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D3.4 Medical application of ionising radiation and radiation protection needs and opportunities in other relevant clinical scenarios

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I. Introduction

The use of ionizing radiation for diagnostic imaging, interventional procedures and radiation therapy has largely increased in the past decades, raising concerns about risks associated with radiation. Children, pregnant women, and patients with chronic conditions who may require frequent radiologic imaging represent a sensitive patient group more prone to the untoward effects of radiation exposure. On the other hand, the use of ionizing radiation for screening examinations requires a very careful justification, as these studies are performed in apparently healthy subjects.

In this context, Task 3.4 was in charge of a series of tasks:

- to identify the needs of research in radiation application and corresponding protection in relevant clinical scenarios not covered in the tasks 3.1 to 3.3, in particular in paediatric patients, pregnant women, chronic diseases, screening programmes, by identifying gaps and possibilities.
- to create a panel for this task including experts from the identified scenarios to ensure that the relevant medical and scientific communities were involved in the definition of the research needs and related priorities.
- to perform a literature research on typical exposures and the state of the art in radiation protection analysed as regards both the technical and procedural aspects.

The composition of partners performing task 3.4 was IBG as task leader and UP, UoC, COCIR, EUC, EMC, and EURAMED as Partners.

II. Methodology

In order to cover in the best way all the main issues, Task Force 3.4 was implemented with a panel of experts and external members according to the clinical scenarios we were requested to consider.

In particular, the following experts were involved:

Task 3.4 Panel composition

IRCCS Burlo Garofolo (IBG)	Claudio Granata Amanda Antonelli
Université Paris (UP)	Guy Frija
COCIR	Riccardo Corridori
University of Crete (UoC)	John Damilakis Eleftherios Tzanis
University Hospital Vall d'Hebron (VHIO)	Jordi Giralt
Nemzeti Népegészségügyi Központ (NNK)	Katalin Lumniczky
European University of Cyprus (EUC)	Christina Iosif (EuC)
Erasmus Universitair Medisch Centrum Rotterdam (EMC)	Mark Konijnenberg (EMC)
European Alliance for Medical Radiation Protection Research (EURAMED)	Klaus Bacher (EURAMED, UGENT)

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Task 3.4 External Members

In addition, task 3.4 nominated additional external experts which accepted their nomination:

- Pierpaolo Alongi, Fondazione Istituto G. Giglio, Cefalu (I)
- Owen Arthurs, Great Ormond Street Hospital, London (UK)
- Erich Sorantin, Medical University of Graz, (A)
- Kimberly Applegate, Emory University, Atlanta GA (USA)
- Sergio Salerno, University of Palermo, (I)
- Massimo Calabrese, Ospedale San Martino, Genova (I)
- Simone Schiaffino, IRCCS Policlinico San Donato, San Donato Milanese (I)
- Paolo De Marco, IRCCS Istituto Europeo di Oncologia, Milano (I)

Online meetings were held with the panel and external members in order to define clinical subspecialties needed (M3-M6). An open web-based survey proposed by the leadership of WP3 was filled in by task 3.4 members in order to compile a list of clinical scenarios relevant to the aims of the task (M6). A final list of relevant clinical scenarios was defined by consensus by task 3.4 members. After a comprehensive review of the literature available, a shortlist of relevant clinical scenarios with related gaps of knowledge and needs of research and possibilities was included in a draft document circulated among Task 3.4 members and a final consensus was obtained (M12)

Different clinical scenarios and the related gaps in knowledge and need of research were presented to other relevant stakeholders at the European Radiation Protection Week Conference, held online in November 2021, for further discussion and feedback (M14) and sent for input to WP6. A preliminary deliverable reporting the results of the task was drafted in August 2022 (M23).

III. Results

Paediatric patients

We decided to focus on children with solid tumors as these are disease entities where ionising radiation is used for treatment and diagnosis regularly. In this context, neuroblastoma represents an excellent scenario for describing the potential research options for improving patient care because it is a relatively frequent paediatric solid tumour and the use of ionizing radiation can be extensive for diagnosis and follow up, as well as for radiation therapy.

Neuroblastoma

Neuroblastoma (NB) is the most common extracranial solid tumour in children and is regarded as the most common malignant tumour in infants [1]. Treatment outcomes vary significantly among patients with NB. Patients with low risk of NB fare well with little or no treatment, whereas high-risk children with metastatic disease have a 5-year-survival of approximately 30-40% despite multimodality therapeutic schedule, including chemotherapy, radiation therapy, stem cell transplantation and immunotherapy that may give rise to significant long-term side-effects [2]. With such heterogeneous clinical scenarios, patient outcome as well as patient radiation exposure may vary greatly during the therapeutic path.

<u>Diagnostic Imaging:</u>

Diagnostic imaging is a core part of the diagnosis, treatment planning as well as staging and follow up of NB patients. The number of radiologic studies can greatly vary according to the stage of the NB disease at diagnosis, being higher in children with a higher stage. Furthermore,

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imaging protocols varies widely depending on local preferences and experience. For 30 children treated for NB, Ahmed et al reported an estimated median cumulative effective dose (CED) due to CT studies of 133 mSv (range, 20 to 209 mSv) [3]. Owens et al recently also reported that the mean CED prerelapse for NB was 125.2 mSv, 64% of which was from CT scans (i.e. 80 mSv). [4]

Morel et al. reported a CED of 30.5 mSv for 66 patients treated in 6 different institutions. The mean CED were twice as high when comparing the centre with the lowest mean CED and the centre with the highest mean CED. Among a similar cohort of patients, the difference could be explained by a lower mean number of CT scans associated with more adapted acquisition [5].

Ozyoruk et al reported median CED of 20 mSv and 11.1 mSv for CT examinations and nuclear medicine examination respectively. However, the study showed great variability in the number of examinations performed: the number of CT scans were in the range of 0-23, while the number of nuclear medicine examinations in the range between 1-5 [6].

Although computed tomography (CT) is an excellent modality largely used in neuroblastoma, magnetic resonance imaging (MRI) should be preferred for diagnosis and staging, if available, due to its intrinsic high contrast and radiation-free images and its capability to provide additional functional information about the tumour. Furthermore, MRI is superior to CT in assessing bone marrow disease and chest wall invasion and should be the default imaging in cases of spinal canal involvement [7]. On the other hand, contrast CT scans should be still preferred for surgical planning in patients who had pre-operative chemotherapy, as MRI can often underestimate disease extent due to the treatment-induced changes: in fact, fibrosis and calcifications result in low T1 and T2 signals in MRI, which renders them less noticeable than at diagnosis [8]. This means ionizing radiation based imaging remains important and needs to be optimized to generate even better diagnostic or treatment planning information with as low as reasonable achievable exposures.

Knowledge about appropriateness and effectiveness of diagnostic imaging - with related dose exposure - during follow-up of survivors is limited. The cumulative exposure can be high, especially in high-risk neuroblastomas.

The lack of evidence for routine surveillance imaging in high-risk patients after remission was highlighted by Morgan et al: the risk of relapse was high and few patients with relapse survived, regardless of the method of detection. [9]. Owens et al, showed that relapsed disease is often detected by symptoms or modality that involve less or no radiation exposure (radiography, ultrasound, MRI) with respect to CT [10]. These findings suggest that surveillance regimens should be reconsidered to avoid long-term sequelae, especially in patients with more favourable outcomes, because surveillance programs that incorporate cross-sectional imaging or ionizing radiation modalities may result in more harm than benefit [11]. Therefore, the justification of routine surveillance imaging – especially with the use ionizing radiation – requires a better validation, possibly through randomised controlled trials.

<u>Nuclear Medical Imaging:</u>
Regarding nuclear imaging for disease diagnosis and staging, 123I-mIBG is currently preferred over 131I-mIBG. On the one hand, it has better physical characteristics: its low gamma energy (159 vs 364 keV) is more suited to conventional gamma-cameras with a better target-to background ratio and a better image resolution. On the other hand, it presents a better dosimetric profile, particularly in the paediatric population, thanks to its shorter half-life (13 hours vs 8 days) and no beta emission which locally deposits substantial amounts of energy but does not contribute to image formation [12].
Ben-Sellem et al showed the additional value of SPECT/CT in terms of the certainty of lesion detection and anatomic localization if compared to planar imaging: in 88% (49 out of 56) of the examinations, SPECT/CT provided additional information which was crucial for the therapeutic decision in 20% of the cases. It allowed a better characterization of the lesion and its

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locoregional extension in 44 cases, a better lymph node staging in 28 cases, the detection of 33 new lesions, and the elimination of 9 false positives. Authors concluded that additional information may justify the slight increment in radiation dose (CT dose contributes, on average, with 12% of the total dose) [13]. Other studies showed the additional value of SPECT/CT images, even if with lower rates of 29% [14], 39% [15] and 41% [16] in terms of additional information provided.

In the evaluation of neuroblastomas, PET tracers have also proven their usefulness: Shahrokhi et al. analysed and prospectively compared 68 Ga-DOTATATE and 131I-mIBG SPECT/CT imaging in a small group of 15 neuroblastomas. 68 Ga-DOTATATE detected more lesions than 131I-mIBG, especially bone metastases [17]. Piccardo et al. objectified that the sensitivity of 18F-DOPA PET/ CT, in staging and in therapeutic assessment of patients with neuroblastoma, was greater than that of 123I-mIBG SPECT/CT [18]. Melzer et al. have shown that 18F-FDG PET/CT is useful in the event of a discrepancy between morphological imaging and 123I-mIBG SPECT [19].

Non-ionizing radiation modalities such as MRI can be effectively used in the management of the disease [20] and it is recommended by current SIOPEN protocols for evaluation of local disease, although more costly and often requiring sedation in younger children. However, care should be taken when using MRI with whole-body diffusion weighted imaging with background body suppression (DWIBS) for detecting bone metastasis, as such MR based imaging shows high false positive rates especially in the skeleton when compared to radioisotopic techniques [21]: In this context, large prospective multicentre cohort studies are needed to validate the role of whole-body MRI with DWIBS sequences as an alternative radiation-free technique to radioisotopic imaging.

Radiation therapy: photon beam therapy

Currently, different international organizations provide their own treatment protocols. For example, the International Society of Pediatric Oncology-Pediatric Oncology in Developing Countries (SIOP-PODC) recommends 21.6 Gy of radiotherapy to the primary tumour bed and residual bone metastases (<6 sites) at the end of the consolidation therapy [22].
The Children's Oncology Group (COG) recommends the application of radiotherapy at a dose of 21.6 Gy after induction chemotherapy and before resection, increasing the dose to 36 Gy for patients with residual lesions after surgery. [23]

The SIOP Europe Neuroblastoma Group (SIOPEN) recommends a dose of 21.6 Gy for the primary tumour completely resected and a randomised study – presently ongoing - of the standard 21.6 Gy dose vs 36 Gy for incompletely resected without systemic radiotherapy for metastases [24].

Therefore, while the current guidelines of most organizations are similar for radiotherapy regimens at the primary site, the exact dose required for postoperative residual disease has not been finally determined, although more aggressive radiotherapy for patients who do not achieve complete macroscopic resection is generally advocated.

Although there are abundant data showing good local control (LC) with 21.6 Gy directed at the primary site, there are few data describing the feasibility and efficacy of RT directed at metastatic sites of the disease as part of the consolidation therapy. Casey et al [25] reported the results of 21.6 Gy of hyperfractionated RT to treat not only the persistent sites of the disease but also previous sites of measurable or bulky disease in complete response, especially those in critical locations such as the skull or weight-bearing bones: the rationale for the latter approach stems from prior experiences showing that the majority of failures occur at previous sites of involvement, even those in complete response to induction therapy. To this regard, randomized controlled trials could be considered.

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Radiation therapy: particle beam therapy

Proton therapy has a significant appeal for the treatment of tumours in young or very young children, especially those tumours occurring in close proximity to vital normal tissues.
Because of the peculiar properties of dose deposition, leading to a reduction of the dose proximal to the target and a lack of an exit dose compared with photons, proton therapy delivers less low-dose radiation to surrounding normal tissues around and beyond the target.
Despite the potential dose savings, previous studies have shown that, for some patients, intensity modulated photon therapy could be preferable over passive-scattered proton therapy, with the possibility of applying a mixed approach [26, 27, 28]

Recent studies reported promising results for local control rate of patients suffering from NB NB: Hill-Kayser et al [29] reports a 5-year control rate of 97% with a median follow-up of 48.7 months for 45 patients. Dose prescription was of 21.6 Gy (relative biological effectiveness) - RBE to primary tumour bed and persistent metastatic sites, with 36 Gy (RBE) to gross residual disease.

Bagley et al [30] published a 5-year local control rate of 87% after a median follow-up of 60.2 months in 8 patients. Primary sites (n = 18) were treated to 21–36 Gy (RBE), and metastatic sites (n = 16) were treated to 21–24 Gy (RBE). The five-year progression-free survival (PFS) was 64%, and the five-year overall survival (OS) was 94%.

Danny Jazmati et al. [31] performed a retrospective analysis of children with high- or intermediate-risk NB who had proton beam theraphy of the primary tumour site performed during the first-line therapy. Doses ranged from 21.0 to 39.6 Gy (RBE). Although the patients received total doses above 30 Gy, in line with the previously mentioned studies, they did not observe relevant toxicity and tumour control rates were high, both for the primary site and the metastases. The authors point out that the excellent disease-related outcomes and absence of late toxicity support the use of this treatment approach for future populations and in future studies.

