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Immune-related Adverse Events on Body CT in Patients with Small-Cell Lung Cancer Treated with Immune-checkpoint inhibitors

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Abstract

Purpose: Investigate the incidence and imaging characteristics of radiologically-evident immune-related adverse events (irAEs) on body CT in patients with small-cell lung cancer (SCLC) treated with immune-checkpoint inhibitors.

Methods: The study included 53 patients with relapsed/refractory SCLC (27 men, 26 women) treated with PD-1/PD-L1 inhibitors alone or in combination with CTLA-4 inhibition, who had baseline and at least one follow-up body CT during therapy. Body CT scans were reviewed to detect and characterize organ-specific irAEs including thyroiditis, pneumonitis, hepatitis, pancreatitis, enteritis, and colitis.

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Results: Nineteen patients (36%) developed radiologically-evident irAEs. The median time from therapy initiation to irAE onset was 7.1 weeks. Pneumonitis and colitis were most common, noted in 9 patients (17%) each. Seven colitis cases demonstrated pancolitis, and two cases showed segmental colitis associated with diverticulosis. The common radiographic patterns of pneumonitis were acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern (n=4) and cryptogenic organizing pneumonia (COP) pattern (n=3). Other irAEs included thyroiditis (n=3), enteritis (n=2), hepatitis (n=1), and pancreatitis (n=1). Older age (p=0.03) and prior radiotherapy to any organ (p=0.03) was associated with overall irAEs. Prior chest radiotherapy was significantly associated with pneumonitis or thyroiditis (p=0.0004).

Conclusion: Radiologically-evident irAEs were noted on body CT in 36% of patients with SCLC treated with immune-checkpoint inhibitors. Colitis and pneumonitis were most common. Prior chest radiotherapy was a predictor of the development of both pneumonitis and thyroiditis. Awareness of risk factors and CT findings of irAEs is important for early detection and accurate diagnosis of potentially serious immunotherapy toxicities.

Keywords

small-cell lung cancer; immune-checkpoint inhibitors; PD-1; PD-L1; immune-related adverse event; computed tomography

Introduction

Small cell lung cancer (SCLC) is an uncommon but highly aggressive subtype of lung cancer associated with poor survival, and its 5-year-survival rate is less than 7%^{1, 2}. This subtype has a distinct neuroendocrine cell origin, which initially responds well to chemotherapy, however, eventually recurs with chemotherapy-resistant disease. Until recently, the standard-of-care treatment for the limited stage SCLC consisted of chemoradiotherapy, and the treatment for the extensive-stage SCLC consisted of chemotherapy alone. This standard treatment strategy has not been changed since the 1980s, and alternative treatment options for SCLC after a failure of standard chemotherapy have been limited^{3, 4}. Recently, immune checkpoint inhibitor therapy has shown promising therapeutic efficacy in SCLC. Nivolumab alone or combination with ipilimumab demonstrated antitumor activity and durable responses in previously treated patients with SCLC who progressed after one or more previous regimens⁵. The addition of atezolizumab to chemotherapy in the first-line treatment of extensive-stage SCLC resulted in significantly longer overall survival and progression-free survival compared to the conventional chemotherapy alone⁶. In the United States, FDA approvals have recently been granted to nivolumab and pembrolizumab (PD-1 inhibitors), as well as to atezolizumab (PD-L1 inhibitor) in combination with carboplatin and etoposide for the treatment of SCLC^{7, 8}.

Immune-related adverse events (irAEs) represent a diverse group of unique toxicities related to immune checkpoint blockade, potentially involving almost any organ systems^{9–15}. These toxicities often involve major organs in the chest, abdomen, and pelvis, including thyroid, lung, liver, pancreas, and gastrointestinal tract, and are associated with unique radiographic manifestations on body CT scans, which can help in irAE detection and monitoring during immune checkpoint inhibitor therapy^{15, 16}. Prior studies described the incidence and

manifestations of irAEs detected on imaging in patients with melanoma and non-small-cell lung cancer^{9, 16}; however, the spectrum of imaging findings of irAEs specifically in patient with SCLC treated with immune checkpoint inhibitors has not been described.

The purpose of the study is to investigate the incidence and imaging characteristics of radiologically-evident irAEs on body CT in patients with SCLC treated with PD-1/PD-L1 inhibitors either alone or in combination with a CTLA-4 inhibitor, and to identify clinical characteristics associated with the development of irAEs in these patients.

