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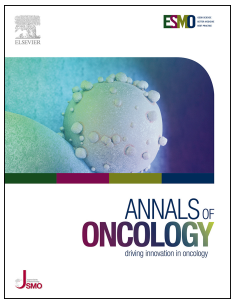

Timing of Radiotherapy (RT) After Radical Prostatectomy (RP): Long-term outcomes in the RADICALS-RT trial [NCT00541047]

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Transparency declaration: All authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

Ethical approval: Appropriate ethical review was in place for each participating country. All participants gave written, informed consent.

Data availability statement: All of the information is publicly available. The dataset and technical appendices are available upon request as per the controlled access approach of the MRC CTU at UCL. Please contact the corresponding author for more information.

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Abstract	300
Background	445
Methods	992
Results	743
Discussion	709
Total	2889

(Word counts cover the body text of each section and excluded the headings and the ending notes; Methods excluding Funding statement)

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ABSTRACT

Background

The optimal timing of radiotherapy (RT) after radical prostatectomy for prostate cancer has been uncertain. RADICALS-RT compared efficacy and safety of adjuvant RT versus an observation policy with salvage RT for PSA failure.

Methods

RADICALS-RT was a randomised controlled trial enrolling patients with ≥1 risk factor (pT3/4, Gleason 7-10, positive margins, pre-op PSA≥10ng/ml) for recurrence after radical prostatectomy. Patients were randomised 1:1 to adjuvant RT ("Adjuvant-RT") or an observation policy with salvage RT for PSA failure ("Salvage-RT") defined as PSA≥0.1ng/ml or 3 consecutive rises. Stratification factors were Gleason score, margin status, planned RT schedule (52.5Gy/20 fractions or 66Gy/33 fractions) and treatment centre. The primary outcome measure was freedom-from-distant metastasis, designed with 80% power to detect an improvement from 90% with Salvage-RT (control) to 95% at 10yr with Adjuvant-RT. Secondary outcome measures were bPFS, freedom-from-non-protocol hormone therapy, safety and patient-reported outcomes. Standard survival analysis methods were used; HR<1 favours Adjuvant-RT.

Findings

Between Oct-2007 and Dec-2016, 1396 participants from UK, Denmark, Canada and Ireland were randomised: 699 Salvage-RT, 697 Adjuvant-RT. Allocated groups were balanced with median age 65yr. 93% (649/697) Adjuvant-RT reported RT within 6m after randomisation;

39% (270/699) Salvage-RT reported RT during follow-up. Median follow-up was 7.8 years. With 80 distant metastasis events, 10yr FFDM was 93% for Adjuvant-RT and 90% for Salvage-RT: HR=0.68 (95%CI 0·43–1·07, p=0·095). Of 109 deaths, 17 were due to prostate cancer. Overall survival was not improved (HR=0.980, 95%CI 0.667–1.440, p=0.917). Adjuvant-RT reported worse urinary and faecal incontinence one year after randomisation (p=0.001); faecal incontinence remained significant after ten years (p=0.017).

Interpretation

Long-term results from RADICALS-RT confirm adjuvant RT after radical prostatectomy increases the risk of urinary and bowel morbidity, but does not meaningfully improve disease control. An observation policy with salvage RT for PSA failure should be the current standard after radical prostatectomy.

Keywords: prostate cancer; radiotherapy; randomised controlled trial; Clinical trial; observational; long-term follow-up

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Highlights:

From 2007 to 2016, 1396 participants were randomised from UK, Denmark, Canada & Ireland to 699 Salvage-RT or 697 Adjuvant-RT.

No evidence of improvement with Adjuvant-RT in FFDM or survival but more toxicity.

An observation policy with salvage RT for PSA failure should be the current standard after radical prostatectomy.

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BACKGROUND

Radical prostatectomy is a standard treatment for localized prostate cancer, and may be followed by post-operative radiotherapy to the prostate bed.[1,2] There has been uncertainty about the optimal timing of radiotherapy after radical prostatectomy. Adjuvant radiotherapy may be given early to those with no evidence of residual disease after surgery in order to reduce the risk of subsequent recurrence. Alternatively, salvage radiotherapy may be given later in the event of recurrent disease. It is possible that adjuvant radiotherapy might be more effective than a policy of salvage radiotherapy for recurrence. However, the salvage policy avoids unnecessary treatment of those cured by surgery alone and so may lead to less treatment-related morbidity.

Two randomised trials of adjuvant radiotherapy after radical prostatectomy were initiated over 30 years ago: The SWOG 8794 trial [3] reported an overall survival benefit for adjuvant radiotherapy, but this survival benefit was not confirmed by the EORTC 22911 trial,[4,5] and expert opinion was divided: At the Advanced Prostate Cancer Consensus Conference (APCCC) 2017, faced with a range of clinical scenarios, 48% of the panel voted in favour of adjuvant radiotherapy and 52% did not.[6]

There have been a further five randomised controlled trials comparing adjuvant radiotherapy versus a policy of salvage radiotherapy for recurrence. Until now, these trials have not been sufficiently large or mature enough to report on long-term outcomes such as overall survival or freedom from distant metastasis. These trials have reported an earlier outcome measure, bPFS. The ARO 96-02 trial [7] and the Finnish Radiation Oncology Group

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trial [8] found that adjuvant radiotherapy reduced the risk of biochemical progression. However, PSA failure at any time was regarded as an event, even in participants who subsequently went on to receive successful salvage radiotherapy. Therefore, a benefit in biochemical progression using this definition demonstrates that radiotherapy has activity but does not shed any light on its optimum timing. The remaining three randomised trials, RADICALS-RT,[9] RAVES[10] and GETUG-16,[11] used a different definition of biochemical progression, requiring PSA failure after radiotherapy. This approach was designed to avoid the limitations of the previous definition but may have introduced a bias in favour of the salvage policy. A meta-analysis of these three trials found no bPFS benefit for adjuvant radiotherapy.[12] Given the lack of robust early surrogate outcome measures, there remains a need to determine the effect of adjuvant radiotherapy on long term outcomes such as freedom from distant metastasis and overall survival.

RADICALS-RT was designed to compare the efficacy and safety of adjuvant radiotherapy after radical prostatectomy versus a policy of observation with early salvage radiotherapy for PSA failure. With the benefit of longer-term follow-up, we now report on the primary outcome measure of freedom-from-distant-metastasis.

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METHODS

Study design and participants

RADICALS is an international, phase III, multi-centre, open-label, randomized controlled trial in prostate cancer. The protocol contains two separate randomisations with overlapping patient groups and was implemented at 138 trial-accredited centres in Canada, Denmark, Ireland and the UK. Participants were randomized shortly after radical prostatectomy between adjuvant and salvage post-operative radiotherapy (RADICALS-RT).

Patients with non-metastatic adenocarcinoma of the prostate were eligible for RADICALS-RT if they had undergone radical prostatectomy, had post-operative PSA≤0.2ng/ml and at least one risk factor from: pathological T-stage 3 or 4; Gleason score 7 to 10; positive margins or pre-operative PSA≥10ng/ml.

