Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial

Christian Carrie, Nicolas Magné, Patricia Burban-Provost, Paul Sargos, Igor Latorzeff, Jean-Léon Lagrange, Stéphane Supiot, Yazid Belkacemi, Didier Peiffert, Nedla Allouache, Bernard M Dubray, Stéphanie Servagi-Vernat, Jean-Philippe Suchaud, Gilles Crehange, Stéphane Guerif, Meryem Brihoum, Nicolas Barbier, Pierre Graff-Cailleaud, Alain Ruffion, Sophie Dussart, Céline Ferlay, Sylvie Chabaud

Lancet Oncol 2019; 20: 1740–49

Published Online October 16, 2019 https://doi.org/10.1016/S1470-2045(19)30486-3

See Comment page 1630

Radiotherapy Department, Léon Bérard Center, Lyon, France (C Carrie MD); **CNRS UMR 5220, INSERM U1044, INSA, University of Lyon, Lyon, France** (C Carrie); **Cellular and Molecular Radiobiology, Lucien Neuwirth Cancer Institute, and Institute of Nuclear Physics of Lyon, Lyon-Sud Faculty of Medicine, Lyon, France** (Prof N Magné MD); **private hospital of Cotes D'armor, Plerin, France** (P Burban-Provost MD); **Radiotherapy Department, Bergonié Institute, Bordeaux, France** (P Sargos MD); **Clinique Pasteur Groupe Oncorad Garonne, Toulouse, France** (I Latorzeff MD); **Henri Mondor Breast Center, Créteil, France** (Prof J-L Lagrange MD); **René Gaudducheau cancer Institute, Nantes, France** (S Supiot PhD); **Department of Radiation Oncology and Henri Mondor Breast Center, University of Paris-Est, Créteil, France** (Prof Y Belkacemi MD); **Lorraine Cancer Institute, Alexis Vautrin Cancer Center, Université de Lorraine, Faculté de Médecine, Vandoeuvre-les-Nancy, France** (Prof D Peiffert MD); **François Baclesse Cancer Center, Caen, France** (N Allouache MD); **Henri Becquerel Cancer Center, Rouen, France** (Prof B M Dubray MD); **Jean Godinot Institute, Reims, France** (S Servagi-Vernat PhD); **Radiotherapy Department, Roanne hospital center, Roanne, France** (J-P Suchaud MD); **Georges-François Leclerc**

Summary

Background Radiotherapy is the standard salvage treatment after radical prostatectomy. To date, the role of androgen deprivation therapy has not been formally shown. In this follow-up study, we aimed to update the results of the GETUG-AFU 16 trial, which assessed the efficacy of radiotherapy plus androgen suppression versus radiotherapy alone.

Methods GETUG-AFU 16 was an open-label, multicentre, phase 3, randomised, controlled trial that enrolled men (aged ≥18 years) with Eastern Cooperative Oncology Group performance status of 0 or 1, with histologically confirmed adenocarcinoma of the prostate (but no previous androgen suppression or pelvic radiotherapy), stage pT2, T3, or T4a (bladder neck involvement only) and pN0 or pNx according to the tumour, node, metastasis (TNM) staging system, whose prostate-specific antigen (PSA) concentration increased from 0·1 ng/mL to between 0·2 ng/mL and 2·0 ng/mL after radical prostatectomy, without evidence of clinical disease. Patients were assigned through central randomisation (1:1) to short-term androgen suppression (subcutaneous injection of 10·8 mg goserelin on the first day of irradiation and 3 months later) plus radiotherapy (3D conformal radiotherapy or intensity modulated radiotherapy of 66 Gy in 33 fractions, 5 days a week for 7 weeks) or radiotherapy alone. Randomisation was stratified using a permuted block method (block sizes of two and four) according to investigational site, radiotherapy modality, and prognosis. The primary endpoint was progression-free survival in the intention-to-treat population. This post-hoc one-shot data collection done 4 years after last data cutoff included patients who were alive at the time of the primary analysis and updated long-term patient status by including dates for first local progression, metastatic disease diagnosis, or death (if any of these had occurred) or the date of the last tumour evaluation or last PSA measurement. Survival at 120 months was reported. Late serious adverse effects were assessed. This trial is registered on ClinicalTrials.gov, NCT00423475.