MATERIALS AND METHODS

Patients

Of the total of 71 patients with SCLC treated with PD-1/PD-L1 inhibitors alone or in combination with CTLA-4 inhibitor between July 2014 and July 2018, 18 patients were excluded due to a lack of baseline or follow-up CT scans (n=18), resulting in 53 patients that constituted final study cohort chart. Patients treated with immunotherapy in combination with chemotherapy were excluded. The medical records and imaging studies were retrospectively reviewed in these patients who had consented to a correlative research study approved by the institutional review board.

Image analysis for irAE detection and characterization

Two radiologists with expertise in cancer imaging (MN and HP) independently reviewed serial body CT scans to identify the imaging findings suggestive of irAEs, according to the pre-defined imaging criteria as published in prior studies^{9–12, 16}. The radiologists were aware that the patients were treated with immune-checkpoint inhibitors for SCLC, however did not have access to other detailed clinical data during the imaging review. CT scans of the chest, abdomen, and pelvis including the baseline scan prior to the initiation of PD-1/PD-L1 inhibitors and serial follow-up scans before starting the next systemic therapy were reviewed for the findings of irAEs, as previously described^{9, 16}. Follow-up CT scans were primarily performed for the purpose of tumor response evaluations, with an interval of 6–12 weeks depending of the clinical protocols; however, additional imaging with a shorter interval was performed if clinically needed to evaluate acute events such as irAE or rapid tumor progression.

The organ-specific irAEs evaluated in this study included thyroiditis, pneumonitis, hepatitis, pancreatitis, enteritis, and colitis, which are representative irAEs involving major body organs with characteristic imaging findings. The imaging criteria used for each of the organ-specific irAEs were as follows; 1) thyroiditis: new enlargement of the thyroid gland or heterogeneous enhancement of the gland¹⁶; 2) pneumonitis: new consolidative, ground glass, or reticular opacities with distributions and appearances that are not consistent with metastasis or other pulmonary conditions, which may be accompanied with centrilobular nodularity or traction bronchiectasis¹²; 3) enteritis and colitis: fluid-filled bowel, mesenteric vessel engorgement, bowel wall thickening (>4mm irrespective of distension) or increased mucosal enhancement¹⁶; 4) hepatitis: hepatomegaly, heterogeneous parenchymal enhancement with areas of low attenuation, or periportal/gallbladder edema¹⁰; 5)

pancreatitis: new focal or diffuse pancreatic enlargement, decreased enhancement of pancreas, or peripancreatic stranding in the absence of a focal lesion suspicious for metastasis¹⁶.

Two radiologists independently assigned scores for the likelihood of an irAE for each of the organ-specific irAEs in each case after the review of serial CT scans, using a 5-point scale: 1=definitely not irAE; 2=probably not irAE; 3=equivocal; 4=probable irAE; and 5=definite irAE^{9, 16}. All cases with scores of 3 or above for any of the organ-specific irAEs were reviewed by consensus of the two original radiologists plus another radiologist (HH), to determine the final score for the irAEs and characterize the specific imaging findings. The patients with a final score of 4 or 5 were considered to be positive for irAEs, as in prior studies^{9, 16}. During the consensus review, the cases positive for colitis were further categorized into two subtypes: diffuse pancolitis or segmental colitis associated with diverticulosis (SCAD)¹¹. Pneumonitis was categorized into four subgroups using the radiographic pattern-based approach that has been used in prior studies of characterization of pneumonitis from immunotherapy and other cancer treatment, which is based on the ATS/ERS international multidisciplinary classification of interstitial pneumonias and the related conditions: acute interstitial pneumonia/acute respiratory distress syndrome (AIP/ARDS) pattern, cryptogenic organizing pneumonia (COP) pattern, non-specific interstitial pneumonia (NSIP) pattern, and hypersensitivity pneumonitis (HP) pattern^{12, 17–21}.

After the completion of the independent and consensus review, the further medical record review was performed to obtain correlative information regarding symptoms, treatment of irAEs, and clinical improvement on follow-up visits.

Statistical analysis

Demographics and clinical characteristics were compared between patients with and without radiologically-evident irAEs. Fisher exact test was used for categorical variables, and Wilcoxon test for continuous variables. All P values were based on a two-sided hypothesis. $P < 0.05$ was considered to be statistically significant.

