Observational Study

CYFRA21-1/TG ratio as an accurate risk factor to predict eye metastasis in nasopharyngeal carcinoma

A STROBE-compliant article

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Abstract

Nasopharyngeal carcinoma (NPC) has a distinctive geographical distribution in China, especially southern China. There are several risk factors for NPC, such as Epstein-Barr virus, genetics, and environmental exposures. Although the incidence of eye metastasis (EM) is lower than metastasis in other body parts, it often indicates poor prognosis.

We assessed several serum biomarkers for their ability to predict EM in NPC. Patients with NPC were selected (n = 963), and were separated into two groups, EM and no eye metastasis. Ten factors were analyzed in both groups including triglyceride (TG), high-density lipoprotein, low-density lipoprotein, alkaline phosphatase, alpha fetoprotein, carbohydrate antigen-199, cancer antigen-153, apolipoproteins AI, apolipoprotein B, and cytokeratin fragment 19 (CYFRA21-1). Independent t tests, binary logistic regression, and receiver operating characteristic curves were used to assess the data.

The EM group had significantly higher CYFRA21-1 and lower TG compared with the no eye metastasis group. Areas under the curve for CYFRA21-1, TG and CYFRA21-1/TG were 0.966, 0.771, and 0.976, respectively. The corresponding cut-off values were 12.12 ng/ml, 0.41 mmol/L, and 13.5. The sensitivity and specificity of CYFRA21-1/TG were 100% and 92.2%, respectively.

The increased ratio of CYFRA21-1 to TG can be an accurate method to detect EM in patients with NPC.

Abbreviations: AUC = area under the curve, CYFRA21-1 = cytokeratin fragment 19, EM = eye metastasis, NEM = non-eye metastasis, NPC = nasopharyngeal carcinoma, ROC = receiver operating characteristic, TG = triglyceride.

Keywords: cytokeratin fragment 19, eye metastasis, primary nasopharyngeal carcinoma, risk factor, triglyceride

1. Introduction

Nasopharyngeal carcinoma (NPC) is a multifactorial, complex disease that originates from the surface epithelium. Most cases of NPC are squamous cell carcinoma.[1] Based on differentiation, NPC can be divided into 3 histological categories: keratinizing, non-keratinizing, and undifferentiated.[2] NPC affects individuals throughout the world, but prevalence rates are especially high in southeast Asia, Greenland, and southern China.[3] In Taiwan, the incidence of NPC is 5.4 cases per 100,000 people.[4]

Due to the abundant blood supply and lymphatic drainage circulation, there are significant differences between NPC and other head and neck tumors, which increases the risk of NPC metastasis to farther distances than in the case of other head and neck tumors.[5,6] The major distal metastasis sites are the bone, lung, liver, and lymph nodes.[7] However, metastasis to the eye is relatively rare. On the basis of existing detection and diagnosis methods, patients with NPC have a 1- and 5-year survival rates of 92% and 70%, respectively, and 20% to 25% of survivors will eventually develop metastatic disease.[8]

NPC has a satisfactory response to radiation therapy; however, if there is distal metastasis and a higher degree of malignancy, a combination of chemotherapy and radiotherapy is required to improve the long-term survival rate. Even with sufficient treatment, almost all metastasis will develop within 3 years. Tumor metastasis becomes the primary determinant of NPC mortality.[16]
Epstein-Barr virus has been closely associated with NPC, and viral DNA in blood circulation is a highly sensitive and specific marker for detecting NPC.\(^{9,10}\) Regrettably, many cases are asymptomatic, some patients are not diagnosed with NPC until the advanced stage, thus has a lower survival rate. The 5-year survival rate for stage IV is only 60%,\(^{11}\) and these patients may not respond to treatment and have a higher incidence of regional recurrence.\(^{11}\) Meanwhile, there are molecular markers used to predict metastasis, probably because of their low sensitivity and specificity.\(^{11}\) It is therefore urgent to identify molecular markers with high specificity and sensitivity, which are immediate and convenient for detection of metastasis. In the present study, we collected data from patients with NPC eye metastasis (EM) and evaluated the blood concentrations of 10 potential factors to clarify their predictive values for detecting EM. We also combined them with triglyceride (TG) and cytokeratin fragment 19 (CYFRA21-1) to obtain the best prediction accuracy.