In summary, these preliminary studies suggest that proton beam therapy is feasible in children with NB with very little acute and early late toxicity and with good control of both primary disease and metastases. However, randomised controlled trials are needed to definie the role of this modality in children with NB.

Nuclear medicine therapy:

Most NBs express the noradrenaline transporter molecule and take up metaiodobenzylguanidine (MIBG), which can be radiolabelled with either ^{123}I or ^{131}I. The therapeutic role of ^{131}I-MIBG as molecular radiotheraphy for NB remains unclear despite extensive clinical experience. A recent systematic review by Wilson et al yelded 30 studies. In 27 of them, the role of ^{131}I-MIBG was assessed in relapsed and refractory disease, whereas in two studies ^{131}I-MIBG was used as induction therapy and in one as consolidation therapy. No randomised controlled trials were available. The objective tumour response rate reported ranged from 0% to 75%, mean 32%. The authors concluded that many studies have demonstrated the activity of ^{131}I-mIBG therapy in neuroblastoma, although the response rates varied widely. In the absence of randomized controlled studies its true effectiveness compared with other treatments remains unknown. Currently, the best available evidence on the efficacy is derived from several single-arm phase II clinical trials as described in the above mentioned meta-analysis [32]. Therefore prospective randomized trials are essential to improve the evidence of the role of ^{131}I-mIBG as therapeutic agent in NB.

Peptide receptor radionuclide therapy (PRRT) which targets the somatostatin receptor SSTR2 using [^{177}Lu]Lu-DOTATATE (LuDO), is widely used in the treatment of somatostatin positive neuroendocrine tumours (NET) in adults with low or moderate proliferation index, established on the immunohistochemical detection of the proliferation related protein Ki-67. PRRT either alone or in combination with additional anticancer agents has shown efficacy in a range of

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other somatostatin-positive cancers, including NB. However, experiences with this kind of therapy for NB have been controversial. A phase IIa trial showed absence of any objective responses, and authors concluded that the use of LuDO, as a single agent at the dose schedule used in this study is not recommended for the treatment of neuroblastoma [33]. Given that other pilot studies showed positive results with possible long-lasting remission [34, 35], the prospective "A phase II trial of 177Lutetium-DOTATATE in children with primary refractory or relapsed high-risk neuroblastoma - LuDO-N" (EudraCTNo: 2020-004445-36, ClinicalTrials.gov Identifier: NCT04903899) tried to evaluate a new dosing schedule of 2 high-activity administration of single agent 177Lu-DOTATATE given 2 weeks apart, prescribed as a personalised whole body radiation absorbed dose, rather than a fixed administered activity. The authors suggest that the failure of other studies might be because the administered activity was too low, and the courses were spread over an excessively long period of time, for a rapidly proliferating tumour. The authors hope that the results from the LuDO-N trial and similar trials on radiopharmaceutical therapy for high-risk neuroblastoma, will generate valuable knowledge, leading to effective therapeutic options that can significantly improve survival in the future [36].

In conclusion, the role of nuclear medicine therapy in NB is still to be defined. New randomised controlled trials should be considered in order to provide a better evidence about its role.

Secondary Neoplasms:

It is known that survivors of high-risk NB are at higher risk of developing secondary malignant neoplasms [37, 38]. High-risk patients receive drugs capable to increase the risk of myelodysplatic syndrome and leukaemia. Radiation therapy plays a pivotal role in high-risk NB treatment, and a dose-response relationship between therapeutic levels of radiation and secondary cancers in adult survivors of childhood cancers is well established [39, 40]. However, an extensive study by Zhen el al [41] on 4338 patients with NB registered in the Surveillance, Epidemiology and End Results (SEER) database could not prove that radiotherapy was an independent risk factors for developing secondary malignant neoplasms. Further epidemiologic research is needed in this regard, based on the creation of larger dedicated international registries and longer follow up . Furthermore, it is unclear whether the combination of radiation therapy with chemotherapy and/or immunotherapy in high-risk NB patients may worsen the unwanted effects of overlapping toxicity profiles.

KEYPOINTS

- There is a persisting lack of standardization in the choice of imaging modality and acquisition protocols among different centres. This issue should be addressed with the creation of specific guidelines as results of close cooperation between of multidisciplinary teams and stakeholders involved in NB management.
- MRI is an effective radiation-free modality for the evaluation of local disease.
- The knowledge on cumulative exposure dose due to diagnostic imaging from diagnosis to end of treatment is limited. Cumulative dose can be very high especially in high-risk neuroblastomas. Dedicated registries and prospective cohort studies should be created, in which dosimetric data and technical parameters of the studies performed should be recorded for later analysis.
- The knowledge on appropriateness and effectiveness of diagnostic imaging - with related dose exposure - during follow up is limited. This needs to be evaluated based on clinical guidelines of necessary information in future studies.
- SPECT/CT may allow additional information which could be crucial for treatment. More research is needed in this regard determining which parameters should be used and what would be the benefit of the additional information.

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- Radiotherapy is an integral part of the multimodality treatment of high-risk neuroblastoma. However, the dose to be delivered to the tumoral bed is still unclear. Hypothesis driven research based on mechanistical evaluations is needed.
- The role of radiotherapy in metastatic disease is controversial and needs further studies based on randomised controlled trials.
- The possible role of proton beam therapy as an alternative technique to conventional photon-based radiotherapy appears promising. Further research about disease-related outcome and late toxicity is needed, based on randomised controlled trials.
- Further research on the opportunities offered by new radioisotopes for nuclear medicine therapy is needed.
- Knowledge on the onset of second malignancies as a consequence of radiation therapy in patients with high-risk NB is limited. Further research is needed based on dedicated international registries and a longer follow-up.

Pregnant women

According to the International Commission on Radiological Protection (ICRP), ‘‘prenatal doses from most correctly performed diagnostic procedures present no measurably increased risk of prenatal or postnatal death, developmental damage including malformation, or impairment of mental development over the background incidence of these entities; life-time cancer risk following in utero exposure is assumed to be similar to that following irradiation in early childhood” [42].

The American College of Radiology established the rule that fetal doses below 100 mGy should not be considered a reason for terminating a pregnancy [43]. The American College of Obstetricians and Gynecologists [44] published the following policy statement: “Women should be counselled that X-ray exposure from a single diagnostic procedure does not result in harmful fetal effects. Specifically, exposure to < 5 rad (50 mGy) has not been associated with an increase in fetal anomalies or pregnancy loss.”

The natural risk for malformations at birth is 4%, According to McCoullough et al. [45], 100 mGy of conceptus dose will only slightly reduce the proportion of children without a malformation from 96% to 95.8%, and similarly, the natural rate of 99.93% of children without cancer during childhood will just marginally decrease to 99.07%; together, 95.93% of children will have neither a malformation nor childhood cancer after 0 mGy, and 94.91% after 100 mGy. This on the other hand means, that instead of 4 children out of 100 (unexposed), 5 children out of 100 (exposed with 100 mGy) will suffer from malformation or childhood cancer meaning an increase of approximately 25% in the number of diseased children. This needs to be discussed by society whether this is seen as acceptable and under which circumstances.

<u>Diagnostic Imaging:</u>
Diagnostic imaging typically delivers doses to the conceptus well below 100 mSv. The imaging of female patients with known pregnancy using ionizing radiation must be justified. Justification is based on the specific benefits and risks for both the mother and the child. The stronger the arguments for a critical situation of one of them the easier is the justification; in contrast, a vague suspicion would not justify an important exposure. When feasible, techniques not involving ionizing radiation should be used (MRI, ultrasound), if they provide the required information without loss of diagnostic information.

The radiation dose absorbed by the fetus cannot be measured directly. The most popular fetal dose estimation methods are based on phantom measurements and/or geometric phantom simulation methods. Fetal radiation dose appears to be related with mother size and is independent of gestational age [46].

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CT examinations are the main source of exposure to the conceptus. Most common conditions that may require CT examinations during pregnancy are pulmonary embolism, trauma, and acute abdomen (abdominal pain, appendicitis).

Recently published data reported a significant increase in the use of CT during pregnancies over the past 21 years (1996–2016) in North America, with approximately 0.8% of pregnancies subjected to examinations, with a four-fold increase in the last 20 years. [47]

Even if CT radiation exposure is significantly higher than conventional x-ray radiography, doses used during routine CT examinations, including abdomino-pelvic scans (single-phase), do not exceed exposures of 100 mGy to the conceptus. In a recent study, the mean in utero doses at different stages of pregnancy were estimated with the use of a suitable anthropomorphic phantom and were calibrated with volumetric CT dose index measurements and Monte Carlo simulation; they varied from 0.04 to 1.04 mGy, from 4.8 to 5.8 mGy, and from 9.8 to 12.6 mGy for CT examinations for pulmonary angiography, abdomino-pelvic and trauma investigations performed with 64-slice CT scanner. Again, all doses were substantially lower than 100 mGy [48].

In addition, ultra-low-dose (ULD) CT protocols may potentially be used for the investigations of pregnant women, with dose levels close to those of conventional radiographs (i.e., effective dose lower than 1 mSv); currently, several technical improvements are being developed to optimise diagnostic performance with ULD CT [49-52]. Here, further research should be performed to try to establish criteria for required image quality and ways to measure such criteria to allow guidelines when ULD CT could be used.

Nuclear Imaging:

Nuclear medicine examinations are usually avoided during pregnancy and their effect depends on the physical properties of the radioisotope, including maternal uptake and excretion, passage of the agent across the blood-placenta barrier, and uptake by the conceptus. Technetium 99m is commonly used in ventilation-perfusion (V/Q) lung scans, when pulmonary embolism is suspected; the absorbed fetal dose in such a case is lower than 5 mGy, which is within the acceptable dose constraints. Conversely, iodine 131 is contraindicated during pregnancy due to its deleterious effects on the fetal thyroid gland; if a thyroid scan is considered necessary, technetium 99 m should be used instead [44]. Nuclear medicine examinations other than V/Q scans are seldomly indicated in pregnancy. Dose estimation coefficients for the most common radiopharmaceuticals are reported in the ICRP Publication 128 [53].

The absorbed dose to the uterus, which is included in the dose tabulations, may be used as a substitute for the absorbed dose to the embryo if the woman is in the first 2–3 months of pregnancy. Similarly, the absorbed dose to the fetus from radioactive substances without placental transfer is expected to be in the same range as the dose to the uterus. For radioactive substances with placental transfer, the absorbed dose to organs and tissues of the mother may, as a first approximation, be taken as representative of the absorbed dose to the corresponding organs and tissues of the fetus [53].

More detailed radiation dose estimates for the fetus from administration of a number of radiopharmaceuticals to women at various stages of pregnancy are given by Russell et al. [54]. Their data illustrate that the majority of studies will probably involve fetal doses of 10 mGy, according to present knowledge. Therapeutic administrations are routinely contra-indicated in the case of pregnancy as this may result in very high fetal doses as well as for breast-feeding women. In addition, beyond 10–13 weeks of gestation, the fetal thyroid may receive extremely high doses in cases of applying a therapy using 131I-iodine [55].

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Radiation Therapy:

Cancer during pregnancy is rare and the knowledge of this special population of patients is pretty limited. Approximately 1 per 1,000 pregnant women will be diagnosed with cancer. The most common one is breast cancer accounting for 30% of all neoplasms. These women will frequently need radiation therapy as well as imaging for staging, including nuclear medicine. Cancer incidence is increasing in pregnant women, which is thought to be due to increasing maternal age. Other common cancers are cervical, lymphoma, melanoma, and thyroid, and most of these would include considering management with radiation therapy during pregnancy. Since the 1970s, radiation therapy of the pelvic region during pregnancy has not been considered an option, due to dose levels in excess of 100 mGy to the embryo/fetus.

The pelvic treatment fields employed for the management of cervical cancer, for example, typically deliver a radiation dose to the tumour site of more than 45 Gy. For such a treatment, the fetus would be partly or entirely included within the treatment volume, and thus receive a radiation dose far in excess of the threshold of 100 mGy. This implies that pelvic radiation therapy during pregnancy may result in severe harmful effects or even lethal consequences for the developing fetus and, therefore, cannot be applied in clinical practice [56].

Thus, the role of radiation therapy during pregnancy is limited to tumours outside the pelvic region. Radiation therapy has been used for the management of several supradiaphragmatic malignancies in pregnant patients such as brain tumours [16-18], head and neck cancer [60-61], breast tumours [62-63] and Hodgkin lymphoma [64-65].

The fetus is always completely excluded from the above treatment fields and therefore receives only an out-of-field dose which is much lower than the dose to the tumour site. The fetal exposure from radiation therapy is due to scattered radiation and leakage through the head of the treatment machine. The fetal dose can be above or below the threshold of 100 mGy, depending on the tumour site and the gestational age at the time of irradiation [66]. The radiation dose to the fetus should always be estimated prior to the start of radition therapy. This dose assessment allows the radiation oncologist and the medical physicist to examine the need and technical possibilities for fetal dose reduction either by using special shielding equipment or by modifying the irradiation parameters.

