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REVIEW

Distinguishing Radiation Pneumonitis from Local Tumour Recurrence Following SBRT for Lung Cancer

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Abstract: Radiation pneumonitis is one of the most common toxicities following SBRT for lung cancer. Although local control rates are good, a recurrent tumour is difficult to distinguish from radiation pneumonitis due to similar size and morphology. Therefore, early detection of a recurrent tumour is challenging, and moreover, it is crucial for affected patients, as early detection enables curative salvage therapy. Promising data exists to solve these challenges for late recurrences, for example, the analysis of high-risk CT features allows prediction of recurrence after 12 months. But particularly in cases of early recurrences and radiation pneumonitis, comprehensive data are lacking. Therefore, the aim of this study was to review the existing literature with special regard to radiological response assessment after stereotactic body radiotherapy and risk factors for predicting radiation pneumonitis or local recurrence.
Keywords: radiation pneumonitis, tumour recurrence, stereotactic body radiotherapy

Plain Language Summary

Radiation pneumonitis is one of the most common toxicities following stereotactic body radiotherapy (SBRT) for lung cancer. It appears within 6 months after SBRT and more than 50% of the patients have corresponding radiological findings, but they are usually asymptomatic. By contrast, local recurrence is less common as local control rates are good. However, distinguishing radiation pneumonitis from a recurrent tumour is challenging due to similar morphology and size. This study aimed to review the literature which investigated predictive factors concerning radiation pneumonitis and local tumour recurrence after SBRT. Indeed, we found promising data. For example, Mattonen and her team reported a computer-aided algorithm for predicting local recurrence within 6 months. Moran and colleagues developed a similar procedure for predicting radiation pneumonitis. Furthermore, the use of positron emission tomography (PET) is encouraging. Huang et al developed a follow-up algorithm for response-assessment after SBRT, in which a PET is recommended in some cases, and Dong et al demonstrated that patients with high metabolic activity (described as SUVmax) before treatment had a worse overall survival. Nevertheless, the interpretation of a PET-scan should be done carefully as there is no optimal SUVmax threshold for predicting local recurrence or radiation pneumonitis. Another approach is to analyse of dosimetric parameters before performing SBRT, and indeed, some parameters seem to be associated with radiation pneumonitis, but again no specific dose constraints are found yet. We found promising data in the literature, but the results are controversial, and a conclusion could not be drawn.

Introduction

Lung cancer is the leading cancer type worldwide with regard to the number of new cases and causes of death.[1] The therapeutic options are surgery, radiosurgery, respectively, ablative (stereotactic) radiotherapy, conventional radiotherapy, chemotherapy or immunotherapy. The

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therapeutic strategy depends on the histological type, tumour stage and the constitution of the patients.[2] In cases of early staged lung cancer (T1-2N0M0), stereotactic body radiotherapy (SBRT) is now a standard treatment option[3] for medically inoperable patients,[4,5] and it is considered to be a safe technique with low rates of severe toxicity.[6] A 3-year local control rate of approximately >90% has been reported.[7,8] Moreover, SBRT could be an option for oligometastatic patients with excellent local control rates and encouraging overall survival,[9] and for operable patients as results are comparable to those from surgery.[10,11]

Radiological changes are commonly seen after SBRT.[12] Compared to conventional fractionated radiotherapy (CRT), SBRT allows the delivery of high doses per fraction while sparing surrounding normal lung tissue. Using volumetric modulated arc therapy (VMAT, Figures 1 and 2) or intensity-modulated radiation therapy (IMRT, 3–8 fractions, Figure 3), a dose distribution highly conformal to the shape of the tumour (high-dose region) and step-down dose gradients at its boundary (low-dose region) can be achieved.[13] Older techniques such as CRT are less conformal to the tumour. It is expected that radiological patterns of radiological changes on a computed tomography (CT) after SBRT are different from those after CRT.[14] On the one hand, CT changes after CRT are limited to the irradiated lung and thus conform to the treatment ports, where a distinct boundary between the irradiated and non-irradiated lung can be seen.[15] On the other hand, due to the more complex dose distribution of SBRT, with highly conformal high-dose region (surrounding the tumour) and large irregular low-dose region (surrounding normal lung tissue, Figures 4, 5, and 6), CT changes do not show distinct boundaries and typically conform to the shape of tumour (Figures 1, 2, and 3).[15]

As reported by Linda et al,[15] the CT changes following SBRT can be divided into an early stage within 6 months (Table 1), mainly related to radiation pneumonitis (RP), and a late stage after 6 months, related to radiation fibrosis. Radiation pneumonitis is one of the most common toxicities after SBRT,[16] up to 50–60% of the patients show acute radiological findings.[17] Most patients usually are asymptomatic (grade 0–1, Common Terminology Criteria of Adverse Events, CTCAE), and reported rates of symptomatic RP (CTCAE grade 2–4) range from 9% to 28%.[18]

Although local control rates are good, one of the most challenging problem is the differentiation of those benign post-SBRT radiological findings from malign local recurrence. They appear as an increase in CT density, and RP might mimic a recurrence due to similar morphology and size[19] making the physicians' decision of salvage treatment options more difficult. Promising data exists to solve these challenges for late recurrences, for example, the analysis of high-risk CT features allows to predict recurrence after 12 months.[20] But particularly in cases of early recurrences and RP, comprehensive data are lacking. Hence, we aimed to review the literature concerning early recurrence and radiation pneumonitis after SBRT for lung cancer.

Methods

Literature Research

We accomplished a comprehensive literature research using the PubMed Database for articles published between January 2006 and April 2019. The following keywords were utilised: Pneumonitis, lung injury, fibrosis, recurrence, relapse, local failure, CT changes, CT appearance, imaging changes, early changes, texture analysis, radiomics, predictive, prognostic and risk factor. These keywords were accompanied by SBRT, SABR and lung cancer. After excluding duplicates, a total of 1078 articles were found. These articles were screened by cross-reading titles and abstracts. Articles directly concerning pneumonitis, fibrosis and recurrence, respectively, predictive factors and imaging findings after SBRT were selected, resulting in about 180 articles for final analysis. Twenty additional studies were included by interest after screening lists of reference. In brief, the following aspects were found:

- general radiographical changes after SBRT
- impact of different treatment techniques
- computed tomography (CT) analysis to distinguish tumour recurrence and radiation pneumonitis
- positron emission tomography (PET) to distinguish tumour recurrence and radiation pneumonitis
- dosimetric factors to predict pneumonitis
- impact of patient-based risk factors

In this review, we report the results as a summary of the most promising data available in the literature we found.

Patients and Creation of the Figures

We retrospectively checked our patient database (from 2018 and 2019) and picked up 11 patients with radiological signs of radiation pneumonitis or tumour recurrence. They are illustrated in 10 figures. CT findings after SBRT are shown in Figures 1–7: Figures 1–3 show radiation pneumonitis after SBRT. Using a deformable image registration, we demonstrate that these findings are conformal to the high dose region. In

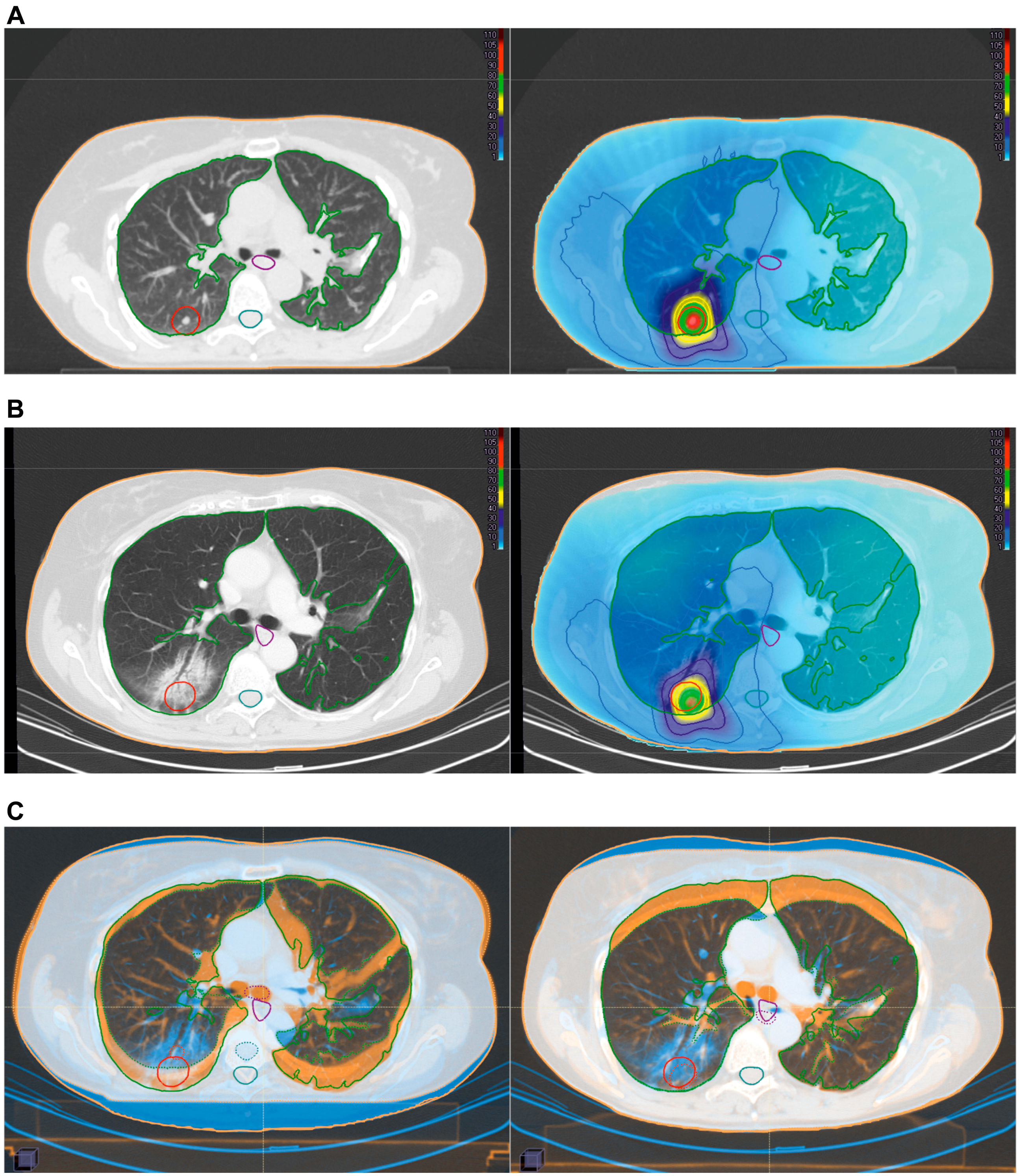

Figure 1 Radiation pneumonitis after SBRT. (**A** left): 74-year-old female patient treated with SBRT for lung metastasis of parathyroid carcinoma (within the red contour). Planning target volume (red contour) and organs at risk: Total lung (green), spinal cord (turquoise), oesophagus (violet). (**A** right): Treatment plan (VMAT-technology, 15 Gy in 3 fractions, total dose 45.0 Gy): Isodose lines (% of total dose) and the dose distribution, high-dose region surrounding the tumour (red, green), step down gradient (yellow, dark blue), and a large low-dose region highlighted in blue. (**B** left): Ground-glass opacities after SBRT, suspected radiation pneumonitis. (**B** right): A deformable image registration was used to correlate the lung changes on follow-up CT-scan with radiation dose distribution. The changes are conformal to the high- and mid-dose region. (**C**): A pre-treatment image (orange, dashed lines) and a follow-up image (blue, solid lines) were fused. A rigid image registration (left) cannot account for lung volume and tumour position changes on follow-up CT-scans. The images do not correlate with each other. The deformable image registration (right) is more accurate than the rigid registration and the images correlate well with each other.

