European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:1869–1877
https://doi.org/10.1007/s00259-019-04388-3

ORIGINAL ARTICLE

PET-detected pneumonitis following curative-intent chemoradiation in non-small cell lung cancer (NSCLC): recognizing patterns and assessing the impact on the predictive ability of FDG-PET/CT response assessment

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Received: 9 March 2019 / Accepted: 31 May 2019 / Published online: 12 June 2019

Abstract

Purpose Inflammatory FDG uptake in the lung (PET-pneumonitis) following curative-intent radiotherapy (RT)/chemo-RT (CRT) in non-small cell lung cancer (NSCLC) can pose a challenge in FDG-PET/CT response assessment. The aim of this study is to describe different patterns of PET-pneumonitis to guide the interpretation of FDG-PET/CT and investigate its association with tumor response and overall survival (OS).

Methods Retrospective analysis was performed on 87 NSCLC patients in three prospective trials who were treated with radical RT ($n = 7$) or CRT ($n = 80$), with baseline and post-treatment FDG-PET/CT. Visual criteria were performed for post-treatment FDG-PET/CT response assessment. The grading of PET-pneumonitis was based on relative lung uptake intensity compared to organs of reference and classified as per Deauville score from grade 1–5. Distribution patterns of PET-pneumonitis were defined as follows: A) patchy/sub-pleural; B) diffuse (involving more than a segment); and C) peripheral (diffusely surrounding a photopenic region).

Results Follow-up FDG-PET/CT scans were performed approximately 3 months (median, 89 days; interquartile range, 79–93) after RT. Overall, PET-pneumonitis was present in 62/87 (71%) of patients, with Deauville 2 or 3 in 12/62 (19%) and 4 or 5 in 50/62 (81%) of patients. The frequency of patterns A, B and C of PET-pneumonitis was 19/62 (31%), 20/62 (32%) and 23/62 (37%), respectively. No association was found between grade or pattern of PET-pneumonitis and overall response at follow-up PET/CT ($p = 0.27$ and $p = 0.56$, respectively). There was also no significant association between PET-pneumonitis and OS (hazard ratio [HR], 1.3; 95% confidence interval [CI], 0.6–2.5; $p = 0.45$). Early FDG-PET/CT response assessment, however, was prognostic for OS (HR, 1.7; 95% CI, 1.2–2.2; $p < 0.001$).

Conclusion PET-pneumonitis is common in early post-CRT/RT, but pattern recognition may assist in response assessment by FDG-PET/CT. While FDG-PET/CT is a powerful tool for response assessment and prognostication, PET-pneumonitis does not appear to confound early response assessment or to independently predict OS.

This article is part of the Topical Collection on Oncology – Chest

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00259-019-04388-3) contains supplementary material, which is available to authorized users.

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Keywords PET-pneumonitis · Radiation pneumonitis · FDG-PET/CT · PET response assessment · Non-small cell lung cancer (NSCLC)

Introduction

The implementation of hybrid imaging with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) has improved imaging accuracy and has become an integral imaging modality for diagnosis and staging, but it is also increasingly used for response assessment and prognostication following curative-intent treatment of advanced non-small cell lung cancer (NSCLC) patients [1, 2]. Early and accurate detection of resistant disease is crucial to allow salvage therapy, particularly with the emergence of targeted therapies and immunotherapy [3]. Salvage surgery may also be possible in patients with clearance of mediastinal lymphadenopathy by chemoradiotherapy [4]. Stereotactic ablative body radiotherapy or surgery may be appropriate for patients who attain local disease control, but have new oligometastasis [5]. Early follow-up of patients can be challenging, however, as treatment-induced inflammatory changes in the normal lung parenchyma (PET-pneumonitis) after radiotherapy (RT) or concurrent chemoradiotherapy (CRT) must be distinguished from residual disease [6–8].

In a recent study, we showed that both qualitative and semiquantitative FDG-PET/CT response criteria provided powerful early post-treatment predictive information [9]. Qualitative response assessment, however, showed a stronger association with overall survival (OS) than did the two semiquantitative criteria: the European Organisation for Research and Treatment of Cancer (EORTC) and PET Response Criteria in Solid Tumors (PERCIST). We speculated that the presence of PET-pneumonitis and difficulty in assigning the residual tumor site in the presence of evolving changes in the lung configuration may have interfered with semiquantitative response assessment and resulted in lower predictive ability. Response assessment is particularly challenging when there is diffuse pneumonitis in the vicinity of the site of the primary tumor. In 2004, we described the importance of pattern recognition in differentiating post-radiation changes from residual disease using standalone PET [6]. With technological advancements in PET imaging, the new generation of cameras have higher sensitivity and spatial resolution, and offer additional opportunities for more accurate anatomical localization of FDG uptake with contemporaneous CT. Furthermore, the past decade has brought dramatic improvements in the planning and delivery of radiation treatments due to technical advancements in delivery tools, computing power, guidance imaging, and motion management [5]. This has led to highly conformal radiation, creating sharper radiation dose gradients and allowing for reduction of radiation dose to non-tumor lung parenchyma, hence reducing the frequency of severe pneumonitis while changing the pneumonitis distribution and pattern [10].

