Original Article
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Oxidized Regenerated Cellulose can be a Cause of False Tumor Recurrence on PET/CT in Patients with Lung Cancer Treated Surgically

Cerrahi Olarak Tedavi Edilen Akciğer Kanserlerinde Okside Rejenere Selüloz, PET/BT'de Yalancı Tümör Nüksünün Bir Sebebi Olabilir

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Abstract

Objectives: Regular follow-up of patients with lung cancer treated surgically is crucial to detect local recurrence or distant metastasis of the tumor. Postoperative follow-ups are performed with thorax computed tomography (CT) and, if necessary, positron emission tomography (PET)/CT. Sometimes, inflammatory tissue reactions due to the materials used during the surgery for hemostasis may cause the appearance of tumor recurrence in imaging modalities. In this study, we presented that oxidized regenerated cellulose (ORC) used intraoperatively may cause false tumor recurrence on PET/CT.

Methods: The records of patients who had local tumor recurrence after lung cancer surgery was reviewed retrospectively. Inclusion criteria were the presence of local recurrence of cancer on PET/CT, specification of using ORC in the surgical notes, and histopathological diagnosis of the recurrence site of tumor was reported as a foreign body reaction. Data of patients were collected according to age, gender, surgery performed, adjuvant therapy status, resolution status and time ORC, and standard uptake value of ^{18}F-fluorodeoxyglucose on PET/CT.

Results: Eleven patients (1 female, 10 males) who met the criteria were included in the study. The median age was 64. Histopathological results of all patients were reported as foreign body reactions. The median detection time of PET/CT positivity after surgery was 139 days (range: 52-208 days). False tumor recurrence was resolved in 8 patients (72.7%) in their control radiological examinations and median resolution time was 334 days (range: 222-762 days). The median maximum standard uptake value of the lesions was 6.2 (1.7-11) on the PET/CT.

Conclusion: ORC used intraoperatively in patients undergoing surgery for lung cancer may cause false tumor recurrence in imaging modalities in postsurgical follow-ups. When tumor recurrence is suspected in the follow-up of these patients, histopathological confirmation is necessary to prevent unnecessary operations and treatments.

Keywords: Lung cancer, positron emission tomography/computed tomography, false recurrence, and oxidized regenerated cellulose

Öz

Amaç: Cerrahi olarak tedavi edilen akciğer kanserli hastaların düzenli takibi, lokal nüks ve uzak metastaz saptanmasında oldukça önemlidir. Postoperatif takipler toraks bilgisayarlı tomografi (BT) ve gerekirse pozitron emisyon tomografisi (PET)/BT ile yapılır. Bazen hemostaz sağlamak

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için ameliyat sırasında kullanılan materyallere bağlı enflamatuvar doku reaksiyonları görüntüleme modalitelerinde tümör nüksü görünümüne neden olabilir. Bu çalışmada intraoperatif kullanılan oksitlenmiş rejenere selülozun (ORS), PET/BT'de yalancı tümör nüksüne neden olabileceğini göstermeyi amaçladık.

Yöntem: Akciğer kanseri cerrahisi sonrası lokal tümör nüksü gelişen hastaların kayıtları geriye dönük olarak incelendi. Dahil edilme kriterleri, PET/BT'de lokal kanser nüksü varlığı, cerrahi notlarda ORS kullanımının belirtilmesi ve tümörün nüks bölgesinin histopatolojik tanısının yabancı cisim reaksiyonu olarak bildirilmesiydi. Hastalara ait yaş, cinsiyet, yapılan cerrahi, adjuvan tedavi durumu, rezolüsyon durumu ve ORC süresi ve PET/BT'deki ^{18}F-florodeoksiglukoz standart uptake değeri verileri toplandı.

Bulgular: Kriterleri karşılayan 11 hasta (1 kadın, 10 erkek) çalışmaya dahil edildi. Ortanca yaş 64 idi. Tüm hastaların histopatolojik raporları yabancı cisim reaksiyonu olarak rapor edildi. Ameliyattan sonra PET/BT pozitifliğinin ortanca tespit süresi 139 gündü (dağılım: 52-208 gün). Kontrol radyolojik incelemelerinde 8 hastada (%72,7) tümör görünümü düzeldi ve ortanca iyileşme süresi 334 gündü (dağılım: 222-762 gün). PET/BT'de lezyonların ortanca maksimum standard tutulum değeri 6,2 idi (dağılım: 1,7-11).

