Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial

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Summary

Background Adjuvant radiotherapy reduces the risk of biochemical progression in prostate cancer patients after radical prostatectomy. We aimed to compare adjuvant versus early salvage radiotherapy after radical prostatectomy, combined with short-term hormonal therapy, in terms of oncological outcomes and tolerance.

Methods GETUG-AFU 17 was a randomised, open-label, multicentre, phase 3 trial done at 46 French hospitals. Men aged at least 18 years who had an Eastern Cooperative Oncology Group performance status of 1 or less, localised adenocarcinoma of the prostate treated with radical prostatectomy, who had pathologically-staged pT3a, pT3b, or pT4a (with bladder neck invasion), pNx (without pelvic lymph nodes dissection), or pN0 (with negative lymph nodes dissection) disease, and who had positive surgical margins were eligible for inclusion in the study. Eligible patients were randomly assigned (1:1) to either immediate adjuvant radiotherapy or delayed salvage radiotherapy at the time of biochemical relapse. Random assignment, by minimisation, was done using web-based software and stratified by Gleason score, pT stage, and centre. All patients received 6 months of triptorelin (intramuscular injection every 3 months). The primary endpoint was event-free survival. Efficacy and safety analyses were done on the intention-to-treat population. The trial is registered with ClinicalTrials.gov, NCT00667069.

Findings Between March 7, 2008, and June 23, 2016, 424 patients were enrolled. We planned to enrol 718 patients, with 359 in each study group. However, on May 20, 2016, the independent data monitoring committee recommended early termination of enrolment because of unexpectedly low event rates. At database lock on Dec 19, 2019, the overall median follow-up time from random assignment was 75 months (IQR 50–100), 74 months (47–100) in the adjuvant radiotherapy group and 78 months (52–101) in the salvage radiotherapy group. In the salvage radiotherapy group, 115 (54%) of 212 patients initiated study treatment after biochemical relapse. 205 (97%) of 212 patients started treatment in the adjuvant group. 5-year event-free survival was 92% (95% CI 86–95) in the adjuvant radiotherapy group and 90% (85–94) in the salvage radiotherapy group (HR 0·81, 95% CI 0·48–1·36; log-rank p=0·42). Acute grade 3 or worse toxic effects occurred in six (3%) of 212 patients in the adjuvant radiotherapy group and in four (2%) of 212 patients in the salvage radiotherapy group. Late grade 2 or worse genitourinary toxicities were reported in 125 (59%) of 212 patients in the adjuvant radiotherapy group and 46 (22%) of 212 patients in the salvage radiotherapy group. Late genitourinary adverse events of grade 2 or worse were reported in 58 (27%) of 212 patients in the adjuvant radiotherapy group versus 14 (7%) of 212 patients in the salvage radiotherapy group (p<0·0001). Late erectile dysfunction was grade 2 or worse in 60 (28%) of 212 in the adjuvant radiotherapy group and 17 (8%) of 212 in the salvage radiotherapy group (p<0·0001).

Interpretation Although our analysis lacked statistical power, we found no benefit for event-free survival in patients assigned to adjuvant radiotherapy compared with patients assigned to salvage radiotherapy. Adjuvant radiotherapy increased the risk of genitourinary toxicity and erectile dysfunction. A policy of early salvage radiotherapy could spare men from overtreatment with radiotherapy and the associated adverse events.

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Introduction

Radical prostatectomy is a standard treatment for patients with localised prostate cancer, showing excellent long-term outcomes.[1] However, a third of patients will have pathological high-risk features, including extracapsular extension, seminal vesicle involvement, or positive surgical margins (R1) on the final pathology report. These risks factors increase the likelihood of biochemical

Research in context

Evidence before this study

Randomised trials comparing adjuvant radiotherapy with observation after radical prostatectomy reported better long-term biochemical control in those receiving radiotherapy. Around a third of patients allocated to observation did not have disease relapse, so adjuvant irradiation for all patients leads to overtreatment. In addition to controversial long-term outcome results, without clear overall survival or metastasis-free survival benefits, the use of adjuvant radiotherapy in daily practice has been limited by an increased incidence of toxic effects. By contrast, despite only retrospective evidence, observation followed by salvage radiotherapy has increasingly been adopted. However, the optimal timing of postoperative radiotherapy remains to be elucidated. No systematic literature search was done.

Added value of the study

Our trial compared adjuvant radiotherapy with early salvage radiotherapy, both combined with short-term hormonal therapy. Adjuvant radiotherapy did not show any benefit compared with the delayed approach but increased the risk of urinary and sexual toxic effects.

Implications of all the available evidence

Salvage radiotherapy could spare men from overtreatment and associated radiotherapy-induced toxic effects. This delayed approach would be preferred unless adjuvant radiotherapy was superior to salvage radiotherapy according to long-term oncological outcomes.

recurrence, providing a rationale for phase 3 adjuvant radiotherapy trials.[2–4]

The SWOG S8794,[3] EORTC 22911,[4] and ARO 96-02/AUO AP 09/95[2] randomised studies compared adjuvant radiotherapy given to the prostate bed without androgen deprivation therapy with observation after radical prostatectomy. These studies, which included patients with high-risk pathology, reported better long-term biochemical control in favour of adjuvant radiotherapy, in addition to controversial long-term outcome results, without clear overall survival or metastasis-free survival benefits.[2–4] Moreover, these trials are difficult to interpret because less than half of patients with disease recurrence in the observation groups received salvage radiotherapy, which is now standard practice.

In these studies assessing adjuvant radiotherapy,[2–4] around a third of patients allocated observation did not have disease relapse. Indeed, we risk overtreating patients by proposing adjuvant radiotherapy for all.[5,6] In daily practice, the use of adjuvant radiotherapy has been restricted by increased incidence of toxic effects and diminished quality of life (QOL).[6,7] By contrast, despite only retrospective evidence supporting efficacy, observation followed by salvage radiotherapy usually at biochemical progression, has increasingly been adopted.[7] The optimal timing of postoperative radiotherapy remains to be elucidated. Three large, multicentre, open-label trials, RADICALS RT,[8] RAVES,[9] and GETUG-AFU 17 were designed to assess whether delayed salvage radiotherapy, given at biochemical relapse, or immediate adjuvant radiotherapy was more appropriate in men with localised prostate cancer after radical prostatectomy. In the GETUG-AFU 17 trial, we aimed to compare adjuvant radiotherapy versus early salvage radiotherapy after radical prostatectomy, combined with short-term hormonal therapy, in terms of oncological outcomes and tolerance.

