European Radiology (2019) 29:3696–3704
https://doi.org/10.1007/s00330-018-5937-6

CHEST

Computed tomography features of local pleural recurrence in patients with malignant pleural mesothelioma treated with intensity-modulated pleural radiation therapy

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Received: 31 July 2018 / Revised: 11 October 2018 / Accepted: 29 November 2018 / Published online: 28 January 2019

Abstract

Objective This study was conducted in order to describe the computed tomography (CT) features of local pleural recurrence in patients with malignant pleural mesothelioma undergoing intensity-modulated pleural radiation therapy (IMPRINT) as part of multimodality treatment.

Methods In this observational study, 58 patients treated with IMPRINT between September 21, 2004, and December 1, 2014 were included. Baseline and follow-up CT scans were qualitatively assessed. On follow-up scans, pleural thickening was categorized as unchanged, decreased, or new/increased. New/increased pleural abnormality was subcategorized as diffuse smooth pleural thickening, diffuse nodular pleural thickening, focal pleural nodule, or multiple pleural nodules. To identify features more frequently present at the time of local recurrence, follow-up scans with local recurrence were matched to four control scans; exact conditional logistic regression was performed.

Results Twenty-one (36%) patients had local pleural recurrence and 20 (34%) patients had nonpleural recurrence; 3 patients had both types of recurrence. The 1-year cumulative incidence rate of local recurrence was 27% (95% confidence interval 15, 39). On follow-up scans, three patterns of pleural abnormality were significantly associated with local recurrence: new/increased multiple pleural nodules (10 (48%) positive scans vs 0 control scans), new/increased diffuse nodular pleural thickening (7 (33%) positive scans vs 1 (1%) control scans), and new/increased focal pleural nodule (3 (14%) positive scans vs 1 (1%) control scan) ($p < 0.001$ for all).

Conclusions Multiple new/increased pleural nodules are the feature most commonly present at local recurrence following IMPRINT; however, any pattern of increased nodular pleural thickening is suspicious.

Key Points

- *In patients with mesothelioma receiving intensity-modulated pleural radiation as part of multimodality therapy, increasing multiple pleural nodules is the computed tomography feature most commonly present at local recurrence.*
- *In these patients, any CT pattern of increased nodular pleural thickening should be considered suspicious for local recurrence.*
- *The most common sites of nonpleural recurrence were lung parenchyma, thoracic lymph nodes, and peritoneum.*

Keywords Malignant mesothelioma · Intensity-modulated radiotherapy · Local neoplasm recurrence · X-ray computed tomography · Pleura

Abbreviations

CIR	Cumulative incidence rate
CT	Computed tomography
FDG	Fluorodeoxyglucose
IMPRINT	Intensity-modulated pleural radiation therapy
IQR	Interquartile range

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MPM	Malignant pleural mesothelioma
mRECIST	Modified response evaluation criteria in solid tumors
MRI	Magnetic resonance imaging
PACS	Picture archiving and communications system
PET	Positron emission tomography

Introduction

Malignant pleural mesothelioma (MPM) is a rare, aggressive thoracic malignancy with poor prognosis [1]. Patients with potentially resectable disease are usually treated with a multimodality approach consisting of surgery, subsequent pleural radiation, followed by systemic chemotherapy [2]. Several studies show that patients undergoing lung-sparing surgical techniques have favorable outcomes compared with those undergoing extrapleural pneumonectomy [3, 4]. This has led to the more frequent use of lung-sparing techniques such as pleurectomy/decortication with adjuvant local radiation therapy used to reduce the risk of local recurrence. Delivering cytotoxic doses of radiation to the entire pleura in patients with intact lungs is challenging. Our institution demonstrated the feasibility of highly conformal hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) as part of lung-sparing multimodality treatment for patients with MPM [5] with studies demonstrating encouraging rates of local control and overall survival [6, 7].

In the context of novel radiotherapy techniques, assessing imaging response and identifying early recurrence may be particularly challenging [8–11]. In MPM, close imaging surveillance of the treated hemithorax is especially vital as treatment failure after multimodality treatment is commonly local [12, 13]. While some quantitative methods have been proposed, including metabolic imaging, volumetric measurements, and a modified version of response evaluation criteria in solid tumors (mRECIST) guidelines, qualitative assessment using computed tomography (CT) of the thorax retains a central role in surveillance after multimodality treatment [14–20].

