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**Short androgen deprivation therapy combined with radiotherapy as salvage treatment for metastatic free survival after radical prostatectomy (GETUG-AFU 16): 112-month follow-up of a phase III randomized trial.**

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Results have been selected for an oral presentation during the ASCO 2019 meeting.

## **ABSTRACT**

### **Background**

Radiotherapy (RT) is the standard salvage treatment after radical prostatectomy (RP). To date, the role of androgen deprivation therapy (ADT) has not been formally demonstrated. This trial assessed the efficacy of RT+ADT vs RT alone in terms of progression-free survival (PFS), metastase-free survival (MFS) and overall survival (OS) in patients with biological relapse after RP. With a median 112-month follow-up, our objective is to update GETUG-AFU 16 results in terms of PFS, to assess MFS, and explored the predictive estimate on OS.

### **Methods**

This open-label, multicentre, phase 3, randomised controlled trial enrolled men (aged  $\geq 18$  years) with ECOG-PS of 0 or 1, with histologically confirmed adenocarcinoma of the prostate (but no previous androgen deprivation therapy or pelvic radiotherapy), stage pT2, T3, or T4a (bladder neck involvement only) and pN0 or pNx, who had rising PSA of  $0 \cdot 2$  to less than  $2 \cdot 0$  ng/mL following radical prostatectomy, without evidence of clinical disease. Patients were centrally randomized (1:1) to ADT (short-term androgen suppression using  $10 \cdot 8$  mg goserelin by subcutaneous injection on the first day of irradiation and 3 months later) added to RT (3D conformal radiotherapy or intensity modulated radiotherapy of 66 Gy in 33 fractions 5 days a week for 7 weeks), or RT alone. Randomisation was stratified using a permuted block method according to investigational site, radiotherapy modality, and prognosis. The primary endpoint was progression-free survival in the intent-to-treat population.(ClinicalTrials.gov NCT00423475). The median follow-up was calculated using a reverse Kaplan-Meier estimate. This post-hoc one-shot data collection performed 4 years after last data cutoff, after a median follow-up of 112-months (IQR 102–123), updated for patient alive at the time of the former analysis, and long-term patient status including dates, for first local progression, for metastatic disease diagnosis, and/or death if any, or indicated the date of the last tumor evaluation and/or last PSA measurement. Survival (95%CI) at 120 months was reported.

### **Findings**

Between Oct 19, 2006, and March 30, 2010, 743 patients were randomly assigned, 374 to radiotherapy alone and 369 to radiotherapy plus goserelin. At the time of data-cutoff (March 2019), the median follow-up was 112 months (IQR 102–123). The 120-month PFS was 64%, 95%CI 58%–69%, and 49%, 95%CI 43%–54% for patients treated with RT+ADT and RT alone, respectively (Stratified logrank test  $p < 0\cdot0001$ ), HR  $0\cdot54$ , 95%CI  $0\cdot43$ – $0\cdot68$ . Tolerance

update reported two second cancers not considered to be related to treatment. No treatment-related death occurred.

### **Interpretations**

The 120-month PFS confirmed results previously reported. Salvage radiotherapy combined with short term ADT significantly reduced risk of biochemical or clinical progression or death compared with salvage radiotherapy alone.

### **Funding**

The trial was supported by the French Health ministry, Astra-Zeneca, la Ligue Contre le Cancer, and La Ligue de Haute-Savoie.

## Introduction

Approximately one third of patients undergoing radical prostatectomy (RP) for prostate cancer have disease recurrence. Biological recurrence defined as detectable levels of serum prostate-specific antigen (PSA) without any clinical evidence of disease and distant metastases may occur in the absence of salvage treatment. The standard treatment for patients with biochemical failure without clinical evidence of disease after RP is salvage radiotherapy; salvage radiotherapy allows to decrease to 75% the risk of distant metastasis, and to delay the need for androgen suppression and related side effects. (1)

Spieler and colleagues recently reported that salvage radiotherapy was associated with favourable outcomes; five-year progression free survival was 68% (95%CI 59.8-74.8%), and PFS rates were 87%, 70%, and 47% in patients with PSA <0.3, 0.3–0.7 and >0.7 ng/mL ( $P<0.0001$ ), respectively. At five years, metastasis free survival was 92.5%, prostate cancer-specific survival 96.4%, and overall survival 94.9%.(2) Five-year cumulative incidences of biochemical recurrence were 42% in patients with PSA concentration less than 0.5 ng/mL, and 56% in patients with PSA greater than 0.5 ng/mL.(3) The metastasis free survival (MFS) at 10 years is 48%.(4;5)

Only half of patients are free of biochemical relapse 5 years after salvage radiotherapy. (6;7) Low- and high-risk groups based on biochemical relapse risk in patients with salvage radiotherapy after RP have been proposed and included time to relapse after surgery, PSA doubling time less than 6 months, PSA level at the time of RT, Gleason >7 and negative surgical margins, or seminal vesicles involvement.(7-9) In the high risk group, the risk of prostate cancer-related death in the absence of treatment was more than 90%, and 17% of patients with biological recurrence after RP died from prostate cancer.(7) In addition, in patients with early (less than 3 years) relapse post-RT and PSA doubling time less than 3 months, the median survival was only 3 years. On the other hand, patients with PSA doubling time >15 months, and relapsing more than 3 years after surgery had a 100% cause-specific survival.(7) Controversy exists regarding the impact of biochemical recurrence on oncological outcomes, and risk stratification is still debatable.(10)

Short term androgen suppression added to salvage radiotherapy had been proposed to improve biochemical relapse-free survival.(11) The randomized trial GETUG-AFU 16 showed a significant improvement of progression free survival (PFS) at 5 years in patients treated with combined short-term ADT plus RT compared to those treated with RT alone, but no impact on OS was demonstrated.(12)

The randomized trial RTOG 9601 enrolling relapsing patients with biochemical relapse identified by persistently elevated PSA after prostatectomy, and true relapse i.e. relapsing patients who were in complete response after surgery showed a better overall survival at 13 years in patients treated with RT combined with 2-year ADT. The magnitude of benefit was increased in patients with PSA concentration greater than 1.5 ng/mL.(13)

The objective of the present article is update GETUG-AFU 16 results in terms of PFS and to assess MFS after a median 112-month follow-up, and confirm the interest of ADT plus RT as salvage treatment in patients with rising PSA after RP.

## **Methods**

### **Study design and participants**

Patients, methods and trial design have previously been published in this journal,(12) and the design of the study is summarized figure 1.

In this open-label multicenter randomized controlled phase 3 trial, men aged 18 or older, with Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1, histologically confirmed prostate adenocarcinoma, stage pT<sub>2</sub> T<sub>3</sub> T<sub>4a</sub> (bladder neck involvement only), pN0 or pNx, were treated by RP in 43 GETUG centers. PSA levels were stable at <0.1 ng/ml for at least 6 months following surgery but then began to rise. PSA levels should be ≥0.2ng/ml to <2ng/ml as confirmed by two repeated tests without evidence of clinical disease according to the international consensus.(8;9) No previous androgen suppression or pelvic irradiation was accepted.

The study was conducted in accordance with the principles of Good Clinical Practices. The protocol was approved by the institutional review board at Centre Léon Bérard, Lyon, France, and the Ethics Committee South East IV, Lyon, France, and the French Agency for the Safety of Health Care Products. Written informed consent was obtained from each patient before enrollment.

The first patient was included on October 19, 2006. The trial was registered with ClinicalTrials.gov on January 18, 2007. This delay was related to time required to implement recently applicable regulation at the national level. However, inclusions were allowed (in compliance with the French law) as soon as the ethics committee approval was received, i.e. on April, 6, 2006. 23 out of the 743 patients were included between October 19, 2006 and January 18, 2007.

### **Randomization and masking**

Patients were randomly assigned in a 1:1 ratio to receive radiotherapy alone (RT alone) or radiotherapy plus six months of ADT. Randomization was stratified according to investigational site, radiotherapy modality (intensity-modulated radiotherapy vs conformational), and prognosis (high vs low risk). The randomization list was done by a statistician at the coordination center who was not involved in the data analysis. Clinicians and patients were not masked to allocation of study treatment.

