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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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Original article

Title: The GETUG-AFU 17 study: a phase III randomised trial comparing adjuvant versus early salvage radiotherapy, combined with short-term androgen deprivation therapy, in men with localised prostate cancer after radical prostatectomy

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Summary

Background Adjuvant radiotherapy (aRT) reduces the risk of biochemical failure in prostate cancer patients following radical prostatectomy (RP). The GETUG-AFU 17 study, compared efficacy and safety of aRT versus early salvage RT (sRT), combined with short-term hormonal therapy.

Methods This open-label, multicentre, phase III, randomised controlled trial, performed in 46 French centres. Patients, ≥ 18 years old and Eastern Cooperative Oncology Group performance status ≤ 1 , with pT3-4 and positive margins, pNx or pN0, with post-operative PSA ≤ 0.1 ng/mL were randomised (by minimisation; 1:1) after RP, to aRT or observation with sRT, combined with 6 months of triptorelin. The primary endpoint was event-free survival (EFS). The incidence of acute and late toxicities were graded using the CTCAE v3.0. This trial is registered with ClinicalTrials.gov number NCT00667069.

Findings Between March 07, 2008, and June 23, 2016, 424 patients were enrolled. We planned to enrol 718 patients. Enrolment was stopped early due to unexpectedly low event rates. Baseline characteristics were well balanced between arms. Median follow-up was 75.3 months (IQR 50–100). At analysis, 115/212 patients (54%) in the sRT Arm had initiated treatment. With 58 events, the 5-year EFS was 92% (95% CI 86–95) in the aRT Arm and 90% (95% CI 85–94) in the sRT Arm (HR=0.81 [95% CI 0.48–1.36]; log-rank test $p=0.42$). Acute grade ≥ 3 toxicities occurred in 6 patients (3%) in the aRT Arm and in 4 (2%) in the sRT Arm. Late grade ≥ 2 genitourinary toxicities were reported in 125 patients (59%) in the aRT Arm and in 46 (22%) in the sRT Arm. Late grade ≥ 2 genitourinary toxicities were worse in the aRT Arm (27% vs 7%; $p<0.0001$). Grade ≥ 2 erectile dysfunction was worse in the aRT Arm ($p<0.0001$).

Interpretation The GETUG-AFU 17 study, although lacking statistical power, showed no benefit in EFS for aRT compared to sRT. aRT increased the risk of genitourinary toxicity and erectile dysfunction. A policy of early sRT could spare men RT and the associated toxicity.

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Key words Adjuvant radiotherapy, salvage radiotherapy, prostate cancer, radical prostatectomy, late toxicity, quality of life.

Key message In the GETUG-AFU 17 multicentre, open label, phase III randomised study, we report no difference in EFS rates between aRT and sRT. aRT significantly increased grade ≥ 2

genitourinary toxicity, and grade ≥ 2 erectile dysfunction compared to sRT. QoL was similar in the arms. Thus, sRT could spare men from RT and its toxicity. The sRT approach should be considered as standard if aRT is not superior to sRT in terms of efficacy.

Research in context

Evidence before this study

Randomised trials comparing adjuvant radiotherapy to observation after radical prostatectomy reported better long-term biochemical control rate in favour of radiotherapy. Approximately a third of patients allocated observation did not have disease relapse, so adjuvant irradiation for all patients leads to overtreatment. In addition to controversial long-term outcomes results, the use of adjuvant radiotherapy in daily practice has been limited by the increased incidence of toxicities reported. In contrast, despite only retrospective evidence, observation then salvage radiotherapy has increasingly been adopted. So, the optimal timing of postoperative radiotherapy remains controversial.

Added value of the study

GETUG-AFU 17 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 toxicity. No systematic literature search was done.

Implications of all the available evidence

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

Introduction

Radical prostatectomy (RP) is a standard treatment for patients with localized prostate cancer, demonstrating excellent long-term outcomes.¹ However, a third of the patients will have pathological high-risk features including extra capsular extension, seminal vesicle involvement and/or positive surgical margins (R1) on the final pathology. These risks factors increase the likelihood of biochemical recurrence, providing a rationale for phase III adjuvant radiotherapy (aRT) trials.²⁻⁴

The Southwest Oncology Group (SWOG) S8794,³ the European Organisation for Research and Treatment of Cancer (EORTC) 22911,⁴ and the German Cancer Society ARO 96-02/AUO AP 09/95² prospective randomised studies compared aRT, given to the prostate bed, without androgen deprivation therapy, to observation after RP. These studies, which included pathological high-risk patients, reported better long-term biochemical control rate in favour of aRT, and controversial long-term outcomes results.²⁻⁴ Moreover, these trials are difficult to interpret, because less than half of patients who recurred in the observation arms received salvage radiotherapy (sRT), a standard in the contemporary era.

In these studies assessing aRT, approximately a third of patients allocated observation did not have disease relapse. Indeed, we risk overtreating patients by proposing aRT to everybody.^{5,6} The use of aRT, in daily practice, has also been limited by the increased incidence of toxicities and diminished quality of life (QoL) reported.^{6,7} In contrast, despite only retrospective evidence supporting efficacy, observation then sRT, proposed at biochemical failure, has increasingly been adopted.⁷ So, the optimal timing of postoperative radiotherapy (RT) remains controversial. Three large multicentre, open-label trials: RADICALS-RT (NCT00541047), RAVES (NCT00860652), and GETUG-AFU 17 (NCT00667069) were designed to assess whether delayed sRT, given at biochemical relapse, or immediate aRT was more appropriate in this setting. We conducted the GETUG-AFU 17 trial to compare aRT versus early sRT following RP, combined with short-term hormonal therapy, in terms of oncological outcomes and tolerance.

Methods

Study design and participants

GETUG-AFU 17 is a randomised, open label, multicentre phase III trial. Men aged ≥ 18 years and with Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 , with localised adenocarcinoma of the prostate, treated with RP with or without pelvic lymph node dissection, pathologically-staged pT3a, pT3b, or pT4a (with bladder neck invasion), pNx (without pelvic lymph nodes dissection) or pN0 (with negative lymph nodes dissection) and with R1 disease were eligible. The PSA level after RP had to be ≤ 0.1 ng/mL and confirmed by a second measurement after 4 weeks. Patients who had surgical or chemical castration, or abnormal testosterone level were ineligible. Patients with positive lymph nodes at pathology were not eligible. The delay between RP and enrolment was limited to 6 months. The study was conducted in accordance with the declaration of Helsinki and received regulatory and ethics approvals. All patients provided written informed consent before participation.