To date, the imaging findings of recurrence in patients undergoing surveillance after treatment for MPM have been described in small retrospective series largely performed on early generation CT scanners, with limited details regarding the CT findings of local recurrence [21–23]. To our knowledge, the radiological features of local pleural recurrences in patients with MPM have yet to be systematically described. Knowledge of the expected appearance and typical locations of early disease recurrence in patients treated with IMPRINT is likely to be of value to radiologists and clinicians, facilitating the prompt initiation of salvage medical therapy after detection of recurrence. The purpose of this study was to describe the CT features of local pleural recurrence in patients who underwent hemithoracic IMPRINT for the treatment of MPM.

Materials and methods

This was an institutional review board-approved, Health Insurance Portability and Accountability Act-compliant retrospective study with a waiver of informed consent, performed at a tertiary oncologic referral center.

Study population

Between September 21, 2004, and December 1, 2014, 108 consecutive patients underwent hemithoracic IMPRINT at our institution for the treatment of MPM. Patients were typically treated with trimodality therapy including platinum/pemetrexed-based chemotherapy, lung-sparing pleurectomy/decortication, and hemithoracic IMPRINT. Patients from this cohort were included in the study if their baseline and follow-up CT imaging were available for review on the institutional picture archiving and communications system (PACS). Fifty patients were excluded as their imaging was not completely available for review. Therefore, 58 patients were included in the final study population.

IMPRINT delivery

The delivery of IMPRINT at our institution has previously been described [5]. Briefly, patients were treated with hemithoracic IMPRINT, typically after lung-sparing surgery with pleurectomy/decortication. Patients were simulated with a CT scan of the chest and treated to a median dose of 4680 cGy in 26 fractions (range 2880 to 5040 cGy) using co-planar beams. Patients were then followed with diagnostic CT scans every three months for the first two years and every six months thereafter. Fifty-three (91%) patients received chemotherapy (18 received adjuvant treatment and 35 received neoadjuvant) and five patients did not. Chemotherapy regimens used were cisplatin and pemetrexed (n = 24), cisplatin–carboplatin–pemetrexed (n = 6), carboplatin–pemetrexed (n = 21), carboplatin–Taxol (n = 1), and cisplatin–pemetrexed–bevacizumab (n = 1).

Image acquisition

CT exams were performed on a 64-slice multidetector CT (Lightspeed VCT or Discovery CT750 HD (both GE Medical Systems)) or a 16-slice multidetector CT (Lightspeed 16, GE Medical Systems). Helical CTs were obtained during full inspiration with the patient in a supine position and with a tube voltage of 120 kVp, auto milliampere yielding a tube current of between 120 and 380 mA, a pitch of 0.984–1.375, and an image reconstruction matrix of 512 × 512. Axial images were reconstructed at slice thicknesses of 1.25 and 5 mm; coronal and sagittal images were reconstructed at a slice thickness of 5 mm. Reflecting local clinical practice, intravenous contrast was ordered at the discretion of referring clinicians. When intravenous contrast was ordered, iohexol 300 mg iodine/mL was administered at a rate of 2.5 ml/s.

Imaging assessment and follow-up

Baseline and follow-up CT images were qualitatively assessed by two radiologists in consensus (reader 1, with 3 years postfellowship experience in thoracic oncologic imaging; reader 2, a current fellow). In cases of lack of consensus, a third radiologist (reader 3, with 20 years postfellowship experience in thoracic oncologic imaging) reviewed the images to adjudicate the findings.

Baseline CT images were first assessed as to whether any radiological gross residual disease remained. When available, baseline preradiation PET/CTs were qualitatively assessed by the study radiologists in conjunction with the diagnostic CT images (preradiation PET/CTs are routinely acquired in our institution to plan the radiation field). If a pleural abnormality consistent with gross residual disease was found, it was subcategorized into one of four imaging patterns: solitary pleural nodule, multiple pleural nodules, diffuse pleural thickening (thickening affecting more than one side of the chest), or focal pleural thickening (thickening affecting only one side of the chest) (Fig. 1a–d). The presence of a pleural effusion and thoracic adenopathy was also recorded.