Abbreviation: VMAT, volumetric modulated arc therapy.

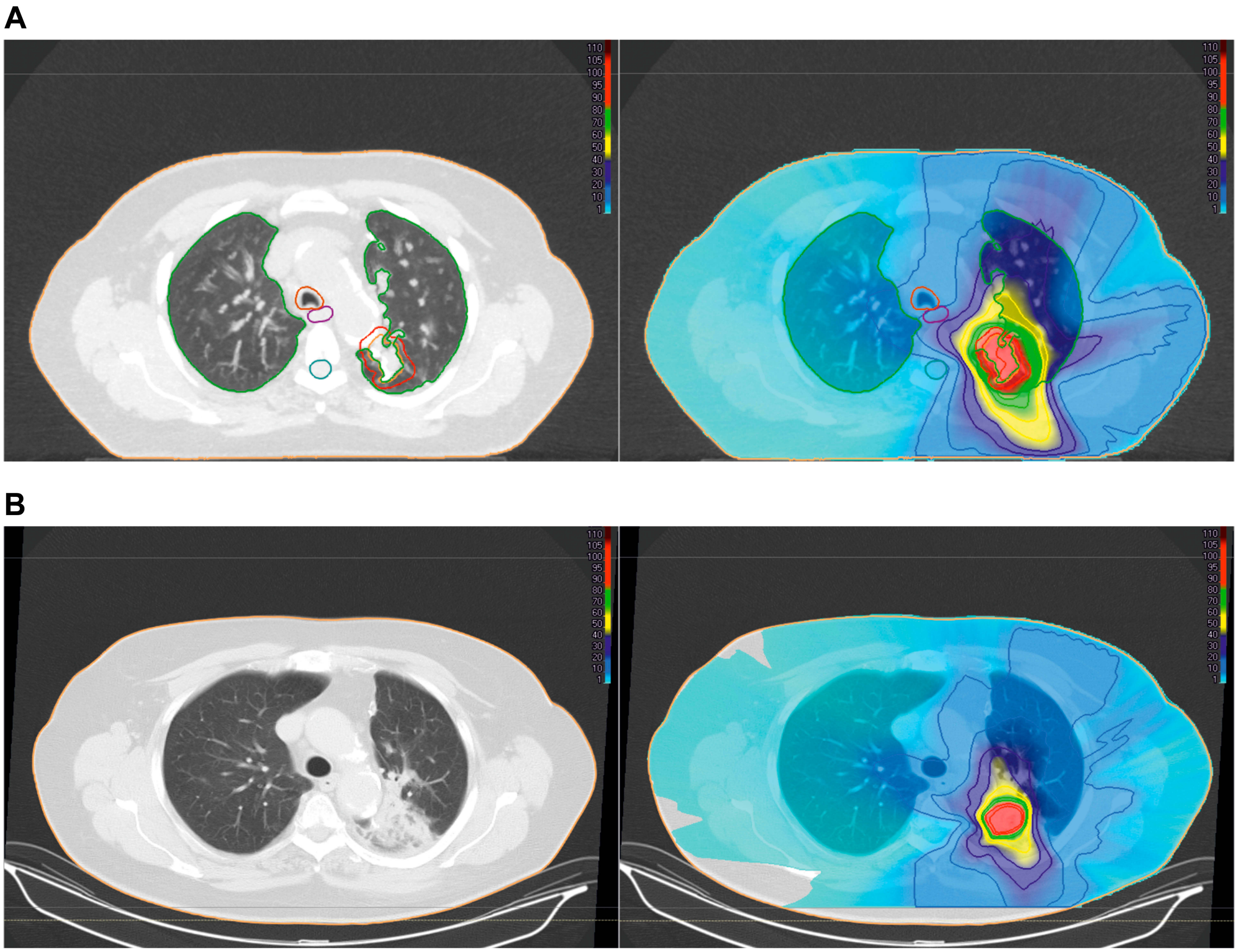

Figure 2 Radiation pneumonitis after SBRT. (**A** left): 78 years old female patient with histologically proven non-small cell lung carcinoma (within the red contour). Planning target volume (red contour) and organs at risk: Total lung (green), spinal cord (turquoise), oesophagus (violet), trachea (orange). (**A** right): Treatment plan (VMAT-technology, 5 Gy in 10 fractions, total dose 50.0 Gy): Isodose lines (% of total dose) and the dose distribution, high-dose region surrounding the tumour (red, green), step down gradient (yellow, dark blue), and a large low-dose region highlighted in blue. (**B** left): Consolidative changes after SBRT, suspect of tumour progression, but radiation pneumonitis was retrospectively diagnosed. (**B** right): A deformable image registration was used to correlate the lung changes on follow-up CT-scan with radiation dose distribution. The changes are conformal to the high-dose region.
Abbreviation: VMAT, volumetric modulated arc therapy.

Figures 4 and 5 we demonstrate local tumour control after SBRT without radiation pneumonitis resp. with discreet signs of radiation pneumonitis. Figure 6 shows a persistent tumour. The patients with radiation pneumonitis (Figures 1 and 2) are shown in Figure 7, too. We illustrate early and late radiological changes following SBRT. PET/CT findings are shown in Figures 8–10: SUVmax associated with radiation pneumonitis is shown in Figures 8 and 9, whereas in Figure 10, we demonstrate that SUVmax is associated with local recurrence.

Incidences of CT Changes Following SBRT for Lung Cancer

The CT changes following SBRT for lung cancer are classified into two stages. The early stage, which is radiation pneumonitis, occurs within 6 months after SBRT[15] with a median time of 17 weeks to the development of first CT changes.[17] A classification system with five patterns of acute CT changes has been proposed by Linda et al[15] and Kimura et al (Table 1)[22] and modified by Dahele et al[17] and Palma et al (Table 2).[21] In brief, the modified categories[21] are diffuse consolidation (dc), patchy consolidation (pc), diffuse ground-glass-opacities (dGGO), patchy ground-glass-opacities (pGGO) and no evidence of changes. Ground-glass-opacities describe an increase in pulmonary attenuation with preserved margins of vessels and airways, whereas within consolidative changes, the vessels and airways cannot be seen.[15,21,22,29] The terms "diffuse" and "patchy" are defined according to size criteria (>5 cm or <5 cm longest axial diameter) or to severity criteria (region contains >50% or <50% abnormal lung).[21]

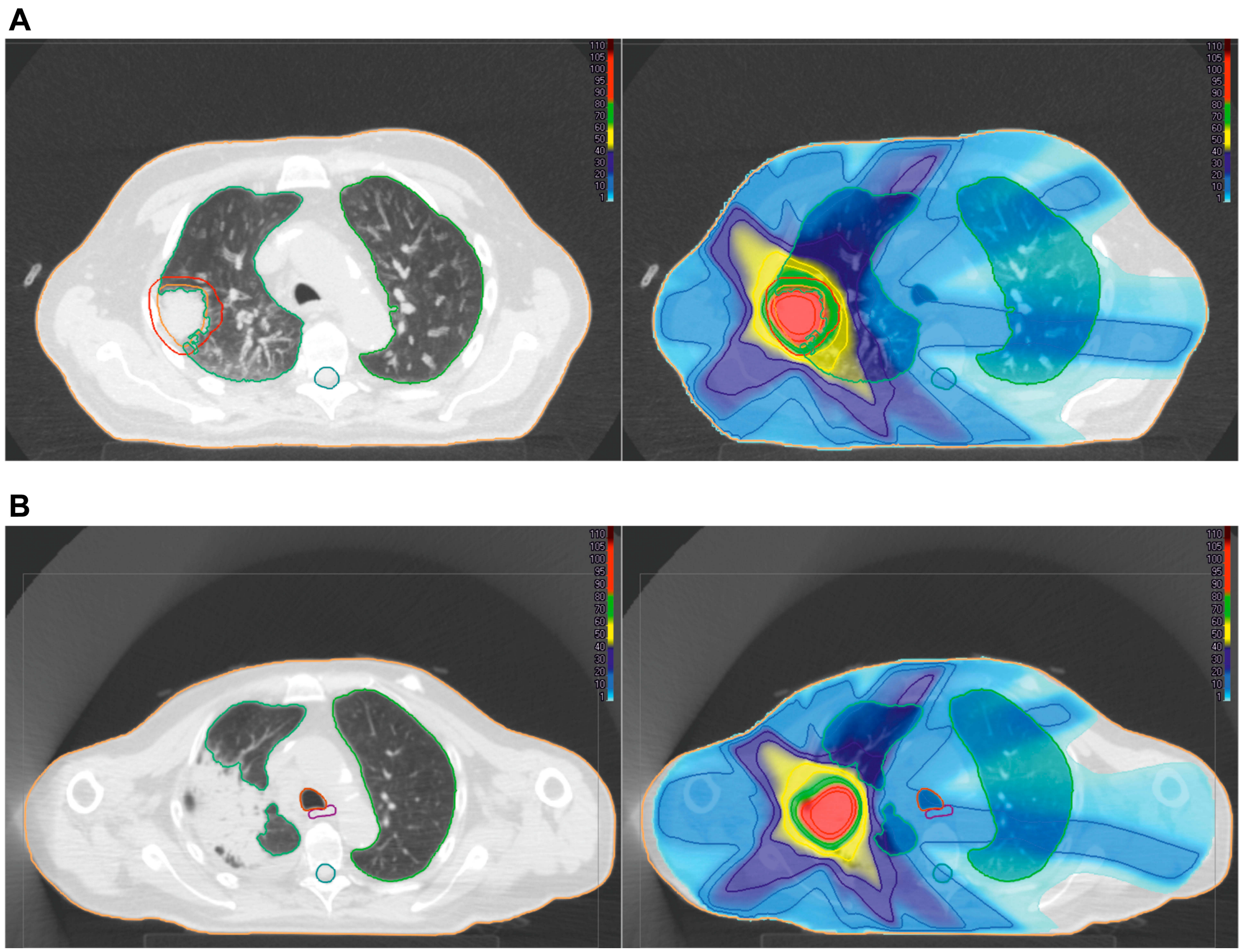

Figure 3 Radiation pneumonitis after SBRT. (**A** left): 80-year-old patient with histologically proven non-small cell lung carcinoma (within the red contour). Planning target volume (red contour) and organs at risk: Total lung (green), spinal cord (turquoise). (**A** right): Treatment plan (IMRT-technology, 9 Gy in 5 fractions, total dose 45.0 Gy): Isodose lines (% of total dose) and the dose distribution, high-dose region surrounding the tumour (red, green), step down gradient (yellow, dark blue). The low-dose region is highlighted in blue. Using IMRT, the lung volume receiving low doses is less compared to VMAT (**B** left): Consolidative changes after SBRT, suspect of tumour progression, but radiation pneumonitis was retrospectively diagnosed. (**B** right): A deformable image registration was used to correlate the lung changes on follow-up CT-scan with radiation dose distribution. The changes are highly conformal to the high-dose region.
Abbreviations: IMRT, intensity-modulated radiotherapy; VMAT, volumetric modulated arc therapy.