2. Patients and methods

2.1. Ethics statement

This study was supported by the Medical Research Ethics Committee of the First Affiliated Hospital of Nanchang University. All subjects signed informed consent forms and agreed to participate in this research. All procedures of this study were conducted in accordance with the Declaration of Helsinki. The IRB approval number is cdyfy2016011.

2.2. Patients

Included patients were all diagnosed with primary NPC (n = 963) between 2002 and 2016. Patients were admitted to the hospital without previous treatment such as surgery or chemotherapy. Patients with primary eye cancer were excluded. Pathological examination of specimens extracted by surgical resection or biopsy was performed to detect primary NPC. Secondary metastasis were diagnosed by computed tomography and magnetic resonance imaging.

2.3. Study design

Clinical data including age, sex, and site of metastasis were collected from the participants’ medical records. Ten tumor markers were investigated, as follows: TG, HDL (high-density lipoprotein), LDL (low-density lipoprotein), ALP (alkaline phosphatase), AFP (alpha fetoprotein), CA199 (carbohydrate antigen-199), CA153 (cancer antigen-153), ApoAI (apolipoprotein AI), ApoB (apolipoprotein B), and CYFRA21-1.

2.4. Statistical analyses

Differences in age, sex, and tumor marker expression levels between the EM and non-EM (NEM) groups were evaluated by independent \(t\) tests. Binary logistic regression was performed to investigate independent risk factors for EM. Receiver operating characteristic (ROC) curves were also plotted, and area under the curve (AUC) values were calculated. The cut-off values, sensitivity, and specificity of risk factors were analyzed. Differences were considered significant at \(P < .05\). All data were analyzed using SPSS 22.0 (IBM, USA) and Excel 2010 software.

3. Results

3.1. Demographic and clinical characteristics

The total number of patients with NPC was 963, 23 in the EM group and 940 in the NEM group. Most participants were male (72.3%), and the mean ages were 52.5 ± 9.4 and 50.6 ± 11.7 years in the EM and NEM groups, respectively (\(P > .05\), \(t\)-test). More details are shown in Table 1 and Figures 1–3. The most common metastasis in the NEM group was to the cervical lymph nodes.

3.2. Risk factors for EM in patients with NPC

To determine whether the 10 tumor markers can be used to discriminate EM from other types of metastasis, we compared their expression levels between the EM and NEM groups. Table 2 shows that TG was significantly decreased and CYFRA21-1 was markedly increased in the EM group compared with the NEM

| Table 1: The clinical characteristics in eye metastasis and non-eye metastasis groups. |
|-----------------------------------------------|
| Characteristics | EM (n = 23) | NEM (n = 940) | \(P\) value |
|-----------------|-------------|--------------|------------|
| Gender          |             |              |            |
| Male            | 16          | 680          |            |
| Female          | 7           | 260          |            |
| Mean age \(^{*}\) | 52.5 ± 9.4  | 50.6 ± 11.7  | .214       |

\(^{*}\) Independent \(t\) test was performed. \(P < .05\) revealed significant difference.

EM = eye metastasis, NEM = non-eye metastasis.

Figure 1. The hematoxylin-eosin staining and Immunohistochemistry images from nasopharyngeal carcinoma patients with eye metastasis. A. Nasopharyngeal carcinoma (HE \(\times 200\)) B. P40+ (SP \(\times 200\)) C. CK+ (SP \(\times 200\)). The tissue was collected from eye metastasis site of nasopharyngeal carcinoma. HE = hematoxylin-eosin, SP = streptavidin-peroxidase.
Figure 2. Example of patients with eye metastasis seen on fundus camera and eye B ultrasonic.

Figure 3. The distribution of patients in Jiangxi Province. There are 11 cities in Jiangxi Province including Nanchang, Jiujiang, Shangrao, Fuzhou, Yichun, Jian, Ganzhou, Jingdezhen, Pingxiang, Xinyu and Yingtan. EM = eye metastasis, NEM = non-eye metastasis.
group ($P < .05$); however, other markers were not significantly different between the two groups ($P > .05$). The binary logistic regression results indicated that TG and CYFRA21-1 could be considered independent factors to predict EM in patients with NPC ($P < .0001$, Table 3).

