GETUG-AFU 31: a phase I/II multi-center study evaluating the efficacy of repeat stereotactic radiation in patients with intraprostatic tumor recurrence after external radiation therapy.

Appendix: statistical model, simulation study

Statistical considerations

A TITE-CRM method with an empiric dose-toxicity model in a Bayesian framework will be used for the dose-finding part of the trial to identify the recommended dose. The target dose-limiting toxicity (DLT) probability is set at p(DLT)=0.25. Three dose levels of SBRT are to be considered: 5 x 5 Gy (DL-1), 5 x 6 Gy (DL1), 6 x 6 Gy (DL2). The starting dose level is 5 x 6 Gy and dose level 5 x 5 Gy will be explored in case of DLT at the starting dose level. DLTs are evaluated during the 18 weeks following the initiation of salvage-SBRT. Observations of patients who have no DLT at the time of the analysis but have not completed the DLT assessment period will be down-weighted in the likelihood, proportionally to the length of follow up.

The Phase I part of the study will include 3 patients at the first dose level. Radiation dose levels for further patients will be defined based on the estimate of the probability of DLT at each dose-level considering all available information accumulated so far. Patients will be treated at the best current estimate of the recommended dose i.e. the dose associated with an estimated probability of DLT the closest to the target 0.25. Patients may eventually be treated at a dose below the dose recommended by the model for safety reasons. The patients can be recruited with no minimal time interval between successive inclusions. Two additional rules will be applied during dose escalation: no dose skipping and no escalation if at least 1 DLT is observed in the last 3 patients.
The dose-escalation part of the study will terminate once 10 patients have been treated and evaluated at a dose currently identified as the recommended dose. Further patients will then be accrued in the expansion cohort, where toxicity data collected over the first 18-week period and DLT assessment will be analyzed approximately every 10 patients with the possibility of modification of the recommended dose, based on model-based estimates.
The Phase II part of the study will need to include 44 patients, including the patients recruited in the dose-finding part of the phase I allocated at the dose level finally identified as the recommended dose. Thus, a minimal sample size of 47 patients will be required in this Phase I/II study (in the case of inclusion of 44 patients at dose level 2 + 3 patients at dose level 1).

Statistical model for dose escalation

A one-parameter empirical power model will be used to assess the relation between the dose level and the probability of DLT: $F(d,\alpha) = p_d^{\exp(\alpha)}$ where $F(d,\alpha)$ is the estimated probability of DLT at dose-level d, p_d is the prior probability of DLT at dose level d, and α is the unknown parameter to be estimated by the model. The vector $\{p_{0d}\}$ represent the initial guesses of toxicity probabilities, reflecting the clinicians' prior belief. The skeleton of initial guesses of toxicity probabilities $\{p_{0d}\}$ is numerically calibrated using the Lee and Cheung approach (ref ClinTrials 2009) and using the getprior function of R, ensuring good design's operating characteristics. After discussion with the clinicians, the delta defining the indifference interval was set at 0.05 (p(DLT)=0.25 +/- 0.05, i.e. indifference interval: 0.20 to 0.30) and the prior MTD (MTD_0) at the 2nd dose level, meaning that the clinicians believe, a priori, that the 2nd dose (6 x 6 Gy) is probably the MTD. This yields a vector of prior probabilities $\{p_{0k}\}$ equal to 0.08, 0.16 and 0.25 for dose level -1 (5 x 5Gy), dose level 1 (5 x 6 Gy) and dose level 2 (6 x 6 Gy). The clinicians confirmed that it was in accordance with their initial guesses. A non-informative prior distribution Normal (0, 1.34) has been assigned for α in the Bayesian

computation. The simulation study below confirmed that the operating characteristics and the behavior of the model defined with these parameters were reasonable.