Randomisation

Eligible patients were randomly allocated (1:1) to either immediate aRT or delayed sRT at the time of biochemical relapse. Clinicians and patients were not masked to the allocation of study treatment. Furthermore, when the GETUG-AFU 17 study was designed, there was evidence that adding short-term hormonal therapy to RT significantly delayed biochemical relapse in patients with localised prostate cancer.^{8,9} Thus, the investigators decided that postoperative RT was combined with short-term hormonal therapy in both arms. Randomisation, by minimisation, was performed using the web-based, TenAléa software, and stratified by Gleason score (with predominant grade of 4 or not), pT stage (pT3a/pT4a versus pT3b), and by centre.

Procedures

In both arms, combined therapy with RT and concomitant hormonal therapy was planned. Hormonal therapy was planned to start within the 2 months before RT. Patients allocated aRT initiated treatment between 3 and 6 months after RP. Those randomly allocated to the sRT Arm started when biochemical relapse occurred.¹⁰

RT was planned in a supine position, the patient having 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.¹¹ Pelvic lymph nodes could be included in a CTV 2, at the physician's discretion. The planned target volume (PTV) was created with an

anisotropic margins: 5 mm posteriorly and 7-10 mm in all others direction. Both three-dimensional conformal RT and intensity-modulated RT were allowed. Three-dimensional conformal RT comprised irradiation in 4 to 6 fields with 6-MV photons. Image-guided RT, in all patients, was based on daily orthogonal kilovoltage radiography or cone-beam computed tomography to verify at least bony alignment. All patients had RT 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), administered by intramuscular injection every 3 months.

All patients had weekly study visits during RT. Following randomisation, visits were planned at 3 and 6 months after completing RT, then every 6 months during the first 2·5 years, and then annually, in both treatment arms. During visits, tumour progression/relapse were assessed by PSA assay, and if PSA had increased, with computed tomography and bone scans. Toxicity was assessed throughout the study. Data concerning adverse events that occurred, grade by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, were collected at each study visit. Patients were considered as having discontinued the study if they withdrew consent or died.

Patients completed the 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 RT, to analyse the QoL variation from baseline in all patients. The EORTC QLQ-C30 assesses 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 QLQ-PR25 assesses five domains: urinary symptoms, bowel symptoms, hormone treatment-related symptoms, sexual activity, and sexual function.

Outcomes

The primary outcome was the event-free survival (EFS): the time interval from randomisation to first documented event, either disease relapse (loco-regional or metastatic), biochemical progression, or death. Biochemical progression was defined as either a PSA level $\geq 0\cdot 4$ ng/mL at least 6 months after completing aRT or sRT, confirmed after 4 weeks, or a PSA level ≥ 1 ng/mL at any time after randomisation, or clinical progression or death from any cause.

Biochemical relapse before initiating sRT, not considered as an event, was defined as a PSA level >0.2 ng/mL confirmed after 4 weeks.¹⁰

The date of the initial increased PSA level was considered the date of biochemical progression. Secondary efficacy outcomes were overall survival (OS) and metastasis-free survival (MFS). MFS was defined as time interval from randomisation to the first documented metastasis or death from any cause. OS was defined as the time interval from randomisation to death from any cause. Secondary safety outcomes included the incidence of acute and late toxicities (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0), QoL evolution from baseline until December 2017 (QLQ-C30 and QLQ-PR25 instruments), and functional dependence in patients older than 75 years (Instrument Activities of Daily Living scale [IADL]). Acute toxicities were those reported during RT up until 3 months after completing RT. All toxicities reported after this time, up until 5 years after RT, were considered as late toxicities. The QoL and IADL instruments were to be completed at enrolment and then at 2 and 5 years after treatment. In addition, patients complete these instruments in December 2017 to allow for the analysis of acute and late toxicities, as well as QoL, reported here.

Statistical analysis

The efficacy and safety analyses were to be performed in the intent-to-treat (ITT) population: all randomised patients according to treatment arm. QoL was analysed in patients with available data. Qualitative data were to be reported as frequency and percentages. Quantitative data were to be reported with mean and associated standard deviation (SD) and median with interquartile range (IQR).

In time-to-event analyses, the date of randomisation would be considered as the date of reference. Patients without events were censored at the last date known to be alive. The median follow-up was to be estimated using the reverse Kaplan-Meier method. EFS, MFS, and OS were to be analysed in each study arm using the Kaplan-Meier method. The survival in the study arms were to be compared using the bilateral logrank test, with the statistical significance level set at 5%. The results were to be presented as rates at various time points with their associated 95% confidence intervals (CI). To assess potential bias resulting from the 3 to 6 months delay between RP and randomisation (3-6 months), a *post-hoc* sensitivity analysis for EFS and OS using the date of RP as reference date for survival were performed.

Acute toxicities (those reported from the start of radiotherapy until 3 months after the last dose) and late toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Statistical comparisons of the incidence of adverse events are exploratory.

The global quality of life scores, as well as each scale/domain of the QLQ-C30 and QLQ-PR25 were calculated according to the scoring manual. Missing data was not replaced. Absolute individual variations from baseline were calculated and median changes from baseline until December 2017 were compared between arms using a non-parametric Kruskal-Wallis test.

The study was designed to show a 10% increase in the 5-year EFS rate, from 60% with early sRT to 70% with aRT (HR=0.70). The α -risk was fixed at 5% and the power at 80%. Under these hypotheses, 242 EFS events were needed at final analysis. Enrolment was planned for 5 years with a final analysis planned 2.5 year after the last patient enrolled. Consequently, the study planned to enrol 718 patients, 359 in each arm. An interim analysis for efficacy and safety was planned after 121 events had occurred. The Peto method for α -adjustment was planned, i.e. a conservative α -threshold of 0.001 at interim analysis to maintain a 5% α -level at final analysis. P-values <0.05 were considered as statistically significant for all outcomes. The study was overseen by a trial steering committee and an independent data monitoring committee (IDMC). Statistical analyses were performed using the SAS software v9.4.

This trial is registered at EudraCT (2007-002495-34) and at ClinicalTrials.gov (NCT00667069).