RESULTS

Overall frequency and clinical predictors of organ-specific irAEs

Median imaging review period was 3.3 months (range, 0.5 – 37.2 months). Median number of baseline and follow-up CT scans that were evaluated in the image review was 5 (range, 2 – 27 studies). Among 53 patients (27 men, 26 women, median age: 65), 19 patients (36%) developed radiologically-evident organ-specific irAEs (Table 1). The median time from the initiation of therapy to the development of irAEs was 7.1 weeks (range, 0.7–44.7 weeks). Among organ-specific irAEs evaluated in the study, pneumonitis and colitis were the most common, noted in 9 patients (17%) each, followed by thyroiditis in 3 patients (6%), and enteritis in 2 patients (4%). Pancreatitis and hepatitis were noted in 1 patient each (2%). Four patients experienced more than one irAE (8%), with two patients experiencing irAEs in three organs and two patients experiencing irAEs in two organs.

The clinical factors listed in Table 1 were studied for the association with irAEs. The 19 patients who experienced irAEs were older than those without irAEs (median age: 67.5 vs. 58 years, respectively, $p=0.0345$). A history of prior radiotherapy to any organ was associated with the development of overall irAEs; 17 of 19 patients with irAEs (89%) had prior radiotherapy, whereas 20 of 34 patients without irAEs (59%) had prior radiotherapy ($p=0.03$). Moreover, prior chest radiotherapy was significantly associated with the development of pneumonitis or thyroiditis ($p=0.0004$). Other demographic and clinical characteristics, including combination regimen using CTLA-4 inhibitor, were not significantly associated with the development of irAE ($p=0.25$). There was no irAE-related death.

Characteristics of individual types of organ-specific irAEs

Colitis—The median time to onset of colitis was 2.6 weeks (range, 0.7–39.9) after initiation of therapy. Among 9 cases of colitis, 7 cases demonstrated diffuse pancolitis (Fig. 1, arrows), and 2 cases showed segmental colitis associated with diverticulosis (SCAD) (Fig. 2). A fluid-filled colon and bowel wall thickening were the most common imaging findings, noted in 7 cases each, followed by increased mucosal enhancement seen in 5 cases, and mesenteric vessel engorgement noted in 4 cases. Three patients with pancolitis had all 4 findings on CT. The development of colitis was not associated with monotherapy or combination therapy ($p=0.46$).

Four of the 9 cases had more than one irAE in addition to colitis, including concurrent thyroiditis and pneumonitis, which developed in a patient 1.5 weeks after colitis ($n=1$), enteritis and hepatitis in one patient which developed at the same time with colitis ($n=1$), enteritis in a patient which developed at the same time as colitis ($n=1$), and pancreatitis which developed 5.6 weeks after colitis in one patient ($n=1$). Among 9 cases, 6 cases were symptomatic and received treatment including systemic corticosteroids ($n=5$) and anti-diarrheal drug ($n=1$), and 3 cases were asymptomatic and managed conservatively. The earliest onset was after 5 days of initiation of therapy, when the patient visited the Emergency Room with acute abdominal pain and CT scan was performed for the assessment of the acute symptom. Follow-up was available on 6 cases, all of which showed improvement clinically and/or radiographically. Three patients deceased before the subsequent follow-up.

Pneumonitis—Nine cases of pneumonitis were identified on CT, with a median time to onset of 12.1 weeks (range, 1.4–44.7) after therapy initiation. Seven out of nine patients were treated with chest radiotherapy previously. Four patients received nivolumab plus ipilimumab combination therapy, whereas 5 patients received PD-1/PD-L1 monotherapy (nivolumab in 3, pembrolizumab in 1, and atezolizumab in 1 patient).

The most common radiographic pattern of pneumonitis was acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern ($n=4$), with bilateral ground-glass opacities (GGO), reticular opacities and consolidations involving all lobes in diffuse distribution in all patients (Fig. 3). The second most common pattern was cryptogenic organizing pneumonia (COP) pattern ($n=3$) predominantly characterized with multifocal

GGO and consolidations. Non-specific interstitial pneumonia (NSIP) pattern was noted in one patient, who demonstrated bilateral lower and peripheral lung distribution accompanying GGO, reticular opacities, consolidation, and traction bronchiectasis. One patient demonstrated a HP pattern with GGO as well as reticular and centrilobular nodularity in both upper lungs. CT findings of pneumonitis were bilateral in 8 patients, whereas one patient had pneumonitis in the entire right lung with superimposed post radiation changes in the right perihilar region from chest radiotherapy performed 3 years ago.