In this manuscript, we describe common patterns of PET-pneumonitis in relation to the metabolic changes in the primary tumor to guide physicians in more accurate interpretation of PET/CT early after radical RT/CRT. The impact of the PET-pneumonitis and its differing patterns on the response evaluation and overall patient outcome were also analyzed.

Materials and methods

Patients

Between 2004 and 2016, three NSCLC prospective trials included patients treated with definitive RT or CRT. Patients eligible for this study had baseline and post-treatment FDG-PET/CT imaging between 1.5 and 4 months after RT. All patients were aged ≥18 years, had an Eastern Cooperative

Table 1 Patient and tumor characteristics

Variable	Statistic	Total ($N = 87$)
Age (years)	Median [range]	68 [46–86]
Sex	Female	30 (35%)
	Male	57 (65%)
Stage at diagnosis	I	7 (8%)
	II	10 (11%)
	IIIA	45 (52%)
	IIIB	25 (29%)
Histology	Adenocarcinoma	36 (41%)
	Large cell	7 (8%)
	NSCLC	13 (15%)
	SCC	31 (36%)
Chemotherapy	Concurrent	80 (92%)
	No chemotherapy	7 (8%)
Chemotherapy type	Carboplatin-Etoposide	1 (1%)
	Carboplatin-Paclitaxel	45 (56%)
	Carboplatin only	3 (3%)
	Cisplatin-Etoposide	31 (39%)
RT dose	50–56 Gy	3 (3%)
	60 Gy	84 (97%)
RT Technique	3D Conformal	80 (92%)
	IMRT	7 (8%)

NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; RT, radiotherapy; 3D, three-dimensional; IMRT, intensity-modulated radiotherapy

Oncology Group (ECOG) performance status of 0–2 and had a histologically or cytologically confirmed NSCLC (Table 1). Approval to conduct this study was granted by our institutional ethics committee (PMCC 17/43R).

Treatment and imaging

All patients were treated to 50–60 Gy three-dimensional conformal or intensity-modulated RT planning according to institutional guidelines. Tumor motion management was based on an FDG-PET/CT planning scan [11] or a four-dimensional (4D) planning CT scan. Concomitant chemotherapy, when indicated, consisted of either cisplatin/etoposide, or carboplatin/paclitaxel. All FDG-PET/CT scans were acquired on an integrated PET/CT scanner including GE Discovery LS, GE Discovery STE (GE Medical Systems, Milwaukee, WI, USA), or Biograph 16 (Siemens Medical Solutions, Erlangen, Germany). Each baseline and post-treatment FDG-PET/CT were performed on the same scanner utilizing a uniform acquisition and processing protocol [11–13].

Response assessment

All analyses were performed using MIM software (MIM 5.4.4; MIM Software, Cleveland, OH, USA). For each patient, on follow-up FDG-PET/CT, visual response evaluation criteria (Peter Mac criteria) were categorized as follows: complete metabolic response (CMR), no tumor uptake or activity in the target tumor similar to that in the mediastinum; partial metabolic response (PMR), any appreciable reduction in the intensity or tumor volume/extent and residual FDG uptake within target tumor greater than mediastinum; stable metabolic disease (SMD), no appreciable change in the intensity or volume/extent of FDG uptake in target tumor; or progressive metabolic disease (PMD), appreciable increase in the intensity or volume/extent of target tumor or new FDG-avid tumor lesion. Response at the primary site and overall response was assessed separately.

Assessment of PET-pneumonitis grade and pattern

PET-pneumonitis was assessed based on the relative intensity (grade) and distribution (pattern) of uptake in the lung parenchyma. The grade of pneumonitis was defined and extrapolated from the reference organs used in the Deauville score as follows: 1) no increased uptake above background, 2) increased uptake above background but equal to or less than mediastinum, 3) above mediastinum but equal to or less than liver, 4) moderately above liver or 5) markedly above liver.

The patterns of PET-pneumonitis were classified as A) subpleural/patchy: in this pattern, the areas of non-tumor lung FDG uptake are separate from the lung tumor and located either in a curvilinear shape in the subpleural/peri-fissural distribution or in a small patch or patches randomly distributed within the lungs, B) diffuse, non-tumor lung FDG uptake diffusely involving at least one segment of the lung. Diffuse uptake either includes the primary tumor site or is located in its vicinity; or C) peripheral, non-tumor lung FDG uptake encircling an area of relatively lower intensity FDG uptake or photopenia, which represents the primary tumor site (Fig. 1). All assessments were the consensus of two experienced nuclear medicine physicians blinded to the clinical outcome.

