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Overview of systemic treatment in recurrent and advanced cervical cancer: a primer for radiologists

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Abstract

Imaging has a central role in surveillance of cervical cancer, guiding decision on when to initiate treatment for recurrent disease and to guide management in advanced cervical cancer. Due to the increased availability of pelvic radiation therapy, the rate of atypical presentation of recurrent disease has increased. Simultaneously, the array of systemic therapies now available for advanced cervical cancer has considerably expanded in the last few years, with therapies now available in mid and low-income countries. While pelvic recurrences are amenable of loco-regional treatment, recurrent disease may present with metastases to the thoracoabdominal organs, lymph nodes, bones, skin and brain, for which systemic treatment represent the standard of care. Besides combined chemotherapy regimens, alternative chemotherapies, biosimilars and immune checkpoint inhibitors are now available, each associated with a definite pattern of response and toxicity. In this review, after describing the typical and atypical presentations of recurrent and advanced cervical carcinoma on cross-sectional imaging, we will discuss systemic treatment for recurrent or advanced disease and their associated radiographic sequelae, in light of the newly available therapies.

Key words: Uterine cervical neoplasms—Neoplasm recurrence—Neoplasm metastases—Diagnostic imaging—Antineoplastic agents—Biosimilar pharmaceuticals

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Cervical cancer is the fourth most common cancer among females worldwide and one of the most common cause of cancer related death in developing countries [1]. Approximately 15–61% of patients with epithelial cervical cancer will develop recurrent disease within 2 years of treatment, and more than 90% of these patients will die from cancer within 5 years [2–5]. Additionally, advanced cervical cancer, constituting only 5% of new diagnoses in the United States, still represents a common presentation of the disease in low and mid income countries [6, 7].

In patients with locally advanced disease, disease surveillance after loco-regional treatment consists of a combination of clinical, laboratory and imaging studies [8]. Imaging has a central role in surveillance, as it guides decision on whether and when to initiate treatment for recurrent disease, defined as local tumor regrowth or the development of distant metastasis discovered 6 months or more after complete regression of the treated lesion [9].

While typical sites of recurrent disease such as pelvis and lymph nodes have been well characterized on imaging, atypical presentations of recurrent disease, involving the liver, adrenal glands, lungs, and osseous structures are known to a lesser degree [10, 11]. In recent years, due to the extensive use of intensive pelvic radiation therapy, recurrent cervical cancer presents more and more commonly with atypical recurrences: it has been estimated that extrapelvic and extranodal disease represent 59.5% of recurrences of cervical cancer [10–13]. Given this shift in presentation of recurrent disease, it is crucial that atypical presentations of recurrent disease are promptly identified on imaging to ensure early diagnosis and appropriate treatment.

Alongside, the array of systemic treatment for recurrent and advanced disease has expanded considerably in the last years [14]. From the platinum-based chemotherapy to the recent FDA approval of pembrolizumab, many systemic therapies are currently available, and many are currently evaluated in phase II or phase III clinical trials, each showing different response pattern and toxicity on imaging studies [14]. In addition, biosimilars have recently been placed on the market, giving renewed hope for treatment of advanced cervical cancer in low and mid income countries, where 85% of cervical cancer cases occur and death rate is 18 times higher [7, 8, 15, 16].

In light of these recent changes in the natural history of cervical cancer, expectations from clinicians towards radiologists have increased: besides early detection of recurrences, radiologists should be knowledgeable of the various treatment lines now available for advanced disease, to correctly interpret treatment response and recognizing adverse events for each systemic drug.

In this review, after introducing typical and atypical presentations of recurrent and advanced cervical carcinoma on cross-sectional imaging, we will discuss systemic treatment options for recurrent or advanced disease and their associated radiographic sequelae.

Recurrent and advanced cervical cancer

Pelvis

Pelvic recurrence may involve the cervix, uterus, vagina, parametria, bladder, ureters, rectum, the pelvic walls and ovaries, commonly resulting from local extension of tumor [11]. Extension to the rectum or bladder represents stage IVA disease according to the FIGO (International Federation of Gynecology and Obstetrics) staging system [17]. Imaging modalities such as CT and MRI have been used to detect early recurrence; however, their detection rate is low, whereas 18F-FDG PET has higher accuracy in detecting recurrences of cervical cancer. Reasons for this include its ability to detect recurrent lesions when anatomy has been distorted after surgery or radiation treatment [12, 18]. However, PET/CT is limited in detecting retrovesical lesions, owing to the clearance of radiotracer into the bladder which may obscure focal FDG uptake [12].

PET/CT demonstrates increased FDG uptake of the bladder or rectal wall, corresponding to nodular thickening on CT or MRI, with possible perivesical or perirectal stranding. Air in the urinary bladder, an indirect sign of fistula, could also be observed. In addition, recurrent cervical cancer can present with tumor-bowel fistula, which can be suspected at imaging when there is gas or oral contrast in a tumor located near a bowel loop, or a tract between tumor and bowel can be demonstrated (Fig. 1). Complications associated with tumor-bowel fistula are: perforation, presenting with peritumoral stranding, free fluid, pneumoperitoneum, peritonitis, oral contrast extravasation on CT or MRI, and superimposed infection with tumor abscess formation. Tumor-bowel fistula can also be associated with the use of bevacizumab [19].

Lymph nodes

Lymphatic involvement is commonly classified into primary and secondary nodal groups where prognosis worsens as nodal involvement progresses from the primary to secondary group. The primary group consists of paracervical, parametrial, internal and external iliac, and obturator nodes. The secondary group consists of the sacral, common iliac, inguinal, and paraaortic nodes [20]. Involvement of supradiaphragmatic nodal stations, such as parabronchial, supraclavicular, and axillary nodes has also been reported, with metastases to the supraclavicular nodes occurring in 11% of cases with distant recurrence [20]. Both CT and MRI have played an important role in identifying recurrent nodal disease via detection of enlarged lymph nodes in these areas (Fig. 2) [11]. 18F-FDG PET can detect malignant involvement of lymph nodes of normal size, with shorter diameter < 1 cm, thus overcoming one of the major limitations of CT and MRI. Various metanalyses have shown that 18F-FDG PET/CT is more sensitive than CT or MRI in detecting lymph node metastasis in patients with cervical cancer [21–23]. However, 18F-FDG PET/CT has limited sensitivity for necrotic lymph nodes and early nodal involvement [12, 18].

Abdomen

The solid organs of the abdomen, such as the liver and adrenal glands, are a frequent site of recurrence and presentation of advanced disease [11, 22, 24, 25]. Liver metastases occur in up to one third of patients with recurrent disease and can present as hypoechoic lesions on ultrasound and as solid lesions with variable enhancement on CT or MRI and focal FDG uptake on PET/CT (Fig. 2) [11, 12].

Peritoneal involvement is present in 5–27% of patients with recurrent cervical cancer [11, 25]. Peritoneal, omental and mesenteric recurrence may present as ascites, implants scalloping the liver contour, peritoneal thickening with nodularity, and soft tissue masses (Figs. 3, 4) [12, 18, 24]. A meticulous search for peritoneal disease should be performed in any patient with cervical cancer, as findings can be subtle, varying from small peritoneal nodules or peritoneal soft tissue stranding, or serosal implants adjacent to the bowel loops, which may cause extrinsic compression of the bowel and various degrees of obstruction. Coronal

