



# Immunotherapy-Related Imaging Findings in Patients with Gynecological Malignancies: What Radiologists Need to Know

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Immunotherapy is an effective treatment option for gynecological malignancies. Radiologists dealing with gynecological patients undergoing treatment with immune checkpoint inhibitors should be aware of unconventional immune-related imaging features for the evaluation of tumor response and immune-related adverse events. In this paper, immune checkpoint inhibitors used for gynecological malignancies and their mechanisms of action are briefly presented. In the second part, patterns of pseudoprogression are illustrated, and different forms of immune-related adverse events are discussed.

**Keywords:** *Checkpoint inhibitors; Pseudoprogression; Adverse drug event; Gynaecological oncology*

## INTRODUCTION

Gynecological malignancies, such as cervical, endometrial, and ovarian cancers, are common. In 2012, cervical cancer was the fourth most frequently diagnosed cancer in female, with 527600 new cases [1]. Instead, for endometrial and ovarian cancers, 319600 and 239000 new cases were registered, respectively [2]. An increase in the prevalence of ovarian cancer is expected by 2035, which accounts for 371000 (+ 55%) new cases and 254000 (+

67%) new deaths [2].

An increase in incidence and mortality must be addressed as an unmet medical need for gynecological patients. Despite advances in surgery, radiation, and chemotherapy, the prognosis for advanced stages of gynecological disease remains poor [3,4].

During the last decade, immunotherapy has revolutionized the field of oncology and has assumed an important role as a standard treatment for several malignancies. The use of immunotherapy has rapidly increased for solid tumor treatment because of its satisfactory results in clinical trials. In 2011, an immune checkpoint inhibitor (ICI) was first approved for the treatment of metastatic melanoma [5]. Since then, ICIs have provided a successful therapeutic option for several solid tumors, including renal cell carcinoma, non-small cell lung cancer (NSCLC), non-Hodgkin's lymphoma, urothelial carcinoma, and hepatocellular carcinoma [6-9]. In this scenario, immunotherapy was thought to be valuable for gynecological malignancies; therefore, several clinical trials have been initiated in recent years [10,11].

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In 2019, pembrolizumab (an anti-programmed cell death protein [PD]-1 agent), in combination with lenvatinib, was approved by the Food and Drug Administration (FDA) for the treatment of advanced endometrial cancer [12]. Currently, several other randomized controlled trials of ICIs are ongoing in Europe (ClinicalTrials.gov Identifier: NCT03737643; NCT03786081; NCT04199104).

Given the growing use of ICIs in gynecologic oncology, radiologists need to develop an increased understanding of imaging findings related to ICIs in daily clinical practice beyond the setting of treatment response evaluation for clinical trials.

This review aims to provide an overview of the most leveraged immunotherapy mechanisms for gynecological cancer and a practical guide for its action during routine follow-up using diagnostic imaging. In particular, we focused on the evaluation of pseudoprogression tumor response patterns (included in the Response Evaluation Criteria in Solid Tumors [iRECIST]) and the imaging findings of the immune-related adverse events (irAEs), which require a prompt diagnosis to establish a specific treatment [13].

### Mechanisms of Action of Immune Checkpoint Inhibitors

The importance of intact immune surveillance in controlling the outgrowth of neoplastic transformations has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissues and a favorable prognosis for various malignancies. In particular, the presence of CD8+ T cells and the CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) ratio correlates with improved prognosis and long-term survival of patients with solid malignancies, such as ovarian, colorectal, and pancreatic cancer, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma [14].

Various cancer immunotherapy methods, including cancer-specific and non-specific immune stimulants, have been developed. For gynecological malignancies, the most frequently used immunotherapeutic agents are ICIs, as shown in Table 1.

ICIs represent an emerging class of non-specific immunotherapy drugs that interfere with immune checkpoint pathways for T-cells [15]. ICIs have been designed to improve anti-cancer immunity. Their targets are molecules that act as checkpoints for balancing immune response regulation. Under physiological conditions,

**Table 1. A List of Currently Most Studied Immune Checkpoint Inhibitors in Gynecological Malignancies**

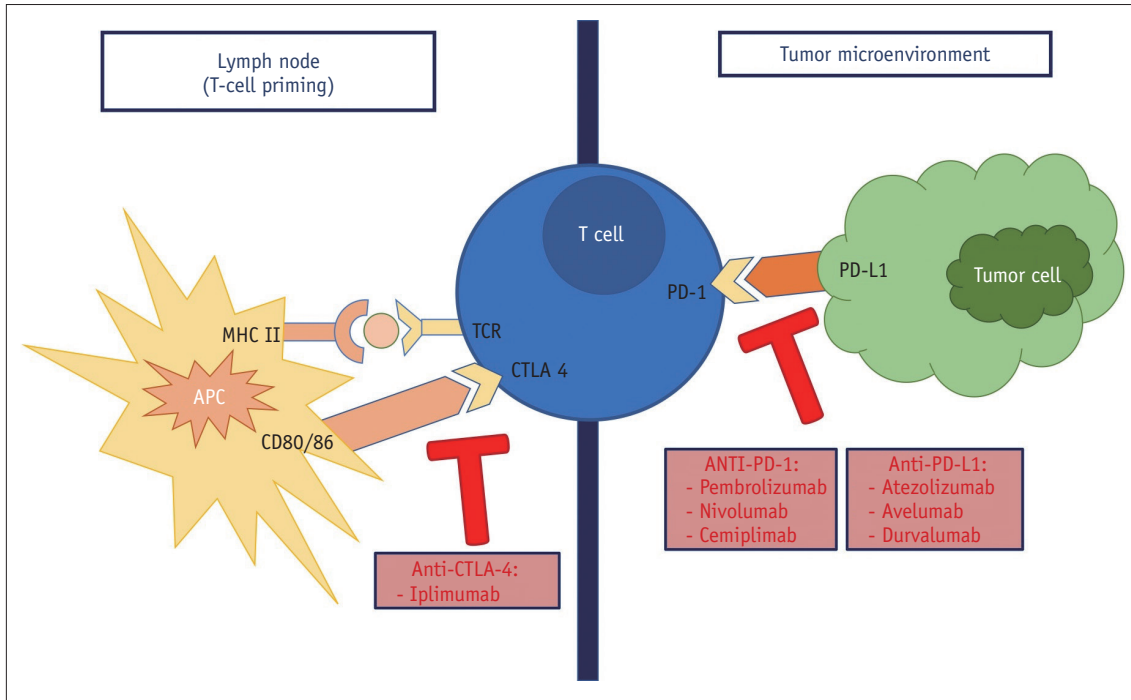
Immune Checkpoint Inhibitor	Molecular Target	Gynecological Malignancies
Pembrolizumab	PD-1	Endometrial, ovarian and cervical cancer
Cemiplimab	PD-1	Cervical cancer
Nivolumab	PD-1	Ovarian cancer
Durvalumab	PD-L1	Ovarian cancer
Avelumab	PD-L1	Endometrial and ovarian cancer
Atezolizumab	PD-L1	Cervical cancer

