Project title: EURopeAn MEDical application and Radiation prOteCtion Concept: strategic research agenda aNd ROadmap interLinking to heaLth and digitisation aspects

Grant Agreement: 899995

Call identifier: NFRP-2019-2020

Topic: NFRP-2019-2020-13 Research roadmap for medical applications of ionising radiation

D3.1 Medical application of ionising radiation and radiation protection in oncology

Leader partner: VHIO

Author(s):	Jordi Giralt, MD, PhD
Work Package:	WP3
Due date:	30/11/2022
Actual delivery date:	30/11/2022
Type:	Report (R)
Dissemination level:	Public (PU)

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

Table of contents

Disclaimer

The opinions stated in this report reflect the opinions of the authors and not the opinion of the European Commission.

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

I. Introduction

Cancers are a group of diseases characterised by uncontrolled growth and spread of abnormal cells. Cancer is caused by external factors such as tobacco consumption, exposure to chemicals, radiation and viruses as well as some internal factors (mutations, hormones, immune conditions). The causes of cancer are diverse and only partially understood.

Cancer has become one of the main causes of death worldwide. GLOBOCAN 2020 estimates the incidence and mortality of cancer produced by the International Agency for Research on Cancer. Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and 10.0 million cancer deaths (9.9 million excl. nonmelanoma skin cancer) occurred in 2020. The global cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020, with a larger increase in transitioning (64% to 95%) versus transitioned (32% to 56%) countries due to demographic changes, although this may be further exacerbated by increasing risk factors associated with globalization and a growing economy. Efforts to build a sustainable infrastructure for the dissemination of cancer prevention measures and provision of cancer care in transitioning countries is critical for global cancer control (1).

Fighting cancer is one of the priorities of the European Union. At present, 3.4 million people in Europe are diagnosed with cancer annually. This number is predicted to increase to more than 4.0 million by 2035. Europe's Beating Cancer Plan aims at reducing the suffering caused by cancer through concrete actions in the areas of prevention, early detection, diagnosis and treatment, and improving the quality of life of cancer patients and survivors (2).

Within EURAMED rocc-n-roll, Task 3.1 analyses the needs of research in ionising radiation application in diagnosis and treatment and corresponding radioprotection (RP) in oncology by identifying gaps and possibilities. To advance in this purpose, the panel members and members of the WP discussed during several virtual meetings what could be the challenges and opportunities. We conducted a survey and based on the results of the survey we developed various recommendations.

II. Methodology

To cover all the main topics in the best way, Task 3.1 was composed by a panel of experts and external members according to the clinical scenarios we were requested to consider. In particular, the following experts were involved:

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

Task 3.1 Panel composition

Name	Center
Laure Fournie	Universite Paris Descartes (UP)
Andrea Rockall	Imperial College (IC)
Katrine Riklund	Umea Universitet (Umu)
Maciej Pech	Otto-Von-Guericke Universitaet Magdeburg (OvGU)
Ursula Nestle	Universitaetsklinikum Freiburg (UKLFR)
Mark Konijnenberg	Erasmus Universitair Medisch Centrum Rotterdam (EMC)
Klaus Bacher	Universiteit Gent (Ugent)
Merce Beltran	Vall d'Hebron Institut of Oncology (VHIO)
Jan-Jakob Sonke	Nederlands Kanker Instituut. Antoni Van Leeuwenhoek (NKI)
Dirk Verellen	European Society of Therapeutic Radiation Oncology (ESTRO)
Marc Benderitter	Institut de Radioprotection et de Surete Nucleaire (IRSN)
Philip Poortmans	European Cancer Organisation (ECCO)
Thomas Brunner	Otto-Von-Guericke Universitaet Magdeburg (OvGU)
Richard Price	European Cancer Organisation (ECCO)
Jonas Teuwen	Nederlands Kanker Instituut. Antoni Van Leeuwenhoek (NKI)
Riccardo Corridori	European Association of Manufacturers of Medical Devices (COCIR)
Jordi Giralt	Vall d'Hebron Institut of Oncology (VHIO)

Online meetings were held with the panel and external members in order to define clinical subspecialties needed (M3-M6). An open web-based survey was discussed and performed by all the members to compile a list of clinical scenarios relevant to the aims of the task.