Randomisation

Participants were randomised within 22 weeks after radical prostatectomy to receive either adjuvant RT to the prostate bed+/- pelvis ("Adjuvant-RT Group"), or close observation with salvage RT to the prostate bed +/- pelvis given in the event of PSA failure, defined as either: (a) two consecutive rising PSA levels with a PSA of greater than 0.1ng/ml, or (b) three consecutive rising PSA levels ("Salvage-RT Policy Group"). Randomisation using a 1:1 allocation was performed centrally using minimisation with a random element which was stratified by Gleason sum score, margin status, RT schedule and study centre.

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Treatment

RT to the prostate bed used a non-randomised dose-fractionation schedule of either 66Gy in 33 fractions or 52.5Gy in 20 fractions. Treatment commenced within 2 months of randomisation and within 26 weeks of radical prostatectomy for Adjuvant-RT, and within 2 months after PSA failure for Salvage-RT. RT could be delayed by up to 2 months further if the patient was also due to receive hormone therapy.

Participants could also receive RT to the pelvic lymph nodes at the investigator's discretion. RT was planned with the patient supine, with empty rectum and comfortably full bladder. Patients could also receive up to 2 years hormone therapy (either an LHRH analogue or bicalutamide 150mg daily) starting before and continuing during and after their post-operative radiotherapy. The duration was either according to clinical judgement or by random allocation through participation in RADICALS-HD[13†] to either no, 6 months or 2 years duration of hormone therapy.

Assessment for efficacy and adverse events

Patients were seen by a site investigator every 4 months from randomisation for 2 years, then 6-monthly until 5 years then annually until 15 years. Clinician-reported data were collected at each follow-up visit on diarrhoea, proctitis, cystitis, haematuria and urethral stricture, graded according to RTOG toxicity score.[14] Data on other adverse events were collected if they met the criteria to be classified as a serious adverse event. Patient-reported data were collected at baseline, 1, 5 and 10 years post-randomisation using standard

† Reference to conference abstract provided; Papers Accepted 15-Mar-2024 – DOIs to follow for updated reference

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questionnaires that included Vaizey (bowel) and ICS-Male-short form (urinary incontinence).

Outcome measures

The full design of RADICALS has been described previously.[15] RADICALS-RT was designed to focus on long-term outcomes; the primary outcome measure was originally disease-specific survival, with freedom-from-distant metastasis (FFDM) as a key secondary outcome measure. Distant metastasis could be bone, liver, lung, distant node or other metastasis, but did not include pelvic nodes. With emerging data of improving patient outcomes from the EORTC 22911 and SWOG 8794 trials, and following discussion with the ongoing RAVES and GETUG-17 trials of radiotherapy timing, it was decided to change the primary outcome of the RADICALS-RT comparison to be freedom-from-distant metastasis (FFDM), which would have greater power at any given time. This change was made with all ethical and regulatory approvals in place, without reference to accumulating comparative data from RADICALS-RT, and was agreed with the Trial Steering Committee (which includes independent members, including the chair) and gained favourable international peer review, through Cancer Research UK.

Secondary outcome measures included initiation of non-protocol hormone therapy, treatment toxicity and patient reported outcomes. To facilitate the ARTISTIC meta-analysis, planned in collaboration with RAVES and GETUG-17, freedom-from-biochemical-progression was added as a secondary outcome measure in 2018, again without reference to the accumulating, comparative data from RADICALS-RT and with the approval of the oversight committees.[12] Biochemical progression-free survival (bPFS) was defined as freedom-from-PSA≥0.4ng/ml following post-operative RT, or PSA>2.0ng/ml at any time, or clinical

progression, initiation of non-protocol hormone therapy or death from any cause.

Sample Size

To target an improvement in participants free of distant metastasis at 10 years from 90% to 95%, with 80% power at a two-sided 5% significance level would require 66 participants with distant metastasis events. This was anticipated to require 1063 participants at an accrual rate of 30 participants per month or 1160 participants at 25 participants per month.

Statistical Analysis

The analysis plan has been published.[16] All analyses are performed on an intention-to-treat basis. The statistical significance of differences between randomised groups were assessed using the log-rank test, and in the absence of evidence of non-proportional hazards, the hazard ratio, from a Cox proportional hazards model, was reported as the measure of effect, with analyses stratified by the stratification factors used at randomisation (except centre). Toxicity data were divided into events reported as occurring within two years after randomisation and subsequently. Within each period, the highest grade of event experienced by participants was compared between randomised groups using the chi-square test. For patient-reported outcomes, groups are compared at one, five and ten years using analysis of covariance, adjusted for baseline score.

One sensitivity analysis was conducted, in which participants who had any metastatic event reported as “suspicious” but which was not subsequently confirmed were assumed to have developed metastasis at that time.

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Trial follow-up concluded on 31-Dec-2021 and the databased was locked on 27-May-2022.

Funding

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RESULTS

Patients

RADICALS-RT recruited 1396 participants over 9 years between November 2007 and December 2016, 697 to the Adjuvant-RT Group and 699 to the Salvage-RT Policy Group (**Figure 1**). Median age was 65 years, median PSA at diagnosis 7.9 ng/ml and 37% (517/1396) had a CAPRA-S score [17] of 6+ (**Table 1**). Median PSA at randomisation was undetectable in both randomised groups. Median follow-up was 7.8 years at end of follow-up (December 2021).

Treatment

Most participants allocated to the Adjuvant-RT Group began treatment, as planned, shortly after randomisation (**Figure 2**). 93% (648/697) Adjuvant-RT Group reported starting RT within 6 months at a median of 4.9 months (IQR 4.1, 5.6 months) after prostatectomy. At the time of analysis, 39% (270/699) of the Salvage-RT Policy Group had now reported starting salvage radiotherapy following PSA failure. In these 270 participants, the median time from randomisation to starting salvage radiotherapy was 1.5 years and their median PSA level at the time of starting salvage radiotherapy was 0.2ng/ml (IQR 0.1, 0.3). A further 12% (82/699) met the protocol definition of PSA failure during follow-up, but had not reported starting salvage radiotherapy at the time of analysis; for these 82 patients, median time from randomisation to PSA failure was 5.2 years .

Most participants who had RT received 66Gy/30f (567, 62%) or 52.5Gy/20f (268, 29%), with similar proportions in both randomised groups. Most participants received RT only to the

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prostate bed, with RT additionally to pelvic lymph nodes in only 3% (21/650) of Salvage-RT Policy Group and 6% (17/270) Adjuvant-RT Group.

Among participants who reported starting RT, 156/650 (24%) of the Adjuvant-RT Group and 72/270 (27%) of the Salvage-RT Policy Group reported use of (neo-) adjuvant hormone therapy, either through co-enrolment in RADICALS-HD or as part of local standard-of-care.

Primary outcome measure – freedom-from-distant metastasis

A primary outcome measure event of distant metastasis or death due to prostate cancer had been reported for 6% (80/1396) of participants at the end of follow-up, with 32 events in the Adjuvant-RT Group and 48 in the Salvage-RT Policy Group (**Figure 3, Table 2**). Of the 48 FFDM events in the Salvage-RT Policy Group, 37 followed after salvage radiotherapy, 7 followed PSA failure without reported salvage radiotherapy, and 4 occurred in the absence of reported PSA failure. 63 participants (28 Adjuvant-RT Group, 35 Salvage-RT Policy Group) reported distant metastasis but remained alive at the end of follow-up; 17 participants (4 Adjuvant-RT Group, 13 Salvage-RT Policy Group) reported metastasis followed by death due to prostate cancer. The difference between randomised groups was not statistically significant (HR=0.681, 95%CI 0.432 to 1.072, p=0.095) for the Adjuvant-RT Group. There was no evidence of non-proportional hazards, p=0.695. Exploratory analyses of consistency of treatment effect on FFDM are depicted in **Figure S1**.