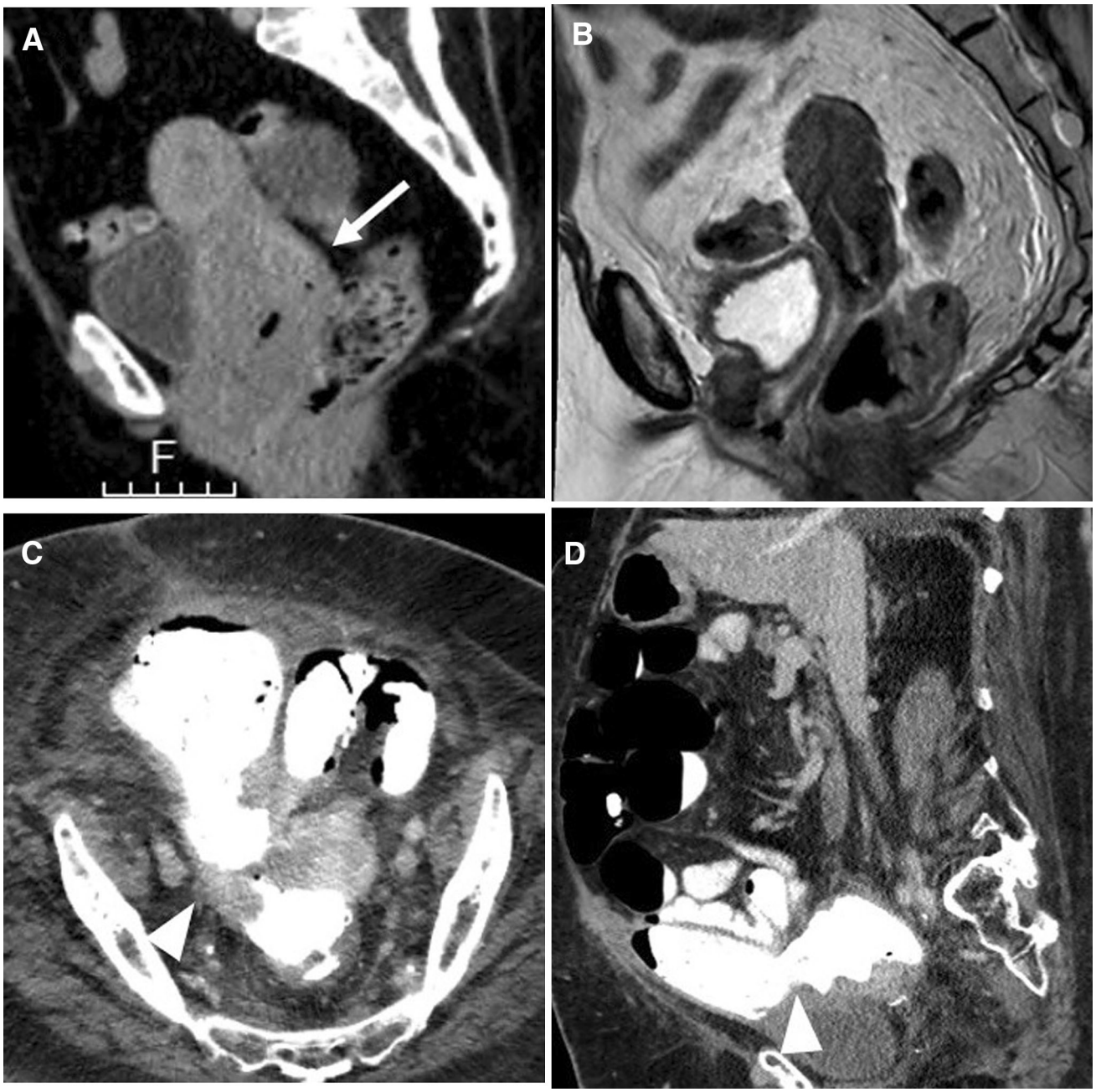


Fig. 1. 71-year-old woman with vaginal bleeding. **A** Sagittal CT image showing a soft tissue mass arising from the cervix. Cervical biopsy demonstrated poorly differentiated carcinoma with serous and clear cell features; patient was treated with carboplatin and Taxol followed by external beam radiation therapy. **B** Coronal T2-weighted MRI image showed homogeneously decreased T2 signal intensity, consistent with treatment response. After 3 years, patient presented with abdominal pain. Axial (**C**) and coronal (**D**) reformatted CT image with intravenous and oral administration of contrast media shows a tract between tumor and a bowel loop (arrowheads), consistent with tumor-bowel fistula.

reformatted CT or PET/CT images or coronal MRI sequences are helpful to identify scalloping of the liver contour and perihepatic implants.

Peritoneal or mesenteric involvement can be associated with the presence of the Sister Joseph nodule, representing umbilical metastasis, arising either from direct extension of tumor to the umbilicus, from the anterior peritoneal surface, or from spread via lymphatic, venous, and ligamentous routes of tumor spread [26].

Thorax

Metastases to the chest are common in patients with recurrent cervical cancer and are frequently associated

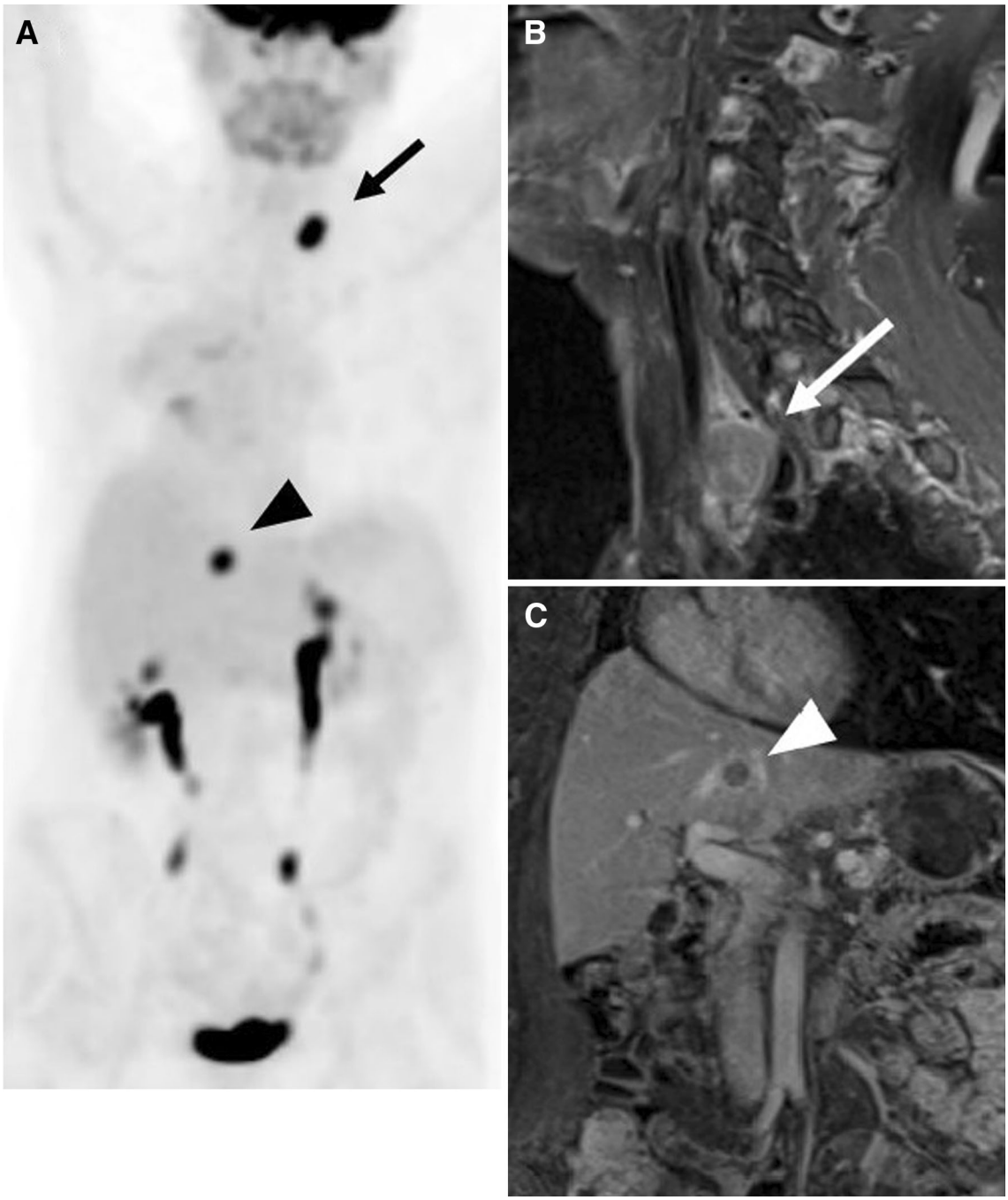


Fig. 2. 57-year-old woman with stage II B high grade squamous cell cervical carcinoma initially treated with chemoradiation. **A** Follow-up PET shows hypermetabolic lesions in the liver (arrowhead) and supraclavicular region (arrow). **B** Sagittal T1-weighted contrast-enhanced MRI image of the neck demonstrates the enhancing enlarged left supraclavicular node (arrow). **C** Coronal T1-weighted contrast-enhanced MRI image of the abdomen demonstrates a peripherally enhancing liver metastasis (arrowhead).

with intra-abdominal metastatic disease [27]. Thoracic metastases manifest as lung nodules, pleural nodules, lymphangitic carcinomatosis, and chest wall masses. Lung metastases occur in 4.2% to 38% of patients with cervical cancer, depending on stage of the disease and type of cervical cancer, occurring more commonly and earlier in patients with adenocarcinoma than in patients with squamous cell cervical cancer [11, 28, 29]. Pulmonary metastases commonly present with pulmonary nodules, which can be multiple, solitary or cavitated, a finding almost always associated with squamous cell cervical cancer type (Figs. 4, 5) [29].

