Medicine®

OPEN

Evaluation of the prognostic value of derived neutrophil/lymphocyte ratio in early stage non-small cell lung cancer patients treated with stereotactic ablative radiotherapy

Xin Wang, MD, Zhi Lou, MD, Lei Zhang, MD, Zhenghong Liu, MD, Jie Zhang, MD, Jia Gao, MD, Yajun Ji, MD*

Abstract

The derived neutrophil-lymphocyte ration (dNLR) is a systemic inflammatory marker.

The present study focusing on the prognostic value of pre-treatment dNLR in patients of early stage non-small cell lung cancer (NSCLC).

From 2012 to 2016, patients with newly diagnosed early stage NSCLC were investigated. Only these who treated with stereotactic ablative radiotherapy (SABR) were enrolled in this study. dNLR was calculated from complete blood count prior to SABR. The optimal cut-off value of dNLR was determined by receiver operating curve. Kaplan–Meier curves and Cox proportional models were used to analyze the impact of pre-treatment dNLR on disease free survival (DFS) and overall survival (OS).

There were 69 patients eligible for analysis, the median follow-up period was 30.9 months. Calculated by receiver operating characteristic curves, the optimal cut off value of dNLR was 1.99. Kaplan–Meier curves demonstrated that a decreased dNLR was correlated with favorable DFS and OS. In univariate analysis, high dNLR was associated with decreased survival; moreover, multivariate analysis revealed that a decreased dNLR was an independent significant favorable prognostic factor for both DFS and OS.

An elevated pre-treatment dNLR may be an independent prognostic biomarker for DFS and OS in patients with early stage NSCLC that are eligible for SABR. dNLR is a reliable, inexpensive, simple, and readily available tool for risk-stratification and should be considered in daily clinical practice.

Abbreviations: 3DCT = 3-dimensional CT, 4DCT = 4-dimensional CT, CBC = complete blood count, DFS = disease free survival, dNLR = derived neutrophil-lymphocyte ration, HR = hazard ratio, ITV = internal target volume, NSCLC = non-small cell lung cancer, OS = overall survival, SABR = stereotactic ablative radiotherapy.

Keywords: derived neutrophil-lymphocyte ration, non-small cell lung cancer, prognostic factor, stereotactic ablative radiotherapy

1. Introduction

Lung cancer is the leading cause of cancer death among males and the second leading cause of cancer death among females across

the world, the most common type of lung cancer is non-small cell lung cancer (NSCLC), which occupied nearly 85%.[1] Over the last 25 years, lung cancer mortality rates have declined.[2] With the implementation of low-dose computed tomography screening, approximately 16% of patients were diagnosed with early stage tumor (T1–2 N0 M0) and the incidence will increase in future.[3] Surgical resection remains the mainstay treatment for early stage NSCLC, however, there were increased risk of surgery for elderly patients or patients combined with comorbidities. Stereotactic ablative radiotherapy (SABR), also known as stereotactic ablative body radiotherapy, has been proved to be an efficacy treatment protocol in medically inoperable early stage NSCLC and oligometastatic lung cancer, obtained favorable local control rates and achieved survival benefits.[4–6] Sun et al reported the efficacy of SABR for clinical stage I NSCLC in a prospective study, with a median follow up of more than 7 years, the incidence of progression free survival and overall survival (OS) were 49.5% and 55.7%, respectively, at 5 years and 38.2% and 47.5%, respectively, at 7 years; in the meantime, there were low level of disease recurrence rates.[7] Furthermore, some investigators exploited the immunologic effects of radiotherapy; SABR contributed to immunogenic death in primary cancer, result in the exposes and release of tumor antigen, priming of tumor specific cytotoxic T cells, and inducing an anticancer

immune response.[8,9] The immune mechanisms of SABR is associated with a favorable disease control.[10] Therefore, clinical tools that are easily available and economically feasible to assess the prognosis of early stage NSCLC patients who received SABR is necessary.