### 3.3. Assessment of the predictive value of CYFRA21-1/TG

To analyze the predictive value of the CYFRA21-1/TG ratio, ROC curves were generated (Figs. 4 and 5). The cut-off values for TG and CYFRA21-1 were 0.41 mmol/L and 12.2 ng/ml, respectively, with AUC values of 0.771 and 0.966. Calculating the ratio of these 2 factors indicated that the sensitivity and specificity were 100% and 92.2%, respectively, and the AUC was 0.976. The results are shown in Table 4. These analyses showed that the CYFRA21-1 to TG ratio may be useful for predicting EM in patients with NPC.

### 4. Discussion

Eye anatomical structure is closely related to the nose and paranasal sinuses, which is associated with corresponding clinical symptoms during the process of invasion and metastasis of NPC. EM of NPC can lead to orbital bone destruction and ophthalmic nerve invasion that can result in the extracocular muscle movement disorders, as well as retinal invasion that can cause vision impairment or loss, diplopia, and other problems. EM is rare because of the lack of the lymphatic vessels in the eyes and orbits. In our department, only 2.3% of patients with NPC had EM.

### Table 2: Comparison of tumor makers between eye metastasis and non-eye metastasis group.

| Tumor marker | EM | NEM | $P$ value |
|--------------|----|-----|-----------|
| TG (mmol/L)  | 0.8±0.2 | 1.5±1.1 | <.0001 |
| HDL (mmol/L)| 1.2±0.5  | 1.3±0.5 | .444 |
| LDL (mmol/L)| 11.0±40.8 | 3.2±10.9 | .366 |
| ALP (U/L)   | 73.3±19.3 | 84.6±50.8 | .287 |
| AFP (ng/ml) | 2.0±2.4  | 1.8±1.1 | .657 |
| CA199 (U/ml)| 10.8±29.3 | 5.4±7.7 | .387 |
| CA153 (U/ml)| 15.5±10.0 | 14.6±15.4 | .786 |
| ApoAI (g/L) | 1.7±0.4  | 1.7±0.9 | .901 |
| ApoB (g/L)  | 1.5±1.3  | 1.1±0.8 | .393 |
| CYFRA21-1 (ng/ml) | 34.1±16.6 | 6.6±12.6 | <.0001 |

Independent t test was performed. $P < .05$ revealed statistical significance.

### Table 3: The binary logistic regression model between eye metastasis and non-eye metastasis group.

| Tumor marker | B   | Exp(B) | $P$ value |
|--------------|-----|--------|-----------|
| TG           | -2.742 | 0.064 | .001     |
| CYFRA21-1    | 0.049 | 1.051 | <.0001 |

The binary logistic analysis was performed. $P < .05$ means significant difference. $B$= coefficient of regression, CYFRA 21-1 = cytokeratin fragment 19, TG = triglyceride.
It is extremely important to identify accurate methods to detect EM in patients with NPC. Due to its undifferentiated or poorly differentiated nature, NPC is highly malignant and may not be diagnosed until the advanced stage. Additionally, EMs in NPC are usually small, and the infiltrating type cannot be detected by conventional imaging techniques unless there is a considerable degree of bone destruction and significant changes in structure density. Therefore, patients with ocular symptoms caused by advanced NPC would be extremely difficult to identify with computed tomography. 

Since we do not fully understand the molecular mechanisms of metastasis and invasion, our treatment approach to NPC is more conservative. NPC treatment is still dominated by radiotherapy. A large accumulative amount of radiation is needed to achieve satisfactory therapeutic effects due to the deep anatomical location of the tumor. However, the tumor is also near the eyes, and radiation can harm ocular structure and function. For patients with NPC, eye discomfort due to EM is indistinguishable from eye problems induced by radiation. As a result, effective biological markers with high specificity and sensitivity would be helpful to determine whether the ocular symptoms were caused by radiation or NPC EM. Depending on the etiology, patients can be treated with appropriate methods to alleviate pain and prolong survival time.

Serological markers have many advantages including minimal invasiveness and convenient acquisition. Although scientists have been aware of a number of serological markers associated with metastasis and prognosis, there are no specific serological markers for EM of NPC. In this study, TG and CYFRA21-1 were found to be useful markers.