Statistical methods

Overall survival was measured from the date of post-treatment FDG-PET/CT to the date of death. Patients alive at the last contact had their survival censored at that date. A linear-by-linear test was used to assess the association between the PET-pneumonitis grade and overall response or response at the primary site. Fisher's exact test and the Kruskal–Wallis test were used to assess the association between presence of PET-pneumonitis and overall response or primary response, respectively. Cox proportional hazard models and Kaplan–Meier methods were used in OS analyses. All statistical analyses were performed in R 3.2.3 (R Core Team, 2015; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and response assessments

Eighty-seven NSCLC patients underwent FDG-PET/CT before and after radical RT ($n = 7$) or CRT ($n = 80$). Eighty-four of 87 patients (97%) received 60 Gy (Table 1). As per usual institutional practice, follow-up FDG-PET/CT scans were performed 2–3 months (median, 89 days; interquartile range, 79–93; range: 47–123) after RT. Of 87 patients, two had only nodal disease with no assessable primary site. Primary response in the 85 patients with assessable primary site were as follows: 42/85 (49%) CMR, 40/85 (47%) PMR, 2/85 (2%) SMD and 1/85 (1%) PMD. Overall response assessment was as follows: 30/87 (35%) CMR, 39/87(45%) PMR, 1/87 (1%) SMD and 17/87 (20%) PMD. The estimated median follow-up was 49 months and the median survival, calculated from the date of the follow-up FDG-PET/CT, was 28 months. Early FDG-PET/CT overall response assessment was prognostic for OS (hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.3–2.2; $p < 0.001$). For complete response analyses, please refer to the prior publication by our group [9].

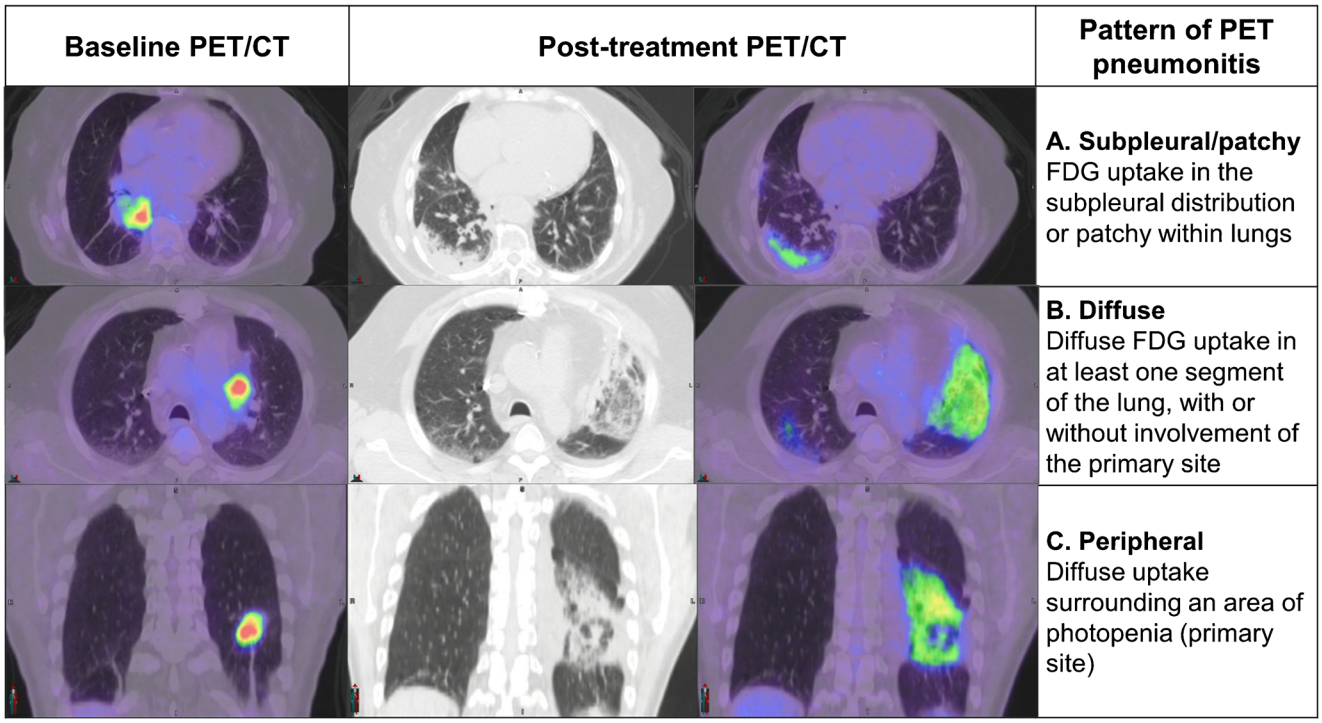

Fig. 1 Illustrative presentation of three patterns of PET-pneumonitis

Grade and pattern of PET-pneumonitis

Overall, PET-pneumonitis was present in 62/87 (71%) of patients. There was no significant difference between the number of days from the completion of RT to follow-up PET/CT in patients with or without PET-pneumonitis, 86.8 days (95% CI, 83.2–90.5) and 83.3 days (95% CI, 75.9–90.7), respectively ($p = 0.38$).

Of the patients with PET-pneumonitis, 12/62 (19%) had Deauville 2–3 and 50/62 (81%) Deauville 4–5. The frequency of the patterns of PET-pneumonitis was as follows: pattern A, 19/62 (31%); pattern B, 20/62 (32%) and pattern C, 23/62 (37%). The proportion of patients with PET-pneumonitis was 11/18 (61%) in patients with PMD or SMD, 27/39 (69%) in PMR and 24/30 (80%) in CMR. Figure 2 provides three representative cases with a diffuse and peripheral pattern of PET-pneumonitis on early follow-up FDG-PET/CT and its relation to the metabolic response at the primary site.