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 12, 2019), the median follow-up was 112 months (IQR 102–123). The 120-month progression-free survival was 64% (95% CI 58–69) for patients treated with radiotherapy plus goserelin and 49% (43–54) for patients treated with radiotherapy alone (hazard ratio 0·54, 0·43–0·68; stratified log-rank test p<0·0001). Two cases of secondary cancer occurred since the primary analysis, but were not considered to be treatment related. No treatment-related deaths occurred.

Interpretation The 120-month progression-free survival confirmed the results from the primary analysis. Salvage radiotherapy combined with short-term androgen suppression significantly reduced risk of biochemical or clinical progression and death compared with salvage radiotherapy alone. The results of the GETUG-AFU 16 trial confirm the efficacy of androgen suppression plus radiotherapy as salvage treatment in patients with increasing PSA concentration after radical prostatectomy for prostate cancer.

Funding The French Health ministry, AstraZeneca, la Ligue Contre le Cancer, and La Ligue de Haute-Savoie.

Introduction

Approximately one third of patients who undergo radical prostatectomy for prostate cancer have disease recurrence. The standard treatment for patients with biochemical recurrence after radical prostatectomy is salvage radiotherapy. Indeed, compared with no salvage therapy, salvage radiotherapy significantly reduces the risk of distant metastasis (hazard ratio [HR] 0·24, 95% CI 0·13–0·45) and allows postponement of long-term androgen deprivation therapy and its related side effects.[1]

Research in context

Evidence before this study

We searched PubMed using the terms "randomised trial", "rising PSA", "radical prostatectomy", and "salvage radiation therapy" for articles published between Jan 1, 1995, and Dec 31, 2018. We also considered the consensus statement on radiotherapy of prostate cancer published in Journal of Clinical Oncology in 1999, the prescribing recommendations from the International Commission on Radiation Units and Measurements published in 1993, and the RTOG 9601 protocol, although this trial enrolled patients with persistently elevated prostate-specific androgen (PSA) concentration after radical prostatectomy. We previously published the first results of the randomised trial GETG-AFU 16, comparing androgen suppression plus radiotherapy versus radiotherapy alone in patients with rising PSA after radical prostatectomy (excluding patients with persistently elevated PSA concentrations after surgery), and showed an improved progression-free survival with the combination treatment at 5 years. Only data on the first progression were collected and metastatic progression could not be adequately captured, so metastasis-free survival was not assessable. RTOG 9601 showed a benefit in overall survival after a 12-year follow-up in patients who received radiotherapy plus two years of antiandrogen therapy compared with patients who received radiotherapy plus placebo.

Added value of this study

Metastasis-free survival was prespecified as secondary endpoint in our trial. This outcome has recently been approved by the US Food and Drug Administration as an endpoint for men with prostate cancer enrolled in clinical trials and has been described as a strong surrogate of overall survival. Participating centres were required to specify for each patient alive at the time of the primary analysis local progression, metastatic progression, and death, to update patient status at nearly 10 years after treatment. Our results confirm the benefit of adding short-term androgen deprivation therapy to salvage radiotherapy on metastasis-free survival in patients with biological recurrence after radical prostatectomy.

Implications of all the available evidence

Salvage radiotherapy combined with short-term androgen suppression significantly improved 120-month metastasis-free survival compared with salvage radiotherapy alone. The GETUG-AFU 16 trial, considered in the context of the results of the RTOG 9601 trial, confirmed the efficacy of androgen suppression plus radiotherapy as salvage treatment for patients with rising PSA after radical prostatectomy.

