Immunohistochemistry of Cytokeratin 7, Cytokeratin 20 and Thyroid Transcription Factor-1 in Metastatic Carcinoma of Cervical Lymph Node Biopsy for Identification of Pulmonary Origin in Rajavithi Hospital

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Background: *One of the most powerful tools used in "the team approach in modern medicine" is immunohistochemistry, a minimally invasive investigative technique which is helpful in many respects, such as in suggesting or defining the primary site of metastatic malignant neoplasms. The panel of Cytokeratin7 (CK7), Cytokeratin20 (CK20) and Thyroid Transcription Factor-1 (TTF-1) is one of the most frequently used, and this study examined expressions of this panel in Rajavithi Hospital in order to assess their significance.*

Objective: *To study the expression of CK7, CK20 and TTF-1 in metastatic carcinoma in neck node biopsy found in the Rajavithi Hospital database, and to assess their effectiveness in identifying pulmonary origin.*

Material and Method: *The Rajavithi Hospital database was searched for all cases of lymph node biopsy in the neck and supraclavicular area for which the pathological diagnosis was metastatic carcinoma. Expressions of CK7, CK20 and TTF-1 were analyzed to measure their sensitivity, specificity, positive predictive values, and negative predictive values.*

Results: *Average age of the subjects, of whom 56.9% were male, was 61.35$\pm$12.9 years. Lung (51.2%), breast (7.3%) and gastrointestinal tract (6.5%) were the three most common organ site origins, and the most common cell type was adenocarcinoma. Expressions are shown in terms of sensitivity (98.4%), specificity (95.0%), positive predictive value (95.4%), negative predictive value (98.3%) and others. The most reliable antibody for identification of pulmonary origin was TTF-1.*

Conclusion: *The immunohistochemistry panel of CK7, CK20 and TTF-1 in the Rajavithi Hospital database is useful as a guide in locating the origin of clinically unknown primary cases of metastatic cervical lymph nodes.*

Keywords: *Immunohistochemistry, Pulmonary origin, CK7, CK20, TTF-1, Rajavithi*

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Before deciding on the medical approach towards treatment of neck mass for which the pathological report is metastatic carcinoma, the most vital information required is the location of the primary site of the neoplasm. Immunohistochemistry (IHC) is a non-invasive investigative technique which can be performed with paraffin block. Pulmonary origin is one of the differential diagnoses, and IHC of a combination of Cytokeratin 7 (CK7), Cytokeratin 20 (CK20) and Thyroid Transcription Factor-1 (TTF-1) is the panel of choice for identifying pulmonary source of cancer. This study examined IHC expressions of CK7, CK20 and TTF-1 of cervical lymph node biopsy specimens in Rajavithi Hospital.

There have been reports of the high specificity and sensitivity of Cytokeratin and TTF-1 for the primary pulmonary system[1-16]. IHC is most effective in differential diagnosis of adenocarcinoma cell types[5,10] and primary or secondary neoplasms[2]. TTF-1 expression shows high specificity for primary lung neoplasms of typical and atypical carcinoids, especially those of peripheral location[1]. TTF-1 also reveals whether or not the metastatic neuroendocrine tumor (NET) originates from the pulmonary system[1-16]. In general, the NET from various primary sites will have similar histopathology findings.

In addition to the use of tissue biopsy specimens, there have been reports of high specificity and sensitivity in detecting metastatic lung cancer using specimens from cytology, effusion body fluids[3,8,9,12],

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and fine-needle aspiration biopsy (FNAB)[11].

TTF-1 is also useful in differential diagnosis of lung cancer and malignant mesothelioma[7]. Cytokeratin and TTF-1 can suggest the pulmonary origin of brain tumor[15] and secondary carcinoma in lymph nodes[14] and is a helpful tool in cases where the primary site of origin is unknown.

In the literature review, there has been no study of the expression of these IHC tests in Rajavithi Hospital or Thailand, and this information could be important for guidance of local practice of this global concept.

Material and Method

Cases were included of cervical and supraclavicular lymph node biopsy in the Rajavithi Hospital database for which the pathological reports were metastatic carcinoma. Cases without CK7, CK20 and TTF-1 tests were excluded. For subjects who met the inclusion criteria, the origin of their neoplasms were identified from specimens taken and from medical records.