Sonuç: Cerrahi olarak tedavi edilen akciğer kanserli hastaların takibinde tümör nüksünden şüphelenildiğinde, gereksiz operasyon ve tedavileri önlemek için histopatolojik doğrulama gereklidir.

Anahtar kelimeler: Akciğer kanseri, pozitron emisyon tomografi bilgisayarlı tomografi, yalancı nüks

Introduction

Surgery is the optimal treatment option for patients with clinically early-stage non-small-cell lung cancer (NSCLC). However, adjuvant treatment such as chemotherapy and/or radiotherapy, may be required depending on the patient's pathological tumor stage, complete resection status, and tumor histopathology. Despite all efforts, the 5-year survival in all stages of NSCLC is less than 50%, and the median expected survival after tumor recurrence has been reported as 11.5 months (1,2,3). Follow-up of patients after surgery for detecting local tumor recurrence or distant metastasis is usually performed with computed tomography (CT) and/or positron emission tomography (PET)/CT. PET/CT is the preferred method for follow-up due to its high sensitivity and specificity for tumor recurrence. Furthermore, it is also a suitable procedure for evaluating the response to adjuvant therapy (4,5). Oxidized regenerated cellulose (ORC) is an absorbable hemostatic material that has long been used for bleeding control in neurosurgery, hepatic surgery, renal surgery, and cardiothoracic surgery. Although some studies in the literature have reported that ORC can cause false tumor recurrence, its PET/CT findings of false tumor recurrence after lung cancer surgery are unclear (6,7,8,9). In this study, we presented ORC used intraoperatively may cause false tumor recurrence on PET/CT.

Materials and Methods

Patient Selection

Following the approval of the Gazi University Ethics Committee (no: 91610558-604.01.02, research code no: 2020-366), the medical records of patients who underwent surgery for NSCLC between January 2018 and August 2020 were examined retrospectively. An informed consent form was obtained from the patients or their relatives included in the study. During the study period, data of patients with cancer recurrence detected on imaging modality, were collected. Inclusion criteria were, detection of local recurrence of lung cancer at the surgical side on PET/CT, specification of using ORC in the surgical notes, and reporting of histopathological diagnosis of biopsy taken from the recurrence site was the foreign body reaction. Patients whose histopathological result were reported as only "non-malignant" were not included in the study. In addition, patients whose follow-up records could not be obtained, and those whose surgical notes did not indicate the use of ORC, were excluded from the study. Data of patients were collected according to age, gender, localization of recurrence, adjuvant therapy status, smoking status, resolution status, total resolution time (day) of agent, maximum standard uptake value (SUV_{max}) on the PET/CT, stage of the tumor, comorbidity status, postoperative complication, and the detection time of false tumor recurrence.

Statistical Analysis

All analyses were performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Due to the small sample size, we only performed descriptive analysis. Descriptive data were expressed in mean ± standard deviation (SD), median (minimum-maximum) or number and frequency. The distribution of numeric variables was evaluated by histogram and Kolmogrov-Smirnov test. The mean ± SD was used for normal distributions and median value with range (minimum-maximum) was used for skewed distributions.

Results

During the study period, we detected 293 patients undergoing surgery for NSCLC in our clinic, and 160 of them (54.7%) required adjuvant treatment. Eleven of the

Table 1. Characteristics of the patients included in the study

Case	Age	Sex	Smoking P/Y	Co-morbidity	Diagnosis	Surgery	Post-op course	Induction therapy	Adjuvant therapy	Localization	PET/CT SUV_{max}	pTNM[1]	Detection time[2] (day)	Resolution time (day)
1	59	M	90	-	TTNA	BLI	Pneumonia	-	CRT	Intercostal	9.6	T1cN2M0	128	Unknown
2	65	M	60	CAD, HT	EBUS-TBNA	RUSL	-	CT	CT	RPT	11	T1cN1M0	120	762
3	69	M	100	COPD	EBUS-TBNA	RUSL	-	-	CT	RPT	6.2	T3N0M0	52	222
4	63	M	30	HT	EBUS-TBNA	V-RUL	-	-	CRT	Hilar	2.9	T1N2M0	208	No resolved (progression)
5	60	F	15	HT, DM	EBUS-TBNA	RUL + S6	-	CT	CRT	SC, RPT	9.3	T1aNoM0	139	519
6	66	M	30	HT, Arrhythmia	T	RML	Pneumonia	-	-	Bronchial stump	5.9	No viable tumor	154	343
7	55	M	60	-	EBUS-TBNA	LP	Pneumonia Pl. effusion	CT	CT	Hilar	2.9	T2bN0M0	149	No resolved
8	62	M	45	CAD	EBUS-TBNA	VRS1	-	-	CT	RPT	6.2	T1bN0M0	149	326
9	64	M	-	HT	EBUS-TBNA	RUL	-	-	CRT	RPT	1.7	T4N2M0	105	316
10	77	M	90	-	EBUS-TBNA	LUL	Pneumonia	-	-	SC	4.4	T2bN0M0	135	431
11	66	M	50	-	EBUS-TBNA	BLI	COVID-19pneumonia	-	CT	SC	10.4	T3N0M0	132	317