Operating characteristics:

The operating characteristics of the proposed design were evaluated using the R titesim function written by Cheung, and considering six different scenarios:

- highly toxic,
- moderately toxic at dose levels -1 and 1, highly toxic at dose level 2
- moderately toxic et every dose level,
- similar with prior probabilities,
- close to the probabilities but a little less toxic,
- little toxic

For the simulation study, we considered that the trial would recruit 47 patients, which is the minimal sample size required in this Phase I/II study.
The following rules were implemented: no dose skipping in escalation, and no escalation if >1 DLT observed among < 3 patients.
For each case, 1000 trials were simulated. The Monte Carlo estimation of the percentage of dose selection, the average number of patients treated at each dose level, the average number of observed DLTs at each dose level demonstrated that the modified CRM design can efficiently identify the MTD, with a reasonable probability of overdosing, and expose few patients to toxicity.
A second set of simulations was performed considering a sample size of 13 patients, which is the minimal expected recruitment in the Phase I part of the study. As expected, the performance is much better when the reassessment is continued during the expansion phase (Phase II part). This is one of the advantages of the CRM method.

Figure 1: Scenarios studied

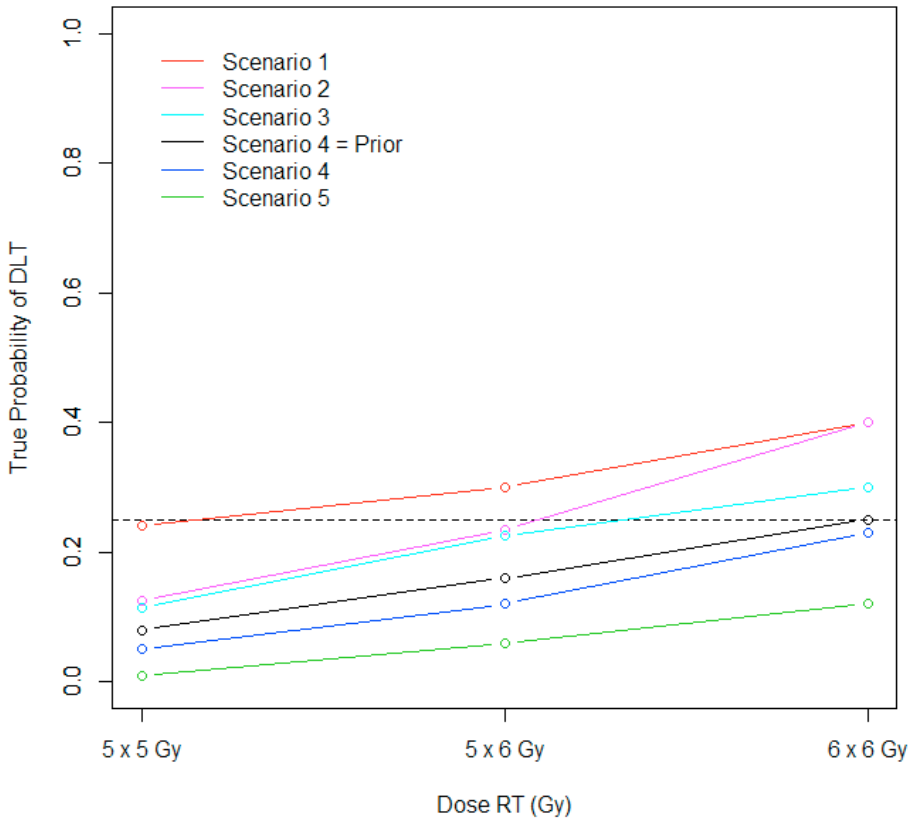
Scenario 1
Scenario 2
Scenario 3
Scenario 4 = Prior
Scenario 4
Scenario 5
True Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
5 x 5 Gy
5 x 6 Gy
6 x 6 Gy
Dose RT (Gy)

Table 1 : Operating characteristics for five different scenarios for the probability of DLT per dose

1a – Simulation for a recruitment of 47 patients (minimal sample size required in this Phase I/II study)

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.24	0.57	23.7	5.7	0.12
1 (5 x 6 Gy)	0.30	0.37	13.4	4.0	0.085
2 (6 x 6 Gy)	0.40	0.06	9.9	4.0	0.085

Expected number of DLTs over the whole trial (47 patients) = 13.7 / trial; 29% patients

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.12	0.12	10.9	1.3	0.03
1 (5 x 6 Gy)	0.23	0.69	21.7	5.1	0.11
2 (6 x 6 Gy)	0.40	0.19	14.4	5.8	0.12