The accurate knowledge of the fetal dose before the patient's treatment is a prerequisite for deciding whether the radiation therapy can be applied during pregnancy.

Fetal doses from previous reports [56] are shown in figure 1.

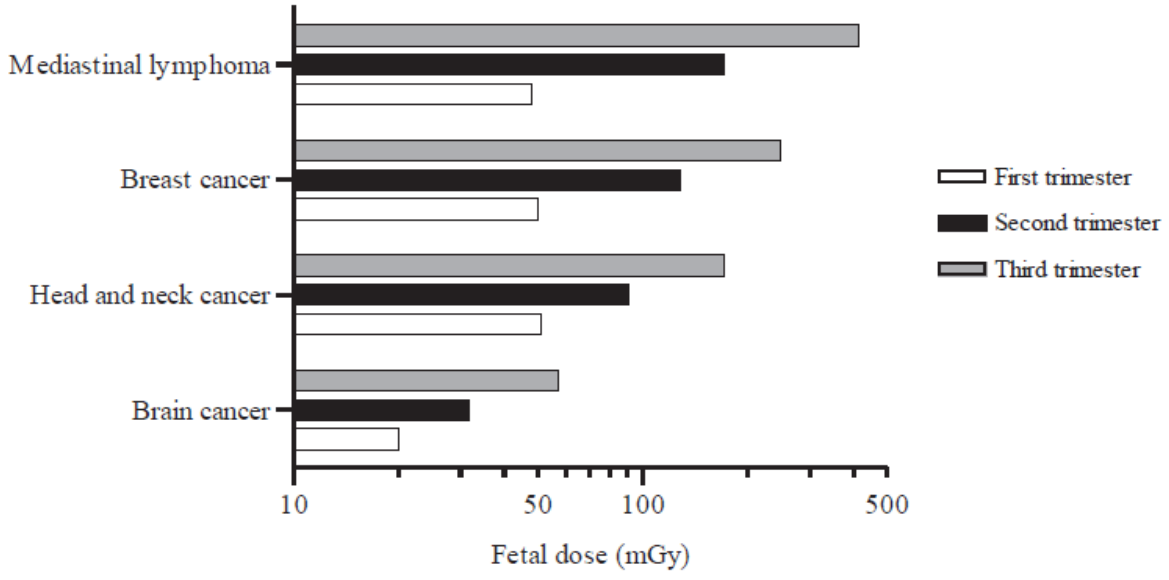

Figure 1 [15]

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Depending on tumour site and period of gestation, doses to the conceptus may or may not exceed the 100 mGy threshold. The fetal dose due to irradiation for a head and neck cancer, breast carcinoma and mediastinal lymphoma can be kept below the threshold value at the first trimester of gestation. However, the fetal dose from radiation therapy for these malignancies may exceed the critical value of 100 mGy at more advanced stages of the pregnancy. Fetal radiation doses of up to 171.0 mGy, 248.0 mGy and 411.3 mGy have been reported for radiation therapy for head and neck cancer, breast cancer, and Hodgkin lymphoma in the mediastinum respectively, during the last three months of pregnancy [56].

Fetal shielding during external photon beam radiotherapy is not only feasible but recommended by the AAPM TG-36 [67]. The Task Group recommended the use of 5-7 cm of lead, subsequent studies found small dose reduction when passing from 5 to 7-8 cm, showing that the fetus can be effectively protected using a lead thickness of 5 cm [68-69].

Several devices have been implemented, allowing protection of the fetus from different directions [70-71], while Podgorask et al demonstrated that many different beam orientations may lead to a fetus dose reduction up to 50% [72].

Other than shielding, it is possible to reduce the dose to the fetus with the appropriate choice of treatment technique and parameters. An increase in field dimension, for instance, leads to a considerable dose elevation, regardless of tumour site and age of gestation [73].

The use of beams with a peak energy higher than 10 MV should be avoided during pregnancy because of the production of neutrons that need to be shielded with appropriate materials other than lead (i.e. borated polyethylene) [74].

Radiation therapy with charged particles could, in principle, reduce the amount of scattered radiation. However, the main contributors to the dose outside the field of treatment are secondary neutrons. For these the biological effectiveness is much higher than secondary photons (RBE for neutrons is energy-dependent and up to 20). Secondary neutrons produced by pencil beam scanning are fewer than those produced by passive scanning techniques, but, because of the high RBE, they still can deliver a significant amount of dose to the fetus, from 2-to-9 times higher than the fetal dose caused by the planning CT [75-77].

The advent of international and national registries for pregnant patients with cancer and a greater commitment to research on this special population has recently shown fewer terminations, fewer caesarean sections, and better maternal-fetal outcomes [78]. A larger implementation of these registries will allow to collect more information in terms of dose exposure to the conceptus and untowards effects.

KEYPOINTS

- Further research is needed to improve estimation of the radiation exposure of the fetus during radiologic imaging, nuclear imaging and maternal radiation therapy.
- Future research on alternative radiation therapy approaches like hadron therapy could be investigated regarding the special effect on pregnant women and the conceptus.
- The creation of national and international registries for pregnant patients with cancer is very much needed in order to gain a better knowledge of this special population, to optimise treatment and to improve maternal and fetal outcomes.

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Screening programs

Justification and optimization are the mainstays of radiation protection. Both of them are especially important in screening programs using ionizing radiation, as a large group of the population is examined regularly, usually to detect cancers in a small proportion of the examined group. We decided to consider lung cancer screening and breast cancer screening because of their large impact on the population.

Lung cancer screening

Lung cancer is the leading cause of death from cancer worldwide and causes more deaths than breast, colorectal, and cervical cancers combined [79]. Only 15% of patients with lung cancer are still alive 5 years after diagnosis, because approximately 70% of patients suffer from advanced disease status at the time of diagnosis [80].

Two large sufficiently powered randomised controlled trials have shown a significant reduction in lung cancer mortality in heavy current or former smokers who were screened with low-dose CT (LDCT), in comparison to chest radiography (NLST) [81] or no-screening (NELSON) [82]. These results were further confirmed by a meta-analysis that included 9 randomised LDCT screening trials enrolling over 96,000 persons, with an estimated mortality reduction of 16% [83].

However, an optimized setup of selection criteria is needed in order to justify the screening inclusion and thus avoid unnecessary imaging in low-risk individuals with related non-justified dose exposure and risk possibly outweighing the benefits. For this reason, two major approaches have been selected for high-risk ever-smokers for LDCT screening. The first is categorical age (age 50/55 to 74/77/80 years), 15/18.8/30 pack-years and time since quitting (10/15 years for former smokers) which is state of the art, as it has been used by NELSON, NLST, US Medicare and Medicaid Services and the US Preventive Services Task Force (USPSTF) as screening criteria, [81,82,84,85]. A second approach is to use risk prediction models that are based on incidence lung cancer risk or risk of lung cancer death. Accurate lung cancer risk prediction models use additional predictors in quantifying risk. Several models have been proposed [86] and identified as being accurate and possibly suitable for guiding selection of individuals for lung cancer screening [87-88], such as the Bach Lung Cancer Death Risk Assessment Tool and the Prostate, Lung, Colorectal, and Ovarian (PLCO) M2012 model [89-91].

To date, the PLCOm2012 is the lung cancer risk prediction model that has been most validated by different research teams in multiple countries around the world, including the US, Germany, Australia, the UK, Canada, and Brazil [86-88, 90-98].

A new prospective study will try to evaluate the comparative accuracy and effectiveness of two promising multivariable risk models for subject selection and nodule management in lung cancer screening [99]: first interim results indicate that the classification accuracy of lung cancer screening outcomes supports the PLCOm2012 criteria over the USPSTF criteria, since the PLCOm2012 criteria detected significantly more lung cancers [100].

Another randomised trial, the Yorkshire Clinical Trial, will compare the performance of PLCOm2012 and USPSTF2013 eligibility criteria, with the additional comparative assessment of a third model, the Liverpool Lung Project (LLPv2) [101].

In general, for all approaches mentioned above, further investigations as well as further optimizations are needed.

What to do when a lung nodule is detected is a key point in terms of patient management. Different approaches have been proposed in order to minimise harm from radiation exposure

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related to imaging studies, invasive procedures, and clinically significant distress [102-103]. A practical approach is to assign patients with lung nodules into one of three categories: routine screening, early recall surveillance at a certain time or referral for a diagnostic workup. Significant variations exist in guidelines for management of lung nodules detected at the baseline and, currently, no protocol can accurately identify all malignant lung nodules while avoiding unnecessary diagnostic workup for benign nodules [104]. Since such nodule management depends on dimension measurements, it is worth noticing that volume estimation via software is software-dependent and can lead to different recall rates [105]. Thus, different recall rates, derived from nodule measurements and management, may lead to a different number of examinations, and, consequently, to different levels of exposure [106].

The PanCan Pulmonary Nodule Malignancy Probability model is the first attempt to personalise nodule management from baseline screening LDCT, using clinical-epidemiological information and nodule information [107]. The prediction tool has been validated by several studies [108-114] and one of its strengths is the identification of low-risk individuals who can undergo the next screening LDCT after 2 years instead of annually [98, 115-116]. In addition, risk-tailored approaches and automatic nodules management with deep learning algorithms may lead to a reduction in unnecessary examinations [117-118].

First results of LDCT in combination with the so-called “liquid-biopsy” have been published, showing the possibilities of personalization in screening intervals [119].

Guidelines on CT requirements for lung cancer screening have been published [120-123].

The American College of Radiology (ACR) recommends using at least 16-slice multi-detector CT scanners (MDCT), whereas the European Society of Thoracic Imaging (ESTI) sets the lower limit at 32-slice and recommends 64-slice MDCT. The total scan time is recommended to be below 10 seconds to cover the total chest within a single breath hold. A tube voltage of 100–120 kVp is acceptable for standard sized patients, whereas a tube voltage of 140 kVp may be used in obese patients. The tube current should be set in conjunction with the tube voltage and pitch to meet certain $CTDI_{vol}$ requirements. The $CTDI_{vol}$ to be met has decreased over the years: in 2014 the ACR reports a level of <3 mGy for standard patient size, while in 2019 ESTI reports levels of <1.6 mGy for patient size up to 80 kg, resulting in an effective radiation dose of approximately 0.7 mSv. The pitch factor is inherent to the system settings since it is based on the rotation time, table feed and output (beam width) of a CT system. The guidelines discourage the use of fixed tube currents, but highly recommend the use of automated tube current modulation based on a patient’s habitus. Moreover, the use of automated tube voltage selection and organ dose modulation is advised. The ACR recommends a pitch between 0.7–1.5, but states that this parameter should be set with the other acquisition parameters mentioned before and the $CTDI_{vol}$.

In contrast to former studies, the current guidelines describe in detail the reconstruction parameters to be used. For a better lung nodule detectability, reconstruction of the CT images is recommended at slice thickness ≤1.0 mm with a slice increment smaller than the slice thickness (≤0.7 mm), but overlapping reconstructions are not mandatory. The field-of-view may be optimised for every patient to include the entire lungs up to 1 cm beyond the rib cage. Standard body or mediastinum/soft tissue and lung kernels should be used and, in addition to this, a medium-sharp (lung) kernel without edge enhancement may be used.

In addition to the radiological societies, a working group of the American Association of Physicists in Medicine (AAPM) developed a set of detailed acquisition protocols for over 30 CT systems of six major vendors for lung cancer screening purposes [124]. These protocols are based on the experience gained with the NLST study and other screening studies by the working group. Similar to the ACR guideline, these protocols should result in radiation dose ($CTDI_{vol}$ ≤3 mGy corresponding to effective doses ≤1.0 mSv) for a standardised patient of 70 kg. However, radiation dose may vary from 0.25 to 5.6 mGy for patients from 50 to 120 kg.

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Recommended acquisition protocols for low dose CT in screening programmes include different values to be chosen in all technical parameters, leading to great variability across institutions [123, 125], in which doses may exceed the recommended $CTDI_{vol}$ value of 3 mGy for a standard patient.

Effective doses are reported to be in the range 0.8-1.5 mSv for medium size participants in the trials initiated between 2001 and 2011.

Regarding cumulative exposure, the COSMOS study reported a median effective dose of 9.3 mSv and 13 mSv at the 10^{th} year of screening for men and women, respectively [126], while the ITALUNG randomised clinical trial reported mean effective doses of 6.2 and 6.8 mSv over 4 years, according to the craniocaudal length of the LDCT examination [127].

Since many lung cancer screening programmes begun in the early 2000s, the CT technology used dates back to 20 years ago.

More recent developments, especially iterative reconstruction algorithms, have allowed for ultralow-dose CT (ULDCT), well below 1 mSv, but the overall diagnostic performance might be affected by such dose decrease [128-131].

Deep learning image reconstruction, however, seems to be able to eliminate all pitfalls in ULDCT, increasing nodule detection rate and improving measurement accuracy [132-133]. However, further research is needed to elaborate the limits of such methods and to evaluate performance more carefully.

Lung cancer screening is a powerful tool to reduce mortality in high-risk human beings. In order to minimise radiation exposure, population selection, nodule management and recall rates, and CT acquisition protocols should be taken into account.