PET-pneumonitis versus overall response and response at the primary site

There was no clear association between grade of PET-pneumonitis and the depth of response at the primary site ($p = 0.067$) (Table 2). Similarly, no association was found between the pattern of PET-pneumonitis and response at the primary site (supplementary table 1). There was no association between grade or pattern of PET-pneumonitis and overall response at early follow-up PET/CT (supplementary table 2 and 3).

PET-pneumonitis versus overall survival

There is no evidence that the presence of PET-pneumonitis on early follow-up FDG-PET/CT is associated with OS of the patients (HR, 1.3; 95% CI, 0.6–2.5; $p = 0.49$. Similarly, no association was found between the grade or pattern of PET-pneumonitis and OS (Table 3). Figure 3 demonstrates Kaplan–Meier curves in patients with or without PET-pneumonitis and their survival by different patterns of PET-pneumonitis.

Discussion

In this study, the presence of PET-pneumonitis on early FDG-PET/CT was not associated with OS of patients with NSCLC treated with RT/CRT. This result is consistent with the previously published study by our group in 2004 [6], in which standalone PET images were used for response assessment and grading of radiation-induced toxicity in non-tumor tissues. PET-pneumonitis usually begins early after radiation and reaches its peak less than 3 months after RT completion [14], a timeline which corresponds to typical response assessment in NSCLC after RT/CRT. Reassuringly, our study showed early FDG-PET/CT response remains prognostic for OS and, as we previously found with standalone FDG-PET, the utility of

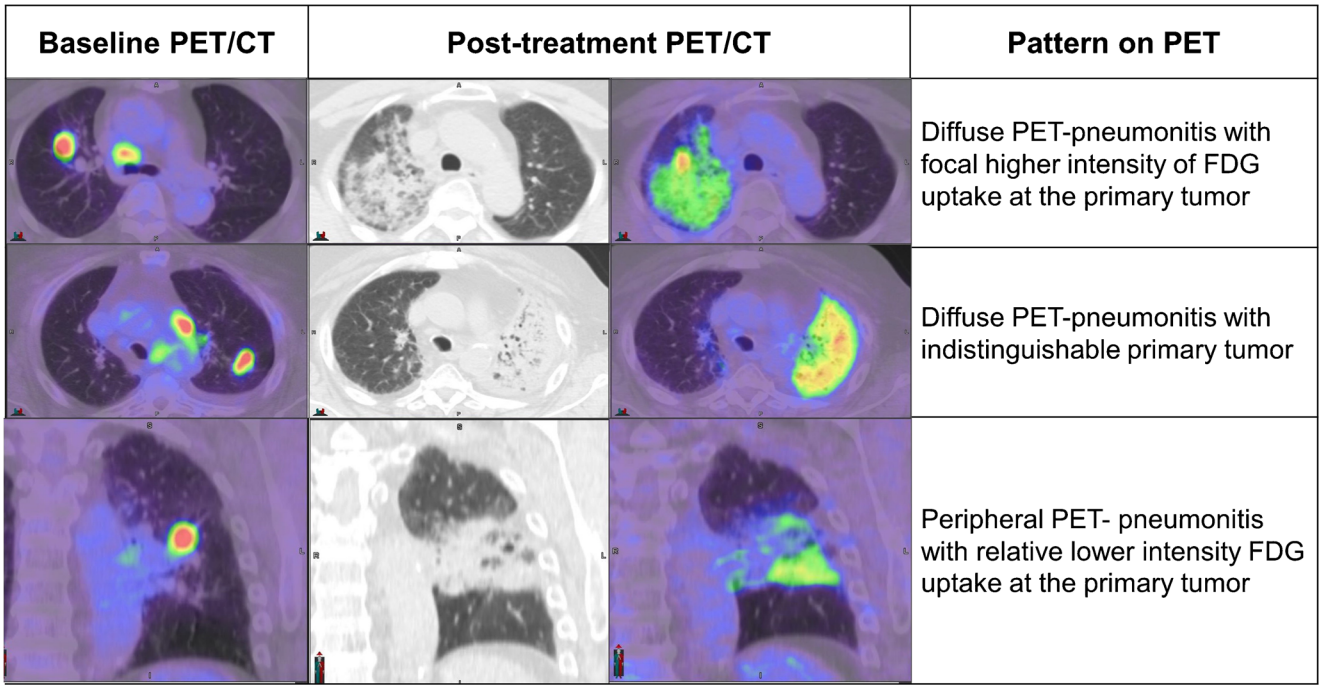

Fig. 2 Top row, diffuse PET-pneumonitis with focal activity above pneumonitis at the primary tumor, indicating residual disease. Middle row, diffuse PET-pneumonitis with the indistinguishable primary site from surrounding pneumonitis, indicating likely inflammatory change but requires further follow-up. Bottom row, peripheral PET-pneumonitis with relative photopenia at the primary tumor, indicating a response to treatment

FDG-PET/CT for response assessment was not confounded by post-radiotherapy changes. This is important especially with the increasing evidence of efficacy of adjuvant immunotherapy [15] and salvage treatments [16], allowing for a personalized, risk-adapted approach based on accurate early response assessment after CRT which may improve patient outcomes.