Follow-up CT images were then assessed and compared with baseline CT images in two broad categories: (i) for evidence of local recurrence (for the purposes of this manuscript, local recurrence refers specifically to local pleural recurrence, and not to other forms of regional recurrence such as nodal metastases) and (ii) for evidence of nonpleural recurrence. Follow-up imaging was reviewed until the criteria for either local or nonpleural recurrence were met (see below), or until the date of last available imaging if the criteria were not met. For the purposes of this manuscript, local recurrence refers specifically to local pleural recurrence, and not to other forms of regional recurrence such as nodal metastases. The pleura/chest wall was qualitatively examined and findings were characterized as one of the following three categories: (1) unchanged pleural thickening/nodule, (2) decreased pleural thickening/nodule, or (3) new or increased pleural thickening/nodule. If a new or increased pleural abnormality was present, it was further subcategorized into one of four imaging patterns: diffuse smooth pleural thickening, diffuse nodular pleural thickening, focal pleural nodule, or multiple pleural nodules (Fig. 2a–d). The presence of a new or increasing chest wall mass and the presence of bone erosion were also documented. Pleural effusion and pericardial effusions, if present, were recorded as being either stable/decreasing or new/increasing. New nodular pericardial thickening was also recorded.

Criteria for recurrence

Local recurrence was defined as (i) a pathology-proven lesion; (ii) a new CT finding of focal pleural nodule, multiple pleural nodules, diffuse nodular pleural thickening, chest wall mass, or bone erosion which was focally fluorodeoxyglucose F-18 (FDG) avid on a subsequent PET/CT; or (iii) new CT finding of focal pleural nodule, multiple pleural nodules, diffuse nodular pleural thickening, chest wall mass, or bone erosion which increased in size on a subsequent CT. Although PET/CT was used to define local recurrence after the identification of suspicious CT findings, it was not used to identify suspicious lesions de novo.

Nonpleural recurrence was defined as (i) a pathology-proven lesion, (ii) new suspicious CT finding (e.g., new peritoneal nodules, lymph nodes newly enlarged > 1.5 cm short axis) which was focally FDG avid on a subsequent PET/CT, or (iii) new suspicious CT finding which increased in size on a subsequent CT. Thoracic nodal metastases, lung parenchymal metastases, metastases in the contralateral thorax, and any extrathoracic metastases were classified as nonpleural recurrence.

Statistical analysis

Time to local recurrence was defined as the interval between the start of IMPRINT to the date of the scan when local recurrence was detected. Death or nonpleural recurrence before local recurrence was treated as competing risks. Patients without any events were censored at the last follow-up. Gray's method was used to examine associations of baseline CT features with time to local recurrence.

We also examined if CT features differed between follow-up scans with local recurrence and follow-up scans without local recurrence. To do this, four follow-up control scans without local recurrence were randomly selected for every scan with local recurrence, matched by time interval between the start of IMPRINT and the scan with a window of ± 2 months. Exact conditional logistic regression was used to test the association between each feature present and local recurrence, and the exact p value from the score test was reported. Due to the limited number of patients with features present, multivariable analysis was not performed.

A test with p value < 0.05 was considered statistically significant. All statistical analyses were performed in software packages SAS 9.4 (SAS Institute Inc., Cary, NC) and R version 3.1 (The R Foundation for Statistical Computing).

Results

Baseline patient characteristics are summarized in Table 1. Baseline CT studies were performed a median of 43 days (interquartile range (IQR) 30–107) after surgery and 17 days (IQR 12–