Methods

Study design and participants

GETUG-AFU 17 was a randomised, open-label, multicentre, phase 3 trial done at 46 French hospitals. Men aged at least 18 years who had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less, localised adenocarcinoma of the prostate treated with radical prostatectomy with or without pelvic lymph node dissection, who had pathologically-staged pT3a, pT3b, or pT4a (with bladder neck invasion), pNx (without pelvic lymph nodes dissection), or pN0 (with negative lymph nodes dissection), and who had positive surgical margins were eligible for inclusion in the study. Patient prostate specific antigen (PSA) after radical prostatectomy had to be 0·1 ng/mL or less and confirmed by a second measurement after 4 weeks. Patients who had surgical or chemical castration, or an abnormal testosterone level were ineligible. Patients with positive lymph nodes at pathology were not eligible. The delay between radical prostatectomy and enrolment was limited to 6 months.

The study was done in accordance with the Declaration of Helsinki and received regulatory and ethics approvals by the Institutional Review Board at Institut Bergonié and the French Agency for the Safety of Health Care Products. All patients provided written informed consent before participation.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to either immediate adjuvant radiotherapy or delayed salvage radiotherapy at the time of biochemical relapse. Random assignment, by minimisation, was done using the web-based TenAléa software version 2 and stratified by Gleason score (predominant grade of 4 *vs* any other grade), pT stage (pT3a or pT4a *vs* pT3b), and centre. Clinicians and patients were not masked to the allocation of study treatment.

Procedures

When the GETUG-AFU 17 study was designed, addition of short-term hormonal therapy to radiotherapy was reported to significantly delay biochemical relapse in patients with localised prostate cancer.[10,11] Thus, the investigators decided that postoperative radiotherapy would be combined with short-term hormonal therapy in both study groups. Hormonal therapy was planned to start within the 2 months before radiotherapy. Patients allocated adjuvant radiotherapy initiated treatment between 3 and 6 months after radical prostatectomy. Patients randomly allocated to the salvage radiotherapy group initiated treatment when biochemical relapse occurred.[12]

Radiotherapy was planned in a supine position, with the patient having a comfortable full bladder and empty rectum. The clinical target volume (CTV) 1 included the prostate bed and was contoured in a similar way to that used in the RTOG 9601 study.[13] Pelvic lymph nodes could be included in a CTV 2, at the physician's discretion. The planned target volume (PTV) was created with anisotropic margins, 5 mm posteriorly and 7–10 mm in all others direction. Both three-dimensional (3D) conformal radiotherapy and intensity-modulated radiotherapy were allowed. Three-dimensional conformal radiotherapy comprised irradiation in 4 to 6 fields with 6-MV photons. In all patients, image-guided radiotherapy was based on daily orthogonal kV radiography or cone-beam CT to verify at least bony alignment. All patients had radiotherapy planned for 7 weeks at a dose of 66 Gy in 33 fractions of 2 Gy, 5 days per week. Pelvic lymph nodes could be treated at a dose of 46 Gy in 23 fractions of 2 Gy, 5 days per week.

Hormonal therapy consisted of 6 months of triptorelin (Decapeptyl 11·25 SR; supplied by Ipsen; Paris, France), administered by intramuscular injection every 3 months.

All patients had weekly study visits during radiotherapy. After random assignment, visits were planned at 3 and 6 months after completing radiotherapy, then every 6 months during the first 2·5 years, and then annually, in both treatment groups. During visits, tumour progression and relapse were assessed by PSA assay and, if PSA had increased, with CT and bone scans. Biochemical progression was defined as either a PSA level of 0·4 ng/mL or greater at least 6 months after completing adjuvant radiotherapy or salvage radiotherapy, confirmed after 4 weeks, or a PSA level of 1 ng/mL or greater at any time after random assignment, or clinical progression or death from any cause. Biochemical relapse before initiating salvage radiotherapy, which was not considered an event for patients in this group, was defined as a PSA level greater than 0·2 ng/mL confirmed after 4 weeks.[12] The date of the initial increased PSA level was considered the date of biochemical progression.

Toxicity was assessed throughout the study. Data concerning adverse events that occurred, graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, were collected at each study visit. Acute toxic effects were those reported during radiotherapy up to 3 months after completion of radiotherapy. All toxic effects reported after this time, up until 5 years after radiotherapy, were considered late toxic effects. Patients were considered to have discontinued the study if they withdrew consent or died.

Patients completed QOL questionnaires during study visits at baseline, then at 2 and 5 years after radiotherapy. Patients were also requested to complete these questionnaires during December, 2017, whether or not they had received radiotherapy, to analyse the QOL variation from baseline in all patients. The EORTC core QOL questionnaire (QLQ-C30) assesses the following 15 health-related QOL scales: global health status (global health-related QOL), five functional scales (physical, role, emotional, cognitive, and social) and nine symptomatic scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The EORTC prostate cancer-specific QOL questionnaire (QLQ-PR25) assesses the following five domains: urinary symptoms, bowel symptoms, hormone treatment-related symptoms, sexual activity, and sexual function.

Outcomes

The primary outcome was event-free survival, assessed as the time from random assignment to the first documented event, either disease relapse (locoregional or metastatic), biochemical progression, or death.

Secondary outcomes were overall survival (defined as the time from randomisation to death from any cause), metastasis-free survival (defined as the time from random assignment to the first documented metastasis or death from any cause), incidence of acute and late toxic effects, change in QOL from baseline until December, 2017 (QLQ-C30 and QLQ-PR25 instruments), and functional dependence in patients older than 75 years (assessed by Instrument Activities of Daily Living scale [IADL]).

Statistical analysis

Statistical comparisons of the incidence of adverse events were exploratory. The study was designed to show a 10% increase in the 5-year event-free survival rate, from 60% with early salvage radiotherapy to 70% with adjuvant radiotherapy (hazard ratio [HR] 0·70). The α was fixed at 5% and the power at 80%. Under these hypotheses, 242 event-free survival events were needed at final analysis. Enrolment was planned to last 5 years, with a final analysis planned 2·5 years after the final patient was enrolled. Consequently, the study planned to enrol 718 patients, with 359 in each group. An interim analysis for efficacy and safety was planned after 121 events had occurred. The Peto method for α adjustment was planned—ie, a conservative α threshold of 0·001 at interim analysis to maintain a 5% α level at final analysis. $p<0·05$ was considered statistically significant.

