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Medical applications of ionising radiation for the diagnosis and treatment of coronavirus-associated lung disease

Statement by the German Commission on Radiological Protection

Adopted at the 310th meeting of the German Commission on Radiological Protection on 9 and 10 February 2021

The German original of this English translation was published in 2021 by the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety under the title:

Strahlenanwendungen in der Diagnostik und Therapie von COVID 19

Stellungnahme der Strahlenschutzkommission

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Preface

Since the start of the global pandemic, a number of publications have suggested using ionising radiation to diagnose or treat a COVID-19 infection. Some proposals call for the use of computed tomography (CT) to screen for presymptomatic SARS-CoV-2-infections, while others suggest radiotherapy to treat COVID-19 pneumonia.

With these proposals in mind, the German Commission on Radiological Protection (SSK) agreed during its 307th meeting on 2 and 3 July 2020 to establish a working group aimed at evaluating the use of ionising radiation in connection with a COVID-19 infection. The working group focussed on radiological protection aspects with a view to using computed tomography to diagnose COVID-19 and when using radiotherapy to treat a COVID-19 pneumonia.

The group started its work on 5 October 2020. Although not commissioned by the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU), representatives of the BMU and the Federal Office for Radiation Protection (BfS) were involved in the consultations.

The working group established to draw up this document, approved by the SSK on 10 February 2021, consists of the following members:

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1 Introduction

The global pandemic due to the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) virus at the beginning of 2020 has had a profound effect on medicine and society. Some of the medical responses to the threat posed by the coronavirus disease (COVID-19), caused by SARS-CoV-2, have a relevance for radiation protection. This has led to conflicting suggestions concerning the use of ionising radiation, chiefly computed tomography (CT) to diagnose a SARS-CoV-2 infection and for follow-up of COVID-19 and radiotherapy to the lungs to treat severe COVID-19 pneumonia.

Given the large number of individuals potentially affected and the potential magnitude of the ionising radiation exposures the German Commission on Radiological Protection (SSK) has deemed it necessary to issue a statement on these two usage scenarios from a radiological protection perspective. Following a review of the available, albeit preliminary, evidence this statement presents the advantages and disadvantages involved in the use of radiation for the diagnosis and treatment of a SARS-CoV-2 infection or COVID-19 illness, along with recommendations to ensure adherence to radiological protection conventions.

2 Statement of the SSK

The SSK issues the following statement:

- The use of CT in asymptomatic persons[1] to diagnose COVID-19 outside of approved studies is not evidentially justified.
- Pursuant to Section 83 (3) of the German Radiation Protection Act (StrlSchG 2017), a CT scan for the diagnosis or follow-up of a COVID-19 pneumonia requires the prior justifying indication from a doctor with the requisite specialist knowledge in radiation protection. To this end, specialist medical associations provide recommendations based on up-to-date findings.
- Given the high radiation exposures involved, and their subsequent risks to long-term health, and in view of the ambiguous pre-clinical and clinical evidence currently available, the SSK does not deem it justified to use radiotherapy to treat a COVID-19 pneumonia, nor is there sufficient evidence to support an attempted individual treatment.
- A COVID-19 pneumonia treatment involving ionising radiation should only be carried out within an approved clinical study that requires a licence as mandated by Section 31 of the German Radiation Protection Act (StrlSchG).
- Any approved use of ionising radiation for COVID-19 patients requires the appropriate radiation protection measures, but measures to protect staff against infection must be implemented to ensure that medical radiotherapy resources remain available for other indications, e. g. diagnosis of other serious illnesses and cancer treatments.

[1] For the purpose of this statement, the term ‘asymptomatic’ refers to a SARS-CoV-2 infection without symptoms. The term ‘asymptomatic’ is not used in the sense of the definition provided in Section 5(16) of the German Radiation Protection Act (StrlSchG), except in Section 4 entitled ‘Legal requirements’.

3 Scientific background

3.1 Coronavirus pandemics

Coronaviruses are a large and widespread family of RNA viruses that largely infect the epithelium of the gastrointestinal tract. Each coronavirus species has an affinity to a specific mammalian host, such as dogs, bats or pigs. However, the viral genome's inherently high mutation rate makes it capable of adapting to new host species. This inherent genetic variability and the resultant swift development of mutated coronavirus strains are beneficial to the survival of the virus. These factors also play a part in evading the host's passive (intrinsic) immune response and in limiting adaptive immune responses to infection or vaccination. Mutated variants of the SARS-CoV-2 virus with increased transmissibility were confirmed recently (Plante et al. 2020).

Close human contact with domesticated and wild animals carrying coronaviruses has led to a series of zoonotic infections. In recent years, coronaviruses transmitted from animal hosts to humans have caused prolonged but localized epidemics in human populations. The first reported epidemic, the Severe Acute Respiratory Syndrome (SARS) outbreak, occurred in 2002 and resulted in over 8,000 deaths in 26 countries (WHO 2003). It is assumed that humans were infected by virus from the Asian palm civet, which had been infected by a coronavirus initially endemic to bats. A second coronavirus epidemic, the Middle East Respiratory Syndrome (MERS) outbreak, occurred in 2004 with camels identified as the probable intermediate host between bats and humans. In this instance, the outbreak has been limited to infections in the Arabian Peninsula, with fewer than 3,000 deaths reported (Chafekar and Fielding 2018). Since the initial outbreaks were reported the SARS virus appears to have disappeared, while MERS virus sporadically resurface in the Gulf region. Forecasters have predicted that increasing globalisation would lead to further coronavirus outbreaks, and this has now proven to be the case with the current COVID-19 pandemic (Fan et al. 2019). Although the primary and intermediate hosts of SARS-CoV-2 have yet to be unequivocally confirmed, the disease is likely to have originated in bats.

SARS-CoV-2 has proven to be highly efficient in colonising the epithelial cells of the human respiratory tract and infection is associated with significant morbidity. The spread of the disease is facilitated as further virus transmission may occur around two days before the onset of symptoms. COVID-19, the disease at the centre of the current pandemic, typically manifests as inflammation of the upper respiratory tract along with a dry cough and fever, and often accompanied by neurological symptoms such as loss of smell and taste. While some cases only suffer mild symptoms, others deteriorate and develop severe symptoms that include life-threatening interstitial pneumonia. These severe cases require intensive care and/or ventilation. In such severe cases the disease typically progresses in multiple phases, where symptoms in the upper respiratory tract may improve for a time before symptoms of pneumonia – chiefly respiratory distress – appear on around the seventh to tenth day of illness.