After online discussion, a final list of relevant clinical scenarios was defined by consensus. 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 3.1 members and a final consensus was obtained.

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.

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

III. Results

III A. Diagnosis

Cancer offers a unique context for medical decisions given not only its variegated forms with evolution of disease but also the need to take into account the individual condition of patients, their ability to receive treatment, and their responses to treatment. Medical imaging, often involving ionising radiation, plays an essential role in nearly all aspects of high-quality cancer care, from preventive measures, including screening and early detection, through diagnosis, therapy selection (following the theranostic route) and treatment planning, monitoring, and follow-up. Data from large prospective studies have shown how imaging can assist in management decisions (3). For example, the US National Oncologic PET Registry has shown that the use of PET leads to substantial changes in the clinical management of 30% of patients across various cancer types (4).

Improve image quality

Image quality improvements can be produced as technical improvements on hardware equipment such as detectors (photon-counting detectors) or radiation dose management (automatic tube current modulation, iterative reconstruction techniques, dynamic collimation, solid-state detectors).

An important recent development is the advent of new X-ray detectors, i.e. for example, photon-counting detectors (PCD) for CT, which have been introduced in recent clinical prototype systems. PCD allows a pixel up to 200 microns pixels at isocentre, which is much smaller than what can be obtained with conventional energy integrating detectors (EID). PCDs also can have a higher quantum efficiency and thus dose efficiency than EID mainly because of electronic noise suppression (5). In addition, the energy-resolving capabilities of these detectors allow generating spectrally resolved imaging techniques, such as quasi mono-energetic images or water/iodine material images as well as K-edge imaging of a contrast agent based on atoms of high atomic number (6).

In the future, molecular imaging with improved spatial and or temporal resolution might further benefit the individualized cancer treatment. For that developments of technologies and methodologies to improve such possibilities will be necessary to foster faster and better cancer treatments.

The use of new radiological devices provides more and better information to make a good diagnosis, however, in some cases it can lead to a significant increase in patient dose. For example, in tomosynthesis based breast scans, due to the increased dose, the risk of breast cancer is approximately 2.5 times higher than in conventional mammography (7). However, it

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

increases detectability by reducing the number of false negatives. In general, the better the image quality, the higher the dose. Justification and optimization are the key to decide when and where better image quality is needed, and both should be considered in all medical imaging protocols (8).

New radiopharmaceuticals and contrast agents

Targeting specific cell membrane and intracellular markers for both diagnostic imaging and radionuclide therapy is a rapidly evolving field in cancer research. Some of these theranostic applications have now found a role in routine clinical practice and have been shown to have a significant impact on patient management (9). Different candidate compounds are targeting novel theranostic targets such as fibroblast activation protein, C-X-C chemokine receptor 4, and gastrin-releasing peptide receptor (10). In addition, several strategies to improve efficacy of radioligand therapy are being evaluated, including dosimetry-based dose optimization, multi receptor targeting, upregulation of target receptors, radiosensitization, pharmacogenomics, and radiation genomics. Several molecular targets are being investigated in ongoing clinical trials and show promise for future implementation. This will also offer potential for new contrast agents e.g. based on nanoparticles for new diagnostic and therapeutic applications.

The rapid introduction of new radionuclides in diagnosis and molecular therapy, some of them with energy spectra and half-lives very different from the usual radionuclides, implies an individualised study of the radiological protection measures to be followed by these patients during the first hours or days after their administration (11). It is difficult to make these recommendations because in many cases the aspects related to the elimination of these radionuclides are not well known (12). The management of radioactive waste from these new radionuclides is another issue to be taken into account in order to protect the environment.