Current CT protocol guidelines set a desirable value of 3 mGy which should not be exceeded for a standard size patient. Development in CT technology may lead to a ULDCT protocol with a ten-fold dose reduction; however, its clinical performance needs to be evaluated thoroughly.

Deep learning reconstruction algorithms might be promising tools to reduce noise without losing nodule detection accuracy. However, potential limitations has to be evaluated very carefully as imgaes might always look nice but data might contain insufficient or wrong information.

KEYPOINTS

- Optimisation of screening selection criteria is needed to improve justification of radiological studies. This point should be addressed with the creation of specific guidelines based on update and refinement of risk models.
- Management of nodule detected on LDCT is a topic of research in order to better justify repeated imaging studies and invasive procedure, and to avoid significant distress. This needs to be further evaluated.
- Combination of liquid biopsy with LDCT is a topic of research, as it could change the management of patients and should be investigated further as hypothesis driven research.
- Guidelines on CT requirements for lung cancer screening are available and need to be periodically updated to reflect the improvements in available technologies. It would be helpful to define image quality requirements as well as requirements on exposure.
- Some data concerning the cumulative exposure during the years of screening for single exposure are available.

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- The possible role of ultra-low dose CT in combination with artificial intelligence-based reconstruction algorithms is a matter of research. Further evaluation as well as research on limitations seems to be mandatory.

Breast cancer screening

Breast cancer (BC) it is the leading cause of cancer related death in women, with 15.5% of all cancer deaths in women and 24.5% of all female cancers worldwide attributed to breast cancer. It is also now the most commonly diagnosed cancer in both sexes with 11.7% incidence, surpassing lung cancer at 11.4%. Globo Cancer Statistics (GLOBOCAN) 2020 ranked breast cancer as the 5th leading cause of cancer death overall, with 685000 deaths [134] worldwide in 2020.

The net increase in breast cancer detection over the past few decades, for both invasive and in-situ cases, has been attributed to longer life expectancy and the introduction of mammography screening. This is especially evident in women > 50 years, which is the starting age for active invitation by most screening programs [135]. Breast screening programs have played an important role in the past three decades by increasing survival rates and reducing mortality rates through early breast cancer detection. The number of benign or small in-situ and invasive cancers are diagnosed 1–3 years earlier with, as opposed to without, breast screening programs [136-137].

Screening mammography is the best method of early detection, and the evidence thus far claims it is most effective in breast cancer mortality reduction for women aged 50–69 years [138]. Upon randomised controlled trials, the reduction in BC mortality due to screening mammography is confirmed for women between 50 and 69 years of age. In 2015, the International Agency for Research on Cancer (IARC) conducted a review of 20 cohort studies and 20 case-control studies: the estimated reduction in BC mortality was 40% for women aged 50–69 years who take up the invitation and 23% when also including those who do not accept the invitation, as a societal effect of the screening policy. From cohort studies, a mortality reduction has also been estimated for women aged 40–49 years and 70–74 years, though the evidence from published studies was considered to be “limited”. Available data did not allow the IARC working group to define an optimal screening interval [138].

Screening programmes differ in both range of population and recall rates: UK screens triennially in the 50-70 years range [139], the U.S. screens biennially for women ≥ 55 years [140], Canada screens every 2-3 years in the 50-74 range [141] and Australia screens biennially in the 50-74 years range [142].

In their position statement, the European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies, strongly support screening mammography of the female population at average breast cancer risk, typically from 50 to 69 years of age.

They consider the extension up to 73 years as a second priority. Screening of younger women, starting as early as 40 years of age, should be evaluated, as a third priority, country by country [142].

The benefit to risk ratio of mammography screening is frequently debated: on the one hand we have a demonstrated reduction in mortality, on the other hand we have risks due to ionizing radiation. To date, there has been no direct evidence that single or cumulative exposures result in radio-induced cancer, but cancers due to exposure to low doses may have long latency period and it may be difficult to discriminate between cancers that are radiation-induced from those that occur naturally [143-144].

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Hooshmand et al [145] estimated a 15:1 benefit-to-risk ratio for annual screening in range 40-49 years and a 62:1 ratio for annual screening in range 40-55, then biennially until 74 years.

Authors assumed an average mean glandular dose of 2.78 mGy for examination (4 projections: 2 craniocaudal and 2 mediolateral oblique). Obviously, those estimates rely on the underlying assumptions made by the authors: if the design of the screening programmes was different, cumulative dose would be different (for example with examinations every 2 or 3 years starting from 50 years).

Warren et al, assuming a mean glandular dose (MGD) of 3 mGy across all thicknesses, reported that the number of deaths caused by radiation-induced cancers is estimated to be around 150 times smaller than the number of lives saved through screening [146].

Loveland et al, in collecting doses of the UK breast-screening programme, showed an MGD of 1.57 mGy for cranio-caudal and 1.75 mGy for medio-lateral oblique views [147].

The work of Ali et al focuses on the estimation of radiation induced breast cancer for different screening programmes: they found a wide range of effective risk, from 42 cases to 1099, over a million people. These differences depend on how the screening programmes are designed but most of all on the commencement age of screening. For instance the highest incidence risk of radiation induced cancer is that of the U.S. screening programme for high-risk women, whereby women may undergo their first examination as early as 30 years of age [148].

Digital breast tomosynthesis (DBT) has been introduced to overcome the intrinsic limitation of tissue superposition in digital mammography (DM), allowing a 3-dimensional localization of a lesion in the breast.

Evidence on clinical performance of DBT is growing as it is known to reduce recall rates in screening and improve detection of abnormalities in women with dense breast tissue, improve diagnosis of benign findings, reduce the number of negative biopsies and assess therapeutic efficacy [149-150]. The study of Gilbert et al, for example, found that DBT increased the sensitivity of 2D mammography in women with dense breasts and the specificity of 2D mammography for all subgroups [151].

DBT tomosynthesis, however, may deliver higher doses to women, due to its intrinsic imaging technique. In DBT, in fact, the X-ray tube rotates over a limited angular range and a low dose exposure of the compressed breast is acquired every few degrees. The average absorbed dose to the glandular tissues is the summation of absorbed doses in the fibro-glandular tissue of the breast from all the multiple low-dose projection images. Tomosynthesis imaging includes multiple parameters that may influence the resulting breast dose. The angular range and number of exposures acquired during a scan are specific to the design of a system and thus these parameters are the same across acquisitions for a particular unit. Different manufacturers of DBT units have adopted quite different settings for these parameters, which are also associated with the detector type used and its design, and whether it is stationary or movable [152].

Artificial Intelligence (AI) in breast screening has been explored in the recent years. A review of the literature performed by Freeman et al, reported results from 12 studies (all retrospective, years of publication 2019-2021), concluding that the role for of AI cannot be evaluated currently with sufficient evidence. The authors show that AI systems are not accurate enough to replace the double reading by radiologists, and underline that, in general, it is unclear which aspects of the breast-screening pathway could benefit from AI. Therefore, they advocate the need for prospective studies with robust designs and large samples to properly evaluate the impact of AI in improving the accuracy for the detection of breast cancer in mammography screening practice. [153]

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In a study by Shoshan et al, AI proved to be effective in excluding true negative DBT images, thus reducing the radiologists' workload by 39%, but these promising results should be readdressed in further prospective studies [154].

In their review, Sechopolous et al concluded that AI performance in real clinical settings could only be evaluated through large-scale screening trials [155].

Breast ultrasound (US) is typically used as a complementary modality, its main advantage being the lack of ionizing radiation. However, as a stand-alone screening technique it lacks specificity, leading to unnecessary recalls and biopsies of benign findings. Thus, improvement in specificity is needed to increase its value as a screening method [156-157].

Colour Doppler, is a well-known technique to improve specificity of US. However, it is usually performed in large vessels that are not present in breast lesion, but with proper image processing and a low flow velocity scale the visualization of smaller vessels appears to be possible. With a better view of the internal microvascular distribution it may be possible to improve specificity: Zhou et al, for example, reported an increase in specificity from 0.70 to 0.85 in Breast Imaging-Reporting and Data System (BIRADS, ACR) 4 categorization [158].

Breast MRI is the imaging technique with the highest sensitivity for cancer detection, even in very dense breasts [159-162]. However, its high costs, the long duration of the examination and the lack of availability could be obstacles to the routine use of breast MRI as a screening tool. Abbreviated MRI, on the other hand, has shorter image acquisition and interpretation times, and this could increase the availability of breast MRI and reduce the costs. The abbreviated protocol includes a pre-contrast examination and one postcontrast T1-weighted examination, along with subtraction images and maximum intensity projection images, halving the number of acquisitions requested by the American College of radiology for accreditation (T2-weighted sequence and pre-contrast, early postcontrast, and delayed postcontrast T1-weighted images) [163]. Studies from Kuhl et al and Leithner et al showed that abbreviated MRI has a comparable diagnostic accuracy to the full protocol but with greatly reduced acquisition and interpretation times [164-165]. A multicentre randomised trial comparing the screening performance of abbreviated breast MRI and DBT in women with dense breasts found the invasive cancer detection rate to be 11.8 per 1000 women with abbreviated breast MRI versus 4.8 per 1000 women using DBT, a difference of seven per 1000 women. Pathology of core or surgical biopsy was the reference standard for cancer detection [166].

Diffusion weighted images could be an added value, as breast cancers show decreased water diffusion due to increased cell density, leading to higher signal intensity on diffusion-weighted images. Several studies show that diffusion-weighted imaging can improve the differentiation between benign and malignant lesions [167-168].

Preliminary studies suggest unenhanced MRI with diffusion weighted MRI may have higher sensitivity than screening mammography for the detection of breast malignancies [169-170]. However, current diffusion-weighted imaging techniques are not sensitive enough to replace contrast-enhanced breast MRI, particularly because the sensitivity for subcentimeter and non-mass lesions is limited. [171-172].

Although breast cancer is one of the few cancers with a well-established screening test using mammography, several authors have investigated whether liquid biopsy can also play a role. Potential applications of liquid biopsy in breast cancer span the entire course of the disease from (early) diagnosis to treatment for metastases. Actually, the ability of liquid biopsy to pick up patients with early-stage disease or even in situ carcinoma remains uncertain. Although highly sensitive assays can detect trace amounts of ctDNA, not all breast cancers will present the same genetic mutations, and the same genetic mutation may be seen in many different cancer types, which may pose challenges to localizing the cancer [173]. In breast cancer, liquid biopsy may play a greater role in monitoring response, determining whether a patient has a

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minimal residual and highlighting the acquisition of mutations that confer resistance to endocrine therapies [173]. However, at present, liquid biopsy is at best an ancillary investigation that complements and builds on results from conventional tissue biopsies. Liquid biopsies in breast cancer have yielded cautiously promising results thus far and the outlook remains optimistic. With time, it is certainly possible that liquid biopsies may play an even greater role in the breast cancer clinic [173] and may reduce the use of radiological screening. An optimal screening setup including all realistic and feasible options shall be developed.

KEYPOINTS

- Justification of screening mammography in woman aged 40-49 and 70-74 years is still matter of debate. Randomised controlled trials should be considered to assess the effectiveness of breast cancer screening in these two age ranges.
- In the age range 50-69, as mortality reduction with screening is no longer matter of debate, an optimal screening interval with mammography has still to be defined. Randomised controlled trials should be considered to define screening intervals that are more efficient.
- The risk of radiation induced breast cancer, albeit low, varies widely according to the design of the screening programme.
- According to current evidence, artificial intelligence in breast cancer screening has not been proven to play a significant role. However, prospective studies with robust designs are needed to properly evaluate its role. First applications as computer aided diagnosis systems to replace the second reader are coming to the market and needs to be evaluated further.
- MRI has the highest sensitivity for cancer detection and could become a game changer, although costs, lack of availability and duration of examination presently hinder its routine use as a screening tool. New, abbreviated protocols could increase the use of MRI as a screening tool. Further controlled studies are needed, But will be out of scope for the EURAMED rocc-n-roll strategic agenda. Evaluations are needed how the society and the health care systems can best benefit from combined approaches.
- An optimal screening setup including all realistic and feasible options that could contribute to the best possible information gathered in a realistic and feasible way shall be developed.

Chronic conditions

Cystic fibrosis represents an excellent example of chronic disease, as it requires frequent radiological studies during its course. Justification and optimization of radiological imaging, frequency, and duration of follow up with radiological imaging, cumulative doses during the course of the disease and alternate radiation-free techniques appear to be the main topics that need to be addressed.

Research is needed to investigate new imaging approaches and corresponding modalities that might help to understand e.g. immunological or inflammatory diseases. Potential examples could be improved nuclear medicine imaging modalities or X-ray fluorescence based imaging using for example nanoparticles as markers. In addition, also new methods for evaluating structural information based on X-ray imaging like dark-field imaging, phase-contrats-imaging or other new approaches will be worse to look at. Such methods could be coupled to AI based evaluations to work with low radiation doses and or elaborate on disease progress.