Nine cases were treated with corticosteroids, while holding PD-1/PD-L1 inhibitors, and three cases were asymptomatic. All cases showed improvement radiologically and/or clinically on follow-up. In terms of the subsequent treatment for SCIC, 3 patients restarted PD-1/PD-L1 inhibitors after the resolution of pneumonitis, 4 patients started conventional chemotherapy, 2 patients started palliative management without any anti-cancer agents due to clinical progression and deterioration of cancer-related symptoms.

Thyroiditis—There were three cases of thyroiditis noted on body CT, with a median time to onset of 5.0 weeks (range, 2.3–5.0). Thyroiditis was the only irAE in two patients, and the other case was accompanying pneumonitis and colitis. All three cases showed new enlargement and heterogeneous enhancement of the thyroid gland on CT (Fig. 4). Thyroid stimulating hormone (TSH) was elevated in all three patients; two patients were asymptomatic and were on observation, and one patient had fatigue and ankle edema related to hypothyroidism and received thyroid hormone replacement therapy.

Enteritis, hepatitis, and pancreatitis—Enteritis, hepatitis, and pancreatitis were accompanying colitis either concurrently or in close temporal proximity. Enteritis was noted in two patients who also had pancolitis, both noted on the same CT scan (time to onset: 2.6 and 12.7 weeks for each irAE, respectively). One patient demonstrated diffuse involvement of the small bowel in addition to the large bowel, with findings of fluid-filled lumen, bowel wall thickening, increased mucosal enhancement and mesenteric vessel engorgement in both small bowel and colon (Fig. 1, asterisks). The other patient had fluid-filled bowel alone in both small bowel and colon.

Hepatitis was noted in one patient who also had enteritis and colitis on the same scan (time to onset: 2.6 weeks), demonstrating hepatomegaly and heterogeneous enhancement with areas of low attenuation and periportal/gallbladder edema on CT scan.

Pancreatitis was noted in one patient who developed colitis 5 weeks prior to the development of pancreatitis. CT scan demonstrated pancreatic enlargement and decreased enhancement of pancreas. Clinically, the patient had abdominal pain associated with pancreatitis, and amylase and lipase were elevated (729 U/L and 1060 U/L, respectively).

Discussion

The incidence of radiologically-evident irAEs was 36% among patients with SCLC who had received PD-1/PD-L1 inhibitors alone or in combination with CTLA-4 inhibitors, and 8% of patients had more than one irAE. Pneumonitis and colitis were the most common irAEs, followed by thyroiditis. Older age and a history of prior radiotherapy to any organ were

associated with the development of irAEs, and the history of prior chest radiotherapy was significantly associated with the development of pneumonitis and thyroiditis. This is the first report that systematically evaluates the radiologically-evident irAEs and describes the imaging characteristics and risk factors in patients with SCLC.

Given the recent FDA approvals of immune-checkpoint inhibitors for the treatment of a wide variety of malignancies, the recognition of irAEs and awareness for their imaging manifestations and risk factors are becoming increasingly important. Treatment with immune checkpoint inhibitors was recently approved for SCLC, but no prior studies have focused on radiologic manifestations of irAEs in this tumor type. According to the prior studies, the incidence of clinically-evident irAEs from anti-PD-1/PD-L1 inhibitors has been reported to be 50–60% for all grade and <10% for grade 3 or higher²².