Artificial intelligence (machine-learning)

Besides its application for technical imaging improvement as noise and artefact reduction, reconstruction etc., artificial intelligence (AI) promises to make great strides in the qualitative interpretation of cancer imaging by expert clinicians, including volumetric delineation of tumours over time, extrapolation of the tumour genotype and biological course from its radiographic phenotype, prediction of clinical outcome, and assessment of the impact of disease and treatment on adjacent organs. AI may automate processes in the initial interpretation of images and shift the clinical workflow of radiographic detection, management decisions on whether to administer an intervention, and subsequent observation to a yet to be envisioned paradigm. Although most studies evaluating AI applications in oncology to date have not been vigorously validated for reproducibility and generalizability, the results do

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

highlight increasingly concerted efforts in pushing AI technology to clinical use and to impact future directions in cancer care (20).

Imaging is not an isolated measure of disease. Increasingly, it is appreciated that the molecular signatures of cancers, including non-invasive blood biomarkers of tumour, have an impact on the outcome of patients with cancer. AI and machine learning will be transformed due to the generation of big digital datasets acquired by means of next generation sequencing (NGS), use of algorithms for image processing, patient-related health records, data arising from large clinical trials and disease predictions. Oncology has been in the forefront to reap the benefits of AI for universal cancer management (21). This includes early detection, tailored or targeted therapy by obtaining genetic information of the patient and predictions of future outcomes.

Integration platforms for diagnostic / Radiomics

Precision medicine requires the ability to classify patients into specialised cohorts that differ in their susceptibility to a particular disease, in the biology of the disease, response to therapy, and so on. Imaging data and, in particular, quantitative imaging features have been identified as a critical source of information when creating such cohorts for precision oncology. Radiomics is an emerging area in quantitative image analysis that aims to relate large-scale extracted imaging information to clinical and biological endpoints (13). The development of quantitative imaging methods along with machine learning has enabled the opportunity to move data science research towards translation for more personalised cancer treatments (14). Accumulating evidence has indeed demonstrated that non-invasive advanced imaging analytics, that is, radiomics, can reveal key components of tumour phenotype for multiple three-dimensional lesions at multiple time points over and beyond the course of treatment.

While radiomics facilitates new possibilities in the field of personalised medicine, some challenges remain. One of the primary obstacles is the lack of big and standardised clinical data (15). Although large amounts of medical imaging data are stored, these data are dispersed across different centres and acquired using different protocols. Access for research purposes is highly restricted by law and ethics. An exhaustive data curation and harmonisation process is still necessary to make it usable for research. Generative adversarial networks open up the possibility of generating synthetic data (16) or domain adaptive algorithms (17) might be able to deal with the shortage of standardised data. Various techniques to visualise deep features have already been put forward by researchers to generate an intuitive understanding. A completely new research area of artificial intelligence (AI) aims to track the decisions made by the intelligent algorithms so that it can be better understood (18). Furthermore, the diagnostic and prognostic power of complex “omics-driven” models is still to be determined in

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

specific populations, and evidence needs to be produced that such methods improve health outcomes (19).

III B. Treatment

Radiotherapy (RT) is the oldest and most used cytotoxic therapy in oncology and contributes to 40-50% of cancer cures (22). Since the emergence of radiotherapy, many technological advances have been made allowing for better anatomic dose targeting. Yet this crucial component of the response to cancer has been largely absent from global health discourse and has received limited domestic and international funding (23).

Over the last few decades, significant improvements in RT have been made. The progressive introduction of intensity-modulated RT (IMRT) and the use of multimodality imaging for target volume and organs at risk delineation, together with the use of altered fractionation regimens, concomitant administration of chemotherapy or targeted agents and advances in the knowledge of cancer biology, have accompanied efficacy improvements in RT.

Heavy particles

Particle therapy uses high-energy charged particles, most usual protons (PT). Their main benefit is a rapid dose fall-off beyond the peak dose or Bragg Peak, which spares healthy tissue, whereas photons (y-rays as well as X-rays) irradiate normal tissues before and after the tumour. Particle therapy can offer increased tumour control as healthy tissue can be avoided enabling dose escalation to some tumours, translating to increased loco-regional control for select patients. PT is more costly compared to the current, best available conventional radiation (24).