Triglyceride (TG) is stored in the lipid droplets as energy to provide ATP by lipolysis. It can form phospholipids and other complex lipids. All cells can synthesize and breakdown TG. One study showed that the expression level of intracellular lipids or the size and/or number of lipid droplets were increased in various cancer cells including breast, prostate, liver, and colon. Similarly, a large-scale cohort study revealed subjects with high TG may have increased risks of rectal and breast cancer. These results indicate that TG may play an important role in providing energy to sustain malignant cell growth and proliferation. Notably, we found decreased blood TG in NPC patients with EM. The occurrence of EM indicates that cancer is in an advanced stage. One possible explanation is that the cancer cells grow rapidly and deplete TG levels, but the mechanism of decreased TG in NPC patients with EM requires further investigation.

CYFRA21-1 is the fragment of cytokeratin 19 in epithelial cells, especially in the pulmonary tissue. It is released into serum during the late S and G2 phases of the cell cycle. When cells become cancerous, metabolism is enhanced, necrosis is accelerated, and abundant CYFRA21-1 is released into the blood. Elevated concentrations of serological markers are closely associated with tumor progression and invasion. CYFRA21-1 has been reported as an independent predictor for small cell lung carcinoma, with elevated serum concentration suggesting a higher risk for patients for developing advanced lung cancer. It is also expressed in various malignant cancers. It was reported that combining CYFRA21-1 and CA125 can be used to detect epithelial ovarian cancer. Patients with head and neck cancer with a high CYFRA21-1 level are more likely to have poor prognosis. Serum CYFRA21-1 level may also be able to predict NPC. Rao et al reported that increased postoperative serum CYFRA21-1 and squamous cell carcinoma antigen may be risk factors for lymph node metastasis and recurrence in patients with laryngeal carcinoma. Serum CYFRA21-1 can also be a prognostic factor for breast cancer liver metastasis.

Our results revealed significantly increased CYFRA21-1 expression in NPC patients with EM. This indicates that the cancer had progressed into an advanced stage, which is in line with previous findings.

In this study, we divided patients with NPC into 2 groups according to the presence of EM. The results showed that serum CYFRA21-1 in patients with EM was significantly increased.
compared with the NEM group, and the cut-off value was 12.12 ng/ml. Meanwhile, serum TG decreased significantly compared with that of patients without metastasis, and the cut-off value was 0.41 mmol/L. To our best knowledge, this is the first time that CYFRA21-1 and TG have been associated with EM in patients with NPC. Since the direction of changes for these two indicators were opposite, we calculated the ratio to obtain more significant data. After generating the ROC curve of the ratio of these 2 markers, we found the sensitivity and specificity of CYFRA21-1/TG were 100% and 92.2%, respectively. Based on these values, we hypothesize that this ratio could be used as an independent indicator for predicting EM in patients with NPC, possibly before it is evident on imaging. There are limitations to our study. First, since it is difficult for NPC to metastasize to eyes, we were only able to analyze a small number of cases. Secondly, all the samples in this study were diagnosed with NPC, we did not perform a comparison between these samples and healthy controls. Thirdly, this was a retrospective study. We had limited information to analyze, and the materials we obtained may also have introduces recall bias. Thus, further investigations are needed to confirm our results. In conclusion, the ratio of serum CYFRA21-1 to TG can be a reliable measure to predict the ocular metastasis of NPC.

**Author contributions**

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**References**

[1] Guo R, Mao YP, Tang LL, et al. The evolution of nasopharyngeal carcinoma staging. Br J Radiol 2019;92:20190244.

[2] Chu MH, Wu JS, Hui EP, et al. Nasopharyngeal carcinoma. Lancet 2016;387:1012–24.

[3] Gao W, Chan YJ, Wong TS. Differential expression of long noncoding RNA in primary and recurrent nasopharyngeal carcinoma. BioMed Res Int 2014;2014:404567.

[4] Chen SW, Chen CH, Tsoa CJ, et al. Nasopharyngeal carcinoma with pericardial metastasis. Kaohsiung J Med Sci 2011;27:289–91.

[5] Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet (London, England) 2005;365:2041–3.