1: According to the 8th tumor-node-metastasis system.
2: Detection time after the surgery.
BLI: Bilobectomy inferior, CAD: Coronary artery diseases, CRT: Chemo-Radiotherapy, COPD: Chronic obstructive pulmonary diseases, CT: Chemotherapy, EBUS-TBNA: Endobronchial ultrasound-guided transbronchial needle aspiration, HT: Hypertension, LP: Left pneumonectomy, LUL: Left upper lobectomy, P/Y: Pack/year, Pl: Pleural, RML: Right middle lobectomy, RPT: Right paratracheal, RUL: Right upper lobectomy, RUSL: Right upper sleeve lobectomy, S6: Lower lobe superior segmentectomy, SC: Subcarinal, T: Thoracotomy, TTNA: Transthoracic needle aspiration, VRS1: VATS right upper anterior segmentectomy, V-RUL: VATS right upper lobectomy

patients who met the inclusion criteria were included in the study. The general characteristics of the patients are given in Table 1. There was 1 female (9.1%) and 10 males (90.9%); the median age was 64 (age range: 55-77). The median SUV_{max} was 6.4 (range: 1.7-11, Figure 1) on PET/CTs. Diagnosis was made with transthoracic tru-cut needle biopsy in 1 patient (9.1%), thoracotomy in 1 patient (9.1%), and EBUS-TBNA in 9 patients (81.8%) (Figure 2a). Histopathological results of all patients were reported as foreign body reactions (Figure 2b). Nine patients (81.8%) received adjuvant therapy. The most common area of false tumor recurrence was the right paratracheal area in 5 patients (45.4%). The median detection time of PET/CT positivity after surgery was 139 days (range: 52-208 days). False tumor images improved in 8 patients (72.7%) in their control radiological examinations. ORC was not resorbed radiologically in 2 patients. The median resolution time of ORC was 334 days (range: 222-762 days). Radiological progression was detected in one patient, and the histopathological report of the biopsy taken by EBUS-TBNA indicated a true tumor recurrence in the same region 18 months after the initial surgery. One of the patients included in the study died and the survival was 31 months. Other patients were alive at the date of the study and the median survival was 34 months (Table 2).

Discussion

In this study, we demonstrated that ORC can cause false tumor recurrence in some patients due to delayed absorption. Tumor recurrence is not rare in patients who underwent surgery for NSCLC. About 40% of all tumor recurrences is isolated in distant metastases, while the remaining recurrences are local or combined (local and distant). The incidence of isolated local tumor recurrence after surgery has been reported to range between 6 and 28% and 20%-40% for stage I and stage II tumors, respectively. Unfortunately, in the case of local tumor recurrence or distant metastasis, treatment success is low and the median survival time is 8.1-18.7 months (7,8). There is no definitive consensus on the postoperative follow-up period and optimal imaging modality

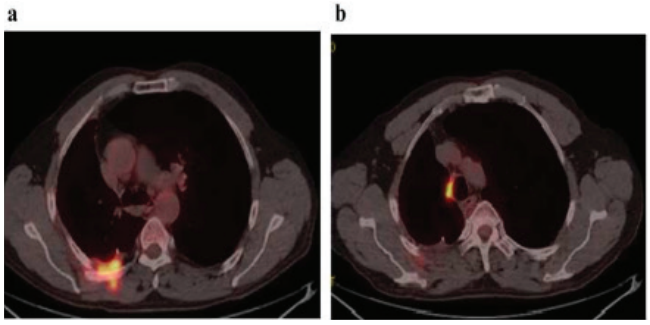


Figure 1. (a) PET/CT image of case 1. A pathological increased uptake at right posterior chest wall with SUV_{max} 9.3. Result of histopathologic examination of biopsy taken by trans-thoracic tru-cut biopsy was foreign body reaction. (b) A pathologic increased uptake (SUV_{max}: 11) was detected at the right paratracheal area on PET/CT of case 2
PET/CT: Positron emission tomography/computed tomography, SUV_{max}: Maximum standard uptake value