Currently, the best available evidence for patients being referred to PT is from retrospective analyses of small single-institutional studies, patient case studies, dosimetric studies or literature reviews. The lack of randomised control trial data as a ‘Gold Standard’ is attributed to methodological and ethical concerns (25). There was a large amount of variability observed in the clinical decision-making tools and dose comparison methods in current use. It is expected that PT patient selection methods will continue to change with developments in proton, the emergence of long-term PT data and the opening of more PT centres (26).

Heavy ion therapy is a unique form of radiotherapy for the treatment of cancer. It deposits ionising radiation in cancer cells via accelerated charged particles that are heavier than protons. Heavy ions have physical properties that make them deposit the dose more accurately

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

and allow the therapeutic heavy ion beam to pass more safely closer to healthy organs on their way to cancers than protons or X-rays could (27). Heavy ions seem to present immunogenic effects such as an increased production of tumour associated antigens and antitumor effects, which may result in reduced ability to metastasize or recur (28). Heavy ions have a considerably greater potential to enhance the therapeutic ratio for many cancer types compared to conventional X-ray and proton radiotherapy. Technological developments and basic and clinical research will be essential to establish the benefits of using spent ions for the treatment of some tumours. This especially includes further investigations about how to determine the actual dose distribution of protons or ions in real patients as the inhomogenities in patients might change the energy deposition and thus the position of the Bragg peak.

FLASH radiotherapy is the delivery of ultra-high dose rate radiation several orders of magnitude higher than what is currently used in conventional clinical radiotherapy and might have the potential to change the future of some cancer treatment. FLASH radiotherapy is stipulated to induce a phenomenon known as the FLASH effect, whereby according to quite a number of animal and cell studies the ultra-high dose rate radiation reduces the normal tissue toxicities commonly associated with conventional radiotherapy, while still maintaining local tumour control. Some few studies could not reproduce such effect.
The FLASH effect has been found in preclinical studies, but there is still a lot to be investigated trying to implement such findings. This holds for both technical and biological research to know if and with what benefit the potential FLASH effect could be used in humans. We need to better understand the mechanisms of action in order to be able to develop a new technology. For that, it will be mandatory to perform further in-vivo and in-vitro studies which are well controlled to better establish the potential advantages of FLASH therapy based on a thorough understanding of the mechanisms. Such investigations should look for spatially and temporally resolved dose distribution, biological effects, volume dependence and intercorrelations between various parameters.

PT may offer the best solution to be able to treat some deep-seated tumours, and there are several high-energy clinical PT facilities already in place that can be modified to generate FLASH dose rates. However, implementation of FLASH protontherapy still has its technical limitations. Significantly more research into FLASH PT is required to be potentially translated into the clinic for the benefit of cancer patients (29). There are also first developments for electron or photon-based FLASH RT. The different forms and effects of FLASH RT need to be investigated and understood better.

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

Imaging integration / IGRT / adaptive RT

In recent decades, technological improvements have allowed the development of techniques that increase the conformity of the prescribed dose to the tumour without affecting normal tissue, such as intensity-modulated radiation therapy (IMRT), volume-modulated arc therapy (VMAT), stereotactic ablative radiotherapy (SABR) and particle therapy. Image guidance is used in all these techniques, and inter- and intrafraction motion control have increasingly become a clinical reality. A guide-line-driven, multidisciplinary approach is of fundamental importance for securing optimal treatment for all patients in an individual approach for each patient, in which the use of radiotherapy is balanced with treatment options provided by other disciplines. Ongoing clinical trials are key in this regard, as they provide the basis for the development of optimal treatment guidelines that support clinical decision making. New hybrid radiotherapy devices that allow precise tumour imaging during radiation, that is, e.g. the recently introduced MR-Linac system, further support clinical radiation oncology. (30)

New radiopharmaceuticals / patient-specific dosimetry

Molecular alterations in malignant disease result in the expression or upregulations of various targets that can be used for imaging and treatment with radiopharmaceuticals or e.g. nanoparticle based pharmaceuticals. This theranostic principle has acquired greater importance in personalised medicine in recent years, particularly in oncology, where advanced tumours can be treated effectively with low side effects (31).