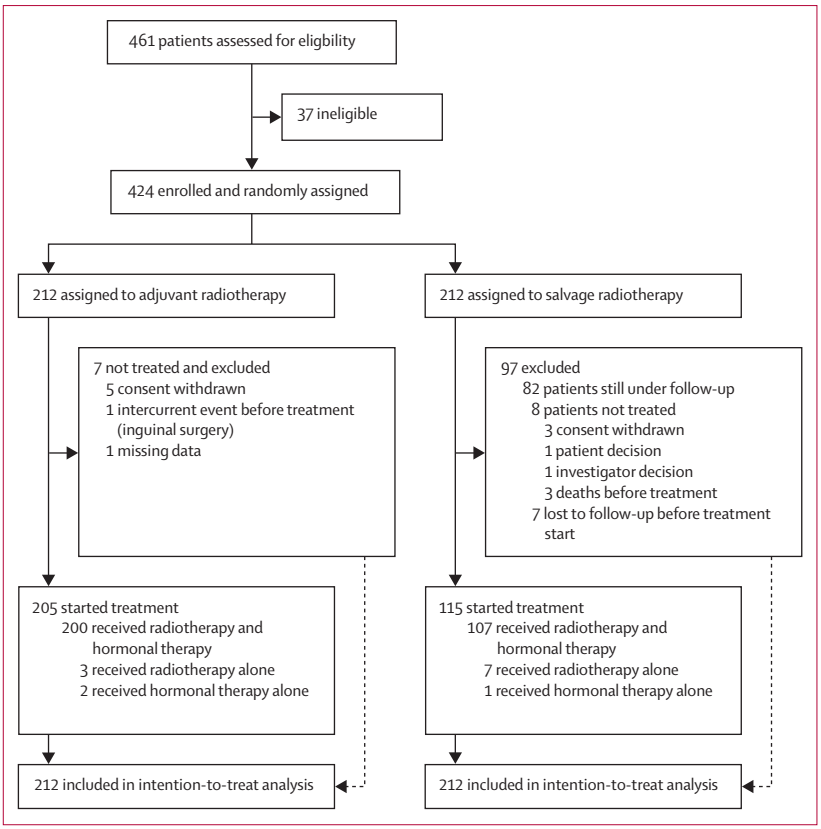

Figure 1: **Trial profile**

See Online for appendix

In time-to-event analyses, the date of randomisation was considered the reference date. Patients without events were censored at the last known date they were alive. Median follow-up was estimated using the reverse Kaplan-Meier method. Event-free survival, metastasis-free survival, and overall survival were analysed in each study group using the Kaplan-Meier method. Survival in the study groups was compared using the bilateral log-rank test, with the significance level set at 5%. Results are presented as survival at various timepoints with their associated 95% CIs. A post-hoc sensitivity analysis for event-free survival and overall survival using the date of radical prostatectomy as the reference date for survival was done to assess potential bias resulting from the 3 to 6 month delay between radical prostatectomy and random assignment.

Efficacy and safety analyses were done on the intention-to-treat population, which comprised all randomly assigned patients according to treatment group. QOL was analysed in patients with available data. Qualitative data were reported as frequency and percentages. Quantitative data were reported as mean and associated SD or median with IQR.

Global QOL scores and each scale or domain of the QLQ-C30 and QLQ-PR25 were calculated according to the scoring manual. Missing data were not replaced. Absolute individual variations from baseline were calculated and median changes from baseline until December, 2017, were compared between study groups using a non-parametric Kruskal-Wallis test.

The study was overseen by a trial steering committee and an independent data monitoring committee (IDMC). Statistical analyses were done using SAS version 9.4.

This trial is registered at EudraCT, number 2007-002495-34 and at ClinicalTrials.gov, number NCT00667069.

Role of the funding source

The study sponsor (Unicancer) was responsible for study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit for publication. PS and PR had access to all the data in the study and had final responsibility for the decision to submit for publication. The funder of the study (Ipsen) conducted a courtesy review of the draft manuscript, but was not involved in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between March 7, 2008, and June 23, 2016, 424 patients were enrolled from 46 French centres (appendix pp 2–3). We planned to enrol 718 patients, with 359 in each study group. However, on May 20, 2016, the IDMC recommended early termination of enrolment because of unexpectedly low event rates. At that time, only 12 (5%) of 242 events needed for the primary outcome analysis had been reported. Consequently, the planned analysis would have been many years away. As our study group had been contacted by the RADICALS team to participate in the ARTISTIC meta-analysis,[14] we decided to use the meta-analysis as the timepoint for our study analysis. When enrolment was stopped, 424 patients had been randomly allocated, 212 to the adjuvant radiotherapy group and 212 to the salvage radiotherapy group (figure 1). Baseline characteristics were similar between the study groups except for hypertension, which was more frequent in the adjuvant radiotherapy group (table 1). The median patient age at random assignment was 63·8 years (IQR 59·7–67·9).

At database lock on Dec 19, 2019, the overall median follow-up time from random assignment was 75 months (IQR 50–100), 74 months (47–100) in the adjuvant radiotherapy group and 78 months (52–101) in the salvage radiotherapy group. In the adjuvant radiotherapy group, 205 (97%) of 212 patients started treatment (figure 1). In the salvage radiotherapy group, 115 (54%) of 212 patients initiated study treatment after biochemical relapse. The median PSA level was 0·24 ng/mL (IQR 0·22–0·29) when salvage radiotherapy was initiated. The median delay between random assignment and radiotherapy was 1·1 months (IQR 0·3–4·4) in the adjuvant radiotherapy group and 23 months (4–100) in the salvage radiotherapy group. 61 (30%) of 203 patients who

received radiotherapy in the adjuvant radiotherapy group had intensity-modulated radiotherapy and 141 (69%) of 203 patients had 3D-conformal radiotherapy; data were missing for one (<1%) patient. 54 (47%) of 114 patients who received radiotherapy in the salvage radiotherapy group had intensity-modulated radiotherapy and 60 (53%) of 114 patients had 3D-conformal radiotherapy; data were missing for one (<1%) patient. All treated patients received radiotherapy to the prostate bed. Pelvic lymph nodes were irradiated in 36 (18%) of 203 patients in the adjuvant radiotherapy group and in 27 (24%) of 114 patients in the salvage radiotherapy group.

The median irradiation dose delivered to the prostate bed was 66 Gy (IQR 66–66) and to the pelvic lymph nodes was 46 Gy (46–46). The median duration of radiotherapy was 7 weeks (6·6–7·3), 7 weeks (6·7–7·3) in the adjuvant radiotherapy group and 7 weeks (6·6–7·3) in the salvage radiotherapy group. The duration of radiotherapy was longer than 8 weeks for six (5%) of 114 patients in the salvage radiotherapy group and seven (3%) of 203 patients in the adjuvant radiotherapy group. The extended duration of radiotherapy was due to acute toxic effects in all except two patients with intercurrent diseases (shingles and bowel obstruction).

