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Original Research

The European Organisation for Research and Treatment of Cancer, State of Science in radiation oncology and priorities for clinical trials meeting report

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Abstract ***Background:*** New technologies and techniques in radiation oncology and imaging offer opportunities to enhance the benefit of loco-regional treatments, expand treatment to new patient populations such as those with oligometastatic disease and decrease normal tissue toxicity. Furthermore, novel agents have become available which may be combined with radiation therapy, and identification of radiation-related biomarkers can be studied to refine treatment prescriptions. Finally, the use of artificial intelligence (AI) capabilities may also improve treatment quality assurance or the ease with which radiation dosing is prescribed. All of these potential advances present both opportunities and challenges for academic clinical researchers. ***Methods:*** Recently, the European Organisation for Research and Treatment of Cancer addressed these topics in a meeting of multiple stakeholders from Europe and North America. The following five themes radiobiology-based biomarkers, new technologies – particularly proton beam therapy, combination systemic and radiation therapy, management of

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oligometastatic disease and AI opportunities in radiation oncology were discussed in a State of Science format to define key controversies, unanswered questions and propose clinical trial priorities for development.

Conclusions: Priorities for clinical trials implementing new science and technologies have been defined. Solutions to integrate the multidimensional complexity of data have been explored. New types of platforms and partnerships can support innovative approaches for clinical research in radiation oncology.

1. Introduction

The field of cancer therapy has seen enormous changes within the last two decades. While much interest has been directed to the emergence of novel systemic therapies which capitalise on evolving biological knowledge of malignancy, there have also been substantial changes in technologies and techniques relevant to radiation and surgical treatments of cancer.

While the regulatory environment requires that new drugs undergo clinical trial evaluation before marketing, the adoption of new technologies is not as constrained. Indeed, to truly evaluate these novel approaches, there must be some degree of training and adoption by health sciences centres to enable clinical trials to take place. As a result, randomised clinical trials addressing the clinical benefit of novel radiation oncology approaches or delivery technologies have been limited. Often new technology simply replaces old based on empiricism or theoretical advantages, often explained by the duration of prospective clinical research not being competitive with the speed of constantly advancing technologies [1]. That being said, academic cancer cooperative groups are ideally suited to provide the infrastructure and access to larger patient populations to support investigation and the clinical trials necessary to rigorously understand the impact of such innovations on outcomes of importance in cancer (survival, toxicity, quality of life, patient-reported outcomes and, increasingly, value for money).

The European Organisation for Research and Treatment of Cancer (EORTC) is one of the oldest organisations conducting such critical research. The Radiation Oncology Group of the EORTC has conducted trials that have shaped practice in breast, lung, head and neck and Genito-Urinary (GU) cancers to name but a few. In addition, EORTC Disease Oriented Groups have thriving radiation oncology members engaged in trial development and conduct.

The rapidly changing landscape of radiation oncology including the emergence of highly conformal radiation techniques, particle therapies, new approaches to management of localised and oligometastatic disease, new discoveries in biology, the rise of artificial intelligence (AI) imaging–based algorithms and emergence of novel drugs available for combination with radiation treatment led the EORTC to sponsor a 'State of Science' meeting to update knowledge and explore research opportunities in radiation oncology. Radiation oncologists from EORTC, the European Society for Radiotherapy and Oncology (ESTRO), Canada and the United States, as well as researchers in particle therapy, radiation biology, immunology, patient-reported outcomes and trial methodology were gathered in September 2018 to review current available evidence supporting practice in various areas, discuss and debate where clinical research should be directed to improve cancer outcomes and to create a menu of priority radiation oncology–based clinical trial questions for further development.

A planning committee created an agenda of priority themes for discussion over a 2-day period, and invited attendees were balanced across therapeutics areas, expertise and European countries (Appendix I). This manuscript summarises key points in the discussion and recommended priority questions and areas for research for study by the EORTC and other organisations.

2. Biology-guided dosing in radiation therapy: where do we stand?

2.1. Current state

Over the last decades, major developments in the use of radiation to treat cancer have been focused on the physically accurate delivery of radiation therapy. This has resulted in the ability to conform radiation dose very precisely to the target of interest thus sparing, as much as possible, surrounding adjacent normal tissues to reduce attendant toxicities. While radiation dosing has become physically accurate, it is lacking in biological precision related to what is known, or yet to be discovered, with respect to specific individual tumour and normal tissue response to radiation. 'Personalized radiation therapy' has, to date, been defined anatomically rather than incorporating the direct or surrogate biomarkers that predict the sensitivity of the tumour and normal tissues [2].

