

Video-assisted thoracoscopic surgery lobectomy for lung cancer versus thoracotomy: a less decrease in sVEGFR2 level after surgery

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Background: Angiogenic and anti-angiogenic factors play an important role in tumor biology and tumor recurrence after surgical resection. Antiangiogenic factors such as vascular endothelial growth factor (VEGF)-receptor 1 (sVEGFR1) and sVEGFR2, two soluble form receptor proteins of VEGF, are critical for angiogenesis. VEGF can be sequestered by soluble forms of these receptors, which result in decreasing VEGF amount available to bind to its receptor on vascular endothelial cell surface. This study aimed to investigate the influences of video-assisted thoracoscopic surgery (VATS) lobectomy and open by thoracotomy for early stage non-small cell lung cancer (NSCLC) on postoperative circulating sVEGFR1 and sVEGFR2 levels.

Methods: Forty-eight lung cancer patients underwent lobectomy through either VATS (n=26) or thoracotomy (n=22). Blood samples were collected from all patients preoperatively and postoperatively on days 1, 3 and 7. ELISA analysis was used to determine the plasma levels of sVEGFR1 and sVEGFR2. Data are reported as means and standard deviations, and were assessed with the Wilcoxon signed-Rank test ($P < 0.05$).

Results: For all patients undergoing lobectomy, postoperative sVEGFR1 levels on days 1 and 3 were markedly increased, while postoperative sVEGFR2 levels on days 1 and 3 were significantly decreased. Moreover, VATS group had significantly higher plasma level of sVEGFR2 postoperative in comparison with open thoracotomy (OT) on day 1 (VATS $6,953 \pm 1,535$ pg/mL; OT $5,874 \pm 1,328$ pg/mL, $P < 0.05$).

Conclusions: Major pulmonary resection for early stage NSCLC resulted in the increased sVEGFR1 and decreased sVEGFR2 productions. VATS is associated with enhanced anti-angiogenic response with higher circulating sVEGFR2 levels compared with that with OT. Such differences in anti-angiogenic response may have an important effect on cancer biology and recurrence after surgery.

Keywords: Video-assisted thoracoscopic; thoracotomy; antiangiogenic factors

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Introduction

Vascular endothelial growth factor (VEGF), the most potent angiogenic factor noted to date, is vital to both wound healing and tumor growth by directly inducing vascular endothelial cell proliferation, migration, tube formation and angiogenesis (1). The plasma level of VEGF rises and reaches the maximal level at two weeks after major surgical injury, and then gradually decreases until four weeks after operation (2). The VEGF family consists of five related homodimeric glycoproteins in mammals, including VEGF-A, B, C, D, E and placenta growth factor (PlGF)-1 and 2 (3). The biological effects of VEGF are mediated by VEGF receptors (VEGFRs), a major type of cell surface receptor, leading to their subsequent hetero- or homo-dimerization and activation through transphosphorylation (4-6).

VEGFR1 and VEGFR2 are the two major VEGF receptors and exhibit high structure similarities. But both receptors have substantial difference such as VEGF-binding properties, signal transduction and angiogenesis (7,8). sVEGFR1 and sVEGFR2 are the soluble forms of each receptor through alternative splicing of VEGFR1 and VEGFR2 mRNA. Due to lack of the intracellular kinase domains, they can't induce signaling transduction. But the presence of extracellular VEGF-binding domains in sVEGFR1 and sVEGFR2 ensure that they can sequester plasma VEGF and decrease the level of free VEGF, thus decreasing pro-angiogenic effect on vascular endothelial cell. sVEGFR1 and sVEGFR2 are considered as negative regulators in the process of angiogenesis by decreasing the availability of VEGF to the endothelial cells (9-11).

Surgical resection remains the standard therapy for lung cancer, however, a high percentage of patients develop recurrences in recent years (12). As mentioned above, the levels of VEGF are progressively increased after surgery for at least two weeks in lung cancer patients. The persistent increase of VEGF level may stimulate the growth of residual tumor in cancer patients and the formation of new blood vessels in solid lung cancer. Therefore, the balance of VEGF and its soluble form of receptors, sVEGFR1 and sVEGFR2, is critical for regulating vessel formation.

Presently, minimally invasive video-assisted thoracoscopic surgery (VATS) and OT are the two major types of thoracic surgery, and pulmonary resection remains the mainstay of treatment for lung cancer patients. Although considerable controversy about the advantages of VATS compared with conventional approach still remains (13), VATS has been used more and more in daily practice for the treatment of

lung cancers especially NSCLC in the last decade (14,15).