They are usually administered in combination to standard chemotherapy or other experimental agents. PD-L1 = programmed cell death protein 1 ligand, PD-1 = programmed cell death protein 1

immune checkpoints are fundamental to maintaining self-tolerance and preventing immune over-activation and host-tissue damage. However, tumor cells take advantage of the mechanisms of host immune system recognition. The goal of an ICI is to reduce immune checkpoint activity to enhance anti-cancer immunity and induce a targeted immune response against cancer cells.

The most relevant immune checkpoints are targets of ICIs: cytotoxic T lymphocyte-associated Protein-4 (CTLA-4), PD-1, and programmed death ligand 1 (PD-L1). CTLA-4 and PD-1 belong to the same CD28 family of T-cell receptors and act as negative regulators of immune responses; hence, the suppression of their activity leads to immune system activation and the mounting of the immune response (Fig. 1) [10]. PD-L1 is a ligand of PD-1 expressed by tumor cells.

PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, which is expressed on the cell surface of activated T-cells under healthy conditions, is to downregulate unwanted or excessive immune responses, including autoimmune reactions [16]. PD-1 is a transmembrane receptor normally expressed on the surface of activated T-cells, Tregs, activated B cells, and natural killer cells. PD-L1 is expressed in different tissues and cancer cells. Anti-PD-1 and anti-PD-L1 antibodies act during the effector phase of the T-cell response [17]. During this phase, PD-1 binds to PD-L1, resulting in T-cell downregulation [18]. In a tumor environment, tumor cells expressing PD-L1 can bind PD-1 receptors of T-cells, inducing T-cell immune tolerance, energy, and apoptosis, which leads to the downregulation of the host immune response [19].



**Fig. 1. Mechanisms of action of CTLA-4 and PD-1.** CTLA-4 binds CD80/86 expressed on antigen-presenting cell, inhibiting T cell. PD-1 binds PD-L1, expressed on tumor cell, resulting in suppression of immune response. APC = antigen-presenting cell, CD = cluster of differentiation, CTLA-4 = cytotoxic T-lymphocyte antigen 4, MHC = major histocompatibility complex, PD-1 = programmed cell death protein 1, PD-L1 = programmed cell death protein 1 ligand, TCR = T-cell receptor

Monoclonal antibodies directed against PD-1 or PD-L1 have been demonstrated to reverse and/or prevent tumor-associated T-cell exhaustion, which promotes the activation of tumor detection and destruction [20].

Several immunohistological studies have demonstrated elevated expression levels of PD-1 and PD-L1 in gynecological malignancies, with estimated expression rates of PD-1 of 75.2% in endometrial cancer, 66.9% in epithelial ovarian cancer, and 63.1% in cervical cancer [19]. The estimated PD-L1 expression level was between 67% and 100% in endometrial cancer [10]. PD-L1 expression may represent an actionable target, but it does not directly translate into treatment response, as studies have shown that it is important to highlight that treatment responses may also occur regardless of tumor PD-L1 status [14].

There is a strong theoretical rationale for adopting immunotherapy in ovarian cancer: the tumor presents with a high PD-L1 expression, an elevated number of TILs, and a neo-antigen load, particularly when harboring homologous recombination deficiency or microsatellite instability-high (MSI-H) [21].

Nevertheless, no immunotherapy agent has been approved so far for ovarian cancer because of the disappointing results of clinical trials [22,23]. However, several phase III

studies are ongoing to clarify the role of immunotherapy in ovarian cancer (ClinicalTrials.gov NCT03737643; NCT03740165).

Regarding cervical cancer, there is a strong rationale for immunotherapy due to the role of the tumor immune environment in cervical HPV-associated tumors. In addition, the tumor tissues of HPV-associated cancers show high PD-1 expressing CD8+ T cells [24]. Pembrolizumab monotherapy demonstrated a long-lasting antitumor activity and manageable safety in patients with advanced cervical cancer. At ASCO in 2016, the preliminary results of the KEYNOTE-028 study on cervical cancer patients were as follows: 17% objective responses and OS of 9 months were reported for pembrolizumab monotherapy in a population of 24 advanced/recurrent cervical cancer patients pre-treated with platinum-based chemotherapy (96%), radiotherapy (92%), and bevacizumab (42%); 38% of the patients received pembrolizumab at least as 4th line chemotherapy [25]. A subsequent phase 2 study, KEYNOTE-158, enrolled 98 patients with pre-treated advanced cervical cancers who received pembrolizumab as a single agent. The overall response rate (ORR) was 13.3%; three patients had CR and 10 patients had PR [26]. Based on these results with pembrolizumab, the US FDA granted an accelerated approval

of pembrolizumab for patients with advanced PD-L1-positive cervical cancer who experienced progression during or after chemotherapy.

