Challenges and opportunities for early phase clinical trials of novel drug–radiotherapy combinations: recommendations from NRG Oncology, the American Society for Radiation Oncology (ASTRO), the American College of Radiology (ACR), the Sarah Cannon Research Institute, and the American College of Radiation Oncology (ACRO)

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NRG Oncology's Developmental Therapeutics and Radiation Therapy Subcommittee assembled an interdisciplinary group of investigators to address barriers to successful early phase clinical trials of novel combination therapies involving radiation. This Policy Review elucidates some of the many challenges associated with study design for early phase trials combining radiotherapy with novel systemic agents, which are distinct from drug–drug combination development and are often overlooked. We also advocate for potential solutions that could mitigate or eliminate some of these barriers, providing examples of specific clinical trial designs that could help facilitate efficient and effective evaluation of novel drug–radiotherapy combinations.

Introduction

Radiotherapy remains a cornerstone of cancer treatment more than a century after it was first used to treat malignant tumours. Radiotherapy is delivered to approximately 60% of patients with cancer overall, including 40% treated with curative intent,[1] and remains one of the most cost-effective cancer therapies.[2] Technological advances have revolutionised radiation delivery, collectively facilitating improved tumour localisation, decreased margin uncertainty, increased target dose delivery, and better sparing of adjacent normal tissue, thereby reducing long-term toxic effects and improving oncologic outcomes.[3–5] Although these improvements in radiation delivery provide meaningful clinical benefits, the next phase of clinical advancement will require harnessing novel therapeutic agents that enhance the biological efficacy of radiotherapy.

The potential for novel drug–radiotherapy combinations is strengthened by an exponential expansion in available systemic therapy agents targeting various biological mechanisms. For example, more than 200 oncology drugs were US Food and Drug Administration (FDA)-approved between 2016 and 2021.[6] Thousands of preclinical studies have leveraged novel drugs to enhance radiotherapy efficacy. Nevertheless, cetuximab in head and neck cancer is the only molecularly targeted drug to receive FDA approval for concomitant delivery with radiotherapy,[7] representing a small number of all patients with cancer. Even this success has been somewhat muted, given that cetuximab–radiotherapy was shown to be inferior to cisplatin–radiotherapy in human papillomavirus-associated oropharyngeal cancer,[8,9] has not improved outcomes when added to standard platinum-based chemoradiation in head and neck squamous cell carcinoma,[10] and has not been beneficial in any other cancer.

Despite limited success to date, combinatorial systemic therapies and radiotherapy can potentially interact in numerous mutually beneficial mechanisms, including tumour radiosensitisation, normal tissue protection, spatial cooperation (radiotherapy targeting locoregional disease and systemic therapy targeting distant micrometastases), potentiation of the immune response, and additive cell death with non-overlapping toxic effects. High-level evidence from clinical trials supports the use of systemic therapies such as cytotoxic chemotherapy or androgen deprivation therapy to improve overall survival in specific cancers (eg, head and neck cancer, cervical cancer, lung cancer, and prostate cancer) when combined with radiotherapy,[11,12] providing strong proof of concept for radiotherapy–systemic therapy synergy. With improved radiation delivery and a rapidly broadening spectrum of available drugs, now is an opportune time to explore novel drug–radiotherapy combinations.

There have been several previous reviews focusing on the clinical development of drug–radiotherapy combinations.[13–16] Although these studies provide excellent broad overviews of drug–radiotherapy development from preclinical investigation to late phase practice-changing trials, most have had less specific focus on the pragmatic issues related to early phase clinical trial design in this space, which are distinct from those arising in clinical trials without radiotherapy. Here, we will explore the key unique challenges in early phase drug–radiotherapy clinical trials and outline actionable solutions for overcoming them.

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Unique challenges of early phase clinical development of novel drug–radiotherapy regimens

Multiple unique challenges specific to developing novel drug–radiotherapy regimens are summarised in panel 1. First, there are multiple limitations in the preclinical data underlying novel drug–radiotherapy trials that potentially reduce their translatability. Current preclinical assays for drug–radiotherapy appear to have limited correlation with clinical reality.[17] Most studies use a small number of decades-old mouse cell lines implanted into syngeneic mouse models or human cell lines implanted into immunodeficient mouse models, both of which have considerable limitations. The regular use of additional, more clinically relevant models to validate results before translation is needed. Additionally, the immune system of young healthy mice, often used in preclinical studies, does not reflect the immune system of our patients, who are often older and overweight. Thus, our current models might inaccurately predict the benefit and toxicity of combining radiotherapy with immunotherapy. Using older or mouse models with obesity for immunotherapy studies can yield results that better reflect clinical efficacy and toxicity.[18,19] In addition to preclinical models that do not accurately recapitulate human cancer biology, the radiation techniques used to treat these models often bear little semblance to radiotherapy regimens used in clinical practice. Furthermore, preclinical studies rarely compare novel drug–radiotherapy combinations against standard of care chemoradiation regimens that will eventually serve as benchmarks in clinical trials. Lastly, many preclinical studies focus on tumour radiosensitisation, largely or entirely ignoring the equally crucial issue of normal tissue radiosensitisation. Multiple groups have made recommendations for improving preclinical studies of drug–radiotherapy combinations.[20–22]

Beyond preclinical data, multiple challenges arise in the clinical development of drug–radiotherapy combinations that are not present for drug trials. For example, early clinical testing of a novel drug is typically initiated in patients with advanced disease who have progressed with standard therapies and have few, if any, therapeutic options. Once safety and efficacy is established in this setting, the novel agent will then be tested in progressively earlier stages of disease. Due to major differences in radiotherapy regimens for metastatic versus localised disease (ie, radiotherapy dose, target volume, use of concurrent systemic therapy, toxicity based on anatomic site, etc), mirroring this traditional drug development process is often not possible for drug–radiotherapy combinations. Testing of curative-intent drug–radiotherapy paradigms typically should be initiated in the curative setting, ideally in groups with less favourable outcomes such that evaluating toxicity thresholds for novel treatments is acceptable.