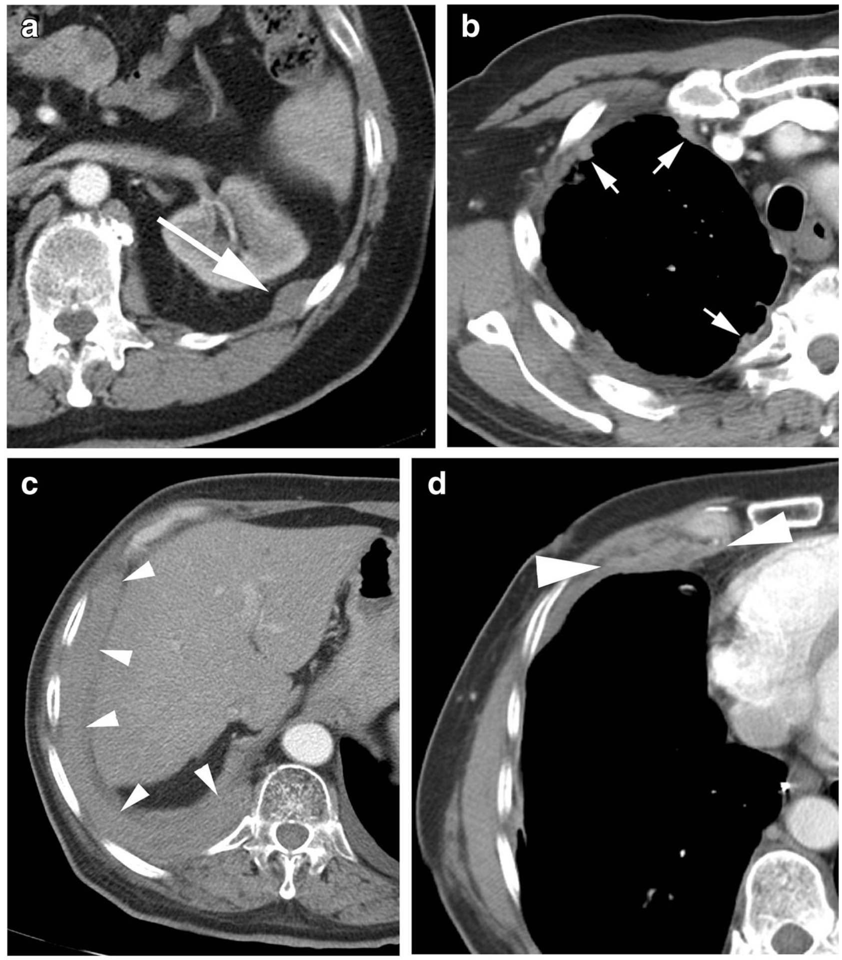

Fig. 1 **a** Pre-IMPRINT axial contrast-enhanced CT image of the lower chest/upper abdomen demonstrating a nodule in the left costodiaphragmatic recess. No other pleural lesion was present. This was classified as a pattern of "solitary pleural nodule." **b** Pre-IMPRINT axial contrast-enhanced CT of the right chest demonstrates multiple small pleural nodules (arrows). Additional nodules were identified at other levels in the thorax. This was classified as a pattern of "multiple pleural nodules." **c** Pre-IMPRINT axial contrast-enhanced CT image of the lower chest demonstrates pleural thickening on more than one side of the right chest (arrowheads). Cases such as this were classified as a pattern of "diffuse pleural thickening." **d** Pre-IMPRINT axial contrast-enhanced CT image of the lower chest demonstrating pleural thickening on one side of the chest (arrowheads), with small volume pleural fluid. This was classified as a pattern of "focal pleural thickening"

21) before IMPRINT. Median imaging follow-up for all patients was 37 weeks (IQR 23–68). Patients received a median of three follow-up CT scans (IQR 2–5). Follow-up CTs which confirmed recurrence were performed a median of 11 weeks (2–23) after first detecting the abnormality on CT. When recurrence was confirmed using PET/CT or with biopsy, the confirmatory test was performed a median of 1 week (1–4) after first detecting the abnormality. Of 289 CT studies that were reviewed, 174 (60%) were performed with intravenous contrast. Fifty-five (95%) patients had baseline preradiation PET/CTs, and these were reviewed by the study radiologists at the same time as baseline preradiation CT images to determine the presence of postsurgical residual disease. Two hundred and twenty (76%) CT studies were CT chest CTs (including the upper abdomen through the level of the adrenals); 61 (21%) studies were CTs of the chest, abdomen, and pelvis; and 8 (3%) studies were CTs of the chest and abdomen.