The incidence of radiologically-evident irAEs has been evaluated in a few previous reports focusing on the cohorts of patients with melanoma and NSCLC^{9, 16, 23}. Tirumani et al reported that the incidence of radiologically-evident irAEs associated with anti-CTLA-4 inhibitor, ipilimumab, in patients with melanoma was approximately 31%¹⁶. Another study by Alessandrino et al reported that the incidence of radiologically-evident abdominal irAEs associated with anti-PD-1/PD-L1 inhibitors was 13%⁹. The overall incidence of 36% in the present study focusing on patients with SCLC treated with PD-1/PD-L1 inhibitors alone or in combination with CTLA-4 inhibitors is higher than both incidences of irAEs in NSCLC patients treated with PD-1/PD-L1 inhibitors and in melanoma patients treated with ipilimumab. Higher incidence of irAEs in SCLC patients may be partly related to frequent concurrent or previous history of radiation therapy which is a part of a current standard of care in SCLC patients, but may also imply immunogenic nature of SCLC or other biological conditions related to SCLC development and progression. Although combination therapy using CTLA-4 inhibitor was shown to be associated with a higher incidence of irAEs compared to PD-1/PD-L1 monotherapy²⁴, no significant differences or trends were noted between monotherapy and combination therapy groups in the present study, likely due to a small number of patients.

Colitis was the one of the most common irAEs in our study, noted in 17% of patients with a median time to onset of 7.1 weeks. All uncommon irAEs including enteritis, hepatitis, and pancreatitis were associated with colitis. These results are consistent with previously reports that colitis is the most common radiologically-evident irAE⁹, and the time of onset is typically <16 weeks from the initial therapy²⁵. CT is an accurate and noninvasive imaging modality for detecting immune-related colitis as well as predicting the need for steroids for the resolution of symptoms²⁶. According to the previous study, CT was highly predictive of colitis (positive predictive value 96%) and highly predictive of the need for steroids to reach resolution of symptoms (positive predictive value 92%)²⁶. In our study, three asymptomatic patients (3/9, 33%) demonstrated obvious colonic wall thickening and mucosal hyperemia on CT scan suggesting radiologically-evident colitis, all of which showed resolution after conservative management. The imaging pattern of immune-related colitis in patients with SCLC was similar to previously described immune-related colitis in other cancers, which is either diffuse pancolitis (7/9 patients, 78%) or SCAD (2/9 patients, 22%)^{9, 11, 16}. Bowel perforation is not common but a serious complication related to immune-related colitis,

especially associated with CTLA-4 inhibitors. Therefore, awareness of this complication with characteristics of imaging features is important for early detection and appropriate management.

Pneumonitis is another irAEs with the highest incidence along with colitis, also noted in 17% of the patient. The incidence is notably higher than previously reported incidences of immune-related pneumonitis, which was 3–5% on anti PD-1/PD-L1 monotherapy in patients with lung cancer, melanoma or renal cell carcinomas, and 6.6% on CTLA-4 and anti PD-1/PD-L1 combination therapy in patients with melanoma^{24, 27, 28}. The spectrum of radiographic patterns of pneumonitis as in the prior studies was noted in patients with SCLC as well, including AIP/ARDS pattern (n=4), COP pattern (n=3), NSIP pattern (n=1), and HP pattern (n=1)^{12, 29, 30}. The incidence of AIP/ARDS pattern appeared somewhat more frequent in SCLC compared to other tumor types, which may be due to the fact that most of patients had received previous radiation therapy, leading to a more extensive pattern of pneumonitis in this specific population. AIP/ARDS pattern has been shown to be a marker of more clinically severe pneumonitis with higher grades¹². In the present SCLC cohort, although the number of pneumonitis cases is too small for further subgroup analyses, one patient required ICU admission for treatment for pneumonitis and the patient had an AIP/ARDS pattern on CT. A particular caution is needed to identify this pattern of pneumonitis in patients with SCLC receiving anti-PD-1/PD-L1 inhibitors.

Thyroiditis is one of the well-known endocrine irAEs along with hypophysitis^{31, 32}. According to a meta-analysis including 38 clinical trials, the incidence of hypothyroidism and hyperthyroidism related to immune checkpoint inhibition was estimated to be 6.6% (95% CI, 5.5%–7.8%) and 2.9% (95% CI, 2.4%–3.7%), respectively³³. Among patients with immune-related thyroiditis, 78% of them initially present as thyrotoxicosis, and 80% of those thyrotoxicosis subsequently developed hypothyroidism^{31–33}. The time to onset of thyrotoxicosis and hypothyroidism was 3–5 weeks and 9–10 weeks, respectively^{31, 32}. The majority of patients who had hypothyroidism required hormonal replacement therapy at the last follow up, suggesting that hypothyroidism might be permanent and require lifelong therapy. Thyroid dysfunction in patients treated with immunotherapy can be unnoticed clinically, because it can be asymptomatic,³¹ or overshadowed by the symptoms of cancer progression, or thyroid stimulating hormone (TSH) is not checked routinely leading to under-diagnosis. Therefore, it is important for radiologists to be familiar with the imaging findings of immune-related thyroiditis for early detection and appropriate management. On medical imaging, immune-related thyroiditis is most commonly detected on Positron Emission Tomography (PET)/CT as new diffuse fluorodeoxyglucose (FDG) uptake in the thyroid gland³⁴. Conventional CT findings can be nonspecific and variable, however we noted that new diffuse enlargement and heterogeneous enhancement of the gland developed after the initiation of immune checkpoint inhibitor therapy is suspicious for immune-related thyroiditis, calling for further evaluation in correlation with laboratory findings.