Because of differences in the classification systems, a specific comparison of acute CT changes among the studies is difficult and incidences may differ:[21] Kimura et al[22] reported incidences of 38.5% (dc), 15.4% (pc and GGO), 11.5% (dGGO), 2.0% (pGGO) and 32.6% (no changes), whereas the incidences reported by Dahele et al[17] were 16% (dc), 24% (pc), 7% (dGGO), 6% (pGGO) and 46% (no changes). The majority of patients have consolidative patterns, GGO is less common and the overall incidence of acute changes is approximately 60%.[20] Due to the dose distribution, these changes correspond to the shape of the tumour and it could be difficult to distinguish those benign findings (Figures 1B, 2B, and 3B) from early local recurrence, especially in cases of diffuse or patchy consolidation.[15] Six months after SBRT, the late stage begins, and CT changes appear as radiation fibrosis.[15] The morphology may change over the years.[17]

Acute RP is shown in Figures 1B, 2B, and 3B. We used a deformable image registration (Figure 1C, right) to correlate the lung changes with the radiation dose distribution. The changes are conformal to the high- and mid-dose region. A rigid registration cannot account for lung volume and tumour position changes on follow-up CT-scans (Figure 1C, left).[23] The deformable image registration is more accurate than the rigid registration and the images correlate well with each other.

Impact of Irradiation Technology

The technical-physical progress of radiation oncology led to distinct changes of dose distribution in patients.

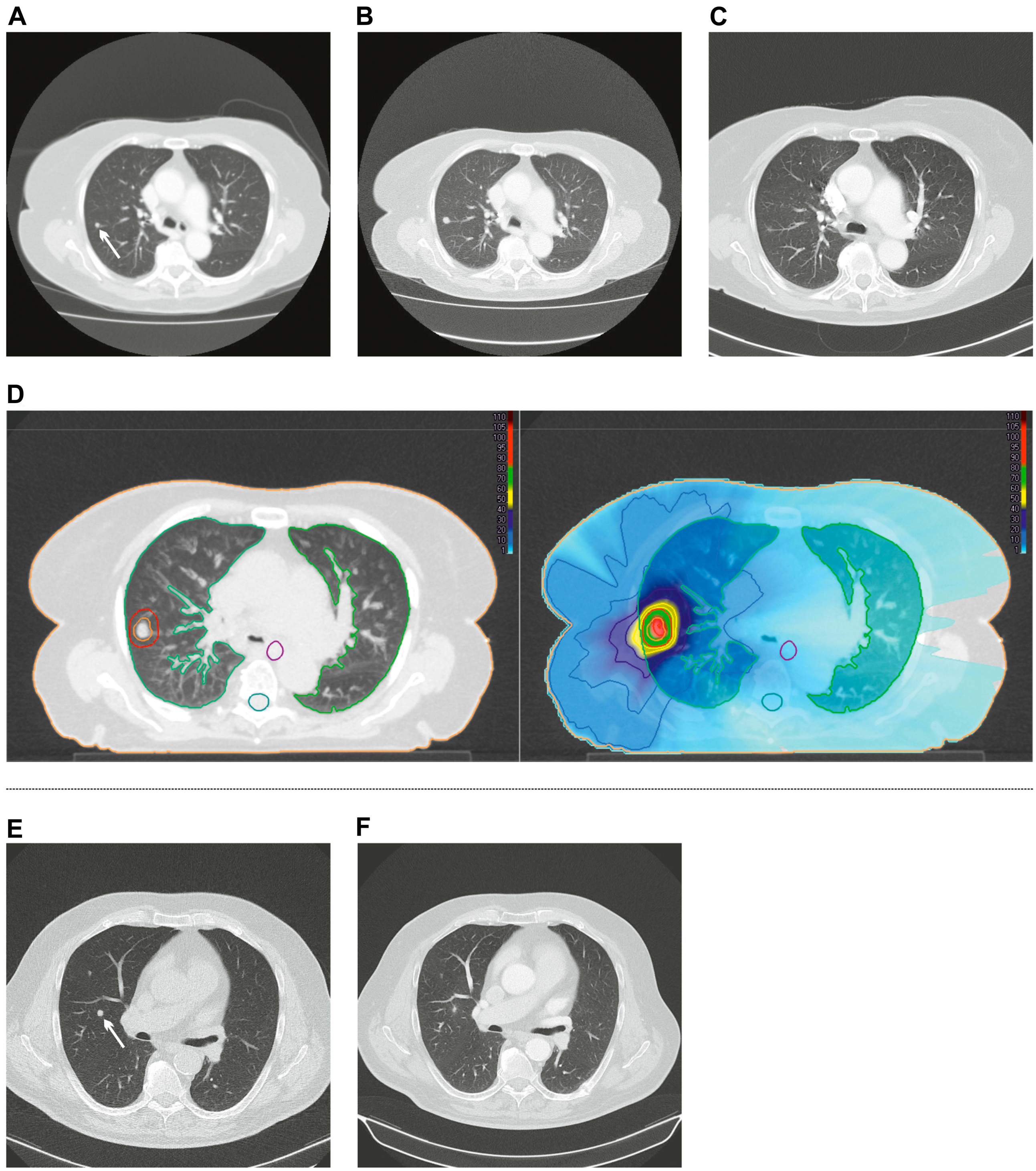

Figure 4 Local control after SBRT. (**A**–**D**): (**A**): 86-year-old woman with a metachronous (5 mm) lung metastasis of colon carcinoma (white arrow). Due to the age, no histological verification was done. (**B**): Follow-up after 3 months. Increase in size to 8 mm, decision for SBRT. (**C**): Tumour response 3 months after SBRT, size decrease by 2 mm, no evidence of radiation pneumonitis. (**D** left): Tumour within the planning target volume (red contour) and organs at risk: Total lung (green), spinal cord (turquoise) and oesophagus (violet).(**D** right): Treament plan: High-dose region surrounding the tumour (red, green), step down gradient (yellow, dark blue), and a large low-dose region highlighted in blue. The patient was treated with a dose of 15 Gy in 3 fractions (total dose 45.0 Gy). (**E** and **F**): Another patient treated with SBRT (7.5 Gy in 8 fractions, total dose 60.0 Gy) for lung metastasis of colon carcinoma (white arrow) had tumour response on follow-up at 3 months after SBRT. No radiation pneumonitis.

Volumetric modulated arc therapy (VMAT, Figures 1A and 2A) improves treatment time by quick dose application, but it tends to increase the volume of normal lung tissue receiving low doses compared to other techniques.[24] Besides VMAT, older techniques such as three-dimensional conformal radiotherapy (3DC-RT) and

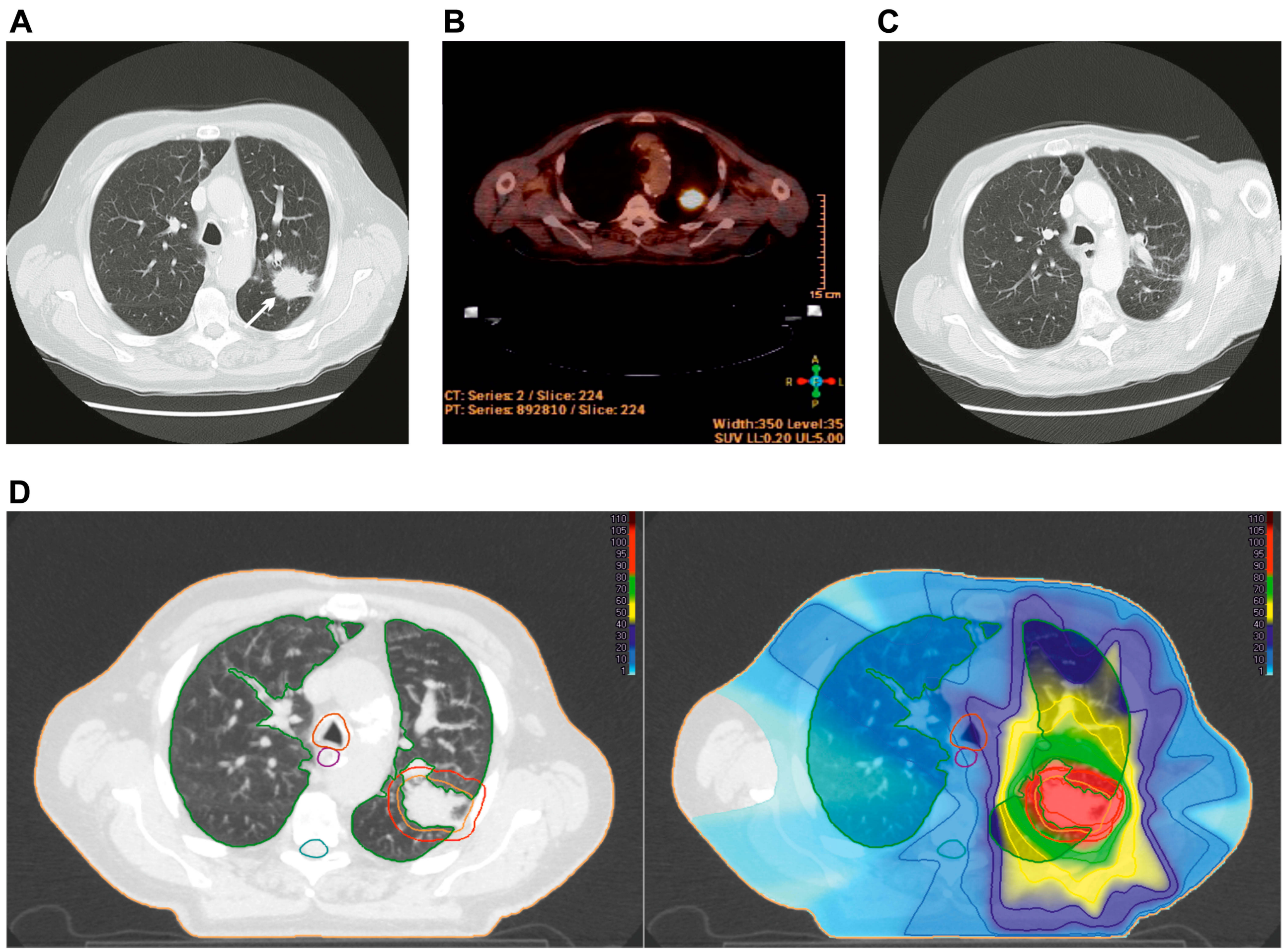

Figure 5 Local control with discreet radiation pneumonitis. (**A**): 78-year-old patient with histologically confirmed non-small cell lung carcinoma (white arrow). Size about 30 mm. (**B**): PET/CT for treatment planning. SUVmax = 14.94. (**C**): Tumour response 3 months after SBRT. Discreet radiation pneumonitis. The patient was asymptomatic. (**D** left): Tumour within the planning target volume (red contour) and organs at risk: Total lung (green), spinal cord (turquoise), oesophagus (violet) and trachea (orange). (**D** right): Treatment plan (IMRT-technology, 12 Gy in 5 fractions, total dose 60.0 Gy): Isodose lines (% of total dose) and the dose distribution, high-dose region surrounding the tumour (red, green), step down gradient (yellow, dark blue), and a large low-dose region highlighted in blue.
Abbreviation: IMRT, intensity-modulated radiotherapy.