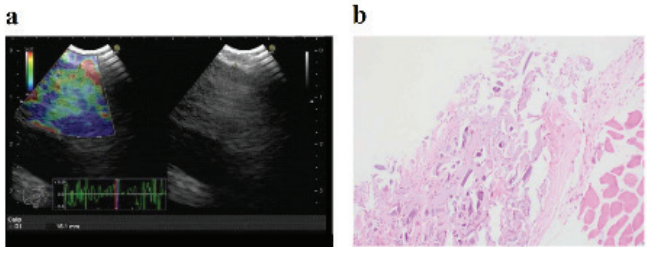


Figure 2. (a) EBUS-image of case 3 shows; indistinct margin, oval shape and heterogeneous echogenicity, partially blue partially non-blue (green, yellow and red) elastographic type in the right paratracheal area. (b) Histopathologically; granulation tissue characterized by numerous multinucleated giant cells is seen in the area adjacent to the normal muscle tissue (hematoxylin-eosin stain x100)
EBUS: Endobronchial ultrasound

Table 2. Survival time, date of surgery, and date of false positivity on PET/CT of patients

Case	Date of surgery	Date of detection	Survivability	Survival time* (month)
1	27/03/2019	02/08/2019	Alive	36
2	13/12/2018	14/04/2019	Exitus	31
3	28/06/2019	19/08/2019	Alive	32
4	11/04/2019	05/11/2019	Alive	35
5	03/07/2019	19/11/2019	Alive	32
6	02/02/2019	06/07/2019	Alive	37
7	08/05/2019	14/10/2019	Alive	34
8	06/04/2019	02/09/2019	Alive	35
9	31/01/2019	16/05/2019	Alive	37
10	31/08/2020	13/01/2021	Alive	18
11	25/08/2020	04/01/2021	Alive	18

*Survival time was calculated according to the current date for living patients. PET/CT: Positron emission tomography/computed tomography

for patients after lung cancer surgery. The common tendency is that patients are followed up with thoraco-abdominal CT or PET/CT at intervals of 3-6 months in the first 2 years, postoperatively. In our department, postsurgical follow-up is performed out in accordance with the National Comprehensive Cancer Network guidelines (radiological follow-up is performed once every 3 months in the first 2 years and PET/CT is performed in the presence of suspected tumor recurrence). The time of local recurrence and distant metastasis after surgery are similar. Boyd et al. (7) reported that the mean durations of distant metastasis and local tumor recurrence were 12.5% and 13.6 months, respectively. However, in our study, the median time of false PET/CT positivity after surgery was 139 days. The possible reason for this difference may be that early radiological tumor recurrence tends to be false positives.

In lung cancer surgery, cellulose hemostatic agents, such as ORC, are placed to provide hemostasis, particularly in the subcarinal and paratracheal areas after lymph node dissection. It may also be necessary to place it in the posterior intercostal space in patients undergoing thoracotomy. ORC is a self-absorbable product and it completely dissolves within 2-4 weeks without causing an inflammatory reaction. However, the reabsorption time of ORC may be prolonged by some reasons, and it may cause inflammation in the localizations where it is placed, thus it may give the appearance of a false tumor recurrence in PET/CT (6,10). The presence of pneumonia or pleural infection in patients during the postoperative period may cause increased inflammation around the materials. Adjuvant treatments (chemotherapy and/or radiotherapy) may also have a similar effect. In our study, most of the patients (81.8%) had a history of adjuvant therapy, and postoperative infection was only considered as the cause of false PET/CT positivity in 2 cases. Some studies in the literature have reported that these agents have the appearance of an abscess on radiological imaging, and their unnecessary use may result in the mediastinal infection (6,10,11). In our series, there were no radiological findings of an abscess, and the histopathological results were incompatible with the infection. In addition, there was no case of mediastinitis related to the use of ORC during the study period.

Study Limitations

This study had some limitations. It is a retrospective, single-center study, and it included few patients. Thus, we could not determine whether there were any correlations between false tumor recurrence and some variables, such as smoking habit, adjuvant/neoadjuvant treatment regimens, and tumor histopathology. However, this study may be

deemed a preliminary report that may inspire researchers to conduct multicenter studies with many patients.