We analysed efficacy in the 424 patients in the intention-to-treat population (212 patients from each study group). For the primary outcome analysis, 58 events were reported, 25 in the adjuvant radiotherapy group (seven with biochemical progression alone, six with biochemical progression associated with disease progression, one with disease progression without biochemical progression, and 11 with death as the first event) and 33 in the salvage radiotherapy group (13 with biochemical progression alone, nine with biochemical progression associated with disease progression, four with disease progression without biochemical progression, and seven with death as the first event). 5-year event-free survival was 92% (95% CI 86–95) in the adjuvant radiotherapy group and 90% (85–94) in the salvage radiotherapy group (HR 0·81, 95% CI 0·48–1·36; log-rank p=0·42; figure 2).

Only the first progressive events were recorded for the analysis. Metastasis-free survival data were not sufficiently mature for comparison of randomised study groups. 11 metastatic progression events were observed, three in the adjuvant radiotherapy group versus eight in the salvage radiotherapy group.

24 (6%) of 424 patients died, 14 (7%) of 212 in the adjuvant radiotherapy group and 10 (5%) of 212 in the salvage radiotherapy group. Four deaths, two in each study group, were due to prostate cancer. Additionally, seven (2%) died from second cancers, three (1%) from cardiovascular problems, one (<1%%) from an infection, and eight (2%) with cause of death unknown. 5-year overall survival was 96% (95% CI 92–98) in the adjuvant radiotherapy groups Arm and 99% (96–100) in the salvage radiotherapy group (HR 1·60, 95% CI 0·71–3·60; p=0·25; figure 2). Similar results were observed using prostatectomy date as the reference date for survival calculation (appendix p 1).

	Adjuvant radiotherapy group (n=212)	Salvage radiotherapy group (n=212)
Age at randomisation, years	63·7 (60·0–67·5)	64·0 (58·8–68·3)
Delay between radical prostatectomy and randomisation, months		
Mean (SD)	3·6 (0·9)	3·5 (0·9)
Median (IQR)	3·4 (3·1–4·1)	3·4 (3–4·1)
Missing data	1	0
Eastern Cooperative Oncology Group performance status		
0	195 (94%)	194 (94%)
1	12 (6%)	13 (6%)
Missing data	5	5
Gleason score		
≤6	21 (10%)	22 (10%)
7	173 (82%)	167 (79%)
3+4	110 (52%)	110 (52%)
4+3	63 (30%)	57 (27%)
≥8	17 (8%)	23 (11%)
Missing data	1	0
Pathological T stage		
pT3a	163 (77%)	163 (77%)
pT3b	45 (21%)	43 (20%)
pT4 (with bladder neck invaded)	3 (1%)	5 (2%)
Missing data	1	1
Pathological N stage		
pN0	153 (73%)	151 (71%)
pNx	58 (27%)	61 (29%)
Missing data	1	0
Hypertension		
Yes	91 (43%)	73 (34%)
No	120 (57%)	139 (66%)
Missing data	1	0
Diabetes		
Yes	30 (14%)	25 (12%)
No	180 (86%)	187 (88%)
Missing data	2	0
Anal-rectal surgery		
Yes	7 (3%)	4 (2%)
No	203 (97%)	208 (98%)
Missing data	2	0
Tobacco smoking		
Yes	33 (16%)	28 (14%)
No	169 (84%)	176 (86%)
Missing data	10	8

Data are median (IQR), n, or n (%), unless otherwise indicated.

Table 1: **Baseline characteristics of the intention-to-treat population**

Acute toxic effects were reported in 184 (87%) of 212 patients in the adjuvant radiotherapy group and 93 (44%) of 212 patients in the in the salvage radiotherapy group (table 2). Of these patients, ten reported adverse events of grade 3 or worse, six (3%) patients in the adjuvant radiotherapy group and four (2%) patients in

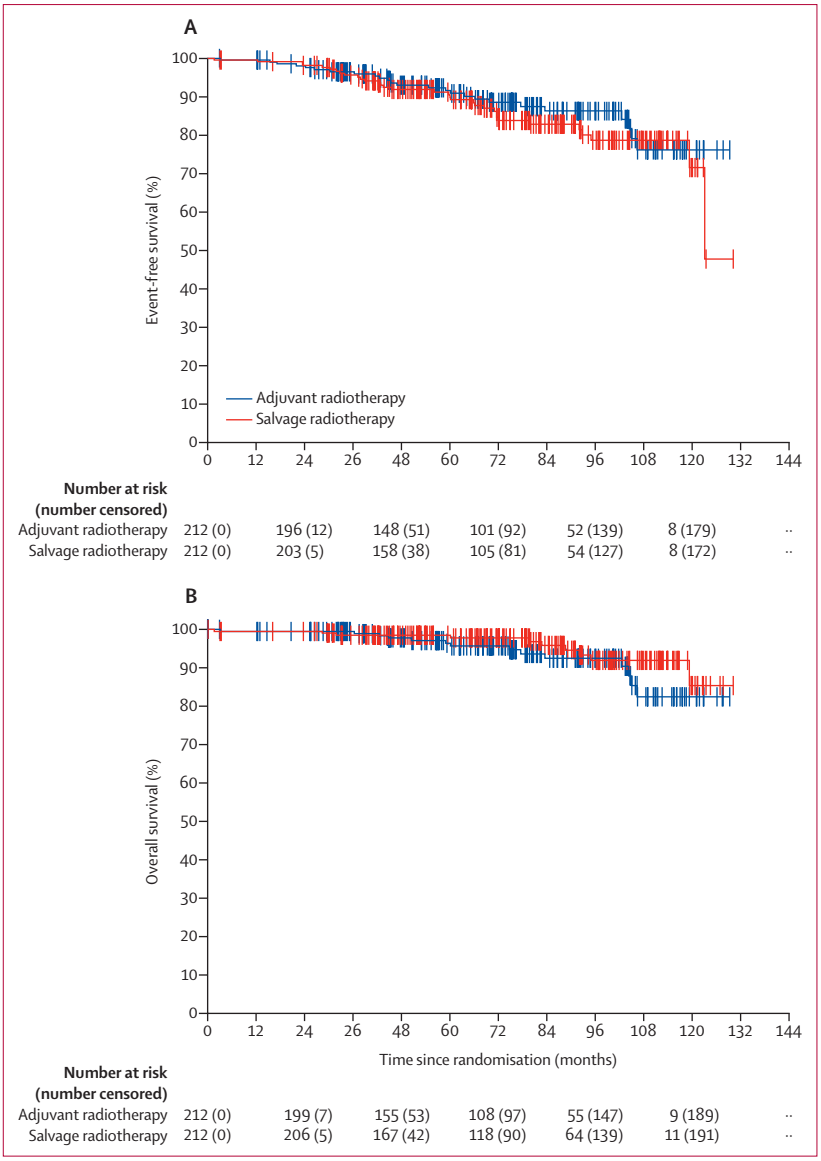

Figure 2: **Event-free survival (A) and overall survival (B) from the date of randomisation**