Incidence of recurrence

At the date of last follow-up, 38 (66%) patients had CT findings consistent with recurrence: 21 (36%) had local recurrence and 20 (34%) had nonpleural recurrence. In three patients (5%), local recurrence and nonpleural recurrence occurred at the same time point. Local recurrence was determined by serial growth on two or more follow-up CTs in 15 (71%) patients, growth on CT with focal FDG avidity on PET in four (19%) patients, and biopsy in two (10%) patients. Three patients had CT findings suspicious for local recurrence but had no imaging follow-up to confirm the findings.

The 1-year cumulative incidence rate (CIR) of local recurrence was 27% (95% confidence interval (CI) 15, 39). Local recurrence occurred after a median follow-up of 35 weeks (IQR 16–66), while nonpleural recurrence occurred after a median follow-up of 38 weeks (IQR 22–64). Thirty-five patients died at last follow-up and median overall survival was 93 weeks (95% CI 59, 110).

Imaging findings

The imaging features on baseline CTs and their relationship to local recurrence are summarized in Table 2. Twenty-seven (47%) patients with radiologically suspected residual pleural disease had a significantly higher 1-year CIR of subsequent

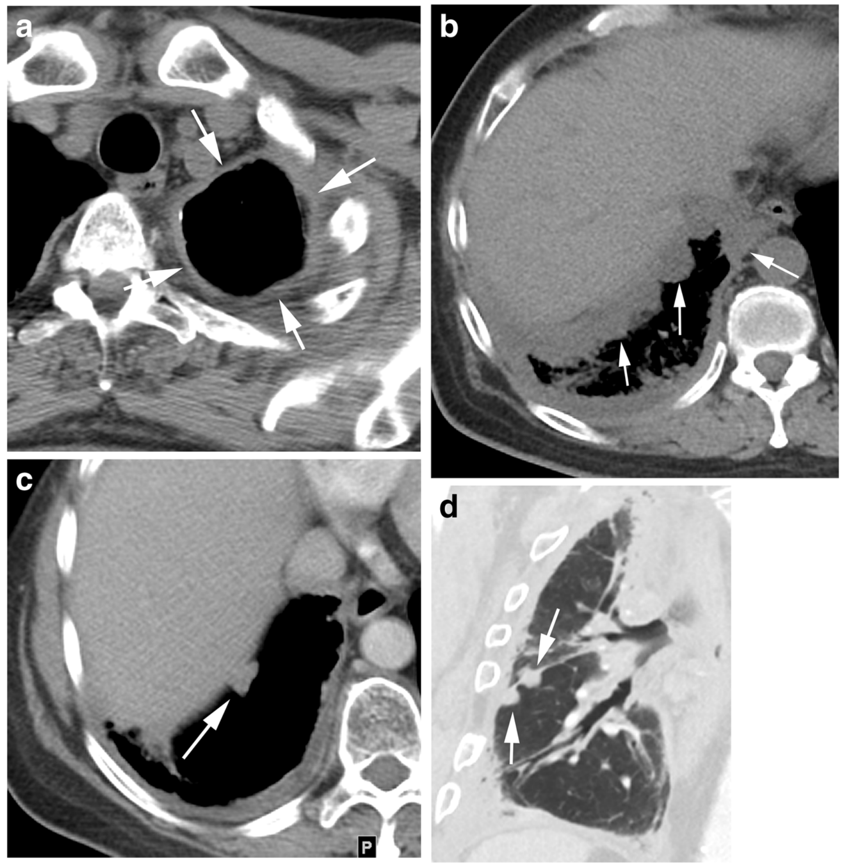

Fig. 2 **a** Post-IMPRINT axial noncontrast CT image of the chest demonstrating smooth circumferential pleural thickening in the left lung apex. Cases such as this were classified as a pattern of "diffuse smooth pleural thickening." **b** Post-IMPRINT axial noncontrast CT image of the chest demonstrating pleural thickening affecting more than one pleural surface with several nodular components (arrows). This was classified as "diffuse nodular pleural thickening." **c** Post-IMPRINT axial-enhanced CT image of the chest demonstrates a focal nodule in the basal right pleura. This was classified as "focal pleural nodule." Smooth thickening of the remaining pleural surfaces and a pleural effusion are also seen. **d** Post-IMPRINT coronal noncontrast CT image of the chest demonstrating two noncontiguous nodules along the pleural/fissural surface in the right thorax. Cases such as this were classified as a pattern of "multiple pleural nodules"

local recurrence compared with those without (0.495 (95% CI 0.295, 0.694) vs 0.07 (95% CI 0, 0.166)).