It is well established that inflammation plays a critical role in carcinogenesis and tumor proliferation.[11] In recent years, systemic inflammation markers such as neutrophil to lymphocyte ratio, C-reactive protein, lymphocyte to monocyte ratio, platelet to lymphocyte ratio, and albumin, have all been demonstrated to correlate with disease outcomes in cancer patients.[12,13] It appeared that the systemic manifestations of inflammation can provide a valuable marker for treatment stratification and prognosis. In addition, some other studies reported the derived neutrophil-lymphocyte ration (dNLR) serve as a simple indicator of systemic inflammation that derived from total neutrophil and white cell counts, can provide prognostic information in variety of malignancies.[14,15] However, the majority of these studies primarily concentrated on surgical resection and definitively chemoradiotherapy, and the prognostic role of pretreatment dNLR in patients who treated with SABR is of very little concern.

dNLR is an inexpensive and readily obtainable index from complete blood count (CBC). The objectives of this study were to investigate the prognostic value of systemic inflammation marker dNLR on disease free survival (DFS) and OS for patients with medically inoperable stage I NSCLC who received SABR. We also attempt to identify the optimal cut-off point of dNLR in these cohort of patients.

2. Patients and methods

2.1. Patients data

From January 2012 to December 2016, medical data of newly diagnosed NSCLC patients were retrospectively analyzed in the First People's Hospital of Lianyungang. All patients were clinically staged by computed tomography, magnetic resonance imaging, and positron emission-CT prior to treatment. Patients were excluded if they met the following criteria: had small cell histologic features, received other anticancer treatment prior to SABR, without curative intention, diagnosed with metastatic lung tumor, combined with other malignancies. There were 73 medical inoperable early stage NSCLC patients who received SABR. Four patients were removed from the final analysis, 1 patient was lost to follow up and 3 patients with unavailable laboratory parameters. The seventh edition of the TNM classification for lung cancer staging was applied. This analysis has been approved by the Institutional Review Board, and written informed consent was obtained from each patient before SABR.

2.2. Treatment

All patients suspected of lung tumor underwent computed tomography scan of the thorax as part of their staging, and the results of the scan were compared to those of staging PET/CT. Magnetic resonance imaging of the brain was used to detect brain metastasis. Blood samples were collected 1 week prior to radiation therapy.

Both 3-dimensional CT and 4-dimensional CT (4DCT) were performed at the time of radiation simulation. During free breathing, the respiratory motion of lung tumor was tracked by the real time position management system. According to the real time position management signal, 10 phase 4DCT image datasets were generated within a respiratory cycle. Maximum intensity projection or average intensity projection CT datasets can be calculated from the 10 phases of the 4DCT to delineate the tumor. Three-dimensional CT datasets are commonly utilized for delineation of the gross target volume, and the maximum intensity projection datasets was used to contour internal target volume (ITV). Based on the combining of gross target volume and ITV, the combined ITV was formed. Using an isotropic 5 mm margin, the planning target volume was generated around the combined ITV. According to tumor size and location, several radiation doses were prescribed. For tumors with a maximum diameters less than 3 cm, they were treated with 48 Gy in 4 fractions; and for tumors larger than 3 cm, the most used treatment strategies include 50 Gy in 5 fractions and 55 Gy in 5 fractions. Daily on-line kilovoltage imaging with weekly cone beam computed tomography were adopted to confirm the tumor position during radiation therapy (Turebeam SN1403 accelerator, Varian Medical Systems, Palo Alto, CA).

2.3. Inflammation biomarkers

Blood samples were drawn 1 week prior to radiation therapy. A CBC was done and inflammation parameters including neutrophil count and lymphocyte were collected. The following formula was used to calculate the derived neutrophil to lymphocyte ratio: dNLR = ANC/(WBC-ANC).[16] Receiver operating characteristic curve was applied to determine the optimal cut-off values of dNLR.

2.4. Follow-Up data

Once the cancer treatment ends, all patients would receive a follow up cancer care plan form the doctor. Patients return to the radiation oncologist for follow up appoints every 3 months during the first 2 years after the completion of treatment, and twice a year after that. In general, a computed tomography imaging of the thorax and up abdomen with contrast was performed, a PET/CT scan and brain magnetic resonance imaging were conducted if necessary.