It is important to note that the tumor response and non-tumor lung tissue response (PET-pneumonitis) to radiation are likely time-dependent phenomena [2, 14]. Some variation was noticed in the timing of post-treatment scanning (range: 47–123 days), although the interquartile range was rather narrow (79–93 days). To ascertain whether the timing of post-treatment PET influenced the detection of PET-pneumonitis, this was compared in patients with or without PET-pneumonitis. Interestingly, the time interval was not significantly different, 86.8 days and 83.3 days in patients with or without PET-pneumonitis, respectively ($p = 0.38$). Despite this possible confounding factor, we did not find a temporal relationship between the metabolic response in the tumor and the PET-pneumonitis at any time point in a given individual patient and more importantly the presence the latter did not appear to impact the response assessment.

Table 2 Response at the primary tumor site by grade of PET-pneumonitis

Grade of PET pneumonitis[π]	Visual PET response at the primary site				Total
	CMR	PMR	SMD	PMD	
1	10 (40.0%)	13 (52.0%)	1 (4.0%)	1 (4.0%)	25
2	2 (40.0%)	2 (40.0%)	1 (20.0%)	0 (0.0%)	5
3	3 (42.9%)	4 (57.1%)	0 (0.0%)	0 (0.0%)	7
4	22 (59.5%)	15 (40.5%)	0 (0.0%)	0 (0.0%)	37
5	5 (45.5%)	6 (54.5%)	0 (0.0%)	0 (0.0%)	11
Total	42 (49.4%)	40 (47.1%)	2 (2.4%)	1 (1.2%)	85*

Linear-by-linear p value = 0.067

*Two out of 87 patients were not assessable for response at the primary site

[π] Grade of pneumonitis is defined by Deauville score 1 to 5

CMR, complete metabolic response; PMR, partial metabolic response; SMD, stable metabolic disease; PMD, progressive metabolic disease

Table 3 Overall survival by grade and pattern of PET-pneumonitis

Variable	Level	*N*	Deaths	Unadjusted		Adjusted*	
				HR	*p* value	HR	p value
PET-pneumonitis	No	25	13	–	0.828	–	0.493
	Yes	62	37	1.1 (0.6–2.0)		1.3 (0.6–2.5)	
PET-pneumonitis grade$^{\pi}$	Per 1 increase in grade	87	50	1.0 (0.8–1.2)	0.823	1.0 (0.8–1.3)	0.824
Pattern of PET-pneumonitis	No pneumonitis	25	13	–	0.996	–	0.650
	Patchy	19	10	1.0 (0.5–2.4)		1.1 (0.5– 2.7)	
	Diffuse	20	13	1.1 (0.5–2.4)		1.1 (0.5– 2.6)	
	Peripheral	23	14	1.1 (0.5–2.3)		1.7 (0.7–3.9)	

N, number of patients; HR, hazard ratio

*Adjusted by PMCC response (ordinal), stage and chemotherapy

$^{\pi}$ PET-pneumonitis grade is defined by Deauville score 1 to 5

There has been increasing interest in whether radiation-induced inflammatory change may impact the response in the tumor. While radiation has direct cytotoxic effects on cancer cells, it is now well established that RT can generate an anti-tumor immune response through effects on the tumor microenvironment via a variety of mechanisms [17, 18]. Synergistic effect of consolidative immunotherapy on improvement outcome following RT has been demonstrated in NSCLC [15, 19]. In addition, biomarker studies have shown an increase in pro-inflammatory cytokines in NSCLC patients during and after RT, which is also associated with pulmonary FDG uptake [20, 21]. The extent to which tumor and normal tissue react to RT, however, depends on multiple factors including altered interactions between the tumor microenvironment including hypoxia, tumor microvasculature, and the complex role of immune reaction and release of immune mediators (cytokines), which may need to be better understood [22].

A limited number of studies have investigated the relationship between the PET-detected inflammatory change and response in the tumor. In a study by Jahangiri et al., a semiquantitative approach was used to measure the global lung metabolic activity on FDG-PET/CT, almost 3 months after photon or proton RT in 39 patients with NSCLC [23]. In this study, radiation-induced inflammation was quantified by subtraction of the tumor metabolic activity from the global lung FDG uptake. The authors reported that while tumor metabolic parameters decreased following RT, non-tumor lung inflammatory FDG uptake increased in the cohort who underwent photon RT. Formal tumor response assessment and treatment outcome was beyond the scope of that study. In 2004, a study was published by our group in 73 patients with NSCLC who were treated with RT, using standalone FDG-PET for response assessment [6]. We reported that increased FDG uptake in normal tissues was associated with a greater likelihood of complete or partial tumor response. Surprisingly, in the current study, we did not find an association between tumor response