[6] Bagatouzou A, Erkalouos E, Michaelides I. Epidural metastasis in nasopharyngeal carcinoma. Strahlenther Onkol 2003;179:123–8.

[7] Li S, Yang J. Nasopharyngeal carcinoma metastasis to the mammary gland: a case report. Oncol Lett 2015;9:275–7.

[8] Chen LC, Chen CC, Liang Y, et al. A novel role for TNFAIP2: its correlation with invasion and metastasis in nasopharyngeal carcinoma. Mod Pathol 2011;24:175–84.

[9] Vo JH, Nei WL, Hu M, et al. Comparison of circulating tumour cells and circulating cell-free Epstein-Barr virus DNA in patients with nasopharyngeal carcinoma undergoing radiotherapy. Sci Rep 2016;6:13.

[10] Xie C, Li H, Yan Y, et al. A nomogram for predicting distant metastasis using nodal-related features among patients with nasopharyngeal carcinoma. Front Oncol 2020;10:616.

[11] Chan KC, Woo JKS, King A, et al. Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer. N Engl J Med 2017;377:513–22.

[12] Liu R, Wang J, Zhang W, et al. Study about eye complication of nasopharyngeal carcinoma. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi= J Clin Otorhinolaryngol Head Neck Surg 2011;25:1123–4. 30.

[13] Zheng LS, Yang JP, Cao Y, et al. SPINK6 promotes metastasis of nasopharyngeal carcinoma via binding and activation of epithelial growth factor receptor. Cancer Res 2017;77:579–89.

[14] Xu Y, Sun Y, Zhao J, et al. Ocular metastasis in lung cancer: a retrospective analysis in a single Chinese hospital and literature review. Zhongguo Fei Ai Za Zhi= Chin J Lung Cancer 2017;20:326–33.

[15] Shields CL, Welch RJ, Malik K, et al. Uveal metastases: clinical features and survival outcome of 2214 tumors in 1111 patients based on primary tumor origin. Middle East Afr J Ophthalmol 2018;25:81–90.

[16] Goto S, Takeda H, Sashara Y, et al. Metastasis of advanced gastric cancer to the extraocular muscle: a case report. J Med Case Rep 2019;13:107.

[17] Ruder AJ, Walsh A, Sollenberger EL, et al. Orbital pheochromocytoma metastasis in 2 patients with known pheochromocytoma. Ophthalmic Plast and Reconstruct Surg 2019;35:e131–4.

[18] Siddiqui MAR, Hussain SZM, Mubarak M. Iris metastasis as the initial presentation of upper gastrointestinal tract carcinoma: a case report. J Med Case Rep 2019;13:367.

[19] Kameniarz L, Armeni E, O’Mahony LF, et al. Orbital metastases from neuroendocrine neoplasms: clinical implications and outcomes. Endocrine 2019;67:483–93.

[20] Welch RJ, Malik K, Mayro EL, et al. Uveal metastasis in 1111 patients: Interval to metastasis and overall survival based on timing of primary cancer diagnosis. Saudi J Ophthalmol 2019;33:229–37.

[21] Chummerpudetsuk R, Tooley AA, Godfrey KJ, et al. Renal medullary carcinoma with metastasis to the temporal fossa and orbit. Ophthalmic Plast Reconstr Surg 2019;35:e149–51.

[22] Min YL, Gong YX, Zhu PW, et al. CEA as a risk factor in predicting uveal metastasis from colorectal cancer. J Cancer 2020;11:51–6.

[23] Pastore MR, D’Alessio R, Cirigliano G, et al. Orbital metastasis as presenting symptom from a prostatic adenocarcinoma. Eur J Ophthalmol 2020;30:N29–P32.

[24] Chacon Gonzalez M, Ibanez Munoz A, Rodriguez Vicente L, et al. Choroidal metastases as initial manifestation of a papillary thyroid carcinoma: a case report. Arch Soc Esp Oftalmol 2020;95:98–74.

[25] Chen KW, Wang WY, Liang WM, et al. The volume of retroperitoneal nodes predicts distant metastasis in patients with advanced nasopharyngeal carcinoma. Oral Oncol 2011;47:1171–5.