2.5. Statistical analysis

All statistical analyses were carried out using SPSS 20.0 (IBM Software Group, Chicago, IL). The primary endpoint of this study was OS, defined from the date of initial diagnosis to date of death or the last follow up. Kaplan–Meier's methodology was used to calculate the survival curves and log-rank test was applied to examine potential differences among the various variables. Univariate and multivariate Cox proportional hazard regression models was used to assess the potential prognostic factors of OS. All statistical analyses were 2 sided, and $P < .05$ was considered to be statistically significant.

3. Results

3.1. Patient characteristics

There were 69 patients diagnosed with early stage NSCLC were identified during the period from June 2012 to October 2016. All patients included in the present analysis were treated with SABR and available for CBC data. The median follows up time was

Table 1

Patient characteristics.

Variable	Frequency
Patients (n)	69
Age (yr)	
Mean	73.26±8.91
Median	74.00
Range	43-91
Sex (n)	
Women	23 (33.3%)
Men	46 (66.7%)
Smoke status	
Ex-smoker	12 (17.4%)
Current smoker	32 (46.4%)
Non-smoker	25 (36.2%)
Histology (n)	
Squamous cell carcinoma	23 (33.3%)
Adenocarcinoma	28 (40.6%)
Unknown	18 (26.1%)
Tumor stage (n)	
T1	48 (69.6%)
T2	21 (30.4%)
Radiotherapy (n)	
48 Gy in 4 factions	17 (24.6%)
50 Gy in 5 factions	26 (37.7%)
55 Gy in 5 factions	12 (17.4%)
Other factions	14 (20.3%)

30.9 months; median age of the eligible patients was 74 years. Most of the patients had pretreatment biopsy and diagnosed with adenocarcinoma histologic features. The proportion of stage T1 disease was about 69.6%, approximately 66.7% of patients were male. Baseline demographics and clinical characteristics are illustrated in Table 1.

3.2. Immune parameters

The immune profiles for the entire patient population were acquired form pretreatment CBC. The median neutrophil count was $4*10^9$ cells/L (range:1.75–$7.0*10^9$ cells/L). The median monocyte count was $0.43*10^9$ cells/L (range:0.15–$0.81*10^9$ cells/L). The median platelet count was $237.66*10^9$ cells/L (range:112.0–$427.0*10^9$ cells/L). The median lymphocyte count was $1.92*10^9$ cells/L (range:0.75–$4.57*10^9$ cells/L). The median serum albumin level was 4.1 g/dL. The calculated median dNLR was 1.99 (range: 0.78–7.84).

3.3. Survival analyses

Receiver operating characteristic curve for dNLR was conducted and the optimal cut-off points was 1.99 of the entire cohort. Based on the calculated cut-off values of dNLR, both DFS and OS were optimally differenced, and patients were divided into t2 groups (high dNLR group [≥1.99] and low dNLR [<1.99] group). Next, we analyzed the 2 groups by Kaplan–Meier survival analysis, the 3-years DFS and OS rates in the low dNLR group were 82.2% and 87.8%, respectively; while the 3-years DFS and OS rates in the high dNLR group were 26.8% and 65.4%, respectively (Figs. 1 and 2). A decreased dNLR were associated with better survival.
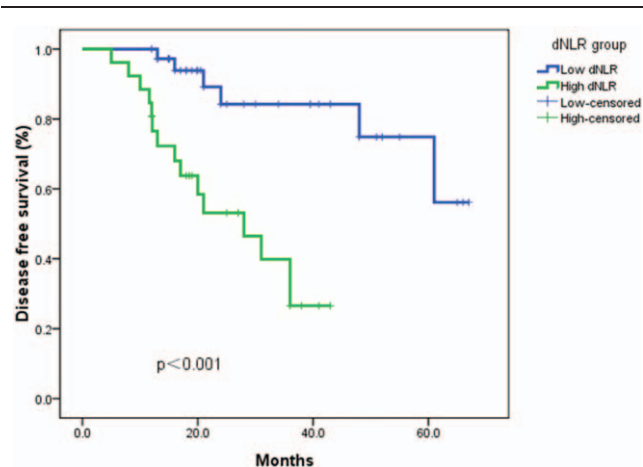

Figure 1. Disease free survival in the low derived neutrophil-lymphocyte ration group and high derived neutrophil-lymphocyte ration group ($P < .01$).