Another challenge for early phase drug–radiotherapy trials is that dose-limiting toxicity (DLT) windows are generally much longer than the 14 to 28-day windows commonly used for drug trials. Standard fractionation schema delivers radiotherapy over 3 to 7 weeks, with many relevant DLTs peaking weeks to months after radiotherapy completion. Thus, drug–radiotherapy DLT evaluation periods of 3–12 months are not uncommon. Long DLT windows constrain the efficiency of early phase clinical trial designs based on a fixed number of evaluable patients, since all DLT data have to be obtained before dose escalation and de-escalation decisions.

A further challenge for novel drug–radiotherapy development is the difficulty extrapolating the safety of a drug–radiotherapy combination from one anatomic site to another due to organ-specific toxic effects. This challenge limits the feasibility of multi-disease site trial designs, such as basket trials, outside of specific sites sharing organs at risk and radiation doses (eg, lung and oesophagus tumours, or gynaecologial and lower gastrointestinal tumours). Additionally, multiple radiotherapy parameters that vary from one disease to another, including volume, fractionation, and timing with respect to drug administration, could affect efficacy and safety.

Although efficacy is not the primary outcome of early phase trials, another challenge is determining preliminary evidence of enhanced activity for drug–radiotherapy combinations. Response rates, which provide insight into the activity of drug–drug combinations, have limited use for drug–radiotherapy combinations due to high response rates from radiotherapy alone in many definitive treatment settings and the absence of measurable disease in the postoperative setting.

Beyond these inherent challenges, the FDA does not provide clear regulatory guidance for obtaining approval for novel drug–radiotherapy combinations. This issue is further complicated due to the late development of these combinations, typically entering clinical testing about 6 years after phase 1 trial results of the drug have been reported.[23] On average, results from phase 1 drug–radiotherapy trials are published approximately 9 years after the drug patent has lapsed,[24] which does not account for phase 2 or 3 trials that require years to conduct in the non-metastatic setting. Given that a drug patent life is 20 years in the USA, the pharmaceutical industry could be disincentivised from pursuing drug–radiotherapy development by these prolonged timelines.

Although a myriad of challenges exists for the clinical development of novel drug–radiotherapy combinations, none are insurmountable either individually or collectively. Actionable and feasible solutions summarised in panel 1 and explored in the remainder of this manuscript are available to facilitate more effective clinical investigations of this treatment paradigm.

Early phase clinical trial design for drug–radiotherapy combinations

Optimal phase 1 drug–radiotherapy clinical trial design has been infrequently examined.[13–16] However, many

***Panel 1*: Key unique challenges to early phase drug–radiotherapy clinical trials and recommendations to overcome these barriers**

Challenge: longer dose-limiting toxicity (DLT) windows are sometimes necessary due to radiotherapy regimens lasting multiple weeks or to monitor for late toxicity

Solutions:

- Use model-based designs that allow continuous enrolment (eg, time-to-event continuous reassessment model)
- Include both acute and late DLT assessment periods
- Utilise multi-drug platform trials that can enrol to different drug–radiotherapy combinations while another drug–radiotherapy cohort is awaiting DLT data

Challenge: often requires initial testing in the curative setting

Solutions:

- Identify populations in each disease site treated with definitive intent with sufficiently poor outcomes to justify novel drug–radiotherapy investigation
- Mandate rigorous radiotherapy quality assurance with centralised real-time review and detailed, site-specific radiotherapy target delineation and organs at risk guidelines can help limit variability due to radiotherapy design differences

Challenge: relevant efficacy endpoints often take many years to evaluate

Solutions:

- Prioritise development of early surrogate endpoints, such as functional imaging response and circulating biomarkers (eg, circulating tumour DNA), that strongly correlate with clinically relevant outcomes.
- Consider using pathological complete response or major pathological response when drug–radiotherapy is used in the neoadjuvant set.

Challenge: lack of biomarkers to direct drug–radiotherapy combinations

Solutions:

- Prioritise biomarker discovery in the preclinical setting
- Collect tumour tissue, ideally both before and after treatment, that can be used to retrospectively identify relevant biomarkers. Collecting tissue after treatment is likely only feasible for patients undergoing preoperative drug–radiotherapy treatment or those with incomplete response to treatment and is typically not possible for patients undergoing postoperative radiotherapy. For patients undergoing definitive radiotherapy without surgery, collection of tissue during radiotherapy (eg, after 1–2 weeks of treatment) is an alternative for easily accessible tumours in clinical situations where post-treatment collection is not feasible
- Collect relevant patient tissue for analysis, including potentially blood, saliva, urine, and stool, for exploratory biomarker correlatives

Challenge: each novel drug–radiotherapy combination typically requires separate clinical testing for each anatomic site

Solutions:

- Site-specific clinical trials generally cannot be avoided for novel drug–radiotherapy combinations due to the anatomic specific of radiation toxicity
- Basket-trial designs across anatomic sites are often less informative for this reason
- For a limited number of sites that share similar organs at risk and radiotherapy regimens (eg, lower gastrointestinal and gynaecological), multi-disease site trials might be feasible

Challenge: lack of regulatory guidance for drug–radiotherapy combination development

Solutions:

- Regulatory agencies should produce guidelines specific to drug–radiotherapy combination regulatory approval given differences from drug–drug development
- National research regulatory institutions should support the use of model-based early phase trials and novel platform-based studies, given the limitations of standard rule-based designs for drug–radiotherapy combinations

Challenge: drug–radiotherapy combinations often studied near end of drug patent life

Solutions:

- Early dialogue between key stakeholders (ie, pharmaceutical companies, academia, and regulators) is needed
- Consider parallel drug and drug–radiotherapy phase 1 trials during development