COVID-19 has been shown to not only affect the respiratory tract and lungs, it may also involve damage to the central nervous system and cardiovascular system, the gastrointestinal tract and the blood vessels. Fatal cases, often present with lymphopenia, thrombosis in terminal vessels, myocarditis, and a dysregulated immune response with a 'cytokine storm' damaging multiple organs (Kniep et al. 2020, Dodt and Schneider 2020, Hemmer et al. 2020).

The World Health Organization (WHO) declared the epidemic a pandemic on 11 March 2020. The high infection rate has overwhelmed the health systems in a number of countries. As of February 2021, the WHO has registered a cumulative total of 106 million cases and 2.3 million

deaths worldwide since the start of the COVID-19 pandemic. The latest figures for the pandemic are available on the WHO website[2] (WHO 2020b).

Germany has registered approximately 2.3 million cases and around 62,000 deaths as of the beginning of February 2021. Current and past figures for the pandemic in Germany are available on the Robert Koch Institute website[3] (in German) (RKI 2020).

Despite expectation that protective measures and vaccinations will slow the spread of the virus over the coming months, it must be taken into account that new SARS-CoV-2 mutations (variants) may emerge that have acquired greater transmissibility, resistance to treatment and the ability to avoid existing immunity. Moreover, future epidemics involving different coronaviruses may well occur and present serious health risks.

3.2 Imaging applications involving ionising radiation for diagnosis and treatment of COVID-19 infections

3.2.1 Current diagnostics

The current method used to diagnose COVID-19 is a reverse transcription polymerase chain reaction (RT-PCR) assay to detect the presence of viral RNA in a transoral or transnasal swab specimen. The sensitivity of detection depends on the quality of the specimen and the current phase of the infection (viral load). If the inflammation of the upper respiratory tract has already subsided, the RT-PCR test may come back negative despite the infection still being present in the lower respiratory tract (Hemmer et al. 2020, Dodt and Schneider 2020). Moreover, some patients do not produce sufficient sputum from which viral RNA can be isolated. In such instances, bronchial secretion would be required to confirm viral RNA via RT-PCR test, meaning that patients must undergo flexible bronchoscopy, bronchoalveolar lavage or suctioning during intubation. These measures are not only invasive, they also put medical staff at an increased risk of infection.

Logistics and internal laboratory processes mean that the results of RT-PCR tests are generally only available after one working day, but often may require several days, bringing a considerable downside to this method. In addition, a steep increase in incidence could lead to global shortages of basic laboratory consumables. This would result in delays to diagnostics and treatments, in turn prolonging the period of time in which infected individuals would transmit virus and thereby extending the burden on the healthcare system.

SARS-CoV-2 rapid antigen tests (lateral flow tests) have been widely available since autumn 2020 and are able to provide results in situ within 30 minutes (Sheridan 2020). However, such tests do not meet full diagnostic accuracy requirements as their validity depends on whether active disease is present, what antigen concentration is present and, more importantly, the quality and time of sampling. Rapid antigen tests have a sensitivity of approximately 90 % and a specificity of around 95 %, although these figures have been provided by the manufacturers using optimal laboratory conditions, rather than point of care use. The Diagnostics Global Health research group at the Tropical Medicine Faculty of the University of Heidelberg in Germany has reviewed and evaluated the risk of systematic bias in currently available independent studies, some of which have already been peer-reviewed, while others are still at the pre-print stage. An overview of the results, including links to the original publications, is available on the following website: https://diagnosticsglobalhealth.org (Denkinger et al. 2020). This study confirms the high specificity provided by manufacturers, but finds that test

[2] https://covid19.who.int/

[3] https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Fallzahlen.html

sensitivity varies a great deal, and is sometimes far lower than stated. The majority of the results ranged between 70 % and 85 %. It is important to note that rapid antigen tests are unsuitable for determining whether a person has been infected as they can only show whether the tested person is currently shedding the virus. If a person has been only recently infected they may test negative but still be capable of transmitting the virus. Rapid antigen tests are designed for testing asymptomatic persons and can be used, e. g. to deny someone who tests positive from entering a high-risk area such as a nursing home, or as a basis for arranging a RT-PCR test.

A detailed description of the metrics of diagnostic testing – specificity and sensitivity – is provided in Annex 1 of this statement.

3.2.2 Rationale for the use of computed tomography of the lung for suspected COVID-19

While projection radiography is less sensitive to pulmonary change, native computed tomography – including low-dose CT (LDCT) – has proven to detect changes in the lung associated with bilateral, multifocal interstitial pneumonia in COVID-19 patients (Heidinger et al. 2020). The extent of the changes become more prominent the more severe the clinical disease (Zhao et al. 2020, Li et al. 2020b). The most commonly reported CT findings are:

- Ground-glass opacity
- Consolidation
- Inverted halo (ground-glass opacity with a surrounding halo of consolidation)
- Interlobular septal thickening
- Crazy paving (a combination of ground-glass opacity and septal thickening)

The use of standardised diagnostic criteria can increase the diagnostic power of the CT scan in COVID-19 cases (Prokop et al. 2020). Nevertheless, the reported changes are by no means specific to COVID-19 pneumonia; they can also be found for example in viral pneumonia of other origin, such as influenza pneumonia or eosinophilic pneumonia. Some findings are less typical of COVID-19 pneumonia, such as the tree-in-bud sign (multiple areas of centrilobular nodules with a linear branching, indicative of illness in the distal airways). Cavitations or pleural effusions may occur at later stages of the illness, particularly in the event of a bacterial superinfection. Pulmonary artery branch sealing due to spontaneous thromboses or embolisms from the large arteries in the vascular system can only be detected with a contrast-enhanced CT scan.

