC) as they may look very much alike. In SCLC p63 is known to be negative whereas it stains positive for squamous cell carcinomas. The small cell variant in the WHO 2004 classification highlights this pitfall. In this study there were 4 cases of SCLC and none of the 4 were positive for p63 (0%). This correlates well with other studies done on larger sample sizes consistently giving the same result as shown in the Table 6.

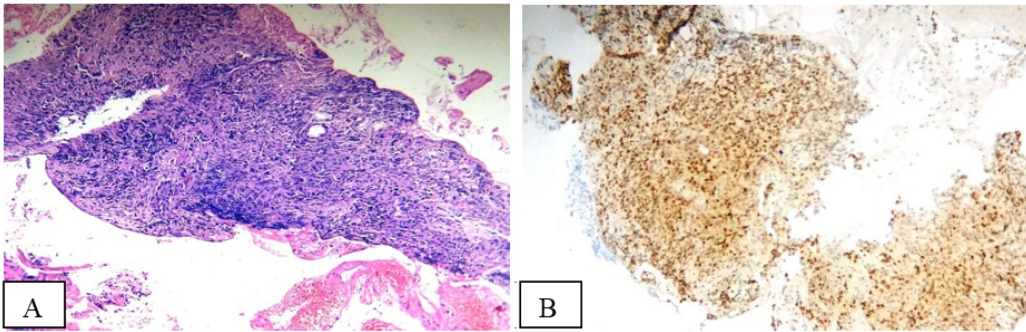


Fig. 1: NSCLC NOS. **A):** shows a poorly differentiated tumor; **B):** the case expressed p63 very strongly (p63 immunostain, X10)

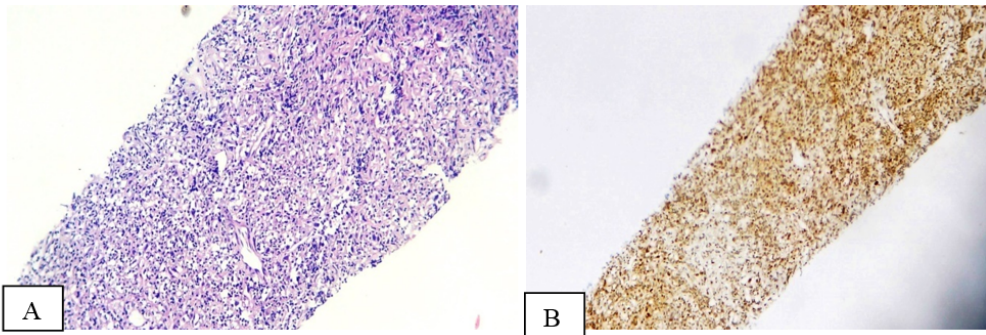


Fig. 2: **A):** NSCLC NOS, (X10); **B):** TTF-1 strongly positive (X10)

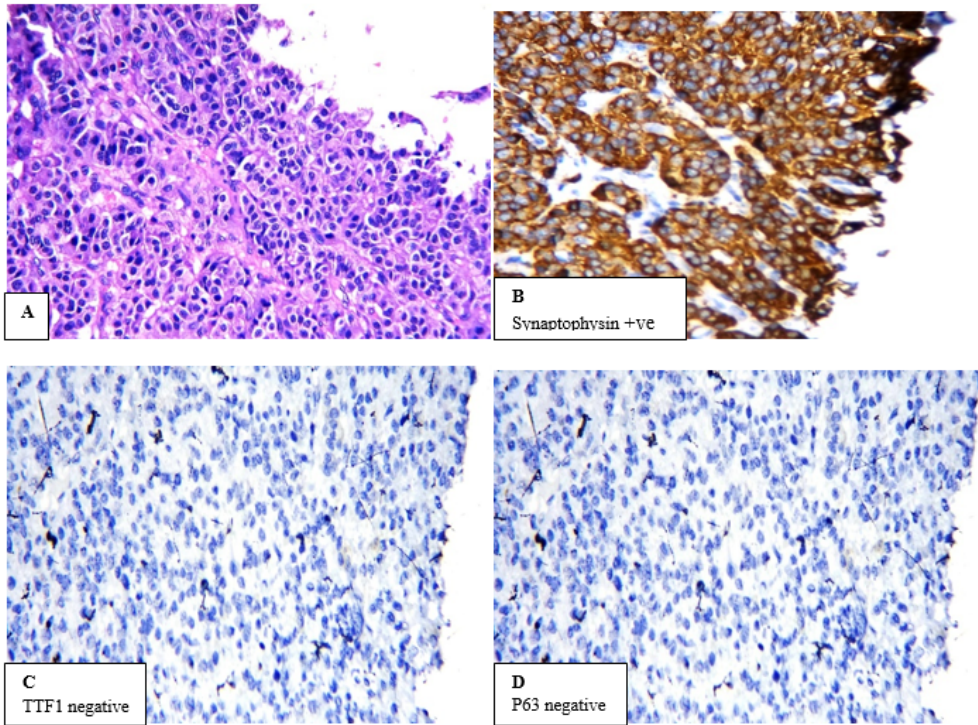


Fig. 3: Smallcell carcinoma, positive for synaptophysin, negative for both TTF-1 and p63