Challenge: preclinical models have limited correlation with clinical practice

Solutions:

- Should include assessment of normal tissue toxicity and radiosensitisation
- Use multiple clinically relevant models (eg, patient-derived xenograft, immunocompetent mice, or orthotopic models)
- Should study novel combination versus the current standard of care that will likely represent the comparator group in a clinical trial
- Optimal timing, dose, and fractionation of radiotherapy and drug should be investigated

of the biggest hurdles of drug–radiotherapy development are directly related to their poor compatibility with standard phase 1 trial designs. For this discussion, we will assume that the radiation dose and timing with respect to the drug is fixed, and the novel drug will be tested at multiple dosing levels. We note that when combining novel radiosensitising drugs with radiotherapy, alternative strategies could be explored, such as using a fixed dose of drug to investigate reductions in radiation dose, duration, or volume. However, such trial designs are currently rare in the phase 1 setting.

Structurally, phase 1 clinical trials in oncology (table) are broadly divided into rule-based (eg, 3+3), model-assisted (eg, Bayesian optimal interval design [BOIN]), and model-based designs (eg, continuous reassessment method [CRM]). Rule-based designs represent the majority of early phase drug–drug combination trials, but they can be prohibitively long for drug–radiotherapy with extended DLT windows. Also, since escalation and de-escalation rules are based on a fixed number of evaluable patients, patients who withdraw or are lost to follow-up without a DLT must be replaced, creating a situation where a single patient withdrawing can add months to the trial duration. Alternatively, model-based designs, such as the time-to-event-CRM, use parametric statistical models of toxicity probability that dynamically incorporate the information from all previously treated patients to predict the DLT probability and make dose determinations.[38,43] Model-based designs also allow more flexibility in determining the target toxicity rate. With the time-to-event-CRM, patients have a weighted contribution to the toxicity probability calculation according to the proportion of the DLT window they have completed. That is, dose escalation and de-escalation decisions can be made using incomplete DLT data after incorporating the amount of follow-up for those patients without a DLT. Time-to-event-CRM has been shown to have superior operating characteristics versus rule-based designs.[44,45] With the time-to-event-CRM, dividing the DLT window into acute and late phases is also possible, with relative weighting in the model set according to the expected likelihood of DLTs in each phase. For example, a 12-month DLT window could have a 3-month acute phase and a 9-month late phase, each contributing 50% to the probability distribution if acute and late toxic effects were thought to occur with equal probability. The disadvantages of this design include substantial infrastructure requirements to allow real-time data collection, software modelling based on incoming data, and dedicated biostatistician support. Additionally, if accrual is rapid and excessive late toxic effects occur, a higher number of patients could be exposed to poorly tolerated doses of drug–radiotherapy compared with other designs. One mitigation strategy is planned accrual suspensions.[46] Restrictions can be placed such that no dose level can be skipped and accrual can be suspended if the probability of toxicity crosses a set threshold.[47]

As a result of the complexities in implementing model-based designs, investigators have proposed model-assisted designs as an alternative. One of the most well established designs is time-to-event-BOIN.[40] Compared with time-to-event-CRM, time-to-event-BOIN is simpler, uses a table for dose escalation and de-escalation decisions instead of a complex mathematical model of the dose–toxicity relationship, and has lower risk of patient overdose.[48] Time-to-event-BOIN has been shown to have similar accuracy to time-to-event-CRM for determining the maximum tolerated dose.[48] Similar to model-based designs, time-to-event-BOIN designs also allow for flexibility in defining the target DLT rate.[36] For example, if the expected baseline grade 3–4 toxicity with radiotherapy alone is 40%, a target of 60% for grade 3–4 toxicity could be used as a threshold to establish drug dose escalation and de-escalation decisions. Thus, time-to-event-BOIN combines the simplicity of rule-based methods with performance characteristics approximating complex model-based approaches.[48]

Beyond the dose escalation and de-escalation schema based on previous designs, an alternative way to mitigate the effect of long DLT windows is to use a platform design that studies multiple drug–radiotherapy combinations simultaneously in a single disease site. Patients can be sequentially enrolled into separate groups with a multiagent platform design, delivering one of several distinct novel drug–radiotherapy combinations. As patients from one drug–radiotherapy combination continue through the DLT window, subsequent patients can be enrolled to receive other novel drug–radiotherapy regimens. Once the other drug-radiotherapy groups have completed enrolment of their current allotment of patients, accrual to the original drug–radiotherapy combination can resume. Such a design, which can be combined with a continuously accruing model-based structure for each group, has multiple beneficial features, including limiting the number of patients simultaneously within the DLT window for a specific drug–radiotherapy combination, avoiding extended openings and closing of the trial, and the ability to include a shared control group for comparing outcomes. The simplest such design is where patients with a single disease type are initially enrolled to receive drug A–radiotherapy.[49] When drug A–radiotherapy suspends accrual for DLT evaluation, subsequent patients can be enrolled to receive drug B–radiotherapy, and vice versa. A more complex platform trial example is the CONCORDE trial for non-small-cell lung cancer that sequentially evaluates five different DNA damage response inhibitors in combination with radiotherapy via a time-to-event-CRM design, comparing outcomes with a shared, concurrently enrolling control group.[50]

Notably, the issues facing drug–radiotherapy combinations are not monolithic across categories of agents. Some classes of agents, such as hormonal therapy, have more orthogonal mechanisms of action to radiotherapy