According to reports from the early stages of the pandemic, native chest CT scans often return pathological findings, also for patients with only mild to moderate symptoms (Guan et al. 2020). Several initial publications have claimed a higher sensitivity of CT scans compared to RT-PCR when testing for COVID-19. This led to some authors recommending the use of CT scans to diagnose COVID-19, especially if waiting times for the results of a RT-PCR test are unjustifiably long due to high demand and bottlenecks in the supply chain or at laboratories (Fang et al. 2020, Ai et al. 2020).

These reports have led to suggestions for the use of chest CT scans in the following scenarios:

- To identify a SARS-CoV-2 infection (screening) in medically asymptomatic persons without any known contact with COVID-19 patients
- To screen for SARS-CoV-2 infection in medically asymptomatic persons who have had contact with COVID-19 patients

- To confirm the diagnosis in symptomatic patients with a previous COVID-19 diagnosis
- To support clinical decision making involving symptomatic patients, such as whether they should be hospitalised, whether therapeutic measures should be administered, or whether they should be discharged from hospital.

3.2.3 Consideration of evidence

Available evidence suggests that CT scans can be used to detect overt COVID-19 and possibly hitherto asymptomatic SARS-CoV-2 infection. Several retrospective studies have compared the power of CT scans to that of RT-PCR testing. A meta-analysis (Kim et al. 2020) involving 68 studies from multiple countries showed a pooled sensitivity of 94 % for CT (ranging from 47 % to 100 %) and 89 % for RT-PCR (ranging from 40 % to 100 %). Pooled specificity for CT was 37 % (ranging from 25 % to 56 %) with a specificity of 100 % being assumed for RT-PCR as the current gold standard, although the numerical value of 99% was assigned in order to compare predictive values. The limited specificity of CT, combined with the differences in prevalence seen among the cohorts of persons tested (ranging from 1 % to 22.9 %), shows that the positive predictive value (PPV)[4] varied across a broad range – 1.5 % to 30.7 % for CT and 43.7 % to 96.4 % for RT-PCR (assuming the 99 % specificity). The negative predictive value (NPV) exceeded 95 %, both for CT and RT-PCR (Kim et al. 2020). Xu et al. (Xu et al. 2020) in their publication have arrived at comparable findings. In the meta-analysis of Kim et al. the German studies (included were studies up to 29th March 2020) had an average prevalence of 5.7 %. This led to a calculated PPV of 8.3 % and an estimated NPV of 99 % for CT, along with an estimated PPV of 84.3 % and an estimated NPV of 99.3 % for RT-PCR (Kim et al. 2020).

All of these comparisons were conducted using retrospective data, thus making them difficult to interpret as it is unclear which patients received a CT scan and whether scans were performed to confirm illness at an early stage where symptoms were unclear, or whether it was on done after manifestation of COVID-19 pneumonia due to severe symptoms with or without confirmation of a SARS-CoV-2 infection. Little is also known about the prevalence of COVID-19 among the group and the respective pre-test probability. Prevalence in particular has a significant influence on the positive predictive value of the test.

The specificity of CT in these studies is low, meaning that pulmonary infiltrates due to COVID-19 cannot be sufficiently distinguished from interstitial pneumonias of other origin. This is of course a major problem during seasonal influenza outbreaks. Studies reported subsequently have reported normal CT findings in approximately 50 % of patients, particularly during the early stages of illness, meaning that the high sensitivity of CT reported in the earlier studies cannot go unchallenged. It remains unclear as to how these discrepancies came about. Possibly the indications used for requesting a CT scan such as the definition of suspicion of illness, or the severity of the symptoms were not consistently applied or have evolved.

A reader study, comparing the results from three radiologists interpreting a common data set, showed that they were able to distinguish between a COVID-19 and a non-COVID-19 pneumonia with an accuracy of 60 % to 83 % (Bai et al. 2020a). It remains to be seen whether the optimized conditions of such a reader study can be equated to real-life circumstances. The same researchers have also reported that the use of a deep-learning algorithm helped improve the accuracy of their diagnosis (Bai et al. 2020b). This suggests that artificial intelligence (AI) could be used to improve diagnostic accuracy, although it has little effect when used to tackle the problem of limited specificity of lung CT scans.

[4] A more detailed description of the metrics of diagnostic testing – sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) – is provided in Annex 1 of this statement.

3.2.4 Consideration of the indications for CT of the lung

As is the case with other types of pneumonia, patients who are strongly suspected of having a COVID-19 pneumonia require a prior justifying indication from a doctor having the requisite specialist knowledge in radiation protection before a CT scan is performed. The requirement being that the results of the CT will have an impact on clinical decisions such that the benefits outweigh the risk. Performing a CT scan on a medically asymptomatic person, even if they had had prior contact with an infected person, is not sufficient justification and is therefore prohibited by German radiation protection law. The SSK also considers the use of CT scanning to be unjustified if it is to be used to clarify a suspicion of COVID-19, or as a supplement to, or substitute for, an RT-PCR test.

On 11 June 2020, the WHO published a rapid advice guide on the use of chest imaging in COVID-19 (WHO 2020a), This was prepared amid the rapidly evolving epidemiological situation in the first half of 2020. At that time, the transmission paths were still unclear and it was not understood that the pandemic would continue to progress. Moreover, the initial lack of personal protective equipment and testing facilities proved to be a major influence in this report. It has since become clearer how the virus is transmitted (e. g. overdispersion[5], superspreading events, aerosol transmission) and – in Germany at least – there are now sufficient respiratory protection and testing facilities available. Table 1 shows how the main recommendations by the 2020 WHO guide compare with the present level of knowledge, and how they are to be interpreted under the prevailing conditions in Germany.

[5] Overdispersion: Overdispersion is a phenomenon involving a high individual-level variation in the distribution of the number of secondary transmissions which may lead to superspreading events.

