Clinics of Surgery

Case Report ISSN 2638-1451 | Volume 6

Elevated STK1p After the Second-Cycle-Chemotherapy Associated with Failure Poor Survival in I-II Stage of NSCLCs- Three Cases Reports

Zhenxin Wang[1], Guoqing Zhang[2], Jin Li[3], Hongbo Ma[3], Ji Zhou[3], Ellen He[3*] and Sven Skog[3]

[1]Department of Oncology, Affiliated Hospital of Suzhou University, Shizi Street 188, Gusu District, Suzhou, China

[2]Department of Oncology, Peking 301 Chinese PLA General Hospital, Fuxing Road 28, Haidian District, Beijing 100853, China

[3]Department of Medicine, Shenzhen Ellen-Sven Precision Medicine Institute, Shenzhen 518057, China

[*]Corresponding authors:

Ellen He (PhD),
Shenzhen Ellen-Sven Precision Medicine Institute,
A301, Bldg.1, 2nd Yinxingzhijie, 1301-76 Guanguang Road, Longhua District, Shenzhen, China,
Tel:+46 739643657; E-mail: ellen.he@sstkmed.org

Received: 20 Oct 2021
Accepted: 06 Nov 2021
Published: 15 Dec 2021
J Short Name: COS

Keywords:

Serum thymidine kinase 1 protein concentration (STK1p); Non-small-cell lung carcinoma (NSCLCs); Serum thymidine kinase 1 protein (STK1p); Response Evaluation Criteria in Solid Tumors (RECST); Stable disease (SD)

Citation:

Ellen He. Elevated STK1p After the Second-Cycle-Chemotherapy Associated with Failure Poor Survival in I-II Stage of NSCLCs- Three Cases Reports. Clin Surg. 2021; 6(10): 1-6

1. Abstract

1.1. Aims: Thymidine Kinase 1(TK1) is a precision protein molecular target for assessment of tumor proliferating rate. This investigation of 3 cases is whether the elevated STK1p after the 2-cycle -chemotherapy is associated with failure poor survival of clinical stage I-II in Non-Small-Cell Lung Carcinomas (NSCLCs).

1.2. Main Methods: The 3 post- operative NSCLCs with clinical stage I-II were confirmed by pathology and followed by individual chemotherapy. The Serum Thymidine Kinase 1 protein (STK1p) was measured using the ECL dot blot assay.

1.3. Results: Although the 3 cases are of early clinical stage I-II, an increasing STK1p following by the second cycle of chemotherapy was observed. The elevated STK1p appeared 3-17 months early as compared the tumor metastasis by CT, and the Response Evaluation Criteria in Solid Tumors was evaluated as stable disease. The 3 patients died due to the failure poor survival.

1.4. Significance: The post-radical resection following by 2 cycle-chemotherapy is important critical-point time to measure STK1p if the value is increasing or decline. The elevated STK1p values can predict an earlier risk of tumor metastasis process than imaging. It can supply a strong advance advice to adapt a new individual treatment for a better prognosis in the NSCLCs in routing clinical setting.

2. Introduction

Lung cancer is the top cause of mortality of both men and women in the world globally, the Non-Small-Cell Lung Cancer (NSCLC) as the most prevalent form [1]. According to the latest annual report of cancer registration in China, in 2015, the number of lung cancer patients was about 733.3/100,000, and the death toll was 610.2/100,000. In addition, lung cancer patients are basically diagnosed late, with an average of 5 years survival rate of ≈15% [2]. Currently, the clinical diagnosis of lung cancer mainly relies on chest X-ray, low dose Computed Tomography (CT) scans for diagnostic lung cancer. The lung cancer screening with LDCT showed a successful performance and can be benefit to reduce the high false positive results [3].

A series of serum-biomarker are available for lung diseases. The Carcinoembryonic Antigen (CEA) and cytokeratin 19 fragment (CYFRA21) are for routing biomarkers of lung cancer. The ROC curve analyses showed combination CEA + CA125, or combination CEA + CY211, are effective for suitable markers for lung cancer screening [4]. However, such combination still not use for the detection of early lung cancer due to low sensitivity and specificity [5] being to the CEA or AFP, such tumor-related biomarker did not directly correlation with tumor proliferating [6, 7, 8]. Therefore, the real promising candidates of biomarkers for early lung cancer screening remain a critical step in the challenging field.