Enteritis is not common, and usually accompanies colitis^{9, 35}. In a previous study reporting the incidence of abdominal irAEs in lung cancer patients, enteritis involving the small bowel was noted in 1.6% (4 enteritis among 18 positive abdominal irAEs). Although rare, immune-related enteritis, especially when associated with CTLA-4, can be clinically severe and have

potential to cause intestinal perforation³⁶, which needs radiologists' attention for early detection along with colitis in patients with SCLC.

Hepatitis is a relatively uncommon irAE, with incidence of 2–5%³⁷. Clinically, immune-related hepatitis can manifest as 1) mild and asymptomatic with mildly elevated liver enzymes or 2) severe with systemic symptoms and markedly increased liver function tests¹⁰. Image findings can be variable, from normal appearance in the mild form to findings of acute hepatitis such as hepatomegaly, periportal edema, and periportal lymphadenopathy in the severe form¹⁰. Pancreatitis is a rare irAEs, with an incidence less than 1%³⁷. Patients can be asymptomatic with elevated amylase/lipase alone. CT demonstrates findings similar to autoimmune pancreatitis such as pancreatic swelling³⁸.

Currently, there is a debate regarding the therapeutic effect and safety of combining radiotherapy and immune-checkpoint inhibitors in lung cancer. A few preclinical studies suggested that radiotherapy could enhance the immune response by secretion of cytokines as well as activation of tumor specific T cells, which leads to a potentially synergistic therapeutic effect^{39–41}. Uncertainties remain regarding increased toxicity, and data are limited. Pulmonary toxicity is one of the main concerns, because pulmonary toxicity related to radiotherapy is a common and well-known dose limiting toxicity and immune-related pneumonitis is a rare but potentially lethal adverse event¹². Additionally, a phenomenon of “radiation recall pneumonitis”, defined as pneumonitis localized to a previously irradiated field after exposure to a systemic agent, can be noted in the previously irradiated lung after initiation of immune-checkpoint inhibitors, which further complicates the issue⁴². In earlier clinical trials in lung cancer, the enrollment of patients who had previous thoracic radiation were limited due to the concern for increasing toxicity^{27, 43, 44}. Most patients with SCLC included in the present study had received prior radiotherapy to the primary lung tumor in the limited stage SCLC, which motivated us to study the association between the prior history of radiotherapy and the development of irAEs, as in a few recent studies on this topic^{45, 46}. Our results showed that the history of radiotherapy to any organ was associated with the development of overall irAEs, the history of chest radiotherapy was associated with the development of pneumonitis and thyroiditis. It is noteworthy that there may be a potential effect of increased toxicity to the organs close to the radiation field. The results also call for increased attention to pneumonitis and thyroiditis in patients with SCLC with a prior history of chest radiotherapy.

Our study has several limitations. First, there were a relatively small number of patients reviewed retrospectively. However, it is important to note that SCLC is less common compared to NSCLC and treatment with immune-checkpoint blockade has only recently been approved. The results of this initial study can provide a basis for further studies with a larger population to validate the results. Second, radiologically-evident irAEs were analyzed on body CT scan alone, because body CT is a standard modality of routine follow-up for patients with SCLC in clinical practice, and thus can be a practical resource for detection of irAEs. The irAEs in the central nervous system were not evaluated in the present study, because not every patient had routine brain MRI in this retrospective cohort, and the findings of immune-related hypophysitis have been previously described in the neuroradiology literature^{47, 48}. Third, not all the cases of radiologically detected irAEs had histologic

confirmation; however, we used the predefined organ-specific imaging criteria that were used on the previous studies to define radiologically-evident irAEs^{9, 16}. It is becoming less frequent to obtain histologic confirmation for the findings of irAEs via invasive tissue sampling in advanced cancer patients including SCLC, and the diagnosis of irAEs is often made by a consensus of multidisciplinary team. Finally, the association of irAEs with treatment efficacy or with survival, described in several prior clinical studies^{49–52} was not investigated in the present study primarily focusing on imaging characterization of organ-specific irAEs.