Cancer Center, Dijon, France (G Crehange PhD); **University hospital of Poitiers, Poitiers, France** (S Guerif MD); **UNICANCER, Paris, France** (M Brihoum MSc); **Catalan Cancer Center, Perpignan, France** (N Barbier MD); **University Institute of Cancer Toulouse-Oncopôle, Toulouse, France** (P Graff-Cailleaud PhD); **Urology Department, Hospices Civils de Lyon, Pierre-Bénite, France** (Prof A Ruffion MD); **and Biostatistics Unit, Clinical Research and Innovation Department, Léon Bérard Cancer Centre, Lyon, France** (S Dussart MD, C Ferlay MSc, S Chabaud MSc)

Correspondence to: Dr Christian Carrie, Radiotherapy Department, Centre Léon Bérard, 69008 Lyon, France **christian.carrie@lyon.unicancer.fr**

Salvage radiotherapy has been shown to be associated with favourable outcomes; 5-year progression-free survival is 68% (95% CI 60–75) in the overall population of patients with persistent or rising concentration of prostate-specific antigen (PSA) after prostatectomy and 87% (71–95) among patients with PSA concentration less than 0·3 ng/mL at the time of biological recurrence, 70% (58–80) among those with PSA concentration of 0·3–0·7 ng/mL, and 47% (31–51) among those with PSA concentration greater than 0·7 ng/mL.[2] At 5 years, metastasis-free survival has been found to be 92·5%, prostate cancer-specific survival 96·4%, and overall survival 94·9%. A 5-year cumulative incidence of biochemical recurrence of 42% was shown in patients with PSA concentration less than 0·5 ng/mL and of 56% in patients with PSA greater than 0·5 ng/mL at the beginning of salvage therapy.[3] Metastasis-free survival at 10 years has been found to be 48%.[4,5]

Only half of patients who have undergone salvage radiotherapy do not have biochemical relapse 5 years after the treatment.[6,7] A classification of the risk of biological recurrence in patients with salvage radiotherapy after radical prostatectomy has been proposed on the basis of time to relapse after surgery, PSA concentration doubling time at the time of relapse (high risk if less than 6 months), PSA concentration at the time of radiotherapy (high risk if PSA concentration is greater than 1 ng/mL), Gleason score (high risk if >7) and surgical margins (high risk if negative margins), or seminal vesicle involvement (high risk if seminal vesicle involvement identified).[7–9] In the high-risk group (defined as meeting one of the high risk criteria mentioned above), the risk of prostate cancer-related death in the absence of salvage treatment was found to be more than 90%, and 17% of patients with biological recurrence after radical prostatectomy died from prostate cancer in the absence of salvage treatment.[7] In addition, in patients with early (<3 years) relapse after salvage radiotherapy and PSA concentration doubling time less than 3 months, the median survival was only 3 years. On the other hand, patients with PSA concentration doubling time longer than 15 months and who relapsed more than 3 years after surgery had a 100% cause-specific survival.[7] Controversy exists regarding the effect 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 randomised controlled trial GETUG-AFU 16 showed a significant improvement of progression-free survival at 5 years in patients treated with combined short-term androgen suppression plus radiotherapy compared with those treated with radiotherapy alone, but no effect on overall survival was found.[12]

The randomised trial RTOG 9601, which enrolled patients with biochemical recurrence identified by persistently elevated PSA concentrations after prostatectomy

and with true relapse (ie, relapsing patients who were in complete response after surgery) showed a better overall survival at 13 years in patients treated with radiotherapy combined with 2-year androgen deprivation therapy than in patients treated with radiotherapy plus placebo. The magnitude of benefit was increased in patients with a PSA concentration greater than 1·5 ng/mL at the time of relapse.[13]

The objective of the present study is to update GETUG-AFU 16 results in terms of progression-free survival and metastasis-free survival 4 years after the original study and to confirm the efficacy of androgen suppression plus radiotherapy as salvage treatment in patients with rising PSA after radical prostatectomy.

