

Received: 2020.02.27
Accepted: 2020.05.18
Available online: 2020.06.18
Published: 2020.08.19

A Review of Clinical and Preclinical Studies on Therapeutic Strategies Using Interleukin-12 in Cancer Therapy and the Protective Role of Interleukin-12 in Hematological Recovery in Chemoradiotherapy

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EFG **Ping Li**
EF **Hong Zhang**
EF **Lina Ji**
EF **Zhi Wang**





Department of Pharmacy, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, P.R. China

Corresponding Author: Zhi Wang, e-mail: wangzhi@qduhospital.cn
Source of support: Self financing

Interleukin-12 (IL-12), a heterodimeric glycoprotein with α and β subunits covalently bonded with a disulfide bond, is a potent anticancer agent. Its action is accomplished through a linkage of the adaptive and innate immune responses. IL-12 can promote the recovery of the hematopoietic system after cancer chemoradiotherapy by stimulating the physiological processes of stem cells, including cell proliferation and differentiation, reconstitution of hematopoietic function, and peripheral blood count recovery. We review therapeutic strategies using IL-12 in clinical studies, including single-agent and combination strategies in hematological tumors and solid tumors, and studies on the protective effects of IL-12 in chemoradiotherapy. This review highlights promising therapeutic strategies based on the anticancer role of IL-12 and the potential protective effects of IL-12 for cancer patients receiving chemoradiotherapy.

MeSH Keywords: Hematologic Neoplasms • Interleukin-12 • Neoplasms, Second Primary

Full-text PDF: <https://www.medscimonit.com/abstract/index/idArt/923855>

 2418  —  —  39



Background

Interleukin-12 (IL-12) can exert antitumor effects by regulating innate immunity, adaptive immunity, and tumor angiogenesis [1–3]. Its antitumor activity is mainly achieved in the following ways. IL-12 can improve the tumor-killing effect of cytotoxic lymphocytes such as cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells [1]. It can also induce or increase the ability of T helper type 1 (Th1) cells to respond to CTLs and enhance the specific immunity of tumor antigens. In addition, IL-12 can increase the production of immunoglobulin G antibodies by stimulating the Th1 response [1]. Moreover, IL-12 stimulates the production of interferon- γ (IFN- γ) by immune cells, tumor necrosis factor- α (TNF- α), and “secondary” pro-inflammatory cytokines that are toxic to tumor cells and can inhibit tumor growth by inhibiting tumor angiogenesis [2]. In addition to the antitumor effects of IL-12, studies have proven that it can enhance hematological recovery after chemoradiotherapy [4–6]. Chemoradiotherapy causes damage to normal tissue cells, bone marrow suppression, and complications such as granulocytopenia and thrombocytopenia [6]. IL-12 can induce the proliferation of long-term hematopoietic stem cells by protecting the bone marrow microenvironment, stimulating the production of cytokines, and enhancing the differentiation of stem cells to progenitor cells, thereby promoting hematological recovery [4–6].

Progress in Therapeutic Strategies of IL-12 Treatment for Cancers

Single-agent therapeutic strategies using IL-12 for cancers

Preclinical animal studies have shown that IL-12 has significant antitumor activity [7–12], which advances the clinical development of IL-12. Preliminary studies have been conducted in humans to assess the safety and effectiveness of intravenous or subcutaneous injection of recombinant human IL-12 (rhIL-12) as a single-agent drug in patients with lymphoma [13–15], melanoma, colon cancer, renal cancer, and ovarian cancer [16]. These studies suggest that IL-12 single-agent therapy is more effective for lymphoma than for other tumors.

Single-agent therapy using IL-12 for cutaneous T-cell lymphoma (CTCL)

CTCL is a type of non-Hodgkin's lymphoma (NHL) that is caused by clonal expansion of T lymphocytes [13,14]. In a phase II study of CTCL [14], 23 patients were enrolled and received rhIL-12, and 10 of the patients completed the 6-month clinical study and continued treatment for 24 months. Patients receiving treatment showed a higher response rate (43%, partial response [PR]; 30%, minimal response [MR]; and 22%, no

response) than the control group. The earliest response began in week 4, and the latest response appeared in week 19. Among the 10 patients who achieved a PR, the median time to the start of the response and response in all 23 patients was 84 days and 94 days, respectively. Five patients received continuous treatment, and 4 of these patients had a MR and 1 achieved a PR. The response of CTCL to IL-12 treatment might be due to the characteristics of CTCL, specifically decreased function of Th1 cells, insufficient production of INF- γ , and the chronic production of Th2 cytokines [14].