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Cystic fibrosis

Cystic fibrosis (CF) is a multisystemic life-limiting disease. CF is caused by an autosomal recessive disorder, and it is characterised by viscid exocrine gland and acinar secretions causing tubular obstruction and bronchiectasis. Irreversible airway disease and lung destruction caused by chronic bacterial infections and inflammation are the most relevant sources of disease-related mortality and morbidity and are responsible for more than 80% of deaths [174]. Modern treatments continue to extend the life expectancy of patients with CF: data from the Cystic Fibrosis Foundation 2019 Patient Registry Annual Data Report shows that the median predicted survival for CF patients in the United States improved from 38 years for those born in 2008 to 48.4 years for those born in 2019 [175]. This significant improvement has been largely achieved by the introduction of prevention and yearly monitoring programmes, which aim to detect disease at an early phase and closely monitor disease progression [176]. The progression of lung disease has been routinely assessed by pulmonary function tests [177], although chest imaging has proven to be more sensitive than pulmonary function tests in the detection of structural lung damage [178]. However, several issues related to the use of chest imaging modalities in CF remain unaddressed. For example, it is unclear when and how different modalities such as chest radiograph, CT and MRI should be used and this variability in practice among centers is the reason of different radiation exposures in patients [179].

Recently, a group of experts in CF imaging founded the iMAging managEment of cySTic fibROsis (MAESTRO) committee, with the aim of outlining the challenges and issues of the practice of imaging in CF through a systematic literature research and producing a series of recommendations [180]. Three different scenarios were considered in this review: first diagnosis, follow-up, and pulmonary exacerbation.

Concerning first diagnosis, the MAESTRO consortium emphasises that CT shows higher sensitivity in detecting early abnormalities than chest radiography, with the main limitation for CT being the absence of protocol harmonization. Furthermore, there is no consensus on what dose level may be considered low and on the optimal timing of the first CT examination. The lower yielding of MRI and the frequent need for sedation in children limit its role at the time of first diagnosis [180].

Concerning follow-up, the MAESTRO consortium advises against the use of chest radiography, as it is often unable to efficiently monitor CF lung disease progression, being less sensitive than CT. To this regard, in view of the progressive increase in life expectancy of the CF population, the risk of radiation exposure could be minimised by an optimised use of CT and an increased utilisation of MRI. The authors emphasise that the lack of guidelines regarding the optimal timing of imaging follow up contributes to the great heterogeneity of imaging protocols among CF centres. In future, imaging follow-up should be patient-tailored and include stratification for risk factors for disease progression, such as chronic bacterial infection and pulmonary exacerbation rate. Such a patient-tailored approach could further reduce the risk of radiation exposure by modifying the imaging interval according to disease status, with longer CT scan intervals in more stable CF patients [180]. Artificial intelligence could play a role in improving the diagnostic performance of chest radiography, thus contributing to limit the cumulative dose due to diagnostic imaging [181]. Artificial intelligence can play a role also in CT imaging, providing automated scoring systems [182].

The MAESTRO consortium emphasises that MRI may become a "one-stop-shop" for CF imaging, thanks to its ability to provide information on lung ventilation, inflammation, perfusion, and structure in a single examination, but is limited by its higher cost compared to CT, and by the need for sedation in uncooperative patients. The benefit afforded by the absence of radiation in MRI technology is particularly important with respect to the potential need for frequent follow-up and the increasing life span of CF patients. More importantly, MRI has a unique advantage over CT, which is the ability to provide information on ventilation,

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inflammation, perfusion, and structure in a single examination. Future studies should focus on MRI protocol harmonisation to foster the development of comparable image quality between CF centres and MRI vendors [180].

Concerning lung ultrasound in patients with CF, the MAESTRO consortium does not support its use for lung disease monitoring as the available evidence is insufficient. Further multi-centre validation studies are needed to assess its potential role [180].

Pulmonary exacerbation is a major determinant of lung function decline and mortality in the CF population. However, the absence of a consensus on the definition of pulmonary exacerbation compromises its optimal clinical management, including the use of imaging for diagnosis and follow-up [183]. The most frequently used imaging modality during exacerbation is chest radiography, despite its poor sensitivity and specificity, especially in patients with severe disease [184]. In this context, CT offers a higher yield but at the cost of a higher dose exposure, and this limits its routine use. With regards to this, the MAESTRO consortium suggests the use of low dose CT protocols in patients with persistent respiratory symptoms despite therapy [180]. Conversely, MRI could offer a valuable alternative thanks to its ability to detect morphological changes related to pulmonary exacerbation with adequate sensitivity and to assess response to treatment [185-187].

Several studies have focused on dose exposure from diagnostic imaging in patients with CF. The study of O'Connell et al. first evaluated the cumulative radiation exposure for 230 CF patients over a long time period (1992-2009). They found that cumulative effective dose (CED) was mainly due to thoracic imaging and abdominal imaging, and that there was an increase of exposure over time which was related to a 5.9-fold increase in the number of CT scans. In particular, in the 10% of patients with the highest CED, 62% of exposure was related to CT scans [188].

O'Reilly et al reported in a retrospective study in 77 children a mean CED of 6.2 mSv [189], while Donadieu et al found a mean CED of 19.5 mSv in their retrospective study on over 80 patients [190].

However, up-to-date scanner and optimised CT protocols may greatly reduce exposure, and a typical 18-year-old patient with CF may receive a CED of approximately 3.5 mSv [191].

Not surprisingly, the average age of the first thoracic CT has decreased dramatically, passing from 20 years for patients born before 1980, to 1.9 years for patients born after 1997 [190], while the median age of death increased by over 0.5 life year per year across US, England and Wales between 1972 and 2009. Given these premises, there is an ongoing requirement for strategies aiming to reduce radiation exposure without affecting diagnostic capabilities.

Iterative reconstruction (IR) has the potential for dose optimisation: when reconstructed with IR, thoracic volumetric images can be diagnostically satisfactory with 40 mAs and a CTDIvol of 3.5 mGy [192].

Several other studies demonstrated that the subjective image quality of low-dose chest CT with IR was similar or improved compared to standard-dose CT [193-194].

Lin et al found that ultra-low dose (ULD) chest CT delivered 94% less dose than LD-CT, but was superior to chest radiography in CF disease quantification, thus being an effective imaging technique for CF surveillance [195-197].

Ernst et al [197] found that the diagnostic quality of a dedicated ULD chest CT was similar to their standard reference CT protocol: median effective dose was 0.05 mSv for adults and 0.04 mSv for children, values which are very close to a chest radiography [197]. Unfortunately, literature addressing CT technical parameters in LD or ULD chest CT is not extensive. Joyce

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et al report the following parameters: 80 kVp, 20 mA, 0.4 s of rotation time, 1.375 as pitch factor, scanning FOV of 32 cm (mean effective dose 0.08 mSv). Images are reconstructed at 3 mm with model-based IR in axial, coronal and sagittal planes, while Willemink et al. [193] report 80 kVp and 28 mAs for a whole chest exams with 0.38 mSv of effective dose. In the study of Ernst et al [197] the ULD protocol presented 80 kVp, 0.4 s rotation time, minimum tube current of 10 mA and images were reconstructed at 0.625 mm slice thickness with model based iterative reconstruction.

The European Cystic Fibrosis Society Clinical Trial Network (ECFS-CTN) developed the Standardised Chest Imaging Framework for Interventions and Personalised Medicine in CF (SCIFI CF) initiative with the purpose of establishing guidelines and recommendations for future chest CT protocols [198]. 16 European centres participated to this initiative with their clinical protocols used over 3 age-specific phantoms. Data were evaluated in terms of dose (CTDIvol) and image quality. The SCIFI CF initiative recommendations for age-dependent CT protocols are reported in Table 1.

TABLE 1 Summary of the recommended guidelines for computed tomography protocols based on this SCIFI CF initiative's findings

Data acquisition mode	Volumetric, helical scan technique
Patient position	Supine with arms above the head
$CTDI_{vol}$[#] for inspiratory scan mGy	
1 year old	0.6
5 years old	1.0
Young adult	2.2
Field of view	As close as possible to the entirety of the lungs without cutting off the lung borders
$CTDI_{vol}$ for expiratory scan	50% lower than inspiratory scan
Tube voltage	Low enough such that the recommended $CTDI_{vol}$ can be reached (*e.g.* 80 kV)
Tube current	Adapt to recommended $CTDI_{vol}$
Pitch	<1, lower limit determined by maximum scan time allowed
Slice thickness	Thinnest slice thickness (*e.g.* 1 mm)
Reconstruction increment	50% overlap (*e.g.* 0.5 mm with 1-mm slice thickness)
Kernel for automated analysis	Sharp reconstruction filter without under- or overshoot at edges, preferably a dedicated kernel for quantitative image analysis
Iterative reconstruction technique	If available, iterative reconstruction techniques can be applied in addition to the requested filtered back-projection techniques
Shielding	Breast shielding by bismuth, for example, is discouraged

SCIFI CF: Standardised Chest Imaging Framework for Interventions and Personalised Medicine in Cystic Fibrosis; $CTDI_{vol}$: volumetric computed tomography dose index. [#]: in 32-cm body phantom.

Table 1

An additional tool for chest imaging could be represented by dark field chest radiography (DFCXR). DFCXR is an emerging imaging technique that exploits the wave character of x-rays by measuring their multiple refractions at material interfaces and allows for an overlay-free, quantitative assessment of the lung's alveolar structure [199]. A normal lung with its many tissue-air interfaces in the alveoli presents a strong, uniform dark-field signal [200]. Any impairment of the alveolar structure that leads to fewer interfaces reduces the dark-field signal. Very recently, DFCXR has been introduced to initial clinical application for the qualitative and quantitative assessment of emphysema in patients with chronic obstructive pulmonary disease [201-202]. These preliminary studies demonstrated a high sensitivity of DFCXR in the detection of structural changes associated with pulmonary emphysema, with an effective dose of 0.035 mSv (lower by about 100 times than chest CT) [202]. Therefore, although at the moment there are no commercial systems available, it is foreseeable that DFCXR could play

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a role in the detection, diagnosis and management of patients with CF. Further research is needed to this regard.

In patients with CF, chronic inflammation plays a fundamental role in causing impairment of lung function. Presently, conventional imaging techniques, neither those using ionizing radiation (CT, PET/CT and PET/MRI) nor those not using ionizing radiation (MRI and US), have progressed to routine clinical use of molecular imaging of inflammation, which could improve disease diagnosis, individualized therapeutic approaches and monitoring of treatment. To this regard, optimized high resolution nuclear medicine approaches or X-ray fluorescence imaging could be promising techniques. Fluorescence imaging is based on the detection of the emission spectrum of a fluorescent molecule that can be activated at a particular site within the body. It is possible to evaluate if the molecule is present, and the intensity of the fluorescence signal can be used to determine the state of the disease [203]. Today, most approaches are based on molecules that are activated by light and also emit light in the visible spectrum or in a similar energy range. Many Fluorescence imaging approaches use near-infrared wavelengths (650-1000 nm), and the near-infrared fluorescence (NIRF) has a number of advantages including good spatial resolution and sensitivity, relative low cost, lack of ionizing radiation and the ability to discriminate multiple fluorescent signals. NIRF imaging can be performed ex vivo on tissue sections and in vivo, either non-invasively or more commonly via intravital microscopy (IVM) or through the use of catheter/probe systems [203]. So far, NIRF fluorescence has been investigated mostly in pre-clinical studies on cardiovascular inflammation disease [203], but its use might be extended to management of other inflammatory conditions, not excluding CF as well. X-ray based fluorescence imaging might be able to combine advantages from optical fluorescence imaging to image the distribution of inflammation with the advantages of X-ray imaging to be able to visualize information from inside the body. Also with X-ray fluorescence imaging the spatial and temporal resolution can be increased compared to nuclear medical imaging techniques.

KEYPOINTS

- International guidelines on CF imaging are very much needed. Clear indications concerning timing and selection of the most appropriate imaging modality should be provided, taking into account the clinical scenario and patient's conditions.
- There is wide variability among the imaging protocols used in patients with CF. As a consequence, dose exposure greatly varies, and the cumulative dose for a single patient can be high. A standardization of technical protocols is very much needed.
- Low-dose and ultra-low-dose CT protocols are an interesting opportunity. However, a clear definition of these protocols is still missing and data concerning the technical parameters are still scarce. Further research based on controlled studies is needed to optimize and harmonize such approaches.
- Artificial intelligence is a relevant aspect of research, as it may play an important role in the diagnosis and scoring of the disease.
- MRI could be a game changer as it may become a "one-stop-shop" for CF imaging: further research is needed to improve and harmonise imaging protocols.
- An additional aspect for CF management and corresponding imaging approaches could be given by dark-field imaging which should be further developed, implemented and evaluated.
- Similarly, in the future new nuclear medicine and X-ray fluorescence imaging might possibly represent a further tool in the management of cystic fibrosis.

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IV. Conclusions & recommendations

In this deliverable, we have reported a series of gaps in knowledge and open issues suggesting the needs of research on the use of medical radiation applications in a series of relevant clinical scenarios concerning children, pregnant women, human beings undergoing screening programmes, and patients with chronic conditions. An evaluation on the related typical exposures and state of the art in radiation protection was also performed.