Methods

Study design and participants

Patients, methods, and trial design have previously been published.[12] In this open-label, multicentre, randomised, controlled, phase 3 trial, men aged 18 years or older, with Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1, histologically confirmed prostate adenocarcinoma, stage pT2, T3, and T4a (bladder neck involvement only) and pN0, or pNx according to the tumour, node, and metastasis (TNM) staging system, were treated by radical prostatectomy in 43 GETUG trial centres. Eligible patients had: PSA concentrations lower than 0·1 ng/mL and stable for at least 6 months following surgery that began to rise after that (to 0·2–2 ng/mL as confirmed by two repeated tests) without evidence of clinical disease according to the international consensus guidelines; life expectancy of 10 years or more; adequate cardiac function, including controlled hypertension; and no known pituitary adenoma.[8,9] Patients who had had previous androgen suppression or pelvic irradiation were excluded. Patients were also excluded if: the initial status at the time of surgery was pN1; histology findings showed cancer other than adenocarcinoma; the patient had another invasive cancer in the previous 5 years; and another antineoplasic treatment was in progress.

The study was done in accordance with the principles of Good Clinical Practices. The protocol was approved by the institutional review board at Centre Léon Bérard (Lyon, France), 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 enrolment.

The first patient was enrolled on Oct 19, 2006. The trial was registered with ClinicalTrials.gov on Jan 18, 2007. This delay was related to slow implementation of recently applicable regulation regarding the central, prospective registration of clinical trials at the national level. However, inclusions were allowed (in compliance with the French law at the time) as soon as the ethics committee approval was received (ie, on April 6, 2006). 23 out of the 743 patients were included between Oct 19, 2006, and Jan 18, 2007.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio by permuted block method (block sizes two and four) to receive either radiotherapy alone (radiotherapy alone group) or radiotherapy plus 6 months of androgen suppression (radiotherapy plus goserelin group). Randomisation was stratified according to investigational site, radiotherapy modality (intensity-modulated radiotherapy *vs* conformational), and prognosis (high *vs* low risk of biological recurrence). The randomisation list was created by a statistician at the coordination centre who was not involved in data analysis. Clinicians and patients were not masked to allocation of study treatment.

Procedures

Initial cancer staging did not include bone scanning, CT, or MRI according to the recommendations at the time of the study for patients with a PSA concentration less than 2 ng/mL. PSA concentration was measured every 6 months for 5 years after radiotherapy and then once per year. No biopsy was required to confirm local or regional relapse, and treatment after relapse was left to the discretion of participating physicians. There was no central review of prostate specimens from surgery. To note, the study did not schedule annual scans or systematic scans. Only patients with biological relapse or reporting pain were subsequently scanned (CT and bone scan). A metastatic event was defined as a progression outside of the prostate bed, therefore any nodal relapse was considered to be a 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 radical prostatectomy 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 groups. Dose was prescribed according to the International Commission on Radiation Units.[15] In addition, patients in the radiotherapy plus goserelin group received goserelin acetate (Astra Zeneca, Courbevoie, France) 10·8 mg by injection on the first day of irradiation and again 3 months later. Per the GETUG group recommendations, patients defined as low-risk had a Gleason score of less than 8, positive surgical margins, PSA doubling time at relapse greater than 6 months, and no seminal vesicle involvement; patients defined as high risk had a Gleason score of 8 or more, negative surgical margins, PSA doubling time at relapse of 6 months or less, and seminal vesicle involvement. PSA concentration doubling time was calculated by dividing the natural log of 2 (0·693) by the slope of the relationship between the log of PSA and time of PSA measurement on three consecutives measurements taken every 2 months.[4]

Data for secondary cancers and serious adverse events potentially related to treatment were collected on an annual basis from medical records and graded according to the Common Terminology Criteria for Adverse Events version 3.

Outcomes

The primary endpoint was progression-free survival, defined as time from randomisation to documented biological recurrence or clinical progression (or both), death from any cause, or censoring at date of last follow-up. At the date of data cutoff (March 12, 2019), we updated progression-free survival. Biochemical relapse was defined in this study as an increase in PSA concentration by more than 0·5 ng/mL compared with the nadir (confirmed by a second PSA measurement). The date of the first increase in PSA concentration recorded was used in survival analyses.