Secondary outcome measures

At the end of trial follow-up 8% (109/1396) participants had died, with 52 deaths in the Adjuvant-RT Group and 57 deaths in the Salvage-RT Policy Group (**Figure 4, Table 2**). The

difference between groups was not statistically significant, HR=0.980 for adjuvant treatment (95%CI 0.667 to 1.440, p=0.917), and there was no evidence of non-proportional hazards, p=0.322. Only 17 deaths were directly attributed to prostate cancer; 4 Adjuvant-RT Group and 13 Salvage-RT Policy Group (**Figure S2**): HR=0.330 for Adjuvant-RT (95%CI 0.107 to 1.023, p=0.044).

We previously reported no difference in biochemical progression-free survival between randomised groups after median 4.9 years follow-up. Here, with median 7.8 years follow-up and 106 further events there was still no evidence of a difference, HR=0.972 for Adjuvant-RT (95%CI 0.758 to 1.247, p=0.822) (**Figure 5, Table 2**).

Non-protocol hormone therapy was initiated by 134 participants during follow-up, 59 in the Adjuvant-RT Group and 75 in the Salvage-RT Policy Group. The difference between groups was not statistically significant, HR=0.832 for Adjuvant-RT (95%CI 0.589 to 1.176, p=0.297) (**Figure 6, Table 2**).

Grade 3 or 4 urethral stricture was reported for 81 participants (6%). Each of the other four routinely-recorded toxicities were reported at grade 3 or 4 for fewer than 5% of participants. Toxicity was more common in the Adjuvant-RT Group, mainly a result of more grade 1 or 2 events, with late toxicity remaining significantly higher (**Table 3**).

From patient-reported outcome measures, (**Figure 7**) the Adjuvant-RT Group reported significantly worse incontinence one year after randomisation (p=0.001), but the difference lessened at later points. Faecal incontinence was statistically significantly worse after one

year in the Adjuvant-RT Group ($p<0.001$), and was also statistically significantly different in participants with an assessment at ten years after randomisation ($p=0.017$).

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DISCUSSION

These long-term results from the RADICALS-RT trial have not shown any statistically significant or clinically meaningful benefit for adjuvant radiotherapy after radical prostatectomy in terms of freedom-from-distant-metastasis. The findings are consistent with those previously-reported on the early outcome measure, bPFS.[9] The results confirm that adjuvant radiotherapy increases the risk of urinary and bowel morbidity. These data strengthen the case for observation after radical prostatectomy, keeping salvage radiotherapy in reserve in the event of recurrent disease.

Most of the secondary efficacy outcomes measures did not show any clear benefit for adjuvant RT: bPFS, time to non-protocol hormone therapy and overall survival were similar in the two arms of the trial. The PCSM result, which may appear intriguing, should be interpreted with considerable caution, given that it is based on only 17 events. Furthermore, it seems implausible that adjuvant RT should improve PCSM without a substantial effect on FFDM or time to non-protocol hormone therapy or both.

RADICALS-RT is the first randomised controlled trial that has both compared adjuvant versus early salvage radiotherapy and that is also sufficiently large and mature to report on freedom-from-distant-metastasis. The two most mature randomised controlled trials, SWOG 8794 and EORTC 22911, did not include early salvage radiotherapy in the control arm, and are therefore of limited relevance to contemporary practice.[3,5] Of the five randomised controlled trials that have compared adjuvant versus early salvage radiotherapy, the other four are not powered to study long-term outcomes such as

freedom-from-distant-metastasis. RADICALS-RT, which is the largest randomized controlled trial of adjuvant radiotherapy after radical prostatectomy, provides the best available evidence regarding the long-term effect of adjuvant radiotherapy on disease control.

RADICALS-RT has several strengths. The patient population, recruited primarily from the UK, Denmark and Canada, is representative of men undergoing radical prostatectomy internationally. The rate of PSA failure after radical prostatectomy alone was relatively high, at around 50%, and therefore suitable for a trial testing the impact of adjuvant radiotherapy. Compliance with allocated treatment and follow-up was high and was consistent across both arms. Outcome measures included not only physician-assessed toxicity, but also patient-reported functional outcomes. The use of (neo-)adjuvant hormone therapy with RT was left to local choice to reflect the breadth of practice at trial initiation with co-enrolment in RADICALS-HD encouraged. Around one quarter of participants reported having (neo-) adjuvant hormone therapy with their RT. While proportionately similar, only around half of participants in the Salvage-RT Policy Group were exposed to RT so the absolute number of participants having hormone therapy with RT was greater in the Adjuvant-RT Group. This may have implications for interpreting the non-protocol hormone therapy data.

RADICALS-RT also has some limitations. Since RADICALS-RT opened, new evidence has suggested that men receiving post-operative radiotherapy benefit from the addition of hormone therapy.[15] While greater use of hormone therapy may have improved outcomes, data from RADICALS-HD suggests that the benefit of hormone therapy is similar, regardless

of radiotherapy timing.[13‡] Similarly, results from the RTOG SPPORT trial[18] suggests a benefit to treating not just the prostate bed, but also the pelvic lymph nodes in men receiving salvage radiotherapy. This option was permitted in RADICALS-RT, but over 95% of participants who had radiotherapy received it to the prostate bed alone. Once again, there is no evidence that pelvic nodal radiotherapy would have a differential effect in the adjuvant or salvage setting. Advances in treatment, such as these, provide another argument in favour of a salvage radiotherapy policy. Given that patients may receive salvage radiotherapy years after their prostatectomy, they may benefit from new knowledge not available in the immediate post-operative period.

The ARTISTIC meta-analysis collaboration was developed to include all the relevant randomized trials of post-operative radiotherapy timing, and, with continued follow-up of all trials, will be powered to report on freedom from distant metastasis and overall survival.[19] The meta-analysis will also enable subgroup analyses to investigate whether any subgroup could be identified to benefit from adjuvant radiotherapy.

The long-term results from the RADICALS-RT trial have not shown any benefit for adjuvant radiotherapy in comparison to a policy of salvage radiotherapy for PSA failure; but adjuvant radiotherapy does increase the risk of urinary and bowel morbidity. These findings add support to a policy of observation after radical prostatectomy, with salvage radiotherapy used in the event of PSA failure.

‡ Reference to conference abstract provided; Papers In Press --- DOIs to follow

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We recognise the efforts of all trial team members at the trials units and hospitals who have supported and engaged with RADICALS. A list of investigators and oversight committee members across the comparisons of the RADICALS protocol is given in the Appendix and on the RADICALS website.[§]

Most importantly, we recognise and thank all of the participants of the trial and the families and friends who supported them. Clinical trials only happen because people choose to join them.