It has been a general assumption that most tumours are more likely to respond or be eradicated by maximising the radiation dose used. However emerging and validated clinical markers and other evidence across diverse tumours have identified that the previous dose paradigm is too broad and inaccurate to apply to all tumour types and patients. This section of the workshop focused on which biology-based predictive biomarkers are validated and ready for evaluation in clinical trials to tailor treatment.

2.2. Questions ready for clinical trial evaluation

Table 1 shows the current landscape of predictive biomarkers to guide radiation therapy. As shown, these are in various stages of validation and clinical development. Both measures of radiosensitivity and hypoxia would appear to be sufficiently validated to derive level I evidence for their use in tailored dose selection in appropriate subpopulations. Two of the most promising predictive biomarkers use RNA expression signatures to classify subpopulations of sensitive and resistant tumours of a given histopathologic type:

a The radiation sensitivity index (RSI-GARD (Genomic Adjusted Radiation Dose)) has been validated across multiple disease sites including different end-points for evaluation. In general, the RSI is bimodal which implies that the delivery of a higher dose of radiation does not necessarily guarantee a greater anti-tumour effect. Indeed, the biological effect may change. For certain patients, a lower than conventional dose could be adequate for tumour control, and for others, even a higher dose would be inadequate.
b The importance of hypoxia is well known in governing response to radiation treatment and has been validated as a predictive biomarker for many tumours (Table 1). Tumour hypoxia can be identified by various measures including the RNA signature (validated) or by hypoxia focused Positron Emission Tomography (PET) or Magnetic Resonance Imaging (MRI) imaging (requires validation).

RSI-GARD and hypoxia markers are ready to be evaluated directly in stratifying tumours for studies in which patients may be randomised to treatment with different radiation doses depending on these predictive biomarkers. Two major types of questions are ready for biology-driven radiation clinical research based on the aforementioned ones and were developed and discussed in the State of Science meeting:

a Randomized trials focused on improving in local control/survival
  o Example – currently curatively treated cancers in stage IIIa patients with Non Small Cell Lung Cancer (NSCLC) would be randomised to standard dose radiation or to tailored radiation dosing (+/– chemotherapy) based on their RSI-GARD and hypoxia signatures. The end-points would include both tumour and toxicity outcomes with the hypothesis being that signature designed treatment would improve tumour outcomes. Specific tumour sites discussed as suitable for this type of trial included not only NSCLC but also HPV-negative head and neck, locally advanced prostate, oesophageal and endometrial cancers. Similar studies could also be relevant for relatively radioresistant tumours where radiation is part of a standard of care (e.g. pancreatic adenocarcinoma, glioblastoma and mesothelioma).

b Randomised trials designed to refine selection of patients for chemoradiation vs. surgery to minimise normal tissue toxicity.
  o Example – Muscle invasive bladder cancer (OR locally advanced rectal cancer). Patients would be randomised between standard approach of chemoradiation or surgery based on current clinical decision rules vs. a RSI-GARD

Table 1
Predictive biomarkers for radiation sensitivity.

		Discovery	Validation	Level 1 evidence
Radiosensitivity	RSI-GARD		Y (many tumours) [3]	
	RNA Sig			
Hypoxia	RNA Sig PET/MRI		Y (many tumours) [4–6]	Y (bladder; head and neck cancer) [4,7]
Genomic	PGA/MTs		(X)	N
Proteomic	P16		(X)	N
	MRE11		(X)	
	MCMT		(X)	
Immune		(X)		N
Imaging	PET FDG		(X)	N
	PET MISO		(X)	
	CBCT		(X)	
Machine learning	Radiomics	(X)		N
Normal tissue	RILA		Y (breast [8]; prostate [9])	N
	Foray	(X)		
	Models ± SNPs	(X)		
	Radiomics			

PGA/MT, Power for Genomic Association Analysis; P16, MRE11, and MCMT are gene coding proteins; PET-FDG, PET-Flurodeoxuglucose; PET-MISO, PET 18F Miso; CBCT, cone beam computed tomography; RILA, radiation-induced CD8 T-lymphocyte apoptosis.

Table 2
Examples of ongoing randomised phase III trials of proton vs. photon therapy.