the salvage radiotherapy group, including three reported serious adverse events (urinary retention, bowel obstruction, and insulin-dependent diabetes). Acute adverse events potentially related to hormonal treatment were hot flushes, asthenia, and hyperhidrosis. Acute genitourinary adverse events of grade 2 or worse were noted in 37 (17%) of 212 patients in the adjuvant radiotherapy group and nine (4%) of 212 patients in the salvage radiotherapy group (p<0·0001). Acute gastrointestinal adverse events of grade 2 or worse were noted in 23 (11%) of 212 patients in the adjuvant radiotherapy group and nine (4%) of 212 patients in the salvage radiotherapy group (p=0·010).

Late toxic effects were reported in 196 (92%) of 212 patients in the adjuvant radiotherapy group and 90 (42%) of 212 patients in the salvage radiotherapy group. These events were grade 2 or worse in 125 (59%) patients in the adjuvant radiotherapy group and in 46 (22%) in the salvage radiotherapy group (table 3).

Late genitourinary adverse events were reported by 155 (73%) of 212 patients in the adjuvant radiotherapy group and 62 (29%) of 212 patients in the salvage radiotherapy group. Late genitourinary adverse events of grade 2 or worse were reported in 58 (27%) of 212 patients in the adjuvant radiotherapy group versus 14 (7%) of 212 patients in the salvage radiotherapy group (p<0·0001), and mainly comprised urinary incontinence, urinary frequency, and haematuria. Late genitourinary toxic effects of grade 3 or worse were reported in 12 (6%) of 212 patients in the adjuvant radiotherapy group and in three (1%) of 212 patients in the salvage radiotherapy group (p=0·018).

Late gastrointestinal adverse events were reported in 94 (44%) of 212 patients in the adjuvant radiotherapy group and in 42 (20%) of 212 patients in the salvage radiotherapy group. These late gastrointestinal toxic events were mainly grade 1–2 rectal haemorrhage, diarrhoea, and proctitis. Late gastrointestinal toxicities (grade 2 or worse) were noted in 17 (8%) of 212 patients in the adjuvant radiotherapy group and in 11 (5%) of 212 patients in the salvage radiotherapy group (p=0·24). Furthermore, late gastrointestinal adverse events of grade 3 or worse were reported in eight (4%) of 212 patients in the adjuvant radiotherapy group and in one (<1%) patient in the salvage radiotherapy group (p=0·044).

Late erectile dysfunction was reported in 77 (36%) of 212 patients in the adjuvant radiotherapy group and in 27 (13%) of 212 patients in the salvage radiotherapy group (p<0·0001). Among these patients, erectile dysfunction was grade 2 or worse in 60 (28%) of 212 in the adjuvant radiotherapy group and 17 (8%) of 212 in the salvage radiotherapy group (p<0·0001), and was grade 3 of worse in nine (4%) patients in the adjuvant radiotherapy group and three patients (1%) in the salvage radiotherapy group (p=0·079).

QOL was evaluated in patients with available data. QoL results for QLQ-C30 and QLQ-PR25 are presented in the appendix (pp 4–7). Functional dependence in older people was not analysed as only three patients completed the IADL scale at baseline.

The change in global health status from enrolment until the QLQ-C30 was completed after radiotherapy and before December, 2017, were similar between treatment groups (p=0·11; appendix pp 5–6). Similarly, the changes in the other domains of the QLQ-C30 were similar in the adjuvant radiotherapy group and salvage radiotherapy group. The functional scales of the QLQ-PR25 remained stable with time (appendix pp 5–6).

During the study, seven patients reported secondary cancers, four (2%) of 212 patients in the adjuvant radiotherapy group (muscle invasive bladder cancer 58 months after initiating radiotherapy, anal canal cancer 66 months after initiating radiotherapy, cancer of the

	Adjuvant radiotherapy group (n=212)			Salvage radiotherapy group (n=212)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Gastrointestinal disorders	112 (53%)	0	0	42 (20%)	1 (<1%)	0
Diarrhoea	60 (28%)	0	0	17 (8%)	0	0
Proctitis	27 (13%)	0	0	6 (3%)	0	0
Anal inflammation	22 (10%)	0	0	5 (2%)	0	0
Intestinal obstruction	0	0	0	0	1 (<1%)	0
General disorders and administration site conditions	100 (47%)	2 (1%)	0	42 (20%)	1 (<1%)	0
Hot flush	81 (38%)	2 (1%)	0	35 (17%)	1 (<1%)	0
Asthenia	41 (19%)	0	0	19 (9%)	0	0
Metabolism and nutrition disorders	0	1 (<1%)	0	0	0	0
Type 2 diabetes	0	1 (<1%)	0	0	0	0
Renal and urinary disorders	143 (67%)	2 (1%)	1 (<1%)	53 (25%)	1 (<1%)	0
Increased urinary frequency	106 (50%)	1 (<1%)	0	37 (17%)	1 (<1%)	0
Urinary incontinence	47 (22%)	1 (<1%)	0	10 (5%)	0	0
Dysuria	32 (15%)	0	0	13 (6%)	0	0
Urinary retention	1 (<1%)	0	1 (<1%)	0	0	0
Reproductive system and breast disorders	16 (8%)	1 (<1%)	0	10 (5%)	1 (<1%)	0
Erectile dysfunction	10 (5%)	1 (<1%)	0	6 (3%)	1 (<1%)	0
Skin and subcutaneous tissue disorders	25 (12%)	0	0	16 (8%)	0	0

There were no deaths due to acute adverse events.

