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Systematic review

A systematic methodology review of phase I radiation dose escalation trials

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ABSTRACT

Background and purpose: The purpose of this review is to evaluate the methodology used in published phase I radiotherapy (RT) dose escalation trials. A specific emphasis was placed on the frequency of reporting late complications as endpoint.

Materials and methods: We performed a systematic literature review using a predefined search strategy to identify all phase I trials reporting on external radiotherapy dose escalation in cancer patients.

Results: Fifty-three trials (phase I: $n = 36$, phase I–II: $n = 17$) fulfilled the inclusion criteria. Of these, 20 used a modified Fibonacci design for the RT dose escalation, but 32 did not specify a design. Late toxicity was variously defined as >3 months ($n = 43$) or > 6 months ($n = 3$) after RT, or not defined ($n = 7$). In only nine studies the maximum tolerated dose (MTD) was related to late toxicity, while only half the studies reported the minimum follow-up period for dose escalation ($n = 26$).

Conclusion: In phase I RT trials, late complications are often not taken into account and there is currently no consensus on the methodology used for radiation dose escalation studies. We therefore propose a decision-tree algorithm which depends on the endpoint selected and whether a validated early surrogate endpoint is available, in order to choose the most appropriate study design.

In the past decades, the delivery of radiation has improved due to the development of advanced technologies, such as intensity-modulated radiotherapy, image-guided radiotherapy, functional imaging and particle therapy. Moreover, to be able to treat more aggressive tumours with radiotherapy (RT), numerous research groups are investigating escalation of radiation dose with these new techniques without increasing the dose to the normal tissues. Dose escalation is usually first investigated in phase I RT trials to establish a safe dose which can be further evaluated in phase II trials. The aim of these phase I trials is to identify toxicities by defining dose-limiting toxicities (DLTs), toxicities described by standardised grading criteria as unacceptable and the maximum tolerated dose (MTD), the dose associated with unacceptable toxicity in a pre-specified proportion of patients.

Various guidelines have been developed [1] for phase I studies testing anti-cancer agents (phase I AC trials). However, phase I RT trials without drugs are fundamentally different in the following ways. (1) The patient population: Whereas phase I AC trials mainly investigate terminal cancer patients with a variety of tumour types which are no longer responding to the standard chemotherapy regimens, phase I RT trials mostly investigate patients with one specific tumour type often treated with curative intent. (2) Treatment variables: phase I AC trials provide the basic pharmacological information which will form the basis to select dosage schedules in further stages of development, whereas phase I RT trials can define universal irradiation target delivery with precise dose mapping of organs at risk. In addition, the definition of DLT (usually 'acute grade 4 haematological toxicity and any grade 3 non-haematological toxicity' in AC trials) cannot be translated into an RT trial. Radiation can cause grade 3 toxicity (e.g. diarrhoea after pelvic radiation, xerostomy after extensive head and neck irradiation, or pneumonitis after lung radiation), which is considered acceptable. (3) Treatment effectiveness: The dose–response relationship for RT follows a sigmoid curve, meaning higher doses lead to higher tumour effectiveness, whereas the dose-response curve for an anti-cancer agent follows a Gaussian course, meaning that a higher dose does not necessarily mean more biological effectiveness. (4) Toxicity: phase I RT trials must not only register acute

Abbreviations: MTD, maximum-tolerated dose; DLT, dose-limiting toxicity; CA, cancer agents; SD, standard deviation; RT, radiotherapy.

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toxicity but also late toxicity which may be caused by radiation-induced damage to normal tissue, thus defining a DLT. This has major implications for the feasibility of certain phase I RT trials, because late toxicity can last for several years [2]. Ideally, trials with anticancer drugs should also include late toxicity, because some agents may induce important long-term side effects. Usually, this is not taken into account, mainly because the selected patient group is unsuitable for this purpose.

All these differences justify more specified guidelines for the design and the reporting of phase I RT trials. As a first step in this process, the general aim of this review was to evaluate the methodology used in the published phase I RT dose escalation trials on cancer patients. More specifically, we wanted to investigate if and how late toxicity was assessed to define the MTD to ultimately provide recommendations on the most appropriate study design for phase I RT trials without drugs.