	Tumour type	Study arms	Sample size	Primary end-point
MDACC Head and neck cancer (US) NCT01893307	Oropharyngeal cancer	• Intensity-modulated proton beam therapy (IMPT) • Intensity-modulated photon therapy (IMRT)	360	Toxicity
NRG Oesophageal cancer (US) NCT03801876	Oesophageal cancer	• Proton Beam therapy paclitaxel Carboplatin Oesophagectomy • Intensity-modulated photon therapy (IMRT) paclitaxel Carboplatin oesophagectomy	300	Overall Survival
RTOG Lung cancer (US) NCT01993810	NSCLC	• Proton beam therapy with concurrent and adjuvant chemo • Photon beam therapy with concurrent and adjuvant chemo	330	Overall Survival Cardiac toxicity and Lymphopenia
NRG Liver cancer (US) NCT03186898	Hepatocellular cancer	• Proton beam therapy • Photon beam therapy	186	Overall Survival
RADCOMP (US) NCT02603341	Post-surgical, locally advanced breast cancer	• Proton beam therapy • Photon beam therapy	1278	Toxicity (Cardiac events)
PARTIQoL (US) NCT01617161	Prostate cancer; low intermediate risk	• Proton beam Therapy • Intensity-modulated photon therapy (IMRT)	400	Toxicity (bowel toxicity)
PAROS (Heidelberg) NCT04083937	Prostate	• Hypofractionated radiotherapy with photons • Hypofractionated radiotherapy with protons • Normofractionated radiotherapy with photons	897	QoL (bowel toxicity)

MDACC, MD Anderson Cancer Center NRG: each letter is the first of the followings National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG); RTOG, the Radiation Therapy Oncology Group; RADCOMP, Radiotherapy Comparative Effectiveness; PARTIQoL, Prostate Advanced Radiation Technologies Investigating Quality of Life; PAROS, Prostate Cancer Patients Treated With Alternative Radiation Oncology Strategies; NSCLC, Non Small Cell Lung Cancer.

and hypoxia-driven treatment assignment. In the bladder cancer example, patients on the experimental arm would be assigned surgery when RSI-GARD score is high and low RSI-GARD score patients would have bladder preserving chemoradiation.

Addressing questions such as those outlined would clarify how best to incorporate these predictive biomarkers into standard practice and decision-making. An increasing issue for prediction is the use of combined modality treatments using radiation therapy in combination with chemotherapy, molecular targeted agents or immunotherapy (refer in the following paragraphs). A 'radiotherapy only' signature may not translate in these settings.

3. How can we address new technologies in the therapeutic armamentarium for optimised patient care/cure – focus on proton therapy

3.1. Current state

The second theme discussed at the State of Science meeting addressed the question of how new radiation technologies should be researched and incorporated into the therapeutic armamentarium to optimise patient care and cure. Currently many new technologies have been incorporated into cancer therapy with only modest levels of clinical evidence for their benefit [1]. The new technologies available include but are not limited to intensity-modulated photon therapy, image guided radiotherapy (IGRT), stereotactic body radiotherapy (SBRT), magnetic resonance-linac (MR-linac) and particle therapies.

The main interest of the participants at the State of Science was on the use of proton therapy so that was the focus of the discussion. This therapy requires substantial investment and infrastructure and is being adopted in many countries because of the preclinical experimental data that proton therapy can reduce normal tissue toxicity [10]. To date, most available data have been based on physical modelling of proton vs. photon beams and/or observational series in the clinic with very limited randomised clinical data identifying whether or not its theoretical benefits are being realised [11–14]. There are several tumour types where the theoretical advantages of proton

therapy are of particular interest: these include but are not limited to childhood brain and spinal cord tumours [15], as well as base of skull tumours, head and neck cancers, uveal tumours and other paediatric cancers.

3.2. Questions ready for clinical trial evaluation

A variety of considerations were discussed in the context of trial designs of proton therapy. These included innovative trial methodologies and use of end-points relevant to patients including quality of life, toxicity and disease outcomes. Given the higher capital and operational cost of this innovative technology, it was considered that health economic parameters must also be incorporated [16]. In addition, translational research questions including biomarkers with radiomics and genetic signatures should be part of such trials. Finally, it was clear that clinical trials of new technologies must always be accompanied by rigorous quality assurance.