Finally, we would like to report a series of techniques/new developments which could become game changers in the above clinical scenarios:

- Photon Counting CT: Studies on the clinical use of photon counting CT are still very scarce or totally missing in the clinical scenarios we considered, due to its very recent commercial availability. Nevertheless, its capability to create extremely high-quality images with a lower dose, spectral separation and material decomposition could significantly change imaging practices in the years to come, also in the scenarios we considered.
- Artificial Intelligence: Artificial intelligence can play an important role in every step of the workflow of radiologic practice, being an excellent tool for its optimization. AI can also improve the detection of areas of pathology in various organs and help in making diagnosis. In the future, we can expect an ever-increasing role in all the scenarios we considered.
- New ionizing radiation based imaging methods like X-ray fluorescence imaging or dark field imaging might allow the generation of new relevant diagnostic information in the future. Corresponding research needs to be set-up as well.

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V. Reference

1. Maris JM, Hogarty MD, et al. Neuroblastoma. Lancet. 2007; 369(9579): 2106-2120.
2. Elzembely MM, Dahlberg AE, et al. Late effects in high-risk neuroblastoma survivors treated with high-dose chemotherapy and stem cell rescue. Pediatr Blood Cancer. 2019; 66(1): e27421.
3. Ahmed BA, Connolly BL, et al. Cumulative effective doses from radiologic procedures for pediatric oncology patients. Pediatrics. 2010; 126(4): e851-858.
4. Owens C, Li BK, et al. Surveillance imaging and radiation exposure in the detection of relapsed neuroblastoma. Pediatr Blood Cancer. 2016. 63(10): 1786–1793.
5. Morel B, Jaudeau-Collart AC, et al. Variability in Imaging Practices and Comparative Cumulative Effective Dose for Neuroblastoma and Nephroblastoma Patients at 6 Pediatric Oncology Centers. J Pediatr Hematol Oncol. 2018; 40(1): 36-42
6. Ozyoruk D, Emir S, et al. Total estimated effective doses from radiologic imaging modalities of children with cancer: a single center experience. World J Pediatr. 2017; 13(3):242-247
7. Littoij AS, de Keizer B. Imaging in Neuroblastoma. Pediatric Radiology. 2022; https://doi.org/10.1007/s00247-022-05489-2
8. Burnand K, Barone G, et al. Preoperative computed tomography scanning for abdominal neuroblastoma is superior to magnetic resonance imaging for safe surgical planning. Pediatr Blood Cancer. 2019; 66(11):e27955.
9. Morgan JE, Walker R, et al. A systematic review of evidence for and against routine surveillance imaging after completing treatment for childhood extracranial solid tumors. Cancer Medicine. 2020; 9:4949–4961.
10. Owens C, Li BK, et al. Surveillance imaging and radiation exposure in the detection of relapsed neuroblastoma. Pediatr Blood Cancer. 2016; 63:1786–1793.
11. McHugh K, Roebuck DJ. Pediatric oncology surveillance imaging: two recommendations. Abandon CT scanning, and randomize to imaging or solely clinical follow-up. Pediatr Blood Cancer. 2014; 61:3–6.
12. Kim YY, Shin HJ, et al. Comparison of effective radiation doses from X-ray, CT, and PET/CT in pediatric patients with neuroblastoma using a dose monitoring program. Diagn Interv Radiol. 2016; 22(4):390–394.
13. Ben-sellem D, Ben-Rejeb N. Does the Incremental Value of 123I-Metaiodobenzylguanidine SPECT/CT over Planar Imaging Justify the Increase in Radiation Exposure? Nuclear Medicine and Molecular Imaging. 2021; 55:173–180.
14. Nadel HR. SPECT/CT in pediatric patient management. Eur J Nucl Med Mol Imaging. 2014; 41:104–114.
15. Liu B, Servaes S, et al. SPECT/CT mIBG imaging is crucial in the follow-up of the patients with high-risk neuroblastoma. Clin Nucl Med. 2018; 43:232–238.
16. Theerakulpisut D, Raruenrom Y, et al. Value of SPECT/CT in diagnostic 131I-mIBG scintigraphy in patients with neuroblastoma. Nucl Med Mol Imaging. 2018; 52:350–358
17. Shahrokhi P, Emami-Ardekani A, et al. 68Ga-DOTATATE PET/CT compared with 131I-MIBG SPECT/CT in the evaluation of neural crest tumors. Asia Ocean J Nucl Med Biol. 2020; 8:8–17.
18. Piccardo A, Morana G, et al. Diagnosis, treatment response, and prognosis: the role of 18F-DOPA PET/CT in children affected by neuroblastoma in comparison with 123I-mIBG scan: the first prospective study. J Nucl Med. 2020; 61:367–374.
19. Melzer HI, Coppenrath E, et al. 123I-MIBG scintigraphy/SPECT versus 18F-FDG PET in paediatric neuroblastoma. Eur J Nucl Med Mol Imaging. 2011; 38:1648–1658.
20. Mohd Zaki F, Moineddin R, et al. Accuracy of precontrast imaging in abdominal magnetic resonance imaging of pediatric oncology patients. Pediatr Radiol. 2016; 46:1684–1693.
21. Hishiguchi H, Ito S, et al. Diagnostic performance of 18F-FDG PET/CT and whole-body diffusion weighted imaging with background body suppression (DWIBS) in detection of lymph node and bone metastases from pediatric neuroblastoma. Annals of Nuclear Medicine. 2018; 32:348–362.

This project has received funding from the Euratom research and training programme 2019-2020 under grant agreement No. 899995.

22. Parikh NS, Howard SC, et al. SIOP-PODC adapted risk stratification and treatment guidelines: recommendations for neuroblastoma in low- and middle-income settings. Pediatric Blood Cancer. 2015; 62:1305–1316.
23. Liu KX, Naranjo A, et al. Prospective Evaluation of Radiation Dose Escalation in Patients with High-Risk Neuroblastoma and Gross Residual Disease After Surgery: A Report from the Children's Oncology Group ANBL0532 Study. J Clin Oncol. 2020; 38:2741–2752.
24. Valteau-Couanet D, Schleiermacher G, et al. High-risk neuroblastoma treatment strategy: The experience of the SIOPEN group. Bull Cancer. 2018; 105(10):918-924.
25. Casey DL, Kushner BH, et al. Dose-escalation is needed for gross disease in high-risk neuroblastoma. Pediatr Blood Cancer. 2018; 65:e27009.
26. Hill-Kayser C, Tochner Z, et al. Proton Versus Photon Radiation Therapy for Patients with High-Risk Neuroblastoma: The Need for a Customized Approach. Pediatr Blood Cancer. 2013; 60:1606–1611.
27. Fuji H, Schneider U, et al. Assessment of organ dose reduction and secondary cancer risk associated with the use of proton beam therapy and intensity modulated radiation therapy in treatment of neuroblastomas. Radiat Oncol. 2013; 8:255.
28. Rombi B, Vennarini S, et al. Proton radiotherapy for pediatric tumors: review of first clinical results. Italian Journal of Pediatrics. 2014; 40:74.
29. Hill-Kayser CE, Tochner Z, et al. Outcomes After Proton Therapy for Treatment of Pediatric High-Risk Neuroblastoma. Int J Radiation Oncol Biol Phys. 2019; 104:401-408.
30. Bagley AF, Grosshans DR, et al. Efficacy of proton therapy in children with high-risk and locally recurrent neuroblastoma. Pediatr Blood Cancer. 2019; 66:e27786.
31. Jazmati, D.; Butzer, S.; et al. Proton Beam Therapy for Children with Neuroblastoma: Experiences from the Prospective KiProReg Registry. Front Oncol. 2021; 10: 617506.
32. Wilson JS, Gains GE, et al. A systematic review of 131I- meta iodobenzylguanidine molecular radiotherapy for neuroblastoma. Eur J Cancer. 2014; 50:801-815
33. Gains JE, Moroz V, et al. A phase IIa trial of molecular radiotherapy with 177-lutetium DOTATATE in children with primary refractory or relapsed high-risk neuroblastoma. Eur J Nucl Med Mol Imaging. 2020; 47:2348-2357.
34. Gains JE, Bomanji JB, Fersht NL, et al. 177Lu-DOTATATE molecular radiotherapy for childhood neuroblastoma. J Nucl Med. 2011; 52:1041–1047.
35. Kong G, Hofman MS, et al. Initial experience with gallium-68 dota-octreotate PET/CT and peptide receptor radionuclide therapy for pediatric patients with refractory metastatic neuroblastoma. J Pediatr Hematol Oncol. 2016; 38:87-96.
36. Sundquist F, Georgantzl K, et al. A Phase II Trial of a Personalized, Dose-Intense Administration Schedule of 177Lutetium-DOTATATE in Children with Primary refractory or relapsed high-risk neuroblastoma–LuDO-N. Front Pediatr. 2022; 10:836230.
37. Applebaum MA, Henderson TO, et al. Second malignancies in patients with NB: the effects of risk-based therapy. Pediatr Blood Cancer. 2015; 62: 128-133.
38. Federico SM, Allewelt HB, et al. Subsequent malignant neoplasms in pediatric patients initially diagnosed with neuroblastoma. J Pediatr Hematol Oncol. 2015; 37: e6-e12.
39. Mertens AC, Yasui Y, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the childhood cancer survivor Study. J Clin Oncol. 2001; 19:3163–3172.
40. Horner MJ, Ries LAG, et al. SEER Cancer Statistics Review, 1975–2006. National Cancer Institute. 2009
41. Zhen H, Guan H, et al. Risk of developing second malignant neoplasms in patients with neuroblastoma: a population study of the US SEER database. Radiation Oncology. 2021; 16:228.
42. ICRP International Commission on Radiological Protection. The 2007 recommendations of the International Commission on Radiological Protection. ICRP Publication 103.
43. ACR American College of Radiology. ACR-SPR practice parameter for imaging pregnant or potentially pregnant adolescents and women with ionizing radiation. 2018; https://www.acr.org/-/media/acr/files/practice-parameters/pregnant-pts.pdf

This project has received funding from the Euratom research and training programme 2019-2020 under grant agreement No. 899995.

44. ACOG Committee on Obstetric Practice. ACOG Committee Opinion. Number 299, September 2004 (replaces No. 158, September 1995). Guidelines for diagnostic imaging during pregnancy. Obstet Gynecol. 2004; 104:647–651.
45. McCollough CH, Schueler BA, et al. Radiation exposure and pregnancy: when should we be concerned? Radiographics. 2007; 27:909–917.
46. Angel E, Wellnitz CV, et al. Radiation dose to the fetus for pregnant patients undergoing multidetectorCT imaging: Monte Carlo simulations estimating fetal dose for a range of gestational age and patient size. Radiology. 2008; 249:220–227.
47. Kwan M, Miglioretti D, et al. Trends in medical imaging during pregnancy in the United States and Ontario, Canada, 1996 to 2016. JAMA Network Open. 2019; 2: e197249.
48. Kelaranta A, Mäkelä T, et al. Fetal radiation dose in three common CT examinations during pregnancy: Monte Carlo study. PhysMed. 2017; 43:199–206.
49. Gervaise A, Gervaise-Henry C, et al. How to perform low-dose computed tomography for renal colic in clinical practice. Diagn Interv Imaging. 2016; 97:393–400.
50. Greffier J, Pereira F, et al. Effect of tin filter-based spectral shaping CT on image quality and radiation dose for routine use on ultra-low-dose CT protocols: a phantom study. Diagn Interv Imaging. 2020; 101:373–381.
51. Beregi JP, Greffier J. Low and ultra-low-dose radiation in CT: opportunities and limitations. Diagn Interv Imaging. 2019; 100:63–64.
52. Martini K, Moon JW, et al. Optimization of acquisition parameters for reduced-dose thoracic CT: a phantom study. Diagn Interv Imaging. 2020; 101:269–279.
53. ICRP International Commission on Radiological Protection. ICRP Publication 128: Radiation Dose to Patients from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances. ICRP Annals of the ICRP. 2015; https://journals.sagepub.com/doi/pdf/10.1177/ANIB_44_2S
54. Russell JR, Stabin MG, et al. Radiation absorbed dose to the embryo/fetus from radiopharmaceuticals. J. Nucl Med. 1997; 73:756-769.
55. Berg G, Nystrom E, et al. Radioiodine treatment of hyperthyroidism in a pregnant woman. J. Nucl Med. 1998; 39:357–361.
56. Mazonakis M, Damilakis J. Estimation and reduction of the radiation dose to the fetus from external beam radiotherapy. Phys Med. 2017; 43:148-152.
57. Sneed PK, Albright NW, et al. Fetal dose estimates for radiotherapy of brain tumors during pregnancy. Int J Radiat Oncol Biol Phys.1995; 32:823–830.
58. Lefebvre L, Doyeux K, et al. Radiotherapy of a glioma in a pregnant woman: evaluation of the fetal dose in conformational 3D or intensity modulated radiation therapy. Cancer Radiother. 2014; 18:763–766.
59. Pantelis E, Antypas C, et al. Radiation dose to the fetus during CyberKnife radiosurgery for a brain tumor in pregnancy. Phys Med. 2016; 32:237–241.
60. Podgorsak MB, Meiler RJ, et al. Technical management of a pregnant patient undergoing radiation therapy to the head and neck. Med Dosim. 1999; 24:121-128.
61. Atabo A, Bradley PJ. Management principles of head and neck cancers during pregnancy: a review and case series. Oral Oncol. 2008; 44:236–241.
62. Ngu SLC, Duval P, et al. Fetal radiation dose in radiotherapy for breast cancer. Australas Radiol. 1992; 36:321–322.
63. Van der Giessen PH. Measurement of the peripheral dose for the tangential breast treatment technique with Co-60 gamma radiation and high energy X-rays. Radiother Oncol. 1997; 42:257–264.
64. Woo SY, Fuller LM, et al. Radiotherapy during pregnancy for clinical stages IA-IIA Hodgkin's disease. Int J Radiat Oncol Biol Phys. 1992; 23:407–412.
65. Nuyttens JJ, Prado KL, et al. Fetal dose during radiotherapy: clinical implementation and review of the literature. Cancer Radiother. 2002; 6:352–357.
66. Kourinou KM, Mazonakis M, et al. Photon-beam radiotherapy in pregnant patients: can the fetal dose be limited to 10 cGy or less? Phys Med. 2015; 31:85–91.
67. Stovall M, Blackwell CR, et al. Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group No. 36. Med Phys. 1995; 22:63–82.