Regular CT of the chest is recommended for patients with stage II–IV cervical cancer during their follow-up

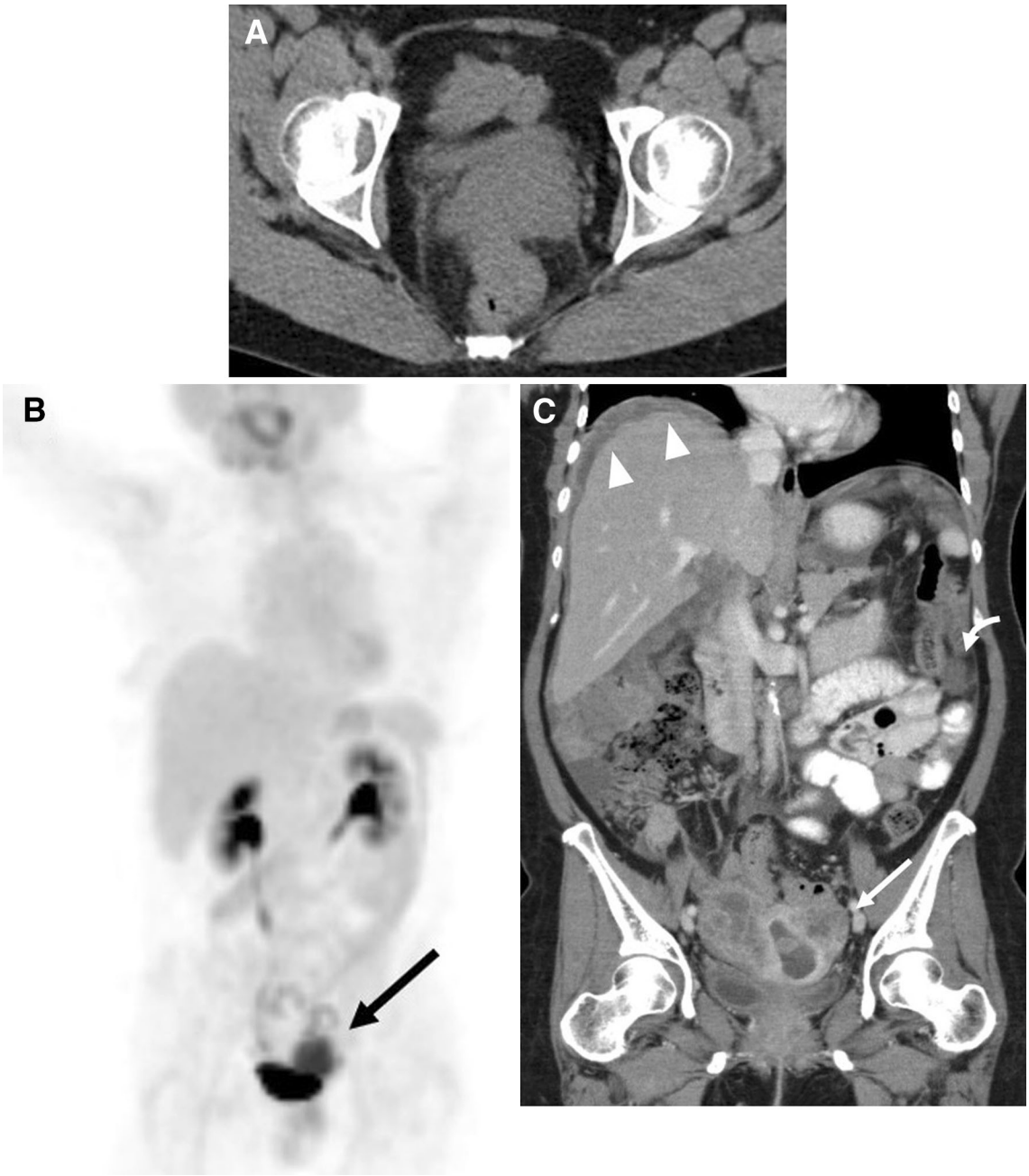


Fig. 3. 48-year-old woman presenting with abnormal vaginal discharge and pelvic discomfort and an enlarged irregular cervix on pelvic exam. The cervix was biopsied, demonstrating adenocarcinoma of the cervix extensively involving the cervical stroma. **A** 18F-FGD PET/CT MIP image shows a hypermetabolic cervical mass with no FDG lymph nodes in pelvis and relative axial CT image (**B**) shows a large cervical mass with adjacent pelvic fat stranding. Patient underwent radiation therapy and six cycles of cisplatin. Follow-up coronal reconstructed CT image (**C**) shows tumor implants in peritoneum and greater omentum in the right and left upper pericolic gutter (curved arrow), around the dome of the liver (arrowhead), and in the pelvis (arrow).

period [30]. This precaution aids in finding lesions early on as lung metastasis may be present for a significant period before becoming symptomatic. Although 18F-FDG PET has relatively high sensitivity in the mediastinum and chest, it has relatively low sensitivity and specificity for lesions in the lung, and PET/CT protocols should include CT of the chest with dedicated lung reconstruction algorithm, since PET has limited sensitivity in detecting micrometastatic lung disease less than 1 cm^3 in volume [12, 18].

Bones

Metastases to the bones have been observed in around 20% of cervical cancer cases, with the lumbar spine being the most frequent site of osseous metastasis [11, 28]. The diagnosis should be confirmed by bone biopsy or by two imaging modalities including a bone scan, CT, FDG-PET, X-ray, and MRI [28]. PET/CT is currently the most accurate imaging method to detect hematogenous bone metastasis in patients with advanced cervical cancer [31–33].

Other

Skin and subcutaneous tissues can be involved in up to 10% of patients with uterine cervical cancer recurrence

Fig. 5. 59-year-old woman presenting with vaginal bleeding and a cervical mass on pelvic exam, with biopsy showing squamous cell carcinoma of the cervix. **A** Initial staging 18F-FDG PET/CT shows a FDG-avid cervical mass, multiple FDG-avid mediastinal lymph nodes, lung nodules, right pelvic node. **B** relative axial CT image of the chest, acquired simultaneously, confirms multiple lung nodules. Patient was treated with external beam radiation therapy and with weekly Cisplatin to pelvic area followed by Cisplatin and Taxol and Pemetrexed for 3 cycles. **C** Restaging CT of the chest acquired 3 months later demonstrates significant decrease in size of the lung nodules. Follow-up CT acquired 6 months later shows significant increase in size of the lung nodules (**D**). Patient was placed on vinorelbine. ▶

