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A different perspective on the correlation between histopathological type and PET-CT SUVmax in non-small cell lung cancer: A retrospective cohort study

Küçük hücreli dışı akciğer kanserinde histopatolojik tip ile PET-BT SUVmax arasındaki korelasyon üzerine farklı bir bakış açısı, Retrospektif kohort çalışma

Özgur Ömer Yıldız [1], İlknur Aytekin Çelik [1]

[1] Yildirim Beyazit University, Faculty of Medicine, Department of Thoracic Surgery, Ankara, Turkey

ORCID ID of the author(s)
ÖÖY: 0000-0001-7314-3131
İAÇ: 0000-0003-0754-680X

Abstract

Aim: In recent years, alternative therapies targeting directly cancer cells and targeted agents have been developed. The aim of this study is to develop a new perspective on alternative therapies on local targets, as identify the correlation between positron emission tomography-computed tomography (PET-CT) SUVmax and histological type of the tumor in non-small cell lung cancers.

Methods: This study is based on the retrospective examination of patients who underwent PET-CT for preoperative staging with non-small cell lung cancer between January 2012 and May 2018. Statistical analyses are made between SUVmax values and histopathological types.

Results: The study is including 448 patients who underwent surgery for non-small cell lung cancer. The average size of the mass was 4.5 cm and the average SUVmax value was calculated as 13.3. The patients were classified into five groups according to their histopathological diagnosis. PET-CT fluorodeoxyglucose (FDG) involvement has been classified for different histopathological types. Statistically significant correlation was identified between the tumor size and histopathological diagnosis. It was found that the difference between SUVmax values of the adenocarcinoma tumors and other types are found statistically significant. SUVmax values have been found mostly between 5-10 in patients with adenocarcinoma and 10-15 in others.

Conclusion: Considering that there are statistically significant differences between PET-CT SUVmax values of tumor cell types, we argue that radiopharmaceuticals which could provide different and local treatment should be used in cancer treatment, they should be combined with alternative therapies such as loco-regional treatment methods, and the studies in that direction should continue in line with the technological developments.

Keywords: Lung cancer, PET-CT, Radiopharmaceutica

Öz

Amaç: Son yıllarda akciğer kanserinin moleküler biyolojisi konusunda yapılan araştırmalar ile kanser hücreleri yanında normal hücreleri de hedef alan sistemik konvansiyonel tedavi yöntemlerinin yanında direk kanser hücrelerini hedef alan tedaviler gelişmiş ve böylece lokal hedefe yönelik ajanlar başlığı altında yeni tedavi alternatifleri üzerine yoğunlaşılmıştır. Bizim çalışmamızda ise amaç lokal hedefe yönelik tedavi alternatifleri konusunda farklı bir kapı aralamak, küçük hücreli dışı akciğer kanserlerinde kitle Pozitron emisyon tomografi-bilgisayarlı tomografi (PET-BT) SUVmax değerinin tümör histolojik tipi ile korelasyon gösterip göstermediğini belirlemektir.

Yöntemler: Çalışmamız, ocak 2012 ile mayıs 2018 yılları arasında preoperatif evreleme amaçlı istenen PET-BT ve sonrasında opere edilen küçük hücreli dışı akciğer kanseri olgularının retrospektif incelenmesi ile oluşturuldu. PET-BT'deki kitlenin SUVmax değeri ve histopatolojik tip kaydedilerek istatistiksel değerlendirme yapıldı.

Bulgular: Çalışmaya KHDAK nedeni ile opere edilen 448 olgu dahil edildi. Olguların ortalama kitle boyutları 4,5cm, ortalama SUVmax değerleri 13,3 olarak hesaplanmıştır. Olgular histopatolojik tanılarına göre 5 grupta toplandı. PET-BT fluorodeoksiglikoz (FDG) tutulum SUVmax değerleri gruplandırıldı ve farklı histopatolojik türde malignitelerin ağırlıklı olarak gösterdikleri tutulum değerleri belirlenmeye çalışıldı. Tümör boyutu ve histopatolojik tanılar ile SUVmax değerleri arasında anlamlı ilişki tespit edildi. Adenokarsinom hücre türüne ait tümörlerin diğer karsinomlara göre PET-BT SUVmax değerlerinin anlamlı düzeyde farklılık gösterdiği tespit edildi. SUVmax değerlerinin ağırlıklı olarak adenokarsinom olgularında 5-10 arası düzeylerde, diğer türlerde genellikle 10-15 arası tutulum gösterdiği belirlendi.