"step-and-shot" intensity-modulated radiation therapy (IMRT, Figure 3A) are in use.[21] A dose distribution highly conformal to the tumour can be achieved (Figure 4D), but because of the differences in dose distribution, different patterns of radiological changes might result.[14] To investigate this assumption, Palma et al[21] compared patterns of acute RP after SBRT with VMAT and 3DC-RT, and they evaluated the severity of clinical RP according to CTCAE v3. The authors reported acute CT changes in 43 of 75 patients (57.3%) which were mainly consolidative, but no significant difference in the pattern of CT changes between VMAT and 3DC-RT was found ($p = 0.47$). Symptomatic pneumonitis was uncommon, only 4 patients (5.3%) had grade 2 or 3 pneumonitis, and again no significant differences were found between them ($p = 0.99$). Similarly, Senthi et al[25] and Badellino et al[14] reported no differences of acute CT changes between VMAT and 3DC-RT ($p=0.23$[25] respectively $p=0.55$[14]) with low rates of severe clinical RP. In conclusion, the techniques are superimposable with low rates of severe clinical pneumonitis.

High-Risk CT Features for Detection of Local Recurrence

CT scans after SBRT are recommended for evaluating tumour response (Figures 4A–C, E, F, 5A, C, 8C, D, and 10D, F), excluding tumour progression (Figures 6A,C and 7A, B) or detecting tumour progression (Figure 10A, C, F, and G), and for detecting benign early (Figure 7C and H) and late radiological changes (Figure 7D–F). Albeit such benign changes

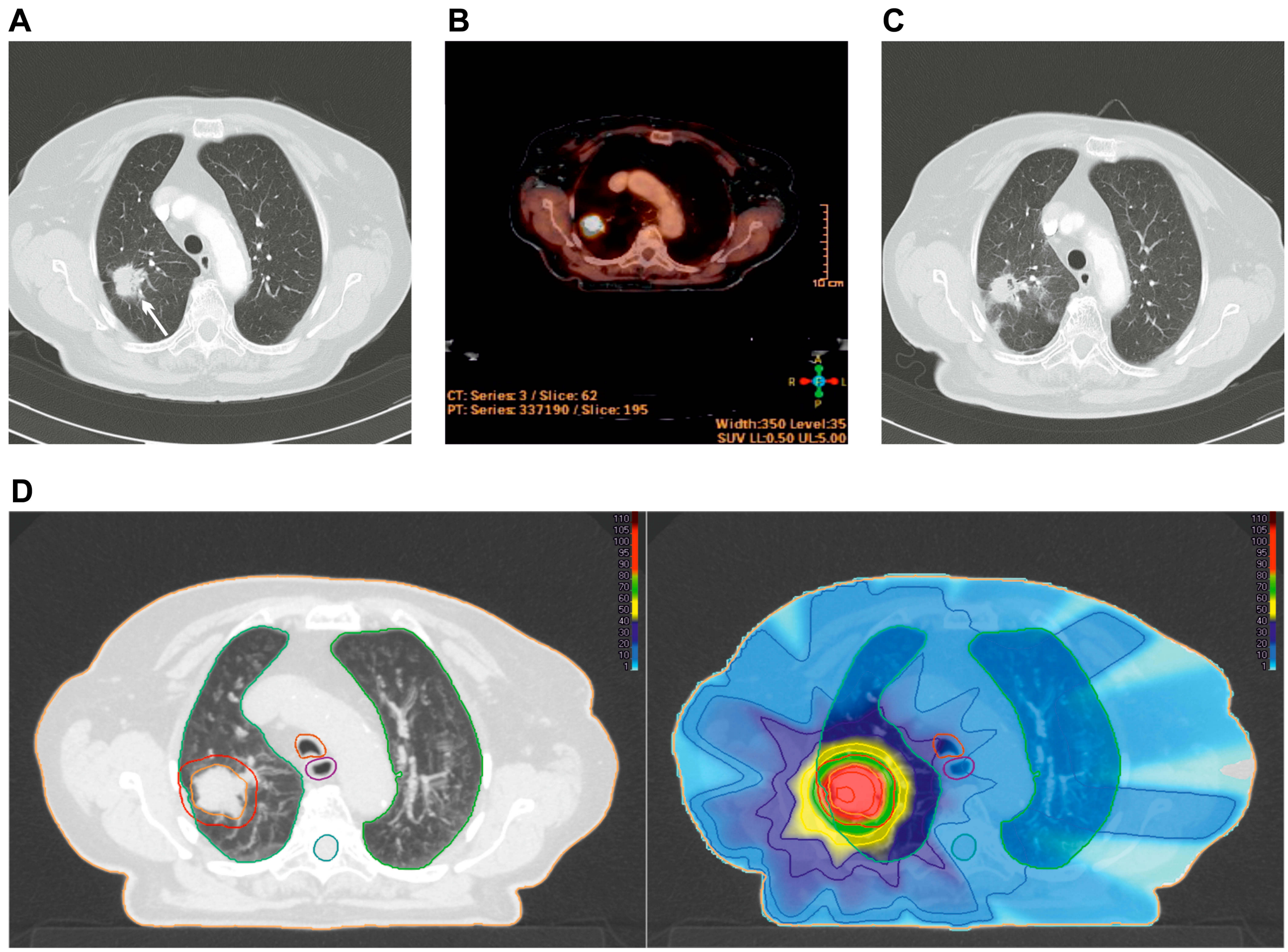

Figure 6 PET for tumour detection. (**A**): 89-year-old female patient with a tumour-related finding on a CT-scan (size 23 mm, white arrow), no histological examination was performed due to poor constitution. (**B**): PET/CT for treatment planning with a SUVmax = 17.1, suspicious of a tumour. SBRT was done. (**C**): Stable disease at 3 months with radiological radiation pneumonitis. On follow-up (at 12 months), the tumour failed to decline (data not shown). (**D** left): Tumour within the planning target volume (red contour) and organs at risk: Total lung (green), spinal cord (turquoise), oesophagus (violet) and trachea (orange). (**D** right): Treatment plan (IMRT-technology, 7 Gy in 5 fractions, total dose 35.0 Gy): Isodose lines (% of total dose) and the dose distribution, high-dose region surrounding the tumour (red, green), step down gradient (yellow, dark blue), and a large low-dose region highlighted in blue.
Abbreviation: IMRT, intensity-modulated radiotherapy.

after SBRT for lung cancer are common, local recurrence is rare.[26] With a median time of 14.9 months, only 4.9% of patients experienced local failure within 2 years.[27] In clinical practice, RECIST criteria 1.1[28] are used for response assessment, but RECIST is not reliable until 15 months post-SBRT.[29] Huang et al[20,30] reported CT findings after SBRT suggestive of recurrence and later defined as high-risk CT features (HRF), including a bulging margin, enlargement after 12 months, loss of air bronchogram, appearance of pleural effusion, linear margin disappearance, enlarging opacity, lymph node enlargement and cranio-caudal growth. The study group[30] matched 12 patients (with pathology proven local recurrence) to 24 patients with benign changes. All these factors were significantly associated with local recurrence ($p < 0.01$). The best indicators were an enlarging opacity after 12 months (sensitivity 100%, specificity 83%) and cranio-caudal growth (sensitivity 92%, specificity 83%). With an increasing number of HRFs, specificity increases and sensitivity decreases. Nevertheless, early detection is disputable. Although some of the HRFs appear 6 months after SBRT, the median time was 22 months for "enlargement after 12 months", respectively, 13 months for "cranio-caudal growth".[30] These results were validated by Peulen et al[31] and Frakulli et al.[19] Huang et al[20,30] also investigated the value of metabolic findings. A normal response is characterised by a stable SUV or a decline to background SUV after SBRT, but a transient increase of SUVmax within 6 months post-SBRT due to acute inflammation of lung tissue is also possible. Especially within the first 6 months after SBRT, recurrence should be considered not until SUVmax is greater than 5.[20] Based on these results, an imaging follow-up algorithm was proposed including the number of HRFs and a SUVmax

Table 1 Early Radiological Changes According to Radiation Pneumonitis After SBRT

Name	Description
Diffuse consolidation	Diffuse, homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls and completely fills the high-dose region. Frequently, air bronchogram can be detected within the area of consolidation, a sign that suggests that the air within affected alveoli has been replaced by exudates and cells.
Diffuse ground-glass opacity	Hazy increased attenuation of lung, with preservation of bronchial and vascular margins, that completely fills the high-dose region.
Patchy consolidation and ground-glass opacity	Patchy areas of hazy and dense increased attenuation of lung, not completely filling the high-dose region.
Patchy ground-glass opacity	Patchy areas of hazy increased attenuation interspersed in normal parenchyma, not completely filling the high-dose region.
No changes	No evidence of increased density within the high-dose region.

Notes: Data from Linda et al[15] and Kimura et al.[22]

threshold of 5.[30] This algorithm might help to detect early recurrences within 6 months, but this is ambiguous regarding the median time of appearance of the benign CT changes.

CT Texture Analysis for Distinguishing Local Recurrence from Radiation Pneumonitis

CT Density Measurements Correlate with CT Changes After SBRT

Palma et al[32] used a deformable registration algorithm for measuring early CT density changes between planning CT and diagnostic follow-up CT 3 months after SBRT for the lung (Figure 1C, right). They found a strong correlation between increased lung density changes in the peritumoral region and the severity of radiological pneumonitis ($p < 0.001$). By contrast, no correlation was found between severity of radiological pneumonitis and the whole ipsilateral lung ($p = 0.22$). In conclusion, the peritumoral region seems to be appropriate for ongoing investigation.

Appearance Measurements Is Superior to Size Measurements

As previously reported, distinguishing local recurrence from benign CT changes is feasible by identification of HRFs on post-SBRT CT, but early detection of local recurrence remains difficult. Delayed detection of local recurrence impairs the opportunities for salvage treatment options considerably. Mattonen et al[29] investigated measures of sizes (mean 3D volume and mean RECIST) and appearance measurements (mean CT density and mean standard deviation of CT density) on the CT for treatment planning and on follow-up CT. Patients were considered to have a recurrent tumour (n=11, pathology proven in n=8) or benign CT changes (n=13, non-recurrent, see[17]). Based on the results of Palma et al,[32] two regions of interest were manually contoured: the consolidative region (increased density without visibility of vessels, Figure 7C) and the ground glass opacities (increased density with visibility of vessels, Figure 7H). Before SBRT, no significant differences were found. Nine months after SBRT, patients with recurrence had significantly denser mean density changes in consolidative region than the non-recurrence patients (– 96.4 ± 32.7HU vs –143.2 ± 28.4HU, $p = 0.046$). Additional, in the GGO at that point of time, the recurrence group had a higher standard deviation of CT density (210.6 ± 14.5HU vs 175.1 ± 18.7HU, $p = 0.0078$). Significant differences in RECIST ($p = 0.028$) and 3D volume ($p = 0.03$) were found 15 months after SBRT. In conclusion, size and appearance measurement may distinguish benign CT changes from recurrence after 9 months, compared to RECIST after 15 months.