### **Procedures**

Initial staging did not include bone scanning or CT or MRI according to the current recommendations at the time of the study for patients with PSA less than 2ng/ml. Semestrial measurement of PSA was performed for 5 years and then every year. No biopsy was required



to confirm local or regional relapse, and treatment after relapse was left to the decision of participating physicians. There was no central review of prostate specimens. To note, the study did not schedule annual scans or systematic scans. Only patients with biological relapse or reporting pain were subsequently scanned (CT scan and bone scan). A metastatic event was defined as a progression outside the prostate bed. As a consequence, any nodal relapse had been considered as metastatic relapse.

According to GETUG recommendations and other GETUG protocols (GETUG01 and GETUG18), the pelvis was irradiated in patients who did not have node dissection during RP and exclusively in those with a risk of nodal involvement greater than 15% according to the Partin table.(14) In such cases, the dose to the pelvis was 46 Gy (2 Gy per fraction). The prescribed irradiation dose to the prostate bed was 66 Gy in 33 fractions, 5 days a week for 7 weeks, in both arms. Dose was prescribed according to the International Commission on Radiation Units.(15) In addition, patients in the RT-goserelin group received goserelin acetate 10.8mg by injection on the first day of irradiation, and a repeated administration 3 months later. Low risk definition as per GETUG group recommendations included Gleason score <8, positive surgical margins, PSA doubling time at relapse >6 months, and no seminal vesicle involvement. PSA doubling time was calculated by natural log 2 (0.693) divided by the slope of the relationship between the log of PSA and time of PSA measurement on 3 consecutive dosages every 2 months spaced by 2 months.(4)

In the previously published GETUG-AFU 16 analysis,(12) only the first event had been collected, therefore MFS could not be analyzed. For example, if the first event was local or regional progression, metastatic progression could not adequately be captured.

OS was predefined as secondary endpoint with assumptions at 10-year. Nevertheless, less than 6% of events were obtained in 2016, and extended follow-up evidenced that maturation required was not achievable. Recent published results from Xie and colleagues (23) proposed to use the MFS as surrogate of OS, and consequently allow to shorten study follow-up to demonstrate treatment efficacy unless cohort eradication is achieved. The on-study amendment (Dec 11, 2008) enlarged study sample size and mentioned that 10-year OS will be explored. End of recruitment occurred in March 2010. Based on inclusion of more than 60% of patients before the end of 2008, we hypothesized that the median 10-year follow-up would have been achieved by the end of 2018, and one-shot update was initiated. 4 years after last data cutoff (Dec 12, 2014) and current database lock was performed on March 12, 2019. Median follow-up calculated by inverse Kaplan-Meier method finally released a 112-month median follow-up. Participating centers were required to update follow-up data for each

patient alive at the time of the former analysis (12). Participating centers updated the dates, for first local progression, for metastatic disease diagnosis, and/or death if any, or indicated the date of the last tumor evaluation and/or last PSA measurement. Subsequent treatment after relapse were not captured and left to the local investigator discretion. Second cancers and serious adverse events potentially related to treatment were collected on an annual basis, and graded according to CTCAE v3.

### **Outcomes**

The primary endpoint was Progression Free Survival (PFS), defined as time from randomization. At the date of data cutoff (March 12, 2019), we updated PFS. The latter was defined as biological or clinical progression (local/regional or distant progression) or death from any cause, or censored when patients were last heard of. Biochemical relapse was defined as an elevation of PSA of more than 0.5 ng/ml compared to the nadir (confirmed by a second PSA measurement). The date of the first PSA elevation recorded is used in survival analyses. Time to nadir of PSA and patients' quality of life and functional dependence 1 year and 5 years after radiotherapy have been reported previously.

Secondary pre-specified outcomes were Metastasis free survival (MFS), OS, acute and late toxicities, time to nadir of PSA, and patients' quality of life and functional dependence 1 year and 5 years after radiotherapy. MFS is defined as time from randomization to documented metastasis or all cause death. OS is measured from the date of random assignment to death from any cause, or censored at the date of last follow-up in patients who were alive.

### **Statistical analysis**

The trial was initially designed to detect a benefit in biochemical and/or clinical PFS from 45% (RT alone) to 60% (RT+ADT) at 5 years, hazard ratio (HR) of 0.64, with 5% two-sided alpha risk and 90% power (466 patients needed). Based on the rapid accrual, and to gain in power for secondary endpoints (OS and MFS) analyses, an on-study amendment (Dec 11, 2008) enlarged the sample size to achieve a 80% power to detect at 10 years a 10% increase (from 75% to 85%) in OS (HR 0.58): 349 cases of progression or death were expected among the total of 738 patients required.

Efficacy endpoints (PFS, MFS, and OS) were analyzed in the intent-to-treat population. The Kaplan-Meier method was used to estimate time-to-event endpoints, and two-sided log-rank tests stratified on randomization factors were used for comparisons between groups. The median follow-up (IQR) was calculated using a reverse Kaplan-Meier estimate. Survival results (associated with 95% confidence interval –CI) are presented at 120 months. The number of patients needed to treat (NNT) to prevent one event (metastasis or death) when

adding ADT to RT was obtained using the risk difference inverse ratio, and used to report the magnitude of the benefit.

Statistical analyses were performed using SAS software (version 9.4). This trial is registered with ClinicalTrials.gov, number NCT00423475.

#### **Role of the funding source**

The sponsor (UNICANCER), French Ministry of Health (PHRC 2005), Astra Zeneca (educational grant and goserelin supply), and La Ligue de Haute-Savoie had no role in study design, collection or interpretation of the data, analysis, or writing the report. The sponsor was involved in data monitoring and pharmacovigilance. Trial conception, data management, analysis, and writing were done by the Clinical Research Department at the Centre Léon Bérard. CC, CF, and SC had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

## Results

Between October 19, 2006 and March 30, 2010, 743 patients were randomized (RT alone: 374; RT+ADT: 369). Patients' characteristics and treatments are detailed in Table 1. Baseline characteristics, treatment, toxicity, and quality of life were previously published in the original report and were not updated for this publication.(12)

Compared with the control group, patients randomised to short-term androgen suppression in addition to salvage radiotherapy were significantly more likely to be free of biochemical or clinical progression at five years (80% vs 62%; HR 0.50; 95% CI 0.38-0.66,  $p < 0.0001$ ). As a reminder, 742 patients were considered in the intent-to-treat analysis; one patient withdrew his consent.

Radiotherapy was used in 738 patients. The median dose to the prostate bed was 66 Gy (IDR 66–66) and the median duration of radiotherapy was 7 weeks (IQR 6.7–7.3) in the two arms. Three patients had a total duration >10 weeks because of acute urinary retention (n=1), intercurrent disease in the second (n=1), and an unknown reason (n=1). Only 119 patients (16%) received nodal pelvic irradiation: 56 [15%] of the 372 in the RT alone group and 63 [17%] of 365 in the combined arm. An up to 50 Gy irradiation of seminal vesicles area was performed exclusively in patients with pT3b stage.

The first injection of goserelin was administered in all but 3 patients in the RT-goserelin group (one patient refused and the injection was inadvertently omitted for two patients). The second injection was given in 351 (96%) out of 366 patients. Out of the 15 patients who did not receive it, 10 patients had refused. For the remaining five, the reasons were injection inadvertently omitted (n=2), toxicity (rash and hypertension) (n=2), and unknown reason (n=1). The median time to nadir PSA was 9.4 months (IQR 7.3–17.5) in the radiotherapy-alone group and 3.0 months (IQR 2.3–7.6) in the radiotherapy-goserelin group.

At the date of data cutoff (March 12, 2019), the median duration of follow-up was 112 months (IQR 102–123) and 307 (41%) PFS events were notified: 120 (33%) and 187 (50%) in RT+ADT and in RT alone arm, respectively. The update of the progression free survival (PFS) showed results similar to those previously reported with a 120-month PFS of 64%, 95%CI 58%–69%, and 49%, 95%CI 43%–54% for patients treated with RT+ADT and RT alone, respectively (Stratified logrank test  $p < 0.0001$ ), HR 0.54, 95%CI 0.43–0.68.(Figure 2)

The subgroup analysis supported these results in favor of RT+ADT arm, with a 120-month-PFS of 61%, 95%CI 51%–70% vs 74%, 95%CI 63%–83%, stratified logrank test  $p = 0.004$ ; HR 0.47, 95%CI 0.28–0.80 for low risk subgroup, and 43%, 95%CI 37%–50% vs 60%,

95%CI 53%–66%, stratified logrank test  $p<0.0001$ - HR 0.56, 95%CI 0.44–0.73 for high risk subgroup.