Secondary prespecified outcomes were metastasis-free survival, overall survival, acute (occurring during treatment and the 6 months that followed) and late (occurring after the first 6 months following treatment) toxic effects, time to nadir of PSA concentration, and patients' quality of life and functional dependence 1 year and 5 years after radiotherapy.[12] Metastasis-free survival was defined as time from randomisation to documented metastasis or all cause death. Overall survival was measured from the date of randomisation to death from any cause or censoring at date of last follow-up. Time to nadir of PSA concentration, patients' quality of life, and patients' functional dependence 1 year and 5 years after radiotherapy were outcomes that have been reported previously.[12]

Statistical analysis

The trial was initially designed to detect a benefit in biochemical or clinical progression-free survival, or both, from 45% (radiotherapy alone) to 60% (radiotherapy plus goserelin) at 5 years, with a hazard ratio (HR) of 0·64, 5% two-sided alpha, and 90% power, for which 466 patients were needed. Because of the rapid accrual, and to increase powering for secondary endpoint analyses (overall survival and metastasis-free survival), a protocol amendment was made during the course of the study (Dec 11, 2008) to increase the sample size to 738 to achieve 80% power to detect an increase by 10 percentage points (from 75% to 85%) in overall survival (HR 0·58) at 10 years.

Overall survival was predefined as a secondary endpoint. The sample size was calculated assuming an increase in overall survival at 10 years ranging from 75% to 85%. However, less than 6% of patients died in 2016, at the time of the primary endpoint analysis, and during an extended follow-up it became evident that survival of these patients was so good that follow-up would need to be extended substantially to analyse overall survival. Based on results published by Xie and colleagues,[16] we decided to use metastasis-free survival as a surrogate for overall survival, which would allow us to shorten the study follow-up time necessary to show treatment efficacy in the case that the entire cohort did not die or was not censored. The protocol amendment made during the study (Dec 11, 2008) increased the sample size and included 10-year overall survival as an additional outcome. End of recruitment occurred in March, 2010. Based on inclusion of more than 60% of patients before the end of 2008, we hypothesised that the median 10-year follow-up would have been achieved by the end of 2018, and a single update was initiated. 4 years after the last data cutoff (Dec 12, 2014), the database was locked on March 12, 2019. Median follow-up was calculated by the inverse Kaplan-Meier method. Participating centres were requested to update follow-up data for each patient alive at the time of the primary analysis.[12] Participating centres updated the dates for first local progression, for metastatic disease diagnosis, or death, if any of these events occurred, or indicated the date of the last tumour evaluation or the last PSA measurement. Subsequent treatments after relapse were not captured and were left to physician's discretion.

In the previously published GETUG-AFU 16 analysis,[12] only the first progression event had been collected, therefore metastasis-free survival could not be analysed (eg, if the first event was local or regional progression, metastatic progression could not adequately be captured).

Efficacy endpoints (progression-free survival, metastasis-free survival, and overall survival) were prespecified and