Table 2: **Acute grade 1 or 2 toxic effects reported in ≥10% of patients and all grade 3 or worse toxic effects graded using the Common Terminology Criteria for Adverse Events version 3.0**

	Adjuvant radiotherapy group (n=212)					Salvage radiotherapy group (n=212)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Cardiac disorders	2 (1%)	2 (1%)	0	0	0	1 (<1%)	0	1 (<1%)	0	0
Angina (unstable)	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0
Gastrointestinal disorders	94 (44%)	86 (41%)	8 (4%)	0	0	42 (20%)	41 (20%)	1 (<1%)	0	0
Rectal haemorrhage	42 (20%)	38 (18%)	4 (2%)	0	0	16 (8%)	16 (8%)	0	0	0
Diarrhoea	25 (12%)	25 (12%)	0	0	0	14 (7%)	14 (7%)	0	0	0
Proctitis	18 (8%)	16 (8%)	2 (1%)	0	0	7 (3%)	7 (3%)	0	0	0
Haemorrhoids	7 (3%)	6 (3%)	1 (<1%)	0	0	2 (1%)	2 (1%)	0	0	0
Upper abdominal pain	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0
Diverticulitis	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Oesophagitis	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
General disorders and administration site conditions	80 (38%)	78 (37%)	2 (1%)	0	0	30 (14%)	30 (14%)	0	0	0
Hot flush	59 (28%)	58 (27%)	1 (<1%)	0	0	20 (9%)	20 (9%)	0	0	0
Asthenia	33 (16%)	33 (16%)	0	0	0	14 (7%)	14 (7%)	0	0	0
Lithiasis	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Infections and infestations	5 (2%)	4 (2%)	1 (<1%)	0	0	1 (<1%)	1 (<1%)	0	0	0
Urinary tract infections	2 (1%)	1 (<1%)	1 (<1%)	0	0	0	0	0	0	0
Injury, poisoning, and procedural complications	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Radiation cystitis	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Investigations	44 (21%)	43 (20%)	0	0	0	14 (7%)	13 (6%)	1 (<1%)	0	0
Weight decrease	41 (19%)	41 (19%)	0	0	0	14 (7%)	13 (6%)	1 (<1%)	0	0
Increased blood creatinine	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	25 (12%)	25 (12%)	0	0	0	11 (5%)	11 (5%)	0	0	0

(Table 3 continues on next page)

	Adjuvant radiotherapy group (n=212)					Salvage radiotherapy group (n=212)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)										
Benign, malignant, and unspecified neoplasms (including cyst and polyps)	18 (8%)	2 (1%)	11 (5%)	1 (<1%)	4 (2%)	11 (5%)	2 (1%)	5 (2%)	1 (<1%)	3 (1%)
Transitional cell carcinoma	5 (2%)	0	4 (2%)	1 (<1%)	0	1 (<1%)	0	1 (<1%)	0	0
Colorectal cancer	2 (1%)	0	1 (<1%)	0	1 (<1%)	2 (1%)	0	0	1 (<1%)	1 (<1%)
Pancreatic adenocarcinoma	0	0	0	0	0	3 (1%)	0	1 (<1%)	0	2 (1%)
Gastric adenocarcinoma	1 (<1%)	0	0	0	1 (<1%)	0	0	0	0	0
Adenocarcinoma of colon	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Anal cancer	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Bladder cancer	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Cholangiocarcinoma	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Chronic lymphocytic leukaemia	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Colorectal adenocarcinoma	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0
Laryngeal cancer	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Lung carcinoma cell type unspecified stage IV	1 (<1%)	0	0	0	1 (<1%)	0	0	0	0	0
Malignant lung neoplasm	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Malignant melanoma	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Myelodysplastic syndrome	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0
Plasma cell myeloma	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Rectal adenocarcinoma	1 (<1%)	0	0	0	1 (<1%)	0	0	0	0	0
Squamous cell carcinoma	0	0	0	0	0	1 (<1%)	0	1 (<1%)	0	0
Nervous system disorders	5 (2%)	4 (2%)	1 (<1%)	0	0	0	0	0	0	0
Generalised tonic-clonal seizure	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0
Renal and urinary disorders	155 (73%)	143 (67%)	12 (6%)	0	0	62 (29%)	59 (28%)	2 (1%)	1 (<1%)	0
Urinary incontinence	116 (55%)	111 (52%)	5 (2%)	0	0	35 (17%)	34 (16)	1 (<1%)	0	0
Urinary frequency	83 (39%)	83 (39%)	0	0	0	31 (15%)	31 (15%)	0	0	0
Haematuria	31 (15%)	26 (12%)	5 (2%)	0	0	10 (5%)	8 (4%)	1 (<1%)	1 (<1%)	0
Dysuria	21 (10%)	20 (9%)	1 (<1%)	0	0	12 (6%)	12 (6%)	0	0	0
Urinary retention	6 (3%)	5 (2%)	1 (<1%)	0	0	5 (2%)	5 (2%)	0	0	0
Micturition disorder	2 (1%)	1 (<1%)	1 (<1%)	0	0	0	0	0	0	0
Reproductive system and breast disorders	86 (41%)	77 (36%)	9 (4%)	0	0	30 (14%)	27 (13%)	3 (1%)	0	0
Erectile dysfunction	77 (36%)	68 (32%)	9 (4%)	0	0	27 (13%)	24 (11%)	3 (1%)	0	0
Skin and subcutaneous tissue disorders	13 (6%)	12 (6%)	1 (<1%)	0	0	4 (2%)	4 (2%)	0	0	0
Rash	5 (2%)	4 (2%)	1 (<1%)	0	0	0	0	0	0	0
Vascular disorders	22 (10%)	19 (9%)	2 (1%)	1 (<1%)	0	10 (5%)	8 (4%)	2 (1%)	0	0
Hypertension	18 (8%)	16 (8%)	2 (1%)	0	0	10 (5%)	8 (4%)	2 (1%)	0	0
Aortic dissection	1 (<1%)	0	0	1 (<1%)	0	0	0	0	0	0
Peripheral arterial occlusive disease	1 (<1%)	0	1 (<1%)	0	0	0	0	0	0	0

***Table 3*: Late toxicities of grade 1 or 2 reported in ≥10% of patients and all grade 3–5 reported in any group, by system organ class and type of toxicity graded using the Common Terminology Criteria for Adverse Events version 3.0**

larynx 86 months after initiating radiotherapy, and transitional cell carcinoma 87 months after initiating radiotherapy) and three (1%) of 212 patients in the salvage radiotherapy group (colorectal cancer 21 months after initiating radiotherapy, kidney cancer 28 months after initiating radiotherapy, and myelodysplastic syndrome 56 months after initiating radiotherapy).

Discussion

In this multicentre, open label, phase 3 randomised trial that compared adjuvant radiotherapy with salvage radiotherapy after radical prostatectomy, event-free survival was not significantly longer in patients who received adjuvant radiotherapy. The number of events in our study was unexpectedly low. Moreover, patients exposed to adjuvant radiotherapy had significantly more acute and late grade 2 or worse genitourinary toxic effects and more grade 2 or worse erectile dysfunction. Changes in global health status were similar between the study groups. Our results suggest that observation after radical prostatectomy, with early salvage radiotherapy when biochemical relapse occurs,

could spare around half of patients from radiotherapy and the related toxic effects.