Role of the funding source

Unicancer, the study sponsor, was responsible for study design, as well as the collection, analysis, and interpretation of the data. In addition, Unicancer was responsible for writing the report and for the decision to submit this article. PS and PR had access to all of the data and made the final decision to submit this article for publication. Ipsen provided financial support for the study, and 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 07, 2008, and June 23, 2016, 424 patients were enrolled from 46 French centres (see appendix p 2-3). The protocol planned to enrol 718 patients, 359 in each study arm. However, on May 20, 2016, an IDMC, recommended early termination of enrolment. At that time, only 12 of the 242 events awaited for the primary outcome analysis had been reported. Consequently, the planned analysis would still require years. Finally, as the GETUG-AFU group was contacted by the RADICALS team to participate in the ARTISTIC meta-analysis it was decided to use the meta-analysis as the time point for our study analysis. When enrolment was stopped, 424 patients had been randomly allocated: 212 to the aRT Arm and 212 to the sRT Arm. Figure 1 presents the study flow chart. Baseline characteristics (table 1) were well balanced between arms except for hypertension that was more frequent in the aRT Arm. In the study population (n=424), 389 patients (94%) were ECOG performance status 0, with a median age at randomisation of 63.8 years (interquartile range [IQR]: 59.7–67.9). The majority of patients had pT3a (326 patients, 77%), pN0 (304, 72%), and a Gleason score of 7 (340, 80%). Hypertension was observed in 164 patients (40%).

(figure 1)

(table 1)

At database lock, on December 19, 2019, median follow-up from randomisation was 75 months (IQR 50–100): 74 (IQR 47–100) in the aRT Arm and 78 (IQR 52–101) in the sRT Arm. In the aRT Arm, 205/212 patients (97%) had started treatment: 200 with RT combined with hormonal therapy, 3 with RT alone, and 2 with only hormonal therapy. Five patients withdrew their consent, one patient was excluded due to intercurrent event (inguinal surgery), and another had missing data. In the sRT Arm, 115/212 patients (54%) had initiated study treatment related to biochemical relapse: 107 with RT combined with hormonal therapy, 7 with RT alone, 1 with only hormonal therapy. Also, 8 patients never started treatment due to consent withdrawal (n=3), investigator decision (n=1), patient decision (n=1), and non-neoplastic death (n=3). Furthermore, 7 patients were lost to follow-up and 82 were still monitored. The median PSA level was 0.24 ng/mL (IQR 0.22–0.29) when sRT was started. The median delay between randomisation and RT was 1.1 months in the aRT Arm and 23 months in the sRT Arm. In the aRT Arm, for patients receiving RT, 61 (30%) had intensity-modulated RT and 141 (70%) 3D-conformal RT; data was missing for 1 patient. Similarly, in the sRT Arm, 54 (48%) had intensity-modulated RT; data was missing for 1 patient. All treated patients received RT to the

prostate bed. Pelvic lymph nodes were irradiated in 36 of 203 (18%) patients in the aRT Arm and in 27 of the 114 treated patients (24%) in the sRT Arm.

The median irradiation dose delivered to the prostate bed was 66 Gy (IQR 66–66) and to the pelvic lymph nodes was 46 Gy (IQR 46–46). The median duration of RT was 7 weeks (IQR 6.6–7.3): 7 weeks (IQR 6.7–7.3) in both arms. The duration of RT was longer than 8 weeks for 6 patients (5%) with sRT and for 7 (3%) with aRT. The extended duration of RT was due to acute toxicities in all except 2 patients with intercurrent diseases: shingles and bowel obstruction.

We analysed efficacy in the 424 patients in the ITT population: 212 patients in both the aRT and sRT Arms. For the primary outcome analysis, 58 events were reported: 25 in the aRT Arm (7 with biochemical progression alone, 6 biochemical progression associated with disease progression, 1 disease progression without biochemical progression, and 11 with death as first event) and 33 in the sRT Arm (13 with biochemical progression alone, 9 biochemical progression associated to disease progression, 4 disease progression without biochemical progression and 7 with death as first event). The 5-year EFS rate was 92% (95% CI 86–95) in the aRT Arm and 90% (95% CI 85–94) in the sRT Arm (HR=0.81 [95% CI 0.48–1.36]; log-rank test $p=0.42$; figure 2A).

At analysis, only the first progressive events were recorded. MFS was not sufficiently mature for comparison of randomised arms. Eleven metastatic progressions were observed, 3 in aRT Arm versus 8 in sRT Arm.

Deaths were observed in 24 patients (6%): 14 (7%) in the aRT Arm and 10 (5%) in the sRT Arm. Four of them were due to prostate cancer, 2 in each arm. In addition, 7 patients died from second cancers, 3 from cardiovascular problems, 1 from an infection, 1 from a trauma after falling, and 8 patients with cause of death unknown. The 5-year OS rate was 96% (95% CI 92–98) in the aRT Arm and 99% (95% CI 96–100) in the sRT Arm (HR=1.60 [95% CI 0.71–3.60]; $p=0.25$; figure 2B). Similar results were observed using prostatectomy date as reference date for survival calculation (appendix p 1).

At analysis, in the ITT population ($n=424$), acute toxicities were reported in 184 patients (87%) in the aRT Arm ($n=212$) and 93 (44%) in the sRT Arm ($n=212$). Of these, 10 reported AEs of grade ≥ 3 including 3 reported serious adverse events (a urinary retention, a bowel obstruction, and an insulin-dependent diabetes). The most frequently acute toxicities are detailed in the table

2. Acute AEs, potentially related to hormonal treatment, were hot flushes, asthenia, and hyperhidrosis. Acute genitourinary AEs of grade ≥ 2 were noted in 37 patients (17%) in the aRT Arm and in 9 (4%) in the sRT Arm ($p < 0.0001$). Acute gastrointestinal AEs of grade ≥ 2 were noted in 23 patients (11%) in the aRT Arm and in 9 (4%) in the sRT Arm ($p = 0.010$).

(table 2)

Late toxicities were reported in 196 patients (92%) in the aRT Arm and in 90 (42%) in the sRT Arm. These were of grade ≥ 2 in 125 patients (59%) in the aRT Arm and in 46 (22%) in the sRT Arm. The most frequently occurring late toxicities are detailed in table 3.

Late genitourinary adverse events, of all grades, were reported by 155 patients (73%) in the aRT Arm and by 62 (29%) in the sRT Arm. Those of grade ≥ 2 in 58 patients (27%) in the aRT Arm versus 14 (7%) in the sRT Arm ($p < 0.0001$): mainly urinary incontinence, urinary frequency, and haematuria. Late genitourinary toxicities of grade ≥ 3 were reported in 12 patients (6%) in the aRT Arm and in 3 (1%) in the sRT Arm ($p = 0.018$).