	Description	Accrual of new patients while DLT data are pending	Advantages	Disadvantages
3 + 3[25-27]	Rule-based design. Three patients are initially enrolled into a given dose cohort. If no DLTs are observed, dose level escalation occurs. If one DLT is observed, a three-patient expansion is used at this dose level. If no patients in this three-patient expansion experience a DLT (ie, one of six total), then dose escalation continues. If two or more of the six patients treated on the dose level have a DLT, then a dose level that is one step lower is considered the MTD and the trial is stopped. The objective is to identify an MTD at which less than 33% of patients have a DLT.	No	Simple, rule-based, historical standard, and low chance of exposing patients to excess DLTs.	Slow (requires full follow-up observation and accrual delays), lack of flexibility if patients are unevaluable (eg, dropouts without a DLT need to be replaced), uses partial information (ie, no data across all dose levels), and often selects the incorrect dose level as the recommended phase 2 dose. The sample sizes used might be excessively small for accurately estimating the true MTD.
Rolling six design[28]	Rule-based design. Allows for accrual of up to six patients concurrently onto a dose level. Decisions as to which dose level to enrol a patient to are based on the number of patients currently enrolled and evaluable, how many have had DLTs, and how many are still in the DLT window at the time of new patient entry.	No	Improved speed compared with a 3 + 3 design that is rule-based.	Could expose more patients to a potentially toxic dose.
CRM[29-31]	Model-based design continuously updates the DLT probabilities using a one-parameter dose–toxicity relationship model and toxicity from cohorts of treated patients. Patients are enrolled and treated in small cohorts (eg, three to six). The dose level closest to the target toxicity level is selected as the MTD.	No	Attempts to minimise the number of patients enrolled at doses with low biological activity without increasing the number of DLTs. Uses all available information efficiently and estimates MTD accurately.	Might expose a large number of patients to considerable toxicity if initial model assumptions are incorrect; interventions to decrease this chance include (1) increasing by only one dose level at a time, (2) treating multiple patients at the MTD, and (3) not escalating the dose level if a DLT was observed in the previous patient. Requires substantial statistical expertise during the design and is operationally more demanding.
Escalation with overdose control[32-34]	Modification on the CRM method with an additional safety criterion—overdose control—that terminates dose escalation if the model predicts the probability that the next dose level exceeds a pre-specified threshold.	No	Improved safety measures over CRM.	Might be over-restrictive of dose escalation and, therefore, increase trial length.
BOIN[35-37]	Model-assisted design with a fixed sample size. Patients are accrued in specified-sized cohorts (eg, one, three, or six). As each cohort is treated, the DLT rate estimate is updated, and an escalation and de-escalation decision is made using all the accumulated data at the current dose level.	No	Provides more flexibility in choosing the target toxicity rate and cohort size (eg, no replacements for dropouts are needed). Superior operating characteristics to standard rule-based designs, such as the 3 + 3 design, lower risk of overdosing than some model-based designs, and similar performance to CRM design.	Slightly higher risk of overdosing than the 3 + 3 design. Uses only accumulated data from the current dose level to appraise the appropriate next dose level, although the sequential nature of the trial design does incorporate some past information in the current decision. Design is not suitable to handle late-onset toxic effects with extended DLT assessment windows.
Time-to-event -CRM[38]	Modification to the CRM design that allows accelerated accrual while patients are still in DLT observation, which is particularly useful if long observation periods are planned to monitor for late toxic effects.	Yes	It allows for the enrolment of new patients while some enrolled patients still have toxicity data pending. Uses data from all dose levels of the dose–toxicity curve model.	Can lead to an excess of patients enrolled under the recommended phase 2 dose.[39] Design is statistically and logistically more complex than time-to-event-BOIN.
Time-to-event -BOIN[40]	Modification of the BOIN design to accommodate late-onset toxic effects. Time-to-event-BOIN allows for dose escalation decisions while toxicity data for some enrolled patients are still pending, by incorporating the amount of follow-up into the decision rules.	Yes	Combines the advantages of time-to-event-CRM design with a rule-based method that simplifies application; escalation rules can be tabulated based on the number of patients, DLTs, and amount of follow-up for patients in DLT observation.	Risk of overdose unless accrual suspension rules are implemented (eg, if >50% of patient DLT outcomes are pending, suspend accrual and wait for additional toxicity data). Uses data from the current dose level to make decisions.
EffTox (phase 2 and 3)[41]	Bayesian model-based trial design with a pre-specified sample size and designed to use both effectiveness and toxicity data simultaneously to establish the optimal dose. Uses the assumptions: (1) previous probability of efficacy or toxicity should be pre-specified for each dose level, and (2) requires the definition of a function to describe the trade-off between efficacy and toxicity.	No, although modified designs might address this[42]	Allows for the establishment of an optimal dose level on the basis of toxicity and efficacy.	Highly complex design requiring active statistical support.

BOIN=Bayesian optimal interval design. CRM=continual reassessment method. DLT=dose-limiting toxicity. MTD=maximum tolerable dose.

Table: **Summary of selected early-stage clinical designs**

and might have less potential for unexpected potentiation of late radiation toxicity. Conversely, molecularly targeted agents, such as DNA damage response inhibitors and cytotoxic agents, generally have a higher potential for radiosensitisation of normal tissue and might require more extended DLT windows than others.

Additionally, phase 1 trials are designed to identify a recommended phase 2 dose by determining the maximum tolerated dose that can be delivered without observing excess toxicity. This dose determination assumes that higher doses are related to higher efficacy. This assumption might not be valid for some drugs or radiotherapy,[51–54] thus, might provide a rationale for using methods that incorporate both efficacy and toxicity in the dose escalation and de-escalation decisions, such as concurrent phase 1 and 2 trials with adaptive Bayesian designs.[41]

In summary, traditional rule-based designs have limitations for early phase drug–radiotherapy clinical trials. More efficient designs that allow for continuous accrual as patients continue with DLT evaluation should be considered when possible. Designing and conducting phase 1 trials with model-based and model-assisted designs requires close collaboration among clinical investigators, biostatisticians, and other stakeholders. In some situations, adaptations of the escalation and de-escalation rules might be needed to ensure patient safety. A safety monitoring plan should be specified in the protocol, and patient-enrolling sites should have sufficient resources to promptly submit safety data to facilitate dose escalation and de-escalation decisions quickly. Last, the trial design is supposed to guide, but not mandate, escalation and de-escalation decisions. Medical experts and the entire study team should participate in and discuss these decisions since patient safety is paramount.