Conclusion

Surgeons should specify whether using ORC and its localization in the surgical notes of patients undergoing pulmonary resections for lung cancer. False tumor recurrence should be considered when radiologic early tumor recurrence is detected in the postsurgical follow-up, particularly in patients receiving adjuvant therapy and those with a history of postoperative infection. Thus, unnecessary treatment and re-surgical interventions can be prevented.

Ethics

Ethics Committee Approval: Gazi University Ethics Committee (no: 91610558-604.01.02, research code no: 2020-366).

Informed Consent: An informed consent form was obtained from the patients or their relatives included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S., A.Ç., N.Y.D., G.A., İ.C.K., Concept: M.S., A.Ç., M.Ş.T., D.Ö., I.A., O.Y., N.Y.D., G.A., İ.C.K., A.İ.T., U.A., Design: M.S., A.Ç., M.Ş.T., D.Ö., I.A., O.Y., N.Y.D., G.A., İ.C.K., A.İ.T., U.A., Data Collection or Processing: M.S., A.Ç., M.Ş.T., D.Ö., I.A., O.Y., N.Y.D., G.A., İ.C.K., A.İ.T., U.A., Analysis or Interpretation: M.S., A.Ç., M.Ş.T., D.Ö., I.A., O.Y., N.Y.D., G.A., İ.C.K., A.İ.T., U.A., Literature Search: M.S., A.Ç., I.A., O.Y., Writing: M.S., A.Ç., O.Y.

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References

1. Martin J, Ginsberg RJ, Venkatraman ES, Bains MS, Downey RJ, Korst RJ, Kris MG, Rusch VW. Long-term results of combined-modality therapy in resectable non-small-cell lung cancer. J Clin Oncol 2002;20:1989-1995.
2. Sekihara K, Hishida T, Yoshida J, Oki T, Omori T, Katsumata S, Ueda T, Miyoshi T, Goto M, Nakasone S, Ichikawa T, Matsuzawa R, Aokage K, Goto K, Tsuboi M. Long-term survival outcome after postoperative recurrence of non-small-cell lung cancer: who is 'cured' from postoperative recurrence? Eur J Cardiothorac Surg 2017;52:522-528.
3. Yuan Q, Wang W, Zhang Q, Wang Y, Chi C, Xu C. Clinical features and prognostic factor of thoracic postoperative oligo-recurrence of non-small-cell lung cancer. Cancer Manag Res 2020;12:1397-1403.
4. Israel O, Kuten A. Early detection of cancer recurrence: 18F-FDG PET/CT can make a difference in diagnosis and patient care. J Nucl Med 2007;48(Suppl 1):28S-35S.
5. Weber WA, Figlin R. Monitoring cancer treatment with PET/CT: does it make a difference? J Nucl Med 2007;48(Suppl 1):36S-44S.
6. Haidari TA, Petersen RH, Skov BG, Ravn J. Oxidized resorbable cellulose (Gelita-cel) causing foreign body reaction in the mediastinum. Interact Cardiovasc Thorac Surg 2018;27:881-883. Erratum in: Interact Cardiovasc Thorac Surg 2019;29:495.
7. Boyd JA, Hubbs JL, Kim DW, Hollis D, Marks LB, Kelsey CR. Timing of local and distant failure in resected lung cancer: implications for reported rates of local failure. J Thorac Oncol 2010;5:211-214.
8. Okami J, Nishiyama K, Fujiwara A, Konishi K, Kanou T, Tokunaga T, Teshima T, Higashiyama M. Radiotherapy for postoperative thoracic lymph node recurrence of non-small-cell lung cancer provides better outcomes if the disease is asymptomatic and a single-station involvement. J Thorac Oncol 2013;8:1417-1424.
9. Williams BA, Sugimura H, Endo C, Nichols FC, Cassivi SD, Allen MS, Pairolero PC, Deschamps C, Yang P. Predicting postrecurrence survival among completely resected nonsmall-cell lung cancer patients. Ann Thorac Surg 2006;81:1021-1027.
10. Melamed JW, Paulson EK, Kliewer MA. Sonographic appearance of oxidized cellulose (Surgicel): pitfall in the diagnosis of postoperative abscess. J Ultrasound Med 1995;14:27-30.
11. Cantero M, Parra LM, Sierra-Marticorena J, Ramos A, Ganga B, Asensio A. Cellulose-derived absorbable hemostatic product as a risk factor for mediastinitis after cardiac surgery. Surg Infect (Larchmt) 2019;20:378-381.