Thymidine Kinase 1 (TK1) was discovered in 1950s. The TK1 is one of salvage enzymes that converts deoxythymidine (dTdR) to deoxythymidine monophosphate (dTMP) and its expression in proliferating cells is closely related to cell cycle, low in G_1 phase, increases in S/G_2 phase and decreases in late G_2/M phase was discovered in 1950s. Therefore, TK1 was as a precision protein molecular target for assessment of tumor proliferating rate [9]. The concentration of Serum Thymidine Kinase (STK1p) in malignant tumor cells is proportional to cell proliferation rate [10-11]. In normal human serum, the STK1p is almost undetectable [12-14]. Based on an enhanced chemiluminescent dot blot assay (Sino-Swed Tongkang Bio-Tech, Inc., Shenzhen, China, www.sstkbiotech.com), the STK1p could be an usful tool in *precise medicine* for prognosis of pre- and malignant cancer, both in oncology clinics and in health screening [9]. The STK1p increased significantly with T-values and with clinical stage and invasiveness. A meta-analysis [15] study on STK1p in early/middle stage of lung carcinoma patients (n=2, 107) showed that the expressions of STK1p increased significantly in the following manner: healthy control group (n=1,694) < benign group (n=272) < carcinoma group (n=1298) ($p<0.00001$), indicating that the half-life of STK1p can monitor the response to the surgery in lung cancer patients, and STK1p could be also used for early detection and distinguish between benign and malignant tumours [15]. Previous reported that STK1p can be used as a reliable factor for prognosis, survival and recurrence in breast cancers [16, 17]. The multivariate COX analysis showed that the STK1p was an independent prognostic factor [16]. A prospective study of local advanced breast cancer patients with neo-adjuvant treatment showed that high STK1p values were positive correlated to clinical stage, tumor size, recurrence and survival [17]. The STK1p can also be used as a prognostic factor of chemotherapy-treated non-Hodgkin's lymphoma patients [18]. The TK1-activity assay (DiviTum, Biovica, Sweden) indicated that the elevated serum TK activity was an independent prognostic factor for survivals of lung cancer. It was found that an increase in TK-activity after the first and second cycle of chemotherapy was significantly associated with treatment failure and poor overall survival [19]. An recently investigation in 127 NSCLCs following a nonrandomized individual adapted treatment demonstrated that low STK1p value correlated significantly to favorable survival in early-middle-stage (I–IIIA) NSCLCs and the COX multi-variate analysis showed that STK1p was an independent prognostic biomarker [5]. A series of literature reviewed that the low score STK1p correlated significantly to favorable survival in early-/middle-stage (I–IIIA) of NSCLCs. In this 3 cases report that we further investigated whether the elevated STK1p after the 2-cycle -chemotherapy associated with failure poor survival of clinical stage I-II in Non-Small-Cell Lung Carcinomas (NSCLCs).

3. Three Cases with Clinical Stage I-II and Died of Long-Term Ineffective Chemotherapy

Based on the ROC analysis, an optimal cut-off STK1p value was set to 0.6 pM after 2-cycle-chemotherapy of NSCLCs and divided into two groups: low STK1p (≤0.6 pM) and elevated STK1p (≥0.6 pM) [5]. The STK1p assay was performed on a commercial kit of Enhanced Chemiluminescence (ECL) dot blot assay to measure the concentration of STK1p as described by Sino-Swed Tong Kang Bio-Tech, Inc., Shenzhen, China (http://www.sstkbiotech.com). The serum samples were taken on the day one-month post-operative or before chemo-treatment and after 2-cycle-chemo-treatment patients. The serum samples were stored at -20˚C until analysis. The STK1p values were at least twice a quality duplicate detection.

3.1. Case 1

A woman with 53 years the patient had no family history of hereditary tumor diseases and personal history of other tumor diseases.

1. Discovery of lung cancer: She had multiple small nodules in right middle lung irregularly by CT examination and then Radical Resection (RR) of upper right lung cancer in 2015-05-04. A histopathological examination was evaluated as NSCLC (mucinous adenocarcinoma, clinical stage IA, tumor size 2.8*3.8. and grade G2). The STK1p was 0.27 pM one month after RR.

2. Chemotherapy: The chemotherapy was carried out using Buck Jane (0.7 mg)+Carboplatin (0.45 mg). However, the STK1 increased to 0.82 pM after 2-cycle-post-chemotherapy, and RECIST (Response Evaluation Criteria in Solid Tumors) was evaluated as Stable Disease (SD). The CT examination showed that the multiple small asymptomatic malignant lung nodules expanded to in both lungs on 2016/01/26.