The imaging features on CTs at the time of local recurrence and on control CTs without local recurrence are summarized in Table 3. Three patterns of pleural/chest wall abnormality were significantly associated with local recurrence: new or increased multiple pleural nodules (10 (48%) local recurrence CTs vs 0 control CTs)), new or increased diffuse nodular pleural thickening (7 (33%) local recurrence CTs vs 1 (1%) control CT), and new or increased focal pleural nodule (3 (14%) local recurrence CTs vs 1 (1%) in control CT) (p values < 0.001, < 0.001, and 0.027, respectively).

New bone erosion and new chest wall mass both occurred in two (10%) local recurrence CTs and in no control CTs, while new pericardial nodularity adjacent to pleural thickening was seen in one (10%) patient at the time of recurrence and in no control CTs, and none of these features could be assessed statistically due to the low incidence of each finding.

Unchanged or decreased pleural thickening was the most common imaging feature on follow-up CTs, visualized at some point in 51 (88%) patients, and was significantly associated with the absence of local recurrence ($p < 0.001$). New or increased diffuse smooth pleural thickening was seen in 10 (17%) patients and in no cases was it noted at the time of local recurrence. Most commonly in these patients (9 (90%) patients), new or increased smooth pleural thickening was noted at one time point during the patients' follow-up, then stabilized. In the ten patients in whom smooth pleural thickening was identified, three (30%) patients had not recurred at last follow-up, five (50%) patients developed subsequent nonpleural recurrence, and two (20%) patients developed subsequent local recurrence. In the latter two patients, one developed superimposed diffuse nodular pleural thickening and 1 developed multiple pleural nodules. In both cases, the superimposed nodular thickening was readily detectable despite the existing smooth pleural thickening. A new/increasing pleural effusion was seen in 17 (29%) patients and was not significantly associated with local recurrence ($p = 0.681$).

The sites of first nonpleural recurrence were as follows: lung parenchyma (8 (40%) patients), thoracic nodes (6 (30%) patients), peritoneum (6 (30%) patients), and bone (1 (5%) patient). Some patients had concomitant nonpleural recurrence at multiple sites.

Discussion

In this study, we assessed the CT imaging appearance in patients undergoing hemithoracic IMPRINT as part of multimodality treatment for MPM and described the imaging

Table 1 Baseline patient characteristics

	N, interquartile range (%)
Sex	
Male	45 (78)
Female	13 (22)
Age (median)	68 (62–73)
Histology	
Epithelioid	49 (85)
Sarcomatoid	2 (3)
Biphasic	7 (12)
Laterality of tumor	
Right	34 (59)
Left	24 (41)
Type of surgery	
Partial pleurectomy	23 (40)
Pleurectomy/decortication	28 (48)
Extended pleurectomy/decortication	5 (9)
Lobectomy	1 (2)
Extent of surgical resection	
R1	30 (52)
R2	28 (48)
Talc pleurodesis prior to radiation	
Yes	17 (29%)
No	41 (71%)

Percentages may not add to 100 due to rounding

R1, cancer cells present microscopically at the resection margin; *R2*, gross pathological examination demonstrates tumor tissue at the resection margin

features associated with local recurrence in this patient cohort. The CT feature most commonly associated with local recurrence was the presence of multiple new or increasing discrete pleural nodules. However, based on our results, any form of increasing pleural nodular thickening should be considered suspicious. Other suspicious imaging features included the presence of a new chest wall mass and bone erosion, both of which were infrequently seen, but always indicated local recurrence.

Increasing smooth pleural thickening was a reassuring imaging feature. It was typically noted at only one time point in follow-up followed by stabilization of the findings. We feel that this pattern of pleural abnormality most likely represented postradiation inflammatory change. Importantly, in patients who developed this pattern of smooth pleural inflammation and subsequently developed pleural recurrence, the pattern of nodular recurrence was readily detectable superimposed on the smooth pleural thickening. Describing the expected imaging findings following treatment with novel forms of radiation therapy is important. For example, early descriptions of the evolution of lung opacities following treatment with SBRT for lung cancer lead to the identification of benign mass-like parenchymal opacities mimicking recurrence [9]. In the current study, no atypical patterns of local recurrence or pleural inflammation were identified. This knowledge will aid radiologists and clinicians in determining their level of suspicion when nodular changes arise during surveillance following IMPRINT from MPM. Identifying nodular changes even in the context of existing inflammation should result in the initiation of a prompt workup to establish the presence of local pleural recurrence (in our institution, this is typically done with PET/CT).