3.4. Prognostic factor analyses

The pretreatment parameters were analyzed to determine whether they would predict for both DFS and OS. On univariate analysis, elevated dNLR predicted for worse DFS ($P = .001$, hazard ratio [HR]=6.69 [95% confidence interval (CI), 2.22–20.16]) and OS ($P = .037$, HR = 4.13 [95% CI, 1.00–17.04]). Then, multivariate analyses were performed to determine the independent prognostic factors for DFS. decreased dNLR ($P = .001$, HR = 6.99 [95% CI, 2.35–21.26]) was correlated with better DFS and OS ($P = .045$, HR = 4.41 [95% CI, 1.04–18.77]) (Table 2). Consequently, dNLR could be used as an independent prognostic marker.

4. Discussion

The current study firstly reports that elevated dNLR was associated with poor survival in patients of early stage NSCLC who received SABR. Our results also suggest that a decreased
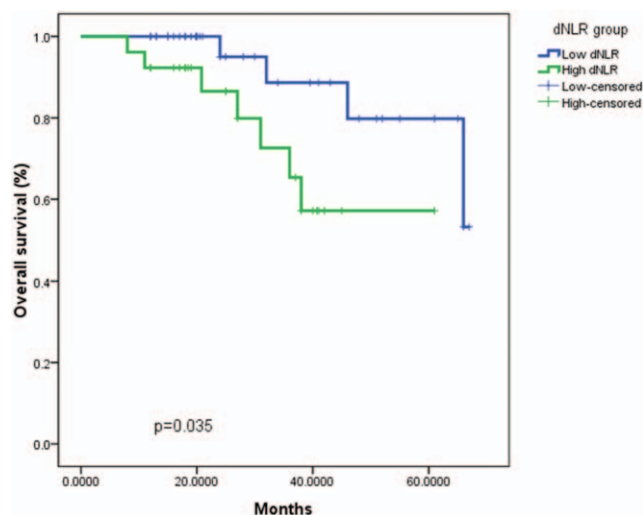

Figure 2. Overall survival in the low derived neutrophil-lymphocyte ration group and high derived neutrophil-lymphocyte ration group ($P = .035$).

Table 2

Cox proportional hazards regression for disease free survival and overall survival.

	DFS Univariate analysis		Multivariate analysis		OS Univariate analysis		Multivariate analysis	
Variable	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Age (>65 vs ≤65)	1.09 (0.36–3.26)	.884			2.50 (0.32–19.80)	.384		
Sex (male vs female)	0.75 (0.25–2.24)	.610			1.12 (0.30–4.25)	.863		
Smoke status (yes vs no)	1.09 (0.42–2.85)	.865			0.58 (0.16–2.08)	.403		
Tumor stage (T1 vs T2)	1.39 (0.57–3.36)	.471			2.22 (0.67–7.38)	.193		
BED (>106Gy vs ≤106 Gy)	1.52 (0.64–3.59)	.340			2.12 (0.64–6.96)	.218		
Complications (yes vs no)	1.34 (0.54–3.33)	.534			0.38 (0.11–1.31)	.125		
dNLR (>1.99 vs ≤1.99)	6.69 (2.22–20.16)	.001	6.99 (2.35–21.26)	.001	4.13 (1.00–17.04)	.037	4.41 (1.04–18.77)	.045

BED = biological effective dose, CI = confidence interval, DFS = disease free survival, dNLR = derived neutrophil to lymphocyte ratio, HR = hazard ratio, OS = overall survival.

dNLR was an independent prognostic factor for this patient population.