Patient-specific dosimetry in radiopharmaceutical therapy (RPT) and particularly for treatment planning is progressively implemented in clinical practice. However, there is al lack in (radio-) biological understanding to address the clinical unmet needs (32). There is a tremendous need to better understand the radiobiology of RPT improving patient care, patient survival, and innovation of new RPT concepts. In addition to the urgent requirement of prospective large data collection, there is the demand of a global and integrated approach to study and understand the biological effects of ionizing radiation in the context of RPT (33).

There has been a growth of interest in, and use of, α-emitting radionuclides in the treatment of cancer because of their higher radiotoxicity per unit of administered activity relative to radionuclides emitting β-, γ-, or x-rays (34). With well-established controls, α-emitting radionuclides can be handled and administered safely for clinical use. Initial investigations have shown that targeted a-therapy with radiolabelled PSMA inhibitors can induce dramatic responses with low toxicity (35)

Several new therapeutic approaches based on antibodies, peptidomimetics, and small molecule compounds have shown promising preclinical and initial clinical results (36). These

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

new radiopharmaceuticals are directed against specific proteins (B7-H3) or saccharides on the surface of tumour cells (CA19-9) but also against proteins produced by tumour stroma cells (FAP). Some of the radiopharmaceuticals are specific for certain tumour diseases whereas others, such as FAPI-04, are potentially suitable for a variety of tumour entities. Besides new targets, novel dose schedules and combination treatments are being studied clinically.

Biology

While radiotherapy has always been a highly personalised cancer treatment regimen, regarding clinical parameters and anatomic dose distribution, biology-driven personalised radiotherapy enables treatment based on the biological characteristics of the tumour and normal tissue, which need to be imaged correspondingly, is currently a promising research area in preclinical and clinical radiation oncology (37). RT doses are prescribed based on the energy absorbed by tissue. However, substantial interpatient heterogeneity exists in the biological effect of a given physical dose of radiotherapy; patients treated uniformly do not have a uniform response. These difference can be quantified at patient level using tumour genomics and, subsequently, the therapeutic approach can be modulated by the treating radiation oncologist (38, 39). The gene expression-based radiosensitivity index (RSI), is a biomarker of tumour radiosensitivity that has been validated in multiple cohorts in different cancer types by classifying patients as either being radiosensitive or radioresistant. (40, 41) Genomic-adjusted radiation dose (GARD) is a novel model that integrates RSI and physical dose of radiation to quantify the biological effect of a given dose in an individual patient. Through a pooled analysis of 11 cancer cohorts, GARD was found to predict the therapeutic benefit of radiotherapy, quantifying the relative benefit of radiotherapy for each individual patient. GARD better defines the likelihood of recurrence and survival than the total dose administered" (42). Two major strategies, acting synergistically, will enable further widening of the therapeutic window of radiation oncology in the era of precision medicine: technology-driven improvement of treatment conformity, including advanced image guidance and particle therapy, and novel biological concepts for personalised treatment, including biomarker-guided prescription, combined treatment modalities and biological adjusted dose.

Even when using the most advanced radiation technologies, the normal tissues of a patient are at risk of longer-term effects of ionizing radiation. These harmful effects are dose-, fractionation-, volume-, and organ-dependent, and should be avoided as much as possible. Not only can they be modified by other therapies and by pre-existing diseases, but they can also be associated with long observation periods and growth, with children being particularly vulnerable patients (43). Elderly patients might also be at increased risk of such late-onset effects since many of these effects add to age-dependent reduction of the reserve capacity of

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

a number of organs at risk (44). Due to an increasing prevalence of cured cancer patients, this has become a matter of concern that should be given a priority in future research

Integration of RT with systemic agents

The benefit of combined treatments of RT and systemic agents in many tumours is well established. Chemoradiation increases dose-intensity through biological modulation. There is a high level of evidence that locoregional control and survival are increased, at the expense of an overlapping toxicity with systemic agents (45). The benefit of chemoradiation is basically based on a dual action: spatial synergistic cooperation between the effect of chemotherapy on eradicating micro metastases and radiotherapy to the localized disease.