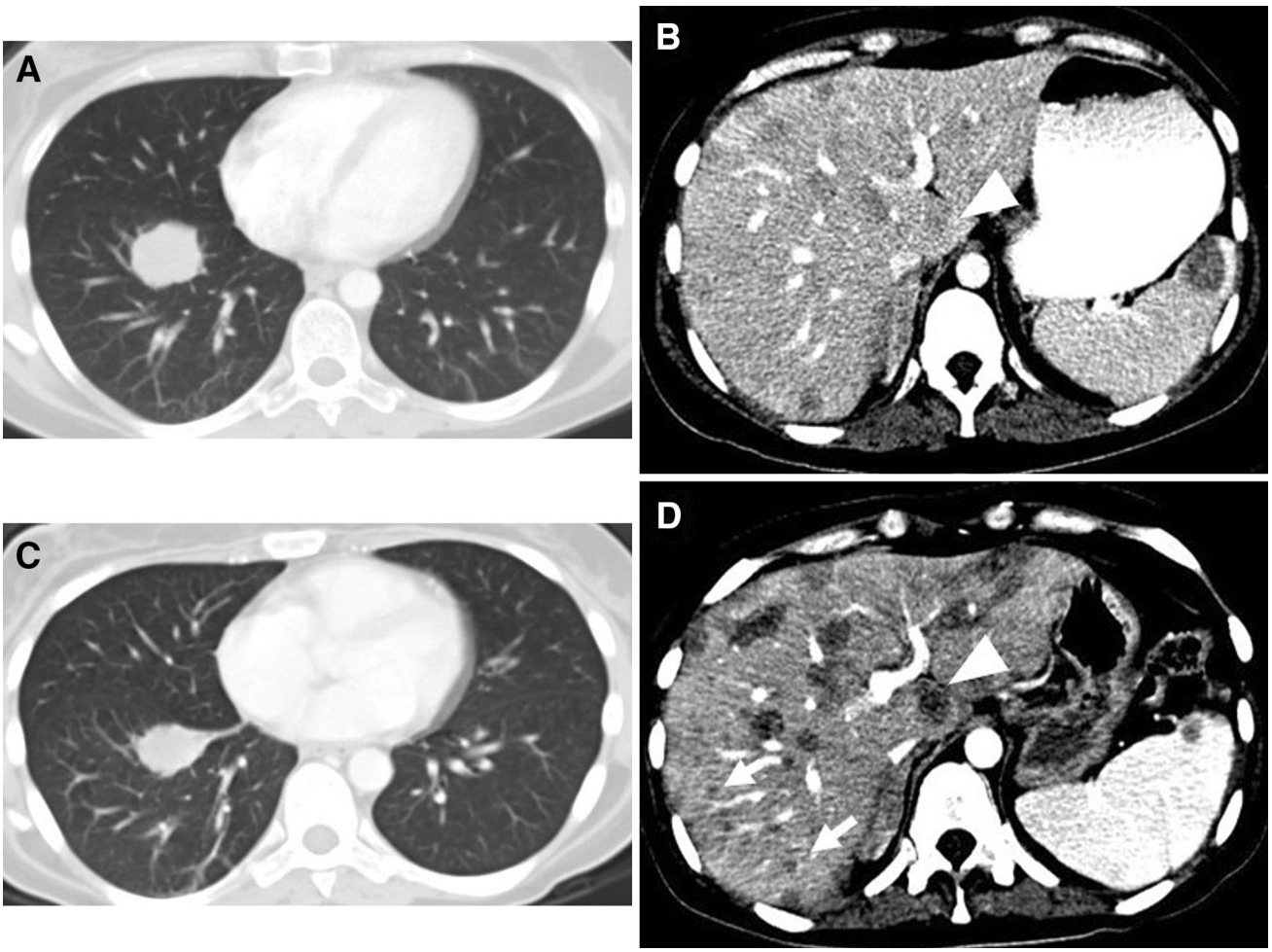
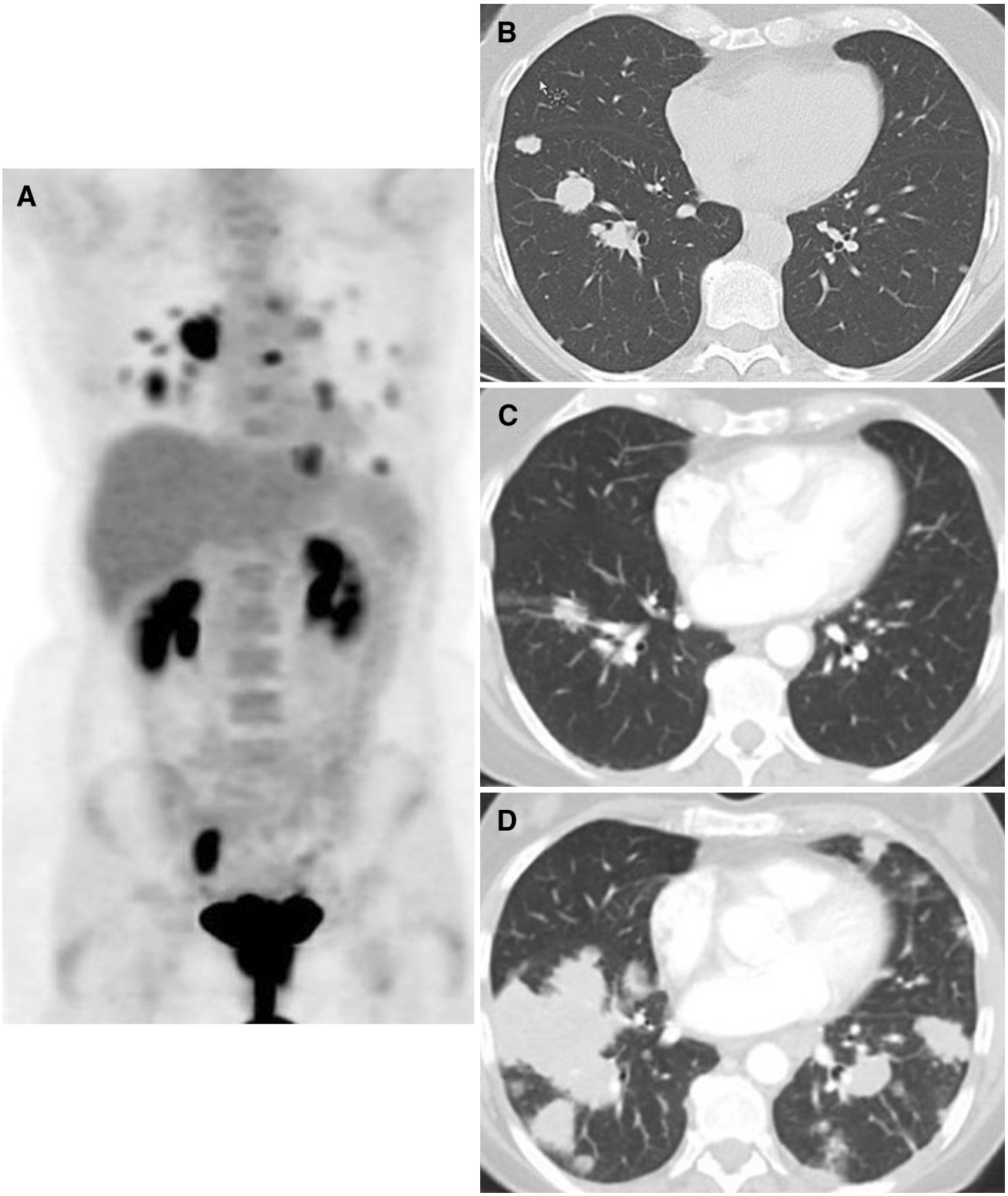