MFS events were diagnosed in 77 (20.9%) patients in RT+ADT vs 106 (28.4%) patients of RT alone group. 120-month MFS was 75%, 95%CI 70–80 vs 69%, 95%CI 63–74 in patient assigned to RT+ADT and RT alone, respectively (stratified log-rank test  $p=0.034$ ), what can be translated into a HR of 0.73, 95%CI 0.54–0.98. No statistically significant difference in subgroups was observed. HR 0.58, 95%CI 0.29–1.17- Stratified log-rank test  $p=0.125$ , and HR 0.77, 95%CI 0.55–1.06- Stratified log-rank test  $p=0.107$  for low and high risk groups, respectively). No treatment-related death occurred.

A total of 97 (13.1%) patients died, 46 (12.5%) in RT+ADT group vs 51 (13.7%) in RT alone. Deaths were due to prostate cancer in 30 patients (RT+ADT:  $n=12$ ; RT alone:  $n=18$ ), to any other cancer ( $n=19$ ), to cardiac causes ( $n=9$ ), to other causes ( $n=25$ ), or to unknown causes ( $n=14$ ). 120-month overall survival was 86% (81–89) and 85% (80–89) for RT+ADT and RT alone, respectively (HR 0.93, 95%CI 0.63–1.39 - two sided  $p=0.73$ ). The rate of death due to cancer was similar in the two arms (4.8 vs 3.3 %), as well as the rate of the onset of a secondary cancer (2.7 vs 2.4 %) in RT alone compared to the combined arm.

Subgroup analysis of MFS is summarized in Figure 3. Subgroup analysis in patients, with or without pelvis irradiation, showed any difference in survival results.

Two cases of second cancers have been reported since the former analysis(12) , not considered as treatment-related. No treatment-related death occurred.

At 120 months, the number of patients needed to treat (NNT) for adding ADT to RT is equal to 14 (19.2% vs 26.3% events in RT+ADT and RT alone arms, respectively). This means that 14 patients on average, need to be treated with ADT added to RT to prevent one metastatic disease or one death.

## Discussion

The final results of the multicenter open label randomized phase 3 trial GETUG-AFU 16 confirmed that the addition of six-month goserelin to salvage radiotherapy led to a better metastatic free survival (MFS) in patients with biochemical relapse after radical prostatectomy.

To date, radical prostatectomy has remained one of the established treatment for localized prostate cancer in men less than 70 years of age. However, biochemical relapse rate at 5 years is 30-70%, depending on the initial staging group. Studies have suggested a potential benefit with salvage radiotherapy through biochemical complete response achieved in half of relapsing patients.(16) One prospective study and many other retrospective analysis strongly suggest a benefit of ADT combined with salvage radiotherapy.(17-20) Even though guidelines show high grade recommendations in favour of salvage radiotherapy, salvage treatment has not been precisely defined yet.

To date, the current prognostic tools included the determination of PSA level and its rising rate over time has long been the sole proof of a silently progressive disease, but it has never been proven that the treatment of rising PSA correlates with overall survival except one randomized trial; Indeed, Shipley and colleagues showed a benefit in overall survival at 13 years in patients with rising PSA or persistent elevated PSA after RP, treated with long-term androgen deprivation therapy and salvage radiotherapy.(13) Despite a long-term median follow-up of nearly 10 years in the present study, a longer follow-up should be necessary to achieve the required number of events, and then to achieve enough power to release significant results in subgroups, or on OS. Improvements of second-line treatments resulted in prolonged survival, even in patients with advanced castration resistant disease.(21;22) The subsequently reduced number of prostate cancer-related deaths imposes a longer term follow-up (over ten years) before an improvement in overall survival can be achieved. Use of MFS in this specific context appears to be particularly appropriate. MFS was recently described as a strong surrogate of overall survival in patients with localized prostate cancer Xie *et al* 2017.(23)

The present trial reports a significant benefit on MFS in the global population with an acceptable tolerance in RT+ADT compared to radiotherapy alone group.

According to Xie and collaborators, our results in MFS showing a HR 0.73, 95%CI 0.54–0.98, should be translated into a predictive estimated HR 0.77, 95%CI 0.62–0.96 on OS. This projection is close to that calculated based on the correlation between PFS and OS (HR 0.71). This trial supported other recently published results.(12) However, some important

differences were observed. Patients in RTOG 9601 had persistent detectable PSA, received longer ADT and more side-effects such as gynecomastia were reported. Moreover half of the patients had a PSA level  $>0.7$  ng/ml at trial inclusion, whereas 80% of the patients in the GETUG-AFU 16 trial had PSA  $<0.5$  ng/ml: The GETUG-AFU 16 confirmed the potential favorable role of adding ADT to RT even in the most favorable group.(12) The RTOG 9601 trial showed that 20 patients had to be treated by a combined approach to prevent one death from prostate cancer. The GETUG-AFU 16 trial states that 14 patients should be treated by adding 6-month ADT to RT to prevent one patient from developing one event (metastatic disease or death) in the ten years.(12)

Pelvic irradiation treatment relative to androgen deprivation therapy did not improve survival in our series contrary to what was discussed in the margins of the SPPORT trial.(24) Pelvis irradiation, PSA doubling time less than 3 months, and the time to biological recurrence after surgery had no impact on survival as previously reported by Freedland and colleagues.(7;16) GETUG-AFU16 limitations include that baseline scans to rule out metastatic disease and follow-up scans to define metastatic events were not centrally reviewed. In addition, CT scan and bone scans were done only in case of relapse and no CT scan were required for follow-up which may introduce a bias since pain tolerance threshold vary from one individual to another. However we assume that this difference was equally balanced in the two arms.

Another limitation is the use of Partin tables which may be debatable. However, we chose these criteria in order to ensure that the decision of pelvic irradiation will be the same in participating centers. Our results used the dose of 66 Gy reported as the standard dose recommended when we designed the trial.(9;16;25) No randomized study reported that an increased dose is more relevant so far.(26;27)

Regarding tolerance data, we exclusively updated serious adverse event in the present follow-up. Nevertheless, one grade 3 treatment-related serious adverse event was reported out of all grade 3 or worse genitourinary events (n=55), and addition of 6-month ADT to RT does not support aggravation of urinary incontinence.(12;28) We can assume that long term toxicity should be acceptable based on the reduced toxicities initially reported.(12) However, only long term data collection would allow to point to a clear conclusion. Current prognostic criteria are not definitively validated. Further harmonization on the stratification according to prognostic factors should be helpful in interpreting data. However, the present data collection did not allow to further reconcile results according to EAU guidelines. The heterogeneity in prognostic group definition can explain differences with EAU propositions.(10)

The GETUG-AFU 16 enrolled more favorable patients compared to those included in RTOG 9601 or other retrospective trials.(6;16) Therefore, the probability to show a benefit in OS with a combined treatment using RT and 6-month androgen deprivation therapy after nearly 10 years median follow-up was reduced. By analogy with RTOG 9601 results, two groups of patients with two complementary approaches could be defined: Patients with high risk of cancer-related death should benefit from a long administration of ADT combined with RT.(13) The benefit/risk balance could be acceptable with regards to related side effects (gynecomastia, osteoporosis, or cardiovascular injury) and OS benefit. Patients at lower risk of cancer-related death should have a shorter ADT as defined by the GETUG-AFU 16, and in accordance with D'Amico and colleagues to prevent the onset of serious deleterious side effects.(29;30)

The GETUG-AFU 16 trial was designed 13 years ago and physics, medical oncology – through improved staging and metastatic disease characterization- and radiotherapy treatments have greatly evolved since the study initiation. In the near future, patient with biological relapse will have MRI examinations, and access to better resolution technologies with PET imaging; recent publications emphasized the importance of PSMA positron tomography with a high impact for radiotherapy planning. GETUG clinical trials currently required local CT scan and MRI for the inclusion of relapsing patients after surgery.(31;32) Therefore, the proportion of patients with biological relapse likely to achieve a metastatic status is reduced, and extended follow-up is required to demonstrate a benefit in OS. The use of MFS, recently proposed as a good surrogate to OS, is especially appropriate in this population of patients with less prostate cancer-related deaths, even after relapse. Beyond treatment impact on overall survival, the time without additional treatment jeopardizing the quality of life should be carefully considered.

In conclusion, GETUG-AFU 16 results confirmed the interest of ADT plus RT as salvage treatment in patients with rising PSA after radical prostatectomy, as evidenced in the RTOG trial for patients with more aggressive relapse.