Sonuç: Tümör hücre tiplerinin PET-BT SUVmax değerleri anlamlı düzeyde farklılık gösterdiklerinden yola çıkılarak PET'te farklı ve lokal tedaviyi sağlayacak radyofarmasötiklerin kullanılması ve değişik alternatifler oluşturulması konusunda teknolojik gelişmeler baz alınarak çalışmalar devam etmelidir.

Anahtar kelimeler: Akciğer kanseri, PET-BT, Radyofarmasötikler

Corresponding author / Sorumlu yazar:
Özgur Ömer Yıldız
Address / Adres: Yıldırım Beyazıt Üniversitesi, Tıp Fakültesi, Bilkent Şehir Hastanesi, Göğüs Cerrahisi Anabilim Dalı, Ankara, Türkiye
e-Mail: dr.ooyildiz@gmail.com

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Introduction

Lung cancer is one of the most important health issues in the world due to increasing incidents and mortality rates. Lung cancer accounts for one third of deaths from cancer. Only 15% of the patients live for 5 years or longer after they are diagnosed. Despite the developments in diagnosis methods and surgical and non-surgical methods, the tumors identified during the diagnosis are not limited to the lungs in the majority of the patients [1]. In patients with non-small cell lung cancer, there is mediastinal lymph node involvement at the time of the diagnosis, and less than 33% of the patients are suitable for surgical resection [2,3].

In recent years, new alternative therapies targeting directly the cancer cells and targeted agents have been developed, in addition to the studies on the molecular biology of lung cancer and systemic conventional therapies targeting both the cancer cells and normal cells. Biophysical methods in lung parenchyma aiming for higher dose medication include embolic confinement or chemo-embolization, selective pulmonary artery perfusion without controlling venous flow, lung suffusion and isolated lung perfusion in which the lung is completely separated from the systemic circulation [4]. The common aim of these techniques is to reduce systemic toxicity for the patients who will undergo chemotherapy in case there is a metastasis from non-small cell lung cancer (NSCLC) or other organ malignancies, as well as to enable higher dose local therapies without the systemic exposure of the chemotherapy agents [5].

The aim of our study is to develop new perspectives on alternative therapies for local targets, to identify whether there is any correlation between positron emission tomography-computed tomography (PET-CT) SUVmax values and the histological type of the tumor in non-small cell lung cancer, and to develop a new perspective for this correlation to support the use of radiopharmaceuticals labelled with molecules effective in local therapy in the foreseeable future.

Materials and methods

This study is based on the retrospective examination of the patients with non-small cell lung cancer, who underwent PET-CT for preoperative staging and surgery, in the clinics we have been working between January 2012 and May 2018. All PET-CT's were taken by the same center. All the evaluations were performed using standard methodology. In this retrospective study, 448 patients who underwent PET-CT for preoperative staging 406 of the patients were (90.6%) male and 42 were female (9.3%).

Preoperative assessment of all patients included anamnesis, physical examination, respiratory function tests, electrocardiography, blood biochemistry and hemogram tests, coagulation tests, postero-anterior and lateral lung graphics, thorax computed tomography and PET-CT. All patients whose tumor size was bigger than 3cm underwent cranial magnetic resonance imaging (MRI) for preoperative staging. Tests and invasive procedures were performed based on TNM staging. Age, gender, preoperative diagnostic tests, location of the mass, SUVmax values of masses and all intrathoracic lymph nodes in PET-CT, operations performed, lymph nodes which were sampled/excised in operation, size of the tumor lesion and tumor type of all patients were recorded in the database.

The areas of FDG accumulation outside normal biodistribution was identified through an evaluation of the F-18 fluorodeoxyglucose (FDG) PET-CT scans. The SUVmax values were calculated.

Statistical analysis

All data are examined statistically; Chi Square, Correlations and One-way Anova analysis methods have been used on SPSS 16 data analysis software. The findings under the $P<0.05$ have been accepted as statistically significant.