In conclusion, radiologically-evident irAEs were noted in 36% of SCLC patients treated with PD-1/PD-L1 inhibitors alone or in combination with CTLA-4 inhibitors on their body CT scans. Colitis and pneumonitis were most common. Older age and the history of previous RT to any organ were associated with development of irAEs. Prior chest radiotherapy was a predictor of the development of pneumonitis or thyroiditis. Awareness of risk factors and specific CT findings of irAEs is important for early detection and accurate diagnosis in patients with SCLC.

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Highlight

- 36% of SCLC patients treated with PD-1/PD-L1 inhibitors had irAE on body CT
- Colitis and pneumonitis were the most common types of irAEs
- Older age and the history of previous radiotherapy were associated with irAEs
- Prior chest radiotherapy was a predictor of with pneumonitis or thyroiditis
- The results call for awareness of risk factors and CT findings of irAEs in SCLC

Figure 1.

A 68-year-old woman who developed diffuse pancolitis and enteritis after starting treatment with nivolumab monotherapy. CT after 2.6 weeks from the start of the immune checkpoint inhibitor therapy showed diffuse wall thickening and mucosal hyperemia of the entire colon (arrows), suggesting pancolitis. Diffuse wall thickening and mucosal hyperemia were also noted in the small bowel loops (asterisks) indicating co-existing enteritis.

Figure 2.

Segmental colitis associated with diverticulosis (SCAD) in a 58-year-old man treated with nivolumab and ipilimumab. a,b) CT after 17.9 weeks from the start of the immune checkpoint inhibitor therapy showed diffuse wall thickening and mucosal hyperemia of the sigmoid colon (arrows) with mesenteric vessel engorgement, demonstrating colitis with a SCAD pattern.

c,d) The patient was asymptomatic, and treated conservatively. Follow-up CT showed resolution of the findings of SCAD in the sigmoid colon (arrows).

Figure 3.

Pneumonitis in a 56-year-old man treated with nivolumab and ipilimumab. CT after 1.4 weeks from the start of the immune checkpoint inhibitor therapy demonstrated diffuse ground glass and reticular opacities throughout both lungs, with areas of consolidation, representing pneumonitis with an acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern.

Figure 4. Thyroiditis in a 71-year-old woman treated with nivolumab and ipilimumab. Compared to baseline CT (a), CT after 5 weeks from the start of the immune checkpoint inhibitor therapy demonstrated new enlargement and heterogeneous enhancement of the thyroid gland (b, arrows), indicating thyroiditis. Elevation of TSH was noted in the laboratory testing.

Table 1.

Patient demographics and disease characteristics

	irAE present (n=19)	irAE not present (n=34)	Total (n=53)
Age (years)			
Median [Range]	67.5 [43–83]	58 [38–84]	65 [38–84]
Gender			
Male	12	15	27
Female	7	19	16
Smoking			
Never	0	2	2
Current or Former	19	32	51
Stage			
Limited	10	9	19
Extensive	9	25	34
History of radiation			
Yes [#]	17	20	37
No	2	14	16
Treatment regimen			
PD-1/PD-L1 monotherapy	9	22 [▲]	31
PD-1/CTLA-4 combination	10 [*]	12 [*]	22
ECOG performance status			
0	2	4	6
1	12	30	42
2	4	0	4
3	1	0	1

Six patients received nivolumab, 2 patients received pembrolizumab, and one patient received atezolizumab.

[▲] Eighteen patients received nivolumab, 3 patients received pembrolizumab, and one patient received atezolizumab.

^{*} All patients in the combination therapy group received nivolumab plus ipilimumab.

[#] 29 received radiotherapy to the chest including 2 patients who also received prophylactic cranial irradiation (PCI), and 8 patients received radiotherapy to the brain alone, either whole brain radiotherapy or stereotactic radiotherapy to brain lesions.