### **Author contributions**

CC, SD, SC contributed to the trial conception and design. All authors contributed to data collection. CF and SC did the statistical analysis and contributed together with SC and CC to data analysis and interpretation. SD, SC, CC, and MB supervised the study. All authors reviewed the manuscript for intellectual content, provided comments, and gave final approval for publication.

### **Declaration of interest**

The sponsor has received grants from Astra Zeneca, La Ligue contre le Cancer, French Health Ministry, and La Ligue de Haute-Savoie. Dr. PEIFFERT reports personal fees from ASTELLAS PHARMA, personal fees from SANOFI AVENTIS FRANCE, personal fees from JANSSEN CILAG, personal fees from TAKEDA, outside the submitted work; Dr. Supiot reports grants, personal fees and non-financial support from janssen , personal fees and non-financial support from Ipsen, personal fees and non-financial support from Takeda, grants, personal fees and non-financial support from Astellas, personal fees and non-financial support from Ferring, grants, personal fees and non-financial support from Astra-Zeneca, outside the submitted work. The other authors declared no conflicts of interest.

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### **Data sharing statement**

Unicancer will share de-identified individual data that underlie the results reported 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 authorization 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 sent to [getug-afu16@unicancer.fr](mailto:getug-afu16@unicancer.fr), from 6 months until 5 years after the publication of this article.

## **Research in context**

### **Evidence before this study**

We searched PubMed with the terms “randomised trial”, “rising PSA”, “radical prostatectomy” and “salvage radiation therapy” between January, 1<sup>st</sup>, 1995 and December 31, 2018. We also considered the consensus statement on radiation therapy of prostate cancer published in Journal of Clinical Oncology in 1999, the prescribing recommendations from the ICRU published in 1993, and the RTOG 96-01 protocol despite the possibility of inclusion of patients with persistent PSA after radical prostatectomy. We previously published the randomised trial GETG-AFU 16, comparing androgen deprivation therapy plus radiotherapy *versus* radiotherapy alone, in patients with rising PSA after radical prostatectomy and excluding patients with persistent elevated PSA after surgery, and showed an improved PFS at 5 years. Only the first progression had been collected, and the metastatic progression could not be adequately captured, therefore Metastatic Free Survival was not analyzed.

### **Added value of this study**

The Metastatic Free Survival was pre-specified as secondary endpoint in our trial, and has recently been approved by the FDA as endpoint for men enrolled in clinical trials, and has been described as a strong surrogate of overall survival. Participating centers were required to specify for each patient alive at the time of the former analysis: local progression, metastatic progression, and death to update patient status at nearly 10 years.

### **Implications of all the available evidence**

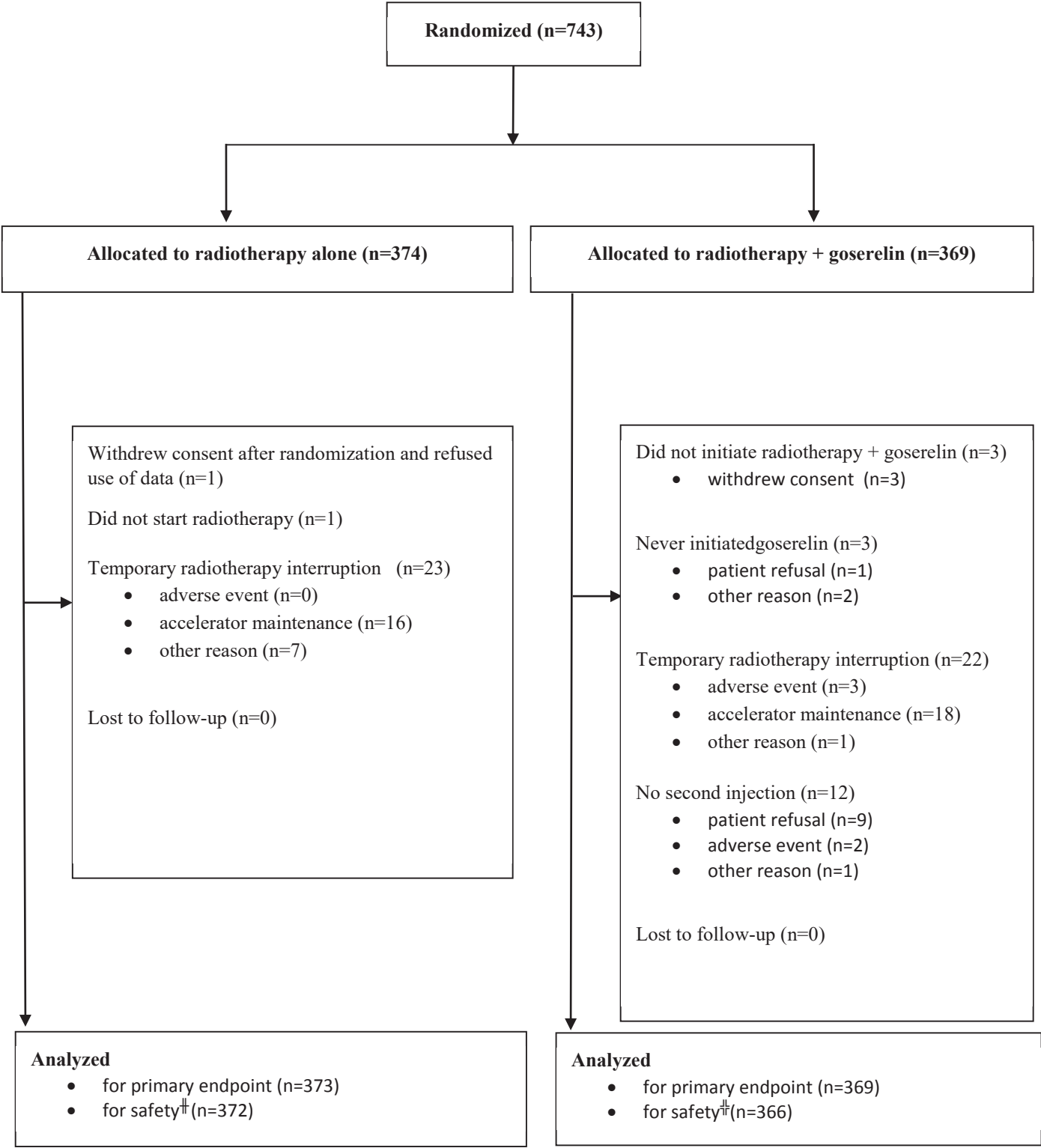
Salvage radiotherapy combined with short term ADT significantly improved 120-month MFS compared with salvage radiotherapy alone. GETUG-AFU 16 considered in the context of RTOG 9601 results, confirmed that this strategy confirmed the interest of ADT plus RT as salvage treatment for patients with rising PSA after radical prostatectomy.

## Reference List

- (1) Boorjian SA, Karnes RJ, Crispen PL, Rangel LJ, Bergstralh EJ, Blute ML. Radiation therapy after radical prostatectomy: impact on metastasis and survival. *J Urol* 2009 Dec;182(6):2708-14.
- (2) Spieler B, Goldstein J, Lawrence YR, et al. Salvage Radiation Therapy for Biochemical Failure Following Radical Prostatectomy. *Isr Med Assoc J* 2017 Jan;19(1):19-24.
- (3) Stish BJ, Pisansky TM, Harmsen WS, et al. Improved Metastasis-Free and Survival Outcomes With Early Salvage Radiotherapy in Men With Detectable Prostate-Specific Antigen After Prostatectomy for Prostate Cancer. *J Clin Oncol* 2016 Nov 10;34(32):3864-71.
- (4) Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999 May 5;281(17):1591-7.
- (5) Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int* 2012 Jan;109(1):32-9.
- (6) Choo R. Salvage radiotherapy for patients with PSA relapse following radical prostatectomy: issues and challenges. *Cancer Res Treat* 2010 Mar;42(1):1-11.
- (7) Freedland SJ, Humphreys EB, Mangold LA et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005 Jul 27;294(4):433-9.
- (8) Freedland SJ, Rumble RB, Finelli A et al. Adjuvant and salvage radiotherapy after prostatectomy: American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2014 Dec 1;32(34):3892-8.
- (9) Stephenson AJ, Kattan MW, Eastham JA et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. *J Clin Oncol* 2006 Aug 20;24(24):3973-8.
- (10) Van den Broeck T, van den Bergh RCN et al. Prognostic Value of Biochemical Recurrence Following Treatment with Curative Intent for Prostate Cancer: A Systematic Review. *Eur Urol* 2019 Jun;75(6):967-87.
- (11) Jang JW, Hwang WT, Guzzo TJ et al. Upfront androgen deprivation therapy with salvage radiation may improve biochemical outcomes in prostate cancer patients with post-prostatectomy rising PSA. *Int J Radiat Oncol Biol Phys* 2012 Aug 1;83(5):1493-9.
- (12) Carrie C, Hasbini A, de Laroche G et al. Salvage radiotherapy for patients with rising. *Lancet Oncol* 2016 Aug;17(8):e315.
- (13) Shipley WU, Seiferheld W, Lukka HR et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. *N Engl J Med* 2017 Feb 2;376(5):417-28.
- (14) Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD. Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology* 2001 Dec;58(6):843-8.
- (15) International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy. Report 50. Bethesda MD: ICRU. 2015. 1993.
- (16) Anscher MS, Clough R, Dodge R. Radiotherapy for a rising prostate-specific antigen after radical prostatectomy: the first 10 years. *Int J Radiat Oncol Biol Phys* 2000 Sep 1;48(2):369-75.
- (17) King CR, Presti JC, Jr., Gill H, Brooks J, Hancock SL. Radiotherapy after radical prostatectomy: does transient androgen suppression improve outcomes? *Int J Radiat Oncol Biol Phys* 2004 Jun 1;59(2):341-7.
- (18) Cheung R, Kamat AM, de CR, et al. Outcome of salvage radiotherapy for biochemical failure after radical prostatectomy with or without hormonal therapy. *Int J Radiat Oncol Biol Phys* 2005 Sep 1;63(1):134-40.