Fig. 4. 37-year-old woman with adenocarcinoma of cervix treated with bevacizumab. Contrast-enhanced CT acquired before starting therapy showing a right lower lobe lung mass (**A**), a splenic lesion and multiple liver lesions (arrowhead) (**B**). Follow-up contrast-enhanced CT shows decreased size of the right lower lobe lung mass (**C**), decrease size of the splenic lesion, and decreased density with apparent increased conspicuity of multiple liver lesions (arrowhead), with new multiple small liver lesions (arrows) (**D**). The apparent increase in conspicuity of the lesion, likely due to intra-tumoral edema occurring in previously isodense areas of the tumor, and the new appearance of hypodense liver lesions, previously not visualized since isoattenuating, represent an unusual pattern of response associated with bevacizumab, termed "pseudoprogression".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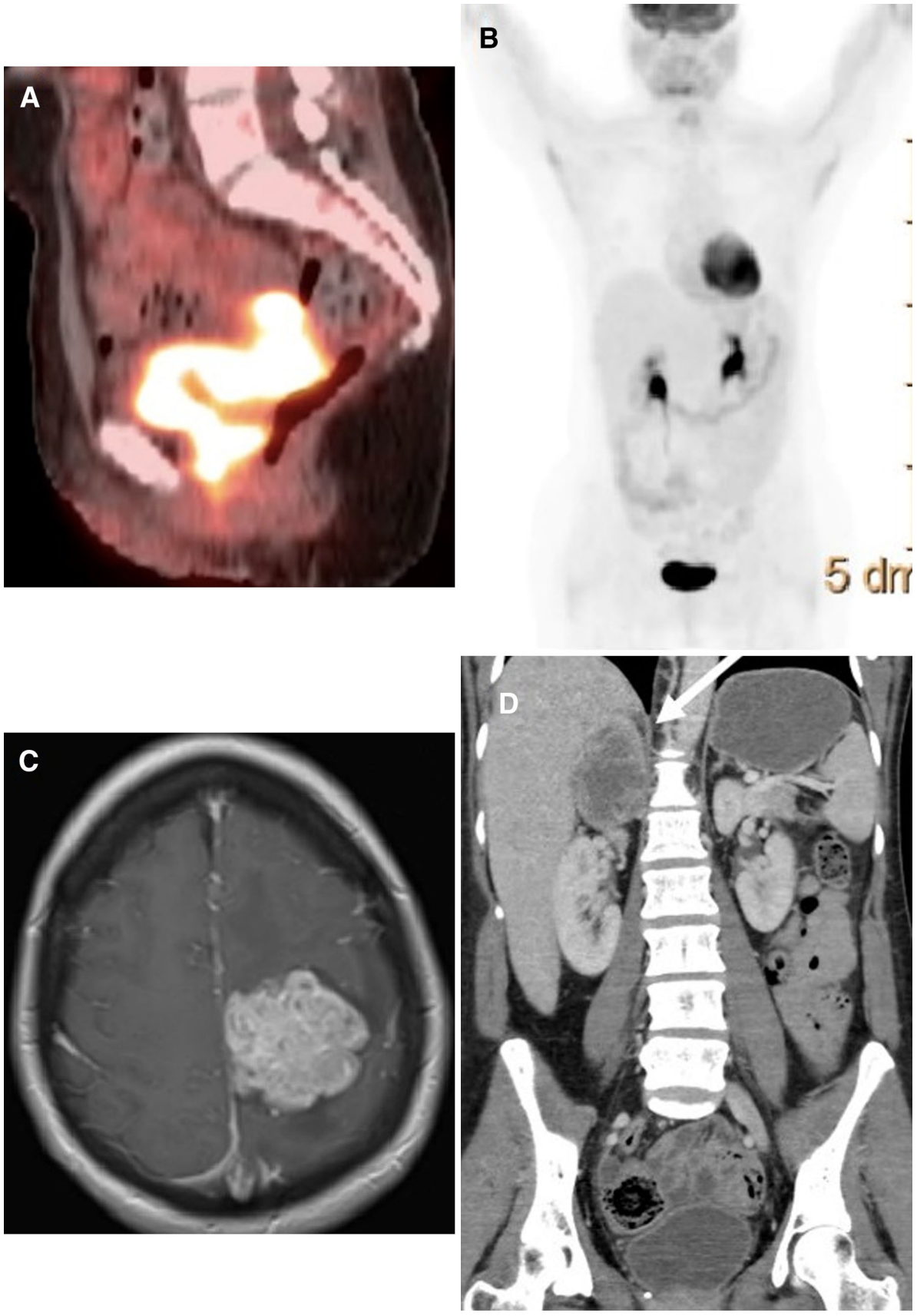
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◀**Fig. 6.** 44-year-old woman presenting with bladder outlet obstruction and an enlarged irregular cervix on pelvic exam, with biopsy showing squamous cell carcinoma of the cervix. **A** Staging PET-CT shows hypermetabolic soft tissue lesion in the cervix, with no additional FDG-avid lesions. Patient was treated with external beam radiation therapy and cisplatin chemotherapy, followed by intracavitary brachytherapy. **B** Restaging PET/CT shows excellent treatment response. 5 years later, patient presented with stroke-like symptoms to the emergency department. Axial T1-weighted contrast-enhanced MRI of the brain (**C**) and restaging CT of the abdomen (**D**) acquired at the time demonstrate respectively a large supratentorial enhancing lesion and a centrally hypodense right adrenal mass (arrow), consistent with recurrences.

[11]. Brain metastases are rare, occurring in 0.5% to 1.2% of cases and quite rare and usually considered incurable [34, 35]. Sites of brain metastases are often located in the supratentorial region and can be either single (50.6%) or multiple (49.4%), presenting as solid lesions with various degrees of enhancement on MRI and perilesional edema (Fig. 6) [36, 37]. In addition, leptomeningeal involvement has been reported [34].

Metastases to the breast and heart, involving the myocardium and the pericardium, have also been reported [38, 39].

Systemic treatment for cervical cancer

While limited stage cancers are treated with surgical resection or radiation therapy (RT), pelvic RT and concurrent cisplatin therapy is the standard of care for locally advanced disease [17, 30, 40]. The purpose of local therapy is to minimize the increased toxicity associated with chemotherapy regimen or to offer treatment when chemotherapy is not readily available and/or there is limited capacity for managing adverse effects women experience from chemotherapy [40].

For recurrent and advanced cervical cancer, doublet chemotherapy became the standard of care, after the (Gynecology Oncology Group) GOG 204 study showed that cisplatin combined with paclitaxel showed improved trends in overall survival (OS) and progression free survival (PFS) when compared with cisplatin combined with other chemotherapy agents [41, 42]. Subsequently results from the GOG 240 trial showed significance for both increased OS and PFS when bevacizumab was added to combination chemotherapy [43]. Consequently, the FDA approved bevacizumab (Avastin) combined with cisplatin/paclitaxel or topotecan/paclitaxel chemotherapy as first-line treatment [44]. While the GOG studies have determined the standard of care for first-line treatment, there is currently no consensus for second-line treatment: as such, patients who progressed on platinum-based first-line therapy can be treated with second-line regimens, included in clinical studies or receive best supportive care measures [14]. The recent FDA approval of pembrolizumab for previously treated advanced or recurrent PD-L1 positive cervical cancer represents another treatment for these patients [45].

Cisplatin

Cisplatin is a metallic platinum-based compound which crosslinks purine bases of DNA and interferes with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis in cancer cells [46, 47]. In 1985, a trial conducted by the GOG determined cisplatin to be the most active single-agent in the setting of recurrent cervical cancer, subsequently superiority of combination therapy with various agents was shown in various trials, with increased overall survival over single-agent cisplatin therapy [48]. Cisplatin toxicities that can be observed on cross-sectional imaging are: acute pancreatitis, presenting with parenchymal enlargement, acute peri-pancreatic fluid collections, and diffuse FDG avidity of the pancreatic parenchyma; hepatotoxicity, in the form of steatosis, with classic increased echogenicity on ultrasound and T1 hypointensity and hypodensity on MRI and CT, and cholestasis, with biliary duct dilation [49, 50]. Platinum-based therapies are also associated with arterial thrombosis, venoocclusive disease, and vascular ischemia, reported in up to 9% of patients treated with these drugs [51, 52].

Topotecan

Topotecan is a cytotoxic agent that works as an inhibitor of topoisomerase I, an enzyme necessary for DNA replication. It acts by forming a stable covalent complex with the DNA/topoisomerase I aggregate leading to breaks in the DNA strand, subsequently resulting in apoptosis and cell death [53]. Since the addition of cisplatin in therapy regimens for cervical cancer, numerous studies have attempted to improve survival rates by incorporating additional cytotoxic drugs. Long et al., in GOG 179, evaluated the combination of cisplatin and topotecan for patients with advanced disease showing slight improvement in median PFS (1.7 months) and median OS (2.9 months) [54].

Topotecan's primary complication is bone marrow suppression. Fatalities due to topotecan-induced neutropenic colitis have also been reported during clinical trials [55]. Neutropenic enterocolitis is classically characterized by transmural inflammation of the cecum, often with involvement of the ascending colon and ileum. Abdominal plain x-rays can show dilated atonic cecum and ascending colon filled with liquid or gas, signs of intramural gas, and small bowel dilation. CT delineates bowel wall thickening, a dilated cecum or other colonic segment, an inflammatory mass, pericolonic inflammation, and pneumatosis intestinalis [56]. Pulmonary toxi-

city can present as interstitial lung disease, organizing pneumonia, diffuse alveolar damage, and in rare cases, constrictive bronchiolitis [57–59]. Risk factors for pulmonary complications include pulmonary fibrosis, lung cancer, exposure to thoracic radiation, use of drugs known to cause pulmonary toxicity, use of colony-stimulating factors, and a history of interstitial lung disease [55].

Paclitaxel

Paclitaxel is a cytotoxic drug that works stabilizing microtubules them against depolymerization. Paclitaxel blocks cells in the G2/M phase of the cell cycle owing to the inability of such cells to form a normal mitotic apparatus and leads to subsequent apoptosis [60, 61]. Moore et al. demonstrated that the addition of paclitaxel resulted in significant improvement in response with an associated modest 2-month improvement in median PFS [62].

Similar to topotecan, neutropenia and thus neutropenic colitis is the principal toxicity in paclitaxel [63]. Paclitaxel has also been associated with pulmonary toxicities such as acute diffuse interstitial pneumonia, subacute diffuse interstitial pneumonitis, pulmonary opacities with peripheral eosinophilia, and pulmonary fibrosis, the most common being interstitial pneumonitis, which can develop days to weeks of receiving paclitaxel [64]. The radiographic features of paclitaxel-induced pneumonitis are nonspecific, showing an increase in reticular markings and interlobular thickening in a patchy or diffuse pattern with or without ground-glass opacities on CT [51, 65].