Little is known about the influences of VATS lobectomy and open by thoracotomy for early stage non-small cell lung cancer (NSCLC) on postoperative circulating sVEGFR1 and sVEGFR2 levels. The purpose of this study was to determine and compare the impact of VATS and OT on the plasma levels of sVEGFR1 and sVEGFR2 during the first week after surgery in lung cancer patients.

Materials and methods

Study population

In this study, 48 patients with stage I NSCLC, who were found solitary pulmonary mass by chest X-ray or CT scan at the First People's hospital of Yunnan Province between January 2013 and June 2014, were recruited. The pathologic classification of lung cancer was confirmed by histological examination. Patients who had received preoperative radiotherapy and chemotherapy were excluded. Written informed consents were given and approval for this study was obtained from the research ethics committee of Kunming University of Science and Technology.

Patients were operated by either VATS (n=26) or OT (n=22). The VATS lobectomy procedure was performed by a standardized three-port anterior approach described by us (16-19). The OT procedure was performed by either the direct anterior approach or the posterolateral approach. Contraindications to the VATS approach include the followings: T3 or T4 lung cancer, tumor larger than 6 cm, centrally placed tumors in the hilum and adherent to vessels, tumors visible in the bronchus. There was no significant difference in baseline variables including age, gender, cancer stage and histology between VATS group and OT group.

Blood sampling, processing and the determination of sVEGFR1 and sVEGFR2 levels

Blood samples were obtained preoperatively (PreOP) within 4 h of surgery and on postoperative days (POD) 1, 3 and 7 for all patients. Plasma was used to evaluate the sVEGFR1 and sVEGFR2 concentration in blood, and EDTA was used as an anticoagulant. Within 30 minutes after the collection, the plasma was isolated via centrifugation at 500 g and stored frozen at -20 °C to avoid loss of bioactive of sVEGFR1 and sVEGFR2. The concentrations of sVEGFR1 and sVEGFR2 were determined by commercially

Table 1 Clinical data

Variables	VATS	OT
Patient number	26	22
Age (years)	61.6±8.2	64.7±10.6
Male/female	17/9	14/8
Tumor diameter (cm)	2.9±0.7	3.5±1.1
Tumor histology		
SCC/Adeno/other	3/19/4	4/15/3
Pathological TNM stage		
I	17	14
IIa	5	4
IIb	4	4
Operative duration (min)	172±41	158±35

VATS, video-assisted thoracoscopic surgery; OT, open thoracotomy; SCC, squamous cell carcinoma; Adeno, adenocarcinoma.

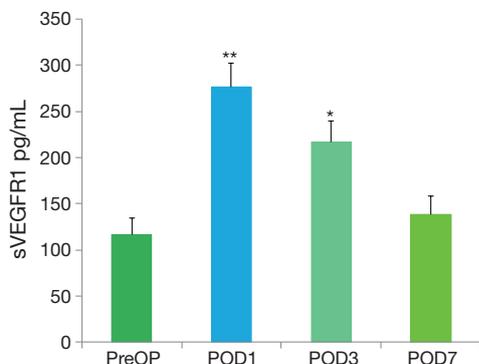


Figure 1 ELISA determined perioperative period plasma sVEGFR1 levels in patients of both VATS and OT groups. The data were reported as the mean value of sVEGFR1 from all patients because there was no significant difference in the levels of sVEGFR1 between VATS and OT groups at any time point measured. **PreOP vs. POD1, 119.5±15.6 vs. 274.6±23.7 pg/mL, P<0.01. *PreOP vs. POD3, 119.5±15.6 vs. 222.5±20.9 pg/mL, P<0.05. VATS, video-assisted thoracoscopic surgery; OT, open thoracotomy; POD, postoperative day; PreOP, preoperatively.

available enzyme-linked immunosorbent assay (ELISA) kits (eBioscience, San Diego, CA, USA). All procedures were performed according to the manufacturer's instructions.

Statistical analyses

SPSS 19.0 statistics package was used for statistical analysis.

The experimental data were reported with means and standard deviations, and compared by independent samples *t*-tests. The non-parametric Mann-Whitney *U*-test was used to analyze clinical variables. All categorical data such as sex and tumor stage were expressed as frequencies and compared by Fisher's exact test. A two-sided P value of less than 0.05 was considered significant.