Dose-limiting toxicity definition for early phase drug–radiotherapy trials

Defining DLTs, one of the central components of early phase trials, can be complex for drug–radiotherapy combinations, given the inherent baseline side-effect profile of standard of care radiation regimens. As an example, in NRG/RTOG 1016, the overall grade 3–4 toxicity rate was seen in 325 (82%) of 398 patients with concurrent cisplatin and radiotherapy for treatment of oropharyngeal cancer.[8] Detecting an increase in toxicity above this baseline level, or directly attributing it to a novel drug–radiotherapy combination, is difficult in a small early phase trial. There are several approaches to addressing this. First, DLTs for drug–radiotherapy trials can focus only on severe and rare toxic events that would be unexpected with standard radiotherapy paradigms, such as extended treatment breaks, life-threatening toxic effects, unexpected side-effects, and treatment-related mortality. For instance, in NRG-HN008, a phase 1 trial of the DNA-dependent protein kinase inhibitor peposertib and radiotherapy in patients with head and neck cancer who were cisplatin-ineligible patients (NCT 04533750), the DLT definition included any grade 3 or greater adverse events that were definitely or might be related to peposertib or radiotherapy that occurred during the DLT observation window, excluding common radiotherapy-related toxic effects (eg, mucositis, dermatitis, dysphagia, etc). The inability to complete at least 80% of the radiotherapy dose or a greater than 1-week delay in radiotherapy due to adverse events definitely or might be related to peposertib, and were also considered DLTs. Alternatively, trial designs can incorporate a background DLT probability based on the radiation dose and dose enhancement factors derived from preclinical studies into a normal tissue complication probability model to estimate the additional effect of an experimental drug on toxicity.[55]

Efficacy endpoints for early phase drug–radiotherapy trials

Although the primary objectives of early phase clinical trials are to assess safety and identify the recommended dose of a given therapy, these studies also provide information about its potential antineoplastic activity. In drug trials, objective response rate is commonly used as an assessment for early evidence of activity. However, given that the goal of radiotherapy in definitive cases is complete eradication of disease and there is no visible tumour to assess for response with postoperative radiotherapy, objective response rate is not a suitable metric for drug–radiotherapy activity. Although locoregional recurrence rates provide the most accurate metric of drug–radiotherapy efficacy, this is suboptimal in early phase trials when trying to efficiently triage the most promising drug–radiotherapy combinations to later phase trials. Therefore, alternative endpoints providing earlier assessments of antitumour activity are needed.

Circulating tumour DNA (ctDNA) holds tremendous potential for rapidly assessing treatment efficacy in solid tumours before relapse or radiographic response in early phase drug–radiotherapy trials. However, careful characterisation of ctDNA responses in each disease setting is required before deployment as an endpoint in clinical trials. Challenges to the use of ctDNA include detectability at low tumour burden levels, technical variability, inability to identify the source of tumour-derived DNA (ie, irradiated tumour *vs* non-irradiated tumour), and reproducibility across different platforms.

Functional imaging assessments are another promising approach that could allow an expedited assessment of drug–radiotherapy activity in early phase clinical trials. Perhaps the most common type of functional imaging used in oncology is fluorodeoxyglucose PET-CT scanning. Changes in tumour fluorodeoxyglucose uptake can be seen as early as the first 1–2 weeks of radiotherapy and correlate with tumour recurrence and overall survival in some diseases.[56,57] Other PET tracers, including but not limited to fluoromisonidazole-based, dotatate-based, fluciclovine-based, and prostate-specific membrane antigen-based agents, could also be useful in various disease contexts. Thus, changes in tracer uptake during or shortly after radiotherapy could provide an early window into the efficacy of a drug–radiotherapy

combination, although the exact imaging timing, optimal cut-point to define a response, and the expected rate of imaging response with standard treatment are context-dependent and need to be established from observational studies before their use in trials. Other imaging techniques, such as multiparametric MRI that includes dynamic contrast enhancement, perfusion, diffusion, and spectroscopy, can also be used for similar purposes.

Where preoperative drug–radiotherapy is used, clinical complete response, pathological complete response rates, or major pathologic response could be early markers of activity. Pathological complete response rate has been used as an endpoint to support accelerated approval of novel systemic agents in early-stage breast cancer.[58]

Special consideration needs to be given to efficacy endpoints in combined radiotherapy–immunotherapy trials. Although traditional radiotherapy trials focus on the local effects of radiotherapy, early phase immunotherapy combination trials are often seeking to evaluate the systemic effects of radiotherapy outside of the irradiated field (abscopal response). Thus, in these trials, it might be important to define specific response criteria measuring endpoints relevant to the questions being asked by the trial. For example, in a recent phase 2 study of immunotherapy either alone or with two different radiotherapy regimens, the goal was to establish if radiotherapy increased the systemic efficacy of immunotherapy.[59] Therefore, the primary outcome was: overall response rate by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, excluding the irradiated lesion. A final consideration in the design of radiotherapy–immunotherapy trials is pseudoprogression, an effect characterised by a transient worsening of tumour appearance on imaging, followed by delayed tumour regression.[60] To help prevent erroneously classifying pseudoprogression as true progression, it is crucial to consider using other response criteria, such as immune-RECIST or independent-related response criteria,[61] or to require confirmation of continued progression on follow-up scans if patients are clinically stable.