Table 1: Comparison of the WHO recommendations (WHO 2020a) and the statement by the SSK on chest imaging in patients with suspected or confirmed COVID-19

	WHO			SSK
	Group of persons	Purpose of medical imaging	WHO recommendation	SSK statement for Germany
R1	For asymptomatic contacts of patients with COVID-19	Confirm SARS-CoV-2 infection	Not recommended	The SSK does not recommend this from a clinical perspective, and it is prohibited due to the lack of a justifying indication
R2.1	For symptomatic patients with suspected COVID-19	Confirm COVID-19	Not recommended when RT-PCR testing is available with timely results	The SSK does not recommend this from a clinical perspective, and it is prohibited due to the lack of a justifying indication
R2.2	For symptomatic patients with suspected COVID-19	Confirm COVID-19	Recommended when (1) RT-PCR testing is not available, (2) RT-PCR testing is available, but results are delayed; and (3) initial RT-PCR testing is negative, but with high clinical suspicion of COVID-19	Only when there is a justifying indication on a case by case basis
R3	For patients with suspected or confirmed COVID-19, not currently hospitalised and with mild symptoms	Decide on hospital admission	Recommended in addition to clinical and laboratory assessment	Only when there is a justifying indication on a case by case basis
R4	For patients with suspected or confirmed COVID-19, not currently hospitalised and with moderate to severe symptoms	Decide on regular ward admission or intensive care unit admission	Recommended in addition to clinical and laboratory assessment	Only when there is a justifying indication on a case by case basis
R5	For patients with suspected or confirmed COVID-19, currently hospitalised and with moderate to severe symptoms	Support decisions on therapeutic management	Recommended in addition to clinical and laboratory assessment	Only when there is a justifying indication on a case by case basis
R6	For hospitalised patients with COVID-19 whose symptoms are resolved	Decide on discharge	Not recommended	Only when there is a justifying indication on a case by case basis

Along with its recommendations, the WHO provides information on which groups of people may benefit from medical imaging. The SSK holds the view that the WHO recommendations should be considered as reference points as to which patients may benefit from medical imaging. However, they should be seen as 'suggestions' at best. As determined by radiological protection legislation s specialist doctor must ensure there is an individual justifying indication, that the benefits outweigh the risk, and that there has been an evaluation of whether the information expected from the scan is required for a pending clinical decision and whether this information can be otherwise obtained without the use of ionising radiation.

Based on current government guidelines a confirmation of pulmonary changes typical of COVID-19 in an individual with symptoms confined to the upper respiratory tract requires no treatment and intervention measures other than those already recommended for individuals without the findings from a CT: home isolation, treatment of the symptoms, and repeat RT-PCR testing if the first test was negative. The ready availability of rapid antigen tests should make it easier to decide whether or not to initiate therapeutic or disease-control measures. At present, there are no known interventions where the findings of a CT scan can avert or mitigate a clinically manifest COVID-19 pneumonia or, at worst, a severe progression of the disease.

The Fleischner Society[6] has provided recommendations on using CT scans in three COVID-19 scenarios, taking into account the widespread availability of RT-PCR and rapid antigen tests, and the pre-test probability of an infection. This probability is considered to be low in the event of a sporadic contact with an infected person, moderate if exposed in a cluster situation, and high if sharing a home with a symptomatic person. Irrespective of risk factors and test results, both the WHO and the Fleischner Society consider moderate to severe symptoms, and a significant deterioration following minor initial symptoms, to be clear indications for a CT scan to obtain a baseline for deciding on how to proceed and to exclude other potential causes. No clear recommendation is provided for indications involving mild symptoms, e. g. if there are only limited risk factors or a high pre-test probability. In such instances, decisions can only be taken on an individual basis.

A CT scan may also be indicated for patients with persistent symptoms after recovering from COVID-19, particularly after temporarily requiring intensive care and/or ventilation, to exclude complications requiring medical intervention.

Various expert scientists, specialist societies (American College of Radiology; The Royal College of Radiologists; Deutsche Röntgengesellschaft) as well as national and international institutions (WHO and the Centers for Disease Control and Prevention) all advise against using CT purely on the suspicion of illness (WHO 2020a, Cleverley et al. 2020, Li et al. 2020a, CDC 2020, RCR 2020, ACR 2020, Revel et al. 2020, Vogel-Claussen et al. 2020). For children, the corresponding specialist societies (Germany Society of Paediatric Radiology, European Society of Paediatric Radiology) each provide their own set of recommendations (Raissaki et al. 2020). However, the use of diagnostic X-ray procedures with symptomatic patients is not affected by this, provided the procedures are required as a baseline in the event of concerns about clinical deterioration, or if they are needed for clinical decisions such as whether to admit a patient to hospital or continue their treatment as an outpatient. Severely ill patients should undergo X-rays and CT scans of the lung as part of the diagnostic process, and they can be requested as a means of responding appropriately to a clinical problem. The general consensus is to avoid performing

[6] The Fleischner Society is an international, multidisciplinary medical society for thoracic radiology, dedicated to the diagnosis and treatment of diseases of the chest. Their recommendations are highly respected internationally and used for a wide range of guidelines on chest imaging.

repeated chest X-rays or CT scans, even in patients in intensive care or patients being ventilated, if there are no specific grounds for doing so (Vogel-Claussen et al. 2020).

3.2.5 Technical recommendations to optimise CT diagnostics for COVID-19

Where possible, low-dose CT scans should be preferred. According to the scan parameters described by Larke et al. (Larke et al. 2011), low-dose computed tomography (LDCT) of the chest leads to a mean organ dose to the lung of up to 4.5 mSv , and a mean effective lung dose of up to 1.4 mSv. Here, gender-specific values must be taken into account. Ongoing and future developments in CT technology may result in further reductions in these values. As the lung has a high intrinsic contrast CT scans can be performed on persons of normal weight using LDCT without any loss of diagnostically important information. A volume CT dose index (CTDIvol) well below 3 mGy should be aimed at for patients of slim to normal stature. Kang et al. were able to show that scans using modern equipment and a low-dose chest CT protocol resulted in a CTDIvol of just 0.4 mGy, whereas the same scanner using the standard CT protocol results in a CTDIvol of approximately 3.4 mGy (Kang et al. 2020). Higher doses may be unavoidable for lung imaging in obese or extremely muscular persons (Kalra et al. 2020). To avoid having to increase the dose, the person being scanned should try to position their arms as far above their head as possible so that the shoulder joints are positioned above the apex of the lungs outside the field. The patient should inhale fully and hold the breath with the scan focussed on the area between the apex of the lungs and the costodiaphragmatic recess, and not on the upper abdominal organs as is the case during a routine chest CT scan. Additional scans during exhalation are not indicated. In contrast to a topographic scan only a single native helical CT is required. Helical CT scanners offer additional ways to reduce the dose by controlling parameters such as pitch, imaging voltage and tube current wherever possible. A slice thickness of 1 mm with overlapping image reconstruction is also recommended. Older scanners may require a larger slice thickness and/or a higher pitch to limit the scan time for patients with respiratory distress who are unable to hold their breath for prolonged periods.