Late gastrointestinal adverse events, all grades were reported in 94 patients (44%) in the aRT Arm and in 42 (20%) in the sRT Arm. These late gastrointestinal toxicities were mainly grade 1-2 rectal haemorrhage, diarrhoea and proctitis in both treatment arms. Late gastrointestinal toxicities (grade ≥ 2) were noted in 17 patients (8%) in the aRT Arm and in 11 (5%) in the sRT Arm ($p = 0.24$). Furthermore, late gastrointestinal AEs of grade ≥ 3 were reported in 8 patients (4%) in the aRT Arm and in 1 patients ($< 1\%$) in the sRT Arm ($p = 0.044$).

The late erectile dysfunction of all grades were reported in 77 patients (36%) in the aRT Arm and in 27 (13%) in the sRT Arm ($p < 0.0001$). Among these, erectile dysfunction was of grade ≥ 2 in 60 patients (28%) in the aRT Arm and in 17 (8%) in the sRT Arm ($p < 0.0001$); and of grade ≥ 3 in 9 (4%) and 3 (1%), respectively ($p = 0.079$).

(table 3)

The evolution of QoL was evaluated in patients with data, see figure 1. QoL results for QLQ-C30 and QLQ-PR25 are available in the appendix p 4-7. The functional dependence in the elderly was not analysed since only 3 patients completed the IADL scale at baseline.

The change in global health status from enrolment until the QLQ-C30 completed after RT and before December 2017 were similar in the treatments arms ($p = 0.11$). Similarly, the changes in the other domains of the QLQ-C30 were similar with aRT and sRT. The functional scales of the QLQ-PR25 remained stable with time.

During the study, 7 patients reported second cancers: 4 in the aRT Arm and 3 in the sRT Arm. In the aRT Arm, patients reported a muscle invasive bladder cancer, an anal canal cancer, a cancer of the larynx, and a transitional cell carcinoma. In the sRT Arm, patients reported a colorectal cancer, a kidney cancer, and a myelodysplastic syndrome. The time intervals to second cancers were 58, 66, 86, and 87 months after initiating RT in the aRT Arm and 21, 28, and 56 months in the sRT Arm.

Discussion

In the GETUG-AFU 17 multicentre, open label, phase III randomised study comparing aRT to sRT after RP, EFS was not significantly prolonged with aRT. The rate of events in our study was unexpectedly low. Moreover, patients exposed to aRT had significantly more acute and late grade ≥ 2 genitourinary toxicity and more grade ≥ 2 erectile dysfunction. The change in global health status were similar in the arms ($p=0.11$). Our results suggest that observation after RP, with early sRT when biochemical relapse occurs, could spare approximately half of the men from RT, and the related toxicity.

At 5 years, more than 90% of patients in the aRT arm were free of progression. In the adjuvant setting, three randomised trials assessing postoperative RT have been completed. Firstly, the EORTC 22911 trial randomised 1005 patients (pT2 R1 or pT3N0) to either aRT, within 4 months of RP, or a wait-and-see strategy. After a median follow-up of 5 years, the biochemical progression-free survival was significantly extended with aRT (74.0%, 98% CI 68.7–79.3) compared to the wait-and-see strategy (52.6%, 98% CI 46.6–58.5, $p=0.0001$).¹² Secondly, the ARO 96-02 trial randomised 307 men, with pT3N0 disease at RP, to aRT or observation. Biochemical progression-free survival after 5 years was significantly extended with aRT (72% [95% CI 65–81] vs 54% [95% CI 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, the probability of patients being without biochemical progression was 20% higher with aRT compared to observation.² Finally, the SWOG S8794 trial randomised 431 patients, with pT3N0 prostate cancer, to aRT or initial observation.³ After a median follow-up of 10.2 years, aRT had a reduced 10-year risk of biochemical treatment failure (42% vs 72%), local failure (7% vs 20%), and distant failure (4% vs 12%) compared with observation. Nevertheless, the results are difficult to interpret due to the lack of timely sRT in the control arms from these trials. The low rate of events in the GETUG-AFU 17 trial, compared to the aRT arm from the “old-fashioned” studies^{3,12,13}, could be related to differences in populations, heterogeneity in radiation techniques and the prescribed dose given to the prostate bed.¹⁴

Furthermore, in localised prostate cancer, adding hormonal therapy to RT reduces biochemical relapse, compared to RT alone.¹⁵⁻¹⁷ In the adjuvant setting, hormonal therapy is not a standard of care, possibly improving our EFS rates.¹⁸ The RADICALS HD trial randomised patients to RT alone (early or deferred) or RT with 6 months of hormonal treatment or RT with 24 months of hormonal treatment. The primary outcome is the disease-specific mortality. This trial will

probably provide an answer concerning the place of postoperative hormonal therapy in this setting.

Early sRT can be curative for patients with biochemical relapse after RP. Whether sRT should be administered alone or combined with hormonal therapy remains controversial. In the last decade, three randomised studies have evaluated hormonal therapy in men receiving sRT after RP. The RTOG 9601, a phase III randomised control trial demonstrated that 24 months of bicalutamide extended survival with a HR=0.77 (95% CI 0.59–0.99).¹¹ The GETUG-AFU 16 study showed that 5-year progression-free survival was prolonged with sRT plus 6 months of goserelin compared to sRT alone (80% [95% CI 75–84] vs 62% [95% CI 57–67]; HR=0.50, 95% CI 0.38–0.66; p<0.0001).¹⁹ These results were confirmed with a 120-month metastasis-free survival rate in favour of the combined arm.²⁰ The NRG Oncology/RTOG 0534 SPPORT trial randomised 1,736 patients to either (i) sRT to the prostate bed, (ii) sRT to the prostate bed with short-term hormonal therapy, or (iii) sRT to the prostate bed and the pelvic lymph nodes with short-term hormonal therapy. SPPORT's population 5-year freedom from progression improved from 71% to 87% when adding both short-term hormonal therapy and pelvic lymph nodes to prostate bed RT (HR=0.45, 95% CI 0.34–0.61).²¹ Similar to the good results in the combined arms from these three trials, we observed a 5-year EFS rate of 90% (95% CI 85–94) in our sRT Arm.^{11,19,21}

The PSA level before sRT may predict who will most benefit from sRT 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 sRT was beneficial, even in the most favourable group.²⁰ However, in a new analysis from the RTOG 9601, examining a subset of patients relapsing after RP with PSA levels ≤ 0.6 ng/mL (n=389), closer to today's standard for early sRT, patients were nearly twice as likely to die from non-cancer causes when bicalutamide was added (HR=1.94; p=0.009). Patients with the lowest PSA levels (0.2–0.3 ng/mL) (n=148) had the greatest risk of death (HR=4.14; 95% CI 1.57–10.89).²² In our study, the median PSA level triggering sRT and short duration hormonal treatment was 0.24 ng/mL, lower than that reported in the Spratt *et al.* analysis. So the added value of hormonal treatment in our early sRT arm is debatable.