A new or increasing pleural effusion was seen with similar frequency in patients with and without local recurrence. While the presence of a worsening effusion should prompt a search for underlying pleural disease, the presence of the effusion itself was not significantly associated with recurrence, and it is likely that in many patients pleural fluid develops as a reactive inflammatory process following radiation.

CT is widely used as an imaging tool in patients receiving multimodality treatment for MPM; however, assessing treatment response can be challenging [16, 24, 25]. The reason for this is multifactorial but includes the presence of evolving posttreatment changes such as lung fibrosis and pleural inflammatory change induced by surgery, radiation, or pleurodesis [26]. In addition, accurate selection and reproducible measurement of pleural lesions over time can be difficult due to the morphology and growth pattern of pleural disease. For example, the most widely used criteria for evaluating tumor response, RECIST 1.1 [27], assumes a roughly spherical shape for any given measured tumor. Given the frequently linear growth patterns seen in MPM as it tracks along the pleural surface, using RECIST 1.1 can lead to significant variability in tumor measurement [16]. Therefore, clinical trials have also used modified RECIST, which differs from RECIST 1.1 in that two linear measurements are obtained perpendicular to the chest wall (rather than along the long axis of the tumor as in RECIST 1.1) at three different levels along the pleural surface [16]. For mRECIST to be used, however, there needs to be measurable pleural disease, and in the majority of patients in this cohort, there was no residual radiologically detectable pleural lesion. In addition, both the RECIST 1.1 and mRECIST guidelines exclude lesions in a previously radiated area. Consequently, qualitative evaluation of the pleural surface plays a central role in disease surveillance.

Magnetic resonance imaging (MRI) and PET/CT have been used as either an alternative or complementary imaging technique in patients with MPM in addition to CT imaging. Compared with CT, MRI has superior soft tissue contrast and has shown some utility for initial staging and in assessing treatment response [28]; however, given CT's widespread availability, speed, and lower cost, the role of MRI for evaluating MPM is limited. PET/CT has an established role in initial diagnosis and is increasingly used during radiation planning [29]. Although some studies have questioned the

Table 2 Imaging findings on baseline CT, obtained after surgery but before IMPRINT, demonstrating the 1-year CIR of local recurrence if a given finding was present

CT findings	*N* (%)	1-year CIR of local recurrence (95% CI)	*p* value
Radiologically suspected residual pleural disease			
Yes	27 (47%)	0.495 (0.295, 0.694)	< 0.001
No	31 (53%)	0.07 (0, 0.166)	
Solitary pleural nodule*			
Yes	3 (11.1%)	0 (0, 0)	0.060
No	24 (88.9%)	0.561 (0.347, 0.774)	
Multiple pleural nodules*			
Yes	15 (55.6%)	0.467 (0.197, 0.736)	0.878
No	12 (44.4%)	0.536 (0.212, 0.86)	
Diffuse pleural thickening*			
Yes	5 (18.5%)	0.6 (0.053, 1)	0.640
No	22 (81.5%)	0.467 (0.245, 0.689)	
Focal pleural thickening*			
Yes	4 (14.8%)	NA (NA, NA)	0.159
No	23 (85.2%)	0.435 (0.224, 0.645)	
Pleural effusion			
Yes	34 (58.6%)	0.149 (0.026, 0.272)	0.212
No	24 (41.4%)	0.454 (0.232, 0.677)	

CIR, cumulative incidence rate; *CT*, computed tomography; *IMPRINT*, intensity-modulated pleural radiation therapy

*These features were only assessed if there was radiologically suspected residual pleural disease

accuracy of PET/CT for local tumor staging [30, 31], the overall staging accuracy of PET/CT is superior to both CT and MRI, particularly for the assessment of locoregional metastases and distant metastatic disease [26, 32]. Its role in evaluating treatment response following multimodality treatment has yet to be fully defined; however, there are a number