On suspicion of venous thromboembolism, a single-phase, contrast-enhanced pulmonary embolism protocol, as established at most radiological institutions, should be used. An additional native phase or dual-energy CT scan, i. e. involving a scanner with two tubes, is not required. As density resolution is most important for this indication, a higher slice thickness (typically 3 mm) and reconstruction involving a soft-tissue algorithm are required along with an edge-preserving algorithm used for the lung parenchyma. With multidetector CT scanners, 1 mm and 3 mm slices can be reconstructed from the raw data of a scan. If this option is not available, the lung parenchyma should be assessed using 3 mm slices without performing an additional 1 mm scan.

3.2.6 Weighing the benefits against the risk of CT of the lung for COVID-19

The risks of a single CT scan are comparatively low for individual persons. However, the extent of the COVID-19 pandemic makes the resulting collective dose relevant in terms of radiological protection, and is compounded by non-radiation risks to medical staff and other clinic personnel. The risk of infection to staff is obvious and depends on the protective equipment as well as how closely they need to work with the patients. Technical staff who, for instance, position patients are unable to avoid bodily contact. Non-COVID-19 patients of the facility, due to their own illness, are often considered to be high-risk persons because an infection would be particularly hazardous to them. Indirect risks may occur when the need to perform CT scans involving (potentially) COVID-19 persons may have a significant negative effect on workflows. By way of example, thorough disinfection and ventilation are required between

individual scans on (potentially) infected persons, in turn increasing the amount of time between scans and possibly leading to bottlenecks for the CT scan needed for other indications.

CT scans on medically asymptomatic persons, even following contact with an infected person, are currently not justified from the clinical standpoint and are prohibited under German radiation protection law. Performing a CT scan purely on the basis of suspected COVID-19 does not provide any significant individual or collective benefit over the stated risks of the radiation exposure as long as the consequences of a positive CT scan do not extend beyond the measures that are already recommended or required by the health authority for a COVID-19 positive individual. This may, however, occur in individual cases (Rubin et al. 2020) and could constitute an individual justifying indication.

In view of the desire to reduce adverse consequences of radiation exposure it makes sense to consider the use of AI in COVID-19 imaging. There are two different types of AI application involved in diagnostic imaging procedures that use ionising radiation. The first is to optimise and accelerate non-linear reconstruction methods to produce diagnostically valid CT images at lower doses than those required for current reconstruction methods. However, this requires prior algorithm training using typical pathological findings from a large number of images. Otherwise, unknown structures could be interpreted as noise and subsequently suppressed or perhaps even exaggerated or imaged in completely the wrong way. The available literature does not yet provide any corresponding approaches for reconstruction algorithms specifically designed for use in CT scans on COVID-19 patients. Irrespective of this, such use of AI is problematic since it is not possible to verify the ‘authenticity’ of the resulting images because the comparatively low radiation dose and high level of noise as a result of using conventional reconstruction methods render it impossible to provide clear reference images.

The second use of AI is to support the diagnostics process by evaluating images in an automated fashion. Section 3.2.3 above provides such an approach gleaned from the literature. However, the low number of cases currently available does not allow for proper evaluation of such an approach. In principle, it may make sense to use AI methods to obtain an automated second opinion, particularly if a large number of scans needs to be evaluated and if the use of AI means that fewer experienced radiologists are required to provide a diagnosis. However, it remains imperative for experienced radiologists to scrutinise automatically generated diagnoses. Automated diagnoses are currently not recommended, particularly given the low number of images available to train the algorithms and the limited knowledge available into the potential characteristics specific to respiratory illnesses associated with COVID-19 patients. AI could be used, for instance, for risk stratification of COVID-19 patients to predict the likelihood of deterioration or to determine possible treatments. It could also be used in tandem with X-ray dark-field imaging (Willer et al. 2018). However, the current state of the pandemic does not allow such studies to be conducted or concluded with a sufficient number of patients and an adequate period of observation.

3.3 Use of radiotherapy for the treatment of COVID-19 infections

3.3.1 Currently available treatments

The general consensus among experts is that the current pandemic will decline once enough of the population becomes immune or has been immunised. To achieve this, large-scale vaccination campaigns have been initiated. During the course of the pandemic, treatment of patients with severe cases of COVID-19 infection has seen significant advancements due to growing knowledge about the course and potential complications of the disease. Increasing clinical experience from intensive care units and regular wards now contributes for example to the early detection of severe progressions and ‘silent hypoxia’ (Hüfner et al. 2020). At the time

of drafting this text, the Association of the Scientific Medical Societies in Germany has issued an S2 Guideline (AWMF 2020) that covers current treatment modalities. Currently, the main evidence-based forms of treatment involve high-flow oxygen therapy (HFOT) and, where possible, non-invasive ventilation, the prone positioning of ventilated patients as early as possible, thromboprophylaxis, antiviral medication with remdesivir during the early phase, and anti-inflammatory treatment with dexamethasone for severe or critical illness. In addition to targeting COVID-19 pneumonia, these treatments also play a central role in addressing the extrapulmonary manifestations and complications which contribute significantly to COVID-19 morbidity.

3.3.2 Possible rationale[7] for using radiotherapy to treat COVID-19 pneumonia

As with other inflammatory diseases (e. g. mastitis, boils), radiotherapy was introduced in the first half of the 20th century to treat bacterial and viral forms of pneumonia (Calabrese and Dhawan 2013). Due to advancements in medical treatment, particularly the development of effective antibiotics at the end of the 1930s and the introduction of antiphlogistic therapy, radiotherapy became less and less important as a treatment for such diseases. Until recently, no more clinical data had been published on the use in pneumonia since the end of the 1940s. However, in 2013 a review of historical literature prompted the suggestion to apply low-dose radiation therapy (LDRT) of the lung to treat pneumonia (Calabrese and Dhawan, 2013). This treatment has become the subject of scientific discussion during the current SARS-CoV-2 pandemic. In this context, the suggested LDRT treatment of COVID-19 patients involves a plan to give a single irradiation to the entire lung at comparably low therapeutic doses ranging between 0.3 Gy to 1.5 Gy. These doses are well below the therapeutic doses generally administered in radiooncology and easily within the clinical tolerance doses for the chest organs, but they still easily exceed the typical doses used in diagnostic applications involving ionising radiation.