3. Chemotherapy continually: An 8 cycles of Dopafi (100mg) in 2016/02/05-2016/ 08/04. In the meantime, the CT examination showed that the multiple small asymptomatic malignant lung nodules in both lungs and slightly larger in 2016-07-06 and 26-12-2016. The Dr. considered the tumor in metastasis.

4. She died 20 months after the continually ineffective treatment. The total time of follow up was 37 months (Figure 1A).

3.2. Case 2

A Man of 78 years the patient had no family history of hereditary tumor diseases and personal history of other tumor diseases.

1. Discovery of lung cancer: He had a right upper adenocarcinoma lung cancer under thoracoscopy by CT examination in 2016-05-29, and RR of upper right lung cancer was performed. Pathology confirmed as NSCLC, clinical stage IIA, tumor size was of 5.5*2 cm and grade G3. The STK1p was 0.1 pM one month after RR.

2. Maintenance therapy: His Dr. used the maintenance therapy with praline plus carboplatin according to the patient individual's physical condition. The STK1p was aggressively increased to 5.29 pM and RECIST was assessed as SD two months after 2-cycle-post-chemotherapy.

3. The maintenance therapy continued from 2016-07-29 to 2018-09-22. The CT examination on 07-12-2017 found that the tumor was metastasizing to hydrothorax (partially encapsulated) and on both sides of the chest and fibrous lesions in the left upper lung, and also observed the liver cysts and left lateral adrenal branch hyperplasia.

4. The patient died 14 months after the ineffective chemotherapy. The total time of follow up was 31 months (Figure 1B).

3.3. Case 3

A Man of 78 years the patient had no family history of hereditary tumor diseases and personal history of other tumor diseases.

1. Neo-chemotherapy: CT examination found that he had left upper lobe lung cancer, clinical stage IB, tumor size was of 3.5*3.0*1.5 cm. The pathology was diagnosed as NSCLC and grade G3. The first, a neo-chemotherapy with Lipitin 270 mg+nedaplatin 120mg, 6 cycles were used in 2013-05-21 to 2013-10-22. It found no nodules in the left upper lobe.

2. Radical Resection (RR): Unfortunately, the patient had a lower right lung cancer and was seen by CT in 2013-12-30. The RR of lower right lung cancer was done on 2014-08-01; The post-operative STK1p value was litter high (0.88 pM) one month after RR as compared to the cut off STK1p value (0.6 pM).

3. Chemotherapy: Of 3 cycles with Dopafi 120 mg + carboplatin 0.4 mg was performed in 2014-11-26 to 2015-01-27. The STK1p was of 0.93 pM, no decline, and the RECIST was evaluated as SD after the 2 cycle- chemotherapy. The PET-CT examination in 2015-02-26 showed that the third and fourth posterior ribs were destroyed and the local pleura was thickened and accompanied with increasing glucose metabolism. It is considered a tumor in metastasizing.

4. Chemotherapies arranged

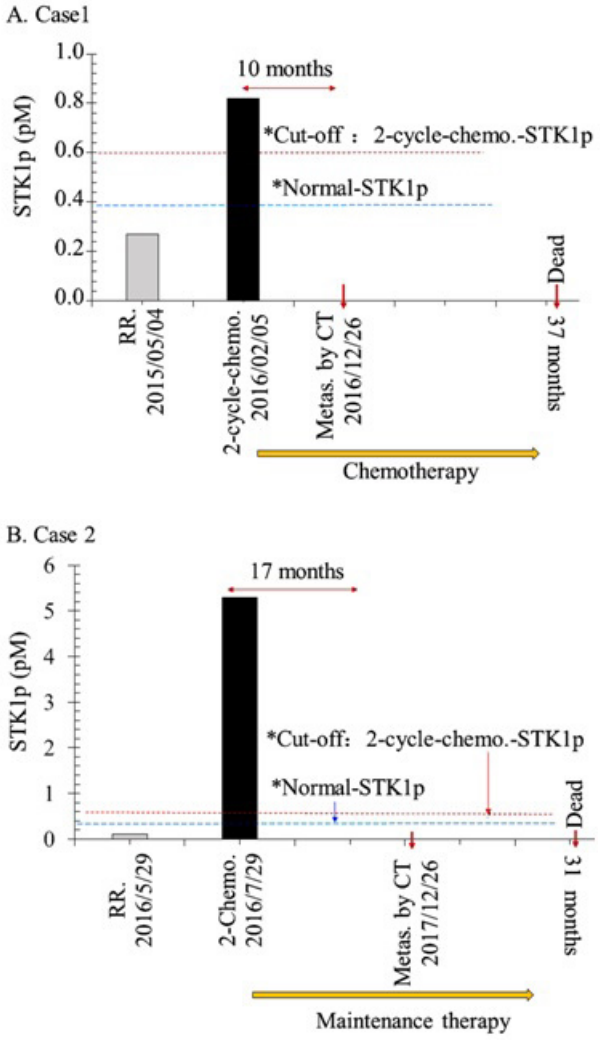
1. Two cycles of gemcitabine 1.6 d1,8, in 2015-03-03 to 2015-05-03.