As noted previously, the theoretical favourable therapeutic ratio of proton vs. photon therapy needs to be confirmed in phase III randomised trials. While this level of evidence is not yet available and several randomised trials are ongoing (for examples, refer Table 2, compiled after the meeting for this report), some centres are currently treating patients with protons outside of randomised clinical trials, and it will be important to set up prospective collection of high-quality data on the toxicity and efficacy outcomes for those patients through the European Proton Therapy Network (www.estro.org/Science/EPTN).

During the State of Science discussions, two major directions for clinical research studies were agreed: The first was to determine whether protons can reduce radiotherapy (RT)-induced morbidity, while maintaining the same or better tumour control/survival (normal tissue complication probability [NTCP] domain). The second was whether proton therapy can improve tumour control and survival (tumour control probability [TCP] domain) in disease sites where the outcome of traditional photon radiation therapy is poor or alternatively where radiation is not in use.

3.2.1. Reduction of RT-induced morbidity

There was strong support to develop and validate, through clinical trials, the use of an NTCP model to predict in individual patients the expected toxicity from proton vs. photon treatment and, based on this, select the preferred type of radiation.

A benefit of protons versus photons in terms of lower rates of radiation-induced toxicity with similar local control can only be obtained when 3 conditions are met: (1) The target dose should be biologically equivalent; (2) The dose to the most relevant organs at risk should be lower (ΔDose) and (3) This ΔDose is expected to translate into a lower rate of toxicity ((ΔNTCP) For example, in head and neck cancer, relevant toxicities (dysphagia, xerostomia, tube feeding dependence, oral mucositis, salivary inflammation and so on) would be predicted from the planned dose received for both the photon and proton plan for the same patient [17]. If no or minimal benefit were to be expected in terms of the modelled toxicity for protons over photons, the patient would be assigned to photon therapy. If there were a substantial reduction in toxicity predicted with protons, the patient would be assigned to proton therapy. A trial to validate (and modify if needed) the NTCP model would be important because, if validated, it could be deployed in clinical decision-making to select patients for proton therapy who might be spared substantial toxicity.

Validation of the model requires prospective clinical studies and is a multistep process. As a first step, observations of patients treated with both photons and protons should allow the subsequent refinement of the model predictions to match observed outcomes; the second step would be a classic Randomised Clinical Trial (RCT) randomising those with a 'meaningful' predicted reduction in toxicity to protons vs. photons. A challenge will be to determine what level of 'toxicity' reduction would make the new technology an acceptable standard in terms of clinical relevance and/or costs. Patient input on reported toxicities will be an important end-point to be incorporated.

Potential tumour types for these trials having a primary goal of reducing morbidity include head and neck cancer, stage IIIC endometrial cancer and low-grade glioma.

3.2.2. Improving tumour control

On the other side of the therapeutic ratio, there is interest in determining if proton therapy and the theoretical ability to safely increase radiation dose to target using this modality could lead to improved tumour control compared with standard photon therapy. Tumour types where normal tissue toxicity limits delivery of high dose radiation are ones where this could be investigated and include oesophageal cancer, glioblastoma, HPV-negative head and neck cancer, sarcoma and chordoma/chondrosarcoma. The appropriate randomised trial design should include standard of care (radiation or chemoradiation) with photons in one arm, with escalated proton dosing in the experimental arm to an approximate equivalent toxicity. Key end-points would be overall survival, tumour control and toxicity.

4. How artificial intelligence may change practice in radiation oncology

AI is the theory and the development of computer systems that are able to perform tasks at a level comparable

Table 3
Randomised phase II trials of local ablative treatment (SBRT) vs control.

Citation	Tumour type	Study arms	Design/sample size	Results Primary end-point Secondary end-point
Gomez DR et al. J Clin. Oncol. 2019 37:1558–65 [27]	NSCLC ≤ 3 metastases without PD after≥3 cycles 1st line systemic Rx	• SBRT or Surgery to all metastatic sites • Maintenance therapy or observation	Randomised phase II/49	PFS 14.2 vs 4.4 mo; p = .022 OS 41.2 vs 17 mo; p = .017
Iyengar P et al. JAMA Oncol. 2018, 4:e173501 [28]	NSCLC ≤ 5 metastases (plus primary) PR or SD after induction chemo	• SBRT to all metastatic sites followed by maintenance chemo • Maintenance chemo	Randomised Phase II/29	PFS 9.7 vs 3.5 mo; p = .01).
Ost P et al. J Clin Oncol 2018, 36:446–453 [29]	Prostate cancer with asymptomatic first recurrence. No prior therapy ≤ 3 metastases	•SBRT to all metastatic sites •Observation	Randomised phase II/62	Androgen deprivation free survival 21 vs 13 mo; p = .11
Palma DA et al, Lancet. 2019; 393:2051–8 [30]	Metastatic solid tumour ≤ 5 metastases	• SBRT to all metastatic sites plus standard of care • Standard of care	Randomised phase II/99	OS 41 vs 28 mo; p = ·09. (NB: 3 treatment-related deaths in SBRT arm)