We have shown that aRT increased the risk of genitourinary and sexual morbidity compared to sRT. Our results accord with those from the three studies comparing aRT to observation: patients allocated aRT reported increased genitourinary toxicities of grade ≥ 2 .^{2,4,23} Our incidences of late grade ≥ 2 genitourinary toxicities are in accordance with those reported in the

aRT arm of the EORTC 22911 study: genitourinary toxicities of grade ≥ 2 were significantly higher with aRT compared to observation (21.3% vs 13.5%; $p=0.003$).⁴ The EORTC 22911 study assessed acute toxicity using the WHO scale and late toxicities with the Late Morbidity Scoring Scheme (RTOG/EORTC), making the comparison with our study difficult. In contrast, the ARO 96–02/AUO AP 09/95 study reported that late genitourinary toxicities (by RTOG scale) were scarce, although more frequent with aRT.² However, urinary incontinence, frequently observed in our study, is not included in the RTOG/EORTC scoring scheme. The Finnish randomised trial also reported high rates of toxicity with aRT compared to RP alone.²⁴ The LENT SOMA Scale, used for grading genitourinary toxicity in this trial, tends to higher grades compared to the CTCAE used in our study.²⁴

For the safety analysis, we need to consider the total dose of RT administered in these studies. We delivered more than the 60 Gy given in the EORTC 22911 and SWOG S8794 trials. This increased dose of RT, has been associated with higher rates of genitourinary toxicity.²⁵ It is also important to highlight the RT techniques used when analysing these results. Indeed, in the SWOG S8794 trial, performed more than 25 years ago, details concerning RT were not reported.³ The EORTC 22911 study used linear accelerators (5–25 MV), using an isocentric technique with non-3-D planning.¹² The ARO 96–02/AUO AP 09/95 study was the first, in this postoperative setting, to propose a 3-D RT approach.¹³ The use of intensity-modulated RT in approximately 40% of our patients could explain our acceptable grade ≥ 2 genitourinary toxicity rate despite the increased RT dose given.^{14,26} It is noteworthy that since RT was delayed with sRT, more patients in the sRT arm benefited from intensity-modulated RT, as this technique became more available in France.²⁷ As we showed in our results, in the literature, the delay between RP and postoperative RT is supposed to influence the risk of long-term AEs. Interestingly, the recovery from urinary incontinence, after RP, occurs at a lower rate in patients after aRT compared to sRT.^{5,6} Our data are also concordant with the GETUG-AFU 16 results, showing late genitourinary adverse events of grade ≥ 3 in 7% of the patients in the combined sRT Arm.¹⁹ Only 4 patients (1.9%) in our sRT arm experienced grade ≥ 3 genitourinary adverse events confirming the good tolerance of the delayed RT approach.

Regarding, the gastrointestinal toxicities reported, they were predominantly of grade 1-2, without significant difference between arms. Likewise, the EORTC 22911 study found around 5% of 10-year grade 3 gastrointestinal toxicities with aRT.⁴ In the GETUG-AFU 16 study, in the sRT combined with hormonal therapy treatment arm, similar to that used in our sRT arm, grade ≥ 3 gastrointestinal events rates were low (2%).¹⁹ These rates are comparable with those

we observed. Similar to the genitourinary toxicity analysis, the use of intensity-modulated RT²⁸ and the toxicity scales used may also influence the interpretation of our results compared to others trials.^{2,4}

We observed that grade ≥ 2 erectile dysfunction was significantly worse in the aRT Arm ($p < 0.0001$). Only the SWOG S8794 trial reported data on sexual function.²³ Van Stam *et al.* showed that men receiving postoperative RT, more than 6 months after RP, experienced better sexual satisfaction compared with those treated within 6 months following surgery, confirming the relation between timing of postoperative RT and sexual tolerance.⁵ Overall, we can expect an increased rate in both acute and late AEs of all grades, and a decreased of QoL, in GETUG-AFU 17 compared to studies without hormonal therapy, owing to the 6-months of hormonal therapy initially delivered concurrent with RT.^{2,4,23,24}

Our analysis of the QLQ-C30 and QLQ-PR25 data found no significant differences between arms, in accordance to the SWOG S8794 trial reporting no differences in intermediate-term QoL between men receiving aRT or with initial observation.²³ Akhtar *et al.* reported favourable long-term QoL and late toxicity following postoperative RT. Patients' QoL were assessed in men treated with post-RP intensity-modulated RT, using the Expanded Prostate Cancer Index Composite (EPIC-26) questionnaire.²⁹

The GETUG-AFU 17 trial has some limitations. Our analysis is limited by the patient accrual not reaching the target, giving a lack of statistical power to strongly conclude on efficacy. In addition, the trial was not powered to study long-term outcomes such as OS and MFS, even with longer follow-up. It is well known that EFS, particularly when PSA driven, is not a surrogate for longer-term outcomes.³⁰ Looking at the older trials of aRT versus observation, they showed large improvements in biochemical progression with RT without showing clear benefit in long-term outcomes. Therefore, from our study, it is very unlikely that results will change consistently in favour of aRT with more follow-up. Finally, regarding the relevance of androgen deprivation added to postoperative RT from the recent literature, our results could be questionable, highlighting potential overtreatment in both arms.

In conclusion, from the GETUG-AFU 17 trial, no difference in EFS rate was shown between aRT and sRT, although the analysis lacked statistical power. Our results show that sRT could spare men from receiving RT and its toxicity. Thus the questions about the best postoperative policy to propose after RP and which patient could still benefit from aRT, are still valid. The publication of the prospective ARTISTIC meta-analysis, including RAVES, RADICALS-RT, and GETUG-AFU 17 trials, will assess the impact of aRT vs early sRT on early, but also long-

term, outcomes in this patient group. Because of the limited power in these trials taken individually, ARTISTIC is a unique opportunity to evaluate the impact of RT timing across patient subgroups.