Appearance Measurements Can Predict Recurrence Within 5 Months

To validate these findings, Mattonen et al conducted an ongoing study.[13] Using the same patients again,[29] the objective of this study was to analyse the accuracy of size and appearance measurements for distinguishing local recurrence from benign CT changes. Once more, the two regions of interest were manually segmented. In the consolidative region, two measures of size (longest axial diameter/RECIST and 3D volume) were taken. A total of nine appearance features were calculated in the GGO: Two first-order texture features (FOF, mean CT density and standard deviation of CT density), and seven second-order texture features (SOF). FOFs are histogram-based features which describe the distribution of values of individual voxels without concern for relationship,[33,34]

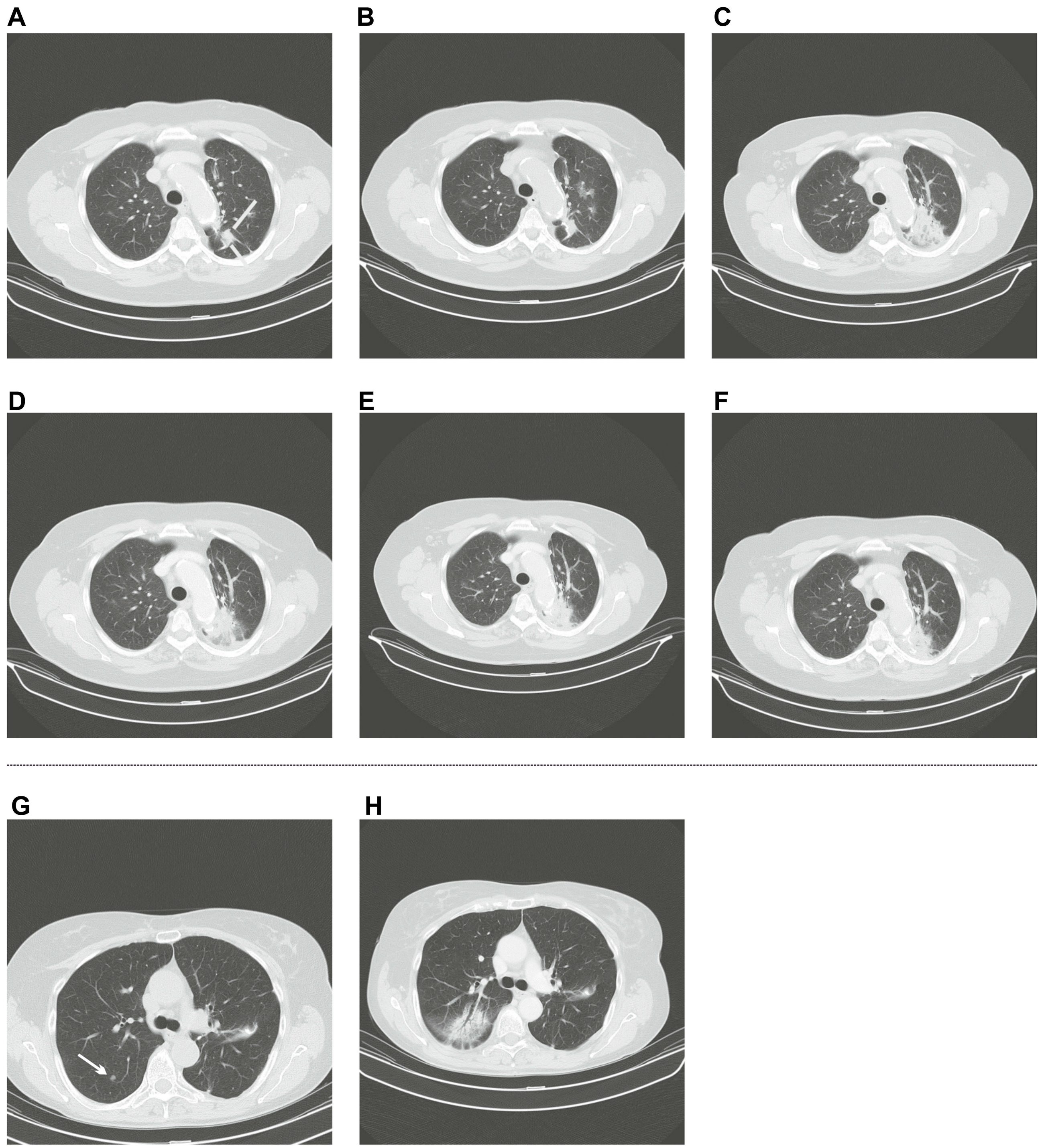

Figure 7 Radiation pneumonitis after SBRT. (**A**–**F**, see Figure 2): Consolidative changes. (**A**): A 78 years old female patient with histologically proven non-small cell lung carcinoma (white lines) was treated with SBRT, 5 Gy in 10 fractions, total dose 50.0 Gy. (**B**): Stable disease 1 month after SBRT. (**C**): Enlarging consolidative changes 5 months after SBRT, suspected tumour progression. Decision to wait. (**D-F**): The CT-changes did not change of time (**D:** 9 months after SBRT, (**E**) 12 months, (**F**) 18 months). Thus, radiation pneumonitis resp. radiation fibrosis was more likely than a recurrent tumour. (**G** and **H**, see Figure 1): Ground-glass opacities. (**G**): A 74-year-old female patient had a parathyroid carcinoma with a lung metastasis (white arrow). SBRT was performed. (**H**): A CT-scan 3 months after SBRT revealed radiographic radiation pneumonitis since ground-glass opacities were seen. No tumour detection at follow-up (images not shown). Thus, radiation pneumonitis was more likely than recurrence of a tumour.

whereas SOFs describe relationships between voxels including a grey-level co-occurrence matrix (GLCM).[33,34] To summarize within 5 months after SBRT, the FOF mean density ($p = 0.035$) and the best performing SOFs energy ($p = 0.036$), entropy ($p = 0.034$) and inertia ($p = 0.036$) were significantly different between the groups. The accuracy of SOF, FOF, 3D volume and RECIST was 77%, 73%, 60% and 57% (two-fold cross-validation). Similar findings resulted within the 5–8 months

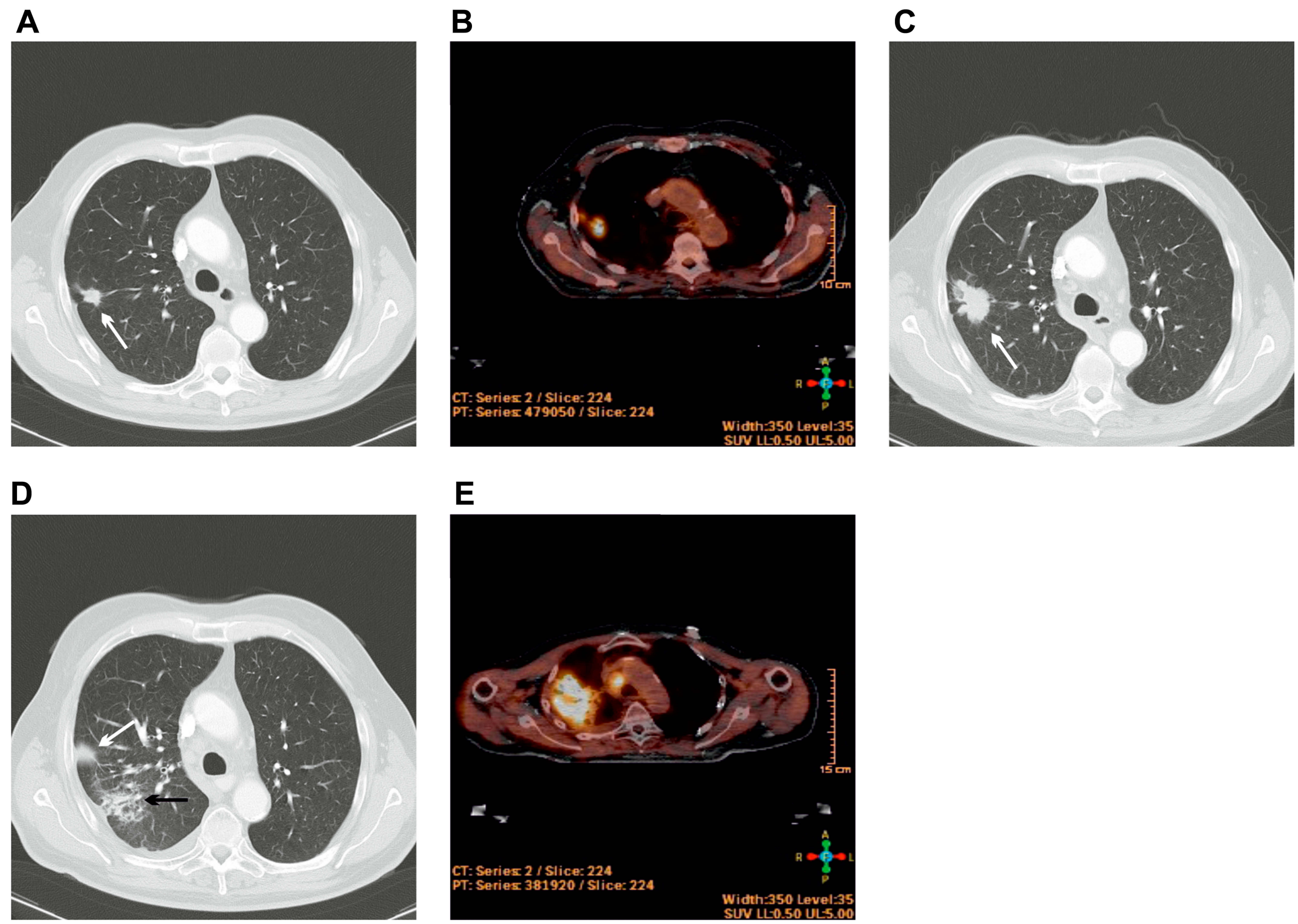

Figure 8 SUVmax persistence associated with radiation pneumonitis (see Figure 3). (**A** and **B**): 80-year-old patient with histologically confirmed non-small cell lung carcinoma (white arrow). CT (size 14 mm) and PET/CT (SUVmax = 7.56) at the time of diagnosis. Therapy was rejected. (**C**): Follow-up 1 year later, enlarging tumour mass (increase in size to 39 mm, white arrow). SBRT was performed (9 Gy in 5 fractions, total dose 45.0 Gy). (**D**): Follow-up 1 month later with radiological radiation pneumonitis (black arrow) and tumour response (white arrow, size 6 mm). (**E**): Increasing consolidation on CT at 3 months, suspect of relapse. PET/CT was performed (SUVmax = 8.27) and a biopsy was taken, but the histology was negative (no malignity). SUVmax persisted without evidence of a recurrent tumour. Radiation pneumonitis was diagnosed. (paratracheal increased metabolic activity with histologically confirmed lymph node metastasis, once again radiotherapy was performed).

interval demonstrating robustness and repeatability. In conclusion, appearance measurements can distinguish local recurrence from benign CT changes within 5 months after SBRT, and this is more accurate than size measurements.

