Chapter 2

PET/CT in Lung Cancer Therapy

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Abstract

Positron Emission Tomography/Computed Tomography (PET/CT) is a new generation modality which gives both functional and morphological information along with CT component performing anatomical imaging, in which positron emitting radioisotopes are used with the aim of functional imaging. PET/CT has been used in the staging and re-staging of lung cancer and also in the evaluation of solitary pulmonary nodules for a long time.

Mediastinal Lymph Node Staging

When MLN staging evaluated with PET/CT generally SUVmax value used and interpretations made depending only on this parameter. There is no cut-off value of that parameter. We think first off all a cut-off value has to be defined.

Radiotheraphy Planning

RT planning with PET/CT ensures giving RT in more effective dose. It may be possible to obtain better results in RT planning by the use of 4D PET/CT compared to 3D planning.

Prognosis

It appears that the presence of prognostic value of SUVmax value in lung cancer. Other metabolic parameters may be consider for this purpose.
PET/CT in Lung Cancer Therapy

Lung cancer is the second most frequent type of cancer in the world and the most common cause of deaths from cancer [1]. Approximately 80-87% of it are non-small cell carcinoma (NSCLC), remaining is small cell lung carcinoma, and as it is known, it is an extremely aggressive tumor with rapid doubling time [2]. Computed Tomography (CT) is used very commonly in lung cancer imaging. However, CT has limitations. The lack of whole body imaging opportunity, it only gives about the morphology of the tumor tissue and its inability to separate atelectasis and malign tissue can be mentioned as the foremost limitations.

Positron Emission Tomography/Computed Tomography (PET/CT) is a new generation modality which gives both functional and morphological information along with CT component performing anatomical imaging, in which positron emitting radioisotopes are used with the aim of functional imaging. PET/CT has been used in the staging and re-staging of lung cancer and also in the evaluation of solitary pulmonary nodules for a long time.

Here, issues such as radiotherapy planning, which especially affects the treatment approach, and its use as a prognostic parameter, and new approaches on mediastinal lymph node (MLN) evaluation with a relatively low accuracy will be discussed rather than the abovementioned usefulness of PET/CT. In addition, M staging will also be briefly discussed and give some usefull information about radiopharmaceuticals.

Radiopharmaceuticals

F18-Flouro Deoxy Glucose (FDG)

F18-Flouro deoxy glucose is the positron-emitting radiopharmaceutical which is most frequently used in cancer imaging. As it is known, it is glucose analogue and shows involvement in these cells depending on the increased glucose use of cancer cells. After entering the cell, it undergoes phosphorylation with hexokinase and turns into F18-Flouro deoxy glucose -6- Phosphate (FDG-6P). Unlike glucose, it cannot proceed to the later stages of glycolysis and is trapped in the cell. Thus, it provides effective information about the functional imaging of the cancer cell. Its half life (T1/2: approximately 110 minutes) which is longer than the other positron-emitting radioisotopes has brought about its easier logistics and therefore its relatively cheapness and the more frequent use of it. Its biggest disadvantage is that it is not specific to tumor tissue and especially its false positivity observed in inflammatory tissues [3].
Some Hypoxia Agents Used in Lung Cancer Imaging

Those Marked with 18F

The most commonly used two compounds are 18F-Fluoromisonidazol (18F-FMISO) and 18F-Flouroazomycine Arabinoside (18F-FAZA). 18F-FMISO is basically a radionuclide which is kept in hypoxic regions of tumors [4]. However, it accumulates in tumor quite slowly and it is necessary to wait for a long time for a good imaging [5]. In addition, its target/ground activity rate is relatively low [6]. Second hypoxia agents is 18F-FAZA, it has higher target/background activity rate compared to 18F-FMISO [7] and probably more useful.

Copper-N Metiltiosemicarbazone (Cu-ATSM)

Cu-ATSM compounds have high redox potential and are kept at the high level in these regions compared to normal tissue depending on its further reduction in hypoxic tissues [8]. Therefore, it has the potential to present useful information about the hypoxia state of the tumor tissue. Its effectiveness was demonstrated in one of the first studies on this subject performed in 2003 [9].