Materials and methods

Identification and selection of studies

We performed a systematic literature review, considering for inclusion full-length papers on phase I RT dose escalation trials identified in the MEDLINE bibliography predefined search strategy. The cut-off date for citation in MEDLINE was 19 November 2007. The following three key terms were used in the search string: 'radiotherapy-dosage', 'radiotherapy' and 'clinical-trial-phase I' (for details see Appendix 1). Phase I–II dose RT dose escalation studies were included if they contained sufficient information on the phase I part of the trial. Two reviewers (GvM, PL) independently assessed the abstracts or, in the event of uncertainty, the full-length articles to determine whether they met the following inclusion criteria: non-randomised phase I trials with radiation dose escalation, the use of external radiotherapy, and the requirement for patients who have histologically or cytologically proven cancer. We did not limit the search in terms of language. Exclusion criteria were randomisation, RT dose escalation combined with dose escalation of drugs, particle therapy, internal RT (e.g. brachytherapy), RT with hyperthermia as co-intervention, Boron Neutron Capture Therapy and radio-immunotherapy.

Data extraction

One reviewer (GvM) extracted the following study items: identifiers, trial location (Northern America, Europe or Asia), study design (single or multicentre), tumour group, phase (I or I–II), design for RT dose escalation (modified Fibonacci or other), increase of RT dose escalation (dose per fraction, number of fractions or both), mean, standard deviation, number of patients per cohort, number of dose levels, dose increment per dose level, definition of period for late toxicity (>3, >6 months or not reported), MTD defined (yes/no) and DLT defined (yes/no). Finally, we scored whether the MTD was related to late toxicity (yes/no/not reported), and the minimum reported follow-up period between different dose escalation levels (<3, 6 or >18 months). If not clearly stated, the study's multicentre structure was inferred from the list of centres supplied by the authors. Data for which reviewer (GvM) was uncertain were independently assessed by a second reviewer (PL). The reviewers discussed any discrepancies together.

Results

Of the 826 studies selected during the search, 685 were excluded by both reviewers because they did not fulfil the selection criteria for the review. After screening the journal papers and holding a consensus meeting, we excluded another 81 studies for the following reasons: dose escalation of RT and dose escalation of drugs ($n = 6$), no dose escalation of RT ($n = 33$), particle therapy ($n = 13$), randomisation ($n = 10$) and other ($n = 19$). There remained 60 articles on 53 different phase I trials examining RT dose escalation in cancer patients: lung ($n = 24$), brain ($n = 4$), prostate ($n = 6$), pancreas ($n = 7$) and other ($n = 12$).

Lung carcinoma

Twenty-four trials (phase I: $n = 17$, phase I–II: $n = 7$) on lung cancer fulfilled the inclusion criteria [3–26]. Most of these trials were performed in Northern America ($n = 20$, 83%) [4–7,10–21,23,24,26,27] details are presented in Appendix 2. Ten (42%) used the modified Fibonacci design for RT dose escalation [3,4,7,10,11,16,18,20,23,24], while the other 14 did not specify design [5,6,8,9,13–15,17,19,21,22,25,26]. Dose escalation was mostly performed by increasing the number of fractions ($n = 15$, 62%) [3–5,10–13,16–18,20–25]. The mean number of patients per cohort was 12 (SD = 12.51, range 4–100) with a mean of four dose levels (SD = 1.01, range 1–9) and a mean dose increment per level of 6 Gy (SD = 3.04 Gy, range 3.6–27.4) (Table 2, Appendix 2).

Late toxicity was not reported in three trials; in the others it was defined as all toxicities detected more than 3 months ($n = 18$) after RT. Definitions of the MTD and DLT were reported in 21 (88%) and 19 (79%) of the trials, respectively. The MTD was related to late complications in 5 (21%) studies [3,6,11,17,19]. The time interval (reported in 16 of the 24 trials) between different dose levels (or minimum follow-up period) was usually 3 months ($n = 12$ (50%)) (Table 3).

Brain, prostate and pancreatic carcinomas

In addition to lung cancer, a large number of phase I RT trials ($n = 17$) were performed to improve the treatment of brain ($n = 4$) [28–32], pancreas ($n = 7$) [33–39] and prostate cancers ($n = 6$) [40–47] (for details per study see Appendix 3). The majority of these studies ($n = 11$, 65% [29,30,33–35,39,40,42,43,45,46]) re-

Table 1
General study details.