Single-agent therapy using IL-12 for NHL and Hodgkin's disease (HD)

A clinical phase II trial of NHL and HD using IL-12 was conducted by Younes et al. [15]. Of the 42 patients receiving IL-12 treatment in this study, 11 received an intravenous injection of IL-12 (250 ng/kg) 5 times a week for 3 weeks, and 31 patients received a subcutaneous injection of IL-12, twice a week. The dosage for the subcutaneous injections was initially 500 ng/kg but was later changed to 300 ng/kg due to dose-related toxicity. Tumor response was determined during the first 8 weeks of treatment and was assessed every 2 to 3 months thereafter. Six of 29 patients had a PR or complete response (CR) (21%), and 10 patients had no disease progression (34%). These results showed that the treatment with IL-12 exerted a therapeutic effect on tumors. Intravenous injection was more effective than subcutaneous injection, with the rates of PR and CR being 40% and 7%, respectively. The severity of the disease was related to the treatment effect. The tumors of all responding patients were relatively small (the largest tumor diameter was <3 cm) [15].

Combined therapeutic strategies using IL-12 for cancer treatment

Considering the limited clinical benefits of rhIL-12 monotherapy, some researchers have conducted clinical trials with IL-12 combined with other antitumor drugs and techniques, and IL-12 has also been employed as an adjuvant therapy for tumor immunotherapy [17–20]. To date, clinical trials on the antitumor effect of IL-12 are mainly in the phase I or II stage. Most treatment strategies focus on the combination of IL-12 with chemoradiotherapy and immunotherapy, and these agents play a synergistic role in cancer treatment.

Use of IL-12 in combination with paclitaxel, trastuzumab, rituximab, and PD-1-targeted therapy

In a study on patients with HER2-positive cancers, such as breast cancer, pancreas cancer, colon cancer, thyroid cancer, esophagus cancer, and stomach cancer, the combined administration of rhIL-12 with paclitaxel and trastuzumab was effective

in 52% of 21 patients (1 patient had CR, 4 patients attained PRs, and there were 6 instances of stable disease) [17]. Patients who had a response to the combined treatment showed increases in the secretion of IFN- γ and several chemokines and activation of the ERK signaling pathway [17]. Given that IL-2 can enhance the activity of NK cells on cell lysis, cytolytic T-cell response, and secretion of IFN- γ from both types of cells [1,2], a clinical trial using IL-12 combined with an anti-CD20 antibody (rituximab) was conducted with patients with refractory NHL [18]. In this clinical study, the researchers aimed to investigate the synergistic effects of IL-2 on rituximab-induced immune-mediated cell lysis. Among 43 patients with refractory NHL treated with combination therapy using IL-12 and rituximab, 29 patients showed responses to the treatment (69%), including 11 CR (25%) and 18 PR (42%) [18]. Therefore, combination therapy of IL-2 and rituximab could benefit patients with refractory NHL. In patients with melanoma given a combination of IL-12 and PD-1-targeted therapy in a 24-week treatment cycle, the disease control rate reached 59%, and 41% (9/22) of patients had a CR [19]. IL-12 greatly reduced the incidence of adverse reactions caused by the administration of the anti-PD-1 antibody alone, and it potentiated the activity of PD-1 antibodies without increasing significant toxicity [19].

Combination therapy using IL-12 and low-dose total skin electron beam therapy (TSEBT) in CTCL

In an ongoing clinical study of IL-12 combined with low-dose TSEBT for CTCL, 150 ng/kg of rhIL-12 was injected subcutaneously on day 2 and day 15 post TSEBT (4 Gy/wk, fractionated; up to 12 Gy), followed by maintenance therapy of 100 ng/kg once every 4 weeks for 6 cycles [20]. The results showed that 5 of the 6 enrolled patients including 4 male patients with an average age of 55 years had evaluable efficacy (of the 5 patients, 1 patient had CR, 2 patients had PR, and 2 patients had stable disease) with a response rate of 60%. Three of the 5 patients had stage IB disease, 1 had stage IIB disease, and 1 had stage IIIB disease. At a median follow-up of 15 weeks, 5 patients were still being studied, and 1 patient dropped out for lichen planus that required topical steroid treatment [20]. These results indicate that rhIL-12 can be administered with low-dose TSEBT in CTCL patients, and exciting clinical results, including CR, can be achieved.