Recently, the results of a phase 1/2 study evaluating nivolumab 240 mg every 2 weeks for vulvar, vaginal, and cervical tumors were published. The cervical cancer patients demonstrated promising clinical activity with a good toxicity profile (ORR 26.3%; progression-free survival 5.5 months) [27].

In endometrial cancer cells, PD-L1 and PD-L2 are considerably overexpressed, which represents the highest expression among gynecologic cancers as well as tumor-infiltrating CD4+ and CD8+ T cells [28]. In addition, some endometrial cancer subtypes (e.g., POLE mutant/hypermutated and MSI-H) express a high tumor mutational burden; therefore, they are highly immunogenic [29].

Approximately 20–30% of patients with endometrial cancer have MSI-H disease and are eligible for checkpoint inhibitor monotherapy. The GARNET trial (ClinicalTrials.gov NCT02715284) demonstrated promising response rates of 42% with dostarlimab (a PD-1 inhibitor) in patients with recurrent or advanced endometrial cancer who had progression during or after platinum-based chemotherapy and had MSI-H tumors [30].

Pembrolizumab provides long-lasting responses in patients with MSI-H cancers and is approved in the US and Japan for the treatment of MSI-H advanced solid tumors. Recently, the combination of pembrolizumab and lenvatinib has been approved by the FDA for advanced endometrial carcinoma without MSI-H or mismatch repair-deficient disease [12]. In a recently published trial, lenvatinib plus pembrolizumab showed promising antitumor activity regardless of MSI status in patients with advanced endometrial carcinoma who had experienced disease progression after prior systemic therapy [31].

## Tumor Response Evaluation and Pseudoprogression (RECIST and iRECIST)

RECIST represents a set of guidelines for tumor response evaluation, and they were first published in 2000 and revised in 2009 as RECIST 1.1 [32]. They represent standard criteria for clinical trial evaluation of tumor response after therapy, but they are not always efficient for patients treated with immunotherapy. Immunotherapy may result in an initial apparent tumor burden increase, which is related to the immune response to tumors rather than cancer cell

growth [33]. However, after an initial increase in the total tumor burden or the appearance of new lesions, a patient may experience a response or a reduction in the total tumor burden [34]. This phenomenon is called pseudoprogression and is mainly due to inflammatory cell infiltration and swelling as a result of enhanced immunity against cancer cells. Therefore, radiologists who perform imaging studies of gynecologic cancer patients undergoing ICI treatment should be familiar with these response patterns and the concept of pseudoprogression.

Pseudoprogression occurs in 9.7% of patients treated with an anti-CTLA-4 agent (ipilimumab) and 0.6–7% of patients with melanoma or NSCLC who are treated with anti-PD-1 agents, such as nivolumab or pembrolizumab [35–38].

Pseudoprogression may occur at any time from the onset of therapy till after the discontinuation of treatment, but it is more common within the first 12 weeks of treatment (Fig. 2) [39]. It is more frequent in younger patients, probably because their immune system provides higher reactivity [38].

According to RECIST 1.1, stable disease is defined as < 20% increase and < 30% reduction in the sum of target lesions, partial response as ≥ 30% reduction in the sum of target lesions, and progressive disease (PD) as ≥ 20% increase in the sum of target lesions and eventual new lesions from the nadir [32].

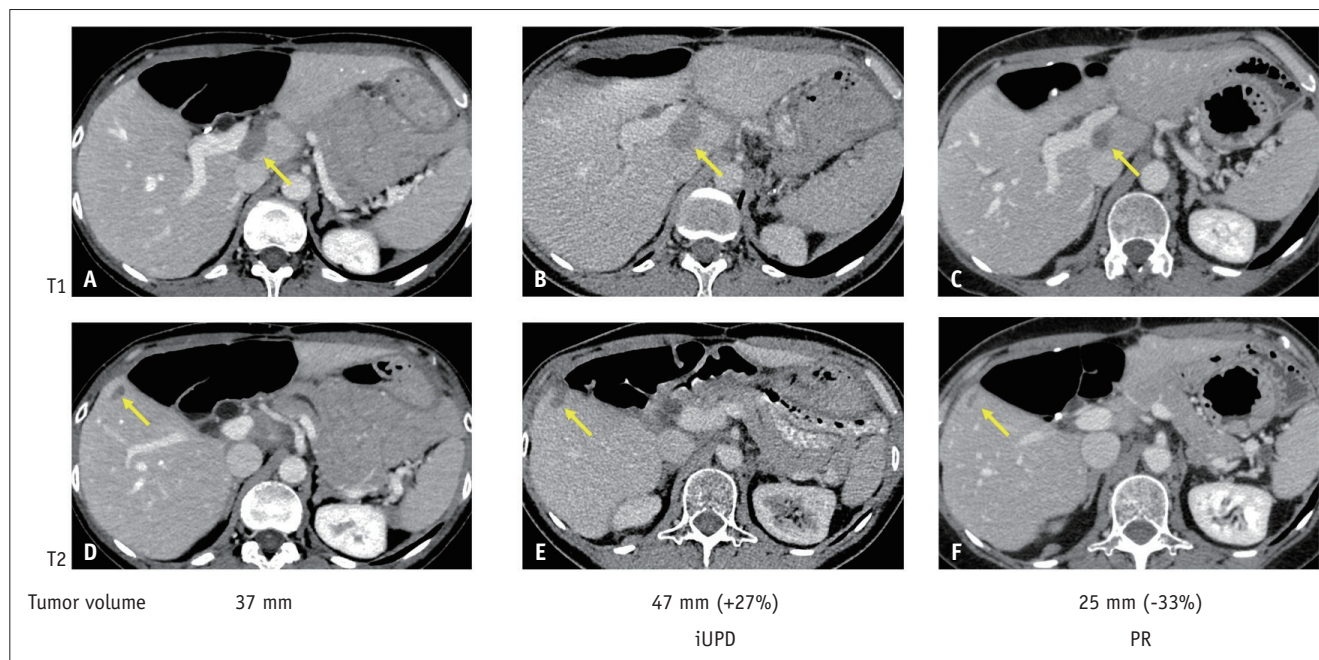
However, RECIST v1.1 fails to identify atypical patterns of tumor response associated with immunotherapy, known as pseudoprogression. Pseudoprogression is defined as an initial increase in tumor size followed by a reduction in tumor burden or an initial reduction in tumor size with the appearance of new lesions, which subsequently regress (Table 2).