The bilateral influence of inflammation and cancer was first reported by Rudolf Virchow in 1863.[17] Over the past few decades, emerging evidence demonstrating the prognostic value of systemic inflammation biomarkers in tumor formation, cancer progression, and metastasis. The systemic inflammation biomarkers including neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio have been well characterized in patients with cancers.[18–20] These biomarkers also have been investigated in early stage NSCLC patients treated with SABR and most of the patients included were elderly individuals.[12,19–21] Recently, dNLR has been investigated as a novel systemic inflammation biomarker in cancer invasion and treatment resistance. Cox et al evaluated the prognostic value of dNLR in patients recruited to the SCOPE1 trial and found an elevated dNLR prior to anticancer therapy was an independent biomarker for OS and progression free survival.[15] Likewise, Yucel et al explored the effect of host inflammation on survival and treatment efficacy by using dNLR, the outcomes showed this new systemic inflammation biomarker can be routinely used in oncogene-addicted NSCLC.[22] In this analysis, we found dNLR as an independent prognosis factor of OS in patients of early stage NSCLC treated with SABR; in the meantime, our finding is the first report that decreased dNLR is associated with better DFS. Furthermore, several research demonstrated the optimal dNLR cut-off value to be 2 and baseline dNLR≥2 was associated with poor OS.[15,16] In the present work, the calculated cut-off value of dNLR was 1.99, and the result was similar to previous studies.

To date, immune evasion plays a key role in tumorigenesis and progression.[23] dNLR reflects host inflammatory status, this metric is reliable, inexpensive, and convenient. An elevated dNLR can lead to increased resting energy expenditure, albumin deficiency, and cachexia.[22] The major implication of dNLR would be to patient stratification, treatment strategies for high risk patient population are different to patients with low risk.[15] In the present analysis, an elevated pretreatment dNLR indicated impaired immune function of individual, and additional anti-cancer strategies are necessary for these patients. Deng et al reported a nomogram established by dNLR and other systematic inflammation biomarkers, the results suggested this nomogram can be used for the prediction of survival and treatment efficacy in patients with cancer.[24] As SABR becomes increasingly used in the management of early stage NSCLC, it is of great importance to use the prognostic model for patient stratification.[25] The low dNLR patients population would be stratified to receive moderate dose of SABR.[26] For high dNLR individuals, increased radiation dose or other treatment strategy may helpful.

There were several inherent limitations in the present analysis. Firstly, the retrospective nature of this study. Secondly, the analysis was conducted in a single medical center and the patient population are relatively small, thus, potential bias may exist. Even though, previous analysis focusing on systemic inflammation biomarkers in early stage NSCLC patients treated with SABR, most of the included patients were more than 65 years old (median age 70–76) and the sample sizes were really small (59–108).[12,19–21] The current study was similar to these studies. Lastly, whilst the present study has validated pretreatment dNLR as a potential prognostic biomarker for early stage NSCLC patients treated with SABR, analysis of other hematological parameters was not performed. Even though, studies reported dNLR in patients treated with SABR are rare, our findings should be interpreted with caution and require to be confirmed in a large randomized prospective analysis.

5. Conclusion

In conclusion, we demonstrated that dNLR as a systemic inflammation biomarker was correlated with DFS and OS in early stage NSCLC patients treated with SABR. It is a readily available tool and could be served as an independent prognostic marker in daily practice. Future clinical trials are needed to determine dNLR as a stratification factor and select eligible patients treated with SABR.

Author contributions

Investigation: Xin Wang, Zhi Lou, Lei Zhang, Zhenghong Liu, Jie Zhang, Jia Gao, Yajun Ji
Methodology: Xin Wang, Zhi Lou, Lei Zhang.
Resources: Xin Wang, Zhenghong Liu, Jie Zhang.
Validation: Lei Zhang, Zhenghong Liu, Jie Zhang, Jia Gao, Yajun Ji.
Visualization: Xin Wang, Zhi Lou, Lei Zhang, Jia Gao, Yajun Ji.
Writing – original draft: Xin Wang, Yajun Ji.

References

[1] Torre LA, Siegel RL, Jemal A. Lung Cancer Statistics. Adv Exp Med Biol 2016;893:1–9.
[2] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7–30.

[3] Aberle DR, Adams AM, et al. National Lung Screening Trial Research TReduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.

[4] Nanda RH, Liu Y, Gillespie TW, et al. Stereotactic body radiation therapy versus no treatment for early stage non-small cell lung cancer in medically inoperable elderly patients: a National Cancer Data Base analysis. Cancer 2015;121:4222–30.