M Staging

The role of FDG-PET/CT in lung cancer staging has long been known. However, one of the biggest disadvantages in this regard is, the difficulty in determining the metastasis that occurred in brain tissue because of its increased glucose metabolism [10]. In a recently published article, while metastasis is most commonly observed in lungs by 63.5% in NSCLC, it is followed by brain by 16.0% and adrenal glands by 7.7%. The metastasis was determined by 3.9% in bone [11]. Looking at these rates, it is seen that FDG-PET/CT has a potential to make detection at high accuracy in the organs on which lung cancer metastasis is frequently seen. In one of the early studies performed in lung cancer staging, Pietarman et al. stated that FDG-PET detected occult metastasis which is about 10% and cannot be detected with other imaging methods as a result of preoperative withdrawal in NSCLC patients [12]. Studies regarding the fact that 18F-fluoride which has begun to be used in recent times is more effective both in revealing the metastatic bone disease and in determining the response of metastatic bone lesions to the treatment in primary pulmonary tumor compared to FDG have begun to emerge [13]. In our opinion, how important the role of PET/CT in M staging will be seen it thought, except for brain.
Nodal Staging

In NSCLC patients, the importance of lymph node (N) staging in treatment selection is known [14]. In lung cancer staging morphologic imaging modalities used frequently. But it is obvious that there is a need for other modalities in this regard because the short-axis length, the criteria of accepting LN as malign, does not have a sufficient accuracy in morphological imaging methods. PET/CT is one of the first of these alternative methods. However, PET/CT’s sensitivity (SE) is given as 61%, specificity (SP) as 98%, positive predictive value (PPV) as 91.7%, negative predictive value (NPV) as 87.5% and an accuracy as 88.2% for nodal staging [16]. Here, low sensitivity and relatively low NPV draw attention. In another study, false negative (FN) result was encountered in one of every four patients with FDG-PET in N2 disease evaluation after neoadjuvant chemotherapy [17]. Taus et al revealed FDG-PET/CT’s sensitivity as 68%, specificity as 86%, PPV as 75% and NPV as 81% [18]. In a meta-analysis published in 2012, PET/CT’s sensitivity was indicated as 46-90% and specificity as 65-90% for N staging in lung cancer. In the same study, the sensitivity was determined to be lower in tuberculosis endemic regions [19]. SE and SP were determined as 71.9% and 89.8% respectively in a meta-analysis in which 14 studies consisting of a total of 2087 patients were included. In the same meta-analysis, sensitivity decreased to 61.0% when nodal station based data was used [20]. In a study carried out by Sivrikoz et al., the sensitivity, specificity, PPV, NPV and accuracy values of FDG-PET/CT in the mediastinal node staging were determined as 72.7%, 97.7%, 88.9%, 93.3% and 92.6% respectively when N2 and N3 patients were only evaluated [16].

When we look at the abovementioned studies, it is seen that SUVmax parameter was generally used in the mediastinal lymph node (MLN) staging and was not sufficient. There is not a consensus which has become clearer regarding what the cut-off value of this parameter should be and the use of some other accuracy-enhancing metabolic parameters except for SUVmax. In their article published in 2015, Mattes et al. revealed the SUVmax median value as 6.2 (range 1.5-20.3) in pathologically positive LN [15]. In another study, Mattes et al. gave the values of 93% sensitivity and 82% specificity when cut-off value was taken as 2.85 for SUVmax and the values of 93% sensitivity and 87% specificity when SUVmaxLN/Tumor was taken as 0.28 [21]. Tournoy et al. determined sensitivity as 76% and specificity as 90% when they took the cut-off value as 2.9, reported SE to be 93% when they took SUVmax/SUVliver ratio as cut-off 1.5 and above [22]. Bryant et al. suggested to take the SUVmax cut-off value as 5.3 [23]. In another study, it was stated that the highest accuracy rate was revealed when it was taken as SUVmax 4.5 [24].

In this regard, there are also studies on dual time FDG-PET/CT’s contribution. As it is known, imaging is performed again following the routine imaging. Generally, an additional imaging of 120 minutes is taken after in-
jection. Basically, it is based on the fact that SUVmax value increases in malign tissues as time passes by and decreases or remains constant in benign tissues. However, in a study published in 2012, it was determined that dual time point FDG-PET/CT had no contribution to mediastinal nodal staging in lung cancer [25]. However, it should be kept in mind that there could be different results in areas where tuberculosis is not common because this study was carried out in tuberculosis - endemic area. In a study published in 2011, patients were divided into two groups as those with pulmonary comorbidity and those without pulmonary comorbidity, and it was reported that dual-time point MLN staging decreased false positive (FP) results in all patients and also led to increase in SP, accuracy and PPV values especially in those with pulmonary comorbidity [26]. Similarly, Uesaka et al. stated that the accuracy value increased in MLN staging when dual time point FDG-PET/CT was used and the increase in specificity was the main factor of it [27]. Takayoshi et al. goes along with him [28].