Table 3 Imaging findings on follow-up CTs, obtained after IMPRINT, comparing features on CTs with local recurrence versus CTs without local recurrence

CT findings	CT studies at time of local recurrence (*N* = 21)	CT studies without local recurrence (*N* = 84)*	*p* value
Stable or decreased pleural thickening			
Yes	1 (5%)	76 (90%)	< 0.001
No	20 (95%)	8 (10%)	
New or increased focal pleural nodule			
Yes	3 (14%)	1 (1%)	0.027
No	18 (86%)	83 (99%)	
New or increased multiple pleural nodules			
Yes	10 (48%)	0 (0%)	< 0.001
No	11 (52%)	84 (100%)	
New or increased diffuse smooth pleural thickening			
Yes	0 (0%)	4 (5%)	0.59
No	21 (100%)	80 (95%)	
New or increased diffuse nodular pleural thickening			
Yes	7 (33%)	1 (1%)	< 0.001
No	14 (67%)	83 (99%)	
New or enlarging pleural effusion			
Yes	3 (14.3%)	7 (8.3%)	0.681
No	18 (85.7%)	77 (91.7%)	

CT, computed tomography; *IMPRINT*, intensity-modulated pleural radiation therapy

*Four follow-up control scans without local recurrence were randomly selected for every scan with local recurrence, matched by time interval between the start of IMPRINT and the scan of studies suggesting that it is an accurate technique for detecting both local and distant recurrence in this setting [13, 33]. Potential limitations to the use of PET/CT include the possibility of intense inflammatory FDG uptake at sites of prior radiation, surgery, and talc pleurodesis [34]. In cases of potentially false-positive inflammatory PET/CT findings, and in areas where access to PET/CT is limited, knowledge of the CT patterns of local recurrence as outlined in the current study is vital.

The pattern of nonpleural recurrence in our cohort is similar to previous reports following multimodality therapy [8, 35] and supports the use of thoracoabdominal CT, rather than thoracic CT alone, as a method for surveying patients with MPM. Although the most common sites of recurrence were in the chest (lung 40% and thoracic nodes 30%), a large minority of patients with nonpleural recurrence had peritoneal metastases (30%). In 20% of the patients, the peritoneum was the only site of metastatic disease at the time of initial recurrence.

Limitations of this study include the fact that only a minority of cases of recurrence were proven pathologically, and in most cases, a progressively enlarging lesion was used as the definition of recurrent disease. Ideally, pathologic confirmation would have been obtained; however, the above definitions of recurrence fit with local clinical practice and were adopted for this study. Another limitation was the variability in the imaging protocols. While the majority of scans were obtained with intravenous contrast, a minority were not. Ideally, all CT examinations would have been performed under the same conditions. The relatively small sample size of 58 patients is an additional limitation. However, MPM is a rare cancer with approximately 3300 cases per year in the USA [36], and achieving a very large sample size is challenging, particularly in the context of a novel treatment. Larger multicenter studies may be needed to more completely describe the clinical and radiological features of similar patient cohorts.

In conclusion, we have provided a systematic description of CT imaging features encountered after surgical resection and hemithoracic IMPRINT for the treatment of MPM. Multiple new or increasing discrete pleural nodules are the CT feature most commonly associated with local recurrence, but the presence of any pattern of new or increasing pleural nodular thickening needs to be treated with a high index of suspicion. Some ancillary imaging findings such as bone erosion or chest wall nodules are useful, if present, but are infrequently seen. The frequency of peritoneal recurrence in our cohort emphasizes the need to image the abdomen during imaging surveillance for MPM. Knowledge of the patterns and imaging appearance of disease recurrence is important for both the radiologist and clinician in the follow-up of these patients.

Funding This research was funded in part through the National Institute of Health/National Cancer Institute Cancer Center Support Grant P30 CA008748.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Michelle Ginsberg.

Conflict of interest The authors of this manuscript declare relationships with the following companies: Merck (Andreas Rimner, not relevant to the submitted work), AstraZeneca (Andreas Rimner, not relevant to the submitted work), and Varian Medical Systems (Andreas Rimner, not relevant to the submitted work).

Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- observational
- performed at one institution

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