Biomarkers for patient selection or toxicity monitoring

Biomarkers are measures of biological processes that provide information regarding prognosis, treatment response, or toxicity probability. Biomarkers can inform selection of systemic therapies in some scenarios, but their role in guiding radiation-based treatment strategies is more obscure. Studies have correlated specific genomic mutations with radioresistance (eg, *KRAS*, *BRAF*, *TP53*, and *NRF2* or *KEAP1*),[62–65] and a gene expression-based radiosensitivity index predicts radiation response in various disease types.[66] However, to date there are no clinically validated predictive biomarkers to guide drug–radiotherapy combination selection. Therefore, preclinical and clinical research for drug–radiotherapy biomarker discovery and validation should be a high priority.

Biomarker evaluation can be measured in various analytes, such as tissue, blood, and saliva, and can be conducted using diverse platforms including next generation sequencing and radiomics, among others. To advance novel therapeutic combinations with radiotherapy, we suggest that all drug–radiotherapy clinical trials collect both putative biomarker data informed by preclinical research and broad next generation sequencing genomic and transcriptomic data for retrospective discovery, with the goal to identify biomarkers that are sufficiently robust to use for future trial design. Ideally, these analytes would be collected both before and after treatment. However, although post-treatment tumour tissue collection is feasible in patients undergoing preoperative drug–radiotherapy, it generally is not possible for patients receiving drug–radiotherapy in the postoperative setting or in non-surgical patients who are expected to have complete eradication of disease at the end of radiotherapy. A potential alternative, at least for non-surgical patients, is to obtain tumour tissue after the first 1–2 weeks of drug–radiotherapy before complete resolution.

Populations to target for early phase trials of novel drug–radiotherapy combinations

Multiple diverse settings exist where novel drug–radiotherapy combinations could be used, including curative-intent radiotherapy (ie, definitive, preoperative, or postoperative settings), oligometastatic disease ablation, primary tumour treatment in patients with de novo metastasis (eg, prostate or nasopharynx), or palliative-intent radiotherapy. Generally, initial clinical testing should occur in the same setting that the drug–radiotherapy combination will ultimately be used, ideally in populations with suboptimal outcomes with standard of care radiotherapy paradigms to justify investigation of a novel regimen with an unknown toxicity profile. Panel 2 lists potential patient populations where early phase drug–radiotherapy trials could be feasible. Once novel drug–radiotherapy combinations have shown safety in these high-risk populations, they can then be tested in broader populations in later phase trials.

Another crucial factor to consider is that radiotherapy has unique organ-specific toxic effects and dose limitations, leading to different possible DLTs in various anatomic sites. Some agents might have less favourable toxicity profiles when combined with radiotherapy in specific sites due to overlapping toxic effects or exacerbation of specific side-effects. For example, a systemic agent that causes mucositis could have acceptable toxicity with radiotherapy in some populations, but not in those with head and neck cancer. Similarly, agents known to cause gastrointestinal distress could have an unfavourable therapeutic ratio with rectal or anal cancer radiotherapy. For these reasons, early phase trials of novel

drug–radiotherapy combinations usually need to be disease site specific.

Moreover, variations in the natural history and patterns of recurrence in different patient populations could drastically change the goals of adding novel drugs to radiotherapy, with important implications both for the types of agents that should be studied and the overall trial design. As an example, glioblastoma multiforme almost never metastasises and produces morbidity and mortality via nearly universal locoregional progression. Thus, radiosensitisers that synergise with and amplify the efficacy of radiotherapy in a tumour-specific manner could be highly desirable. By contrast, in stereotactic ablative radiotherapy for oligometastatic cancers, local control rates are above 90%, but distant progression at untreated sites of microscopic disease is a central challenge. Therefore, radiosensitising agents might have less use in this setting compared with systemic agents capable of eradicating micrometastatic disease on their own. Although these are simply two of many possible clinical scenarios, they illustrate the need to design each early phase drug–radiotherapy trial specifically for the disease site and clinical context that it is being studied.

***Panel 2*: Examples of potential populations to evaluate novel drug–radiotherapy combinations**

Definitive setting with low locoregional control

- TNM stage T4 or N3 human papillomavirus-negative head and neck squamous cell carcinoma
- High grade glioma, including glioblastoma
- Unresectable oesophageal squamous cell carcinoma or adenocarcinoma
- Unresectable stage IIIB, IIIC non-small-cell lung cancer
- Unresectable salivary cancer
- Anaplastic thyroid cancer
- Unresectable pancreatic cancer or hepatobiliary cancers
- Inoperable cancer of the uterine cervix
- Rectal adenocarcinoma, planning for non-operative management
- Unresectable sarcoma (eg, osteosarcoma, Ewings, or soft tissue)

Neoadjuvant setting

- Oesophagogastric or rectal cancer (TNM stage T3, T4, or LN+)
- Retroperitoneal soft tissue sarcoma
- Borderline resectable pancreatic or hepatobiliary cancer

Adjuvant setting

- High-risk oral cavity cancer
- High-risk cutaneous squamous cell carcinoma in immunosuppressed patients
- High grade glioma, including glioblastoma

Oligometastatic disease

- Breast, colorectal, head and neck squamous cell carcinoma, non-small-cell lung cancer, prostate, and sarcoma

Patients who are ineligible to receive standard of care therapy

- Cisplatin-ineligible locally advanced head and neck squamous cell carcinoma
- Locoregionally recurrent head and neck squamous cell carcinoma
- Medically inoperable uterine cancer
- Recurrent small-cell lung cancer