Radiomics-Based Assessment Using a Semiautomatic Segmentation Algorithm for Distinguishing Local Recurrence from Radiation Pneumonitis

Semiautomatic Segmentation Algorithm Is Time Sparing

Radiomics describes the extraction of large amounts of image features from radiographic images and the analysis of these data for decision support.[33,35] The extracted features are calculated within a region of interest,[34] for example, the consolidative region or the GGO. In clinical practice, delineation of the consolidative regions tends to be simple, but contouring of the GGO is time-consuming and more difficult. Even though robustness to the variability of manually GGO delineation was reported,[13] delineation takes time and an interoperator variability is expected due to barely recognizable boundaries of GGO.[36] Using a semiautomatic segmented periconsolidative region, which is an expansion of the consolidative region, time can be saved. As this region intends to retrieve GGO tissue, results comparable to manually contoured GGO are achieved.[37,38]

Semiautomatic Segmentation Algorithm Allows Distinguishing Within 6 Months

Mattonen et al established a semiautomatic segmentation algorithm for early prediction of lung cancer recurrence after SBRT using second-order features.[37] First, accuracy of recurrence

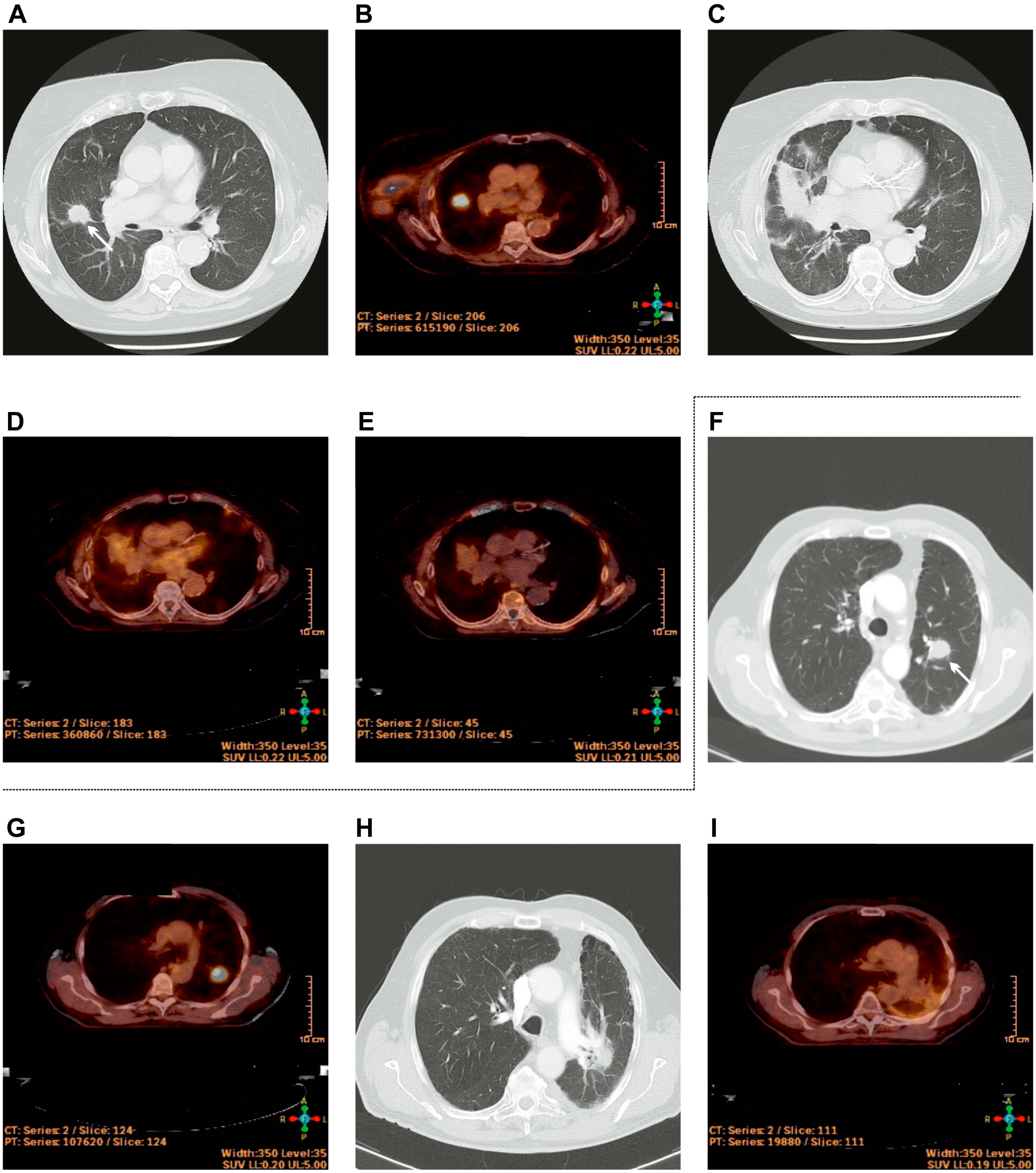

Figure 9 PET/CT for distinguishing radiation pneumonitis from local recurrence. (**A-E**): (**A** and **B**): 82-year-old female patient with histologically confirmed non-small cell lung cancer. CT (size 17 mm, white arrow) and PET/CT (SUVmax = 12.74) at the time of diagnosis. SBRT was done with a dose of 7.5 Gy in 8 fractions (total dose 60.0 Gy). (**C**): On follow-up 3 months after SBRT, a CT-scan was suspect of tumour progression (consolidative region, size 39 mm). (**D**): A PET/CT at this time point was done, SUVmax was 5.25. A biopsy was taken, but it was negative. A follow-up PET was recommended. (**E**): At 6 months after SBRT, SUVmax (= 2.25) declined. Thus, elevated SUVmax was recognized and radiation pneumonitis was retrospectively diagnosed. (**F–I**): (**F** and **G**): 80-year-old patient treated with SBRT. Lesion size was 22 mm (white arrow) and the SUVmax was 16.38. The dose was 7.5 Gy in 7 fractions (total dose 52.5 Gy). (**H**): A CT 3 months after SBRT was suspect of tumour progression and a PET was recommended. (**I**): SUVmax was 3.51 at 6 months after SBRT. A recurrent tumour resp. tumour progression was unlikely and radiation pneumonitis was diagnosed. On follow-up, the CT changes did not change (data not shown).

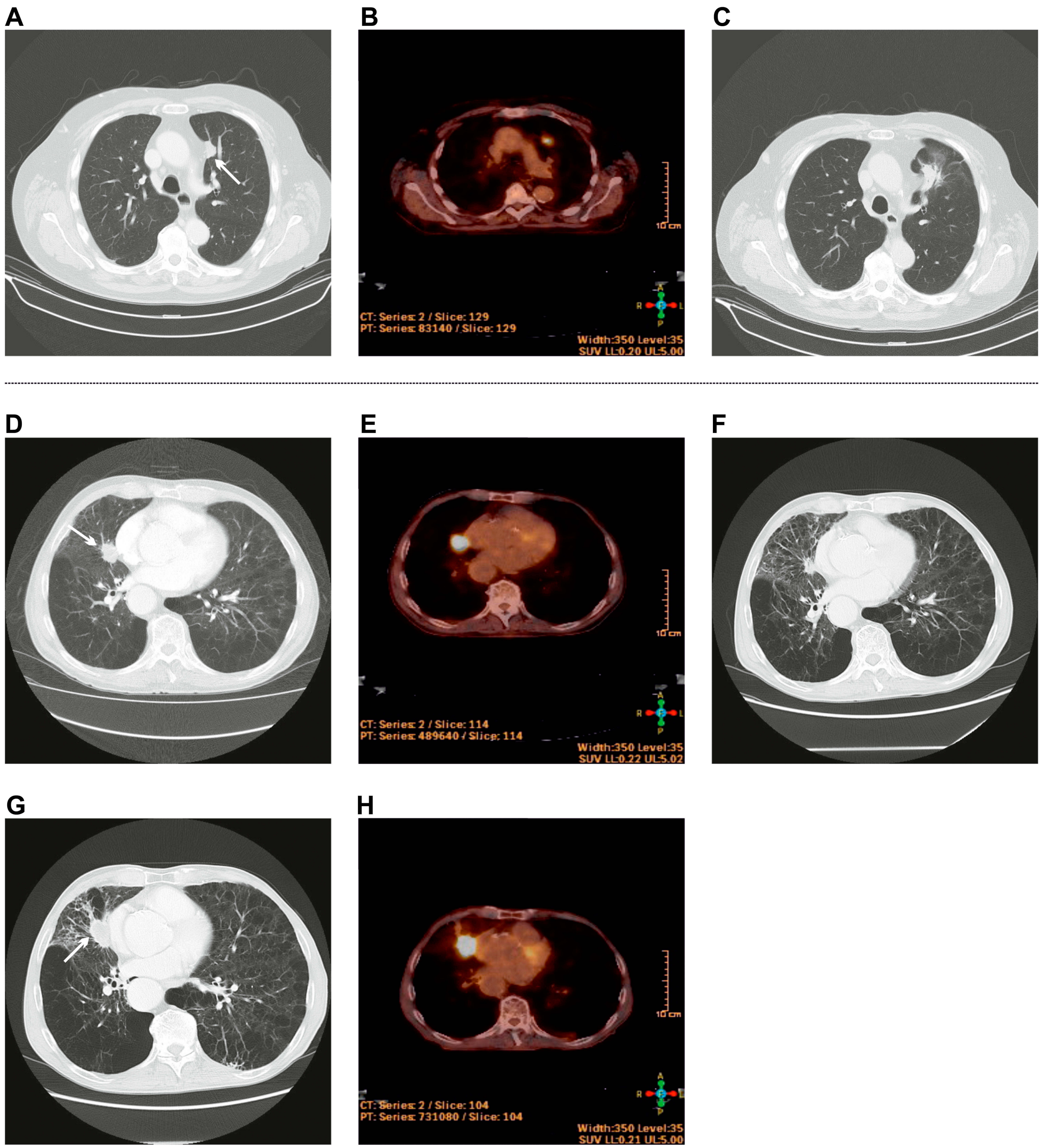

Figure 10 SUVmax persistence associated with local recurrence. (**A**–**C**): (**A**) A 79-year-old patient had a tumour-related finding on a CT (size 18 mm, white arrow). (**B**) The patient refused histological confirmation and a PET was performed. SUVmax was 7.56. (**C**) 2 months after SBRT (7.5 Gy in 7 fractions, total dose 52.5 Gy), the size increased (27 mm), and SUVmax raised to 8.01 (images not shown). Tumour progression was histologically confirmed, but the patient refused salvage treatment. (**D**–**H**): (**D** and **E**) 75-year-old patient with histologically confirmed non-small cell lung cancer. CT (size 24 mm, white arrow) and PET/CT (SUVmax = 13.75) at the time of diagnosis. The patient had a severe COPD resp. emphysema. SBRT was done with a dose of 5 Gy in 10 fractions (total dose 50.0 Gy). (**F**) Tumour response (size 17 mm), no evidence of RP. (**G**) 6 months after SBRT, new tumour growth (30 mm, white arrow) was detected and histologically confirmed. (**H**) PET/CT for treatment planning was done (SUVmax = 18.31). SUVmax failed to decline. Salvage-treatment was done.

prediction was tested[36] with a patient database previously used.[29] The longest axial diameter (RECIST) of the consolidative region was manually measured and the periconsolidative region was automatically calculated and delineated by adding a margin of 16 mm to the axial diameter. For control, manual delineation of the GGO was done. As a result,

Table 2 Modified Classification of Early Radiological Changes After SBRT

Name	Description
Diffuse consolidation	Consolidation more than 5 cm in largest dimension. The involved region contains more consolidation than aerated lung
Patchy consolidation	Consolidation less than 5 cm in largest dimension and/or the involved region contains less consolidation than aerated lung
Diffuse GGO	More than 5 cm of GGO, (without consolidation). The involved region contains more GGO than normal lung,
Patchy GGO	Less than 5 cm of GGO, (without consolidation), and/or the involved region contains less GGO than normal lung
No changes	No new abnormalities. Includes patients with tumours that are stable, regressing or resolved, or fibrosis in the position of the original tumour that is not larger than the original tumour

Notes: Data from Palma et al[21] and Dahele et al.[17]

the semiautomatic algorithm was not inferior to manually delineation, with low interoperator variability and a trend to yield better accuracy. The ongoing study[39] tested the accuracy with more patients (45 patients, local recurrence: n = 15, benign changes: n = 30, see[17,30]) and a larger radiomic feature set (22 first-order features and 22 second-order features). The physicians assessed post-treatment CT scans and were asked to decide whether a scan was suspect for recurrence or not. Median time to the first detection of recurrence was 15.5 months with a moderate level of agreement across the observers, mean error was 35%, false positive rate 1% and false negative rate 99%. Within 6 months after SBRT, the physicians were unable to detect recurrences. By contrast, the algorithm demonstrated good performance with a mean error of 24%, a false positive rate of 24% and a false negative rate of 23%. Within 6 months, radiomic assessment using a semiautomatic algorithm demonstrates excellent results, and this is superior to the physicians' ability to distinguish local relapse or pneumonitis.