To date, all, with one notable exception, targeted agents investigated as radiosensitizers have failed to demonstrate an improvement in outcome. Only a phase III study proved the concept of increasing local control with manageable increase in toxicity through targeting the epidermal growth factor receptor (EGFR) (46). Numerous agents are being developed in combination with radiotherapy. However, specific tumour radiosensitizers are lacking and radiosensitizers carry a risk of increasing in-field toxicity. There is a need to investigate the combination of RT with the new biological agents that are being incorporated into cancer treatment.

Radiotherapy modulates the immune system by producing a range of effects including local inflammatory reaction, T-cells promotion, and provoking an enhanced host immune response against tumour cells (47). These localised processes can even be improved by triggering the immune system through immunotherapy. Preclinical studies have shown that different forms of immunotherapy can act as a local sensitizer for RT with good local control rates. Local effects were observed in a variety of tumour types, with different RT doses and fractionation schedules (48).

Several prospective clinical trials have shown promising improvements in survival for patients with oligometastatic disease with the use of metastasis-directed therapies when compared with standard-of-care systemic therapy alone. For example, in the SABR-COMET trial, compared standard-of-care systemic therapy with (n=66) or without (n=33) stereotactic ablative radiotherapy (SABR). After a median follow-up of about 2 years, median overall survival was increased in the group that received SABR (41 months) compared with that in the control group (28 months). In this regard, the combination of radiotherapy and immunotherapy for patients with widely spread metastases has gained considerable interest (49). However, maximising the synergistic impact of radioimmunotherapy necessitates a better understanding of the heterogeneity of the clinically defined metastatic sites.

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

Radiomics could allow evaluation of immune infiltration of tumours and, thus, lead to the identification of novel predictors of the efficacy of immunotherapy. Sun et al. (5) developed a radiomic signature of immune infiltration of tumours and assess the ability of this signature to predict clinical outcomes in patients treated with anti-PD-1 or anti-PD-L1 immunotherapy (50). These findings suggest the potential for non-invasive biomarker development in immunotherapy and the possibility to combined SABR with immunotherapy based on this biomarker.

IV. Conclusions & recommendations

In this deliverable we have reported a series of gaps in knowledge and open issues suggesting the needs of research about the use of medical radiation applications in cancer. The medical applications of ionizing radiation in oncology are very broad and play a fundamental role in diagnosis and treatment. Technological advances and a better understanding of biology open large areas of knowledge and research needs.

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

- Integrated diagnostics
- Photon counting CT
- Improved molecular imaging
- Theragnostics with new radiopharmaceuticals and particles
- Artificial intelligence / Machine learning
- Radiomics
- Heavy particle therapy
- Flash therapy
- Alpha-particle therapy
- Combined therapies