Progress in the Understanding of the Role of IL-12 in Hematological Recovery After Radiation

Protective effect of recombinant mouse (rm) IL-12 on mice receiving radiation

IL-12 stimulates bone marrow hematopoiesis and peripheral blood count recovery in irradiated mice and can prolong the

survival period of radiation-injured mice [4,5]. In a study conducted by Chen et al. [4], mice were given a single intravenous injection of IL-12 at 48, 36, 24, or 12 h before receiving lethal doses of radiation and at 1, 12, 24, or 36 h after radiation. This study showed that the long-term survival rates (>1 year) of mice given IL-12 24 h before and 1 h after irradiation were 91.4% and 75%, respectively, while all mice in the control group died within 25 days after irradiation. Evaluation of the bone marrow pathology of the mice revealed that the bone marrow composition of the IL-12-treated mice recovered to normal on the 14th day after radiation, indicating that IL-12 could stimulate bone marrow hematopoiesis. IL-12 was also found to promote peripheral blood count recovery in the mice receiving irradiation [4]. It is worth noting that IL-12 promoted the recovery of cells in whole blood. Moreover, Basile et al. [5] found that the effect of IL-12 on survival rate was not significantly affected by radiation dose in mice. In their study, mice received 3 different doses (8.6, 8.8, or 9.0 Gy) of total body irradiation for 24 h, and significant improvement in survival rate was shown in the mice that received a single dose of IL-12 (20 ng) by injection. The survival rates of the placebo groups were 20%, 10%, and 0%, respectively, much lower than those of the groups receiving IL-2 (80%, 60%, and 70%, respectively) [5]. There were no substantial differences in the survival rates of mice that received a single injection of IL-12 at the same dose but different radiation doses, suggesting that radiation dose did not significantly influence the efficacy of IL-12 [5].

IL-12 promotes hematological recovery and exerts synergistic anticancer effects in tumor-bearing mice receiving chemoradiation

To investigate the role of IL-12 on the hematological recovery of tumor-bearing mice, Basile et al. [6] established 2 tumor-bearing mouse models, the EL4 lymphoma model and the Lewis lung cancer model, which were given radiotherapy and chemotherapy. In both mouse models, compared with a granulocyte-colony stimulating factor (G-CSF) group and a control group, the IL-12 group exhibited significant hematopoietic recovery of each blood cell type and reduced tumor growth. IL-12 combined with cyclophosphamide treatment resulted in a significant reduction in tumor volume, but no significant tumor reduction was achieved with G-CSF treatment. Furthermore, radiotherapy and chemotherapy combined with IL-12 increased the tumor-free rate in the mice [6]. These results indicate that IL-12 exhibits a synergistic antitumor effect with radiotherapy and chemotherapeutics while restoring hematopoietic function.

IL-12 protects against radiation better than G-CSF in nonhuman primates

In a study using nonhuman primates that received radiation treatment as well as rhIL-12 or G-CSF, Gluzman-Poltorak et al. [21]

showed that counts for neutrophils, platelets, and red blood cells in the polar phase were significantly increased and the incidence of severe neutropenia and severe thrombocytopenia was significantly reduced in the rhIL-12 group compared with the G-CSF group. The study confirmed that a single administration of rhIL-12 could promote bone marrow regeneration and restore hematopoiesis, and the effect was stronger than that of G-CSF in the irradiated animals. Another preclinical study revealed that the survival rate of animals exposed to irradiation was closely correlated with the trough values of blood cells [22]. Blood cell analysis revealed that the median values of lymphocytes, neutrophils, and platelets in all surviving animals in the control group, the IL-12 group, and the G-CSF group were significantly greater than the values in the animals that died [22]. In further analysis of mortality and the receiver operating characteristic (ROC) curve, the positive predictive value (the percentage of actual animal deaths as a percentage of the predicted deaths) was calculated using a lymphocyte threshold of $0.08 \times 10^9/L$. The control group had a positive predictive value of 97.2%, while the rhIL-12 group had a positive predictive value of 92.5%, indicating that the lymphocyte number was a strong predictor of mortality. Neutrophils and platelets were also strong predictors of mortality [22]. These results suggest that promoting early bone marrow regeneration and increasing the trough value of all major types of blood cells, especially lymphocytes, neutrophils, and platelets, could be the main mechanism by which rhIL-12 reduces the lethal effect of severe bone marrow suppression caused by radiation.