OS = overall survival; PFS = progression-free survival; SBRT = stereotactic (ablative) body radiation therapy; PD = progressive disease; PR = partial response; SD = Stable Disease; NSCLC = Non Small Cell Lung Cancer.

with human intelligence, a termed coined by John McCarthy in the 1950s and the inventor of the computer programming language Lisp. AI has evolved tremendously from the days of Lisp into modern Python programming offered by major high-tech companies. AI is generally data driven and requires input of large data sets and is the computational vehicle for big data analytics [18]. Modern data science covers both big data, as well as AI including machine learning algorithms and its latest advances represented by deep learning algorithms [19].

There are two potential areas highlighted where AI could significantly impact the practice of radiation oncology.

- The first is in the practical aspects of radiation planning and delivery. For example, image analysis can be used for tumour/normal tissue segmentation and treatment plans can be developed based on models build on prior treatment plans thus liberating radiation personnel from time-consuming tasks around the image segmentation and planning processes.
- The second and related area is in the use of such systems to provide review and quality assurance (RTQA) of treatment plans performed in more traditional ways and to provide remote services for RTQA.

There are of course also important research opportunities for use of AI and deep learning algorithms most significantly for modelling [20,21] but also for the analysis of large clinical, biological or radiomics data sets.

While no specific plans for clinical research questions examining AI outputs were developed during the State of Science meeting, some directions were discussed as important for clinical research groups such as the EORTC. These groups are ideally placed to focus on generating new potential AI applications from their research data sets and also validating AI applications from other groups and commercial entities on their independent data sets.

5. Targeting oligometastatic disease – who can we cure?

5.1. Current state

Metastases account for most cancer-related mortality. Despite advances in systemic therapy, the therapeutic approach most widely applied in this cancer stage, most patients with metastases from solid tumours are still considered incurable. Historically, localised modalities such as surgical resection and radiation were generally used with palliative intent. However, in the last two decades, it has been hypothesised that some patients may have truly limited (oligometastatic) tumour spread or tumour with limited capacity to spread and that such patients might be cured or have survival extended through ablative approaches (radiation or surgery) to the metastatic site(s) [22].

To date, while there is no universally accepted definition of what constitutes 'oligometastatic' disease, several parallel developments in the last few years have led to the rapid expansion of study and use of ablative therapy for apparent oligometastatic disease. These developments include improved imaging modalities allowing earlier and more accurate detection of metastasis with lower tumour burden [23–25], as well as the

Table 4
Randomized phase III trials evaluating SBRT in addition to standard of care.

	Tumour type	Study arms	Design	Sample size	Primary end-point
NCT02685397	Castrate-resistant prostate cancer ≤ 5 metastases	• SBRT to all metastatic sites + LHRH agonist + enzalutamide • LHRH agonist + enzalutamide	Phase II/III	130 (ph II) 374 (ph III)	PFS
NCT02089100	First-line metastatic breast cancer; ≤ 5 metastases	• SBRT to all metastatic sites + systemic therapy • Systemic therapy	Phase III	280	PFS
NCT03784755	Hormone-sensitive prostate cancer ≤ 5 metastases	• SBRT to all metastatic sites and untreated primary if present + standard systemic therapy • SBRT to untreated primary if present + standard systemic therapy	Phase III	410	Failure-free Survival
NCT02759783 (CORE trial)	Prostate cancer Breast cancer NSCLC ≤ 3 metastases	• SBRT to all metastases + standard of care • Standard of care	Phase II/III	230 (ph II) TBD (ph III) for each tumour type	PFS (ph II)
NCT02364557	Breast cancer ≤ 4 metastases	• SBRT or surgery to all metastatic sites + standard of care • Standard of care	Phase II/III	402	PFS (ph II) OS (ph III)
NCT03862911	Oligometastases (1−3)	• SBRT to all metastases + standard of care • Standard of care	Phase III	297	OS
NCT04115007	Hormone-sensitive prostate cancer ≤ 5 metastases	• SBRT to all metastases + standard of care • Standard of care	Phase III	350	Castrate-resistant prostate cancer free survival
NCT03721341	Oligometastases (4−10)	• SBRT to all metastases + standard of care • Standard of care	Phase III	159	OS
NCT02893332	EGFR-mutated metastatic NSCLC ≤5 metastases	• SBRT to all metastases + TKI • TKI	Phase III	200	PFS