[26] Zhao Y, Wang Y, Zeng S, et al. LMP1 expression is positively associated with metastasis of nasopharyngeal carcinoma: evidence from a meta-analysis. J Clin Pathol 2012;65:41–5.

[27] Cai Y, Li J, Lu A, et al. Increased serum levels of macrophage inflammatory protein-3alpha and cystatin a predict a poor prognosis of nasopharyngeal carcinoma. Medicine 2014;93:e123.

[28] Zheng J, Li J, Xu L, et al. Phosphorylated Msk1 and eIF4E are associated with lymph node metastasis and poor prognosis of nasopharyngeal carcinoma. PloS One 2014;9:e89220.

[29] Tang Q, Hu QY, Piao YF, et al. Correlation between pretreatment serum LDL-cholesterol levels and prognosis in nasopharyngeal carcinoma patients. Oncol Targets Ther 2016;9:2585–91.

[30] Hu K, Xie X, Wang R, et al. Association of the rs2071559(T/C) polymorphism with lymphatic metastasis in patients with nasopharyngeal carcinoma. Oncology Lett 2017;14:7681–6.

[31] Chen S, Youhong T, Tan Y, et al. EGRF-PKM2 signaling promotes the metastatic potential of nasopharyngeal carcinoma through induction of FOSL1 and ANTXR2. Carcinogenesis 2019;41:723–33.

[32] Lee KY, Seah LL, Tow S, et al. Nasopharyngeal carcinoma with orbital involvement. Ophthalmic Plast Reconstr Surg 2008;24:185–9.

[33] Lin KT, Lee SY, Liu SC, et al. Risk of ocular complications following radiation therapy in patients with nasopharyngeal carcinoma. Laryngoscope 2019;130:1270–7.

[34] Balaban S, Lee LS, Schreuder M, et al. Obesity and cancer progression: is there a role of fatty acid metabolism? BioMed Res Int 2013;2013:274585.

[35] Sun H, Huang X, Wang Z, et al. Triglyceride-to-high density lipoprotein cholesterol ratio predicts clinical outcomes in patients with gastric cancer. J Cancer 2019;10:829–36.
Dal Bello MG, Filiberti RA, Alama A, et al. The role of CEA, CYFRA21-1 and NSE in monitoring tumor response to Nivolumab in advanced non-small cell lung cancer (NSCLC) patients. J Transl Med 2019;17:74.

Jin C, Yang M, Han X, et al. Evaluation of the value of preoperative CYFRA21-1 in the diagnosis and prognosis of epithelial ovarian cancer in conjunction with CA125. J Ovarian Res 2019;12:114.

Sunpaweravong S, Puntawibul P, Sunpaweravong P, et al. Correlation between serum SCCA and CYFRA 2 1-1, tissue Ki-67, and clinicopathological factors in patients with esophageal squamous cell carcinoma. J Med Assoc Thailand 2016;99:331–7.

Molina R, Auge JM, Filella X, et al. Pro-gastrin-releasing peptide (proGRP) in patients with benign and malignant diseases: comparison with CEA, SCC, CYFRA 21-1 and NSE in patients with lung cancer. Anticancer Res 2005;25:3317–8.

Zhang L, Liu D, Li L, et al. The important role of circulating CYFRA21-1 in metastasis diagnosis and prognostic value compared with carcinoembryonic antigen and neuron-specific enolase in lung cancer patients. BMC Cancer 2017;17:96.

Liu L, Xie W, Xue P, et al. Diagnostic accuracy and prognostic applications of CYFRA 21-1 in head and neck cancer: a systematic review and meta-analysis. PloS One 2019;14: e0216561.

Song XM, Wang ZJ, Cao WJ, et al. The value of circulating CYFRA21-1 expression in patients with nasopharyngeal carcinoma: a study of 529 subjects. Int J Clin Oncol 2016;21:1038–45.

Rao LH, Zhang L, Tian L, et al. The clinical significance of CEA, Cyfra21-1 and SCC in laryngeal carcinoma's clinicopathological parameters. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi = J Clin Otorhinolaryngol Head Neck Surg 2017;31:1182–6.

Treska V, Topolcan O, Zoubkova V, et al. Perioperative tumour marker levels as prognostic factors for surgical treatment of breast cancer liver metastases. Anticancer Res 2018;38:3647–52.