IL-12 stimulates bone marrow hematopoietic progenitor cells to expand *in vitro*

Fardoun-Joalland et al. [23] and Grafte et al. [24] studied the *in vitro* efficacy of IL-12, using normal human peripheral blood and bone marrow mononuclear cells, respectively. They showed that in combination with rhIL-3, erythropoietin, or G-CSF, rhIL-12 could significantly enhance the formation of cell colonies. In colony culture experiments, Jacobsen et al. [25] showed that the combination of FLT3 and IL-12 or IL-11 significantly stimulated the expansion of mouse bone marrow hematopoietic progenitor cells *in vitro* [25].

Mechanism underlying the stimulatory effect of IL-12 on hematological recovery

Regarding the mechanism by which IL-12 stimulates hematopoiesis, IL-12 has been shown to act through IFN- γ . IL-12 induces

production of IFN- γ through the Stat4 pathway, and IFN- γ then acts on hematopoietic stem cells [26]. However, studies have shown that IFN- γ plays a dual role (stimulatory/inhibitory) in hematopoiesis [27–29]. The toxicity of IL-12 is related to the excessive production of IFN- γ , suggesting that the effect of IL-12 on hematological recovery may be dose related: Low doses of IL-12 can promote hematopoiesis, while high doses of IL-12 inhibit hematopoiesis by inducing excessive IFN- γ production and toxic reactions [26–29].

Concluding Remarks

Earlier nonclinical studies showed a better therapeutic effect of IL-12 alone than clinical studies using IL-12. The difference in the efficacy between the 2 types of trials is likely caused by the requirement of IL-12 for pre-existing antitumor immune responses in clinical studies, as newly vaccinated experimental animals were generally used in the nonclinical studies [30–32]. However, cancer patients in clinical trials have immune deficiency due to previous treatments and the long-term effects of disease [30,31]. Moreover, the main limiting factor for the clinical application of IL-12 monotherapy in solid tumors is the low level of IL-12 infiltration in the tumor microenvironment. The combination of IL-12 with other antitumor drugs and therapeutic techniques seems to overcome this problem [33]. Despite the potent antitumor effect of IL-12, the toxicity caused by systemic delivery of IL-12 limits its clinical application [34]. Recent studies have focused on the improvement of delivery methods, optimization of doses, and gene therapy with IL-12 [34–36]. IL-12 has been proven to have an ideal therapeutic effect on pancytopenia caused by severe radiation injury [37,38]. The high incidence of hematological toxicity caused by radiotherapy and chemotherapy often leads to the interruption of treatment due to the inhibition of hematopoietic function in cancer patients [38,39]. The development of IL-12 drug is of great significance for the treatment of decreased blood cell counts after radiotherapy and chemotherapy in cancer patients. It thus has the potential to become a blockbuster drug that overcomes the limit of hematological recovery in cancer patients receiving chemoradiotherapy, which will also benefit combination therapies using IL-2 for cancers.

Conflict of interest

None.

References:

1. Lasek W, Zagożdżon R, Jakobisiak M: Interleukin 12: Still a promising candidate for tumor immunotherapy. *Cancer Immunol Immunother*, 2014; 63(5): 419–35
2. Hagberg N, Joëlsson M, Leonard D et al: The STAT4 SLE risk allele rs7574865[T] is associated with increased IL-12-induced IFN- γ production in T cells from patients with SLE. *Ann Rheum Dis*, 2018; 77: 1070–77
3. Wang Y, Fan KT, Li JM et al: The regulation and activity of interleukin-12. *Front Biosci*, 2012; 4: 888–99
4. Chen T, Burke KA, Zhan Y et al: IL-12 facilitates both the recovery of endogenous hematopoiesis and the engraftment of stem cells after ionizing radiation. *Exp Hematol*, 2007; 35: 203–13
5. Basile LA, Ellefson D, Gluzman-Poltorak Z et al: HemaMaxTM, a recombinant human interleukin-12, is a potent mitigator of acute radiation injury in mice and non-human primates. *PLoS One*, 2012; 7: e30434
6. Basile LA, Gallaher TK, Shibata D et al: Multilineage hematopoietic recovery with concomitant antitumor effects using low dose Interleukin-12 in myelosuppressed tumor-bearing mice. *J Transl Med*, 2008; 6: 26
7. El-Shemi AG, Ashshi AM, Na Y et al: Combined therapy with oncolytic adenoviruses encoding TRAIL and IL-12 genes markedly suppressed human hepatocellular carcinoma both *in vitro* and in an orthotopic transplanted mouse model. *Exp Clin Cancer Res*, 2016; 35: 96
8. Yue T, Zheng X, Dou Y et al: Interleukin 12 shows a better curative effect on lung cancer than paclitaxel and cisplatin doublet chemotherapy. *BMC Cancer*, 2016; 16: 665
9. Bermúdez-Morales VH, Fierros-Zarate G, García-Meléndrez C et al: *In vivo* antitumor effect of an HPV-specific promoter driving IL-12 expression in a HPV 16-positive murine model of cervical cancer. *J Cancer*, 2016; 7: 1950–59
10. Ciomber A, Smagur A, Mitrus I et al: Antitumor effects of recombinant antivascular protein ABRa-VEGF121 combined with IL-12 gene therapy. *Arch Immunol Ther Exp*, 2014; 62: 161–68
11. Eckert F, Jelas I, Oehme M et al: Tumour targeted IL-12 combined with local irradiation leads to systemic tumor control via abscopal effects *in vivo*. *Oncoimmunology*, 2017; 6: e1323161
12. Fallon JK, Vandever AJ, Schlom J et al: Enhanced antitumor effects by combining an IL-12/anti-DNA fusion protein with avelumab, an anti-PD-L1 antibody. *Oncotarget*, 2017; 8: 20558–71
13. Rook A, Wood GS, Yoo EK et al: Interleukin-12 therapy of cutaneous T-cell lymphoma induces lesion regression and cytotoxic T-cell responses. *Blood*, 1999; 94: 902–8
14. Duvic M, Sherman ML, Wood GS et al: A phase II open-label study of recombinant human interleukin-12 in patients with stage IA, IB, or IIA mycosis fungoides. *J Am Acad Dermatol*, 2006; 55: 807–13
15. Younes A, Pro B, Robertson MJ et al: Phase II clinical trial of interleukin-12 in patients with relapsed and refractory non-Hodgkin's lymphoma and Hodgkin's disease. *Clin Cancer Res*, 2004; 10: 5432–38
16. Tuguez S, Burkhard SH, Ohs I et al: New insights into IL-12-mediated tumor suppression. *Cell Death Differ*, 2015; 22: 237–46
17. Bekaii-Saab TS, Roda JM, Guenterberg KD et al: A phase I trial of paclitaxel and trastuzumab in combination with interleukin-12 in patients with HER2/neu-expressing malignancies. *Mol Cancer Ther*, 2009; 8: 2983–91
18. Ansell SM, Witzig TE, Kurtin PJ et al: Phase I study of interleukin-12 in combination with rituximab in patients with B-cell non-Hodgkin lymphoma. *Blood*, 2002; 99: 67–74
19. Canton DA, Shirley S, Wright J et al: Melanoma treatment with intratumoral electroporation of tavokinogene telseplasmid (pIL-12, tavokinogene telseplasmid). *Immunotherapy*, 2017; 9: 1309–21
20. Kim YH, Hoppe RT, Rook AH et al: A single-arm PHASE 2A study of NM-IL-12 (rHu-IL12) in patients with mycosis fungoides-type CTCL (MF) undergoing low-dose TOTAL skin electron BEAM therapy (LD-TSEBT). *Blood*, 2016; 128: 4165