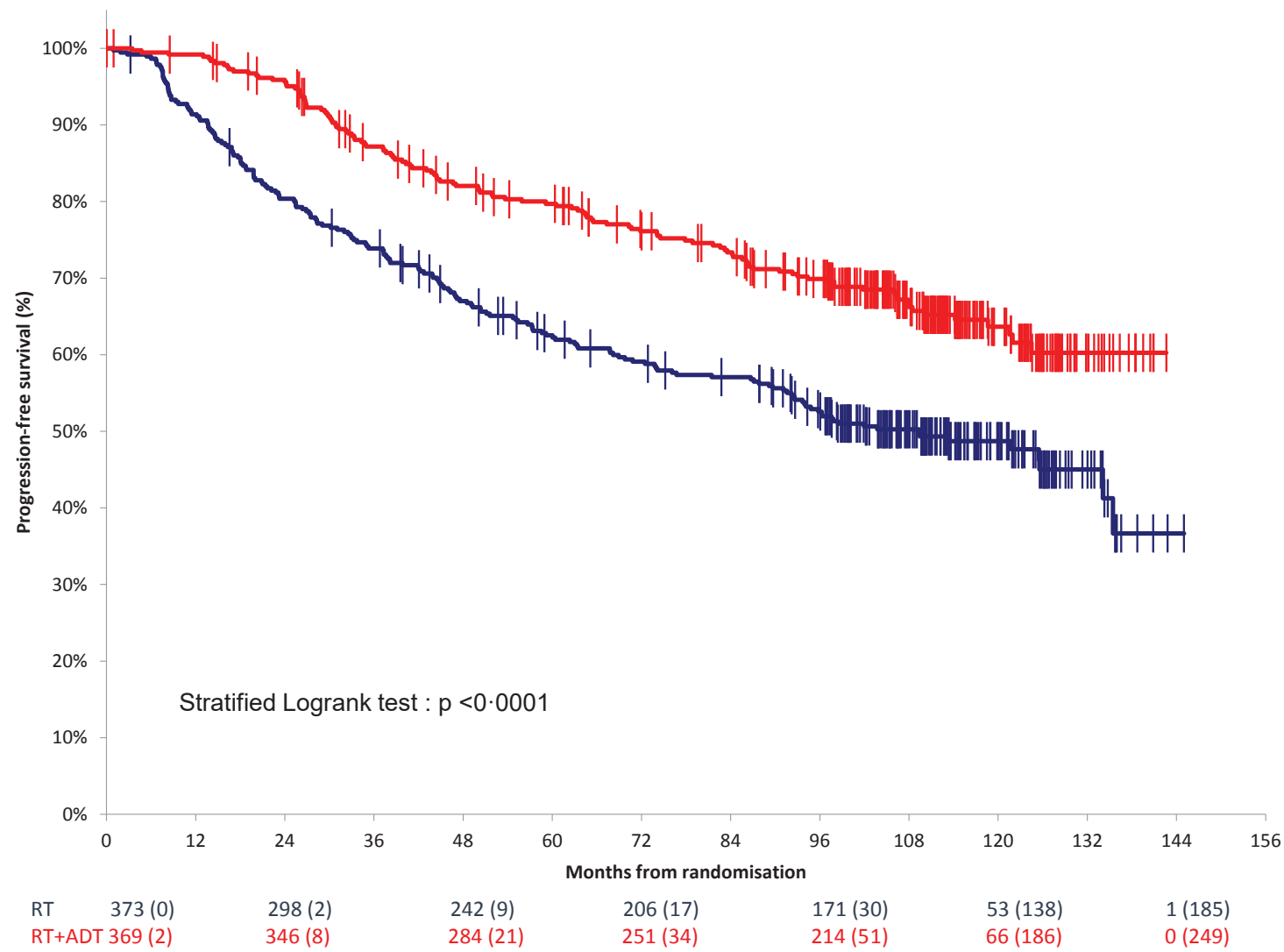
- (19) Katz MS, Zelefsky MJ, Venkatraman ES, Fuks Z, Hummer A, Leibel SA. Predictors of biochemical outcome with salvage conformal radiotherapy after radical prostatectomy for prostate cancer. *J Clin Oncol* 2003 Feb 1;21(3):483-9.
- (20) Soto DE, Passarelli MN, Daignault S, Sandler HM. Concurrent androgen deprivation therapy during salvage prostate radiotherapy improves treatment outcomes in high-risk patients. *Int J Radiat Oncol Biol Phys* 2012 Mar 1;82(3):1227-32.
- (21) Mateo J, Carreira S, Sandhu S, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N Engl J Med* 2015 Oct 29;373(18):1697-708.
- (22) Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2017 Jul 27;377(4):352-60.
- (23) Xie W, Regan MM, Buyse M, et al. Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. *J Clin Oncol* 2017 Sep 20;35(27):3097-104.
- (24) A.Pollack, T.G.Karrison, A.G.Balogh, et al. Short Term Androgen Deprivation Therapy Without or With Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiotherapy: The NRG Oncology/RTOG 0534 SPPORT Trial. *International Journal of Radiation Oncology* 102[5], 1605. 2018.
- (25) Cox JD, Gallagher MJ, Hammond EH, Kaplan RS, Schellhammer PF. Consensus statements on radiation therapy of prostate cancer: guidelines for prostate re-biopsy after radiation and for radiation therapy with rising prostate-specific antigen levels after radical prostatectomy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *J Clin Oncol* 1999 Apr;17(4):1155.
- (26) Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. *Eur Urol* 2017 Apr;71(4):630-42.
- (27) Kishan AU, Tendulkar RD, Tran PT, et al. Optimizing the Timing of Salvage Postprostatectomy Radiotherapy and the Use of Concurrent Hormonal Therapy for Prostate Cancer. *Eur Urol Oncol* 2018 May;1(1):3-18.
- (28) Adam M, Tennstedt P, Lanwehr D, et al. Functional Outcomes and Quality of Life After Radical Prostatectomy Only Versus a Combination of Prostatectomy with Radiation and Hormonal Therapy. *Eur Urol* 2017 Mar;71(3):330-6.
- (29) Giacalone NJ, Wu J, Chen MH, et al. Prostate-Specific Antigen Failure and Risk of Death Within Comorbidity Subgroups Among Men With Unfavorable-Risk Prostate Cancer Treated in a Randomized Trial. *J Clin Oncol* 2016 Nov 1;34(31):3781-6.
- (30) D'Amico AV. Can short-term hormone therapy for rising PSA prolong survival? *Lancet Oncol* 2016 Jun;17(6):687-8.
- (31) Gupta SK, Watson T, Denham J, et al. Prostate-Specific Membrane Antigen Positron Emission Tomography-Computed Tomography for Prostate Cancer: Distribution of Disease and Implications for Radiation Therapy Planning. *Int J Radiat Oncol Biol Phys* 2017 Nov 1;99(3):701-9.
- (32) Calais J, Kishan AU, Cao M, et al. Potential Impact of (68)Ga-PSMA-11 PET/CT on the Planning of Definitive Radiation Therapy for Prostate Cancer. *J Nucl Med* 2018 Nov;59(11):1714-21.