Imaging Features from Pre-Treatment Planning CT and Post-Treatment First Follow-Up CT at 3 Months Correlate with Outcome

Other authors suggested a prognostic model based on a pre-treatment[40] or post-treatment CT-scan at 3 months,[41] which includes clinical data (like TNM-Stage or ECOG performance status), manually scored 2D semantic features (like pleural retraction or longest axial diameter) and comprehensive computer-derived 3D radiomic features. Dependent on their individual risk score, patients had either a high or low risk of recurrence. Recent studies validated that radiomics-based pre-treatment CT analysis[42–45] or PET/CT analysis[46] correlates with overall survival (OS) and local control (LC) respectively, local recurrence. Similar, CT-based radiomics analysis correlates with radiation pneumonitis.[47] All in all, radiomics is an emerging feature for predicting outcome after SBRT, but due to different use of first- and second-order features as well as the lack of standardized protocols, routine use in clinical practice remains difficult.

Impact of 18-FDG-PET/CT Findings

The maximum standard uptake value (SUVmax) of 18-fluorodeoxyglucose (18-FDG) is a measure for tumour glucose metabolism (Figures 5, 6, 8, 9B, G, and 10B, E) and it might correlate with prognostic features,[48] but an elevated FDG-uptake value is also associated with an inflammation like RP (Figure 8E).[49] In clinical practice lung cancer diagnosis is based on a CT scan of the chest (Figures 5A, 6A, 7A, G, 8A, 9A, F, and 10A, D), ideally proven by a biopsy, and a PET/CT is more accurate than a CT for mediastinal lymph node staging[50] and it is useful for treatment planning (Figures 5B, D and 6B, D).[51] Therefore, the staging of lung cancer should include PET/CT.[52] Otherwise, a PET/CT can help if a diagnosis of lung cancer is uncertain, especially in cases in which biopsy is not feasible due to poor constitution of the patient (Figure 6A and B).[53] After treatment, response assessment is performed using CT and RECIST criteria,[49] and a PET/CT is recommended once recurrence is suspected on a follow-up CT scan (Figures 9C, D, H, I, and 10G, H).[53] Over the last decade, several studies investigated the use of 18-FDG-PET/CT in terms of predicting tumour response, overall survival, recurrence and pulmonary toxicities like radiation pneumonitis.[8]

Relevance of Pre-Treatment SUVmax

Several studies correlated pre-treatment SUVmax (Table 3) with overall survival or local control rates. Some studies found a significant correlation,[48,54-58] but other studies did not.[52,59-61] It is noteworthy that the reported threshold of SUVmax for predicting OS or LC differs among the studies. Two meta-analyses[8,62] revealed that patients with high levels of pre-treatment SUVmax had worse overall survival ($p<0.001$) and worse local control rates ($p<0.001$), but the prognostic value remains heterogeneous due to unknown optimal SUVmax threshold.[63]

Table 3 Selected Studies Reporting on Pre-Treatment or Post-Treatment SUVmax

Study	**Main Findings**
Pre-Treatment SUVmax	
Hoopes et al[52]	Pre-SUVmax not correlated with OS or LC hypermetabolic activity may persist 2 years without recurrence
Burdick et al[59]	Pre-SUVmax not correlated with OS
Takeda et al[54]	Pre-SUVmax correlated with LC threshold: pre-SUVmax = 6 (p<0.01)
Satoh et al[60]	Pre-SUVmax not correlated with OS or LC
Clarke et al[55]	Pre-SUVmax correlated with LC/recurrence post-SUVmax correlated with LC/recurrence threshold: pre-SUVmax = 5 (p=0.0002) resp. post-SUVmax = 2
Vu et al[61]	Pre-SUVmax not correlated with OS or LC/recurrence
Takeda et al[56]	Pre-SUVmax correlated with OS or LC/recurrence threshold: pre-SUVmax = 2.55 (OS, p<0.001) resp. 3.35 (LC, p<0.001)
Kohutek et al[48]	Pre-SUVmax correlated with OS or LC threshold: pre-SUVmax = 3.0 (OS, p<0.001 resp. LC, p<0.003)
Tanaka et al[57]	Pre-SUVmax correlated with recurrence threshold: pre-SUVmax = 8.0
Chaudhuri et al[71]	Pre-SUV non-irradiated lung predicts radiation pneumonitis
Mazzola et al[58]	Pre-SUVmax predicts complete response at 6 months after SBRT threshold: pre-SUVmax = 5 (p<0.001)
Pierson et al[63]	Pre-SUVmax not correlated with outcome
Post-Treatment SUVmax	
Matsuo et al[66]	Post-SUVmax within 6 months tends to be high without indicating recurrence
Henderson et al[67]	Post-SUVmax at 12 months is slightly elevated without evidence of recurrence median post-SUVmax = 6.04 (at 2 weeks) resp. 2.80 (at 26 weeks) low pre-SUVmax might increase after SBRT within 2 weeks high pre-SUVmax commonly declines within 2 weeks after SBRT
Dahele et al[65]	Post-SUVmax reduction of 3.6 (relative 64%) correlates with tumor response
Bollineni et al[49]	Post-SUVmax (at 3 months) correlated with LC threshold: post-SUVmax = 5.0 (p=0.02)
Takeda et al[68]	Post-SUVmax (at 12 months) correlated with LC threshold: post-SUVmax = 3.2 (early image*) resp. 4.2 (delayed image*)
Essler et al[69]	Post-SUVmax (at 12 months) correlated with LC threshold: post-SUVmax = 5.48 (p=0.009)
Tyran et al[64]	Post-SUVmax (at 3 months) correlated with LC no threshold found
Pierson et al[63]	Post-SUVmax not correlated with outcome

Notes: *Dual-time-point: image registration 60 mins (early) and 120 mins (delayed) after injection of 18-FDG.
Abbreviations: SUV, standard uptake value; OS, overall survival; LC, local control; pre-SUVmax, pre-treatment SUVmax; post-SUVmax, post-treatment SUVmax.

Relevance of Post-Treatment SUVmax

Early post-treatment SUVmax (Table 3) at 3 months was investigated. SUVmax seems to be associated with local control resp. local recurrence.[49,64] For example, Huang et al[20,30] suggested an imaging follow-up algorithm that recommends salvage therapy if SUVmax is greater than five. A decrease of SUVmax is associated with tumour response (Figure 9B, E, G, and I),[65] but elevated SUV values might persist after SBRT without evidence for local recurrence (Figure 8E).[66,67] Furthermore, late post-treatment SUVmax (Table 3) at 12 months was associated with local control,[68–70] but hypermetabolic activity might persist without evidence of a recurrent tumour.[52] Once again, the reported thresholds are varying.[63]

Relevance of PET/CT for Predicting Radiation Pneumonitis

We found only one study correlating pre-treatment SUV in the non-target lung with the risk of symptomatic radiation pneumonitis following SBRT.[71] Twenty-eight patients with symptomatic RP (grade ≥ 2, CTCAE 4.03) and 57 without RP (grade 0–1) were compared. Non-target volume was defined as “total lung volume minus PTV” (total non-target lung volume), respectively, “ipsilateral lung volume minus PTV” (ipsilateral non-target lung volume). Mean lung dose (MLD) and SUV were significantly associated with the risk of developing symptomatic RP, and a model for risk stratification was proposed. Thus, SUV of non-target lung might be predictive for radiation pneumonitis.

Relevance of Metabolic Tumour Volume (MTV) and Total Lesion Glycolysis (TLG) for Predicting Radiation Pneumonitis

SUVmax is a histogram-based parameter which measures the hottest voxel in a region of interest, for example, within the region of a tumour, but it is does not correlate with its size. Thus, some authors argue that volume-based parameters like MTV and TLG might better correlate with overall survival or local control than SUVmax. The metabolic tumour volume (MTV) is the total lung volume with an SUV greater than 2.5, defined as the sum of voxels with SUV > 2.5, whereas the total lesion glycolysis (TLG) is the product of MTV and SUVmean.[72] Indeed, Takahashi et al[73] and Dosani et al[74] found that MTV and TLG are predictive for overall survival and local control, but in contrast, other studies[58,75] found no correlation. Intriguingly, Mazzola et al[58] found an increase of MTV over time. This may correlate with the inflammation of the lung parenchyma after SBRT. In conclusion, predicting tumour control is ambiguous, but MTV might be predictive for radiation pneumonitis.

Limitations of PET/CT

National guidelines recommend a PET/CT for tumour staging (for example, the United States NCCN guideline or the German S3-guideline of non-small-lung-cancer) since elevated SUVmax is suspect of malignity. PET/CT for predicting radiation pneumonitis after conventional radiotherapy is well investigated,[71] and PET/CT might be useful for response assessment following SBRT, but some limitations must be discussed. SUVmax associated with local recurrence may fail to decline (Figure 10H),[20] but high post-treatment SUVmax (mean SUVmax = 4.9 at 6 months) without evidence of recurrence (Figure 8E) was reported,[66] and metabolic activity (range SUVmax 2.5–5.07) might persist (Figure 9I).[52] Furthermore, transient increase due to radiation pneumonitis which disappeared after complete remission was also reported.[20] Thus, elevated post-SBRT SUVmax should not be considered for local treatment failure.[67] Otherwise, if a follow-up CT-scan (Figure 9C) is suspicious for recurrence and post-SBRT SUVmax is greater than 5 (Figure 9D),[30] respectively, pre-treatment SUVmax was low and post-SBRT SUVmax is less than five,[20] a recurrent tumour could be considered.[20,30] Moreover, pre- or post-treatment SUVmax might be correlated with overall survival and local tumour control, but the reported thresholds of SUVmax differ among the studies. That is why some authors argue to interpret PET imaging findings for 2 years after SBRT carefully,[64] and a follow-up PET/CT is not recommended for response assessment.[53] One major reason for these differences might be the lack of standardization of obtaining the SUVmax.[63] The studies[48,49,52,54–60,65–67] reported several PET-protocols with regard to the use of different PET-scanner, fasting time before injection of 18-FDG (4−6 hrs), blood sugar concentration (<140–<200 mg/dl), activity of 18-FDG (3–6 MBq) and waiting time between injection and image registration (40–60 mins). The result is poor agreement between the studies.[76]

Impact of Dosimetric Factors for Predicting Radiation Pneumonitis

BED Greater Than 100 Archives Local Control

Among others, the therapy planning has two goals. On the one hand, the prescribed dose should cover the planning target volume (PTV), on the other hand, the dose constraints of the organs at risk (OAR) should be respected. To compare different dose schedules, the biologically effective dose (BED) based on the linear quadratic model is used.[77] Although this model might be inappropriate in radiosurgery,[78] a BED (α/β-ratio = 10, BED_{10}) higher than 100 Gy prescribed to the encompassing isodose is recommended in several national guidelines[77,79] to archive local tumour control. In most studies, the majority of patients were treated with a $BED_{10} > 100$ Gy[79] resulting in good local control.