Results

Clinical finding

In this study, a total of 48 NSCLC patients met the study criteria and were recruited. Twenty six of them were in the VATS group and 22 were in the OT group. There were no significant demographic differences between these two groups (Table 1). The duration of surgery for patients of both VATS and OT groups were not significantly different in this study, although there was a weak tendency towards a slightly longer procedure for VATS. The number and location of lymph nodes dissected were comparable between the two groups. No blood transfusion was required in the surgical procedures for any patients, and there was no perioperative mortality or severe complications after surgery.

Effect of different treatments on sVEGFR1 level

No significant difference was observed in the levels of sVEGFR1 between VATS and OT groups at any time point measured, so the data were reported as the mean value of sVEGFR1 from all patients. The mean levels of sVEGFR1 detected in all patients at each time point are presented in Figure 1. The mean preoperative sVEGFR1 value or baseline for all patients was 119.5±15.6 pg/mL. The mean sVEGFR1 levels on POD1 (274.6±23.7 pg/mL, P<0.01), on POD3 (222.5±20.9 pg/mL, P<0.05) were significantly higher than the preoperative result (Figure 1). No significant difference was observed between the POD7 time point and the baseline.

Effect of different treatments on sVEGFR2 level

The mean sVEGFR2 levels detected in both VATS group and OT group at each time point are presented in Figure 2. When compared with preoperative sVEGFR2 basal level (VATS, 8,556.3±1,627.5 pg/mL; OT, 8,621.1±2,060.7 pg/mL), significant decreases were noted in both groups on POD1

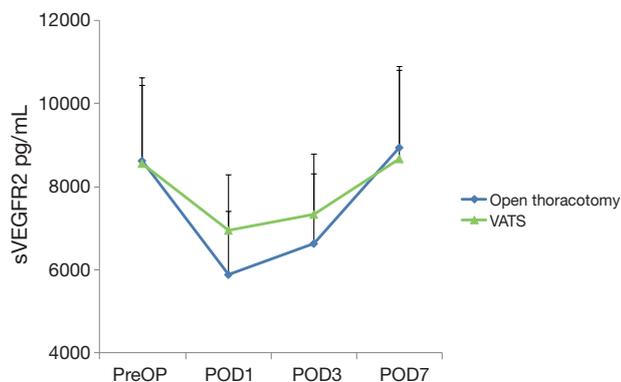


Figure 2 Comparison of the perioperative period plasma sVEGFR2 levels between VATS group and OT group. There were significant decreases in both groups on POD1 (VATS, $6,753.5 \pm 1,535.9$ pg/mL, $P < 0.05$; OT, $6,640.1 \pm 1,452.3$ pg/mL, $P < 0.01$) and on POD3 (VATS, $7,336.4 \pm 1,672.5$ pg/mL, $P < 0.05$; OT, $6,640.1 \pm 1,452.3$ pg/mL, $P < 0.05$) in comparison with preoperative sVEGFR2 basal level (VATS, $8,556.3 \pm 1,627.5$ pg/mL; OT, $8,621.1 \pm 2,060.7$ pg/mL). In addition, sVEGFR2 level in VATS group decreased less than in OT group on POD1 ($P < 0.05$), no significant difference in sVEGFR2 levels was observed between two groups on POD3, On POD7, sVEGFR2 had a tendency to return to normal level in both groups. VATS, video-assisted thoracoscopic surgery; OT, open thoracotomy; POD, postoperative day.

(VATS, $6,753.5 \pm 1,535.9$ pg/mL, $P < 0.05$; OT, $6,640.1 \pm 1,452.3$ pg/mL, $P < 0.01$), on POD3 (VATS, $7,336.4 \pm 1,672.5$ pg/mL, $P < 0.05$; OT, $6,640.1 \pm 1,452.3$ pg/mL, $P < 0.05$). Furthermore, there was a significant difference in the level of sVEGFR2 between the two groups on POD1 ($P < 0.05$), sVEGFR2 level in VATS group decreased less than in OT group. While no significant difference was observed on POD3. On POD7, sVEGFR2 had a tendency to return to normal level in both groups.