Results

In the hospital-based population in this study, the mean age was 61.35±12.90 years old, range 12-87 years, and 56.9% of the subjects were male. The majority of subjects worked as contractors (41.5%), household workers (35.8%) or farmers (7.3%), and most were alive (83.7%). Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics (n=123)

	Number	Percent
Age (years)		
Mean±SD (min-max)	61.35±12.90 (20-87)	
Gender		
Male	70	56.9
Female	53	43.1
Occupation		
Government officer	5	4.1
Business	8	6.5
Household	44	35.8
Contractor	51	41.5
Farmer	9	7.3
Monk	4	3.3
Others	2	1.6
Status		
Alive	103	83.7
Dead	20	16.3

The origin, morphology and topology of the subjects are presented in Table 2. The lung was the most commonly found organ site (51.2%), followed by the breast (7.3%) and GI tract (6.5%). However, it was found that in 14.6 percent of cases, the organ of origin could not be determined. Metastatic adenocarcinoma was the most frequently observed morphology (72.4%), and pulmonary adenocarcinoma was the cell type of lung cancer which benefitted most from the studied panel[2-10]. All lymph nodes were of the neck, and more than half of these were supraclavicular lymph nodes (52.0%).

Markers for metastatic carcinoma included CK7, CK20 and TTF-1. These markers have a high sensitivity and specificity in diagnostic testing of cancers which originate in the lung**,** as shown in Table 3. The most reliable antibody for identifying pulmonary origin was TTF-1 which showed high sensitivity (98.4%) and accuracy (96.7%), and these results are consistent with the findings of almost all previous studies[1-16]. A combination of two markers, CK7 (+) and TTF1 (+), had the highest sensitivity (98.4%) of combinations used.

Table 2. Origin, Morphology and Topography (n = 123)

	Frequency	Percent
Origin		
Lung	63	51.2
Breast	9	7.3
GI tract	8	6.5
Pancreatobiliary	6	4.9
Ovary	5	4.1
Head &neck	4	3.3
Liver	4	3.3
Thyroid	4	3.3
Stomach	4	3.3
Bile duct	1	0.8
Extranodal	1	0.8
Fibrous tissue	1	0.8
Prostate	1	0.8
Breast	1	0.8
Pancreas	1	0.8
Indeterminate	18	14.6
Morphology		
Metastatic carcinoma	31	25.2
Metastatic squamous cell CA	3	2.4
Metastatic adenocarcinoma	89	72.4
Topography		
Cervical lymph node	59	48.0
Supraclavicular lymph node	64	52.0

Table 3. Diagnostic test of cancer from lung origin (n=123)

Antibodies	Origin		Sen (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
	Lung	Not Lung					
CK7							
Pos (Lung)	63	52	100.0	13.3	54.8	100.0	57.7
Neg (Not Lung)	0	8					
CK20							
Neg (Lung)	56	34	88.9	43.3	62.2	78.8	66.7
Post (Not Lung)	7	26					
TTF1							
Pos (Lung)	62	3	98.4	95.0	95.4	98.3	96.7
Neg (Not Lung)	1	57					
CK7(Pos)CK20 (Neg)							
(Lung)	56	28	88.9	53.3	66.7	82.1	71.5
(Not Lung)	7	32					
CK20(Neg)TTF1(Pos)							
(Lung)	55	1	87.3	98.3	98.2	88.1	92.7
(Not Lung)	8	59					
CK7(Pos)TTF1							
(Lung)	62	2	98.4	96.7	96.9	98.3	97.6
(Not Lung)	1	58					
CK7(Pos)/CK20(Neg)/TTF1(Pos)							
Pos (Lung)	63	31	100.0	48.3	67.0	100.0	74.8
Neg (Not Lung)	0	29					

Discussion

Table 1 shows the baseline characteristics of the subjects studied, and their data is typical of Rajavithi Hospital patients who present with neck mass, so, the results may be applied to other Rajavithi Hospital patients.

Almost half of the involved organs of origin in table 2 are, interestingly, non-lung. Therefore, the data group shows no selection bias for any organ origin. The number of cases by cell type is in keeping with the usual incidence of lung cancer. The studied metastatic carcinoma cases were nodes of the neck area.

The expression of CK7, CK20 and TTF-1 in Rajavithi Hospital is shown in table 3. The most reliable antibody for pulmonary origin was TTF-1 (98.4% sensitivity and 95% specificity). The sensitivity of TTF-1 in lung adenocarcinoma in other reported series ranged from 57.5% to 76%. Jorge S. Reis-Filho et al., found that TIF-1 was a highly specific marker for primary lung adenocarcinomas with sensitivity of 61.53% and specificity of 100%[2], while the present study yielded a sensitivity higher than that found by those authors. A combination of CK7 and TTF-1 is particularly useful for diagnostic testing of cancer originating from the lung because CK7 and TTF expression are significantly more frequent in adenocarcinomas of primary lung, pulmonary and breast origin than in those of gastrointestinal (GI) origin[17].