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Contributors

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

Declaration of interests

PS and IL declares receiving honoraria, providing medical advice, and participating on boards for Astellas, Bayer, Bouchara, Ferring, Ipsen, Janssen, Sanofi, and Takeda. SS declares to have received funding from Jansen, Astra-Zeneca, and Astellas, as well as 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 conflicts of interest.

Data sharing statement

Unicancer will share de-identified individual data that underlie the results reported in this article under the following conditions: the data shared will be limit 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 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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Figures

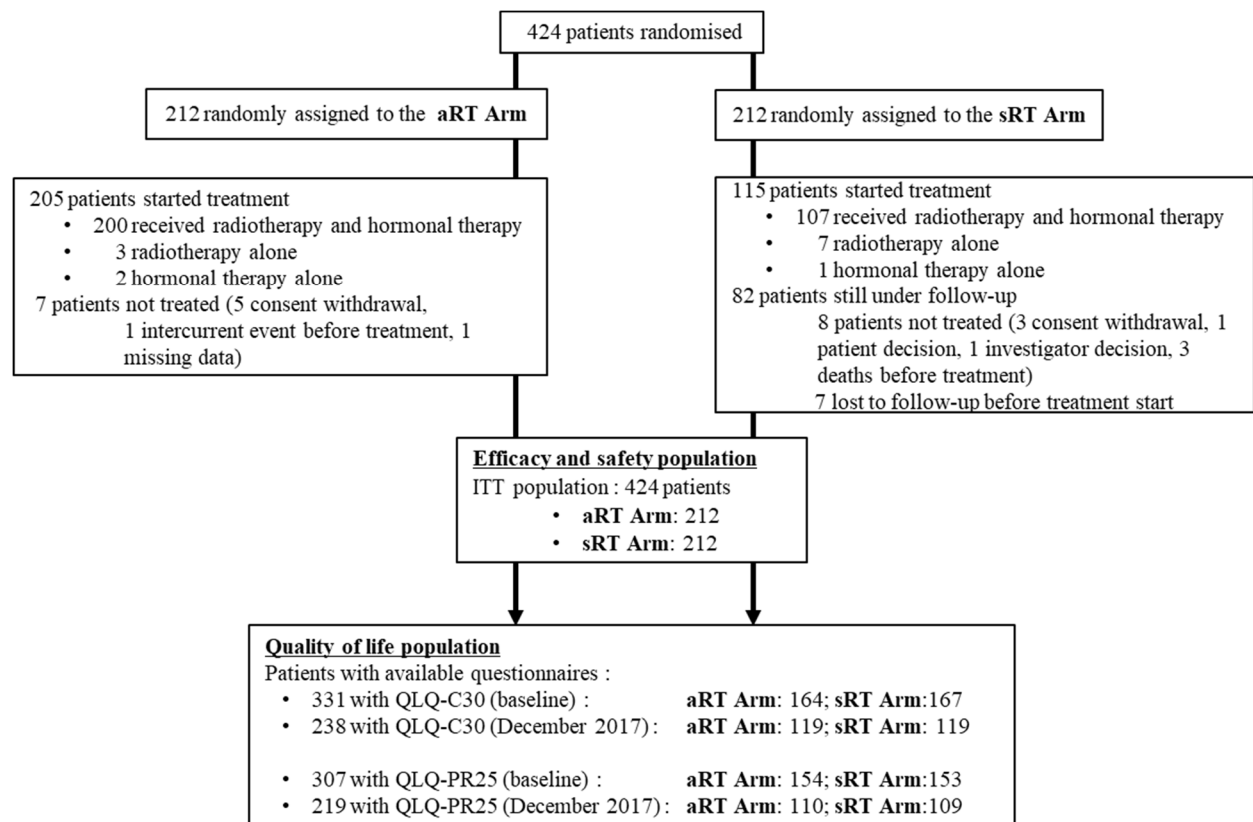
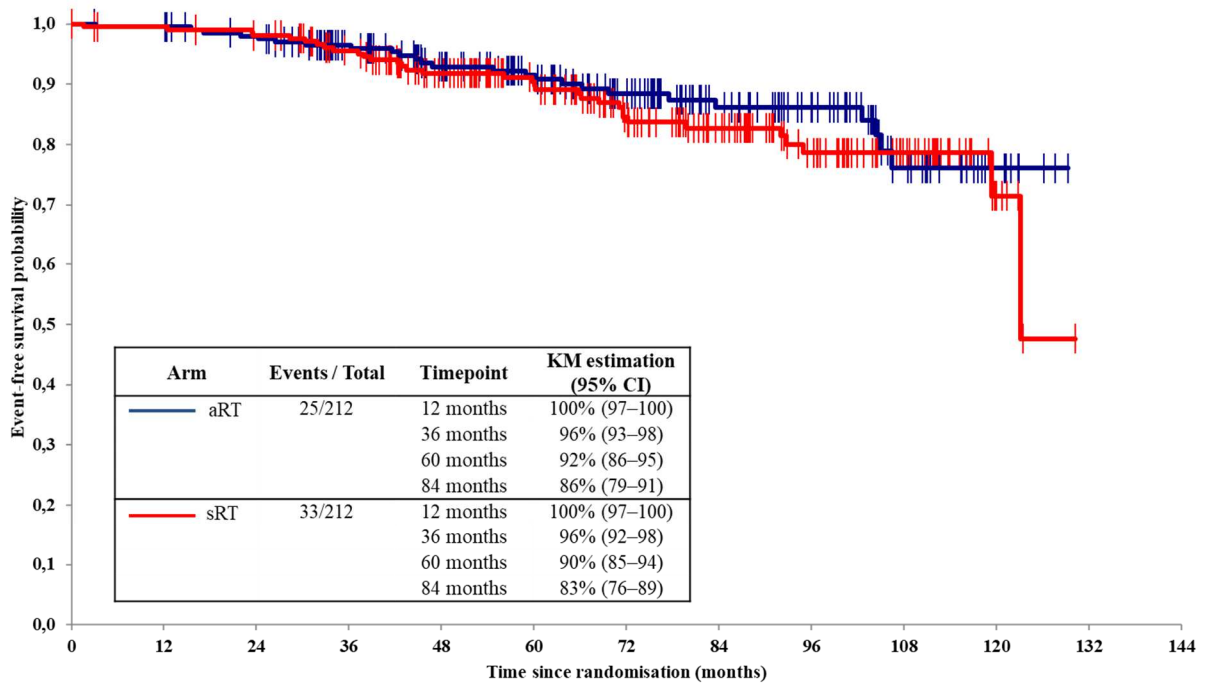


Figure 1: Trial profile

aRT=adjuvant radiotherapy; sRT=salvage radiotherapy; ITT=intent-to-treat; QLQ=quality of life questionnaire.