Expected number of DLTs over the whole trial (47 patients) = 12.1 / trial; 26% patients

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.12	0.08	8.0	1.0	0.02
1 (5 x 6 Gy)	0.23	0.52	17.0	3.9	0.08
2 (6 x 6 Gy)	0.30	0.40	22.0	6.7	0.14

Expected number of DLTs over the whole trial (47 patients) = 11.6 / trial; 24% patients

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.08	0.006	3.2	0.3	0.01
1 (5 x 6 Gy)	0.16	0.22	11.3	1.8	0.04
2 (6 x 6 Gy)	0.25	0.78	32.5	8.2	0.17

Expected number of DLTs over the whole trial (47 patients) = 10.3 / trial; 22% patients

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.05	0.001	2.2	0.1	0.002
1 (5 x 6 Gy)	0.12	0.09	8.4	1.0	0.02
2 (6 x 6 Gy)	0.23	0.91	36.4	8.4	0.18

Expected number of DLTs over the whole trial (47 patients) = 9.5 / trial; 20% patients

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT *
-1 (5 x 5 Gy)	0.01	0	0.8	0.003	<0.001
1 (5 x 6 Gy)	0.06	0	2.3	0.1	0.002
2 (6 x 6 Gy)	0.12	1.0	43.9	5.3	0.113

Expected number of DLTs over the whole trial (47 patients) = 5.4 / trial; 11.5% patients

*% of DLT: mean n. of DLT / total number of patients

1b – Simulation for a recruitment of 13 patients (minimal sample size required in the Phase I part of the study)

The grey row represents the true MTD (proba(DLT) closest to the target of 0.25.

SCENARIO 1 : highly toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.24	0.52	4.7	1.1	0.08
1 (5 x 6 Gy)	0.30	0.27	2.7	0.8	0.06
2 (6 x 6 Gy)	0.40	0.21	5.6	2.2	0.17

Expected number of DLTs over the whole trial (13 patients) = 4.1 / trial; 31% patients

SCENARIO 2: moderately toxic at dose levels -1 and 1, highly toxic at dose level 2

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.12	0.30	3.8	0.5	0.04
1 (5 x 6 Gy)	0.23	0.39	3.2	0.7	0.05
2 (6 x 6 Gy)	0.40	0.31	6.0	2.4	0.19

Expected number of DLTs over the whole trial (13 patients) = 3.6 / trial; 28% patients

SCENARIO 3: moderately toxic at every dose level

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.12	0.21	3.0	0.4	0.03
1 (5 x 6 Gy)	0.23	0.33	3.0	0.7	0.05
2 (6 x 6 Gy)	0.30	0.46	7.0	2.1	0.17

Expected number of DLTs over the whole trial (13 patients) = 3.2 / trial; 25% patients

SCENARIO 4 : true proba(DLT) = prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.08	0.09	2.1	0.2	0.02
1 (5 x 6 Gy)	0.16	0.27	2.8	0.5	0.04
2 (6 x 6 Gy)	0.25	0.64	8.0	2.0	0.15

Expected number of DLTs over the whole trial (13 patients) = 2.7 / trial; 21% patients

SCENARIO 5: little less toxic than prior probabilities

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.05	0.05	1.6	0.1	0.01
1 (5 x 6 Gy)	0.12	0.21	2.7	0.3	0.02
2 (6 x 6 Gy)	0.23	0.74	8.7	2.0	0.15

Expected number of DLTs over the whole trial (13 patients) = 2.4 / trial; 18% patients

SCENARIO 6: little toxic

Dose level	True proba(DLT)	% of dose selection	Mean n. of patients	Mean n. of DLT	% of DLT*
-1 (5 x 5 Gy)	0.01	0.004	0.6	0.01	0.001
1 (5 x 6 Gy)	0.06	0.04	1.8	0.09	0.007
2 (6 x 6 Gy)	0.12	0.96	10.6	1.3	0.10

Expected number of DLTs over the whole trial (13 patients) = 1.4 / trial; 11% patients

*% of DLT: mean n. of DLT / total number of patients