When MLN staging evaluated with PET/CT generally SUVmax value used as abovementioned and interpretations made depending only on this parameter. Moreover, a cut-off value, which has become clearer in this regard, could not be determined. We think first off all a cut-off value has to be defined. In addition, it is seen that SUVmaxLN/tumor, SUVmaxLN/liver ratios and dual time point imaging have potential to improve accuracy. Here, it should be kept in mind that dual time point imaging cannot bring benefit in tuberculosis-endemic areas. We think there is a need for studies which are multicentric, prospective and have a high number of patients.

There is one more thing have to be said. The results are more promising in early stage lung cancer patients. For instance, Li et al. pointed out the high NPV value (91%) of FDG-PET/CT in early stage NSCLC patients [29]. Similarly, in a study carried out in 2007, it was stated that direct surgical operation could be performed without the need for invasive diagnostic methods in patients with normal mediastinal node result in FDG-PET/CT imaging [22]. We think those results are assertive and they have to be need studies which similar cohort.

RT (Radiotheraphy) Planning

In NSCLC, RT planning is mostly done with CT; but, some problems may occur frequently in this practice, such as target volume contouring, tumor/atelectasis separation, e.g [30]. In particular, the fact that atelectasis area cannot be distinguished by CT may affect the effective dose during RT when the amount of radiation received by normal tissue is taken into account. The radiation exposure of normal lung tissue may cause bronchoalveolar fibrosis, vascular endothelial pathologies and may disrupt the perfusion and ventilation [31]. Therefore, the purpose should be that, given irradiation of the tumor tissue in effective doses while exposing the normal tissue to radiation as little as possible. It is stated that the use of PET/CT contrib-
utes to giving optimal radiation dose to tumor tissue by ensuring the tumor/atelectasis separation [32-34].

As it is known, better tumor control is ensured as the radiation dose given to tumor tissue increases [35,36]. In studies carried out, it was stated that PET/CT taken before RT significantly decreased the target volume and thus ensured to give RT in more effective doses to tumor by decreasing the radiation dose to be taken by normal tissue [37,38]. Vojti et al. found median GTV as 61 cm³ and PTV as 320 cm³ when they calculated using CT, and found these values significantly less when they performed the same process using PET/CT (median GTV PET/CT=52.5 cm³, median PTV PET/CT=267.7 cm³) [30]. In a study carried out by Brianzoni et al., the target volume was changed for RT in 44% of patients with PET/CT. Among all patients, while the target volume of 24% of them increased according to CT and the target volume decreased 20% of them [39]. On the other hand, De Ruyscher et al. determined that the target volume was decreased in great majority of patients as a result of PET/CT, and consequently delivered dose increased from 55.2Gy to 68.9 Gy and the radiation dose taken by oesophagus and lung decreased [37]. In a study published in 2015, while the average volume was determined as 6.2 cm³ when tumor contouring before RT was performed with 4DCT-ITV in peripheral lung tumors, it was determined as 8.6 cm³ when tumor contouring was performed with 4DPET/CT, and the difference was found statistically significant. In the same study, no significant difference was determined in central lesions [40]. As it is seen from the studies carried out, it seems that doing RT planning with PET/CT ensures giving RT in more effective dose. As it is mentioned above, the irradiation of tumor in more effective doses is important for tumor control. It is seen that, there is need for studies with a high number of patients regarding the effect of RT planning done with PET/CT as well as this modality’s effects on survey.

Except for its effect on primary tumor target volume, PET/CT can change the mediastinal node irradiation plan. In their study carried out in 2011, Van Loon et al. stated that the use of PET/CT imaging for RT planning could decrease the elective nodal failure [41]. However, Kanzaki et al. demonstrated in their study, which was published in the same year, that PET/CT could not detect occult mediastinal metastasis in 11% of the patients [42]. Similarly, in their study published in 2016, Nygard et al. identified failure in planning made by looking at the FDG PET/CT results due to LNs which were considered to be outside RT area in 11/81 (14%) patients [43]. In our opinion, it is necessary to be careful while making MLN irradiation plan due to PET/CT’s weakness in showing micrometastasis. The positive PET/CT result to MLN should be included in the irradiation field and the possibility of micrometastasis should be kept in mind for FDG negative LNs.

A side from PET/CT can change the MLN staging, it can reveal the presence of distant metastasis because it al-
allows for whole body imaging. Lin et al. determined that FDG-PET/CT affected the treatment plan by increasing the staging in approximately 35% of patients before RT [44]. In a similar prospective study, the curative treatment was given up because the treatment plan of each of four RT radical candidate patients after PET/CT [45].

Another point that should be mentioned here is the duration between PET/CT imaging and the start time of RT. In their study published in 2015, Konert et al. stated that RT should be started within 4 weeks at the maximum after PET/CT, otherwise primary tumor area and mediastinal node irradiation may not be sufficient [46].