This project has received funding from the Euratom research and training programme 2019-2020 under grant agreement No. 899995.

68. Mazonakis M, Tzedakis A, et al. Radiotherapy for supradiaphragmatic Hodgkin's disease: determination of the proper fetal shielding conditions using Monte Carlo methodology. Phys Med. 2011; 27:181–187.
69. Mazonakis M, Tzedakis A, et al. Monte Carlo simulation of radiotherapy for breast cancer in pregnant patients: how to reduce the radiation dose and risks to fetus? Radiat Prot Dosimetry. 2017; 175:10–16.
70. Nuyttens JJ, Prado KL, et al. Fetal dose during radiotherapy: clinical implementation and review of the literature. Cancer Radiother. 2002; 6:352–357.
71. Owrangi AM, Roberts DA, et al. Revisiting fetal dose during radiation therapy: evaluating treatment technique and a custom shield. J Appl Clin Med Phys. 2016; 17:34–46.
72. Podgorsak MB, Meiler RJ, Kowal H, et al. Technical management of a pregnant patient undergoing radiation therapy to the head and neck. Med Dosim 1999; 24:121–128
73. Mazonakis M, Lyraraki E, et al. Conceptus dose from involved-field radiotherapy for Hodgkin's lymphoma on a linear accelerator equipped with MLCs. Strahlenther Onkol. 2009; 185: 355–363.
74. Roy SC, Sandison GA. Shielding for neutron scattered dose to the fetus in patients treated with 18 MV X-ray beams. Med Phys. 2000; 27:1800–1803.
75. Yeom YS, Griffin KT, et al. Fetal dose from proton pencil beam scanning craniospinal irradiation during pregnancy: A Monte Carlo study. Phys Med Biol. 2022; 67(3):10.1088/1361-6560/ac4b38.
76. Wong Ym, Koh CWY, et al. A review on fetal dose in Radiotherapy: A historical to contemporary perspective. Phys Med. 2023, 105:102513.
77. Wang X, Poenisch F, et al. Spot scanning proton therapy minimizes neutron dose in the setting of radiation therapy administered during pregnancy. J Appl Clin Med Phys. 2016; 17: 366-376.
78. Wolters V, Heimovaara J, et al. Management of pregnancy in women with cancer. Int. J. Gynecol. Cancer. 2021; 31:314–322.
79. Bray F, Ferlay J, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68:394-424.
80. Siegel RL, Miller KD, et al. Cancer statistics, 2018. CA Cancer J Clin. 2018; 68:7-30.
81. The National Lung Screening Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011; 365:395-409.
82. de Koning HJ, van der Aalst CM, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020; 382:503-513.
83. Hoffman RM, Atallah RP, et al. Lung Cancer Screening with Low-Dose CT: a Meta-Analysis. J Gen Intern Med. 2020; 35:3015-3025.
84. Centers for Medicare & Medicaid Services. Final National Coverage Determination on Screening for Lung Cancer with Low Dose Computed Tomography (LDCT). 2015; www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=274
85. Moyer VA, U.S. Preventive Services Task Force. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014; 160: 330-338.
86. Tammemägi MC. Application of risk prediction models to lung cancer screening: a review. J Thorac Imaging. 2015; 30:88-100.
87. Tammemägi MC. Selecting lung cancer screenees using risk prediction models - where do we go from here. Transl Lung Cancer Res. 2018; 7:243-253.
88. Ten Haaf K, Bastani M, et al. A comparative modeling analysis of risk-based lung cancer screening strategies. J Natl Cancer Inst. 2020; 112:466-479.
89. Tammemägi MC, Katki HA, et al. Selection criteria for lung-cancer screening. N Engl J Med. 2013; 368:728-736.
90. Bach PB, Kattan MW, et al. Variations in lung cancer risk among smokers. J Natl Cancer Inst. 2003; 95:470-478.
91. Katki HA, Kovalchik SA, et al. Development and validation of risk models to select ever-smokers for CT lung cancer screening. JAMA. 2016; 315:2300-2311.

This project has received funding from the Euratom research and training programme 2019-2020 under grant agreement No. 899995.

92. Tammemagi MC, Schmidt H, et al. Participant selection for lung cancer screening by risk modelling (the Pan-Canadian Early Detection of Lung Cancer [PanCan] study): a single-arm, prospective study. Lancet Oncol 2017; 18:1523-1531
93. Crosbie PA, Balata H, et al. Implementing lung cancer screening: baseline results from a community-based 'lung health check' pilot in deprived areas of Manchester. Thorax. 2019; 74:405-409.
94. Katki HA, Kovalchik SA, et al. Implications of nine risk prediction models for selecting ever-smokers for computed tomography lung cancer screening. Ann Intern Med. 2018; 169:10-19.
95. Li K, Husing A, et al. Selecting high-risk individuals for lung cancer screening: a prospective evaluation of existing risk models and eligibility criteria in the German EPIC cohort. Cancer Prev Res. 2015; 8:777-785.
96. Hüsing A, Kaaks R. Risk prediction models versus simplified selection criteria to determine eligibility for lung cancer screening: an analysis of German federal-wide survey and incidence data. Eur J Epidemiol. 2020; 35:899-912.
97. Weber M, Yap S, et al. Identifying high risk individuals for targeted lung cancer screening: independent validation of the PLCOM2012 risk prediction tool. Int J Cancer. 2017; 141:242-253.
98. Ten Haaf K, Jeon J, et al. Risk prediction models for selection of lung cancer screening candidates: a retrospective validation study. PLoS Med. 2017; 14: e1002277.
99. Lim KP, Marshall H, et al. Protocol and rationale for the International Lung Screening Trial. Ann Am Thorac Soc. 2020; 17:503-512.
100. Lam S, Myers R, et al. PL02.02 Lung cancer screenee selection by USPSTF versus PLCOm2012 criteria - interim ILST findings. J Thorac Oncol. 2019; 14:S4-S5.
101. Crosbie PA, Gabe R, et al. Yorkshire Lung Screening Trial (YLST): protocol for a randomised controlled trial to evaluate invitation to community-based low-dose CT screening for lung cancer versus usual care in a targeted population at risk. BMJ Open. 2020; 10:e037075.
102. Loverdos K, Fotiadis A, et al. Lung nodules: A comprehensive review on current approach and management. Ann Thorac Med. 2019; 14:226-238.
103. Heuvelmans MA, Walter JE, et al. Management of baseline and new sub-solid nodules in CT lung cancer screening. Expert Rev Respir Med. 2018; 12:1-3.
104. Lam S, Tammemagi M. Contemporary issues in the implementation of lung cancer screening. Eur Respir Rev. 2021; 30(161):200288.
105. Soo E, Edey AJ, et al. Impact of choice of volumetry software and nodule management guidelines on recall rates in lung cancer screening. Eur J Radiol. 2019; 120:108646.
106. Henschke CI, Yip R, et al. CT screening for lung cancer: comparison of three baseline screening protocols. Eur Radiol. 2019; 29:5217-5226.
107. McWilliams A, Tammemagi MC, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013; 369: 910-919.
108. González Maldonaldo S, Delorme S, et al. Evaluation of prediction models for identifying malignancy in pulmonary nodules detected via low-dose computed tomography. JAMA Netw Open. 2020; 3:e1921221.
109. Schultz EM, Sanders GD, et al. Validation of two models to estimate the probability of malignancy in patients with solitary pulmonary nodules. Thorax. 2008; 63:335-341.
110. Al-Ameri A, Malhotra P, et al. Risk of malignancy in pulmonary nodules: a validation study of four prediction models. Lung Cancer. 2015; 89:27-30.
111. Winkler Wille MM, van Riel SJ, et al. Predictive accuracy of the PanCan lung cancer risk prediction model - external validation based on CT from the Danish Lung Cancer Screening Trial. Eur Radiol. 2015; 25:3093-3099.
112. Zhao H, Marshall HM, et al. Screen-detected subsolid pulmonary nodules: long-term follow-up and application of the PanCan lung cancer risk prediction model. Br J Radiol. 2016; 89:20160016.
113. van Riel SJ, Ciompi F, et al. Malignancy risk estimation of screen-detected nodules at baseline CT: comparison of the PanCan model, Lung-RADS and NCCN guidelines. Eur Radiol. 2017; 27:4019-4029.

This project has received funding from the Euratom research and training programme 2019-2020 under grant agreement No. 899995.

114. Nair VS, Sundaram V, et al. Accuracy of models to identify lung nodule cancer risk in the National Lung Screening Trial. Am J Respir Crit Care Med. 2018; 197:1220-1223.
115. Tammemagi MC, Lam S. Screening for lung cancer using low dose computed tomography. BMJ. 2014; 348:g2253.
116. Myers R, Mayo JR, et al. Evaluation of the clinical utility of the PanCan, EU-NELSON and Lung-RADS protocols for management of screen detected lung nodules at baseline. J Thorac Oncol. 2019; 14:S288-S289.
117. Ciompi F, Chung K. Towards automatic pulmonary nodule management in lung cancer screening with deep learning. Sci Rep. 2017; 7:46479.
118. Adams SJ, Mondal P, et al. Development and Cost Analysis of a Lung Nodule Management Strategy Combining Artificial Intelligence and Lung-RADS for Baseline Lung Cancer Screening. J Am Coll Radiol. 2021; 18:741-751.
119. Pastorino U, Boeri M, et al. Baseline computed tomography screening and blood microRNA predict lung cancer risk and define adequate intervals in the BioMILD trial. Ann Oncol. 2022; 33(4):395-405.
120. American College of Radiology. ACR - STR Practice Guideline for the Performance and Reporting of Lung Cancer Screening Thoracic Computed Tomography (CT). 2019; Practice Parameter. 1076:1-12.
121. Adult Lung Cancer Screening Technical Specifications 2014. Available here: https://www.acraccreditation.org/-/media/ACRAccreditation/Documents/LCS/Lung-Cancer-Screening-Technical-Specifications.pdf?la=en</eref>
122. Revel MP. Chest CT for Lung Cancer Screening -Technical standards [Internet]. European society of thoracic imaging; 2020. Available online: https://www.myesti.org/content-esti/uploads/ESTI-LCS-technicalstandards_2019-06-14.pdf
123. Vonder M, Dorrius DM, et al. Latest CT technologies in lung cancer screening: protocols and radiation dose reduction. Transl Lung Cancer Res. 2021; 10:1154-1164.
124. American Association of Physicists in Medicine (AAPM). Lung Cancer Screening CT Protocols Version 5.1. 2019; Available online: https://www.aapm.org/pubs/CTProtocols/documents/LungCancerScreeningCT.pdf
125. Demb J, Chu P, et al. Analysis of Computed Tomography Radiation Doses Used for Lung Cancer Screening Scans. JAMA Intern Med. 2019; 179:1650-1657.
126. Rampinelli C, De Marco P, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. BMJ. 2017; 356:j347.
127. Mascalchi M, Mazzoni LN, et al. Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT. Br J Radiol. 2012; 85:1134-1139.
128. Zhang M, Qi W, et al. Screening for lung cancer using sub-millisievert chest CT with iterative reconstruction algorithm: Image quality and nodule detectability. Br J Radiol. 2018; 91:20170658.
129. Martini K, Ottlinger T, et al. Lung cancer screening with submillisievert chest CT: Potential pitfalls of pulmonary findings in different readers with various experience levels. Eur J Radiol. 2019; 121:108720.
130. Ye K, Zhu Q, et al. A feasibility study of pulmonary nodule detection by ultralow-dose CT with adaptive statistical iterative reconstruction-V technique. Eur J Radiol. 2019; 119:108652.
131. Huber A, Landau J, et al. Performance of ultralow-dose CT with iterative reconstruction in lung cancer screening: limiting radiation exposure to the equivalent of conventional chest X-ray imaging. Eur Radiol. 2016; 26:3643-3652.
132. Jang B, Li N, et al. Deep Learning Reconstruction Shows Better Lung Nodule Detection for Ultra-Low-Dose Chest CT. Radiology. 2022; 303:202-212.
133. Murchison JT, Ritchie G, et al. Validation of a deep learning computer aided system for CT based lung nodule detection, classification, and growth rate estimation in a routine clinical population. PLoS One. 2022; 17:e0266799.
134. Sung H, Ferlay J, et al. Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71:209-249.