Table 3: Comparison with other studies done of TTF-1 in adenocarcinoma of the lung

	Tissue	Number of cases	Methods	Comments
Pelosi G, Frassetto F, Pasini F, <i>et al</i> ⁴	Lung adenocarcinomas	97	IHC	70 out of 97 (72%) cases of lung adenocarcinoma were positive for TTF-1
Sturm N, Lantuejoul S, Laverriere M, <i>et al</i> ⁵	Lung adenocarcinomas	26	IHC	23 out of 26 (88%) cases of lung adenocarcinoma were positive for TTF-1
Amin MB, Tamboli P, Merchant SH, <i>et al</i> . ⁶	Study of Micropapillary adenocarcinoma of the lung	15	IHC	12 out of 15 (80%) of the cases of micropapillary lung adenocarcinoma were positive for TTF-1
Stenhouse G, Fyfe N, King G, Chapman A, Kerr KM. ⁷	Pulmonary adenocarcinoma	128	IHC	110 out of 128 (86%) of the pulmonary adenocarcinoma were positive
Srodon M, Westra WH. ⁸	Brain metastases from lung primary	11	IHC	All 11 cases (100%) of metastatic lesions from a lung primary stained positive for TTF-1
Saad RS, Liu YL, Han H, Landreneau RJ, Silverman JF. ⁹	Pulmonary adenocarcinomas	50	IHC	37 out of the 50 cases (74%) of pulmonary adenocarcinomas stained positive for TTF-1
This study	Pulmonary adenocarcinomas	7	IHC	All 7 expressed TTF1 exclusively (100%)

Table 4: Comparison with other studies done for TTF-1 in small cell carcinoma of the lung

	Tissue	No of cases	Methods	Comments
Cheuk W, Kwan MY, Suster S, Chan JK. ¹⁰	Small cell carcinoma of the lung	52	IHC	43 out of the 52 cases (83%) of small cell carcinoma expressed TTF-1
Hecht JL, Pinkus JL, Weinstein LJ. ¹¹	Small cell carcinoma of the lung	4	IHC	1 out of the 4 cases (25%) of small cell carcinoma expressed TTF-1
Yatabe Y, Mitsudomi T, Takahashi T. ¹²	Small cell carcinoma of the lung	12	IHC	11 out of 12 cases (92%) of small cell carcinoma expressed TTF-1
Srodon M, Westra WH. ⁸	Brain metastasis of small cell carcinoma of the lung	7	IHC	6 of the 7 cases (86%) expressed TTF-1
This study	Small cell carcinoma of the lung	4	IHC	2 out of the 4 cases expressed TTF-1 (50%)

Table 5: Comparison studies of p63 in squamous cell carcinoma

Reference/	Tissue	No of cases	Methods	Comments
Wu M, Wang B, Gil J, <i>et al</i> . ¹⁴	Pulmonary squamous cell carcinoma	13	IHC	13 out of 13 cases (100%) of pulmonary SCC stained positive for p63 ^[130]
Zhang H, Liu J, Cagle PT, <i>et al</i> . ¹⁵	Pulmonary squamous cell carcinoma	28	IHC	28 out of 28 cases (100%) of pulmonary SCC stained positive for p63
Kalhor N, Zander DS, Liu J. ¹⁶	Pulmonary squamous cell carcinoma	13	IHC	13 out of 13 cases (100%) of pulmonary SCC expressed p63
Kargi A, Gurel D, Tuna B. ¹⁷	Pulmonary squamous cell carcinoma	39	IHC	32 out of the 39 cases (82%) of pulmonary SCC expressed p63
Loo PS, Thomas SC, Nicolson MC, Fyfe MN, Kerr KM. ¹⁸	Pulmonary squamous cell carcinoma	23	IHC	21 out of the 23 cases (91%) of pulmonary SCC expressed p63
Wu M, Szporn AH, Zhang D, <i>et al</i> . ¹⁹	Pulmonary squamous cell carcinoma	4	IHC	All 4 cases (100%) of pulmonary SCC expressed p63
This study	Pulmonary squamous cell carcinoma	15	IHC	13 out of the 15 cases expressed the p63 marker (87%).