OS = overall survival; PFS = progression-free survival; SBRT = stereotactic (ablative) body radiation therapy; TKI = tyrosine kinase inhibitor; EGFR = Epidermal Growth Factor; LHRH = luteinizing hormone-releasing hormone; NSCLC = Non Small Cell Lung Cancer.

development of non-surgical approaches such as high dose/ablative therapy using SBRT, allowing focused high dose radiation treatment with fewer side-effects [26], as well as seamless integration into systemic therapies.

Several small phase II randomised trials have been reported in the oligometastatic setting, signalling benefits in outcomes meriting further evaluation (Table 3) [27–31].

Along with these developments, despite the lack of any adequately powered phase III randomised studies showing survival benefits, some guidelines have been modified to recommend ablative therapies for oligometastatic disease (defined variably) in several cancer types (e.g. colorectal cancer, sarcoma, non-small cell lung cancer, renal cell cancer, prostate cancer, germ cell cancer and some paediatric cancers and breast cancer) [32,33]. As a result, the use of radical local treatment for oligometastases using SBRT has increased markedly. A worldwide survey conducted in more than 1000 radiation oncologists reported that more than 60% of all responders were already offering SBRT for oligometastatic disease [34].

The increasing use of SBRT for this indication in practice settings makes designing trials to definitively document the potential benefits of radical treatment of limited metastatic disease a complex problem [35]. Adding to this complexity is that fact that the spectrum of oligometastases is broad and diverse in terms of cancer type, biology, timing of development, previous treatments for the primary cancer, imaging used for detection of oligometastases and the number, location and size of oligometastatic lesions [36]. Clinical trials evaluating ablative therapy must in addition consider the integration of local treatment into a systemic treatment strategy. The optimal choice of radiation dose/fractionation for radical local treatment is also unknown, and finally relevant clinical end-points need agreement and definition. For example, the use of the proximal end-point of progression-free survival is problematic when clearly patients whose disease is untreated will have progression detected earlier than those whose disease is ablated. The real question is whether such treatment changes the ultimate trajectory of disease and impacts overall survival. Finally, the impact of adoption of this as a standard of care could have wide ranging impact on surveillance protocols of potentially curatively treated patients. If it is believed early diagnosis and treatment of oligometastatic disease is standard, new follow-up protocols will need evaluation that could have impacts on cancer care costs and patient burden. Fortunately, several randomised phase III trials are ongoing (examples shown in Table 4, identified through a search in Clinicaltrials.gov database) and so some of these questions will be addressed.

5.2. Discussion and priority questions

While it was acknowledged that phase III evidence was currently lacking and would be required to address some of the uncertainties noted, some of radiation oncologists participating in the State of Science meeting were uncomfortable with randomising patients to standard of care vs. ablative therapy for tumours in which guidelines were already changing (e.g. breast, prostate, colorectal cancer). These were however the following research priorities identified:

i. For groups and institutions willing and able to do so, collaboration with planned/ongoing randomised phase III trials of oligometastatic disease in common solid tumours is encouraged to ensure these are completed rapidly and answers to questions about impact on survival, which patient groups are most likely to benefit are addressed.
ii. For less common solid tumours, basket-type trials evaluating the impact of ablative oligometastatic treatments would be of value.
iii. For patients not enrolled on prospective trials, priority should be given to registering patients undergoing oligometastatic radiation therapy on the OligoCare platform of E^2RADIatE, developed by the EORTC-ESTRO Radiation Infrastructure for Europe. This pragmatic observational pan-European cohort will accumulate data on patients undergoing radiation to oligometastatic disease as part of their treatment trajectory and allow assessment of factors affecting their selection for treatment and their overall survival, patterns of care and patterns of outcomes
iv. Economic analyses will be critical to include in any prospective trials of oligometastatic SBRT, particularly the impact of enhanced surveillance for the early detection of small burden metastatic disease, and its response assessment to ablative radiation therapy that would be a consequence of adopting this approach as a standard of care.