In this context, several modified response criteria have been proposed, including immune-related response criteria, immune-related RECIST, immune-modified RECIST, and immune RECIST [13,33,35].

The RECIST group proposed iRECIST, which is a modified criterion for immunotherapy [13]. In the case of tumor progression (“PD”), iRECIST incorporated the term “unconfirmed progressive disease (iUPD)” to facilitate the differentiation of true tumor progression from pseudoprogression, whereby the initially unconfirmed PD is confirmed during follow-up after 4–8 weeks for reassessment before it can be called PD.

iUPD is characterized by:

- ≥ 20% increase in tumor volume from the nadir



**Fig. 2. iRECIST criteria for evaluation of a 51-year-old female with ovarian cancer treated with pembrolizumab (anti PD-1).**  
**A, D.** Baseline CT shows two peritoneal subglissonian metastases (arrows; T1: 17 mm; T2: 10 mm). **B, E.** On a 3-month follow-up, both lesions enlarged with an increase of 27% of the target lesions leading to an iUPD according to iRECIST. **C, F.** After 8 weeks, both lesions decreased in size, compared to baseline examination (-33%). iRECIST = included in the Response Evaluation Criteria in Solid Tumors, iUPD = unconfirmed progressive disease, PD-1 = programmed cell death protein 1, PR = partial response

**Table 2. Comparison of Tumor Response Evaluation Criteria: RECIST 1.1 and iRECIST**

Type of Criteria	Measurement	Target Lesions (No.)	SD Criteria (Sum of Target Lesions)	PR Criteria (Sum of Target Lesions)	PD Criteria (Sum of Target Lesions)	PD Confirmation	New Lesion
RECIST 1.1 (2009) [32]	Unidimensional (LA, SA for nodes)	5 (max 2/organ): LA ≥ 10 mm; nodes (SA ≥ 15 mm)	< 20% increase and < 30% reduction	≥ 30% reduction	PD: ≥ 20% increase	Not required	Defines PD
iRECIST (2017) [13]	Unidimensional (LA, SA for nodes)	5 (max 2/organ): LA ≥ 10 mm; nodes (SA ≥ 15 mm)	< 20% increase and < 30% reduction	≥ 30% reduction	iUPD: ≥ 20% increase	Scan after 4-8 weeks	Defines iUPD, PD confirmation necessary

iRECIST = included in the RECIST, iUPD = unconfirmed progressive disease, LA = long axis, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SA = short axis, SD = stable disease

- A non-target lesion progression
  - The appearance of new lesions
- PD is confirmed after 4–8 weeks in cases with the following:
- Target lesions increase in size by ≥ 5 mm.
  - Significant increase in non-target lesions previously classified as iUPD
  - New lesion increase by ≥ 5 mm or an increase in the number of new lesions

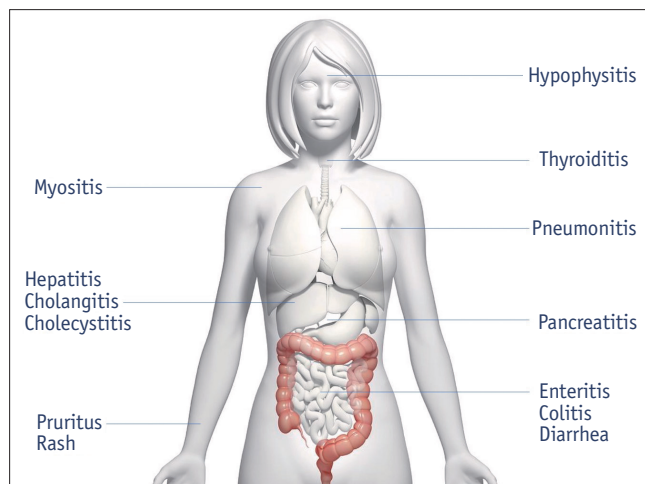
Currently, RECIST 1.1 remains the standard for tumor response evaluation in clinical practice. iRECIST is valuable

for immunotherapy response evaluation during ICI clinical trials (Table 2) [40].

### Immune-Related Adverse Events (irAEs)

Immunotherapy enhances immune activity and may be responsible for the dysregulation of immune homeostasis in other organs, leading to specific toxicities defined as irAEs. The global incidence of irAEs in patients treated with anti-PD-1/PD-L1 agents was reported to be approximately 27% in a meta-analysis conducted in 2017 [41]. The incidence of severe irAEs has been reported to be 6%. The

incidence of irAEs was 8.25% with nivolumab, 5.10% with pembrolizumab, and 5.28% with atezolizumab [41]. irAEs usually occur at the onset of therapy; nonetheless, they can occur at any time, even after treatment cessation [42]. The management of irAEs generally requires the discontinuation of immunotherapy and steroid administration. IrAEs involve several organs and tissues, with a wide range of imaging findings [43]. The most common irAEs are fatigue, diarrhea, pruritus, rash, and colitis followed by pneumonitis and hepatitis (Fig. 3) [34]. Some adverse events may be asymptomatic and can only be detected during imaging studies. Radiologists should be familiar with imaging features suggestive of irAEs, as they can occur in up to 17% of patients receiving immunotherapy [33]. Some of these irAEs are life-threatening and require prompt recognition because radiological findings may precede clinical manifestations [44].