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

REFERENCES

1. Sung, Ferlay J, Siegel R et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries CA Cancer J Clin; 2021 May;71(3):209-249.
2. Europe's Beating Cancer Plan - European Unionhttps://health.ec.europa.eu › eu_cancer-plan_en_0
3. Hricak H, Abdel-Wahab M, Atun R, et al. Medical imaging and nuclear medicine: a Lancet Oncology Commission. Lancet Oncol. 2021 Apr;22(4):e136-e172
4. Hillner BE, Siegel BA, Liu D, et al. Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: initial results from the National Oncologic PET Registry. J Clin Oncol. 2008 May 1;26(13):2155-61
5. Si-Mohamed SA, Miailhes J, Rodesch PA, et. Spectral Photon-Counting CT Technology in Chest Imaging. J Clin Med. 2021 Dec 9;10(24):5757
6. Sawall S., Amato C., Klein L., Wehrse E., Maier J., Kachelrieß M. Toward molecular imaging using spectral photon-counting computed tomography? Curr. Opin. Chem. Biol. 2021;63:163–170.
7. Gilbert FJ, Tucker L, Gillan MGC, 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
8. Sechopoulos I. A review of breast tomosynthesis. Part I. The image acquisition process. Med Phys 2013;40(1):014301
9. Jadvar, H., Chen, X., Cai, W. & Mahmood, U. Radiotheranostics in cancer diagnosis and management. Radiology 286, 388-400 (2018).
10. Te Beek E, Burggraaf J, Teunissen J, Vriens D. Clinical Pharmacology of Radiotheranostics in Oncology. Clin Pharmacol Ther. 2022 Apr 3
11. Aerts A, Eberlein U, Holm S, et al. EANM position paper on the role of radiobiology in nuclear medicine. Eur J Nucl Med Mol Imaging. 2021 Oct;48(11):3365-3377
12. Yonekura Y, Mattsson S, Flux G et al. ICRP Publication 140: Radiological Protection in Therapy with Radiopharmaceuticals. Ann ICRP 2019 Sep;48(1):5-95.
13. Avanzo M, Stancanello J, El Naqa I, “Beyond imaging: The promise of radiomics,” Phys. Med 38, 122–139 (2017).
14. Lambin P, Rios-Velazquez E, Leijenaar R, et al. “Radiomics: extracting more information from medical images using advanced feature analysis,” Eur. J. Cancer 48, 441–446 (2012).
15. Rogers W, Thulasi Seetha S, Refaee TAG, et al. Radiomics: from qualitative to quantitative imaging. Br J Radiol. 2020 Apr;93(1108):20190948.
16. Mahmood F, Chen R, Durr NJ. Unsupervised reverse domain adaptation for synthetic medical images via Adversarial training. IEEE Trans Med Imaging 2018; 37: 2572–81
17. Wang Q, Milletari F, Nguyen HV, et al. Domain adaptation and representation transfer and medical image learning with less labels and imperfect data: first MICCAI workshop, dart 2019, and first International workshop, MIL3ID 2019, Shenzhen, held in conjunction with MICCAI 2019, Shenzhen, China, October 13 and 17, 2019, proceedings. Springer Nature 2019; 254
18. Holzinger A. Explainable AI (ex-AI) [Internet. Informatik-Spektrum. 2018; 41: 138–43
19. Saracci R. Epidemiology in Wonderland: big data and precision medicine. Eur J Epidemiol 2018; 33: 245–57.
20. Wenya Linda Bi WL, Hosny A, Schabath MB, et al. Artificial intelligence in cancer imaging: Clinical challenges and Applications. CA Cancer J Clin. 2019 Mar;69(2):127-157.