2. Two cycles of gemcitabine 1.4d1, 8+ nedaplatin 100mg in 2016-03-26 to 2016-05-03. The CT examination observed tumor metastasis in 2016-03-10, including the multiple asymptomatic malignant lung nodules, multiple right ribs and thoracic vertebrae.

5. Continued chemotherapy

1. Two cycles with vinorn 40mg d1, 30mg d5 + vinorn 100mg was done in 2016-06-01 to 2016-07-23.

2. The patient died 15 months after the long-term ineffective treatment. The total time of follow up was 59 months (Figure 1C).



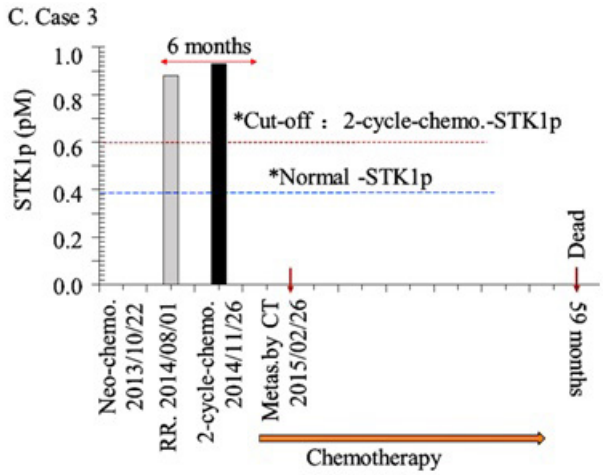


Figure 1. The elevated STK1p after the second cycle of chemotherapy associated with poor survival in 3 NSCLCs. *2-cycle-chemo-STK1p: The optimal cut-off STK1p value was set to 0.6 pM post-2-cycle chemotherapy of NSCLCs [5]; *Normal-STK1p: The Normal-STK1p values were excluded all tumor diseases, moderate/severe proliferative diseases, virus-infectious, severe inflammation diseases, also including the obese, un-normal values of blood, urea or fecal, it may contain some proliferating/chronic diseases in relation with the tumor diseases. The mean and median STK1p values of 0.36-0.38 and 0.37-38 pM, respectively [9, 20].

4. Discussion

A recent investigation explored that the beginning 2 cycles of chemotherapy treatment were an effective time point. The cut off of STK1p (0.6 pM) is a useful monitoring factor to assess the prognosis of NSCLCs [5].

In this case study, an elevated STK1p was detected after the 2-cycle-chemotherapy (STK1p=0.82 pM) as compared to the cut off of STK1p value (0.6 pM) (Figure 1A). The STK1p presented early 10 months as compared to the tumor metastasis by CT. In case 2, the STK1p was intensively increased to 5.29 pM after the 2-cycle-chemotherapy, it was 17 months early as compared CT (Figure 1B). In case 3, the post-operative STK1p value was already littered high (0.88 pM) and did not decline after the 2-cycle-chemotherapy (STK1p=0.93 pM) (Figure 1C), the elevated STK1p appeared 3 months early as compared to the tumor metastasis by CT. All 3 cases were assessed as SD score after the 2-cycle-chemotherapy, which implied that RR+ Individual chemotherapy did not effective and the continued chemotherapy did not give the patent any benefit.

Previous studies published on the prognosis of breast cancer patients proved that STK1p level increased 3 [16] to18 months [17] early than the discovery of visible cancer by imaging, it supports our study. As well as we know that cancer is a chronic disease due to abnormal growth. Every cancer arises from a precancer, although not all precancers lead to cancer. Over time, the number of percancer cells must be abnormally proliferate, and achieve excess numbers [21]. If all precancers were detected early, the risk to further develop into malignancy would be reduced extensively. For example a case report showed that a 72 years old woman was diagnosed as precancer (ground-glass opacity) in the lung while the STK1p value was high of 3.9 pM, however,3 lung tumor-related markers were negative (CEA (-) Cyfra19 (-) NSE (-). The STK1p continued to rise to above 10-13 pM, while CT and 3 markers were still normal. The patient underwent right lobectomy and systemic lymphadenectomy under thoracoscopicpy 4 months after the discovery of lung cancer by CT. Pathology investigation confirmed the presence of lung adenocarcinoma (moderate differentiation). The STK1p value declined to at low level (1.3 pM) one month after surgery, no metastasis or recurrence by CT assessment so far [20].