6. Combining radiotherapy with novel agents

6.1. Current state

The use of concurrent systemic therapy – notably standard antineoplastic chemotherapy – in combination with radiation has been the subject of many years of study and is now part of the standard of care in multiple tumour types.

While there is substantial interest in evaluating novel agents (e.g. targeted therapies, immune oncology drugs) in combination with radiation, there is debate about the best preclinical models, dosing and schedule information on which to base subsequent clinical trials. Furthermore, there are complexities in defining the optimal clinical settings in which to conduct combination studies, how to

Table 5
Clinical priorities and clinical trials in radiation oncology – consolidated recommendations.

Clinical priority	Objectives	Type of tumour of interest	Trial design
Biology optimisation for more precision	Improve local control	Non–small cell lung cancer, HPV – head and neck cancer Locally advanced prostate cancer, oesophageal cancer Endometrial Cancer	Randomisation between standard treatment and allocation based on radiation sensitivity index or hypoxia markers
	Patient selection for chemoradiotherapy vs surgery	Muscle invasive bladder cancer, locally advanced rectal cancer, head and neck cancer	Allocation of patients or chemoradiation based on radiation sensitivity index to surgery
New technologies for better care (particles)	Reduction of morbidity	Head and neck cancer, endometrial cancer, low-grade glioma	NTCP: model prediction through cohorts followed by trials for predicted reduction in toxicity
	Improving tumour control without increasing normal tissue toxicities	Oesophageal cancer, glioblastoma HPV – head and neck cancer sarcoma Chordoma	Standard of care vs escalating proton dosing
Artificial intelligence to benefit patients	Improving precision of radiation delivery	As applicable	Embedding validation of AI on clinical trials
	Monitoring quality assurance	As applicable	
Oligometastatic patients: improving cure	Assessing the impact of ablative treatment	Rare solid tumours Other tumours	Basket trial Prospective registry to document patterns of care and outcome
Novel agents combination	The added value of combination with mechanism-based agents (IO, targeted agents…)	Rectal cancer, oesophageal cancer	Window of opportunity in the neoadjuvant setting

NTCP, normal tissue complication probability; AI, artificial intelligence; IO, Immuno-Oncology.

determine limiting toxicities (when both acute and late effects may be seen) and the key intermediate efficacy end-points which can determine if new combinations warrant randomised evaluation. A final hurdle is that trials of new drugs in combination with radiation are often of little interest to pharmaceutical industry, meaning access to such drugs (even for academic groups that can fund the work) has been a challenge. Nevertheless, the State of Science attendees highlighted the importance of developing novel combinations with radiation, with a goal of improving cancer outcome.

Immunotherapy was the therapeutic class of greatest interest to pursue by those attending the State of Science meeting. Immune-based cancer treatments have been studied for decades, but it is only the last few years that progress has been made in identifying new agents (e.g. anti-CTLA4 antibodies, and PD1/PDL1 targeted agents) of substantial clinical impact. Despite these agents being relative newcomers to the clinic, numerous preclinical studies have shown combining these drugs with radiation might yield synergistic effects [37]. The theoretical mechanisms for this are several including but not limited to the following: radiation-induced cell damage may expose tumour antigens that may lead to cytotoxic T-cell activation [38] and radiation-induced changes to the microenvironment may facilitate infiltration of immune cells. Such preclinical information provides a compelling rationale for combining radiation with immune oncology agents.

6.2. Discussion and priority questions

There was general agreement that phase I and II combination trials of immunotherapy and radiation should be 'window of opportunity' designs in locally advanced cancers where neoadjuvant (chemo)radiation followed by surgery is a general standard and where early end-points such as pathological complete response would be available as suitable end-points on which to make decisions about further development. In addition, where pathological

response rates may be significantly increased, avoidance of surgery might be considered an end-point of value. Another advantage to studying combination treatment in this setting is that pre- and post-treatment tissue samples could be studied to document changes in biologic measures relevant to radiation sensitivity. Pre- and post-treatment imaging could also be incorporated. Such studies could use an 'addition' or 'substitution' design wherein the novel agent could be either added to current therapy or substituted for standard systemic chemotherapy given in combination with radiation, which would be selected would depend on the clinical context and strength of the (preclinical) science.