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

21. Dlamini Z, Francies FZ, Hull R, Marima R. Artificial intelligence (AI) and big data in cancer and precision oncology. Comput Struct Biotechnol J. 2020 Aug 28;18:2300-2311
22. Atun R, Jaffray DA, Barton MB, et al. (2015) Expanding global access to radiotherapy. Lancet Oncol 16, 1153–1186.
23. Zubizarreta EH, Fidarova E, Healy B, Rosenblatt E. Need for radiotherapy in low and middle income countries—the silent crisis continues. Clin Oncol (R Coll Radiol) 2015; 27: 107–14.
24. Verma V, Mishra MV, Simone CB. Cost-effectiveness of proton beam therapy for oncologic management. Int J Radiat Oncol Bio Phys 2018; 101 (2 Supplement 1): E20.
25. Ahern V. Selecting patients for proton beam therapy. J Med Radiat Sci 2021; 68: 2–
26. Zientara N, Giles E, Le H, and Short M. A scoping review of patient selection methods for proton therapy. J Med Radiat Sci 69 (2022) 108–121
27. Durante M, Debus J and Loeffler JS. Physics and biomedical challenges of cancer therapy with accelerated heavy ions. Nat Rev Phys. 2021 December ; 3(12): 777–790.
28. Park SS, Dong H, Liu X, et al. Pd-1Restrains Radiotherapy-Induced Abscopal Effect. Cancer Immunol Res. 2015; 3:610–9.
29. Hughes JR, Parsons JL. FLASH Radiotherapy: Current Knowledge and Future Insights Using Proton-Beam Therapy. Int J Mol Sci. 2020 Sep 5;21(18):6492
30. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. Lancet Oncol. 2020; 21:E18–E28.
31. Kelkar SS, Reineke TM. Theranostics: combining imaging and therapy. Bioconjug Chem. 2011;22:1879–1903.
32. Aerts A, Eberlein U, Holm S, et al. EANM position paper on the role of radiobiology in nuclear medicine. Eur J Nucl Med Mol Imaging. 2021;48:3365–77.
33. Pouget JP, Konijnenberg M, Eberlein U, et al. An EANM position paper on advancing radiobiology for shaping the future of nuclear medicine. Eur J Nucl Med Mol Imaging 2022 https://doi.org/10.1007/s00259-022-05934-2
34. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213–223.
35. Kratochwil C, Bruchertseifer F, Giesel FL, et al. 225Ac-PSMA-617 for PSMAtargeted alpha-radiation therapy of metastatic castration-resistant prostate cancer. J Nucl Med. 2016;57:1941–1944
36. Langbein T, Weber WA, and Eiber M. Future of Theranostics: An Outlook on Precision Oncology in Nuclear Medicine. J Nucl Med 2019; 60:13S–19S
37. Baumann M, Krause M, Overgaard J, et al. Radiation oncology in the era of precision medicine. Nat Rev Cancer 2016;16:234–249.
38. Eschrich SA, Pramana J, Zhang H, et al. A gene expression model of intrinsic tumor radiosensitivity: prediction of response and prognosis after chemoradiation. *Int J Radiat Oncol Biol Phys* 2009; **75:** 489–96.
39. Scott JG, Berglund A, Schell MJ, et al. A genome-based model for adjusting radiotherapy dose (GARD): a retrospective, cohort-based study. *Lancet Oncol* 2017; **18:** 202–11.
40. Eschrich SA, Fulp WJ, Pawitan Y, et al. Validation of a radiosensitivity molecular signature in breast cancer. *Clin Cancer Res* 2012; **18:** 5134–43.
41. Mohammadi H, Prince A, Figura NB, et al. Using the radiosensitivity index (RSI) to predict pelvic failure in endometrial cancer treated with adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys* 2020; **106:** 496–502.

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

42. Scott JG, Sedor G, Ellsworth P, et al. Pan-cancer prediction of radiotherapy benefit using genomic-adjusted radiation dose (GARD): a cohort-based pooled analysis. Lancet Oncol 2021; 22: 1221–29
43. Lambrecht M, Eekers DBP, Alapetite C, et al. (2018) Work package 1 of the taskforce "European Particle Therapy Network" of ESTRO. Radiation dose constraints for organs at risk in neuro-oncology; the European Particle Therapy Network consensus. Radiother Oncol. 2018;128;26–36.
44. Bentzen SM Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. Nat Rev Cancer 2006;9:702–713.
45. Chargari C, Clemenson C, Martins I, Perfettini J-L, Deutsch E. Understanding the functions of tumor stroma in resistance to ionizing radiation: emerging targets for pharmacological modulation. Drug Resist Updat Rev Comment Antimicrob Anticancer Chemother 2013;16:10–21.
46. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21–8.
47. Van Limbergen EJ, De Ruysscher DK, Olivo Pimentel V, et al. Combining radiotherapy with Immunotherapy: the past, the present and the future. Br J Radiol 2017;90:20170157
48. Vanneste BGL, Van Limbergen EJ, Dubois L et al. Immunotherapy as sensitizer for local radiotherapy. ONCOIMMUNOLOGY 2020, VOL. 9, NO. 1, e1832760
49. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. Lancet. 2019 May 18;393(10185):2051-2058
50. Sun R, Limkin EJ, Vakalopoulou M, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. Lancet Oncol 2018; 19(9): 1180-1191

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