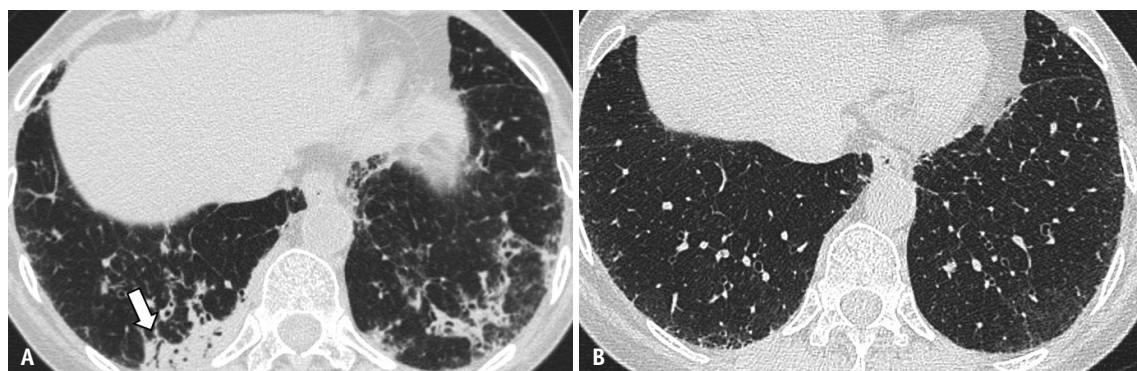
**Fig. 3. Most common immune-related adverse events in female.**

**Pneumonitis**

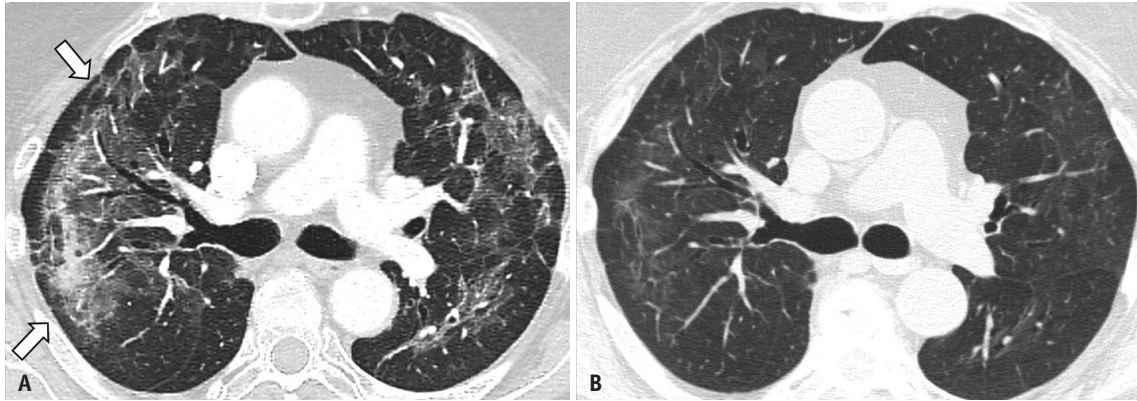
Pneumonitis is one of the most frequent irAEs, especially in patients receiving ICIs in combination, and it occurs in approximately 5% of patients treated with anti-PD-1/PD-L1 agents [45]. Despite the restricted availability of data on ICIs as a result of their recent introduction, different CT patterns for ICI-related pneumonitis have been described [46].

Organizing pneumonia (OP) is the most frequent presentation of ICI-therapy-related pneumonitis in the largest cohort currently available, to our knowledge [47]. OP manifests as patchy bilateral consolidative or ground-glass opacities or a combination of both, with peribronchovascular or subpleural distribution and predominant involvement of the lower lobes (Fig. 4). Air bronchograms are usually observed for opacities [46]. A possible marker for OP is a round consolidative opacity surrounding a central ground-glass area observed as a reversed halo or atoll sign [48]. The nodular presentation can include small nodules, mostly in a peribronchovascular distribution, to mass-like nodules with spiculated margins mimicking a malignancy [49]. Differential diagnoses for ICI-related OP include cryptogenic pneumonia, COVID-19 pneumonia [50], and other infections (such as invasive aspergillosis). Clinical and laboratory findings are required to differentiate these conditions from OP [46].

Non-specific interstitial pneumonia (NSIP) is the second most common presentation of ICI-related pneumonitis (Fig. 5). NSIP presents with bilateral and symmetric ground-glass and reticular opacities with lower lobe predominance [46]. A specific finding is subpleural sparing of the posterior lower lobes [49], which also allows its differentiation from infections.



**Fig. 4. Pneumonitis with an organizing pneumonia pattern.** 57-year-old female with cervical cancer in treatment with atezolizumab showing mild dyspnea. **A.** Follow-up CT scan performed 5 weeks after atezolizumab initiation shows bilateral lower lobes consolidative opacities. **B.** CT scan performed 4 weeks after atezolizumab interruption and corticosteroids administration shows pneumonitis resolution with residual subpleural reticular opacities.



**Fig. 5. Pneumonitis with a NSIP pattern.** 72 year-old female with ovarian cancer in treatment with durvalumab showing no significant respiratory symptoms  
**A.** Follow-up CT scan performed 6 weeks after durvalumab initiation shows bilateral confluent ground-glass and reticular opacities with subpleural sparing (arrows). **B.** CT scan performed 4 weeks after durvalumab interruption and corticosteroids administration shows partial resolution of NSIP. NSIP = non-specific interstitial pneumonia

Hypersensitivity pneumonitis (HP) is less common in patients with ICI-related pneumonitis. Imaging findings are the same as those for HP observed in other conditions, and they include diffuse or upper lobe prevalent centrilobular ground-glass nodules and, sometimes, air trapping [45]. Clinical and anamnestic findings can help distinguish ICI-related HP from HP associated with allergen exposure [46].