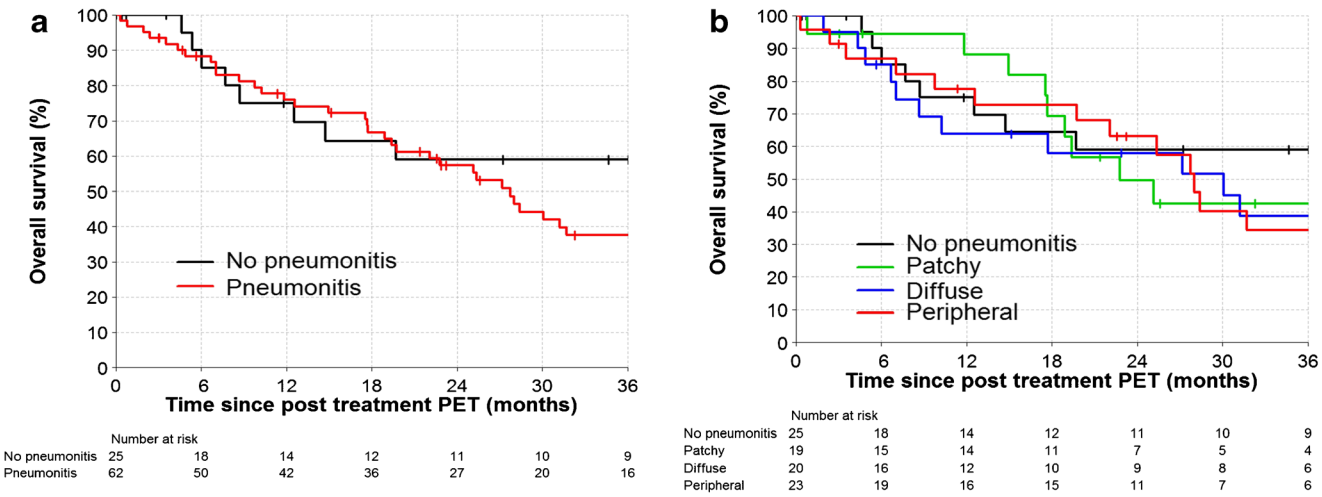

Fig. 3 Kaplan–Meier method of the depiction of overall survival in patients with or without PET-pneumonitis (A) and by the pattern of PET-pneumonitis (B)

and pattern of PET-pneumonitis. This was despite using the rather similar definition of different patterns of PET-pneumonitis. We also graded the PET-pneumonitis based on its relative intensity to organs of reference, with a higher score indicating higher metabolic activity. However, on linear-by-linear association, this did not yield a statistically significant correlation with tumor response. Although not completely understood, potential reasons for this outcome may be explained, at least partly, by the advances in PET cameras with higher sensitivity and resolution of newer generation PET/CT cameras compared to standalone PET, which may allow detection of more subtle degrees of PET-pneumonitis. There have also been significant technological advances in radiotherapy administration over the last decade that may have altered the relationship between dose delivered into the tumor and the surrounding lung. Multiple studies have shown the RT technique may influence the normal lung response on FDG-PET [24, 25]. Even though the 3D conformal RT was the predominant technique in our cohort, in recent years the number of fields has increased due to the use of CT planning and the weight of each radiation field are better optimized to achieve better conformality. In further studies, however, it would important to evaluate the effect of treatment volumes and dosimetric parameters on PET-pneumonitis grade and pattern.

The other potential explanation and limitations of this study were the relatively low number of patients with SMD or PMD compared to other categories of response. Only 3/87 patients had SMD or PMD at the primary site, indicating the efficacy of modern regimens for local disease control. However, 18/87 patients had SMD or PMD in overall response assessment, indicating a higher proportion of more distant failure. Together these factors may have underpowered statistical analysis in these subgroups and may have contributed to the lack of association between tumor response and PET-pneumonitis. However, the association between metabolic inflammatory change and tumor response may need to further be reassessed in studies with a larger cohort of patients.

In a recent study using the same cohort of patients, we showed that the visual criteria were superior to semiquantitative criteria in distinguishing the responders [9]. We speculated that the lower discriminative ability of the semiquantitative criteria could be explained by the confounding impact of PET-pneumonitis on standardized uptake value (SUV) measurements. The qualitative visual analysis of PET images is still the principal methodology used for the response assessment in clinical practice. Visual assessment is dependent upon the contrast between metabolic activity in the tumor and background activity as well as pattern distribution of FDG activity. By categorizing the PET-pneumonitis distribution patterns, independent of metabolic changes at the primary site of the tumor, we have tried to provide a visual framework to facilitate more accurate interpretation of FDG-PET/CT images. We recognize that the diffuse pattern of PET-pneumonitis poses a significant interpretational challenge, especially when it incorporates the primary tumor or is localized in its proximity, which leads to lower tumor-to-background ratio. In some cases, tumor-to-background ratio, albeit lower, may still be appreciable. As depicted in Fig. 2 (top and bottom row), the relative intensity of the treated primary tumor site compared to pneumonitis has created a perceptible tumor-to-background contrast sufficient to identify both the residual and responding tumor, compared to the surrounding inflammatory change. Loss of tumor to background contrast could also be seen (Fig. 2 middle row), which may pose a significant interpretational challenge. Although in our experience this may be an inflammatory change in the lungs, a further confirmatory study may be warranted. In addition, pattern recognition can be implemented in semiquantitative response criteria through machine-learning [26]. Incorporation of pattern recognition in semiquantitative criteria may be of even more importance as strict application of the semiquantitative measurements is challenging due to difficulty in the accurate assignment of the region of interest and image co-registration in evolving alteration of the lung configuration following RT/CRT.