Figure 1: Enrollment, randomization and follow-up of patients.

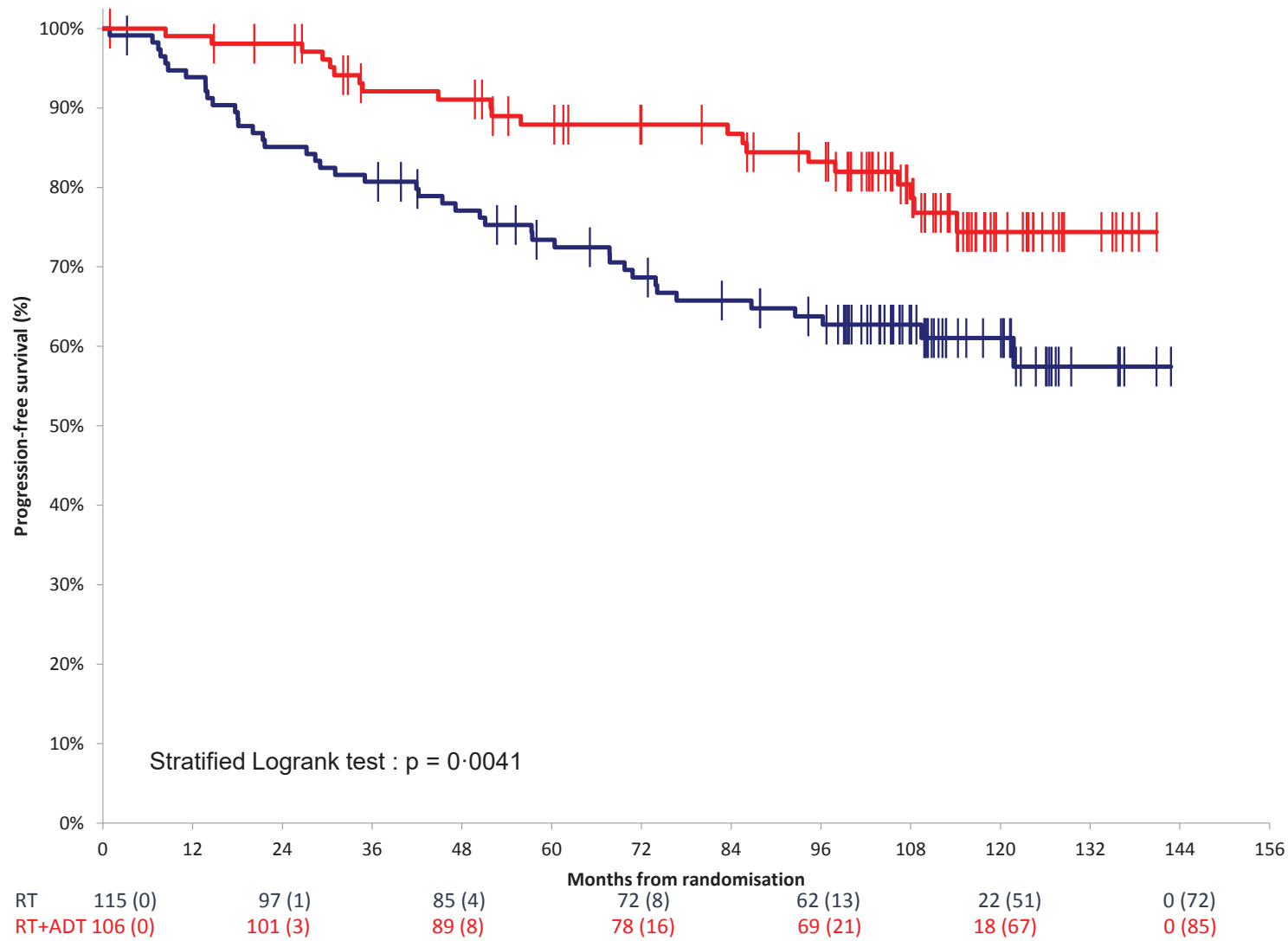


‡ only patients who received at least one dose of radiotherapy were analysed, ‡ only patients who received at least one dose of radiotherapy or one injection of goserelin were analysed.

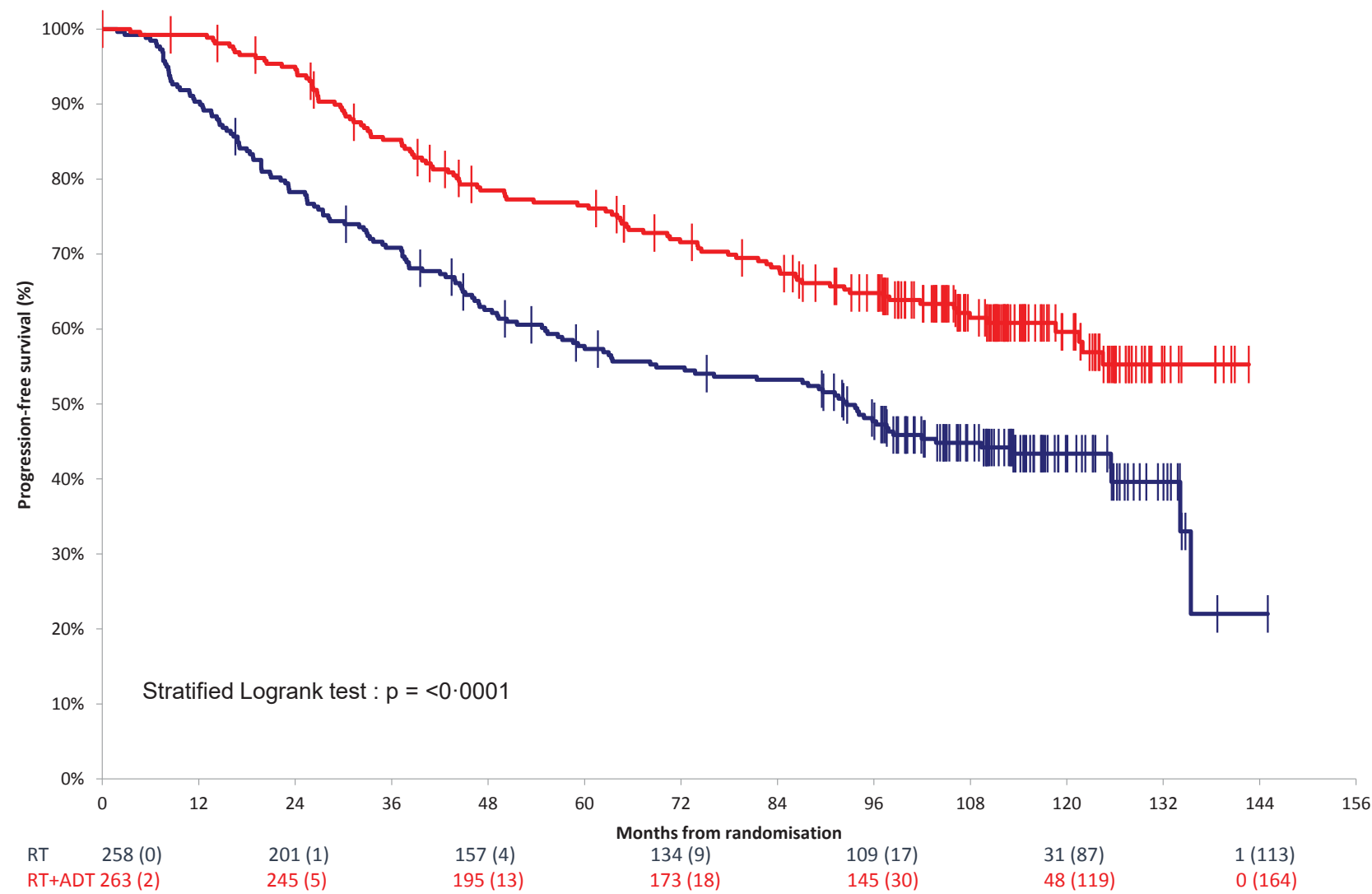
Figure  
A : Progression Free Survival : All patients