Acute interstitial pneumonia (AIP)-acute respiratory distress syndrome (ARDS) is uncommon in ICI-related pneumonitis, but it manifests with a severe clinical presentation. AIP-ARDS features include geographic or diffuse ground-glass or consolidative opacities involving most of the lungs. Lobular sparing areas can be visualized; interlobular septal thickening and a crazy-paving pattern may also be observed [47].

Bronchiolitis is rare and, consequently, not well-described. Typically, bronchiolitis manifests as an area of centrilobular nodularity, often with a tree-in-bud arrangement. Wall thickening of the adjacent bronchi is frequently observed. Focal consolidative and ground-glass opacities are infrequently associated findings [51].

### Sarcoid-Like Reaction

A sarcoid-like reaction includes hilar and mediastinal lymphadenopathy and is usually associated with pulmonary granulomatosis. It occurs in 5–7% of patients treated with ipilimumab (anti-CTLA-4); to our knowledge, sarcoid-like reactions are very rare, with only a few case reports available in the literature; however, sarcoid-like reactions should be kept in mind in newly developing mediastinal and hilar adenopathy in the appropriate clinical setting. In these cases, this reaction should be recognized as an immunologic

reaction rather than a sign of disease progression [52–54]. Imaging features on CT include hilar and mediastinal lymphadenopathy associated with pulmonary peri-lymphatic nodules with a predominance in the upper lobes [46]. Hilar and mediastinal lymphadenopathies may appear hypermetabolic on PET/CT and mimic nodal metastases.

### Enteritis and Colitis

ICI-related colitis or enteritis are among the most prevalent and potentially severe irAEs (Figs. 6, 7). A recent meta-analysis reported an incidence of 0.3–1.1% in patients treated with anti-PD-1/PD-L1 agents [55]. ICI-related colitis usually occurs within 6–18 weeks after the initiation of therapy [56]. On CT, an inflammatory pattern is detectable as wall thickening, mucosal enhancement, air-fluid levels, perivisceral stranding, and mesenteric hyperemia. Perforation is an uncommon complication requiring early identification for prompt treatment [57]. Two different patterns of ICI-related colitis are described: 1) diffuse and 2) segmental colitis. Diffuse colitis is reported to be more frequent (75% of cases) and is characterized by mild and diffuse wall thickening with or without colonic distension and mesenteric vessel engorgement. Segmental colitis is associated with diverticulosis (SCAD) and has been observed in 25% of cases. An SCAD pattern includes moderate wall thickening and localized perivisceral inflammation in a large bowel segment in which diverticulosis is present [43]. Colitis should be correctly identified and reported because different treatment options are indicated: 1) steroids for diffuse colitis and 2) steroids and antibiotics for segmental colitis [57].

### Pancreatitis

ICI-related pancreatitis is a rare complication with an incidence of 1–4% [58], and it can be clinically silent with an asymptomatic serum lipase/amylase increase or present with typical clinical symptoms of acute pancreatitis (Fig. 8). The biological and physio-pathological aspects of ICI pancreatitis are still unknown; ICI-related pancreatitis seems to be more common in patients with other associated adverse events [59]. Some studies have shown that immunotherapy-related pancreatitis is occult on imaging; however, imaging could play a potential role in the diagnosis, severity assessment, and recognition of possible complications. Contrast-enhanced CT provides a global assessment of the disease, and MRI plays a supplementary role [60].

On imaging, ICI-related pancreatitis presents with characteristics similar to those of traditional interstitial edematous pancreatitis and generally appears in several forms:

- On CT, it appears as a pancreatic enlargement and focal or segmental hypo-enhancement, which is surrounded by fat

stranding. Necrosis is rare in ICI-related pancreatitis [59].

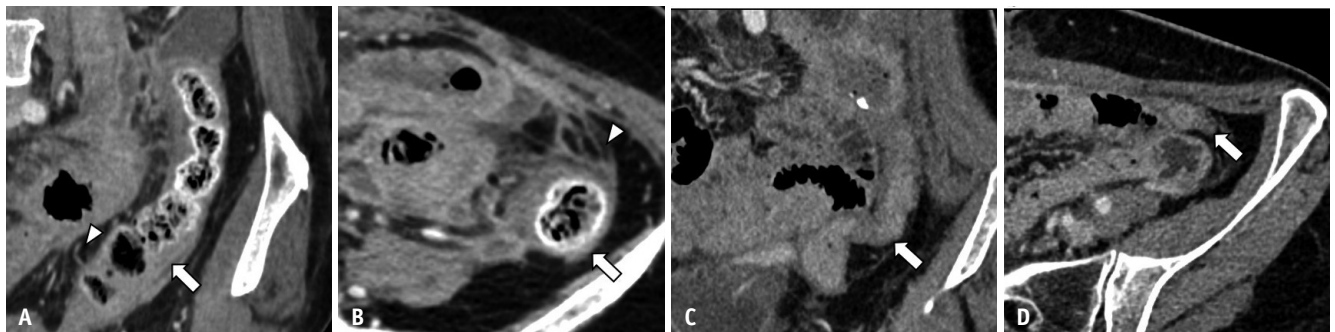
- On MRI, the edematous regions appear relatively hypointense relative to the liver on pre-contrast T1-weighted fat-suppressed images and slightly hyperintense relative to the liver on T2-weighted images, and a restriction of the signal on diffusion-weighted images can be observed [61].

- On PET/CT, increased fluorodeoxyglucose (FDG) uptake throughout the pancreas is observed [62].

Differential diagnoses, including autoimmune pancreatitis [63] and pancreatic metastases [64], represent a potential imaging pitfall for radiologists because depicting and interpreting the features described above is crucial to guiding correct patient management.