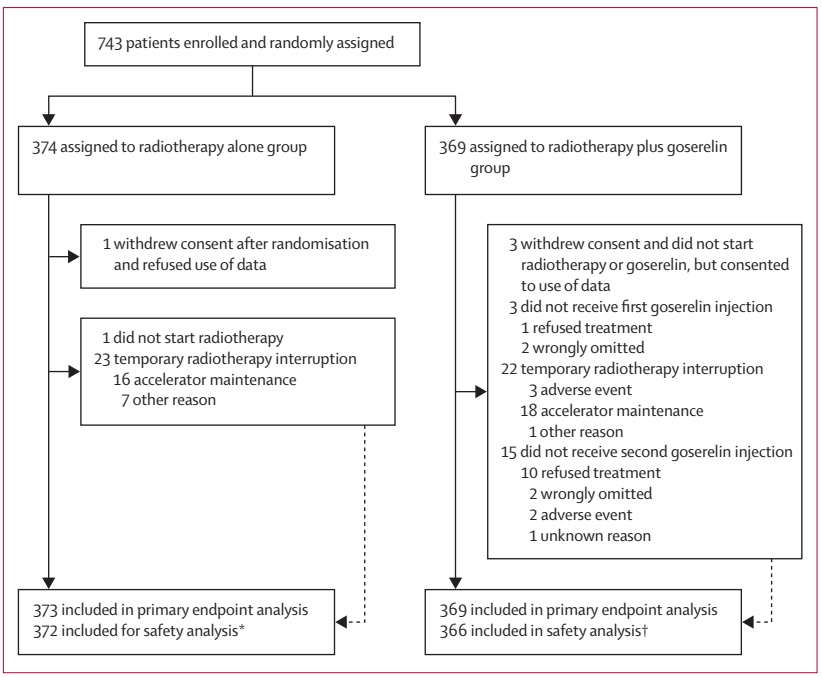

Figure 1: **Study profile**
*Only patients who received at least one dose of radiotherapy were analysed. †Only patients who received at least one dose of radiotherapy or one injection of goserelin were analysed.

	Radiotherapy alone group (n=373)	Radiotherapy plus goserelin group (n=369)
Median age (years)	66·8 (61·5–71·9)	69·5 (62·9–72·1)
Gleason score <8		
Yes	332 (89%)	329 (89%)
No	41 (11%)	40 (11%)
pT (TNM 2005)*		
pT2a	37 (10%)	29 (8%)
pT2b	76 (20%)	75 (20%)
pT2c	88 (24%)	92 (25%)
pT3a	121 (33%)	127 (35%)
pT3b	50 (13%)	44 (12%)
pT4 bladder neck involvement	0	1 (<1%)
pN (TNM 2005)		
pN0	274 (73%)	273 (74%)
pNx	99 (27%)	96 (26%)
Positive surgical margins	196 (53%)	175 (47%)
No seminal vesicle involvement	318 (85%)	312 (85%)
PSA doubling time >6 months	276 (74%)	270 (73%)
Stratified prognosis factor		
Low risk	115 (31%)	106 (29%)
High risk	258 (69%)	263 (71%)
ECOG performance status†		
0	345 (96%)	329 (94%)
1	13 (4%)	22 (6%)
Median PSA concentration before randomisation (ng/mL)‡	0·3 (0·2–0·5)	0·3 (0·2–0·5)
Median time between surgery and relapse (months)‡	30 (19–52)	34 (21–53)
Median pre-surgery PSA concentration (ng/mL)§	8·1 (6·1–11·6)	8·4 (6·0–12·2)

Data are n (%) and median (IQR). Percentages may not sum to 100 because of rounding. TNM=Tumour, Node, Metastasis classification. ECOG=Eastern Cooperative Oncology Group performance status. PSA=prostate-specific antigen. *2 missing values. †33 missing values. ‡4 missing values. §169 missing values.

Table: **Baseline characteristics**

analysed in the intention-to-treat population. We also did post-hoc analyses of progression-free survival in the high-risk and low-risk subgrups and a post-hoc subgroup analysis of metastasis-free survival (Gleason score <8 *vs* ≥8, positive *vs* negative surgical margin, involvement *vs* no involvement of seminal vescicle, PSA doubling time >6 months *vs* ≤6 months). The Kaplan-Meier method was used to estimate time-to-event endpoints, and two-sided log-rank tests stratified on randomisation 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% CIs) are presented at 120 months. The number of patients needed to treat to prevent one event (metastasis or death) when adding androgen suppression to radiotherapy was obtained using the risk difference inverse ratio and used to report the magnitude of the benefit.

Statistical analyses were done with SAS software (version 9.4).

This trial is registered with ClinicalTrials.gov, NCT00423475.