Results

The study included 448 patients that underwent surgery for non-small cell lung cancer. 406 of the patients were male (90.6%) and 42 of the patients were female (9.3%) with an average age of 58.9 (8.99) (26-87). In all patients, the size of the mass and FDG involvement (SUVmax) were recorded. According to this, the average size of the masses was calculated as 4.5 (2.3) cm (0.4-20) and the average SUVmax value was calculated as 13.35 (6.18). The patients were classified in 5 groups according to the histopathological diagnosis, which included squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, large cell carcinoma and other types. PET-CT FDG involvement SUVmax values have been classified and involvement values with malignancy in different histopathological types have tried to be identified (Table 1).

Table 1: PET-CT SUVmax values according to histopathological types

SUVmax groups	SCC n (%)	ADENO n (%)	ADENOSCC n (%)	LARGE n (%)	Others n (%)	Total n
0-5	2 (0.93)	18 (11.11)	1 (2.7)	0 (0.0)	0 (0.0)	21
5-10	46 (21.49)	55 (33.95)	4 (10.81)	4 (17.39)	3 (25)	112
10-15	78 (36.44)	61 (37.65)	13 (35.13)	10 (43.47)	5 (41.66)	167
15-20	57 (26.63)	19 (11.72)	12 (32.43)	5 (21.73)	1 (8.33)	94
20-25	20 (9.34)	6 (3.7)	5 (13.51)	3 (13.04)	1 (8.33)	35
25-30	6 (2.8)	1 (0.61)	0 (0.0)	1 (4.34)	2 (16.66)	10
30-35	3 (1.4)	1 (0.61)	2 (5.4)	0 (0.0)	0 (0.0)	6
35-40	0 (0.0)	1 (0.61)	0 (0.0)	0 (0.0)	0 (0.0)	1
40-45	2 (0.93)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2
Total	214 (100)	162 (100)	37 (100)	23 (100)	12 (100)	448

SCC: Squamous cell carcinoma, ADENO: Adenocarcinoma, ADENOSCC: Adenosquamous carcinoma, LARGE: Large cell carcinoma

Significant correlation was identified between the tumor size and the histopathological diagnoses and the SUVmax values. 214 of the patients (47.8%) was operated for small cell cancer, 162 of them (36.2%) adenocarcinoma, 37 of them (8.3%) for adenosquamous carcinoma and 23 (5.1%) for large cell carcinoma and 12 (2.7%) for other malignancies. PET-CT SUVmax values of the patients were compared with the histopathological diagnoses.

Significant relation was found between the tumor size and the diagnoses types, and the SUVmax values in Chi Square analysis. Positive correlation was found between the tumor diameter and the SUVmax values when compared with Correlations analysis (Table 2).

When the diagnoses types and SUVmax values were compared using the One-way Anova method, it was found that the difference between the PET-CT SUVmax values of tumors containing adenocarcinoma cell types and squamous or adenosquamous carcinoma is statistically significant (Table 2).

In the analysis done through classification of SUV values, it was found that the involvement level in all malignancy types is at 10 -15 SUVmax value level. In the second frequency,

it was found that adenocarcinoma patients showed involvement between 5-10 SUVmax values and other malignancies showed 15 SUVmax value.

Table 2: Comparison of SUV max values found in adenocarcinoma with other cell types

Dependent Variable	(I) Tumor type	(J) Tumor type	Mean Difference (I-J)	Std. Error	*P*-value	95% Confidence Interval	
						Lower Bound	Upper Bound
SUVmax	Adeno	SCC	-3.45*	0.62	<0.001	-5.14	-1.75
		Other	-3.91	1.78	0.18	-8.78	0.97
		Large	-3.72*	1.33	0.04	-7.35	-0.09
		Adeno-squamous	-4.51*	1.08	<0.001	-7.48	-1.54

SCC: squamous cell carcinoma

Discussion

Our knowledge on survival ways of tumor cells, their genetics and resistance to drugs have increased in recent years. Possible reason for the negative results on some tumors after surgery and chemotherapy is their resistance to chemotherapy agents and the failure of drugs to reach the effective concentration level in the tumor mass [4,5]. This shows that there is a need for new chemotherapy agents and a method to transfer them inside the lung tissue in a more effective way. There is an increasing interest in the methods aiming for higher drug doses in lung parenchyma.