[5] Kosmidis S, Katsochi D. Advanced radiation techniques: stereotactic body radiation therapy (SBRT) in early stage inoperable lung cancer disease. Pract Radiat Oncol 2013;3:S16.

[6] Sun B, Brooks ED, Komaki R, et al. Long-term outcomes of salvage stereotactic ablative radiotherapy for isolated lung recurrence of non-small cell lung cancer: a phase II clinical trial. J Thorac Oncol 2017;12:983–92.

[7] Sun B, Brooks ED, Komaki RU, et al. 7-year follow-up after stereotactic ablative radiotherapy for patients with stage I non-small cell lung cancer: results of a phase 2 clinical trial. Cancer 2017;123:3031–9.

[8] Herrera FG, Bourhis J, Coukos G. Radiotherapy combination opportunities leveraging immunity for the next oncology practice. CA Cancer J Clin 2017;67:65–85.

[9] Schaue D, Ratikan JA, Iwamoto KS, et al. Maximizing tumor immunity with fractionated radiation. Int J Radiat Oncol Biol Phys 2012;83:1306–10.

[10] Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. Blood 2009;114:589–95.

[11] McMillan DC. Cancer and systemic inflammation: stage the tumour and stage the host. Br J Cancer 2013;109:529.

[12] Luo H, Ge H, Cui Y, et al. Systemic inflammation biomarkers predict survival in patients of early stage non-small cell lung cancer treated with stereotactic ablative radiotherapy - a single center experience. J Cancer 2018;9:182–8.

[13] Alagappan M, Pollom EL, von Eyben R, et al. Albumin and neutrophil-lymphocyte ratio (NLR) predict survival in patients with pancreatic adenocarcinoma treated with SBRT. Am J Clin Oncol 2016;41:242–7.

[14] Mezquita L, Auclin E, Ferrara R, et al. Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. JAMA Oncol 2018;4:351–7.

[15] Cox S, Hurt C, Grenader T, et al. The prognostic value of derived neutrophil to lymphocyte ratio in oesophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol 2017;125:154–9.

[16] Proctor MJ, McMillan DC, Morrison DS, et al. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. Br J Cancer 2012;107:695–9.

[17] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.

[18] Hu P, Shen H, Wang G, et al. Prognostic significance of systemic inflammation-based lymphocyte- monocyte ratio in patients with lung cancer: based on a large cohort study. PLoS One 2014;9:e108062.

[19] Cannon NA, Meyer J, Iyengar P, et al. Neutrophil-lymphocyte and platelet-lymphocyte ratios as prognostic factors after stereotactic radiation therapy for early-stage non-small-cell lung cancer. J Thorac Oncol 2015;10:280–5.

[20] Giuliani M, Sampson LR, Wong O, et al. Prognostic value of pretreatment circulating neutrophils, monocytes, and lymphocytes on outcomes in lung stereotactic body radiotherapy. Curr Oncol 2016;23:e362–8.

[21] Shaverdian N, Veruttipong D, Wang J, et al. Pretreatment immune parameters predict for overall survival and toxicity in early-stage non-small-cell lung cancer patients treated with stereotactic body radiation therapy. Clin Lung Cancer 2016;17:39–46.

[22] Yucel S, Bilgin B. The prognostic values of systemic immune-inflammation index and derived neutrophil-lymphocyte ratio in EGFR-mutant advanced non-small cell lung cancer. J Oncol Pharm Pract 2020;1078155220913106.

[23] Yarmarkovich M, Farrel A, Sison A3rd, et al. Immunogenicity and immune silence in human cancer. Front Immunol 2020;11:69.

[24] Deng Q, He B, Liu X, et al. Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. J Transl Med 2015;13:66.

[25] Zhou Z, Folkert M, Cannon N, et al. Predicting distant failure in early stage NSCLC treated with SBRT using clinical parameters. Radiother Oncol 2016;119:501–4.

[26] Luo H, Cui Y, Song H, et al. Should stereotactic body radiotherapy doses be adjusted according to tumor size in early-stage non-small-cell lung cancer? A systematic review and meta-analysis. Future Oncol 2019;15:3071–9.