At 5 years, more than 90% of patients in the adjuvant radiotherapy group had not progressed. In the adjuvant setting, three randomised trials assessing postoperative radiotherapy have been completed.[2,3,15] First, the EORTC 22911 trial[15] randomly assigned 1005 patients (pT2 R1 or pT3N0) to either adjuvant radiotherapy within 4 months of radical prostatectomy or a wait-and-see strategy. After a median follow-up of 5 years, biochemical progression-free survival was significantly extended with adjuvant radiotherapy (74·0%, 98% CI 68·7–79·3) compared with the wait-and-see strategy (52·6%, 46·6–58·5, p=0·0001). Second, the ARO 96-02 trial[2] randomly assigned 307 men with pT3N0 disease at radical prostatectomy to adjuvant radiotherapy or observation. Biochemical progression-free survival after 5 years was significantly extended in patients who received adjuvant radiotherapy (72%, 95% CI 65–81 *vs* 54%, 45–63; HR 0·53, 95% CI 0·37–0·79; p=0·0015). This benefit was confirmed after a median follow-up of 110 months, when the probability of patients being without biochemical progression was 20% higher with adjuvant radiotherapy compared with observation. Finally, the SWOG S8794 trial[3] randomly assigned 431 patients with pT3N0 prostate cancer to adjuvant radiotherapy or initial observation. After a median follow-up of 10·2 years, patients who received adjuvant radiotherapy had a reduced 10-year risk of biochemical treatment progression (42% *vs* 72%), local progression (7% *vs* 20%), and distant progression (4% *vs* 12%) compared with patients assigned to observation. Nevertheless, these results are difficult to interpret because of the lack of timely salvage radiotherapy in the control groups from these trials.[2,3,15] The low number of events in the GETUG-AFU 17 trial compared with adjuvant radiotherapy groups from previous studies[3,15,16] could be due to differences in populations, heterogeneity in radiation techniques, and the prescribed dose given to the prostate bed.[17]

Furthermore, in localised prostate cancer, adding hormonal therapy to radiotherapy reduces biochemical relapse compared with radiotherapy alone.[18–20] In the adjuvant setting, hormonal therapy is not a standard of care, possibly improving event-free survival in our study.[21] The RADICALS HD trial (NCT00541047) randomly assigned patients to radiotherapy alone (early or deferred), radiotherapy with 6 months of hormonal treatment, or radiotherapy with 24 months of hormonal treatment. The primary outcome is disease-specific mortality, and this trial could provide an further information concerning the place of postoperative hormonal therapy in this setting.

Early salvage radiotherapy can be curative for patients with biochemical relapse after radical prostatectomy. Whether salvage radiotherapy should be administered alone or combined with hormonal therapy remains unclear. In the past decade, three randomised studies have evaluated hormonal therapy in men receiving salvage radiotherapy after radical prostatectomy. RTOG 9601,[13] a phase 3 randomised controlled trial showed that 24 months of bicalutamide extended survival (HR 0·77, 95% CI 0·59–0·99). The GETUG-AFU 16 study[22] showed that 5-year progression-free survival was prolonged with salvage radiotherapy plus 6 months of goserelin compared with salvage radiotherapy alone (80%, 95% CI 75–84 *vs* 62%, 95% CI 57–67; HR 0·50, 95% CI 0·38–0·66; p<0·0001). These results were supported by 120-month metastasis-free survival in favour of the combined radiotherapy group.[23] The NRG Oncology/RTOG 0534 SPPORT trial[24] randomly assigned 1736 patients to either salvage radiotherapy to the prostate bed, salvage radiotherapy to the prostate bed with short-term hormonal therapy, or salvage radiotherapy to the prostate bed and the pelvic lymph nodes with short-term hormonal therapy. 5-year progression-free survival improved from 71% to 87% when adding both short-term hormonal therapy and pelvic lymph nodes to prostate bed radiotherapy (HR 0·45, 95% CI 0·34–0·61).[24] Similar to the results in the combined radiotherapy groups from these three trials, we observed 5-year event-free survival of 90% (95% CI 85–94) in our salvage radiotherapy group.[13,22,24]

The PSA level before salvage radiotherapy might predict who will most benefit from salvage radiotherapy and whether hormonal therapy should be added in terms of PSA-driven and long-term outcomes. The GETUG-AFU 16 multivariate analysis showed that adding goserelin to salvage radiotherapy was beneficial, even in the low-risk group, defined as patients with a Gleason score lower than 8, positive surgical margins, PSA doubling time at relapse of more than 6 months, and no seminal vesicle involvement.[23] However, in an analysis from RTOG 9601[25] that examined 389 patients who relapsed after radical prostatectomy with PSA levels of 0·6 ng/mL or less, which is closer to today's standard for early salvage radiotherapy, patients were almost twice as likely to die from non-cancer causes when bicalutamide was added (HR 1·94, 95% CI 1·17–3·20); p=0·009). 148 patients with the lowest PSA levels (0·2–0·3 ng/mL) had the greatest risk of death (HR 4·14, 95% CI 1·57–10·89).[25] In our study, the median PSA level triggering salvage radiotherapy and short-duration hormonal treatment was 0·24 ng/mL, lower than that reported in the Spratt and colleagues analysis.[25] Therefore, the added value of hormonal treatment for patients in our early salvage radiotherapy group is debatable.

We showed that adjuvant radiotherapy increased the risk of genitourinary and sexual morbidity compared with salvage radiotherapy. Our results support those from three studies that compared adjuvant radiotherapy with observation,[2,4,26] in which patients allocated to adjuvant radiotherapy reported increased genitourinary toxic effects of grade 2 or worse. Our incidence of late grade 2 or worse genitourinary toxicities is in accordance with that reported in the adjuvant radiotherapy group of the

EORTC 22911 study, in which genitourinary toxic effects of grade 2 or worse were significantly higher with adjuvant radiotherapy compared with observation (21·3% [95% CI 17·5–16·6] *vs* 13·5% [10·4–16·6]; p=0·003).[4] The EORTC 22911 study[2] assessed acute toxicity using the WHO scale and late toxic effects with the Late Morbidity Scoring Scheme (RTOG/EORTC), making comparison with our study difficult. By contrast, the ARO 96–02/AUO AP 09/95 study[16] reported that late genitourinary toxic effects (per the RTOG scale) were scarce, although more frequent with adjuvant radiotherapy. However, urinary incontinence, which was frequently observed in our study, is not included in the RTOG/EORTC scoring scheme. Another randomised trial also reported high rates of toxicity with adjuvant radiotherapy compared with radical prostatectomy alone.[27] The LENT SOMA scale, which was used for grading genitourinary toxicity in this trial, tends to higher grades compared to the CTCAE criteria used in our study.[27]