We suggest that it is very important to note that elevated STK1p values predict an earlier risk of tumor metastasis than imaging. It can be given strong advance advice how to improve the individual adapted treatment for a better prognosis in the patient's further.

More recently, the immunotherapy revolution, specifically, the development of Immune Checkpoint Inhibitors (ICIs), such as PD-L1 expression can improve treatment at advantage lung cancer and lead to clinical benefit. A meta-analysis revealed that immunotherapy plus chemotherapy is an effective option as a first-line treatment for lung cancer (n= 4, 887). The NSCLC patients administered combined therapy exhibited higher PFS and OS than patients treated with chemotherapy alone (P<0.001). Moreover, as the expression of PD-L1 increased, the PFS and OS benefits were more significant [22]. However, it is challenging to obtain serial biopsies during a course of therapy to monitor the PD-L1 expression in intrathoracic tumors. Isolation of CTCs from peripheral blood can provide a minimally invasive method to monitor PD-L1 expression on tumor cells over time [23], the protocol was complicated and time-consuming. We suggest using STK1p assay for monitoring treatment Since it is simple, and low cost.

Precision molecular medicine with many biomarker tests are available or under development for several lung diseases. So far, few biomarkers are in early widespread clinical use. It is mandatory to show the performance of these biomarkers for the monitoring and prognosis in early lung tumors, such, precancers (ground-glass opacity preaches), malignant tumors (asymptomatic malignant lung nodules, invisible small tumor or early localized tumors) [21], which are potential to use monitoring and prognosis of personalized targeted therapies. TK1 is one of the precise molecule targets for monitoring and prognostic factor, specifically, for early detection of the growth rate of invisible small tumors. STK1p assay is also noninvasive and low cost [9]. We propose that STK1p combined with imaging or another biomarkers might be a more reliable assessment for the development of premalignancy or diseases associated with the risk process of lung cancer. There would be no or very limited lung cancer development in the future if the premalignancy or early tumors were treated in time.

5. Conclusion

STK1p value has benefit to early discovery premalignancy or invisible tumors and gives Dr's advice to adopt a reasonable treatment in time. The post-radical resection followed by
2 cycle-chemotherapy is an important critical-point time to measure STK1p if the value is increasing or declining. Since elevated STK1p values predict an earlier risk of tumor metastasis than imaging it can be given strong advance advice on how to adapt a new individual treatment for a better prognosis in the NSCLCs and also other cancer patient's further.

6. Ethical Approval

This study is under the ethical standards in the 1964 Declaration of Helsinki and its later amendments. The Ethical approval supervised by the national ethical guidelines of China and approved by the Peking 301 Chinese PLA General Hospital's Ethics Committee (Ethic No. S2015-036-01).

7. Financial & Competing Interests Disclosure

This project was supported by Science and Technology Projects of JiangSu city (SS201631).