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[§] https://www.mrcctu.ucl.ac.uk/media/1811/radicals-protocol-version-60-14-dec-2018_signed.pdf

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COMPETING INTERESTS

CCP reports advisory board for AAA and Blue Earth Therapeutics and ITM Oncologics. **PMP** reports personal fees for participation on Advisory Board for AAA Nordic, MSD, Pfizer Denmark and Bayer A/S Denmark. **CNC** reports advisory board for Abbvie; and invited speaker for Bayer and Knight Pharmaceuticals. **NDJ** reports personal fees for participation on Advisory Board for AstraZeneca, Bayer, Janssen, Merck, Novartis and Sanofi; institutional fees for Expert Testimony for Janssen and Sanofi; personal fees for being an Invited Speaker for Merck Sharp & Dohme (UK) Limited. **FS** reports advisory board for Astellas, AstraZeneca, Bayer, BMS, Janssen, Merck, Myovant, Novartis and Pfizer; Local PI for Amgen, Astellas, Bayer, BMS, Janssen, Merck, Novartis, Pfizer, Sanofi; Coordinating PI for AstraZeneca. **LCB** reports a previous role, unrelated to the present manuscript, part funded by NIHR BRC. **AMZ** reports personal fees from Pfizer, Janssen, Astellas, MSD and EUSA Pharma; and support for attendance of a conference from Bayer. **MRS** reports speaker fees from Janssen, Eli Lilly and Eisai; and research grants from Astellas, Clovis Oncology, Janssen, Novartis, Pfizer and Sanofi.
All other authors have declared no conflicts of interest, unless they have been submitted directly through the ESMO Portal.

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TABLES AND FIGURES

Figure 1: Accrual to RADICALS-RT and patient progress through trial

Figure 2: Proportion starting radiotherapy over time
Blue = Salvage-RT Policy Group
Red = Adjuvant-RT Group

Figure 3: Freedom from distant metastasis
Blue = Salvage-RT Policy Group
Red = Adjuvant-RT Group

Figure 4: Overall survival
Blue = Salvage-RT Policy Group
Red = Adjuvant-RT Group

Figure 5: Biochemical progression-free survival
Blue = Salvage-RT Policy Group
Red = Adjuvant-RT Group

Figure 6: Initiation of non-protocol hormone therapy
Blue = Salvage-RT Policy Group
Red = Adjuvant-RT Group

Figure 7: Incontinence ratings
Blue = Salvage-RT Policy Group
Red = Adjuvant-RT Group

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CONTRIBUTIONS

CCP was the chief investigator

CCP, MRS, NWC, HGK, CC, and MKBP were responsible for trial design

CCP, MRS, NWC, HGK, MKBP were grant holders (UK) and CC, FS, WP were grant holders (Canada)

CCP, NWC, ADC, HGK, PMP, CC, WC, JL, WP, HP, AS, PN, LB, RP, HP, FS, MKBP, and MRS were TMG members

CCP, ADC, MRS, and MKBP were responsible for the analysis plan

ADC and MRS did the final analyses

CCP, ADC and MRS wrote essential sections of the manuscript

All authors collated data, interpreted data, and edited, reviewed, and approved the final manuscript

All authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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RADICALS INVESTIGATORS

See appendix

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Table 1: Patient Characteristics, n (%) unless indicated

	Salvage-RT		Adjuvant-RT		All	
	N	%	N	%	N	%
	699	(100)	697	(100)	1396	(100)
Age						
Years*	65 (60,68)		65 (60,68)		65 (60,68)	
PSA at diagnosis						
ng/ml*	8 (5.6,11.6)		7.8 (5.8,11.4)		7.9 (5.7,11.5)	
Gleason score						
GS <7	48	(7)	48	(7)	96	(7)
GS 3+4	338	(48)	349	(50)	687	(49)
GS 4+3	190	(27)	188	(27)	378	(27)
GS ≥8	123	(18)	112	(16)	235	(17)
Pathologic T-stage						
pT2	176	(25)	163	(23)	339	(24)
pT3a	390	(56)	408	(59)	798	(57)
pT3b	129	(18)	121	(17)	250	(18)
pT4	4	(1)	5	(1)	9	(1)
Positive margins						
Present	444	(64)	439	(63)	883	(63)
Absent	255	(36)	258	(37)	513	(37)
Lymph node involvement						
N1	28	(4)	38	(5)	66	(5)
N0	374	(54)	336	(48)	710	(51)
Nx	297	(42)	322	(46)	619	(44)
missing	*0*		*1*		*1*	
CAPRA-S score						
Low (0 to 2)	55	(8)	58	(8)	113	(8)
Intermediate (3 to 5)	384	(55)	382	(55)	766	(55)
High (6+)	260	(37)	257	(37)	517	(37)
Country						
England	573	(82)	574	(82)	1147	(82)
Denmark	92	(13)	95	(14)	187	(13)
Canada	28	(4)	22	(3)	50	(4)
Republic of Ireland	6	(1)	6	(1)	12	(1)

* median (IQR)

CAPRA = Cancer of the Prostate Risk Assessment
GS = Gleason score
N = Nodal status
T = Tumour stage

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Table 2. Primary and Secondary Outcome Measures

	Salvage-RT (n=699)		Adjuvant-RT (n=697)	
Freedom-from-distant-metastasis				
Events	48	(6.9%)	32	(4.6%)
Metastasis, no PCa death	35		28	
Prostate cancer death	13		4	
Hazard ratio*			HR = 0.681	(0.432, 1.072)
Log-rank p-value*			0.095	
Proportional hazards p-value **			0.695	
RMST† (95%CI)	9.61	(9.49, 9.72)	9.72	(9.62, 9.82)
10-year event free for FFDM	89.6%		92.7%	
Overall survival				
Events	57	(8.2%)	52	(7.5%)
Hazard ratio*			HR = 0.980	(0.667, 1.440)
Log-rank p-value*			0.917	
Proportional hazards p-value **			0.322	
RMST† (95%CI)	9.58	(9.47, 9.69)	9.56	(9.44, 9.68)
10-year survival	87.4%		87.6%	
Prostate-cancer specific mortality				
Events	13		4	
Hazard ratio*			HR = 0.330	(0.107 to 1.023)
Log-rank p-value*			0.044	
Proportional hazards p-value **			0.765	
RMST† (95%CI)	9.90	(9.85, 9.96)	9.97	(9.94, 10.0)
10-year event free for FFDM	97.1%		99.2%	
Initiation of non-protocol HT				
Events	75	(10.7%)	59	(8.5%)
Hazard ratio*			HR = 0.832	(0.589, 1.176)
Log-rank p-value*			0.297	
Proportional hazards p-value **			0.854	
RMST† (95%CI)	9.30	(9.15, 9.46)	9.43	(9.29, 9.57)
10-year event free for FFDM	85.4%		88.9%	
Biochemical PFS				
Events	135	(19.3%)	125	(17.9%)
Hazard ratio*			HR = 0.972	(0.758, 1.247)
Log-rank p-value*			0.822	
Proportional hazards p-value **			0.527	
RMST† (95%CI)	8.70	(8.50, 8.90)	8.72	(8.51, 8.93)
10-year event free survival	75.0%		76.4%	

* adjusted for randomisation stratification factors,
** Grambsch-Therneau test of non-proportional hazards,
† Restricted mean survival time (standard error).