For safety analyses, we should consider the total dose of radiotherapy administered in previous studies. We delivered more than the 60 Gy given in the EORTC 22911 and SWOG S8794 trials. This increased dose of radiotherapy has been associated with increased genitourinary toxicity.[28] We should also highlight the radiotherapy techniques used when analysing these results. Indeed, in the SWOG S8794 trial, done more than 25 years ago, details concerning radiotherapy were not reported.[3] The EORTC 22911 study used linear accelerators (5–25 MV), using an isocentric technique with non-3D planning.[15] The ARO 96–02/AUO AP 09/95 study was the first in this postoperative setting to propose a 3D radiotherapy approach.[16] The use of intensity-modulated radiotherapy in around 40% of the patients in our study could explain our acceptable incidence of grade 2 or worse genitourinary toxic effects despite the increased radiotherapy dose.[17,29] Since radiotherapy was delayed with salvage radiotherapy, more patients in the salvage radiotherapy group in our study benefited from intensity-modulated radiotherapy as this technique became more available in France.[30] As we showed in our results, the delay between radical prostatectomy and postoperative radiotherapy influenced the risk of long-term adverse events. Recovery from urinary incontinence after radical prostatectomy occurs at a lower rate in patients after adjuvant radiotherapy compared with salvage radiotherapy.[5,6] Our data are also concordant with GETUG-AFU 16 results,[22] which showed late genitourinary adverse events of grade 3 or worse in 7% of patients in the combined salvage radiotherapy group. Only four patients in our salvage radiotherapy group had grade 3 or worse genitourinary adverse events, supporting good tolerance of the delayed radiotherapy approach.

Reported gastrointestinal toxic effects were predominantly grade 1–2, without a significant difference between the study groups. Likewise, the EORTC 22911 study found around 5% of 10-year grade 3 gastrointestinal toxic effects with adjuvant radiotherapy.[4] In the GETUG-AFU 16 study, grade 3 or worse gastrointestinal events were rare (2%) in the salvage radiotherapy combined with hormonal therapy treatment group, which was similar to our salvage radiotherapy group.[22] These incidences are similar to those reported in the current study. Similar to the genitourinary toxicity analysis, the use of intensity-modulated radiotheray[31] and the toxicity scale used might also affect the interpretation of our results compared with other trials.[2,4]

We observed that grade 2 or worse erectile dysfunction was significantly worse in the adjuvant radiotherapy group compared with the salvage radiotherapy group. Only the SWOG S8794 trial reported data on sexual function.[26] van Stam and colleagues[5] showed that men receiving postoperative radiotherapy more than 6 months after radical prostatectomy had better sexual satisfaction than did those treated within 6 months of surgery, confirming the association between timing of postoperative radiotherapy and sexual tolerance. Overall, we expect increased acute and late adverse events of all grades and decreased QOL in GETUG-AFU 17 compared with studies without hormonal therapy, due to the 6 months of hormonal therapy initially delivered with radiotherapy.[2,4,26,27]

Our analysis of the QLQ-C30 and QLQ-PR25 data found no significant differences between the study group, in accordance with the SWOG S8794 trial that reported no differences in intermediate-term QOL between men receiving adjuvant radiotherapy or with initial observation.[26] Akthar and colleagues[32] reported favourable long-term QOL and late toxicity after postoperative radiotherapy. Patient QOL was assessed in men treated with intensity-modulated radiotherapy after radical prostatectomy, using the Expanded Prostate Cancer Index Composite questionnaire.[32]

Our trial has some limitations. Our analysis is limited by patient accrual not reaching the target, giving a lack of statistical power to reach conclusions on efficacy. Additionally, the trial was not powered to study long-term outcomes such as overall survival and metastasis-free survival, even with longer follow-up. Event-free survival, particularly when PSA driven, is not a surrogate for longer-term outcomes.[33] Previous trials of adjuvant radiotherapy versus observation showed large improvements in biochemical progression with radiotherapy, without showing a clear benefit in long-term outcomes.[2,3,15] Therefore, it is very unlikely that our results will change consistently in favour of adjuvant radiotherapy with longer follow-up. Finally, our results could be questionable in terms of the addition of androgen deprivation to postoperative radiotherapy, highlighting potential overtreatment in both study groups.

In conclusion, we found no difference in event-free survival between patients treated with adjuvant radiotherapy and patients treated with salvage radiotherapy, although our analysis lacked statistical power. Our results show that salvage radiotherapy could spare men from receiving radiotherapy and its associated toxic effects.

Thus, questions over the best postoperative policy to propose after radical prostatectomy and which patients could still benefit from adjuvant radiotherapy remain valid. Publication of the prospective ARTISTIC meta-analysis,[14] including the RAVES,[9] RADICALS RT,[8] and GETUG-AFU 17 trials, will assess the effect of adjuvant radiotherapy versus early salvage radiotherapy on early and long-term, outcomes in this patient group; because of the restricted power in these trials individually, ARTISTIC is a unique opportunity to evaluate the effect of radiotherapy timing across patient subgroups.

Contributors

PR was the principal investigators for the study. SC and PR designed the trial. PS, SC, IL, NM, AB, SS, DP, MSA, OG, PGC, MSi, PBe, PBa, YB, DA, MSo, and PR contributed to the acquisition, analysis, and interpretation of the data. MB and SC were responsible for trial management, and the acquisition and analysis of data. The manuscript was drafted by PS, SC, and PR, and all other authors critically reviewed and revised the manuscript. All authors approved the final version of the manuscript before submission.

Declaration of interests

PS and IL declaresreceiving honoraria, providing medical advice, and participating on boards for Astellas, Bayer, Bouchara, Ferring, Ipsen, Janssen, Sanofi, and Takeda. SS declares funding from Jansen, AstraZeneca, and Astellas, and personal fees and non-financial support from Jansen, Astellas, Ipsen, Takeda, Bouchara-Recordati, and Sanofi. DA received honoraria from NovaGray. All other authors declare no competing interests.

Data sharing

Unicancer (Paris, France) will share de-identified individual data that underlie the results reported in this Article under the following conditions: the data shared will be limited to that required for independent mandated verification of the published results, the reviewer will need authorisation from Unicancer for personal access, and data will only be transferred after signing of a data access agreement. A decision concerning the sharing of other study documents, including the protocol and statistical analysis plan, will be examined upon request. Unicancer will consider access to study data upon written detailed request, from 6 months until 5 years after the publication of this Article.

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