B : Progression Free Survival : Low-risk subgroup patients

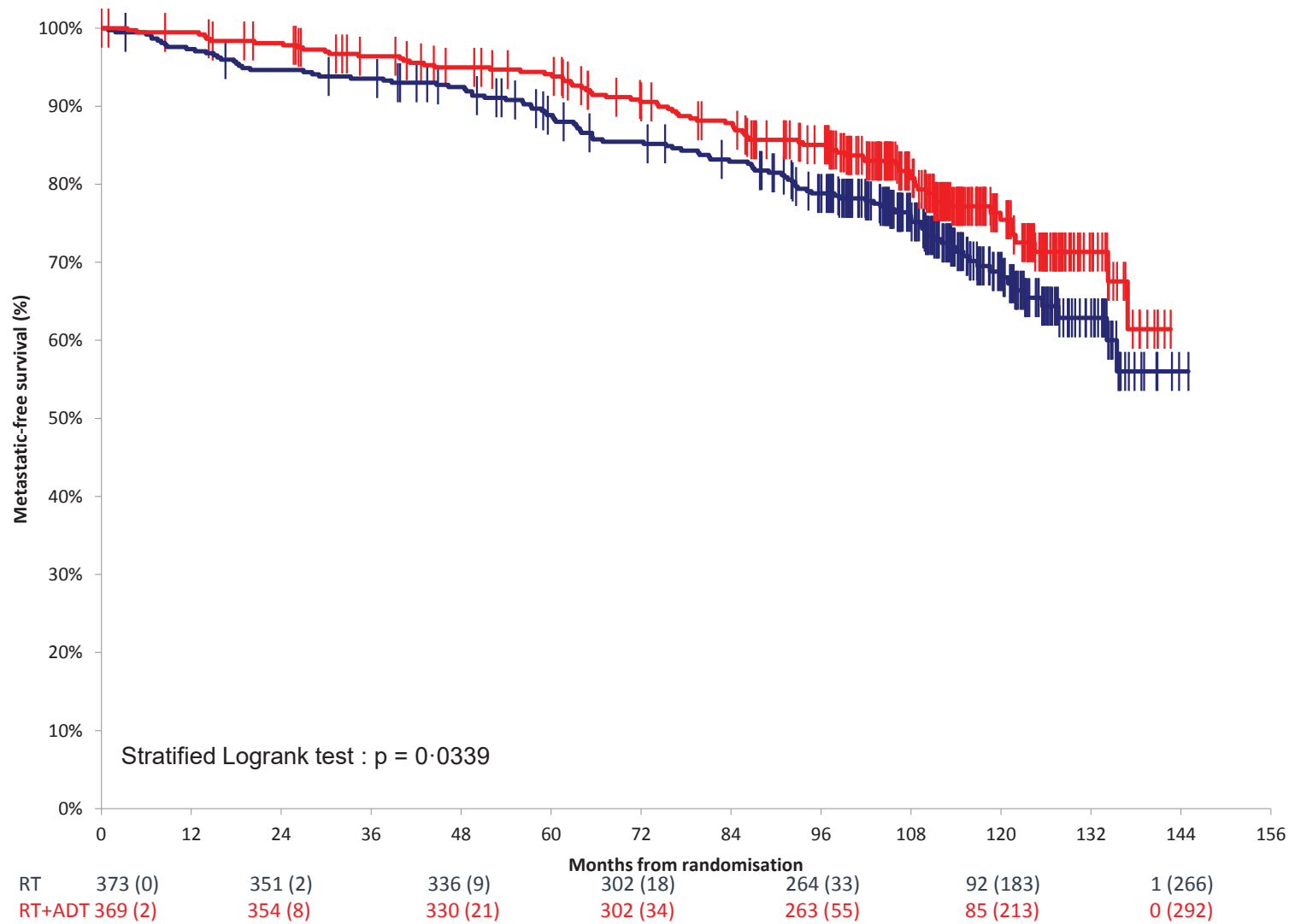


C : Progression Free Survival : High-risk subgroup patients

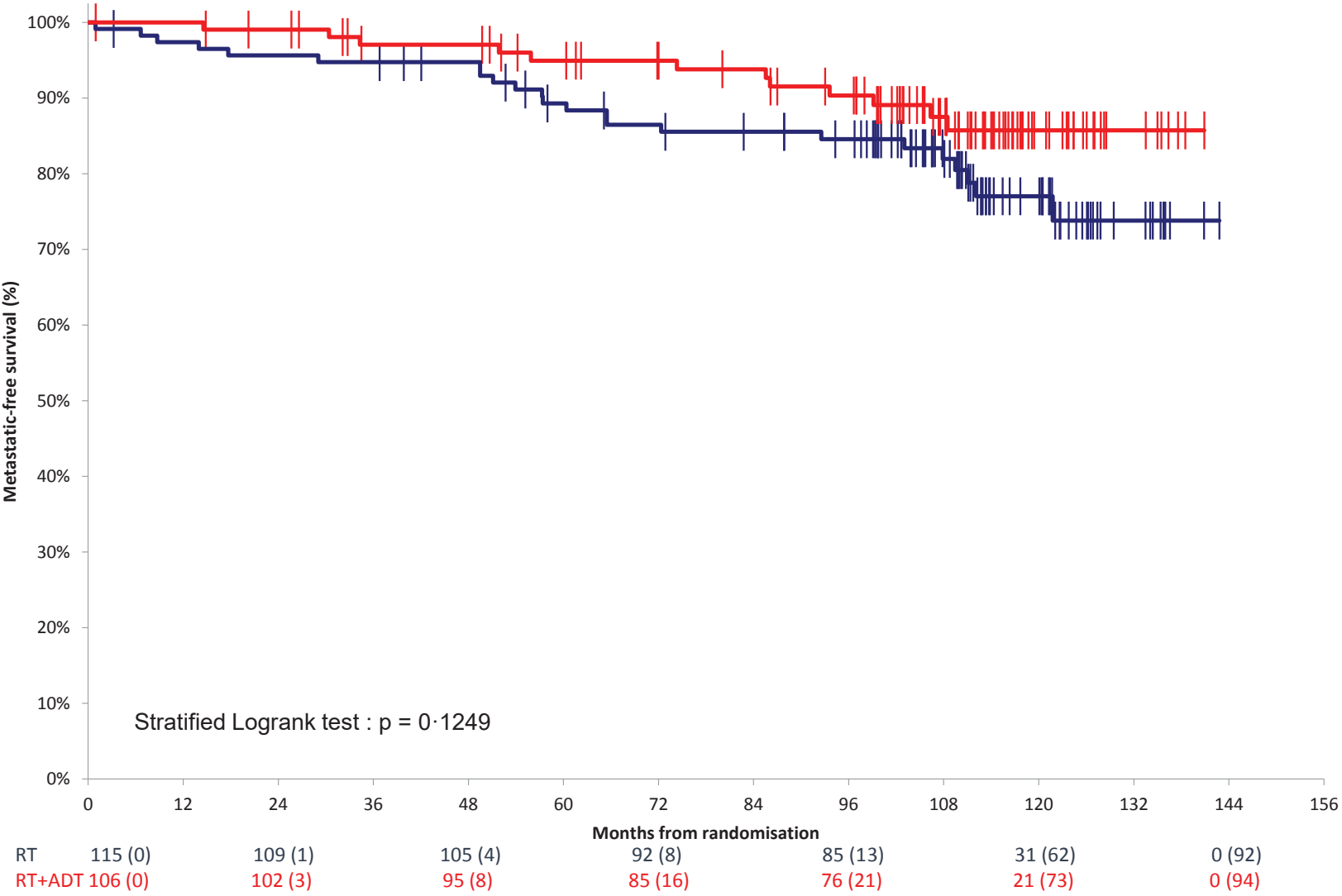




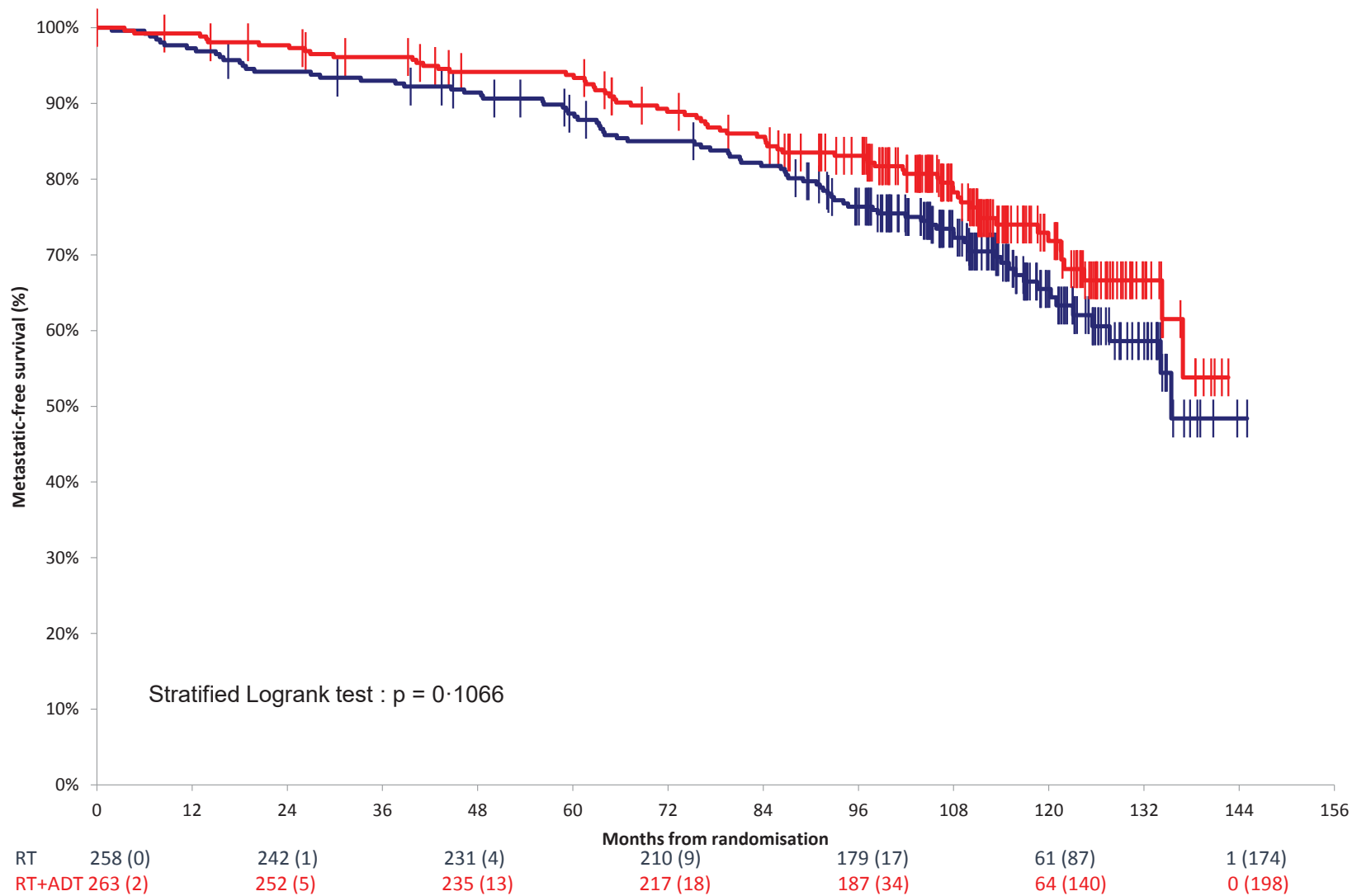
D : Metastatic Free Survival : All patients

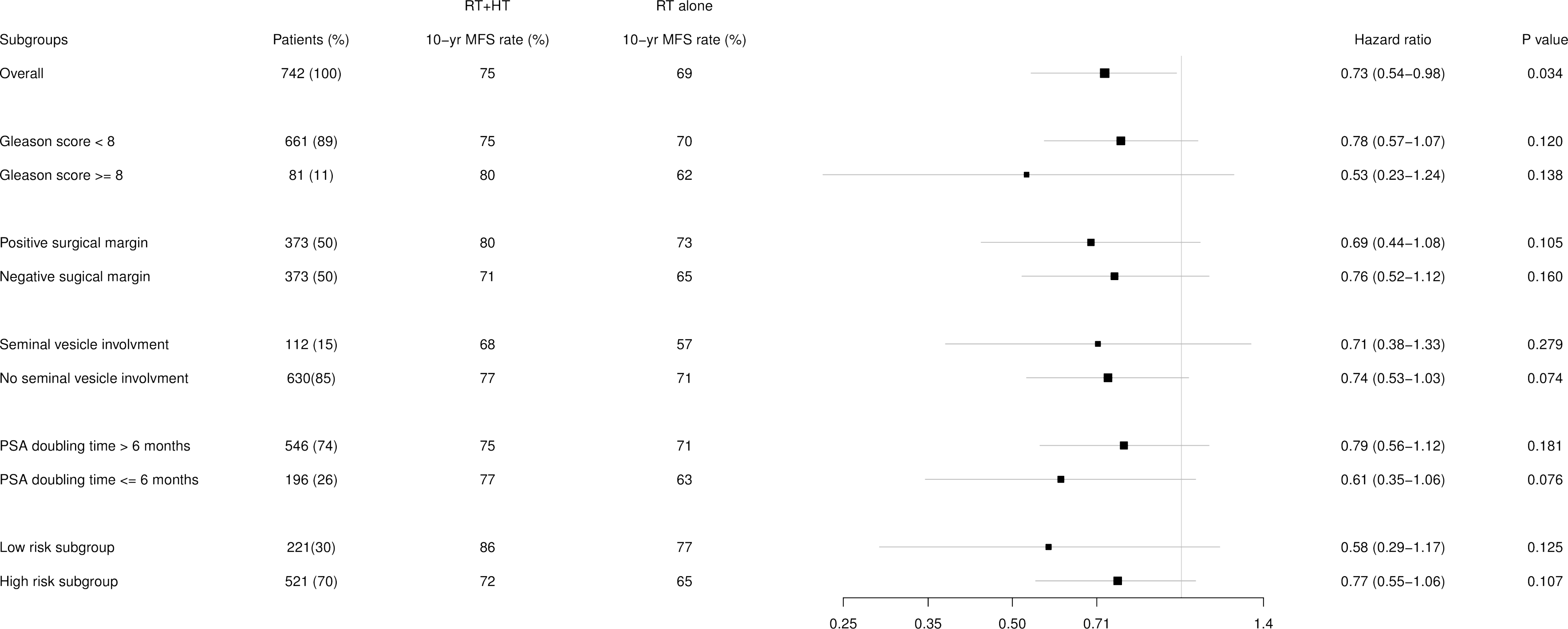


E : Metastatic Free Survival : Low-risk subgroup patients



F : Metastatic Free Survival : High-risk subgroup patients





**Table 1. Characteristics of the Patients at Baseline.** ECOG: Eastern Cooperative Oncology Group performance status. PSA: prostate specific antigen. Data are n% and median with range (min-max).

Characteristics	Radiotherapy alone N=373	Radiotherapy + goserelin N=369	Total population N=742
Age (years)			
Median	67	67	67
Range	52–85	49–80	49–85
Gleason score <8	332 (89)	329 (89)	661 (89)
Yes	332 (89)	329 (89)	661 (89)
No	41 (11)	40 (11)	81 (11)
pT (TNM 2005) †			
pT2a	37 (10)	29 (8)	66 (9)
pT2b	76 (20)	75 (20)	151 (20)
pT2c	88 (24)	92 (25)	180 (24)