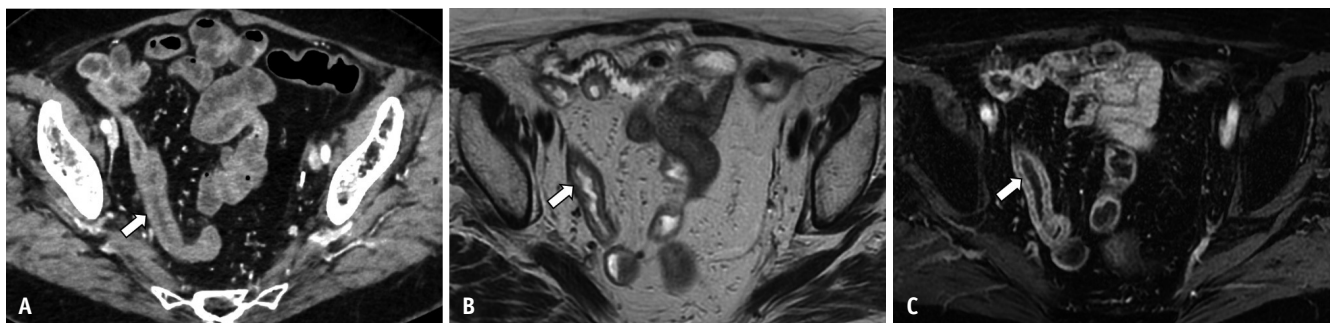
### Hepatitis

Hepatitis is a rare irAE, with incidence rates varying from 1% to 3% [65]. ICI-induced hepatitis can present with an asymptomatic increase in aspartate aminotransferase, alanine aminotransferase, and bilirubin serum levels.



**Fig. 6. Colitis.** 58-year-old female with ovarian cancer presenting at emergency department with abdominal pain and diarrhea, 10 weeks after Pembrolizumab initiation.

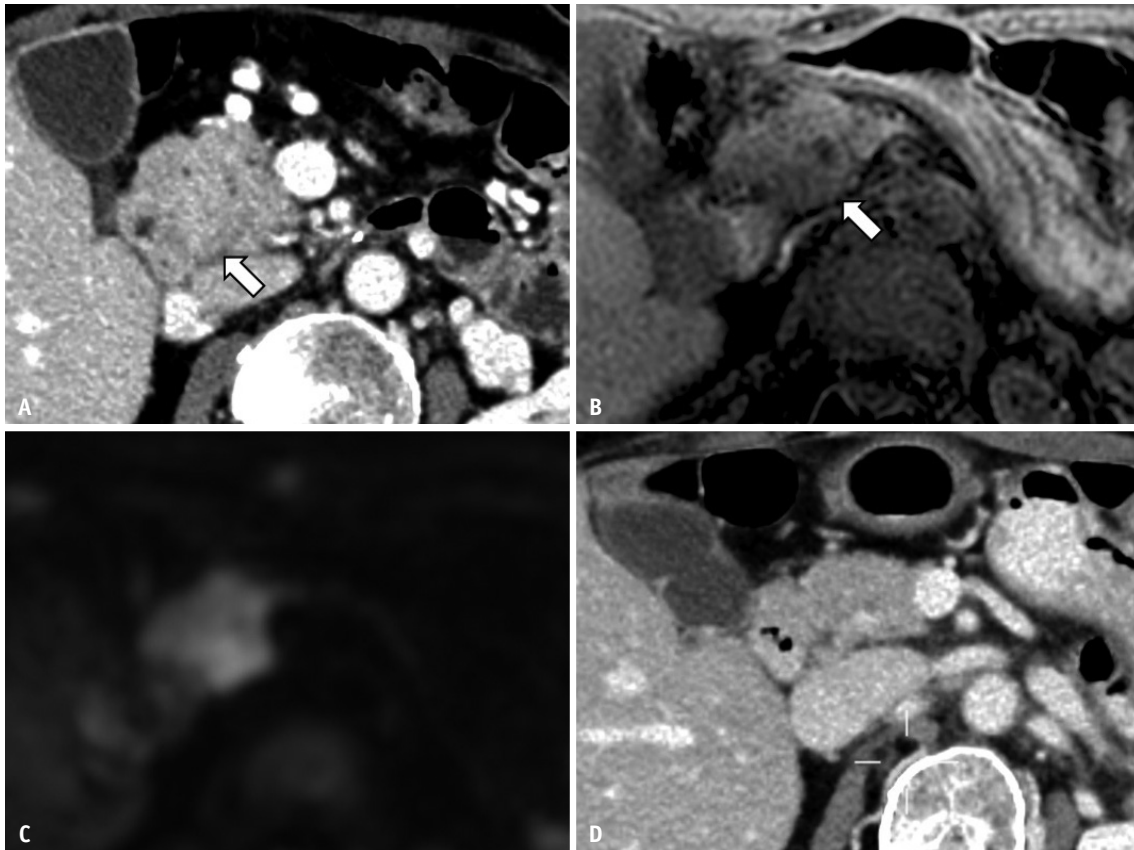
**A, B.** Coronal (A) and axial (B) contrast-enhanced abdominal CT show wall thickening of the descending colon (arrows) and surrounding fat stranding (arrowheads). **C, D.** Coronal (C) and axial (D) contrast-enhanced CT image, acquired 6 weeks after pembrolizumab interruption and corticosteroids administration shows normal appearance of descending colon (arrows).



**Fig. 7. Enteritis.** 73-year-old female with endometrial cancer in treatment performing follow-up CT and pelvis MRI.

**A.** Follow-up CT scan performed 15 weeks after Pembrolizumab initiation shows wall thickening of an ileal loop (arrow). **B.** Axial fast spin echo T2-weighted images shows wall thickening and mild hyperintensity of submucosal layer (arrow), representing oedema. **C.** Axial T1-weighted fat-sat post-gadolinium images better show stratified pattern of the ileal wall thickening with mucosal enhancement (arrow) and low-intensity submucosal oedema.