In daily practice, the panel of these three antibodies may be useful in the case of unknown primary site, especially in non-lung cases where integrated results can suggest their histogenesis. Our results concerning TTF-1 and cytokeratin expression in lung tumors are in agreement with other reports in the literature[4,11,12,14].

In concordance with Jerome Marson V et al[4] this study found Cytokeratin and TTF-1 expression to be correlated with the histological type and grade of lung tumors, and Yatabe Y, found that TTF-I was a good marker for proving or excluding the possibility of lung origin of adenocarcinomas[10].

Conclusion

The results of this study of expressions of the panel of CK7, CK20 and TTF-1 in Rajavithi Hospital are consistent with almost all studies in the international literature and confirm the appropriateness of past and

present approaches and practices.

What is already known on this topic?

Panels of Cytokeratin and TTF-1 are useful in detecting pulmonary origin in many kinds of specimen, yielding high specificity and sensitivity.

What this study adds?

The results of this study in Rajavithi Hospital are compatible with the data in the literature concerning tissue specimens of neck nodes. Thus, the effectiveness of the past and present approaches and practice is evident and useful in guiding further management.

Potential conflicts of interest

None.

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ผลอิมมูโนฮีสโตเคมิสตรีของ Cytokeratin 7, Cytokeratin 20 Thyroid Transcription Factor-1 ในชิ้นเนื้อไบออปซี่ต่อมน้ำเหลืองที่คอที่มีการแพร่กระจายของมะเร็งชนิด Carcinoma

ฐิติ กวักเพชรย์

ภูมิหลัง: หนึ่งในความสำคัญของการดูแลผู้ป่วยเป็นคณะทำงานในการแพทย์สมัยใหม่ คือ การใช้อิมมูโนฮีสโตเคมิสตรี ซึ่งเป็นการตรวจเพิ่มที่ไม่ลุกล้ำร่างกายผู้ป่วยเพิ่มเติม ซึ่งใช้ได้ในหลายกรณี กรณีหนึ่งเช่น ใช้เพื่อหาปฐมภูมิของมะเร็ง ซึ่งในบริบทนี้ ชุดการทดสอบของ Cytokeratin 7 (CK7), Cytokeratin 20 (CK20) และ Thyroid Transcription Factor-1 (TTF-1) เป็นชุด (panel) ที่นิยมใช้กันมากที่สุดชุดหนึ่ง จึงได้ศึกษาผลอิมมูโนฮีสโตเคมิสตรีของทั้งสามแอนติ้บอดี้ในสิ่งส่งตรวจของโรงพยาบาลราชวิถีเพื่อดูนัยสำคัญของผลการศึกษา

วัตถุประสงค์: เพื่อศึกษา expression ของ CK7, CK20 และ TTF-1 ในไบออปซี่ต่อมน้ำเหลืองที่คอที่มีการแพร่กระจายของมะเร็งชนิด Carcinoma ของโรงพยาบาลราชวิถี

วัสดุและวิธีการ: รวบรวมไบออปซี่ต่อมน้ำเหลืองที่คอของโรงพยาบาลราชวิถี ทุกรายที่มีการแพร่กระจายของมะเร็งชนิด Carcinoma และคัดเฉพาะรายที่มีการส่งตรวจ CK7, CK20 and TTF-1 ด้วยเพื่อนำมาวิเคราะห์ต่อไป

ผลการศึกษา: อายุเฉลี่ยกลุ่มตัวอย่างคือ 61.35±12.9 ปี เป็นเพศชาย 56.9% อวัยวะต้นกำเนิดสามอันดับแรก คือ ปอด (51.2%) เต้านม (7.3%) และทางเดินอาหาร (6.5%) และชนิดของมะเร็งที่มากที่สุดในการศึกษานี้ คือ ชนิด adenocarcinoma ผลการศึกษาและการวิเคราะห์ถึงความไว (98.4%) ความเฉพาะเจาะจง (95.0%) positive predictive value (95.4%), negative predictive value (98.3%) และอื่น ๆ โดยได้แสดงในตารางซึ่งพบว่า TTF-1 จะดีที่สุดในการบ่งชี้มะเร็งปฐมภูมิ จากปอด

สรุป: ชุดอิมมูโนฮีสโตเคมิสตรี (CK7, CK20 and TTF-1) ในโรงพยาบาลราชวิถีมีประโยชน์ในการบ่งชี้แหล่งกำเนิดมะเร็งปฐมภูมิของมะเร็งที่กระจายมาที่ต่อมน้ำเหลืองที่คอซึ่ง TTF-1 จะดีที่สุดทั้ง sensitivity และ specificity