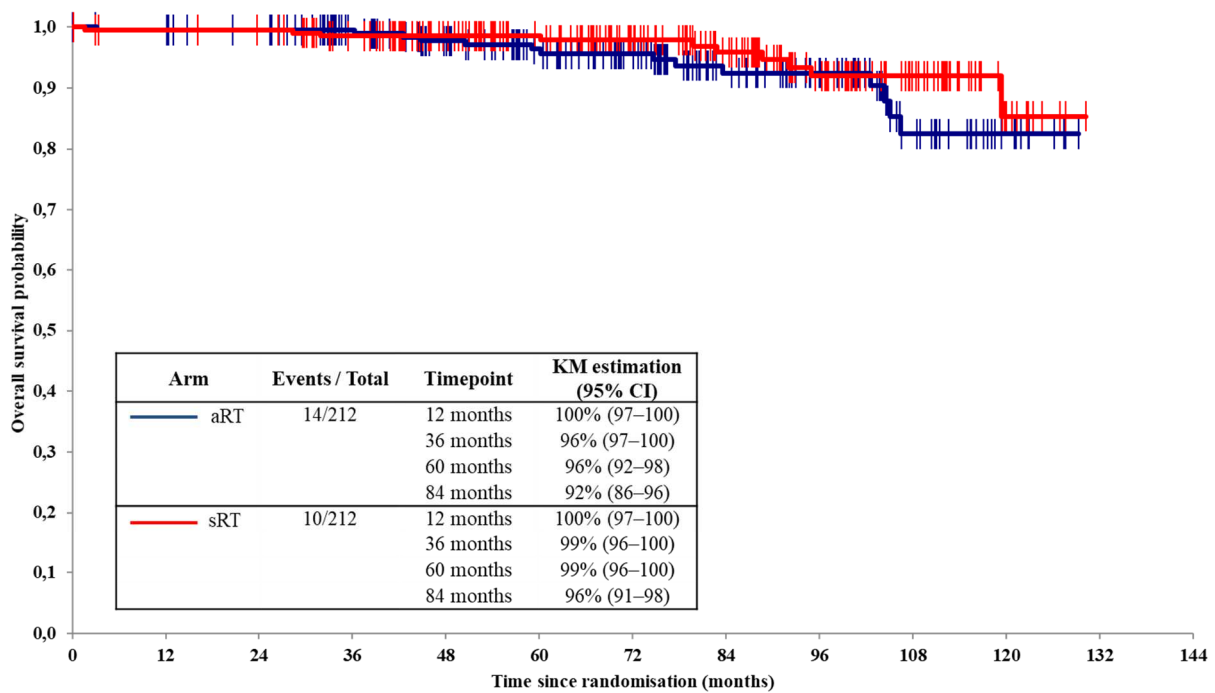
A



Patients at risk (number censored):

212 (0)	196 (12)	148 (51)	101 (92)	52 (139)	8 (179)
212 (0)	203 (5)	158 (38)	105 (81)	54 (127)	8 (172)

B



Patients at risk (number censored):

212 (0)	199 (7)	155 (53)	108 (97)	55 (147)	9 (189)
212 (0)	206 (5)	167 (42)	118 (90)	64 (139)	11 (191)

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

CI=confidence interval; KM Est=Kaplan-Meier estimation; aRT=adjuvant radiotherapy; NE=not evaluable; sRT=salvage radiotherapy

Tables

	aRT Arm (n=212)	sRT Arm (n=212)
Age at randomisation (years)		
Median (IQR)	63.7 (60.0–67.5)	64.0 (58.8–68.3)
Delay between RP 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
ECOG 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

Table 1: Baseline characteristics of the intent-to-treat population (n=424)

System organ class								
Type de toxicité	aRT Arm (n=212)				sRT Arm (n=212)			
	Any grade	1-2	3	4	Any grade	1-2	3	4
Gastrointestinal disorders	112 (53%)	112 (53%)	0 (0%)	0 (0%)	43 (20%)	42 (20%)	1 (<1%)	0 (0%)
Diarrhoea	60 (28%)	60 (28%)	0 (0%)	0 (0%)	17 (8%)	17 (8%)	0 (0%)	0 (0%)
Proctitis	27 (13%)	27(13%)	0 (0%)	0 (0%)	6 (3%)	6 (3%)	0 (0%)	0 (0%)
Anal inflammation	22 (10%)	22 (10%)	0 (0%)	0 (0%)	5 (2%)	5 (2%)	0 (0%)	0 (0%)
Intestinal obstruction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
General disorders and administration site conditions	102 (48%)	100(47%)	2 (1%)	0 (0%)	43 (20%)	42 (20%)	1 (<1%)	0 (0%)
Hot flush	83 (39%)	81 (38%)	2 (1%)	0 (0%)	36 (17%)	35 (17%)	1 (<1%)	0 (0%)
Asthenia	41 (19%)	41(19%)	0 (0%)	0 (0%)	19 (9%)	19 (9%)	0 (0%)	0 (0%)
Metabolism and nutrition disorders	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Type 2 diabetes mellitus	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal and urinary disorders	146 (69%)	143 (67%)	2 (1%)	1 (<1%)	57 (27%)	53 (25%)	1 (<1%)	0 (0%)
Urinary frequency	107 (50%)	106 (50%)	1 (<1%)	0 (0%)	38 (18%)	37 (17%)	1 (<1%)	0 (0%)
Urinary incontinence	48 (23%)	47 (22%)	1 (<1%)	0 (0%)	10 (5%)	10 (5%)	0 (0%)	0 (0%)
Dysuria	32 (15%)	32 (15%)	0 (0%)	0 (0%)	13 (6%)	13 (6%)	0 (0%)	0 (0%)
Urinary retention	2 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Reproductive system and breast disorders	17 (8%)	16 (8%)	1 (<1%)	0 (0%)	11 (5%°)	10 (5%)	1 (<1%)	0 (0%)
Erectile dysfunction	11 (5%)	10 (5%)	1 (<1%)	0 (0%)	7 (3%)	6 (3%)	1 (<1%)	0 (0%)
Skin and subcutaneous tissue disorders	25 (12%)	25 (12%)	0 (0%)	0 (0%)	16 (8%)	16 (8%)	0 (0%)	0 (0%)

Table 2: Acute toxicities of grade 1 or 2 reported in ≥10% of patients and all grade 3-5 reported in any arm, by system organ class and type of toxicity graded using the CTCAE v3.0.