Tumour type	Number	Trial location number			Study design number		Phase number	
		Northern America	Europe	Asia	Single centre	Multicentre	I	I–II
LSSCLC	4	4	0	0	0	4	4	0
NSCLC	20	16	3	1	11	9	13	7
Subtotal (%)	24 (100)	20 (83)	3 (12)	1 (4)	11 (46)	13 (54)	17 (71)	7 (29)
Brain	4	3	1	0	1	3	2	2
Pancreatic	7	4	1	2	5	2	4	3
Prostate	6	5	0	1	1	5	5	1
Subtotal (%)	17 (100)	12 (71)	2 (12)	3 (18)	7 (41)	10 (59)	11 (65)	6 (35)
Various	12 (100)	9 (75)	3 (25)	0 (0)	4 (33)	8 (67)	8 (67)	4 (33)
Total (%)	53 (100)	41 (77)	8 (15)	4 (8)	22 (42)	31 (58)	36 (68)	17 (32)

Table 2
Study details of RT dose escalation schemes.

Tumour type	Number	Design of RT dose escalation number				Increase of RT dose escalation number				Number of patients per cohort Mean (SD)	Number of dose levels Mean (SD)	Dose increment per level (Gy) Mean (SD)
		Modified Fibonacci	CRM	Other	Not reported	Number of fractions	Dose per fraction	Both*	Not reported			
LSSCLC	4	2	0	2	0	2	1	1	0	7 (2.78)	5 (2.63)	5 (1.34)
NSCLC	20	8	0	11	1	13	4	2	1	18 (20.47)	3 (1.20)	7 (5.64)
Subtotal (%)	24 (100)	10 (42)	0(0)	13 (54)	1 (4)	15 (62)	5 (21)	3 (12)	1 (4)	12 (12.51)	4 (1.01)	6 (3.04)
Brain	4	1	0	3	0	1	2	1	0	15 (18.55)	4 (1.50)	5 (1.79)
Pancreatic	7	5	0	2	0	4	3	0	0	89 (67.86)	3 (0.84)	5 (0.30)
Prostate	6	1	0	5	0	4	0	1	1	7 (5.41)	4 (1.68)	6 (3.10)
Subtotal (%)	17 (100)	7 (41)	0 (0)	10 (59)	0 (0)	9 (53)	5 (29)	2 (12)	1 (6)	37 (32.90)	4 (0.44)	5 (1.40)
Various	12 (100)	3 (25)	1 (8)	8 (67)	0 (0)	8 (67)	3 (25)	0 (0)	1 (8)	22 (25.08)	3 (1.08)	4 (2.15)
Total (%)	53 (100)	20 (38)	1 (2)	31 (58)	1 (2)	32 (60)	13 (25)	5 (9)	3 (6)	26 (23.50)	4 (0.63)	5 (1.84)

* Both = RT dose escalation by increase of number of fractions or dose per fraction.

Table 3
Details of study outcome definition.

Tumour type		Late toxicity			MTD		DLT		MTD related to late toxicity			Minimum follow-up period			
		>3 months	>6 months	Not reported	Yes	No	Yes	No	Yes	No	Not reported	⩽3 months	6 months	⩾18 months	Not reported
LSSCLC	4	3	0	1	3	1	3	1	0	1	3	2	0	0	2
NSCLC	20	18*	0	2	18	2	16	4	5	9	6	10	4**	0	6
Subtotal (%)	24 (100)	21 (88)	0 (0)	3 (12)	21 (88)	3 (12)	19 (79)	5 (21)	5 (21)	10 (42)	9 (37)	12 (50)	4 (17)	0 (0)	8 (33)
Brain	4	2	0	2	1	3	2	2	0	0	4	0	0	0	4
Pancreatic	7	6	1	0	6	1	6	1	1	2	4	2	0	1	4
Prostate	6	6	0	0	2	4	2	4	1	0	5	0	0	1	5
Subtotal (%)	17 (100)	14 (82)	1 (6)	2 (12)	9 (53)	8 (47)	10 (59)	7 (41)	2 (12)	2 (12)	13 (76)	2 (12)	0 (0)	2 (12)	13 (76)
Various	12 (100)	8 (67)	2 (17)	2 (17)	8 (67)	4 (33)	9 (75)	3 (25)	2 (17)	3 (25)	7 (58)	3 (25)	3 (25)	0 (0)	6 (50)
Total (%)	53 (100)	43 (81)	3 (6)	7 (13)	38 (72)	15 (28)	38 (72)	15 (28)	9 (17)	15 (28)	29 (55)	17 (32)	7 (13)	2 (4)	27 (51)

MTD = maximum tolerated dose defined, DLT = dose-limiting toxicity defined, NR = not reported.
* One study reported >6 weeks, one study reported >4 months.
** One study reported a 6–12 month min follow-up period.

ported only safety and toxicity data. In general, the trials were performed as multicentre studies (n = 10, 59%) [28,29,31–36,38,43] in the Northern America (n = 12, 71%) [28–30,33–37,40,44–48] (Table 1). Seven (41%) used the modified Fibonacci design for RT dose escalation [30,33,34,37–39,41]; in the other ten (59%) no specific design was used [28,29,31,32,35,36,40,42,43,45,46].