FFDM = Freedom-from-distant-metastasis
HT = Hormone therapy
PCa = Prostate cancer
PFS = Progression-free survival
RMST = Restricted-mean "survival" time

Table 3: RTOG toxicity scale*, n (%) unless indicated

	Early (<2years)							Late (2+ years)						
	All		Salvage-RT		Adjuvant-RT			All		Salvage-RT		Adjuvant-RT		
	N	%	N	%	N	%	p**	N	%	N	%	N	%	p**
	1379	(100)	697	(100)	682	(100)		1343	(100)	681	(100)	662	(100)	
Diarrhoea														
Grade 1 or 2	398	(29)	127	(18)	271	(40)	<0.001	184	(14)	64	(9)	120	(18)	<0.001
Grade 3	16	(1)	4	(1)	12	(2)		7	(1)	2	(<1)	5	(1)	
Grade 4	0	(0)	0	(0)	0	(0)		1	(<1)	0	(0)	1	(<1)	
Proctitis														
Grade 1 or 2	216	(16)	52	(7)	164	(24)	<0.001	130	(10)	43	(6)	87	(13)	<0.001
Grade 3	11	(1)	3	(<1)	8	(1)		10	(1)	2	(<1)	8	(1)	
Grade 4	0	(0)	0	(0)	0	(0)		0	(0)	0	(0)	0	(0)	
Cystitis														
Grade 1 or 2	284	(21)	96	(14)	188	(28)	<0.001	141	(11)	50	(7)	91	(14)	0.001
Grade 3	20	(1)	6	(1)	14	(2)		14	(1)	7	(1)	7	(1)	
Grade 4	1	(<1)	0	(0)	1	(<1)		0	(0)	0	(0)	0	(0)	
Haematuria														
Grade 1 or 2	130	(9)	37	(5)	93	(14)	<0.001	129	(10)	31	(5)	98	(15)	<0.001
Grade 3	29	(2)	5	(1)	24	(4)		35	(3)	5	(1)	30	(5)	
Grade 4	0	(0)	0	(0)	0	(0)		0	(0)	0	(0)	0	(0)	
Urethral stricture														
Grade 1 or 2	73	(5)	22	(3)	51	(8)	0.001	66	(5)	22	(3)	44	(7)	<0.001
Grade 3	76	(6)	32	(5)	44	(6)		55	(4)	19	(3)	36	(5)	
Grade 4	5	(<1)	3	(<1)	2	(<1)		3	(<1)	3	(<1)	0	(0)	

* No Grade 5 events reported

** Adjuvant vs Salvage, chi-square test

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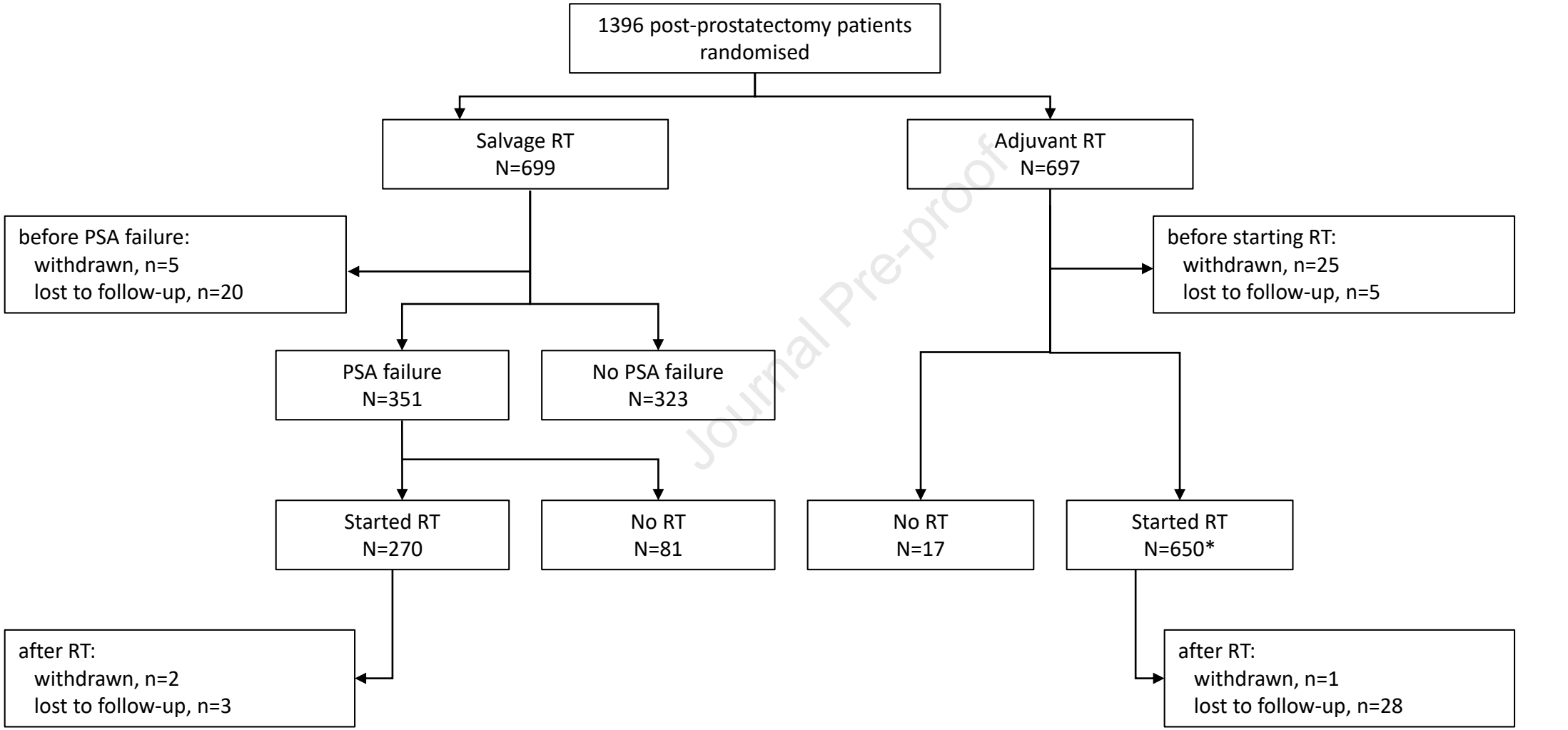
Figure 1: Accrual to RADICALS-RT and patient progress through trial