Vinorelbine

Vinorelbine is a semi-synthetic vinca-alkaloid agent which stimulates microtubule depolymerization and mitotic spindle destruction, blocking cells at the G2/M phase [66]. Vinorelbine has moderate activity in patients with persistent or recurrent cervical carcinoma, with better response rate for squamous cell carcinoma compared to adenocarcinoma [66–68]. Main toxicities associated with vinorelbine are hematologic, pulmonary and neurologic. Neutropenia and its complications has been observed in up to 52% of patients with weekly IV vinorelbine [69]. Vinorelbine associated pneumonitis may present with diffuse ground-glass and reticular opacities [58].

Gemcitabine

Gemcitabine is a nucleoside analog of deoxycytidine which is phosphorylated into its active form once inside a cell. From there, it is incorporated into DNA on the end of an elongating strand and inhibits DNA polymerases from proceeding. This process inhibits the cell from growing and eventually causes cell death [70]. Regarding its efficacy in cervical cancer, although generally inferior to cisplatin as a single-agent, when used concurrently with cisplatin and/or radiation therapy, has higher objective response rates and improves survival [71].

Gemcitabine's most prominent toxicities include neutropenia, thrombocytopenia, anemia and gastrointestinal side effects [71]. Gemcitabine-induced pulmonary toxicities are also common, with an incidence rate of 23%., ranging from mild (dyspnea and bronchospasm) to severe (pulmonary fibrosis and acute respiratory distress syndrome) toxicity [72]. These complications and their related radiologic features are important to distinguish early as they may be potentially fatal or have significant detriment on quality of life if not treated promptly [71]. Consideration of capillary leak syndrome in the differential diagnosis of new-onset interstitial pulmonary edema after gemcitabine use is vital. Furthermore, gemcitabine is associated with increased risk of thromboembolic events, presenting with accelerated arterial or venous thrombosis, the latter being more common [52].

Bevacizumab

Bevacizumab is a humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal IgG antibody. By inhibiting VEGF, bevacizumab's use leads to reduction in microvascular growth of tumor blood vessels and thus limits the blood supply to tumor tissues [73]. Besides cervical cancer, in combination therapy, bevacizumab is approved for the treatment of advanced colorectal can-

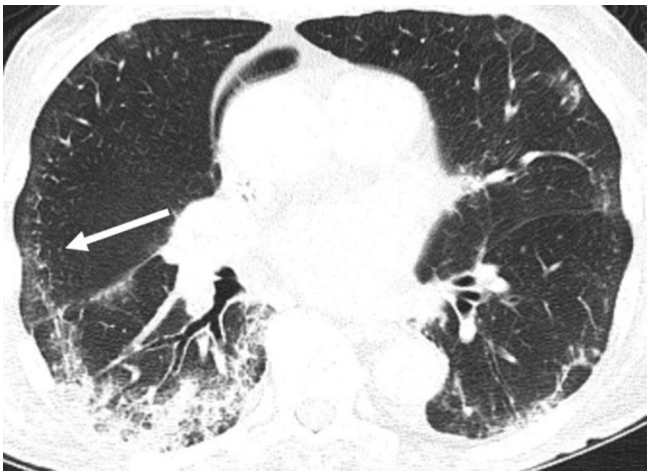

Fig. 7. 79-year-old woman with advanced cervical adenocarcinoma treated with pembrolizumab, with moderate liver function test elevation. Restaging CT of the chest shows peripheral ground-glass opacities with subpleural sparing consistent with an NSIP pattern (arrow), not visible on prior scans (not shown). Findings were thought to be related to immune-mediated pneumonitis.

cer, advanced non-small cell lung cancer, metastatic breast cancer, and advanced renal cell cancer [73, 74].

Differently from traditional chemotherapy agents used for cervical cancer, bevacizumab may show decrease in attenuation of solid lesions, or new cavitation of lung nodules, representing a decrease in vascularity [75]. These changes can occur with or without concurrent lesion change in size, and represent treatment response [75, 76]. Bevacizumab has also been associated with unusual patterns of response, which may represent a potential source of confusion for the radiologist, including the presence an increase in size despite a decrease in attenuation, due to intra-tumoral edema occurring in previously isodense areas of the tumor; and the new appearance of hypodense liver lesions, previously not visualized since isoattenuating, named ''pseudoprogression''. In these cases, decision to change treatment should be deferred until after a follow-up study, which will show stabilization or improvement in case of pseudoprogression (Fig. 4) [75, 77].

Bevacizumab has many potential toxicities ranging from hypertension to thrombosis, hemorrhage, wound complications and colonic perforations [78]. Of these, gastrointestinal perforation is an infrequent but potentially fatal toxicity which can lead to peritonitis requiring emergency operative intervention [79]. Often times, patients with peritoneal signs will have emergent surgery without the need for imaging; however, CT can be very helpful in guiding surgical intervention if the site of perforation is unclear [80]. Additionally, there is an inherent risk of bleeding with any VEGF-targeted agents. Most commonly, this is grade 1 epistaxis, but serious, and in some cases, fatal hemorrhagic events, including hemoptysis, gastrointestinal bleeding, hematemesis, intracerebral hemorrhage, and vaginal bleeding, have occurred [81]. It is crucial for the source of bleeding to be identified on imaging so that correct management can be applied. Cholecystitis, pancreatitis, hepatic steatosis and posterior reverse encephalopathy syndrome have also been reported [75, 82, 83].

Immune checkpoint inhibitors

Cervical cancer treatment with standard systemic chemotherapy doublets, such as those mentioned above, have had overall dismal PFS and response rates. Nonetheless, the integration of bevacizumab-based triplet therapy in the first-line setting for treatment of recurrent or metastatic disease has allowed response rates to approach 50% [84]. However, other mechanisms of therapy are still being identified. For instance, it is believed that human papillomavirus, the number one risk factor for acquiring cervical cancer, can escape host immune-mediated identification and eradication by inducing expression of programmed death-ligand 1 (PD-L1). This is evidenced by the upregulation of PD-L1 in cervical cancer [84, 85]. This has developed the consideration of the use of immune checkpoint inhibitors in cervical cancer treatment.

A single-arm, multi-cohort phase II trial called KEYNOTE-158 investigated pembrolizumab, a PD-1 inhibitor, for the treatment of cervical cancer. In this trial, patients with advanced cervical squamous cell cancer with noted progression or intolerance to standard therapy received pembrolizumab monotherapy for 2 years or until progression or toxicity. Distinctly, the response rate seemed to strengthen with an increase in follow-up: those initially enrolled had a response rate of 17% which increased to 27% in patients who had follow-up greater than 27 weeks [86]. Based on the results of this trial granted the FDA approved pembrolizumab in PD-1 positive recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.

Immune checkpoint inhibitors are associated with specific patterns of treatment response, with possible decrease in size of baseline lesion by 12 weeks; with slow steady decline in tumor burden after initial stability of the lesions; with initial increase in lesion size or appearance of new lesions followed by response [87].

Immune checkpoint inhibitors are typically associated with a unique spectrum of side effects termed immune-related adverse events (irAEs). These include dermatologic, gastrointestinal, hepatic, endocrine, myositis, and sarcoid-like reactions [88]. Of these, gastrointestinal toxicities are observed in up to 20% of cases and can present with enteritis, diffuse colitis and segmental colitis associated with diverticulosis (SCAD) [89, 90]. Diffuse colitis or enteritis is characterized by mesenteric vessel engorgement with either fluid-filled bowel loops or mild diffuse or segmental bowel wall thickening. SCAD occurs in a pre-existing segment of diverticulosis and is characterized by segmental wall thickening with associated pericolonic fat stranding [90].

Immune-related hepatitis is a rare adverse event presenting with mild hepatomegaly, periportal and gallbladder edema, periportal lymphadenopathy, diffusely hypoattenuating liver parenchyma or heterogeneous parenchymal enhancement [91, 92].

Pembrolizumab associated pneumonitis is an uncommon but potentially fatal complication with a spectrum of CT presentation, presenting with cryptogenic organizing pneumonia, or with peripheral basilar subpleural ground-glass changes and interlobular septal thickening mimicking nonspecific interstitial pneumonia (NSIP) (Fig. 7) [93]. Other irAE observed are pancreatitis, thyroiditis, myositis, hypophysitis, presenting with focal FDG uptake in the affected organs on PET/CT and classic imaging appearance on CT or MRI.