Dose escalation was performed in nine of these studies by increasing the number of fractions (53%) [31,34,36,38,39,41,43,46,47], and in five studies by increasing the dose per fraction (29%) [28,30,33,35,37]. In two studies, both the number of fractions and the dose per fraction were increased (12%) [29,32,40]. The mean number of patients per cohort was 37 (SD = 32.90, range 4–186), the mean number of dose levels was 4 (SD = 0.44, range 2–7) and the mean dose increment per level was 5 (SD = 1.40, range 1–10) (Table 2 and Appendix 3). Late toxicity in almost all studies was defined as occurring 3 months or more after treatment (n = 14, 82%). The MTD was defined in nine (53%) studies [30,33–35,37–39,41,43], and the DLT in ten (59%) [29,30,33–35,37–39,41,43]. In only two studies (12%) late toxicity was used to define the MTD [39,45]. Finally, four studies (24%) reported details on the minimum follow-up period for dose escalation [33,36,39,45] (Table 3).

Other carcinomas

The remaining 12 phase I RT trials reported data on head and neck (n = 2) [49,50], oesophagus (n = 1) [51], breast (n = 1) [52], haematological (n = 1) [53], lymphoma or Hodgkin's (n = 1) [54], bone metastases (n = 1) [55], liver metastases (n = 2) [56,57], rectal (n = 2) [58,59] and cervical cancers (n = 1) [60] (see Appendix 4 for details per study). These studies were also mostly performed as multicentre trials (n = 8, 67%) [49,50,55–62] in the USA (n = 9, 75%) [53–60,62,63], and reported only the phase I study results (n = 8, 67%) [49,52,54,56–60].

The design for RT dose escalation was not specified in eight of these studies (67%) [49,50,52,54–56,59–62]; three used a modified Fibonacci design (25%) [51,53,57]; and one used the continual reassessment method (CRM) [58]. For RT dose escalation, in most studies the number of fractions was increased (n = 8, 67%) [51–56,59–62], while three studies used dose per fraction (25%) [49,50,57]. The mean number of patients per cohort, the number of dose levels, and the dose increment per level were 22 (SD = 25.08, range 3–58), 3 (SD = 1.08, range 1–5) and 7 Gy (SD = 8.97 Gy, range 2–5), respectively (Table 2).

A period of over 3 months was most commonly used to define late toxicity (n = 8, 67%) [50–53,55,56,58,59,61,62]. Eight (67%) and nine (75%) of the studies reported definitions for MTD and DLT, respectively; however, only two [56,59] used late toxicity data to define MTD. Six studies (50%) reported the period used between different dose levels (Table 3) [49,53,54,56,59,63] .

Discussion

To our knowledge, this is the first review which investigates the methodology used in phase I RT dose escalation trials. Those stud-

ies which did report a design for RT dose escalation usually used the classical modified Fibonacci design ($n = 20$, 38%). Two-thirds of the studies provided essential study definitions such as MTD and DLT, but only nine (17%) related late toxicity to MTD. Importantly, only 26 studies (49%) reported the minimum follow-up period to assess late toxicity.