* 1 pt started RT >1yr after randomisation

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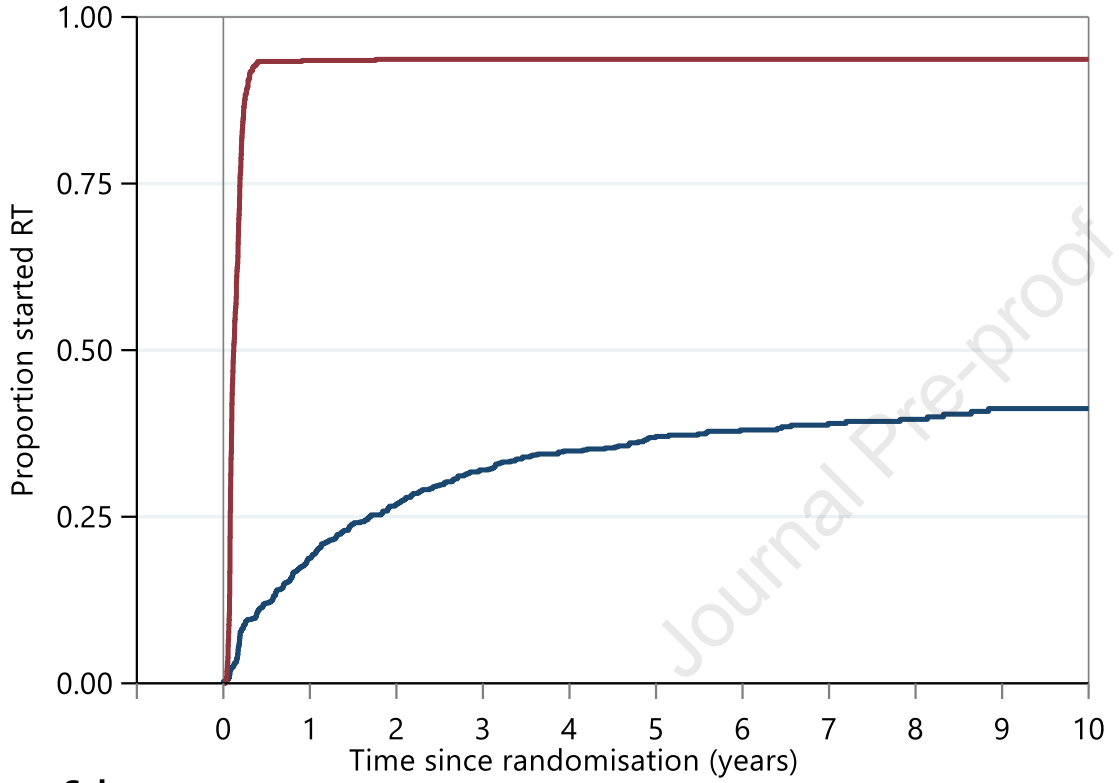
Figure 2: Time to starting RT



Salvage											
At-risk	699	565	501	458	431	377	300	236	179	126	68
Censored	0	3	11	19	27	67	139	199	254	303	361
RT start	0	131	187	222	241	255	260	264	266	270	270
Adjuvant											
At-risk	697	43	40	39	38	35	23	20	16	14	14
Censored	0	5	7	8	9	12	24	27	31	33	33
RT start	0	649	650	650	650	650	650	650	650	650	650

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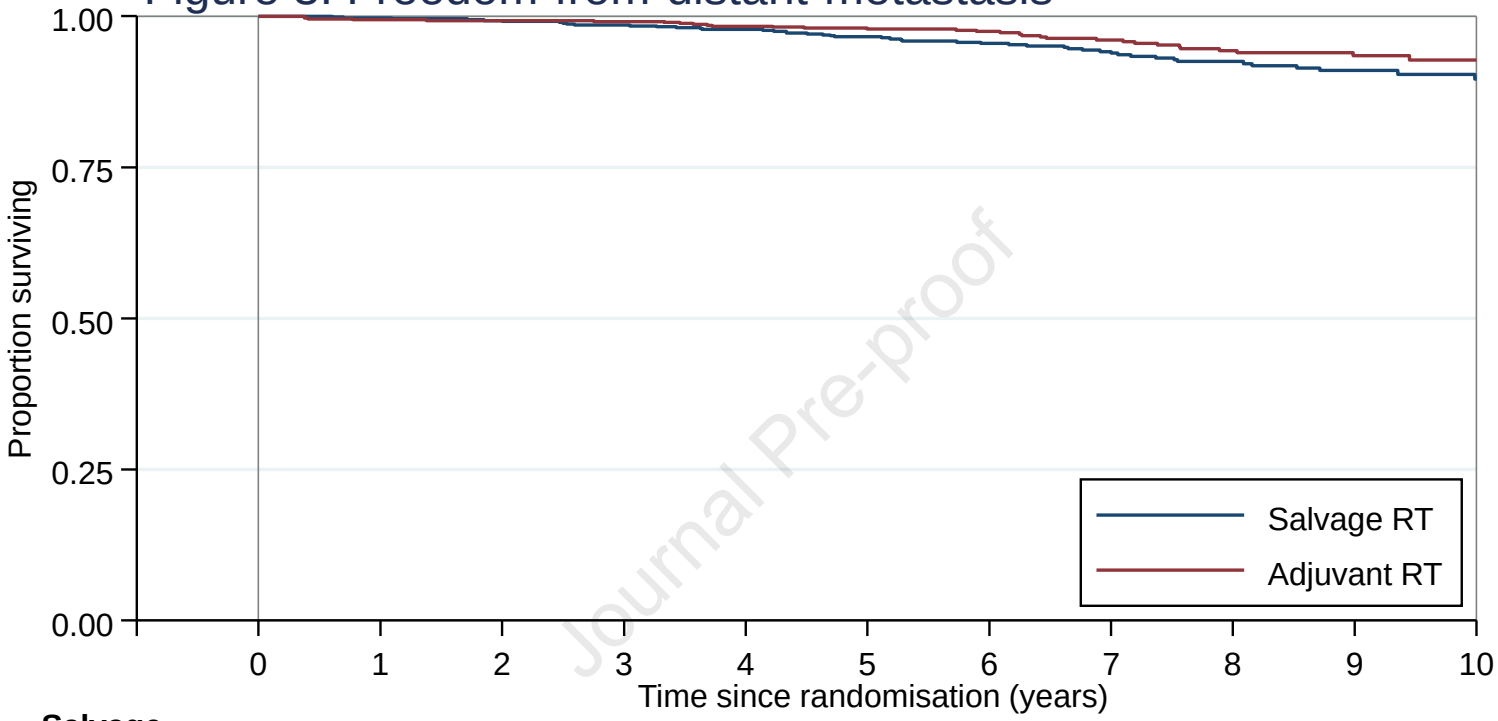
Figure 3: Freedom-from-distant-metastasis



Salvage											
At-risk	699	693	683	666	656	589	476	380	293	201	111
Censored	0	4	11	23	28	87	194	284	365	453	541
Event	0	2	5	10	15	23	29	35	41	45	47
Adjuvant											
At-risk	697	671	664	651	635	584	471	372	282	185	102
Censored	0	22	28	40	51	99	210	303	387	482	564
Event	0	4	5	6	11	14	16	22	28	30	31