Furthermore, PET-CT imaging is now a routine practice, based on the idea that cancer needs more energy, hence uses more glucose compared to the normal tissues. The most frequently used compound in PET imaging is FDG labelled with Fluorine (F)-18. SUVmax is a semi-quantitative indicator showing radioactively labelled glucoses uptake of the tumor tissue, and determining prognostic factors such as tumor differentiation. FDG PET-CT has been successful in identifying and monitoring malign tumors [6]. Other PET radiopharmaceuticals have been used in some tumors with lower FDG affinity and lower glucoses metabolism. Among the most typical examples are Ga-68 PSMA in prostate cancer, Ga-68 DOTA-TATE and F-18 FDOPA in neuroendocrine tumors and F-18 fluorocholine in hepatocellular cancer. PET-CT with different radiopharmaceuticals showing different biological features of neoplastic tissue is used for primary tumor diagnosis and characterization, in particular for staging, and re-staging, determining relapse, identifying response to therapy, and planning radiotherapy in thoracic tumors [7,8]. As it can be seen, specific radiopharmaceuticals are used for different tumors and there are new developments with significant progress in this area.

The main aim of the methods that aim for higher dose drug targeting in lung parenchyma, such as embolic trapping or chemoembolization, selective pulmonary artery perfusion without controlling venous flow (SPAP), lung suffusion and isolated lung perfusion in which lung is completely separated from systemic circulation, is to deliver chemotherapeutic agents to the isolated lungs and to eliminate systemic side effects, as well as to reach maximum concentration level in the target tissue [5]. Isolated perfusion methods in cancer treatment that was first published by Creech et al. in 1959 have been supported with other studies but these studies have not been popular to this date [4,9].

Changing SUVmax values according to the histological types in NSCLC, which we aimed to show in this study, can offer a new approach in developing targeted therapies. Such a study has not been conducted yet. Existing studies mostly focused on prognostic significance of SUVmax value and changes in SUVmax values according to histological types. There are studies evaluating the correlation between SUVmax and histological subtypes of NSCLC, which found SUVmax value of adenocarcinoma significantly low compared to other subtypes [10-12]. In Turkey, the study conducted by Yalcınkaya et al. [13] found that there is a statistically significant difference between the average SUVmax value of adenocarcinoma which is 13.27 and that of squamous carcinoma which is 16.11.

Similar to the other studies, the SUV max values in adenocarcinoma patients were significantly low in our study as well. Based on that, if the radiopharmaceutical agent accumulation in NSCLC subtypes show differences, we believe that chemotherapeutic agents can be delivered to the target tissue labelled with a radionuclide, and reach to a sufficient concentration level in the target tissue. Besides, if it is used together with methods such as isolated lung perfusion which aims to increase treatment success by reaching at maximum chemotherapeutic drug dose in the target tissue, it can be possible to provide treatment with the most efficient dose, by determining the chemotherapy dose in proportion to involvement level identified according to the tumor subtypes, and with minimum side effects.

Parallel to the developing technology, PET-CT modality which provides functional information at molecular level and in vivo, and enables us to conduct a non-invasive examination about the biological behavior of the tumor in both morphological and functional senses. This study supports the studies which argue that PET-CT images contain more information than considered and provide opportunities such as developing individualized treatment plans in the clinical practice.

Conclusion

Depending on the features of PET radiopharmaceuticals, different biochemical, metabolic or functional parameters can be imaged in vivo. But the routine practice is monitoring the glucose metabolism, which is the most accepted and used parameter. FDG compound labelled with F-18 is utilized for this reason. There are also radiopharmaceuticals specific to the organ and the tumor. It is possible to achieve the minimum dose, the minimum systemic side effects and the maximum response by combining special radiopharmaceuticals that have been developed for the treatment of target organs and chemotherapeutical agents.

Considering that there are statistically significant differences between PET-CT SUVmax values of tumor cell types, we argue that radiopharmaceuticals which could provide different and local treatment should be used in cancer treatment, they should be combined with alternative therapies such as loco-regional treatment methods, and the studies in that direction should continue in line with the technological developments.

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