Rectal cancer was identified as an optimal model. Discussions focused on developing a platform to study multiple questions (different drugs, doses, radiation prescription) in a series of non-randomised sequential trials; selecting one or more promising regimens for phase III comparisons. Alternatively, innovative adaptive designs may be used advantageously to compare several combinations across several arms of the same trial, allowing the best arm according to the efficacy to be enriched.

There was overlap noted with discussions in the radiobiology session where the choice of optimal radiotherapy for combined studies would use validated predictive markers. The attendees felt it might be efficient to incorporate this concept into combined modality studies of novel agents.

7. Conclusions: where do we go from here?

Demonstrating evidence for changing practice in cancer medicine needs clear questions, robust methodology and end-points and committed clinical researchers. Therapeutic progress should be the result of identifying and solving key public health questions. In oncology multi-disciplinarity, optimising not only systemic and locoregional treatments but also translational disciplines is central to patient management. In the era of precision oncology, biomarkers and constantly evolving technology, solid evidence for treatment options need a thorough assessment of high-quality complex data sets. Efficient access to patients alongside new solutions for clinical research needs constant adaptation to the changing environment. The first objective through the evaluation of the State of Science in radiation oncology was to identify priorities for clinical trials while assessing the integration of new technologies including AI and translational science. The second objective was to identify solutions and clinical trials which would integrate the multi-dimensional complexity of data to deliver evidence for these clinical priorities (Table 5). It demonstrated that it needs international cooperation and cross-cutting science to define the scientific strategy, reform approaches to data handling and re-engineer the process of cooperation integrating all required expertise. To improve the therapeutic ratio for patients whose therapy includes radiation treatment, the priorities have been identified as optimising combination therapies with emerging systemic treatments, understanding the role of particle therapy, refining dose fractionation and dose delivery and integrating tumour and normal tissue biology and incorporating strategies that use AI. The European EORTC-ESTRO Radiation Infrastructure for Europe E^2RADIatE is a pan European registry which integrates specific cohorts for oligometastatic patients and patient treated with protons, based on which prospective clinical trials are being developed to address some of these public health questions. Delivering evidence to improve survival and quality of life of patients with cancer is at the heart of such initiative and central to the mission of such State of Science exercise. The major identified risk is the sustainability for such independent platform, which can only succeed if it offers ease of use and a substantial added value to the community, willing therefore to stimulate and support its use. Governments and supranational funding agencies should support such initiative and align in the best interest of patients and society, establishing therapeutic strategies which truly make a difference.

Conflict of interest statement

P.O. reports receiving institute research funding from Merck, Bayer, and Varian; receiving consultancy honoraria or serving as advisory board member (institute)—Ferring, BMS, Janssen and Bayer and receiving travel grants Ferring. E.D. reports receiving grants and personal fees from Boerhinger, grants from AMAZONAWS, grants and personal fees from Roche, grants and personal fees from AZD, grants from BMS, grants from MSD, personal fees from AMGEN and personal fees from ACCURAY, outside the submitted work. All other authors declare no conflict of interest.

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Appendix. State of Science attendees

Last name	First name	Institution	Country
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Ducreux	Michel	Institut Gustave Roussy	FR
Eisenhauer[2]	Elizabeth	Queens University	CA
El Naqa	Issam	University of Michigan	USA
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Fournier	Béatrice	EORTC Headquarters	BE
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Haustermans	Karin	UZ Leuven	BE
Herrera	Fernanda	Centre Hospitalier Universitaire Vaudois	CH
Hurkmans[1]	Coen	Catharina Ziekenhuis	NL
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Illidge	Timothy	The University of Manchester	UK
Jaffray	David	University Health Network and University of Toronto	CA
Kaidar-Person	Orit	Rambam Health Care Campus	IL
Kirkby	Karen	The University of Manchester	UK
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Russell	Nicola	The Netherlands Cancer Institute	NL
Scott	Jacob	The Cleveland Clinic	USA
Span	Paul	Radboud University Medical Center Nijmegem	NL
Thomas[2]	Gillian	Sunnybrook Health Sciences Centre	CA
Tombal[2]	Bertrand	Cliniques Universitaires Saint-Luc	BE
Van Limbergen	Evert	Maastricht University	NL
Weber[1]	Damien	Paul Scherrer Institute, ETH Domain	CH
West	Catharine	The University of Manchester	UK
Woodruff	Henry	Maastricht University	NL

[1] Working Group Leader.
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