Analysis time

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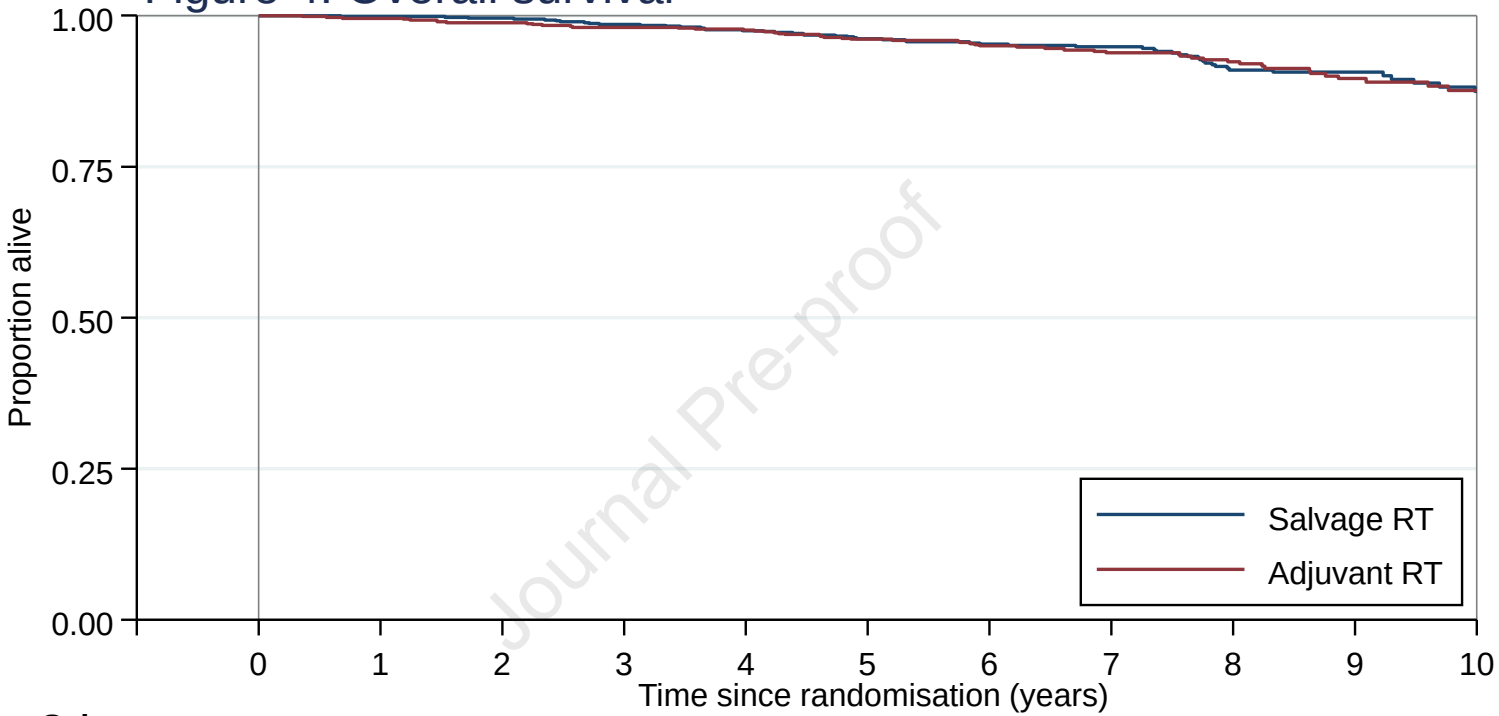
Figure 4: Overall survival



Salvage											
At-risk	699	695	687	675	665	602	488	394	302	211	115
Censored	0	3	9	14	17	71	180	272	350	440	531
Event	0	1	3	10	17	26	31	33	47	48	53
Adjuvant											
At-risk	697	674	666	654	643	591	476	379	290	188	104
Censored	0	20	23	30	38	80	189	281	365	460	541
Event	0	3	8	13	16	26	32	37	42	49	52

Analysis time

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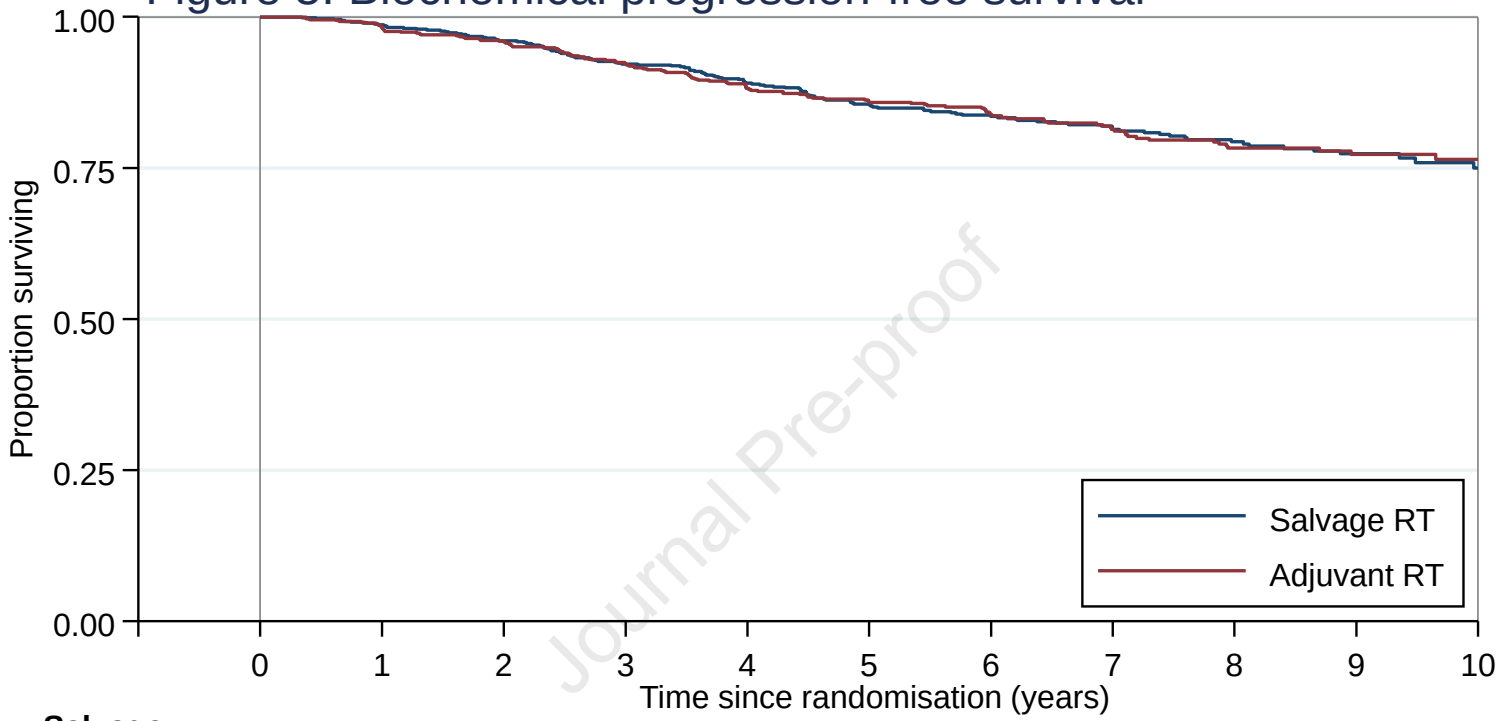
Figure 5: Biochemical progression-free survival



Salvage											
At-risk	699	679	650	615	587	488	396	305	235	139	75
Censored	0	11	22	31	38	115	196	278	341	432	493
Event	0	9	27	53	74	96	107	116	123	128	131
Adjuvant											
At-risk	697	659	638	600	563	481	386	296	212	130	60
Censored	0	26	32	45	56	124	209	289	363	443	512
Event	0	12	27	52	78	92	102	112	122	124	125