21. Gluzman-Poltorak Z, Vainstein V, Basile LA: Recombinant interleukin-12, but not granulocyte-colony stimulating factor, improves survival in lethally irradiated nonhuman primates in the absence of supportive care: Evidence for the development of a frontline radiation medical countermeasure. *Am J Hematol*, 2014; 89: 868–73
22. Gluzman-Poltorak Z, Vainstein V, Basile LA: Association of hematological nadirs and survival in a nonhuman primate model of hematopoietic syndrome of acute radiation syndrome. *Radiat Res*, 2015; 184: 226–30
23. Fardoun-Joalland D, Teixeira-Lebrun G, Lenormand B et al: Synergism of interleukin-12 and interleukin-3 on development of hematopoietic progenitors. *Eur J Haematol*, 2010; 54: 172–75
24. Grafte S, Lévêque C, Paysant J et al: IL-12 indirectly enhances proliferation of 5-FU-treated human hematopoietic peripheral blood CD34+ cells. *Am J Hematol*, 1998; 58: 183–88
25. Jacobsen SE: The FLT3 ligand potently and directly stimulates the growth and expansion of primitive murine bone marrow progenitor cells *in vitro*: Synergistic interactions with interleukin (IL) 11, IL-12, and other hematopoietic growth factors. *J Exp Med*, 1995; 181: 1357–63
26. Broxmeyer HE, Bruns HA, Zhang S et al: Th1 cells regulate hematopoietic progenitor cell homeostasis by production of oncostatin M. *Immunity*, 2002; 16: 815–25
27. Maciejewski J, Selleri C, Anderson S et al: Fas antigen expression on CD34+ human marrow cells is induced by interferon gamma and tumor necrosis factor alpha and potentiates cytokine-mediated hematopoietic suppression *in vitro*. *Blood*, 1995; 85: 3183–90
28. Zoumbos NC, Gascon P, Djou JY et al: Interferon is a mediator of hematopoietic suppression in aplastic anemia *in vitro* and possibly *in vivo*. *Proc Natl Acad Sci USA*, 1985; 82: 188–92
29. Zhao X, Gliang R: Brief report: Interferon-gamma induces expansion of Lin(-) Sca-1(+)C-Kit(+) cells. *Stem Cells*, 2010; 28: 122–26
30. Zhang L, Feng D, Hu Y et al: IL-12 augments antitumor responses to cycled chemotherapy. *J Immunother*, 2015; 38: 137–44
31. Gokhale MS, Vainstein V, Tom J, et al: Single low-dose rHuIL-12 safely triggers multilineage hematopoietic and immune-mediated effects. *Exp Hematol Oncol*, 2014; 3: 11
32. Ruan S, McKinley L, Zheng M et al: Interleukin-12 and host defense against murine pneumocystis pneumonia. *Infect Immun*, 2008; 76: 2130–37
33. Deplanque G, Shabafrouz K, Obeid M: Can local radiotherapy and IL-12 synergize to overcome the immunosuppressive tumor microenvironment and allow “*in situ* tumor vaccination”? *Cancer Immunol Immunother*, 2017; 66: 833–40
34. Lupi LA, Delella FK, Cuciolo MS et al: P-MAPA and interleukin-12 reduce cell migration/invasion and attenuate the toll-like receptor-mediated inflammatory response in ovarian cancer SKOV-3 cells: A preliminary study. *Molecules*, 2019; 25(1): 5
35. Li J, Lin W, Chen H et al: Dual-target IL-12-containing nanoparticles enhance T cell functions for cancer immunotherapy. *Cell Immunol*, 2020; 349: 104042
36. Chiocca EA, Yu JS, Lukas RV et al: Regulatable interleukin-12 gene therapy in patients with recurrent high-grade glioma: Results of a phase I trial. *Sci Transl Med*, 2019; 11(505): eaaw5680
37. Mills BN, Connolly KA, Ye J et al: Stereotactic body radiation and interleukin-12 combination therapy eradicates pancreatic tumors by repolarizing the immune microenvironment. *Cell Rep*, 2019; 29: 406–21
38. Guo N, Wang WQ, Gong XJ et al: Study of recombinant human interleukin-12 for treatment of complications after radiotherapy for tumor patients. *World J Clin Oncol*, 2017; 8: 158–67
39. Umeda Y, Tsujikawa T, Anzai M et al: The vertebral 3'-deoxy-3'-18F-fluorothymidine uptake predicts the hematological toxicity after systemic chemotherapy in patients with lung cancer. *Eur Radiol*, 2019; 29: 3908–17