Designs used for RT dose escalation

Our review confirms the finding of another review assessing phase I AC trials that the modified Fibonacci design is the most commonly used method for dose escalation [64]. Also called the 3 + 3 design, in which patients are treated in cohorts of three, with the first cohort at a specified starting dose. In this design, the dose is escalated according to the modified Fibonacci sequence in which dose increments become gradually lower as the MTD is approached (e.g., dose increases of 100%, 65%, 50%, 40%, and 30–35% thereafter). The dose escalation is continued in cohorts of three patients until typically two DLTs are seen in a maximum of six patients. If 1/3 toxicity is observed in the first cohort, three more patients are treated at the same level; if 2/3 or 3/3 toxicities are observed, the current level is declared to exceed the MTD. This design has substantial benefits but does have a few important drawbacks. In an ideal design, the number of patients treated at sub-therapeutic doses is minimized to prevent unnecessary toxicity. The modified Fibonacci escalation scheme however, can lead to multiple dose escalations involving dozens of patients before the MTD is defined. As a consequence, most patients are treated with potentially biologically inactive doses [65]. Moreover, the Fibonacci design only uses information from the most recent one or two cohorts, ignoring data from earlier patients. Next, as compared to alternative statistical designs (see below), it takes a considerable time to reach the MTD, resulting in a delayed completion of the trial. These weaknesses of the Fibonacci design indicate the need for more efficient approaches to safety trials. Trial designs less frequently used include the excess recruitment design (ERD) and the continual reassessment method (CRM) [66], or its variants such as time-to-event CRM (TITE-CRM) [67]. The ERD uses a rule that decides on the accrual of each individual eligible patient making it possible to account for the situation where it is unclear whether patients under observation will be evaluated. The (TITE)-CRM approach is Bayesian oriented. In the TITE-CRM methodology, if the trial progresses and the patients do not experience toxicities at different doses, the estimates of toxicity probability are recalculated using a Bayesian expectation and subsequent patients are assigned doses according to the principle of always treating at the target dose [68]. Dose escalation is reassessed after each patient. Therefore, the risk of treating several consecutive patients at too high a dose is limited.

In the current review, none of the identified studies used the ERD design whereas only one study used the (TITE)-CRM method [58], though it is increasingly used in phase I AC studies [69]. One strength of this method is its strong statistical property: the CRM provides a greater chance of identifying the correct dose compared to the modified Fibonacci method [70]. Another strength is its flexibility: it uses dynamic dose increments and cohort sizes. In addition, the dose escalations can be varied more rapidly: when no toxicity is experienced in the initial dose, the level can be quickly increased; likewise, when moderate toxicity is experienced, the escalation dose can be adapted in escalation speed [69].

Late toxicity and the maximum tolerated dose

In evaluating how safe a particular RT dose is, it is important to investigate also late toxicity for defining MTD. The value of early toxicity effects is limited as they are mostly transient; in other words, the affected tissue will recover and the symptoms and signs will improve [2]. Unlike acute toxicity, late toxicity tends to be irreversible or even progressive in severity, and may affect the quality of life or compromise the survival benefits of the RT therapy. In our review, only 9 of the 56 studies based their MTD on late toxicity parameters. However, as the minimum follow-up in only two of these studies was more than 18 months, it is likely that not all late toxicity data are scored before a RT dose is increased or an MTD defined. As a consequence, one could argue the plausibility that some studies will lead to the use of regimens that were subsequently found to be unacceptable due to delayed injuries. Unfortunately, we failed to identify the frequency with which the studies identify an inadequate regimen due to the lack of those data. One of the causes of this could be the known "publication bias": trials with negative results are most often not published. The limited percentage of studies which use late toxicity in evaluating RT doses in our review may be related to the many drawbacks of reporting and interpreting (late) toxicity data:

- One may argue that the development of a new RT treatment approach is unacceptably slowed by the need to wait for late toxicity results to mature [2]. For instance, most late toxicities in the head and neck will develop within the first 3 years of treatment, though a few appear or progress after this period [71].
- Reporting toxicity is difficult as numerous steps in the reporting process can influence the reliability of the data. First, late toxicity assessment of a given treatment may depend on the toxicity scale used, and the MTD will therefore depend on the criteria established for the DLT [72]. For example, in prospective evaluations of oropharynx carcinoma and breast cancer patients, LENT/SOMA scores were found to be more accurate than RTOG/EORTC [73,74] and NCI-CTC scoring systems [73]. Critics claim that the RTOG late toxicity scoring criteria do not contain sufficient objective descriptors and endpoints [71]. Secondly, monitoring toxicity in trials is complex: the clinical staff must aggregate not only objective data on toxicity (e.g. laboratorial values and physical examinations) but also subjective patient information (i.e. symptoms). Therefore, the process of data collection is vulnerable to errors of misinterpretation and omission [75]. Third, there are a number of potential sources for reporting variability including the frequency and intensity of protocol-directed toxicity evaluations, limited guidance or standards for safety data reporting, and variations in methods for summarising and presenting results [2]. Also, late toxicity is a competing event of survival; in other words, patients subject to mild treatment and low survival will have a lower visible toxicity. Another reason why late toxicity is not used for evaluation in many phase I RT trials is that, for specific types of cancer, late toxicity is not a relevant outcome measure. For instance, the life expectancy for most of the patients with brain metastasis is very low, and therefore, many such patients die before late toxicity occurs.