The main acute pathophysiological changes that may develop during the course of severe SARS-CoV-2 disease are as follows:

- Loss of structural integrity/functionality of the blood vessels and activation of blood clotting cascades (Teuwen et al. 2020).
- Dysregulation of the immune response (Merad and Martin 2020, Tay et al. 2020, Agrati et al. 2020, Huang et al. 2020) that may affect the outcome of the disease. The initial inhibition of interferon release has an immunosuppressive effect due to abnormal development of myeloid cells, manifesting in excessive activation of phagocytes, cytotoxins and inflammatory immunocytes.
- Onset of excessive inflammation, known as a ‘cytokine storm’ (Teuwen et al. 2020).

LDRT of the lung is suggested to have a beneficial effect due to the following mechanisms:

- Inhibition of expression and release of inflammatory cytokines (Abdollahi et al. 2020). This is also the aim of other non-radiotherapy treatments used or in planning/testing for COVID-19 (Zhang et al. 2020, Schett et al. 2020). A rationale for this is provided below in the description about the anti-inflammatory effect of LDRT
- Optimisation of immune system activity, particularly in terms of the ratio of activated to non-activated immunocytes, abnormal polarisation of macrophages, and possible apoptosis of infiltrating immunocytes. Modulation of signal paths linked to the production of antiviral type 1 interferon clearly requires further investigation;

[7] For the purpose of this statement, rationale means justifying consideration.

nevertheless, there is a rationale for these hypotheses owing to the fact that modulation of the immune system was observed following LDRT on humans with inflammation and in the animal model (Rödel et al. 2012b)

3.3.2.1 Consideration of evidence

Low-dose irradiation of pneumonia: clinical data

In their review from 2013, Calabrese and Dhawan (Calabrese and Dhawan 2013) list a series of clinical studies on various forms of experimental pneumonia that were published during the first half of the 20th century. These studies involving a total of 863 patients reported a high number of cured patients, but also presented the following problems:

- There were no control groups as it was considered unethical not to treat an ill person. Instead, a comparison was drawn with mortality rates for untreated patients in the clinic or local area
- Doses were determined by irradiating boils (ulcerous inflammation of hair follicles, generally caused by staphylococcus aureus)
- The irradiation equipment in the individual studies had different technical properties

In view of these points it is unwise to consider the evidence from these studies as having been evaluated sufficiently rigorously (Salomaa et al. 2020; Kirsch et al. 2020).

The rationale for using LDRT to specifically treat COVID-19 pneumonia was recently published by teams in North America and Iran, the latter having been affected heavily during the first wave of the pandemic (Ghadimi-Moghadam et al. 2020). The latter authors made a case for the proposed treatment by referring to the lack of deleterious health effects seen in populations living in areas with very high naturally background radiation. The therapy concept was also supported in Canada (Kirkby and Mackenzie 2020). Several review articles, planning initiatives and case reports have been published in recent months (Del Castillo et al. 2020), and multiple clinical studies have been initiated. Ameri et al. (Ameri et al. 2020) recently reported on an initial prospective single-arm non-blinded case series from Tehran where five patients over the age of 60, who were receiving oxygen due to COVID-19 pneumonia, were given LDRT of the lung with a dose of 0.5 Gy. At the same time, these patients were treated with anticoagulants and dexamethasone as per the current guidelines. The patients were not given any antiviral medication. In three out of five cases the patient saw an improvement in their condition, while two patients died, one of whom withdrew their consent to take part in the study after receiving treatment. The authors concluded that the study produced promising results given the response rate of 80 %. However, the editors of the International Journal of Radiation Oncology, Biology and Physics were far more reserved in an accompanying editorial (Kirsch 2020) where they concluded that radiotherapy with this indication is unlikely to be used for anything other than clinical studies, particularly given that antiviral and antiphlogistic treatment is now available and vaccines are also expected to be available soon.

In the prospective REDACTED study published in December 2020 (Hess et al. 2020), ten patients requiring oxygen, but not intubated or receiving antiviral medication, were given LDRT with a dose of 1.5 Gy. The results of this treatment were compared with a cohort of the same size that was selected in a blinded fashion from a non-interventional study populations and comparable in terms of age (LDRT: median age of 78, control: median age of 75) and comorbidities. Six members of the control group received antiviral medication. In patients who received LDRT, the median time until clinical recovery was reduced significantly from 12 to 3 days ($p = 0.048$). After 28 days, 90 % of the patients in both cohorts were still alive and no acute toxicity was reported. The authors concluded that additional studies are justified.

One difficulty arising in connection with preventive treatment involving LDRT is the relatively small window of time in which the treatment may be beneficial rather than counterproductive. Owing to pathophysiological considerations, this window of time may be between the first occurrence of symptoms with pathological relevance (e. g. shortness of breath, onset of alveolar inflammation, changes visible on a CT scan, biomarkers requiring clinical validation such as lymphopenia, activated macrophages/monocytes, MDSC, cytotoxic CD8+, IL-6 and IL-10 release) and the occurrence of acute lung failure with all its associated complications (insufficient supply of oxygen to the lung, severe alveolar inflammation) (Tharmalingam et al. 2020). One conceivable option would be to stratify COVID-19 patients by using AI on CT scans. Similar stratification or an early decision for or against certain therapeutic measures could be performed via AI evaluation of the biomarkers mentioned above (for further literature, see Dhall et al. 2020, Wertz et al. 2020, Goyal et al. 2019).

Phase I clinical trials involving LDRT for COVID-19 pneumonia are currently being conducted in several countries (USA, Spain, Iran, Italy, Finland, India) (Salomaa et al. 2020; Prasanna et al. 2020). These trials are non-randomised and generally only conducted in one medical centre. Planning for the trials includes partial transition to randomised phase II trials involving around 1,000 patients worldwide (Prasanna et al. 2020).