Analysis time

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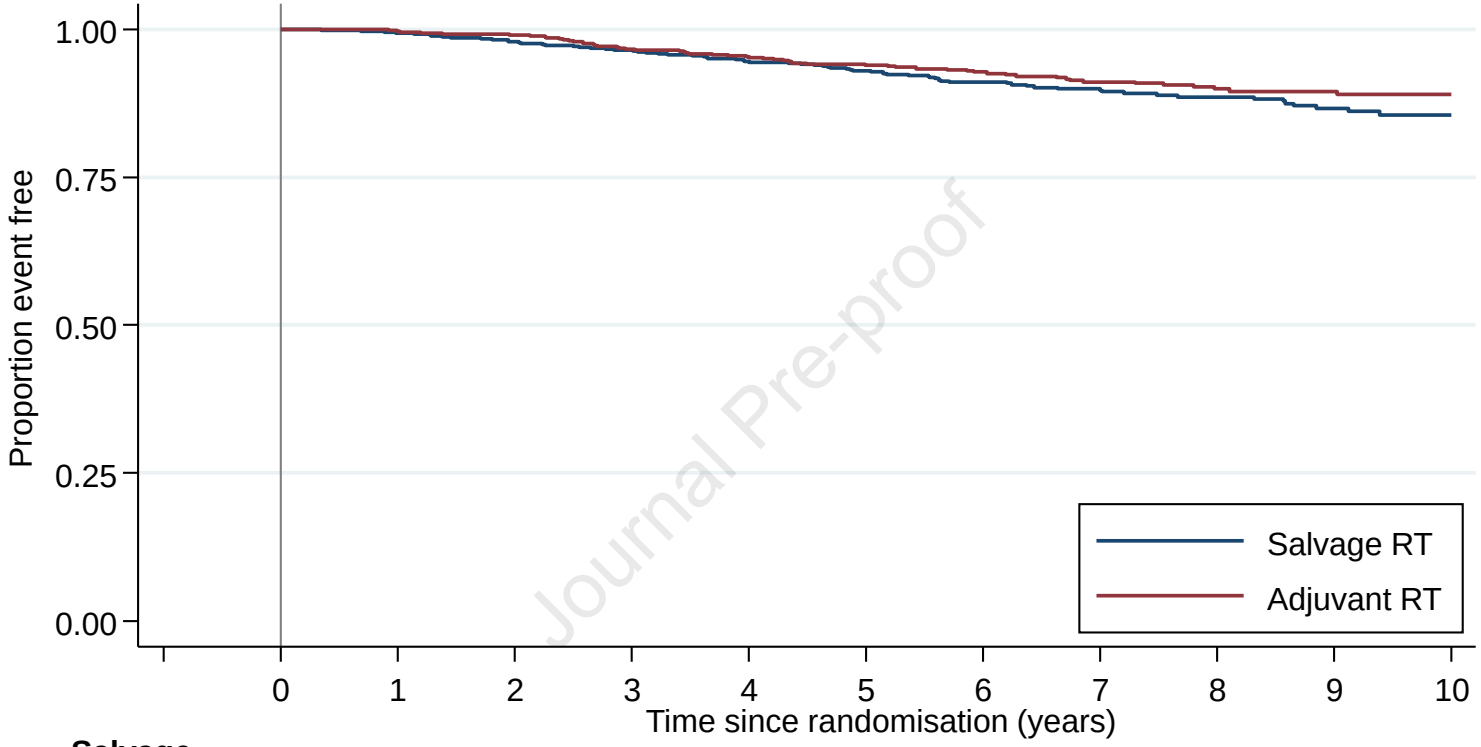
Figure 6: Initiation of non-protocol hormone therapy



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Salvage											
At-risk	699	690	672	651	630	561	447	358	279	191	103
Censored	0	4	12	24	32	90	194	278	352	435	521
Event	0	5	15	24	37	48	58	63	68	73	75
Adjuvant											
At-risk	697	672	659	632	613	556	448	352	267	172	94
Censored	0	23	31	43	53	101	203	292	373	467	544
Event	0	2	7	22	31	40	46	53	57	58	59

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Figure 7: Incontinence ratings

Figure 7A
ICS urinary incontinence score

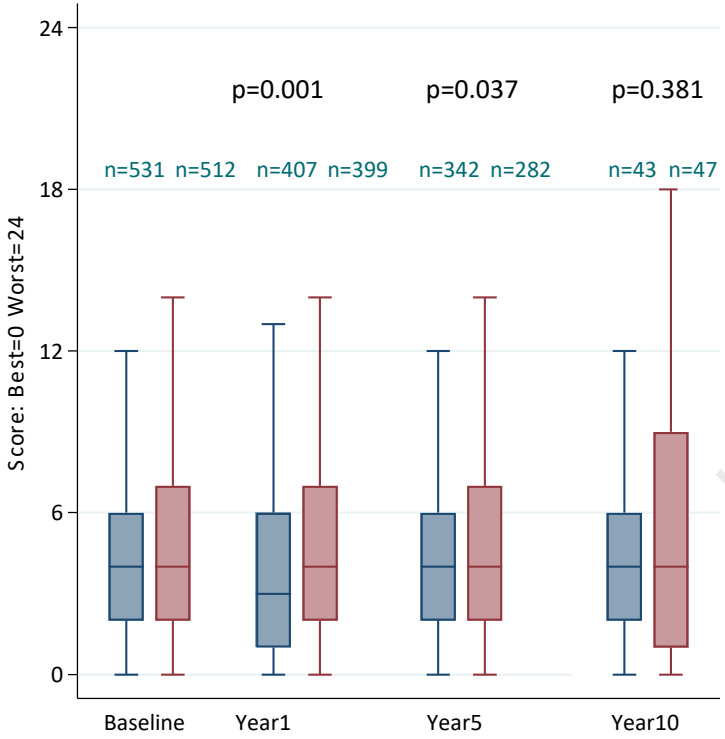
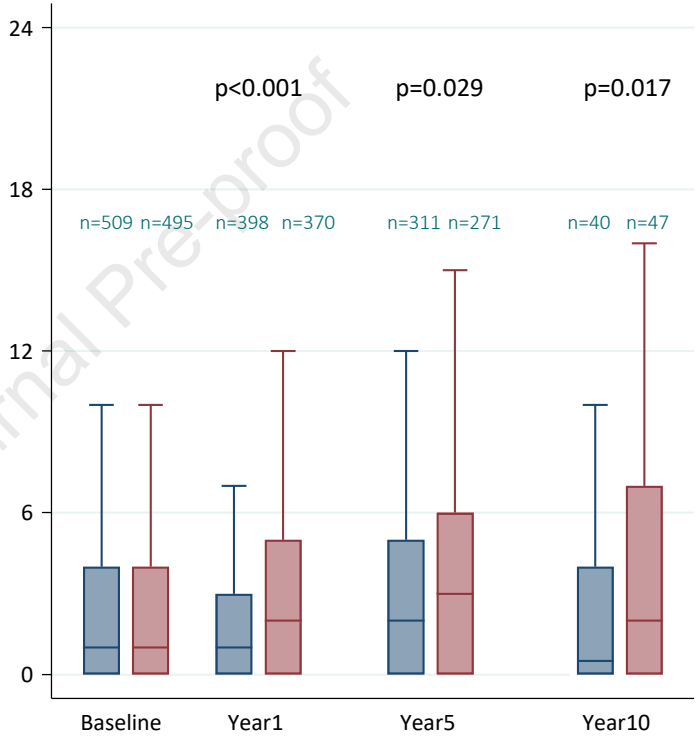


Figure 7B
Vaizey faecal incontinence score



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Blue = Salvage; red = adjuvant