Role of the funding source

The funder of the study was involved in data monitoring and pharmacovigilance but played no role in study design, data collection, data analysis, data interpretation, or writing of the report. CC, CF, and SC had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Oct 19, 2006, and March 30, 2010, 743 patients were randomly assigned to receive either radiotherapy alone (n=374) or radiotherapy plus goserelin (n=369; figure 1). Baseline characteristics, treatment, toxicity, and quality of life have been published previously (table).[12] Since one patient in the radiotherapy alone group withdrew consent, 742 patients were included in the intention-to-treat analysis (373 patients in the radiotherapy alone group and 369 patients in the radiotherapy plus goserelin group).

738 patients received radiotherapy. The median dose to the prostate bed was 66 Gy (IQR 66–66) and the median duration of radiotherapy was 7 weeks (6·7–7·3) in the two groups. Three patients (<1%) had a total duration of more than 10 weeks because of acute urinary retention (n=1), intercurrent disease (n=1), and an unknown reason (n=1). Only 119 patients (16%) received nodal pelvic irradiation: 56 (15%) of 372 patients in the radiotherapy alone group and 63 (17%) of 365 patients in the radiotherapy plus goserelin group. Data for nodal pelvic irradiation was missing for one patient in the radiotherapy plus goserelin group. An irradiation of up to 50 Gy of the seminal vesicles area was performed exclusively in patients with stage pT3b disease.

The first injection of goserelin was administered in all but three patients (n=363 [99%]) in the radiotherapy plus goserelin group (one patient refused and the injection was inadvertently omitted for two patients). The second injection was given in 351 (96%) of 366 patients. Of the 15 patients who did not receive it, 10 patients had refused, in two patients the injection was inadvertently omitted, two patients had toxic effects (rash and hypertension), and in one patient the reason was unknown. The median time to nadir PSA was 9·4 months (IQR 7·3–17·5) in the radiotherapy alone group and 3·0 months (2·3–7·6) in the radiotherapy plus goserelin group.

At 5 years, significantly more patients randomly assigned to the radiotherapy plus goserelin group than patients assigned to the radiotherapy alone group were free of biochemical or clinical progression (80% [95% CI 75–84] in the radiotherapy plus goserelin group