Pre-clinical data on low-dose irradiation for experimental pneumonia

In their summary of past pre-clinical works, Calabrese and Dhawan (Calabrese and Dhawan 2013) refer to four sets of studies that involved the following model systems:

- Bacterial pneumonia induced in guinea pigs or dogs (conducted by two different groups of researchers)
- Virally – but not SARS-CoV-2-induced – pneumonia in cats and mice (conducted by a single group of researchers)

The end point was generally mortality (Fried 1941; Baylin et al. 1946, Lieberman et al. 1941; Dubin et al. 1946).

In 2020, Little et al. reanalysed data from 13 of these studies. In six of these studies, inoculation took place prior to irradiation (Little et al. 2020). Little et al. concluded that the results are contradictory or statistically insignificant, pointing out that these retrospective studies cited as evidence by Calabrese and Dhawan do not provide any evidence that COVID-19 mortality would be decreased following LDRT.

There is generally far less data available as a basis for justifying LDRT treatment for pneumonia compared to the amount of data available to justify the use of LDRT for the treatment of chronic inflammatory diseases. However, this form of treatment involves modulation of inflammatory responses, albeit with completely different medical conditions (Rödel et al. 2020) and should be clearly distinguished from the effect of radiation on non-inflammatory diseases (Deloch et al. 2018b).

The search for suitable animal models for a SARS-CoV-2 infection has been ramped up in recent months, with proposals including primates, hamsters and transgenic mice to express the human angiotensin-converting enzyme 2 (ACE2) receptor used by SARS-CoV-2 to gain entry to the cell. The receptor-binding domain of the human SARS-CoV-2 virus has been genetically modified to enable infection of mice (Leist et al. 2020). Infecting mice with the wild-type virus is only partially possible, with the human pathogenesis of the disease not occurring in mice. There are currently no results available from studies on the effectiveness of LDRT in any of these newer animal models (Kirsch et al. 2020).

Clinical analogy: radiotherapy for chronic inflammatory diseases

For several decades now, LDRT has been used in Germany and a number of Eastern European countries to treat painful degenerative musculoskeletal disorders and chronic joint inflammation such as osteoarthritis, rheumatoid arthritis and hyperproliferative disorders (Minten et al. 2016). Based on a survey conducted in Germany, an estimated 9,000 patients per year received LDRT at the end of the 1990s (Leer et al. 1998).

Despite this relatively broad spectrum of use, the effectiveness of the treatment has often been a matter of controversy, particularly in recent times. Clinical studies, predominantly retrospective in nature, demonstrate non-significant (Mahler et al. 2019; Minten et al. 2018; Minten et al. 2016) or significant anti-inflammatory effects (Donaubauer et al. 2020b; Juniku et al. 2019; Seegenschmiedt et al. 2015). More recent blinded, randomised studies (Minten et al. 2018) have failed to demonstrate any positive effect from LDRT. To meet the standards for evidence-based medicine additional prospective randomised studies are needed that include a larger number of patients, follow-up lasting more than three months, and a limit on the medical condition included (Ott et al. 2019).

Pre-clinical studies indicate that LDRT has a dose-dependent anti-inflammatory effect (Frey et al. 2009, Deloch et al. 2018a) and, together with data from *in vitro e*xperiments, deliver findings into the potential underlying mechanisms (Rödel et al. 2012a). These mechanisms are assumed to be an LDRT-induced, suppression of cytokine release and a restoration of a balance between oxidative stress and antioxidative defence in cells (Large et al. 2014; Rödel et al. 2002). Both of these mechanisms lead to reduced adhesion of immunocytes to the vascular endothelium, which equates to a decreased inflammatory response (Erbeldinger et al. 2017; Hildebrandt et al. 2002; Arenas et al. 2006) with reduced cytokine release (Rödel et al. 2012a). They also cause an increase in immunosuppressive and anti-inflammatory T cells (T-regs) while inducing an anti-inflammatory phenotype in macrophages (Wunderlich et al. 2015). Irradiation also influences the proliferation and activity of various cells types involved in the pathogenesis of the treated diseases (Donaubauer et al. 2020a; Deloch et al. 2019; Rödel et al. 2017).

3.3.3 Risks of LDRT to the lung

Concerns about the potential negative effects of LDRT to the lung has given rise to a number of investigations into the subject (Prasanna et al. 2020).

Potential negative effects include the following:

- Risk of cancer in irradiated organs
- Risk of cardiovascular diseases and vascular damage
- Risk of unfavourable progression of the virus

A recently published work by Arruda et al. provides highly detailed estimates on the risk of cardiovascular damage, along with stochastic risks for various thoracic organs based on LDRT dose, age and sex. Arruda et al. consider a 2 % additional risk of cardiovascular mortality and cancer to be inacceptable, while an additional risk below 1 % was considered acceptable. The authors hold that prescribed LDRT doses of less than 0.5 Gy are an acceptable cardiovascular risk, while doses of 0.7 Gy are acceptable for all of the cancer risks included in their work. The authors consider doses of 1 Gy or higher to be unacceptable, except in the case of the risk of lung cancer in patients over the age of 60 (Arruda et al. 2020).

It is also important to consider the risks to other persons not suffering from COVID-19. In an analysis published in November 2020, Lai et al. (Lai et al. 2020) used data from the British National Health Service (NHS) to estimate that a significant increase in cancer mortality can be expected over the coming months and years which is attributable solely to global efforts to

tackle the pandemic. While this initial assumption only focuses on postponing diagnoses and acute treatment, many oncological centres are experiencing treatment bottlenecks due to the pandemic. Even in a robust healthcare system the large number of COVID-19 patients potentially competing for radiotherapy resources could prove highly detrimental to the outcome for cancer patients, particularly in view of the need for the disruptive infection prevention and control measures required for staff and oncological patients not suffering from COVID-19. Despite taking every precaution to prevent infection, this represents an unnecessary risk of infection for both patients and staff.