Dosimetric Factors Predicting Radiation Pneumonitis After SBRT

The tissue and organs have different tolerance towards radiation-induced injury. Beside the PTV, a biologically based classification system was suggested which defines the deterministic risk volume (DRV) and the stochastic risk volume (SRV). The DRV is exposed to doses which exceed a specific tolerance to radiotherapy without resulting in compulsory side effects. These are the organs at risk. Above a specific dose threshold, side effects develop, and the extent of damage increases with increasing doses. In the SRV, a specific threshold does not exist, and a minimal dose might result in side effects. The damage probability increases with the doses, mainly resulting in tumour induction.[24] By optimizing the treatment plan, side effects can be minimized. Several studies (Table 4) attempted to find risk factors for predicting symptomatic radiation pneumonitis (grade $\geq$ 2, CTCAE) with focus on volume and dose of SBRT like the PTV, MLD (mean lung dose) or V20 (percentage of lung volume exceeding 20 Gy). Age, gender, tumour location and dose scheme do not correlate with radiation pneumonitis,[6,80-82] confirmed by a pooled analysis of the literature.[83] Regarding the dosimetric factors, the results are controversial. The studies (Table 4) reported variable correlations between the risk of RP and several dosimetric factors. The pooled analysis[83] showed that MLD and V20 were significantly correlated with the risk of RP, but the study group failed to ascertain specific dose constraints. The underlying causes could be differences in target definition (like planning target volume) or lung volume definition (whole or ipsilateral lung volume) and the use of different algorithm for dose calculation.[83] Furthermore, using different number of fractions and dose, one would expect different biological effects,[83] although the dose scheme was not correlated with RP.[82] A meta-analysis[16] could show a relationship between the dosimetric factors and symptomatic RP, and several dose constraints were reported, but the authors suggest to conduct more studies for clarification. However, it is worth mentioning that a 4D-CT for treatment planning,[82] cone beam CT, real-time tumour tracking[84] and respiratory gating[85] might reduce the risk of severe RP. In conclusion, different dose schemes gain comparable local control rates, and dosimetric factors with focus on volume and dose are predictive for RP, but specific dose constraints are lacking, and further studies are needed to clarify.

Impact of Patient-Based Specific Risk Factors

Clinical Parameters

As reported above, age, gender and the location of the tumour (central or peripheral, upper or lower lung) are usually not associated with an increased risk of radiation pneumonitis. The concurrent use of angiotensin-converting enzyme inhibitor might reduce the risk of RP.[86,87]

Tumour Size

With increasing tumour size, the lung volume receiving low doses extends. Thus, it is expected that larger tumours are associated with worse local control and higher incidences of severe radiation pneumonitis.[88] However, the literature is controversial. Tumours above 5 cm diameter[7] had a lower 1-year local control rate (>5 cm 79.8% vs <5 cm 98.2%, $p=0.01$), but other studies[89,90] suggested similar local control rates using the same threshold. Similarly some studies correlated radiation pneumonitis with T-stage ($p=0.031$), respectively, tumour size,[6] albeit other studies found no correlation.[7]

Pre-Existing Pulmonary Injury and Serum KL-6 Level

Chronic obstructive pulmonary disease (COPD) is not correlated with RP (Figure 10D), and SBRT might be a treatment option for operable patients with higher risk for pulmonary toxicity following surgery.[91] Patients with interstitial lung changes (IC) have a higher risk for idiopathic pulmonary fibrosis (one of the seven idiopathic interstitial pneumonias) as IC is one of the major criteria for diagnosis (American Thoracic Society and European Respiratory Society 2002). Thus, patients with IC might have a higher risk for RP following SBRT. Indeed, Yamashita et al[92] reported a high incidence of severe RP (grade $\geq$ 4) in patients with IC ($p < 0.0001$) and high levels of KL-6 (Krebs von den Lungen-6, $p < 0.0001$). KL-6 is a glycoprotein which is indicative of

Table 4 Selected Studies Reporting on Dosimetric Factors for Predicting Symptomatic Radiation Pneumonitis

Study	PTV	MLD	V20	CTCAE Grade	Incidence, Median Time to Onset of RP
Guckenberger et al[80] no specific threshold	(+) p=0.02[a]	(+) p<0.05[a] (IL)	(+) p<0.05[a]	≥ °2	°0-1: 81.3% °2: 16% median time 5 months
Takeda et al[81] no specific threshold	(-) p=0.84[a]	(-) p=0.81[a] (TL)	(-) p=0.49[a]	°0-2 vs °3	°0-1: 79% (°0: 27.2%, °1: 51.8%) °2: 15.8% °3: 5.2% median time 4.3 months (°1-2) and 2.2 months (°3)
Matsuo et al[98] Threshold PTV: 37.7mL (11.1% vs 34.5% for ≥ 2°) Threshold V20: 5.8% (15% vs 42.9% for ≥ 2°)	(+) p=0.02[b]	(-) p=0.11[b] (TL)	(+) p=0.03[b]	°0-1 vs ≥ °2	°0-1: 79.7% °2: 18.9% °3: 1.4% median time 4.5 months (°2-3)
Barriger et al[99] Threshold MLD: 4 Gy (4.3% vs 17.6% for ≥ °2) Threshold V20: 4% (4.3% vs 16.4% for ≥ 2°)	(-) p=0.18[b]	(+) p=0.02[b] (TL)	(+) p=0.03[b]	°0-1 vs ≥ °2	°0-1: 90.8% (°0: 83.2%, °1: 7.6%) °2: 6.8% °3: 2.0% °4: 0.4% median time 8.4 months (°1) and 3.5 months (°2-4)
Bongers et al[100] Threshold MLD: 3.6 Gy	n.r.	(+) p=0.006[a] (CL) p=0.02[a] (TL)	n.r.	°0-2 vs ≥ °3	°3: 10% median time 6 months (°3)
Kanemoto et al[6] no specific threshold	(+) p=0.037[a]	n.r.	(+) p=0.02[a]	°0-1 vs ≥ °2	°0-1: 87.0% (°0: 21.2%, °1: 65.8%) °2: 11.3% °3: 1.7% median time 4.2 months (°1) and 2.5 months (°2-3)
Kim et al[82] Threshold PTV: 14.35 mL (8.6% vs 27.0% for ≥ °2)	(+) p=0.042[b]	(-) p=0.541[b] (TL)	(-) p = 0.222[b]	°0-1 vs ≥ °2	°0-1: 81.9% °2: 15.3% °3: 2.8% median time 3.5 months (°2-3)
Parker et al[7] Threshold TL MLD: 5.1 Gy (6.1% vs 26.9% for ≥ °2) Threshold TL V20: 6.7% (5.6% vs 25.8% for ≥ °2) Threshold IL MLD: 8.6 Gy (5.6% vs 26.7% for ≥ °2) Threshold IL V20: 14.9% (5.6% vs 27.6% ≥ °2)	(-) p=0.37[a]	(+) p=0.02[a] (TL) p<0.01[a] (IL)	(+) p=0.02[a] (TL) p=0.01[a] (IL)	°0-1 vs ≥ °2	°0-1: 90.8% (°0: 43.4%, °1: 47.4%) °2: 6.9% °3: 2.3% median time 3.5 months (°2-3)

Notes: (+) significant, (-) not significant, [a]p value based on comparison of the CTCAE-groups (column 5), [b]p value based on the reported threshold (column 1).
Abbreviations: n.r., not reported; TL, total lung; IL, ipsilateral lung; CL, contralateral lung; RP, radiation pneumonitis.

interstitial pneumonia. Raised serum levels are found in cases with activated interstitial pneumonia.[18] Subsequent studies[93] suggested that patients with IC were at higher risk for RP, and this was correlated with worse overall survival. Dosimetric factors of the IC-patients were not different from those of the non-IC-patients (nIC, $p > 0.1$). Yoshitake et al[94] validated these results: The cumulative incidence of RP (grade ≥ 2) at 6 months was 44.4% compared to 4.1% in patients without IC (p<0.0001). Overall survival at 2 years was worse (IC-patients: 49.6% vs nIC-patients: 86.7%, p = 0.0005). IC-patients had higher levels of KL-6 ($p < 0.001$), and dosimetric factors were not significantly different between the two groups (MLD p = 0.571 and V20 p = 0.698). However, patients had a significant higher risk of RP when KL-6 was greater 600 U/mL (IC: 83.5% vs nIC: 25.0%, p = 0.017) and when MLD was greater 4 Gy (70% vs 12.5%, p = 0.038). V20 did not correlate with an increased risk of RP (p = 0.210).[94] In conclusion, patients with high levels of KL-6 and interstitial changes may develop severe radiation pneumonitis. They should not receive SBRT,[18] and if not possible, these patients should be carefully monitored after SBRT.[95] Detection of interstitial changes can avoid lethal radiation pneumonitis (grade 5).[91]

Conclusions

Radiation pneumonitis (Figures 1–3) is one of the most common toxicities following SBRT for lung cancer, and more than 50% of the patients have corresponding radiological findings, but they are usually asymptomatic. By contrast, local recurrence is less common as local control rates are good (Figures 4 and 5). Nevertheless, distinguishing radiation pneumonitis (Figures 7–9) from early local recurrence (Figure 10) is challenging. In particular, Figure 9 shows that a CT with findings suspect of a recurrent tumour is not necessarily associated with relapse. Promising data were reported by Mattonen et al. They established a semiautomatic algorithm for distinguishing local recurrence from benign CT changes within 6 months. The use of radiomics improved the results, but since standard proceeding protocols are lacking, the routine use in clinical practice remains difficult. Furthermore, various studies investigated the utility of SUVmax. In general, PET/CT is useful for tumour detection (Figure 6) and higher values of SUVmax are associated with worse local control, but elevated values of SUVmax following SBRT are correlated with recurrence (Figure 10) as well as with radiation pneumonitis (Figure 8). Due to the lack of standardization of PET-CT-scans, an optimal threshold of SUVmax could not be found yet. Since SBRT induces vascular damage in addition to DNA-double-strand breakages,[96] some authors argued to use hybrid PET and CT perfusion imaging.[3,97] CT perfusion imaging is a dynamic contrast-enhanced CT technique which correlates with tumour angiogenesis and microvessel density[97] and may observe the destruction of blood vessels.[3] Unfortunately, studies are rare. Dosimetric factors might be better to avoid radiation pneumonitis or recurrence. Optimizing the treatment plan, the risk of radiation pneumonitis might be reduced, and at the same time, good local tumour control can be achieved, but specific dose constraints are missing. One major problem is the retrospective nature of the reported studies and the used patient database. Histological verification of tumour is inconsistent, and definition of tumour recurrence varies among the reported studies. This might result in selection bias. In summary, we found promising data to predict local recurrence or radiation pneumonitis, but this data remains controversial. This underlines the need for prospective randomized trials. Ongoing studies might improve the reported findings. However, radiation pneumonitis is common, and local recurrence is rare. For decision-making, patients who are suspected of a recurrent tumour should be introduced at the interdisciplinary tumour conference, which should be attended by radiologists and surgeons as well as haematology oncologists and radio oncologists.

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Disclosure

The authors report no conflicts of interest in this work.

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