This project has received funding from the Euratom research and training programme 2019-2020 under grant agreement No. 899995.

135. Howlader N, Noone AM, et al. SEER Cancer Statistics Review, 1975-2010. Bethesda, MD; National Cancer Institute. Updated 2013; Available online: https://seer.cancer.gov/archive/csr/1975_2010/#contents
136. BreastScreen Australia Evaluation Taskforce. Breast Screen Australia Evaluation. Evaluation final report. Canberra: Australian Government Department of Health and Ageing. 2009; Report No.: Screening Monograph No.1/2009. Available online: http://cancerscreening.gov.au/internet/screening/publishing.nsf/ Content/programme-evaluation
137. DeSantis C, Ma J, et al. Breast cancer statistics. CA Cancer J Clin. 2014; 64:52-62.
138. Lauby-Secretan B, Scoccianti C, et al. Breast-Cancer screening - Viewpoint of the IARC working group. N Engl J Med. 2015; 372:2353-2358.
139. Cancer Research UK, Breast screening, Cancer Research UK. 2017; Available from: https://about-cancer. cancerresearchuk.org/about-cancer/breast-cancer/getting-diagnosed/ screening/breast-screening
140. Smith RA, Andrews KS, et al. Cancer screening in the United States, 2018: a review of current American cancer society guidelines and current issues in cancer screening. CA Cancer J Clin. 2018; 68(4):297-316.
141. Tonelli M, Connor Gorber S, et al. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. Can Med Assoc J (CMAJ). 2011; 183:1991-2001.
142. Australian Institute of Health and Welfare (AIHW). Breast Screen Australia monitoring report 2020. AIHW, Australian Government. 2020; Available from: https://www.aihw.gov.au/reports/ cancer-screening/breastscreen-australia-monitoring-report-2020/summary
143. Hendrick RE . Radiation doses and cancer risks from breast imaging studies. Radiology. 2010; 257:246-253.
144. Bosmans H, Marshall N. Radiation doses and risks associated with mammographic screening. Curr Radiol Rep. 2013; 1:30-38.
145. Hooshmand S, Reed WM, et al. A review of screening mammography: The benefits and radiation risks put into perspective. J Med Imaging Radiation Sc. 2022; 53:147-158.
146. Warren L, Dance DR, et al, Radiation risk of breast screening in England with digital mammography. BJR. 2016; 89(1067): 2015897.
147. Loveland J, Young KC, et al. Radiation doses in the United Kingdom breast screening programmes 2016-2019. Br J Radiol. 2022; 95(1135):20211400.
148. Ali RMK, Englan A, et al. Effective lifetime radiation risk for a number of national mammography screening programmes. Radiography 2018; 24:240-246.
149. Good WF, Abrams GS, et al. Digital breast tomosynthesis: a pilot observer study. Am J Roentgenol. 2008; 190:865-9.
150. Svahn TM, Houssami N, et al. Review of radiation dose estimates in digital breast tomosynthesis relative to those in two-view full-field digital mammography. Breast. 2015; 24(2):93-9.
151. Gilbert FJ, Tucker L, et al. Accuracy of Digital Breast Tomosynthesis for Depicting Breast Cancer Subgroups in a UK Retrospective Reading Study (TOMMY Trial). Radiology. 2015; 277:697-706.
152. Sechopoulos I. A review of breast tomosynthesis. Part I. The image acquisition process. Med Phys. 2013;40(1):014301.
153. Freeman K, Geppert J, et al. Use of artificial intelligence for image analysis in breast cancer screening programmes: systematic review of test accuracy. BMJ. 2021; 734:n1872.
154. Shoshan Y, Bakalo R, et al. Artificial Intelligence for Reducing Workload in Breast Cancer Screening with Digital Breast Tomosynthesis. Radiology. 2022; 303(1):69-77.
155. Sechopolous I, Teuwen J, et al. Artificial Intelligence for Breast Cancer Detection in Mammography and Digital Breast Tomosynthesis: state of the art. Semin Cancer Biol. 2021; 72:214-225.
156. Ohuchi N, Suzuki A, et al. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. Lancet. 2016; 387:341-348.

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157. Weigert JM. The Connecticut Experiment; The Third Installment: 4 Years of Screening Women with Dense Breasts with Bilateral Ultrasound. Breast J. 2017; 23:34-39.
158. Zhu YC, Zu DM, et al. A comparative study on superb microvascular imaging and conventional ultrasonography in differentiating BI-RADS 4 breast lesions. Oncol Lett. 2019; 18:3202-3210.
159. Mann RM, Cho N, et al. Breast MRI: State of the Art. Radiology. 2019; 292:520-536.
160. Taylor JS, Tofts PS, et al. MR imaging of tumor microcirculation: promise for the new millennium. J Magn Reson Imaging. 1999; 10:903-907.
161. Sung JS, Stamler S, et al. Breast Cancers Detected at Screening MR Imaging and Mammography in Patients at High Risk: Method of Detection Reflects Tumor Histopathologic Results. Radiology. 2016; 280:716-722.
162. Bakker MF, de Lange SV, et al. Supplemental MRI Screening for Women with Extremely Dense Breast Tissue. N Engl J Med. 2019; 381:2091-2102.
163. Breast magnetic resonance imaging (MRI) accreditation program requirements. American College of Radiology. Available online: https://www.acraccreditation.org/modalities/breast-mri. Accessed August 31, 2022
164. Kuhl CK, Schrading S, et al. Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection - A novel approach to breast cancer screening with MRI. J Clin Oncol. 2014; 32: 2304-2310.
165. Leithner D, Moy L, et al. Abbreviated MRI of the Breast: Does It Provide Value? J Magn Reson Imaging. 2019; 49:e85-e100.
166. Comstock CE, Gatsonis C, et al. Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection Among Women with Dense Breasts Undergoing Screening. JAMA. 2020; 323:746-756.
167. Shi RY, Yao QY, et al. Breast Lesions: Diagnosis Using Diffusion Weighted Imaging at 1.5T and 3.0T-Systematic Review and Meta-analysis. Clin Breast Cancer. 2018; 18:e305-e320.
168. Baltzer P, Mann RM, et al. Diffusion-weighted imaging of the breast-a consensus and mission statement from the EUSOBI International Breast Diffusion-Weighted Imaging working group. Eur Radiol. 2020; 30:1436-1450.
169. Yabuuchi H, Matsuo Y, et al. Detection of non-palpable breast cancer in asymptomatic women by using unenhanced diffusion-weighted and T2-weighted MR imaging: comparison with mammography and dynamic contrast-enhanced MR imaging. Eur Radiol. 2011; 21:11-17.
170. Kazama T, Kuroki Y, et al. Diffusion-weighted MRI as an adjunct to mammography in women under 50 years of age: an initial study. J Magn Reson Imaging. 2012; 36:139-144.
171. Amornsiripanitch N, Bickelhaupt S, et al. Diffusion-weighted MRI for Unenhanced Breast Cancer Screening. Radiology. 2019; 293(3):504-520.
172. Pinker K, Moy L, et al. Diffusion-Weighted Imaging With Apparent Diffusion Coefficient Mapping for Breast Cancer Detection as a Stand-Alone Parameter: Comparison With Dynamic Contrast-Enhanced and Multiparametric Magnetic Resonance Imaging. Invest Radiol. 2018; 53:587-595.
173. Tay TKY, Tan PH. Liquid biopsy in Breast Cancer. Arch Patol Lab Med. 2021; 145:678-686
174. Egan ME. Genetics of cystic fibrosis: clinical implications. Clin Chest Med. 2016; 37: 9-16.
175. Cystic Fibrosis Foundation. Patient Registry Annual Data Report. 2020. Available from: www.cff.org/sites/default/files/2021-10/2019-Patient-Registry-Annual-Data-Report.pdf
176. Bell SC, Mall MA, et al. The future of cystic fibrosis care: a global perspective. Lancet Respir Med. 2020; 8: 65-124.
177. Wagener JS, Elkin EP, et al. Pulmonary function outcomes for assessing cystic fibrosis care. J Cyst Fibros. 2015; 14: 376-383.
178. de Jong PA, Nakano Y, et al. Progressive damage on high resolution computed tomography despite stable lung function in cystic fibrosis. Eur Respir J. 2004; 23: 93-97.
179. Kuo W, Ciet P, et al. Monitoring cystic fibrosis lung disease by computed tomography. Radiation risk in perspective. Am J Respir Crit Care Med. 2014; 189: 1328-1336.

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180. Ciet PL, Bertolo S, et al. State-of-the-art review of lung imaging in cystic fibrosis with recommendations for pulmonologists and radiologists from the "iMAging managEment of cySTic fibROsis" (MAESTRO) consortium. Eur Respir Rev. 2022; 31:210173.
181. Lee MZ, Cai W, et al. Fully automated scoring of chest radiographs in cystic fibrosis. Annu Int Conf IEEE Eng Med Biol Soc. 2013; 2013: 3965-3968.
182. Dournes G, Hall CS, et al. Artificial intelligence in CT for quantifying lung changes in the era of CFTR modulators. Eur Respir J. 2022; 59(3):2100844.
183. Tiddens HAWM, Stick SM, et al. Respiratory tract exacerbations revisited: ventilation, inflammation, perfusion, and structure (VIPS) monitoring to redefine treatment. Pediatr Pulmonol. 2015; 50: Suppl 40, S57-S65.
184. Greene KE, Takasugi JE, et al. Radiographic changes in acute exacerbations of cystic fibrosis in adults: a pilot study. AJR Am J Roentgenol. 1994; 163:557-562.
185. Benlala I, Hocke F, et al. Quantification of MRI T2-weighted high signal volume in cystic fibrosis: a pilot study. Radiology. 2020; 294: 186-196.
186. Ciet P, Serra G, et al. Diffusion weighted imaging in cystic fibrosis disease: beyond morphological imaging. Eur Radiol. 2016; 26: 3830-3839.
187. Ciet P, Bertolo S, et al. Detection and monitoring of lung inflammation in cystic fibrosis during respiratory tract exacerbation using diffusion-weighted magnetic resonance imaging. Eur Respir J. 2017; 50:1601437.
188. O'Connell OJ, McWilliams S, et al. Radiologic imaging in cystic fibrosis: cumulative effective dose and changing trends over 2 decades. Chest. 2012; 141: 1575-1583.
189. O'Reilly R, Ryan S, et al. Cumulative radiation exposure in children with cystic fibrosis. Ir Med J. 2010; 103:43e6.
190. Donadieu J, Roudier C, et al. Estimation of the radiation dose from thoracic CT scans in a cystic fibrosis population. Chest. 2007; 132:1233e8.
191. Ward R, Carrol WD, et al. Radiation dose from common radiological investigations and cumulative exposure in children with cystic fibrosis: an observational study from a single UK centre. BMJ Open. 2017; 21;7:e017548.
192. Singh S, Kalra MK, et al. Adaptive statistical iterative reconstruction technique for radiation dose reduction in chest CT: a pilot study. Radiology. 2011; 259:565e73.
193. Willemink MJ, de Jong PA. Pediatric Chest Computed Tomography at a Radiation Dose Approaching a Chest Radiograph. Am J Respir Crit Care Med. 2013; 188:626-627.
194. Mieville FA, Berteloot L, et al. Model-based iterative reconstruction in pediatric chest CT: assessment of image quality in a prospective study of children with cystic fibrosis. Pediatr Radiol. 2013; 43:558-567.
195. Lin S, Lin M, et al. Efficacy of model-based iterative reconstruction in cystic fibrosis assessment using CT. Clin Radiol. 2019; 74:569.e19-569.e27.
196. Lin S, Lin M, et al. Image quality comparison between model-based iterative reconstruction and adaptive statistical iterative reconstruction chest computed tomography in cystic fibrosis patients. J Med Imaging Radiat Oncol. 2019; 63:602-609.
197. Ernst CW, Basten IA, et al. Pulmonary Disease in cystic Fibrosis: Assessment with Chest CT at Chest Radiography Dose Levels. Radiology. 2014; 273:597-605.
198. Kuo W, Kemmer-van de Corput MPC, et al. Multicentre chest computed tomography standardisation in children and adolescents with cystic fibrosis: the way forward. Eur Respir J. 2016; 47:1706-1717.
199. Pfeiffer F, Bech M, et al. Hard-X-ray dark-field imaging using a grating interferometer. Nat Mater. 2008; 7:134-137.
200. Gassert FT, Urban T, et al. X-ray dark-field chest imaging: qualitative and quantitative results in healthy humans. Radiology. 2021; 301:38 -395.
201. Urban T, Gassert FT, et al. Qualitative and quantitative assessment of emphysema using dark-field chest radiography. Radiology. 2022; 303:119-127.
202. Willer K, Fingerle AA, et al. X-ray dark-field chest imaging for detection and quantification of emphysema in patients with chronic obstructive pulmonary disease: a diagnostic accuracy study. Lancet Digit Health. 2021; 3:e733 - e744.
203. MacRitchie N, Frleta-Gilchrist M, et al. Molecular imaging of inflammation - Current and emerging technologies for diagnosis and treatment. Pharmacol Ther. 2020; 211:107550.

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