3.3.4 Risk-benefit analysis

The potential benefit of LDRT of the lung should be weighed against the aforementioned risks and progression of the disease without irradiation of the lung. However, the benefit that is to be taken into consideration should include evidence from a clinical study on the use of LDRT for COVID-19 pneumonia, it should also involve the question of which additional measures can be taken to stop the spread of the disease (see Section 3.3.1.) and which additional measures could be taken in the future based on current activities. Examples here include optimised medication courses and, above all, vaccination campaigns. Providing a full evaluation of the current outlook in this respect extends far beyond the scope of this statement, meaning that it is currently not possible to deliver a risk-benefit analysis specifically for LDRT of the lung for COVID-19 pneumonia. In view of the radiation risks involved, the SSK considers a treatment involving ionising radiation can only be justified within the context of clinical studies.

4 Legal requirements

In accordance with Section 83 (1) of the German Radiation Protection Act (StrlSchG), ionising radiation or radioactive substances may only be applied on people (hereafter referred to as *use of ionising radiation on people*) when it is:

(1) in connection with *medical exposure*, or

(2) in connection with the exposure of the public in order to examine a person in cases envisaged or permitted by the law or in accordance with general occupational health and safety regulations, or in accordance with other countries' provisions on immigration (*non-medical use*).

Among other things (cf. Section 2 (8) StrlSchG), the term *medical exposure* includes the use of ionising radiation on:

- a patient as part of his or her medical or dental examination or treatment
- an asymptomatic individual to screen for a certain illness
- a person for the purposes of medical research

Examinations involving X-irradiation under the German Infection Protection Act (IfSG 2000) are not covered by the term medical exposure, but by the term non-medical use (Section 83 (1) (2) StrlSchG).

Use of ionising radiation on people must deliver a sufficient benefit. When evaluating whether the use in question delivers sufficient benefit, its overall potential diagnostic or therapeutic benefit, including the direct health benefit for the individual and the benefit for society, must be weighed against the potential harm to the individual resulting from the exposure (Section 83 (2) StrlSchG).

In principle, in accordance with Section 83 (3) StrlSchG, *use of ionising radiation on people* may only take place after a medical doctor or dentist who possesses the requisite specialist knowledge in radiation protection has decided that, and by what means, the use is to be effected (*justifying indication*). In addition, in accordance with Section 119 (1) of the German Radiation Protection Ordinance (StrlSchV 2018), the medical doctor or dentist issuing the justifying indication must ensure that the intended use of ionising radiation on people is a recognised procedure compatible with the requirements of medical science, or that it is an *attempt to cure* a person for which the medical doctor or dentist must provide sufficient grounds for doing so.

The duty to *issue justifying indication* in accordance with Section (83) (3) StrlSchG shall not apply to examinations involving X-radiation under the German Infection Protection Act (Infektionsschutzgesetz), or to uses on people for the purpose of medical research in accordance with Section 31(1) or Section 32(1). Such uses for medical research require approval from the Federal Office for Radiation Protection (BfS); alternatively, the BfS must be notified in written or electronic form prior to such uses.

The German Radiation Protection Act defines *screening* as the use of X-radiation or radioactive substances in connection with medical exposure in order to examine persons who do not exhibit any symptoms of disease or any concrete suspicion of disease (*asymptomatic individuals*) in order to detect a specific disease (Section 5 (16) StrlSchG). Here, a distinction is made between screening for non-communicable diseases (e. g. breast cancer screening) and screening for communicable diseases in parts of the country or for population groups with above-average incidence of disease. In accordance with Section 84 (4) StrlSchG, the latter type of screening shall only be permissible where the *Land*'s highest competent health authority, in agreement with that *Land*'s highest radiation protection authority, has authorised screening for public health reasons.

As with any *use of ionising radiation on people*, exposure for the purpose or examining or treating COVID-19 is subject to the legal requirements set out in the German Radiation Protection Act (StrlSchG) and German Radiation Protection Ordinance (StrlSchV).

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6 Abbreviations

ACE2 receptor	Angiotensin-converting enzyme 2 receptor
ACR	American College of Radiology
COVID-19	Coronavirus disease
CT	Computed tomography
CTDIvol	Volume computed tomography dose index
DRG	German Radiological Society
AI	Artificial intelligence
LDCT	Low-dose CT
LDRT	Low-dose radiation therapy
NHS	National Health Service in the UK
NPV	Negative predictive value
PPV	Positive predictive value
RCR	The Royal College of Radiologists
RNA	Ribonucleic acid
RT-PCR	Reverse transcription-polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

Annex

A-1 Metrics of diagnostic testing

Diagnostic tests such as RT-PCR or CT typically involve two metrics – sensitivity and specificity. Sensitivity is the probability of a diseased person being correctly classified as diseased (true positive / (true positive + false negative)), while specificity is the probability of a non-diseased person actually being classified as disease-free (true negative / (true negative + false positive)).

The extent to which a test is reliable in any given situation is generally expressed by way of the positive and negative predictive value (PPV and NPV). PPV is the probability of a person with a positive test actually having the disease (true positive / (true positive + false positive))[8]. NPV is the probability of a person with a negative test actually being disease-free (true negative / (true negative + false negative)). However, PPV and NPV not only depend upon the validity of the test, but also the prevalence of the disease in the tested population. Initially, prevalence can only be estimated, meaning the lower the prevalence, the lower the PPV and the less certain a positive test can be considered to be correct. Even with a comparatively specific test, a true positive is contrasted by a significant number of false positives. This is illustrated in the tables below that provide a calculation of predictive value at 50 % and 5 % prevalence. For illustration the test has a sensitivity and a specificity of 90 %.

Calculation of predictive value at 50% prevalence:

	Test +	Test -	Total
Infection	450	50	500
No infection	50	450	500
Total	500	500	1,000

PPV = 450 / 500 = 90%; NPV = 450 / 500 = 90%

Calculation of predictive value at 5% prevalence:

	Test +	Test -	Total
Infection	45	5	50
No infection	95	855	950
Total	140	860	1,000

PPV = 45/140 = 32 %; NPV = 855/860 = 98 %

[8] The definition of PPV means that it cannot be calculated correctly for a test to be used as a gold standard (and no false negatives can occur with a formal sensitivity of 100%) because it will always be 100%. As a sensitivity of 100% is derived solely from the definition of a gold standard, but is not realistic, Kim et al. (Kim et al. 2020) used a sensitivity of 99% in their work to calculate the predictive value for the gold standard, RT-PCR.