Another important point is that the tumor moves along with respiration and affects the RT area. It has been reported in the literature that higher rates of malignant cells are observed around GTV in high risk lung tumors especially in terms of macroscopic spread, and PET/CT showed CTV less than as it was in these tumors. It was reported that CTV was calculated correctly in low risk tumors [47]. In a study published in 2014, the use of respiratory-gated PET/CT was proposed in the solution of this problem, and thus it was stated that a more accurate target volume could be calculated [48]. The same proposal was also made by Konert et al. one year later [46].

In our opinion, it may be possible to obtain better results in RT planning by the use of 4D PET/CT compared to 3D planning. However, it is certain that studies with a high number of patients in this regard are needed.

The last point that should be mentioned about RT and PET/CT is the hypoxia imaging in tumor. The study carried out by Toma-Dasu et al. with FMISO-PET suggests that hypoxic agents can be used in RT planning [49]. Bollineni et al. used FAZA as the hypoxia agent. In this study, the imaging performed in the 2nd week was stated to be more appropriate method in hypoxia-directed dose escalation strategies compared to FAZA-PET/CT performed before the treatment [50]. There is a need for studies concerning which is this radionuclide should be used and when it is appropriate to perform PET/CT imaging for this purpose.

Response to KT

As it is known, the treatment response was mainly performed with anatomical imaging methods before the introduction of PET/CT’s clinical use. The biggest problem in this method was the problems experienced in decision-making and evaluation due to the inability to make distinction of necrotic and residual tumor tissue [51]. However, it was stated that the change in the metabolic parameters of the tumor tissue correlated with chemotherapy response and clinical outcomes [52,53].

The studies on this subject are mainly focused on SUVmax value. The fact that SUVmax and MTV could predict the response to treatment in PET/CT imaging performed before and after concurrent chemoradiotherapy in local advanced NSCLC patients was suggested by
Huang et al. [54]. Cerfolio et al. gave SE and SP ratios of the decrease in SUVmax value by 80% or more in NSCLC patients administered with neoadjuvant KT as 90% and 100% in the evaluation of complete pathological response [55]. In a study published in 2015, it was stated that a decrease below 35% in SUVmax should be evaluated as the absence of treatment response in PET/CT imaging performed after 2 cure KT and KT regime was proposed to be changed in such cases [56]. In their article published in 2016, Ripley et al. analyzed the persistent N2 disease detection with PET/CT after postinduction KT. In this study, SE, SP, accuracy, PPV and NPV values were identified as 59%, 55%, 57%, 66% and 47% respectively, and it was stated that the fact that SUVmax in N2 node was 3.3 and above increased the persistent N2 disease risk [57]. In a meta-analysis, 83% SE, 84% SP, 74% PPV and 91% NPV were determined in predicting the response of FDG-PET imaging to neoadjuvant KT in NSCLC patients [58].

Consequently, it is seen that the decrease in SUVmax value can be taken as criteria in evaluating chemotherapy response. However, we think there is a need for multicentric and prospective publications with greater number of patients concerning how many cures after the chemotherapy PET/CT should be performed and what rate reduction is acceptable in SUVmax as partial or complete response.

Prognostic Value

The importance of prognostic parameters for the treatment method of lung cancer patients has long been known. However, it is stated that TNM stage is not an excellent prognostic marker completely by itself or along with clinical factors [59]. PET/CT’s potential to give information about the metabolism of tumor tissue suggests that it can be used for this purpose. In this regard, Lee et al. determined in their study published in 2013 that the prognosis of NSCLC patients with high SUVmax values was poor [60]. Casali et al. demonstrated that high FDG uptake was associated with poor prognosis in NSCLC patients [61]. In another study, it was stated that SUVmax had prognostic value in early stage NSCLC patients [62]. In a meta-analysis conducted by European Lung Cancer Working Party in 2008, the prognostic value of the primary SUVmax value in NSCLC patients was indicated [63]. The unclear point seems what the cut-off value should be, not whether SUVmax has predictive value.