System organ class										
Type de toxicity	aRT Arm (n=212)					sRT Arm (n=212)				
	Any grade	1-2	3	4	5	Any grade	1-2	3	4	5
Cardiac disorders	2 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Angina (unstable)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Gastrointestinal disorders	94 (44%)	86 (41)	8 (4%)	0 (0%)	0 (0%)	42 (20%)	41 (20%)	1 (<1%)	0 (0%)	0 (0%)
Rectal haemorrhage	42 (20%)	38 (18%)	4 (2%)	0 (0%)	0 (0%)	16 (8%)	16 (8%)	0 (0%)	0 (0%)	0 (0%)
Diarrhoea	25 (12%)	25 (12%)	0 (0%)	0 (0%)	0 (0%)	14 (7%)	14 (7%)	0 (0%)	0 (0%)	0 (0%)
Proctitis	18 (8%)	16 (8%)	2 (1%)	0 (0%)	0 (0%)	7 (3%)	7 (3%)	0 (0%)	0 (0%)	0 (0%)
Haemorrhoids	7 (3%)	6 (3%)	1 (<1%)	0 (0%)	0 (0%)	2 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Upper abdominal pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Diverticulitis	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Oesophagitis	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
General disorders and administration site conditions	80 (38%)	78 (37%)	2 (1%)	0 (0%)	0 (0%)	30 (14%)	30 (14%)	0 (0%)	0 (0%)	0 (0%)
Hot flush	59 (28%)	58 (27%)	1 (<1%)	0 (0%)	0 (0%)	20 (9%)	20 (9%)	0 (0%)	0 (0%)	0 (0%)
Asthenia	33 (16%)	33 (16%)	0 (0%)	0 (0%)	0 (0%)	14 (7%)	14 (7%)	0 (0%)	0 (0%)	0 (0%)
Lithiasis	1 (<1%)		1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infections and infestations	5 (2%)	4 (2%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Urinary tract infections	2 (1%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Injury, poisoning, and procedural complications	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cystitis radiation	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Investigations	44 (21%)	43 (20%)	0 (0%)	0 (0%)	0 (0%)	14 (7%)	13 (6%)	1 (<1%)	0 (0%)	0 (0%)
Weight decrease	41 (19%)	41 (19%)	0 (0%)	0 (0%)	0 (0%)	14 (7%)	13 (6%)	1 (<1%)	0 (0%)	0 (0%)
Blood creatinine increased	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	25 (12%)	25 (12%)	0 (0%)	0 (0%)	0 (0%)	11 (5%)	11 (5%)	0 (0%)	0 (0%)	0 (0%)
Neoplasms benign, malignant and unspecified (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 (0%)	4 (2%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Colorectal cancer	2 (1%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	2 (1%)	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)
Adenocarcinoma pancreas	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)	0 (0%)	1 (<1%)	0 (0%)	2 (1%)
Adenocarcinoma gastric	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Adenocarcinoma of colon	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anal cancer	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bladder cancer	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cholangiocarcinoma	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chronic lymphocytic leukaemia	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Colorectal adenocarcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Laryngeal cancer	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

System organ class										
Type de toxicity	aRT Arm (n=212)					sRT Arm (n=212)				
	Any grade	1-2	3	4	5	Any grade	1-2	3	4	5
Lung carcinoma cell type unspecified stage IV	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lung neoplasm malignant	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Malignant melanoma	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myelodysplastic syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Plasma cell myeloma	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rectal adenocarcinoma	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Squamous cell carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Nervous system disorders	5 (2%)	4 (2%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Generalised tonic-clonal seizure	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal and urinary disorders	155 (73%)	143 (67%)	12 (6%)	0 (0%)	0 (0%)	62 (29%)	59 (28%)	2 (1%)	1 (<1%)	0 (0%)
Urinary incontinence	116 (55%)	111 (52%)	5 (2%)	0 (0%)	0 (0%)	35 (17%)	34 (16%)	1 (<1%)	0 (0%)	0 (0%)
Urinary frequency	83 (39%)	83 (39%)	0 (0%)	0 (0%)	0 (0%)	31 (15%°)	31 (15%)	0 (0%)	0 (0%)	0 (0%)
Haematuria	31 (15%)	26 (12%)	5 (2%)	0 (0%)	0 (0%)	10 (5%)	8 (4%)	1 (<1%)	1 (<1%)	0 (0%)
Dysuria	21 (10%)	20 (9%)	1 (<1%)	0 (0%)	0 (0%)	12 (6%)	12 (6%)	0 (0%)	0 (0%)	0 (0%)
Urinary retention	6 (3%)	5 (2%)	1 (<1%)	0 (0%)	0 (0%)	5 (2%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)
Micturition disorder	2 (1%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Reproductive system and breast disorders	86 (41%)	77 (36%)	9 (4%)	0 (0%)	0 (0%)	30 (14%)	27 (13%)	3 (1%)	0 (0%)	0 (0%)
Erectile dysfunction	77 (36%)	68 (32%)	9 (4%)	0 (0%)	0 (0%)	27 (13%)	24 (11%)	3 (1%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	13 (6%)	12 (6%)	1 (<1%)	0 (0%)	0 (0%)	4 (2%)	4 (2%)	0 (0%)	0 (0%)	0 (0%)
Rash	5 (2%)	4 (2%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	22 (10%)	19 (9%)	2 (1%)	1 (<1%)	0 (0%)	10 (5%)	8 (4%)	2 (1%)	0 (0%)	0 (0%)
Hypertension	18 (8%)	16 (8%)	2 (1%)	0 (0%)	0 (0%)	10 (5%)	8 (4%)	2 (1%)	0 (0%)	0 (0%)
Aortic dissection	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Peripheral arterial occlusive disease	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (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 arm, by system organ class and type of toxicity graded using the CTCAE v3.0.