Sarcoid-like findings with new or enlarging thoracic or abdominal nodes are commonly observed and should be correctly interpreted. In these cases, decision to change treatment should be deferred until after a follow-

up study, which will show decreased size or FDG avidity of the sarcoid nodes [94].

Conclusion

Given the improvement in loco-regional therapies for cervical cancer, more and more patients are currently living with recurrent and advanced cervical cancer. In the past years, the number of therapies available has increased considerably for these patients. Radiologists should be familiar with presentation of recurrent and advanced cervical cancer, the array of systemic therapy available, along with their pattern of treatment response and their adverse events.

Compliance with ethical standards

Funding No funding was received for this study.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Statement of informed consent is not applicable since the manuscript does not contain any patient data.

References

1. American Cancer Society. Global burden of cancer in women (2018) Current status, trends, and interventions. Atlanta: American Cancer Society; 2018. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-burden-of-cancer-in-women.pdf. Accessed 18 July 2018
2. Adegoke O, Kulasingam S, Virnig B (2002) Cervical cancer trends in the United States: a 35-year population-based analysis. J Womens Health 21(10):1031–1037
3. Fagundes H, Perez CA, Grigsby PW, Lockett M (1992) Distant metastases after irradiation alone in carcinoma of the uterine cervix. Int J Radiat Oncol 24(2):197–204
4. Elit L, Fyles AW, Devries MC, et al. (2009) Follow-up for women after treatment for cervical cancer: a systematic review. Gynecol Oncol 114(3):528–535
5. Peiretti M, Zapardiel I, Zanagnolo V, et al. (2012) Management of recurrent cervical cancer: a review of the literature. Surg Oncol 21(2):e59–e66
6. Sreedevi A, Javed R, Dinesh A (2015) Epidemiology of cervical cancer with special focus on India. Int J Womens Health 7:405–414
7. LaVigne AW, Triedman SA, Randall TC, Trimble EL, Viswanathan AN (2017) Cervical cancer in low and middle income countries: addressing barriers to radiotherapy delivery. Gynecol Oncol Rep 22:16–20
8. Charakorn C, Thadanipon K, Chaijindaratana S, et al. (2018) The association between serum squamous cell carcinoma antigen and recurrence and survival of patients with cervical squamous cell carcinoma: a systematic review and meta-analysis. Gynecol Oncol 150(1):190–200
9. Quinn MA, Benedet JL, Odicino F, et al. (2006) Carcinoma of the cervix uteri. FIGO 26th Annual Report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet 95(S1):S43–103
10. Kim TH, Kim MH, Kim BJ, et al. (2017) Prognostic importance of the site of recurrence in patients with metastatic recurrent cervical cancer. Int J Radiat Oncol 98(5):1124–1131
11. Fulcher AS, O'Sullivan SG, Segreti EM, Kavanagh BD (1999) Recurrent cervical carcinoma: typical and atypical manifestations. RadioGraphics 19(S1):S103–S116
12. Son H, Kositwattanarerk A, Hayes MP, et al. (2010) PET/CT evaluation of cervical cancer: spectrum of disease. Radiographics 30(5):1251–1268
13. Kavanagh BD, Gieschen HL, Schmidt-Ullrich RK, et al. (1997) A pilot study of concomitant boost accelerated superfractionated radiotherapy for stage III cancer of the uterine cervix. Int J Radiat Oncol Biol Phys 38(3):561–568
14. Boussios S, Seraj E, Zarkavelis G, et al. (2016) Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: where do we stand? A literature review. Crit Rev Oncol Hematol 108:164–174
15. Monk BJ, Huh WK, Rosenberg JA, Jacobs I (2017) Will bevacizumab biosimilars impact the value of systemic therapy in gynecologic cancers? Gynecol Oncol Res Pract 4:7
16. U. S. Food and Drug Administration/Center for Drug Evaluation and Research (2018) FDA approves first biosimilar for cancer treatment. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm576096.htm. Accessed 18 July 2018
17. FIGO Committee on Gynecologic Oncology (2014) FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet 125(2):97–98
18. Ryu SY, Kim MH, Choi SC, Choi CW, Lee KH (2003) Detection of early recurrence with 18F-FDG PET in patients with cervical cancer. J Nucl Med 44(3):347–352
19. Tirumani SH, Baez JC, Jagannathan JP, Shinagare AB, Ramaiya NH (2013) Tumor-bowel fistula: what radiologists should know. Abdom Imaging 38(5):1014–1023
20. Sotto LSJ, Graham JB, Pickren JW (1960) Postmortem findings in cancer of the cervix: an analysis of 108 autopsies in the past 5 years. Am J Obstet Gynecol 80(4):791–794
21. Choi HJ, Roh JW, Seo SS, et al. (2006) Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. Cancer 106(4):914–922
22. Wang H, Li QK, Auster M, Gong G (2018) PET and CT features differentiating infectious/inflammatory from malignant mediastinal lymphadenopathy: a correlated study with endobronchial ultrasound-guided transbronchial needle aspiration. Radiol Infect Dis 5(1):7–13
23. Sugawara Y, Eisbruch A, Kosuda S, et al. (1999) Evaluation of FDG PET in patients with cervical cancer. J Nucl Med 40(7):1125–1131
24. Jeong YY, Kang HK, Chung TW, Seo JJ, Park JG (2003) Uterine cervical carcinoma after therapy: CT and MR imaging findings. RadioGraphics 23(4):969–981
25. Badib AO, Kurohara SS, Webster JH, Pickren JW (1968) Metastasis to organs in carcinoma of the uterine cervix. Cancer 21:434–439
26. Flynn VT, Spurrett BR (1969) Sister Joseph's nodule. Med J Aust 1:728–730
27. Avdalovic M, Chan A (2004) Thoracic manifestations of common nonpulmonary malignancies of women. Clin Chest Med 25(2):379–390
28. Li H, Wu X, Cheng X (2016) Advances in diagnosis and treatment of metastatic cervical cancer. J Gynecol Oncol 27(4):e43
29. Martínez-Jiménez S, Rosado-de-Christenson ML, Walker CM, et al. (2014) Imaging features of thoracic metastases from gynecologic neoplasms. Radiographics 34(6):1742–1754
30. National Comprehensive Cancer Network (2018) Cervical cancer. Version 2.2018. https://www.nccn.org/professionals/physician_gls/default.aspx#site. Accessed 18 July 2018
31. Kumar R, Gupta R, Khullar S, et al. (2000) Bone scanning for bone metastasis in carcinoma cervix. J Assoc Phys India 48(8):808–810
32. du Toit JP, Grove DV (1987) Radioisotope bone scanning for the detection of occult bony metastases in invasive cervical carcinoma. Gynecol Oncol 28(2):215–219
33. Hirnle P, Mittmann KP, Schmidt B, Pfeiffer KH (1990) Indications for radioisotope bone scanning in staging of cervical cancer. Arch Gynecol Obstet 248(1):21–23
34. Chura JC, Shukla K, Argenta PA (2007) Brain metastasis from cervical carcinoma. Int J Gynecol Cancer 17(1):141–146