Table 6: Comparison with other studies done with p63 and small cell carcinoma

	Tissue	Number of cases	Methods	Comments
Wu M, Wang B, Gil J, <i>et al.</i> ¹⁴	Pulmonary smallcell carcinoma	23	IHC	None of the 23 cases (0%) of pulmonary small cell carcinoma stained positive for p63
Zhang H, Liu J, Cagle PT, <i>et al.</i> ¹⁵	Pulmonary smallcell carcinoma	28	IHC	None of the 28 cases (0%) of pulmonary small cell carcinoma stained positive for p63
Kalhor N, Zander DS, Liu J. ¹⁶	Pulmonary smallcell carcinoma	13	IHC	None of the 13 cases (0%) of pulmonary small cell carcinoma stained positive for p63
Wu M, Szporn AH, Zhang D, <i>et al.</i> ¹⁹	Pulmonary smallcell carcinoma	16	IHC	None of the 16 cases (0%) of pulmonary small cell carcinoma stained positive for p63
Kargi A, Gurel D, Tuna B. ¹⁷	Pulmonary smallcell carcinoma	28	IHC	None of the 28 cases (0%) of pulmonary small cell carcinoma stained positive for p63
This study	Pulmonary smallcell carcinoma	4	IHC	None of the 4 cases expressed the p63 marker (0%).

4.3. P63 and adenocarcinoma

Out of the 7 cases of adenocarcinoma, none (0%) of them were positive for p63. The marker p63 is seen to be consistently negative in many of the studies conducted like the study conducted by Shtilbans V, Szporn AH, Wu M, Burstein DE.²⁰

5. Conclusion

To conclude the immunohistochemical study of lung biopsies is a descriptive study carried out in the department of pathology at a tertiary health care centre, Bangalore, between August 2012 to August 2014. A total of 40 biopsies were studied.

The preliminary results with H&E : 12 cases had a definitive diagnosis, as follows:

4(10%) were small cell lung cancer (SCLC), 3(7.5%) were squamous cell carcinoma (SCC), 5 (12%)were adenocarcinoma (ADC),

14 cases had a probable diagnosis as follows: 12 were diagnosed as NSCLC favor squamous cell carcinoma, 2 were diagnosed as NSCLC favor adenocarcinoma,

13 cases had no clear morphology on Hand E, Which were diagnosed as NSCLC NOS, and 01 case was LCNEC.

Following the Immunohistochemical analysis the final diagnosis was very different, The 12 definitive cases were confirmed and remained the same with 4 cases (10%) of SCLC, 3 cases (7.5%) of SCC, 5 cases of adenocarcinoma,

The NOS /Probable diagnosis group: 15 cases diagnosed as NSCLC favor SCC, 9 cases were diagnosed as NSCLC favor adenocarcinoma and 4 remained as NSCLC NOS. There was a significant reduction in the number of cases diagnosed as NSCLC NOS. This is important

because treatment for SCC and ADC differ vastly. Another important finding was p63 not staining small cell carcinomas, this helps to distinguish between NSCLC and SCLC given the existence of the poorly differentiated, small cell variant of squamous cell carcinoma.

In this study it was found that TTF-1 was very specific for adenocarcinomas. It was also found that p63 did not stain any case suspected to be an adenocarcinoma. P63 was found to be very specific for SCC, staining 13 out of the 15 cases (87%).

4 cases of SCLC were also stained positive by synaptophysin; this is 100% of the cases.

So both markers TTF-1 and p63 work well together to give us very important and reliable data so help us get a very important conclusive diagnosis. These two markers proved very helpful in diagnosing the cases of lung cancer with certainty. The biopsy material is often very limited, so only a few markers can be used as opposed to resection specimens where a number of sections can be taken. So using the correct markers is very important.

Therefore this study gives additional proof to the reliability and necessity of using these two makers in the diagnosis of a lung carcinoma on a biopsy, considering the limited tissue available.

6. Summary

P63 was found to be highly specific for SCC, with 13 out of the 15 cases expressing it, TTF-1 was found to be highly specific for adenocarcinoma staining all the 7 cases suspected to be adenocarcinoma. In particular there were 13 cases diagnosed as NSCLC NOS on H&E, out of the 13 cases, 9 of them were given significantly better clarity in their diagnosis following IHC, they were diagnosed favoring

adenocarcinoma or SCC. 4 of the cases did not take up either of the markers so they remained as NSCLC NOS. The number of cases in this category reduced from 32.5% to 10%, which is a reduction of 22.5%. This is important because the treatment for SCC and adenocarcinoma is very different, and both these entities behave very differently.

Both p63 and TTF-1 have been found to be an invaluable part of the diagnostic process for a lung biopsy.

7. Source of interest

None.

8. Conflict of interest

None.

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Cite this article: Vidya K , Saraf S. IHC–The need of the hour in classifying lung tumours effectively on guided biopsies!. *Indian J Pathol Oncol* 2019;6(4):615–621.