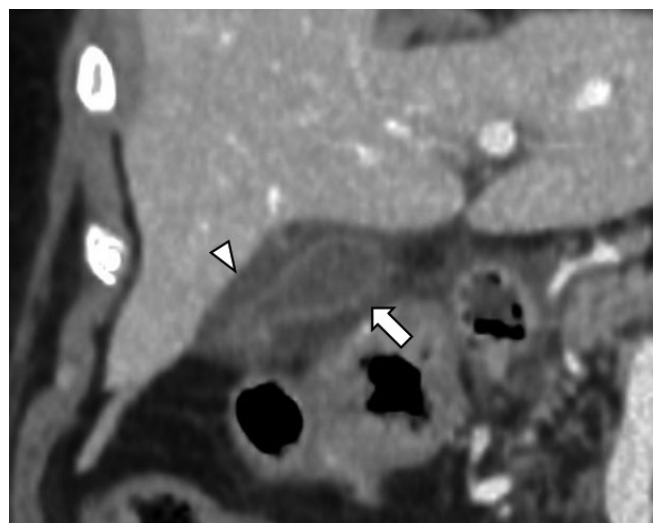
**Fig. 8. Pancreatitis.** 66-year-old female with cervix cancer presenting at emergency department with right abdominal pain, 10 weeks after Atezolizumab initiation.

**A.** Contrast-enhanced CT scan shows pancreatic head enlargement associated to focal hypo-enhancement (arrow). **B.** Axial T1-weighted fat-sat images clearly show focal hypointensity on pancreatic head (arrow). **C.** Diffusion-weighted images shows significant diffusion restriction in the pancreatic head. **D.** CT scan performed 6 weeks after treatment interruption and corticosteroids administration shows normal appearance of the pancreas.

Hepatitis generally occurs within the first two months after treatment onset [64]. The diagnosis is based on laboratory results, and imaging does not play a primary role. Trans-abdominal ultrasound (US) can show focal or global structural changes in the liver parenchyma with heterogeneous echogenicity. Imaging features that can be underlined on CT and MRI are hepatomegaly, heterogeneous parenchymal enhancement with low attenuation areas, periportal edema, lymphadenopathy, and ascites [66].

**Cholangitis and Cholecystitis**

Some ICI-related cholangitis cases have been reported in the literature as rare and serious irAEs in metastatic lung cancer patients treated with nivolumab [67]. On imaging, ICI-related cholangitis shows dilation, wall thickening, and hypervascularity of the intra- and extrahepatic bile ducts. Signs of cholecystitis can coexist with pericholecystic fluid collections (Fig. 9).



**Fig. 9. Cholecystitis.** 71-year-old female with ovarian cancer presenting at emergency department with right upper abdominal pain, 12 weeks after pembrolizumab initiation. Coronal-reconstructed abdominal CT scan shows mucosal enhancement (arrow) and pericholecystic fluid collection (arrowhead).

### Neuromuscular irAEs

ICI-related myositis is the most common neuromuscular complication [68]. In a large study, the incidence of myositis was 0.7% with both anti-CTLA-4 and anti-PD-1/PD-L1 agents [69]. Neuromuscular complications of ICI therapy are the most frequent neurological manifestations, with myasthenia gravis being characterized as the most common PD-1 inhibitor-associated neuromuscular complication [38,39]. ICI-therapy-induced Guillain-Barré syndrome is another severe irAE of the peripheral nervous system. Its clinical presentation is characterized by diffuse and bilateral myalgia, possibly involving several muscle groups. On MRI, STIR sequences show hyperintense muscle signals representing inflammatory edema and necrotic changes observed on muscle biopsy [68]. ICI-related myositis is infrequently associated with myasthenia gravis [70].

### Thyroiditis, Hypophysitis, Adrenalitis

Endocrine involvement is common in patients receiving anti-CTLA-4 and anti-PD-L1 antibodies, with incidence rates varying from 5% to 10% [64]. Endocrine dysfunctions include thyroiditis, hypophysitis, and adrenalitis, and patients are generally symptomatic. Hypophysitis is identifiable on CT as an enlargement of the pituitary gland, but the gold standard is MRI, which shows diffuse and symmetric enlargement with homogeneous contrast enhancement [71]. Thyroid gland involvement has been demonstrated in patients treated with nivolumab [72] manifesting clinical symptoms of hypo- or hyperthyroidism. Thyroid involvement occurs more frequently in female [73]. The gold standard for detecting thyroiditis is US, and images show heterogeneous echogenicity and marked hypervascularity on Doppler analysis. Thyroiditis can be demonstrated with 18FDG-PET examination because thyroiditis shows an intense, diffuse radiotracer uptake into the thyroid gland. Adrenalitis should be suspected if bilateral adrenal gland enlargement with nodularity is observed on CT after ICI treatment initiation. Differential diagnoses include adrenal metastases [64].

## CONCLUSION

ICIs are becoming promising treatments for cancer and gynecological tumors; their use is expected to yield favorable overall and progression-free survival. Radiologists need to be familiar with the peculiarities of immunotherapy agents.

The iRECIST application is currently limited to some

clinical trials, but all radiologists caring for gynecological patients who observe an apparent disease progression before regression should be aware of pseudoprogression tumor response patterns during follow-up scans. Moreover, irAEs can occur during immunotherapy treatment, and radiologists should identify and report adverse events to guide patient management. Since irAEs can mostly occur at any time during treatment, the differential diagnoses should always be considered, and multidisciplinary collaboration is required to ensure appropriate diagnosis and optimal management.

In conclusion, radiologists should promptly identify atypical tumor response patterns and common adverse events associated with ICIs. In this context, radiologic signs, such as thyroiditis, myositis, and colitis, of more frequent ICI-related gynecological cancers should be considered.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

### Author Contributions

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