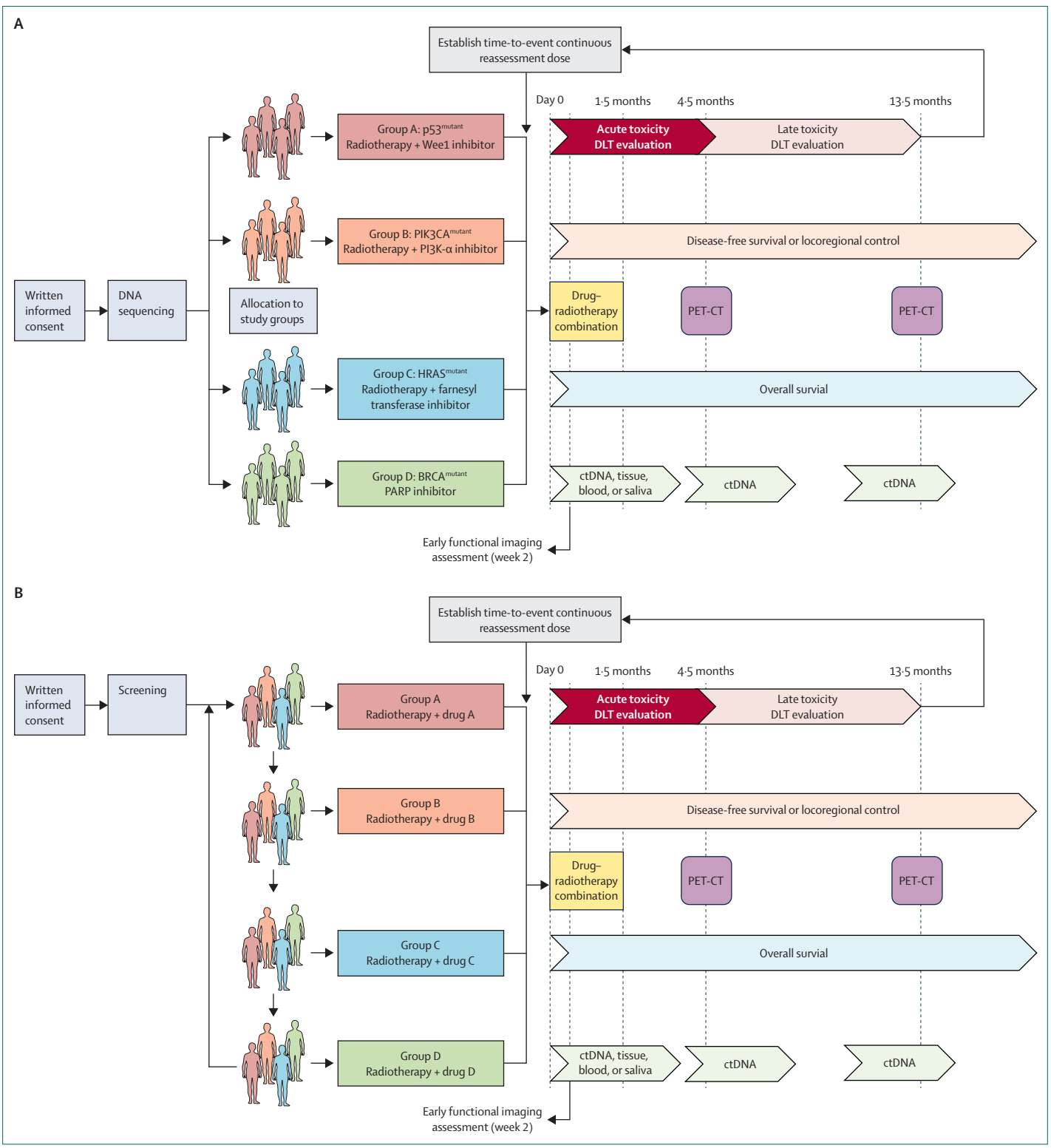
Recommendations for overcoming the challenges of novel drug–radiotherapy early phase trials

Although a myriad of challenges exist that are inherent to early phase drug–radiotherapy trials that are distinct from trials that do not involve concomitant radiotherapy, all are surmountable. Leveraging existing clinical trial networks and infrastructure with standardised radiation and drug delivery capabilities is key to accelerating the development of these early phase drug–radiotherapy studies. Multi-institutional cooperative groups are ideally positioned to lead model-based and model-assisted, multi-drug platform early phase trials. These groups have the extensive infrastructure and high-level statistical support necessary to maximise the efficiency and probability of success for early phase drug–radiotherapy trials. For example, the Developmental Therapeutics Radiation Therapy subcommittee of NRG Oncology is tasked with developing early phase clinical trials that incorporate radiotherapy within the National Clinical Trials Network,

***Figure:* Hypothetical early phase drug–radiotherapy multi-arm platform clinical trial designs that address many challenges inherent to drug–radiotherapy trials**

In these examples, both trials enrol patients with human papillomavirus-negative locally advanced head and neck squamous cell carcinoma undergoing 7 weeks of definitive radiotherapy, but ineligible for cisplatin-based chemotherapy. The trials use a time-to-event continuous reassessment design for dose decisions and a 13·5 month DLT window with 4·5 month acute (75% weighting) and 9 month late (25% weighting) toxicity assessment periods. An early functional imaging assessment (eg, fluorodeoxyglucose PET-CT, fluoromisonidazole, or multiparametric MRI) and ctDNA can be obtained at week 2 of drug–radiotherapy to assess to early treatment response. Tissue, blood, and saliva are collected and stored for biomarker discovery and translational correlatives. Notably, these trials could also include an additional randomly assigned standard of care group (ie, radiotherapy alone) that enrols concomitantly and serves as a comparator to the experimental groups for both efficacy and toxicity. (A) Patients undergo genomic screening and are enrolled on individual drug–radiotherapy groups based on pre-defined biomarkers (RADMatch). (B) Patients with clinical factors and radiosensitivity index biomarkers predicting high risk of locoregional recurrence are enrolled initially to a specific radiosensitising drug–radiotherapy combination (radiotherapy + drug A). When a pre-specified number of patients have been enrolled, subsequent patients join on another radiosensitising drug–radiotherapy combination (radiotherapy + drug B) while patients on radiotherapy + drug A progress through the DLT window. Similarly, after radiotherapy + drug B enrols a pre-specified number of patients, subsequent patients are registered to receive radiotherapy + drug C followed by radiotherapy + drug D, until eventually returning to enrol for radiotherapy + drug A. ct-DNA=circulating tumour DNA. DLT=dose-limiting toxicity.