35. Cormio G, Pellegrino A, Landoni F, et al. (1996) Brain metastases from cervical carcinoma. Tumori 82(4):394–396
36. Piura E, Piura B (2012) Brain metastases from cervical carcinoma: overview of pertinent literature. Eur J Gynaecol Oncol 33(6):567–573
37. Fetcko K, Gondim DD, Bonnin JM, Dey M (2017) Cervical cancer metastasis to the brain: a case report and review of literature. Surg Neurol Int 8:181
38. Malviya VK, Casselberry JM, Parekh N, Deppe G (1990) Pericardial metastases in squamous cell cancer of the cervix: a report of two cases. J Reprod Med 35(1):49–52
39. Pannu HK, Corl FM, Fishman EK (2001) CT evaluation of cervical cancer: spectrum of disease. Radiographics 21(5):1155–1168
40. Chuang LT, Temin S, Camacho R, et al. (2016) Management and care of women with invasive cervical cancer: American Society of Clinical Oncology resource-stratified clinical practice guideline. J Glob Oncol 2(5):311–340
41. Monk BJ, Tewari KS (2014) Evidence-based therapy for recurrent cervical cancer. J Clin Oncol 32(25):2687–2690
42. Monk BJ, Sill MW, McMeekin DS, et al. (2009) Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 27(28):4649–4655
43. Tewari KS, Sill MW, Long HJ, et al. (2014) Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 370(8):734–743
44. U. S. Food and Drug Administration/Center for Drug Evaluation and Research (2014) Avastin (bevacizumab). Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125085s301lbl.pdf. Accessed 18 July 2018
45. U. S. Food and Drug Administration/Center for Drug Evaluation and Research (2018) FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm610572.htm. Accessed 18 July 2018
46. Dasari S, Tchounwou PB (2014) Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol 740:364–378
47. Rosenberg B, Camp LV, Krigas T (1965) Inhibition of cell division in escherichia coli by electrolysis products from a platinum electrode. Nature 205(4972):698–699
48. Bonomi P, Blessing JA, Stehman FB, et al. (1985) Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 3(8):1079–1085
49. King PD, Perry MC (2001) Hepatotoxicity of chemotherapy. Oncologist 6(2):162–176
50. Trivedi CD, Pitchumoni CS (2005) Drug-induced pancreatitis: an update. J Clin Gastroenterol 39(8):709–716
51. Torrisi JM, Schwartz LH, Gollub MJ, et al. (2011) CT findings of chemotherapy-induced toxicity: what radiologists need to know about the clinical and radiologic manifestations of chemotherapy toxicity. Radiology 258(1):41–56
52. Rohatgi S, Jagannathan JP, Rosenthal MH, et al. (2014) Vascular toxicity associated with chemotherapy and molecular targeted therapy: what should a radiologist know? AJR 203(6):1353–1362
53. Kollmannsberger C, Mross K, Jakob A, Kanz L, Bokemeyer C (1999) Topotecan: a novel topoisomerase I inhibitor: pharmacology and clinical experience. Oncology 56(1):1–12
54. Long HJ, Bundy BN, Grendys EC, et al. (2005) Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol 23(21):4626–4633
55. Pubchem (2018) Topotecan. https://pubchem.ncbi.nlm.nih.gov/compound/60700. Accessed 18 May 2018
56. Rodrigues FG, Dasilva G, Wexner SD (2017) Neutropenic enterocolitis. World J Gastroenterol 23(1):42–47
57. Maitland ML, Wilcox R, Hogarth DK, et al. (2006) Diffuse alveolar damage after a single dose of topotecan in a patient with pulmonary fibrosis and small cell lung cancer. Lung Cancer 54(2):243–245
58. Rossi SE, Erasmus JJ, McAdams HP, Sporn TA, Goodman PC (2000) Pulmonary drug toxicity: radiologic and pathologic manifestations. RadioGraphics 20(5):1245–1259
59. Edgerton CC, Gilman M, Roth BJ (2004) Topotecan-induced bronchiolitis. South Med J 97(7):699–701
60. Horwitz SB (1994) Taxol (paclitaxel): mechanisms of action. Ann Oncol 5(S6):S3–S6
61. Kampan NC, Madondo MT, McNally OM, Quinn M, Plebanski M (2015) Paclitaxel and its evolving role in the management of ovarian cancer. BioMed Res Int 2015:413076
62. Moore DH, Blessing JA, McQuellon RP, et al. (2004) Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 22(15):3113–3119
63. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC (1993) Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol 20(4S3):1–15
64. Bielopolski D, Evron E, Moreh-Rahav O, et al. (2017) Paclitaxel-induced pneumonitis in patients with breast cancer: case series and review of the literature. J Chemother 29(2):113–117
65. Tamiya A, Naito T, Miura S, et al. (2012) Interstitial lung disease associated with docetaxel in patients with advanced non-small cell lung cancer. Anticancer Res 32(3):1103–1106
66. Capasso A (2012) Vinorelbine in cancer therapy. Curr Drug Targets 13(8):1065–1071
67. Morris M, Brader KR, Levenback C, et al. (1998) Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix. J Clin Oncol 16(3):1094–1098
68. Muggia FM, Blessing JA, Method M, et al. (2004) Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 92(2):639–643
69. Gregory RK, Smith IE (2000) Vinorelbine: a clinical review. Br J Cancer 82(12):1907–1913
70. Plunkett W, Huang P, Xu YZ, et al. (1995) Gemcitabine: metabolism, mechanisms of action, and self-potentiation. Semin Oncol 22(4S11):3–10
71. Mutch DG, Bloss JD (2003) Gemcitabine in cervical cancer. Gynecol Oncol 90:S8–S15
72. Chi D-C, Brogan F, Turenne I, et al. (2012) Gemcitabine-induced pulmonary toxicity. Anticancer Res 32(9):4147–4149
73. Shih T, Lindley C (2006) Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. Clin Ther 28(11):1779–1802
74. Krill LS, Tewari KS (2015) Integration of bevacizumab with chemotherapy doublets for advanced cervical cancer. Expert Opin Pharmacother 16(5):675–683
75. Tirumani SH, Fairchild A, Krajewski KM, et al. (2015) Anti-VEGF molecular targeted therapies in common solid malignancies: comprehensive update for radiologists. Radiographics 35(2):455–474
76. Howard SA, Krajewski KM, Thornton E, et al. (2012) Decade of molecular targeted therapy: abdominal manifestations of drug toxicities—what radiologists should know. AJR 199(1):58–64
77. Shinagare AB, Jagannathan JP, Krajewski KM, Ramaiya NH (2013) Liver metastases in the era of molecular targeted therapy: new faces of treatment response. AJR 201(1):W15–W28
78. Odia Y, Shih JH, Kreisl TN, Fine HA (2014) Bevacizumab-related toxicities in the National Cancer Institute malignant glioma trial cohort. J Neurooncol 120(2):431–440
79. Han ES, Monk BJ (2007) What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? Gynecol Oncol 105(1):3–6
80. Singh J, Steward M, Booth T, Mukhtar H, Murray D (2010) Evolution of imaging for abdominal perforation. Ann R Coll Surg Engl 92(3):182–188
81. Hang XF, Xu WS, Wang JX, et al. (2011) Risk of high-grade bleeding in patients with cancer treated with bevacizumab: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 67(6):613–623
82. Tirumani SH, Jagannathan JP, Shinagare AB, et al. (2013) Acute pancreatitis associated with molecular targeted therapies: a retrospective review of the clinico-radiological features, management and outcome. Pancreatology 13(5):461–467
83. Tirumani SH, Krajewski KM, Shinagare AB, Jagannathan JP, Ramaiya NH (2014) Gallbladder complications associated with molecular targeted therapies: clinical and imaging features. Clin Imaging 38(1):50–55

84. Wolford JE, Tewari KS (2017) Highlights from the gynecologic oncology track at the 2017 Annual Meeting of the American Society of Clinical Oncology. J Gynecol Oncol 28(5):e74
85. Hollebecque A, Meyer T, Moore KN, et al. (2017) An open-label, multicohort, phase I/II study of nivolumab in patients with virus-associated tumors (CheckMate 358): efficacy and safety in recurrent or metastatic (R/M) cervical, vaginal, and vulvar cancers. J Clin Oncol 35(15S):5504
86. Schellens JH, Marabelle A, Zeigenfuss S, et al. (2017) Pembrolizumab for previously treated advanced cervical squamous cell cancer: preliminary results from the phase 2 KEYNOTE-158 study. J Clin Oncol 35:5514
87. Wolchok JD, Hoos A, O'Day S, et al. (2009) Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 15(23):7412–7420
88. Naidoo J, Page DB, Li BT, et al. (2015) Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 26(12):2375–2391
89. Mekki A, Dercle L, Lichtenstein P, et al. (2018) Detection of immune-related adverse events by medical imaging in patients treated with anti-programmed cell death 1. Eur J Cancer 96:91–104
90. Kim KW, Ramaiya NH, Krajewski KM, et al. (2013) Ipilimumab-associated colitis: CT findings. AJR 200(5):W468–474
91. Kim KW, Ramaiya NH, Krajewski KM, et al. (2013) Ipilimumab associated hepatitis: imaging and clinicopathologic findings. Invest New Drugs 31(4):1071–1077
92. Alessandrino F, Tirumani SH, Krajewski KM, et al. (2017) Imaging of hepatic toxicity of systemic therapy in a tertiary cancer centre: chemotherapy, haematopoietic stem cell transplantation, molecular targeted therapies, and immune checkpoint inhibitors. Clin Radiol 72(7):521–533
93. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS (2016) Incidence of programmed cell death 1 inhibitor-related pneumonitis in patients with advanced cancer: a systematic review and meta-analysis. JAMA Oncol 2(12):1607–1616
94. Gkiozos I, Kopitopoulou A, Kalkanis A, et al. (2018) Sarcoidosis-like reactions induced by checkpoint inhibitors. J Thorac Oncol. https://doi.org/10.1016/j.jtho.2018.04.031