Goodgame et al. determined that SUVmax had predictive value in preoperative PET imaging in early stage NSCLC. In this study, SUVmax 5.5 cut-off was given [64]. In another study, it was stated that SUVmax>9.5 value was an independent prognostic factor in patients with lung adenocarcinoma and associated with overall survival (OS) and disease free survival (DFS) [65]. In their article published in 2014, Ulger et al. gave 3-year OS ratio as 42% in
the group in which SUVmax value was 10.7> in local advanced NSCLC patients and as 23% in the group in which it was 10.7< and they stated that FDG uptake had independent predictive value [66]. SUVmax cut-off value was taken as 13 in Stage IIIA patients administered with surgical operation after neoadjuvant chemotherapy, and the survival in patients with FDG uptake below this value was demonstrated to be statistically significantly better [67]. SUVmax>12.9 value was also determined as an independent predictor indicating short DFS for large cell neuroendocrine carcinoma (LCNEC) [68]. Nair et al. stated that the fact that primary tumor SUVmax value is 7 and above is a risk factor for metastasis free survival [69]. In a study published in 2013, stage IA lung adenocarcinoma patients were evaluated, and it was reported that there was a relationship between primary tumor SUVmax and tumor aggressiveness and nodal metastasis, and this parameter could be evaluated as a prognostic factor indicating PFS [70]. Kishimoto et al. demonstrated that SUVmax value was one of two independent prognostic factors along with the pathologic stage for recurrence for all lung cancer subtypes [71].

It appears that the presence of prognostic value of SUVmax value in lung cancer has been clearly demonstrated. However, it is not possible to evaluate all of the studies within the same category. There are large numbers of studies performed on patients in the same stage and in the same histopathological subgroup. Therefore, it is obvious that there is a need for determining separate SUVmax cut-off value for each group by the studies to be created by homogeneous patient groups.

In this regard, some metabolic parameters were also analyzed except for SUVmax. In one of them, Takeda et al. analyzed the usefulness of dual time point FDG PET/CT in demonstrating the presence of local failure in patients who received stereotactic body radiotherapy (SBRT). In this study, a statistically significant difference was found in early and late images and Retension Index (RI) between recurrent and non-recurrent diseases [72]. Similar results were also demonstrated by Satoha et al. and it was stated in a multivariate analysis that high RI value was a risk factor for distant metastasis [73]. Im et al. determined that MTV which is another metabolic parameter could be used as a prognostic factor in NSCLC patients [74]. In a study published in 2013, it was demonstrated that MTV and TLG was an independent prognostic parameter for OS in NSCLC patients [75]. In another study published in 2015, it was demonstrated that there was a relationship between the recurrence risk and a decrease of 29.7% and below in MTV in PET/CT imaging performed before and after treatment in local advanced stage NSCLC [76].

The number of prognosis evaluation studies performed with RI and MTV-TLG parameters is less compared to studies that evaluated SUVmax. However, the abovementioned results are promising and we believe that the number of publications on this subject should be increased.
The last point that should be mentioned is the prognosis relationship with hypoxic agents. The response of treatment and hypoxia in tumor tissue relationship with prognosis has long been known. The determination of tumor hypoxia with PET/CT and the relationship of its results with prognostic parameters are new subjects. In their study published in this field in 2016, Kinoshita et al. performed prognosis evaluation with two hypoxia agents 18F-FAZA and 62Cu-ATSM PET/CT results. In this study, when 18F-FAZA and OS correlation was analyzed, while sensitivity and specificity was determined as 84.1% and 57.1%, these values were found as 80.0%, 65.0% for PFS. OS sensitivity and specificity values were found as 70.0% and 66.7% for 62Cu-ATSM, and the same parameters were found as 64.3% and 75.0% for PFS [77]. It is obvious that there is a need for increasing the number of studies in this regard.

Unlike the relationship of NSCLC prognosis and PET/CT results described above, it was reported by Gomez et al. that there was not a relationship between prognosis and PET/CT metabolic parameters in Limited Stage-SCLC patients [78]. In another study, Whole body MTV and OS and PFS relationship in Extensive Stage-SCLC was analyzed, and it was demonstrated that OS and PFS durations of patients with high WBMTV values were shorter [79]. Zhu et al. achieved the same result in SCLC and prognosis relationship for MTV [80]. However, Ong et al. determined in their study that there was not a significant relationship between MTV, TLG and SUV mean and prognosis in LS-SCLC patients [81]. In our opinion, the number of studies in this regard is small, and the subject should be clarified by multicentric and prospective studies including high number of patients.

Result

1. The weakest aspect of PET/CT in lung cancer staging is the MLN staging which is performed based on SUVmax value. In this regard, it may be possible to increase the accuracy rate by taking different parameters except for SUVmax.

2. PET/CT’s advantage is clear in RT planning. It seems possible that especially the planning done with respiratory-gated can allow for giving more effective doses to malignant tissues and exposing normal tissues to less radiation.

3. It seems that metabolic PET parameters will have significant contributions in prognosis evaluation. However, it is obvious that there is a need for studies consisting of homogeneous groups with higher number of patients.
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