a vast network of academic and community sites. The National Clinical Trials Network has a strong history of conducting biomarker-driven multi-arm platform trials, such as NCI-MATCH, ComboMATCH, and LungMAP for targeted systemic therapies and drug combinations. Although biomarker-driven platform trial



designs for drug–radiotherapy combinations need to be distinct from drug-only trials for the reasons outlined in this Personal View, there are several potential avenues for National Clinical Trials Network-supported drug–radiotherapy platform trials. For instance, a RadMATCH platform combining radiotherapy with drugs targeting genomic determinants of radiation resistance or other therapeutic vulnerabilities could enrol biomarker-selected patients into a multi-arm, multi-drug–radiotherapy combination trial to test not only the safety, but also preliminary efficacy of the combinations (figure A).

Another potential National Clinical Trials Network-supported multi-arm platform design well suited for drug–radiotherapy combinations that use systemic agents expected to have broader activity, such as DNA-damage repair-inhibiting radiosensitisers, apoptosis-modifying drugs, and cytotoxic agents, evaluates multiple drug–radiotherapy combinations sequentially in a single disease site before dose modification and cycling back to earlier drug–radiotherapy combinations (figure B). This design mitigates many of the biggest hurdles to initial drug–radiotherapy toxicity evaluation, allowing continuous enrolment of patients to various combinations while limiting the number exposed to any specific drug–radiotherapy combination dose level, even when using longer DLT evaluation periods. This design could also use radiosensitivity-based biomarkers, such as preferentially enrolling patients with low radiation sensitivity index scores, for eligibility.[66]

Innovative platform trial designs combining novel drugs and radiotherapy are starting to emerge internationally. For example, the RAINBO clinical trial programme being run in Europe and Canada is a platform of four clinical trials for postoperative therapy following surgery for patients with endometrial cancer.[67] Patients are enrolled in one of the four trials investigating novel treatment strategies depending on their molecular status. Three of the four trials are investigating the combination of postoperative radiotherapy with or without non-chemotherapeutic systemic agents. Although this platform consists primarily of phase 3 clinical trials and does not deliver radiosensitising drugs concomitantly with radiotherapy, a similar platform could be applied to early phase drug–radiotherapy trials as in the proposed RADMATCH design (figure A). A second innovative design is the CONCORDE trial from the UK for non-small-cell lung cancer,[50] which is similar to the design we propose in figure B. The CONCORDE platform is testing five novel DNA-damage inhibitors in combination with radiation and uses several of the solutions proposed in this Personal View to facilitate efficient drug–radiotherapy design. We urge the Cancer Therapy Evaluation Program and the National Cancer Institute to endorse and support similar innovative platform designs for drug–radiotherapy in the USA via the National Clinical Trials Network mechanism.

Novel drug–radiotherapy combinations will require equally novel and adaptable clinical trial designs to ensure efficient early phase clinical trials. Multi-institutional cooperative group structures are uniquely well suited to design, implement, and oversee these multi-drug–radiotherapy combination early phase platform trials requiring large numbers of screened patients for enrolment and extensive collaboration with the pharmaceutical industry, clinicians, biostatisticians, and research professionals. However, further investment in supportive clinical trial infrastructure and biostatistical support will be instrumental in facilitating the conduct of this important niche of clinical trials in the future.

Conclusion

Moving forward, the alignment of clinicians, multi-institutional cooperative groups, stakeholders, and existing federal clinical trial infrastructure is crucial to ensure our ability to develop the next generation of drug–radiotherapy combinations. A collective understanding of the unique but often overlooked challenges in early phase drug–radiotherapy development is essential. Collaboration is also required to adopt rational and practical solutions to overcome these challenges. Simply extrapolating clinical trial designs and regulatory principles from drug–drug combinations is unlikely to lead to efficient or successful drug–radiotherapy development. Further improvements in cancer outcomes will be contingent on our ability to conduct efficient clinical trials that combine the latest in radiotherapeutic approaches with innovative systemic therapies.

Contributors

ZSZ: conceptualisation, writing the original draft, review, editing, and supervision. SS: conceptualisation, methods, resources, writing the original draft, review, and editing. SKJ: conceptualisation, methods, investigation, writing the original draft, review, editing, and supervision. KRP: writing the original draft, review, and editing. RJK: conceptualisation, writing the draft, review, and editing. TMW: conceptualisation, writing the original draft, review, editing, and supervision. MX-W: conceptualisation, data curation, writing the draft, review, and editing. PAT-S: writing the original draft. AMM: writing the original draft, review, and editing. JM: conceptualisation, methods, validation, formal analysis, investigation, writing the original draft, review, editing, visualisation, supervision, and project administration. SEF: writing the original draft, review, and editing. JMB: writing the draft, review, and editing. SPP: conceptualisation, methods, investigation, resources, writing the original draft, review, editing, supervision, and project administration. SHL: conceptualisation, methods, formal analysis, investigation, resources, writing the original draft, review, editing, visualisation, and supervision. All authors agree to be accountable for all aspects of the work, which includes ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

JMB received grants or contracts from the National Institutes of Health (NIH); royalties or licences from UpToDate; and has a leadership or fiduciary role in other board, society, committee, or advocacy group (paid or unpaid) for the American Society for Radiation Oncology (ASTRO) and is on the Board of Directors as Science Council Chair. SEF reports ongoing research with Novartis and Bayer; received consulting fees from Lantheas, Progenics, Blue Earth, Bayer, Astellas, Pfizer, and Jaansen;

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