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J. Clin. 2019; 69: 7-34.
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China. CA Cancer J Clin. 2016; 66(2): 115-32.
3. Zhao H, Zhu Q, Zhang C, Li J, Wei M, Qin Y, et al. Tocilizumab combined with favipiravir in the treatment of COVID-19: A multicenter trial in a small sample size. Biomed Pharmacother. 2021; 133:110825.
4. Yang Q, Zhang P, Wu R, Lu K, Zhou H. Identifying the best marker combination in CEA, CA125, CY211, NSE, and SCC for lung cancer screening by combining ROC curve and logistic regression analyses: is it feasible? Dis. Markers. 2018; 1: 1-12.
5. Wang Z, Zhang G, Li Z, Li J, Ma H, Hei A et al. STK1p as a prognostic biomarker for overall survival in non-small-cell lung carcinoma, based on real-world data. Future Sci OA. 2021; 7(3): FSO661.
6. Wu JT. Circulating Tumor Markers of the New Millennium 584. AACC Press, NY, USA. 2002; 115-117.
7. Wang Y, Jiang X, Dong S, Shen J, Yu H, Zhou J, et al. Serum TK1 is a more reliable marker than CEA and AFP for cancer screening survey in a study of 56,286 people. Cancer Biomark. 2016; 11:529-536.
8. Wang Y, Jiang X, Wang S, Yu H, Zhang T, Xu S, et al. Serological TK1 predict pre-cancer in routine health screenings of 56,178 people. Cancer Biomark. 2018; 22: 237-247.
9. Skog S, He E, Haghdoost S. Prevention and early detection of human tumour. LAP lambert academic publishing, Schaltungsdienst Lange O.H.G., Berlin. 2017.
10. Kauffman MG, Kelly TJ. Cell cycle regulation of thymidine kinase: residues near the carboxyl terminus are essential for the specific degradation of the enzyme at mitosis. Mol. Cell. Biol. 1991; 11: 2538-2546.
11. Weagel EG, Burrup W, Kovtun R, Velazquez EJ, Felsted AM, Townsend MH, et al. Correction to: membrane expression of thymidine kinase 1 and potential clinical relevance in lung, breast, and colorectal malignancies. Cancer Cell Int. 2019; 19:29.
12. Gronowitz JS, Hagberg H, Kallander CF, Simonsson B. The use of serum deoxythymidine kinase as a prognostic marker, and in the monitoring of patients with non-Hodgkin's lymphoma. Br. J. Cancer. 1983; 47:487-495.
13. Topolcan O, Lubos Holubec L. The role of thymidine kinase in cancer diseases. Expert Opin. Med. Diagn. 2008; 2: 129-140.
14. Chen Y, Ying M, Chen Y, Hu M, Lin Y, Chen D, et al. Serum thymidine kinase 1 correlates to clinical stages and clinical reactions and monitors the outcome of therapy of 1,247 cancer patients in routine clinical settings. Int. J. Clin Oncol. 2010; 15(4): 359-368.
15. Lou X, Zhou J, Ma H, Xu S, He E, Skog S. The half-life of serum thymidine kinase 1 concentration is an important tool for monitoring surgical response in patients with lung cancer: a meta-analysis. Genet. Test. Mol. Biomarkers. 2017; 21(8):471-478.
16. He Q, Fornander T, Johansson H, Johansson U, Hu GZ, Rutqvist LE. Thymidine kinase 1 in serum predicts increased risk of distant or loco-regional recurrence following surgery in patients with early breast cancer. Anticancer Res. 2006; 26(6C): 4753-4759.
17. Chen F, Tang L, Xia T, He E, Hu G, Li Y. Serum thymidine kinase 1 levels predict cancer-free survival following neoadjuvant, surgical and adjuvant treatment of patients with locally advanced breast cancer. Mol. Clin. Oncol. 2013; 1(5): 894-902.
18. Pan Z, Ji X, Shi Y, Zhou J, He E, Skog S. Serum thymidine kinase 1 concentration as a prognostic factor of chemotherapy-treated non-Hodgkin's lymphoma patients. J Cancer Res. Clin. Oncol. 2010; 136(8): 1193–1199.

19. Nisman B, Nechushtan H, Biran H, Gantz-Sorotsky H, Peled N, Gronowitz S. Serum thymidine kinase 1 activity in the prognosis and monitoring of chemotherapy in lung cancer patients: a brief report. Thorac. Oncol. 2014; 9:1568-1572.
20. Chen ZH, Wang Y, Chen G. Chapter 21. Serum-biomarker thymidine kinase 1 for early discovery of tumour process of 160,086 participants using a sensitive immune-ECL-dot-blot detection system. In: Advances in Sensors: Reviews, Volume 6. Yurish SY (Ed.). International Frequency Sensor Association Publishing, Barcelona, Spain, 529–540 (2018).
21. Berman JJ, Moore G. Precancer: The Beginning and the End of Cancer. Massachusett. Jones and Bartlett Publishers. 2010.
22. Shen K, Cui J, Wei Y, Chen X, Liu G, Gao X, et al. Effectiveness and safety of PD-1/PD-L1 or CTLA4 inhibitors combined with chemotherapy as a first-line treatment for lung cancer: a meta-analysis. J Thorac. Dis. 2018; 10: 6636-6652.
23. Wang Y, Kim TH, Fouladdel S, Zhang Z, Soni P, Qin A. PD-L1 Expression in Circulating Tumor Cells Increases during Radio(chemo)therapy and Indicates Poor Prognosis in Non-small Cell Lung Cancer. Sci Rep. 2019; 9: 566.