pT3a	121 (33)	127 (35)	248 (34)
pT3b	50 (13)	44 (12)	94 (13)
pT4 bladder neck involvement	0 (0)	1 (0)	1 (0)
pN			
pNO	274 (74)	273 (74)	547 (74)
pNX	99 (27)	96 (26)	195 (26)
Positive surgical margins	196 (53)	175 (47)	371 (50)
No seminal vesicle involvement	318 (85)	312 (85)	630 (85)
PSA doubling time >6 months	276 (74)	270 (73)	546 (74)
Stratified Prognosis factor			
Low risk	115 (30.8%)	106 (28.7%)	221 (29.8%)
High risk	258 (69.2%)	263 (71.3%)	521 (70.2%)
ECOG Performance status ‡			
0	345 (96)	329 (94)	674 (95)
1	13 (4)	22 (6)	35 (5)
PSA before randomization (ng/ml)			
¶			
Median	0.30	0.30	0.30
Range	0–14	0–8	0–14
Median time between surgery and relapse (months) ¶			
Median	29.99	33.98	31.19
Range	0–162	2–166	0–166
Pre-surgery PSA (ng/ml) ¶			
Median	8.10	8.35	8.20
Range	0–46	0–800	0–800

\*There were no significant differences between the groups in any of the characteristics listed.

Percentages may not sum to 100 because of rounding

† 2 missing values; ‡ 33 missing values; ¶ 4 missing values; ¶ 169 missing values