These drawbacks support the development and use of alternative endpoints for defining RT-induced late toxicity. One such alternative may be biomarkers, as they can have a predictive value for radiation-induced cell damage: for example, a correlation between radiation-induced epithelia cell loss and plasma citrulline level has been demonstrated in mice [76]. Another alternative is the increased expression of serum cytokines. IL-6 is an indicator for late pulmonary toxicity [77,78] and augmented IL-6 and TGF-β_1 levels are possibly related to RT-induced lung damage [77]. Finally, the early surrogate endpoint of rectal bleeding has been found to be predictive for RT-induced late toxicity in rectal cancer patients [79,80].

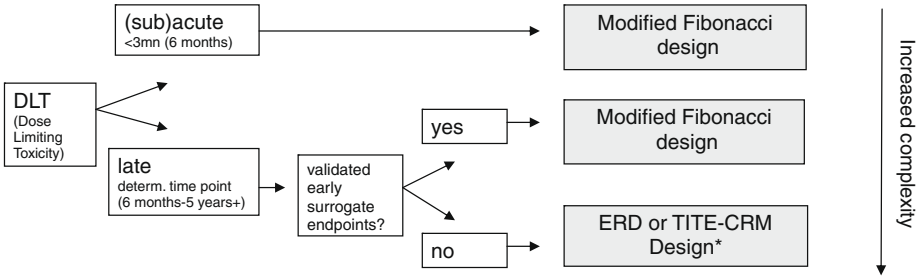

Fig. 1. Flowchart design phase I trials RT. Abbreviations: ERD = excess recruitment design, TITE-CRM = time-to-event continual reasssesment method * [67,68,81].

Limitations

The sample of studies considered here is likely to be somewhat biased. Limiting the search to journals in a single database means that it may not represent an exhaustive review of all relevant publications. Furthermore, the standards of journals cited by MEDLINE are likely to be higher than those of non-MEDLINE journals, thus producing an over-optimistic view of the methods used in phase I RT trials. Furthermore, we are fully aware that trials with adverse effects are often not published. However, even with some approximation, we believe the current review gives reasonable indication of the methods used in current phase I RT studies.

Recommendations for future research

The above considerations suggest that guidelines for the design and reporting of phase I RT trials in medical journals would be welcome. Special attention should be paid to the design and use of the most adequate dose escalation schemes, and the use of new designs for RT dose escalation (such as a time-to-event continual reassessment method) needs to be further assessed. In addition, to resolve the problems of late toxicity as a study outcome, more research is needed to investigate early surrogate endpoints for late toxicity, such as the cytokines, IL-6 and TGF-β_1.

On the basis of our results, it is clear that there is no consensus on the methodology used for phase I radiation dose escalation trials. Surprisingly, only nine (17%) of the trials used late toxicity data to proceed to the next dose level or to define MTD. The increasing use of new technologies allowing dose escalation (such as IMRT, protons and carbon ions) makes it highly desirable to develop a consensus on phase I trial methodology and to validate surrogate endpoint markers of late toxicity since the methods used to assess chemotherapy dose-limiting toxicities are at current inappropriate for assessing the toxicity of radiotherapy and chemo-radiation regimens.

We propose a decision-tree based on the current evidence in order to select the most appropriate design for RT phase I studies (Fig. 1). If (sub)acute toxicity is the endpoint of the study, the often used modified Fibonacci design will be adequate. However if late toxicity must be assessed, which is often the case with dose escalation trials, two scenarios are possible: (a) if validated early surrogate endpoints are available (e.g. a dosimetric parameter such as mean lung dose), then a modified Fibonacci design is acceptable and straightforward; or (b) if no validated early surrogate endpoints are available, then we recommend more complex designs such as the ERD and the TITE-CRM, which will shorten the duration of the entire trial and efficiently uses patient information throughout the study. In all situations, we recommend including a late toxicity primary or secondary endpoint in any subsequent phase 2 trial.

We conclude that in phase I RT trials without drugs, late complications are often not taken into account and there is currently no consensus on the methodology used for radiation dose escalation studies. We therefore suggest a decision-tree in order to, depending on the endpoint and the existence of validated early surrogate endpoints, choose the most appropriate study design.

Competing interests

The authors declare that they have no competing interests.

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None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2010.02.009.

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