Discussion

Lung cancer remains the leading cause of cancer death in the world. VATS has completely revolutionized modern thoracic surgery. In the past 20 years, VATS lobectomy technique transform from an experimental procedure to the standard of care for patients with early stage NSCLC (20). Potential benefits of VATS for lung cancer resections compared to OT include smaller incision, less pain, less blood loss, reduced postoperative complications, shortened length of stay and hospital cost reduction (21-23). The potential advantages following VATS major lung resection

have given rise to numerous speculations on the possible mechanisms, including weakened acute inflammatory responses (24), better preserved immune functions resulting in improved tumor immune-surveillance (25,26), alterations to tumor microenvironment and its effect on tumor angiogenesis.

Angiogenesis is essential for tumor growth and metastasis, and VEGF is presently the most potent inducers of angiogenesis. The VEGF release after surgery may have undesirable effects on residual tumor cells, and could promote tumor growth and metastasis formation (4). Previous studies have shown there was significantly higher level of circulating VEGF at POD3 in the Open group in comparison with the VATS group (1). VEGF exerts its function by binding to VEGFR on endothelial cells. The VEGF binding sites on the soluble and EC-bound VEGFR are identical. So it is assumed that once VEGF is bound to sVEGFR, it cannot bind to EC-bound VEGFR, sVEGFR are thought to sequester plasma VEGF and counteract the functions of VEGF.

In recent years, many researches are attempting to investigate the relationship between sVEGFRs and cancer, and the role of sVEGFRs in the formation of metastasis. The results of some studies have shown significantly higher levels of sVEGFR1 and sVEGFR2 in the plasma of women with breast cancer than in the control group (27,28), higher concentrations of sVEGFR1 in malignant pleural effusion than in benign pleural effusion (29). Additionally, other studies indicated that the high levels of sVEGFR1 or the high ration of sVEGFR1:VEGF within tumor tissue and in plasma correlated with high stage of cancer or worst prognosis, although the potential mechanisms remain unknown (30).

In this study, we found an early increase in circulating sVEGFR1 level, whereas a great decrease in sVEGFR2 level after surgery in both groups. Furthermore, a less sVEGFR2 decrease was observed in VATS group when compared with Open group. This study also found that the plasma sVEGFR2 level was greater than the corresponding sVEGFR1 level at all time points, and this phenomenon has been observed in patients following major colorectal surgery (9,10). Thus, it is demonstrated that the effect of the decrease in sVEGFR2 level predominates over the effect of the increase in sVEGFR1 level during the early postoperative days with respect to the total soluble receptor concentration. Moreover, VATS had little impact on the level of sVEGFR2 in comparison with OT, sVEGFR2 level was maintained at a constant concentration to sequester

and discourage angiogenesis in the perioperative period following VATS. The less impact of VATS on the level of anti-angiogenic factor sVEGFR2 may be one of the potential mechanisms supporting advantages of VATS lobectomy.

However, it is notable that numerous cytokines and cofactors including neuropilin-1, neuropilin-2 and heparin differentially modulate the affinity of VEGF for VEGFR1 and VEGFR2 or sVEGFR1 and sVEGFR2 (9). Without measuring the levels of these molecules during the first postoperative days, so it is difficult to evaluate the exact effects of sVEGFRs on free plasma VEGF. In addition, it is reported that there is higher level of sVEGFR2 on the endothelial cell membrane in comparison with sVEGFR1 (10), we did not investigate the impact of different types of surgery on endothelial cell surface expression of VEGFR1 and VEGFR2, so it remains unknown whether the relative portion of VEGFRs in the endothelial cell membrane changes responding to surgical procedures. Selection bias is another important factor to affect the accuracy of research results, because it is impossible to ethically make a prospective and randomized comparison between VATS and open lobectomy. Perioperative investigations concerning these aspects will lead to better characterization of the effect of surgical procedures on early postoperative plasma protein composition with respect to angiogenesis and tumor growth.

Conclusions

In conclusion, major lung resection for early stage NSCLC is associated with changes in postoperative anti-angiogenic factors sVEGFR1 and sVEGFR2 levels. Dramatic increase of sVEGFR1 levels and great decrease of sVEGFR2 levels were observed in both VATS group and OT group. More important, there was a less decrease of sVEGFR2 level in VATS group when compared with OT group. Minimally invasive VATS approach resulted in relatively stronger antiangiogenic response in the early postoperative period in comparison with the OT approach. The effect of postoperative changes in anti-angiogenic factors on tumor angiogenesis after lung cancer surgery warrants further research.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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