Conclusions

PET-detected pneumonitis is common in early post-CRT/RT, but with careful visual assessment, recognizing the different patterns of PET-pneumonitis, the impact on response assessment is minimal. While FDG-PET/CT post-CRT/RT in NSCLC is a powerful tool for response assessment and prognostication, the presence of PET-pneumonitis appears not to be associated with early response or OS.

Funding No funding was received for this study. However, the ^{18}F-FLT/^{18}F-FDG study (Australian Clinical Trials Registry: ACTRN12611001283965) work was supported by the National Health and Medical Research Council (NHMRC) (grant number APP1003895) and the Victorian Cancer Agency. The ^{68}Ga-Ventilation/perfusion PET (Universal Trial Number: U1111-1138-4421) study was supported by funding from the NHMRC (grant number APP1038399) and from the Cancer Australia Priority-driven Collaborative Cancer Research Scheme (Project No. 1060919). Professor Hicks is supported by an NHMRC Practitioner Fellowship (APP1108050).

Compliance with ethical standards

Conflict of interest We wish to confirm that there are no known conflicts of interest associated with this publication. A Iravani, GA Turgeon, T Akhurst, JW Callahan, M Bressel, SJ Everitt and MP Mac Manus have no disclosure. Through his institution, DL Ball has an advisory role for Pfizer Australia. RJ Hicks has ownership interest in Telix Radiopharmaceuticals. Through his institution, S Siva has an advisory role for Astellas Pharmaceuticals and Janssen Pharmaceuticals and receives research funding from Varian Medical Systems and Merck Sharp & Dohme Pharmaceuticals. S Siva received speakers' bureau, travel/accommodations/expenses from Bristol-Myers Squibb Pharmaceuticals as well as travel/accommodation/expenses from Astellas Pharmaceuticals.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The registration number for the prospective studies were as follows, PET-planning study: Peter Mac protocol 03/55; the ^{18}F-FLT/^{18}F-FDG study: Australian Clinical Trials Registry no. ACTRN12611001283965; and the ^{68}Ga-ventilation/perfusion PET study: universal trial number U1111-1138-4421. The Peter MacCallum Cancer Clinical Research and Ethics Committee approved this retrospective study and waived the requirement to obtain informed consent (approval number: PMCC 17/43R). All patients had previously provided written informed consent to undergo their respective prospective studies.

References

1. Hicks RJ. Role of 18F-FDG PET in assessment of response in non-small cell lung cancer. J Nucl Med Off Publ Soc Nucl Med. 2009;50(Suppl 1):31S–42S. https://doi.org/10.2967/jnumed.108.057216.
2. Mac Manus MP, Hicks RJ, Matthews JP, McKenzie A, Rischin D, Salminen EK, et al. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2003;21:1285–92. https://doi.org/10.1200/JCO.2003.07.054.
3. Gotwals P, Cameron S, Cipolletta D, Cremasco V, Crystal A, Hewes B, et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. Nat Rev Cancer. 2017;17:286–301. https://doi.org/10.1038/nrc.2017.17.
4. Van Breussegem A, Hendriks JM, Lauwers P, Van Schil PE. Salvage surgery after high-dose radiotherapy. J Thorac Dis. 2017;9:S193–200. https://doi.org/10.21037/jtd.2017.03.88.
5. Bergsma DP, Salama JK, Singh DP, Chmura SJ, Milano MT. Radiotherapy for oligometastatic lung cancer. Front Oncol. 2017;7:210. https://doi.org/10.3389/fonc.2017.00210.
6. Hicks RJ, Mac Manus MP, Matthews JP, Hogg A, Binns D, Rischin D, et al. Early FDG-PET imaging after radical radiotherapy for non-small-cell lung cancer: inflammatory changes in normal tissues correlate with tumor response and do not confound therapeutic response evaluation. Int J Radiat Oncol Biol Phys. 2004;60:412–8. https://doi.org/10.1016/j.ijrobp.2004.03.036.
7. Caulo A, Mirsadraee S, Maggi F, Leccisotti L, van Beek EJ, Bonomo L. Integrated imaging of non-small cell lung cancer recurrence: CT and PET-CT findings, possible pitfalls and risk of recurrence criteria. Eur Radiol. 2012;22:588–606. https://doi.org/10.1007/s00330-011-2299-8.
8. Sudarski S, Henzler T, Schoenberg SO. Post-therapeutic positron emission tomography/computed tomography for early detection of non-small cell lung cancer recurrence. Transl Lung Cancer Res. 2013;2:295–303. https://doi.org/10.3978/j.issn.2218-6751.2013.05.02.
9. Turgeon G, Iravani A, Akhurst T, Beaulieu A, Callahan J, Bressel M, et al. What FDG-PET response-assessment method best predicts survival after curative-intent chemoradiation in non-small cell lung cancer (NSCLC): EORTC, PERCIST, Peter Mac or Deauville criteria? J Nucl Med. 2018. https://doi.org/10.2967/jnumed.118.214148.
10. Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35:56–62. https://doi.org/10.1200/JCO.2016.69.1378.
11. Mac Manus MP, Everitt S, Bayne M, Ball D, Plumridge N, Binns D, et al. The use of fused PET/CT images for patient selection and radical radiotherapy target volume definition in patients with non-small cell lung cancer: results of a prospective study with mature survival data. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2013;106:292–8. https://doi.org/10.1016/j.radonc.2012.12.018.
12. Everitt S, Ball D, Hicks RJ, Callahan J, Plumridge N, Trinh J, et al. Prospective study of serial imaging comparing fluorodeoxyglucose positron emission tomography (PET) and fluorothymidine PET during radical chemoradiation for non-small cell lung cancer: reduction of detectable proliferation associated with worse survival. Int J Radiat Oncol Biol Phys. 2017;99:947–55. https://doi.org/10.1016/j.ijrobp.2017.07.035.
13. Siva S, Callahan J, Kron T, Martin OA, MacManus MP, Ball DL, et al. A prospective observational study of Gallium-68 ventilation and perfusion PET/CT during and after radiotherapy in patients with non-small cell lung cancer. BMC Cancer. 2014;14:740. https://doi.org/10.1186/1471-2407-14-740.
14. De Ruysscher D, Houben A, Aerts HJ, Dehing C, Wanders R, Ollers M, et al. Increased (18)F-deoxyglucose uptake in the lung during the first weeks of radiotherapy is correlated with subsequent radiation-induced lung toxicity (RILT): a prospective pilot study. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2009;91:415–20. https://doi.org/10.1016/j.radonc.2009.01.004.
15. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017;377:1919–29. https://doi.org/10.1056/NEJMoa1709937.
16. Arnett AL, Packard AT, Mara K, Mansfield AS, Wigle DA, Haddock MG, et al. FDG-PET parameters as predictors of pathologic response and nodal clearance in patients with stage III non-small cell lung cancer receiving neoadjuvant chemoradiation and surgery. Practical Radiat Oncol. 2017;7:e531–e41. https://doi.org/10.1016/j.prro.2017.04.013.
17. Badiyan SN, Roach MC, Chuong MD, Rice SR, Onyeuku NE, Remick J, et al. Combining immunotherapy with radiation therapy in thoracic oncology. J Thorac Dis. 2018;10:S2492–S507. https://doi.org/10.21037/jtd.2018.05.73.
18. Turgeon GA, Weickhardt A, Azad AA, Solomon B, Siva S. Radiotherapy and immunotherapy: a synergistic effect in cancer care. Med J Aust. 2019;210:47–53. https://doi.org/10.5694/mja2.12046.
19. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379:2342–50. https://doi.org/10.1056/NEJMoa1809697.
20. Siva S, MacManus M, Kron T, Best N, Smith J, Lobachevsky P, et al. A pattern of early radiation-induced inflammatory cytokine expression is associated with lung toxicity in patients with non-small cell lung cancer. PLoS One. 2014;9:e109560. https://doi.org/10.1371/journal.pone.0109560.
21. Abravan A, Eide HA, Knudtsen IS, Londalen AM, Helland A, Malinen E. Assessment of pulmonary (18)F-FDG-PET uptake and cytokine profiles in non-small cell lung cancer patients treated with radiotherapy and erlotinib. Clin Transl Radiat Oncol. 2017;4:57–63. https://doi.org/10.1016/j.ctro.2017.04.002.
22. Weller A, O'Brien MER, Ahmed M, Popat S, Bhosle J, McDonald F, et al. Mechanism and non-mechanism based imaging biomarkers for assessing biological response to treatment in non-small cell lung cancer. Eur J Cancer. 2016;59:65–78. https://doi.org/10.1016/j.ejca.2016.02.017.
23. Jahangiri P, Pournazari K, Torigian DA, Werner TJ, Swisher-McClure S, Simone CB 2nd, et al. A prospective study of the feasibility of FDG-PET/CT imaging to quantify radiation-induced lung inflammation in locally advanced non-small cell lung cancer patients receiving proton or photon radiotherapy. Eur J Nucl Med

Mol Imaging. 2019;46:206–16. https://doi.org/10.1007/s00259-018-4154-5.
24. Guerrero T, Johnson V, Hart J, Pan T, Khan M, Luo D, et al. Radiation pneumonitis: local dose versus [18F]-fluorodeoxyglucose uptake response in irradiated lung. Int J Radiat Oncol Biol Phys. 2007;68:1030–5. https://doi.org/10.1016/j.ijrobp.2007.01.031.
25. Siva S, Callahan JW, Kron T, Chesson B, Barnett SA, Macmanus MP, et al. Respiratory-gated (4D) FDG-PET detects tumour and normal lung response after stereotactic radiotherapy for pulmonary metastases. Acta Oncol. 2015;54:1105–12. https://doi.org/10.3109/0284186X.2015.1027409.
26. Ypsilantis PP, Siddique M, Sohn HM, Davies A, Cook G, Goh V, et al. Predicting response to neoadjuvant chemotherapy with PET imaging using convolutional neural networks. PLoS One. 2015;10:e0137036. https://doi.org/10.1371/journal.pone.0137036.