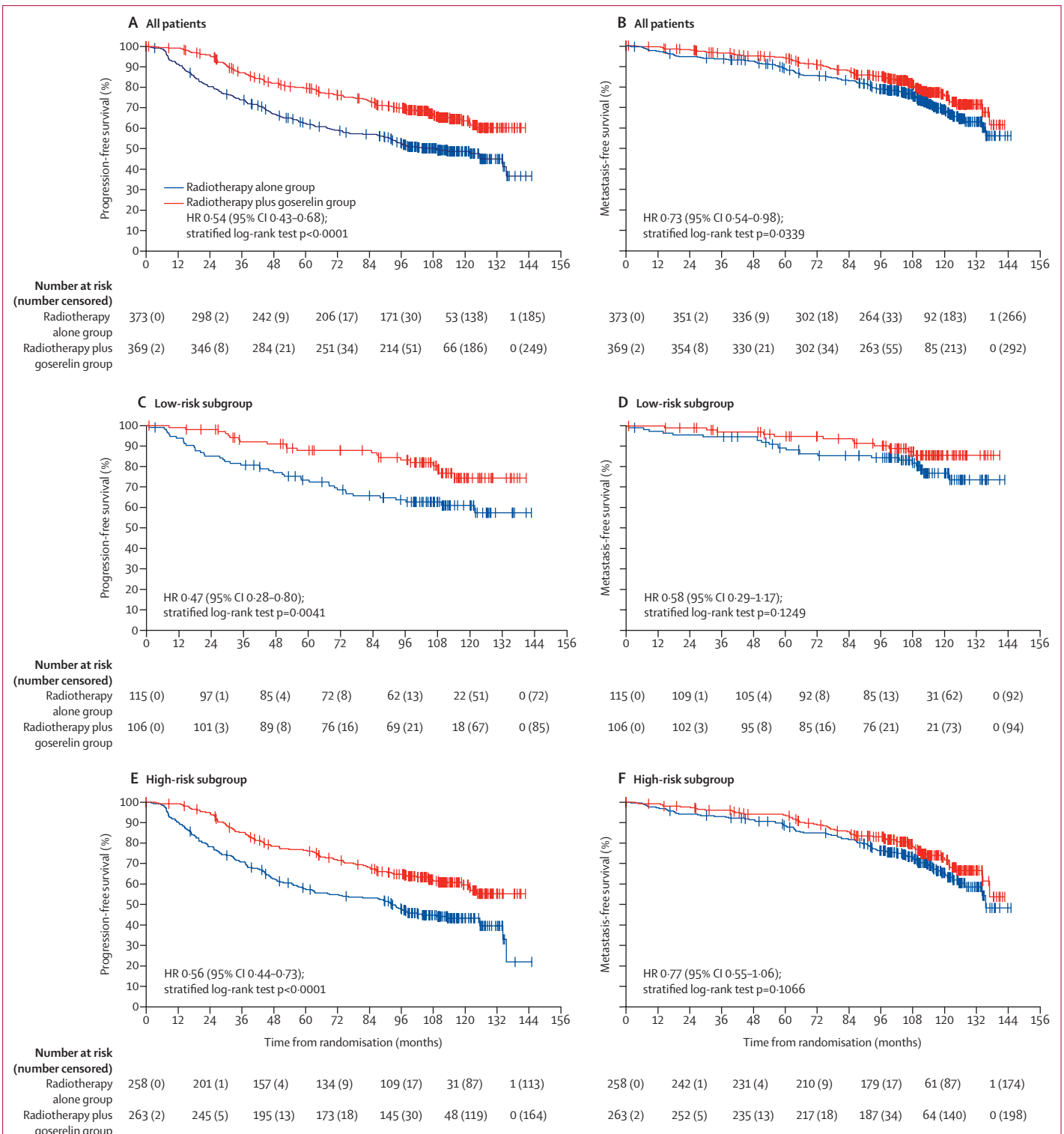

***Figure 2*: Kaplan-Meier plots for progression-free survival (A, C, and E) and metastasis-free survival (B, D, and F)**
Progression-free survival in (A) the overall population, in the subgroups of patients at (C) low or (E) high risk of biological or metastatic recurrence or prostate-cancer related death. Metastasis-free survival (B) in the overall population and in the subgroups of patients at (D) low or (F) high risk of biological or metastatic recurrence or prostate-cancer related death. HR=hazard ratio.

	n (%)	10-year MFS (95% CI)		Hazard ratio (95% CI)	p value
		Radiotherapy plus goserelin group	Radiotherapy alone group		
Gleason score <8	661 (89%)	75% (69–80)	70% (64–75)	0·78 (0·57–1·07)	0·120
Gleason score ≥8	81 (11%)	80% (61–90)	62% (43–76)	0·53 (0·23–1·24)	0·138
Positive surgical margin	373 (50%)	80% (72–86)	73% (64–79)	0·69 (0·44–1·08)	0·105
Negative sugical margin	373 (50%)	71% (63–78)	65% (56–72)	0·76 (0·52–1·12)	0·160
Seminal vesicle involvement	112 (15%)	68% (52–80)	57% (42–70)	0·71 (0·38–1·33)	0·279
No seminal vesicle involvement	630 (85%)	77% (70–82)	71% (64–76)	0·74 (0·53–1·03)	0·074
PSA doubling time >6 months	546 (74%)	75% (68–81)	71% (64–77)	0·79 (0·56–1·12)	0·181
PSA doubling time ≤6 months	196 (26%)	77% (64–85)	63% (50–73)	0·61 (0·35–1·06)	0·076
Low-risk subgroup	221(30%)	86% (76–92)	77% (67–85)	0·58 (0·29–1·17)	0·125
High-risk subgroup	521 (70%)	72% (65–78)	65% (58–72)	0·77 (0·55–1·06)	0·107
Overall	**742 (100%)**	**75% (70–80)**	**69% (63–74)**	**0·73 (0·54–0·98)**	**0·034**

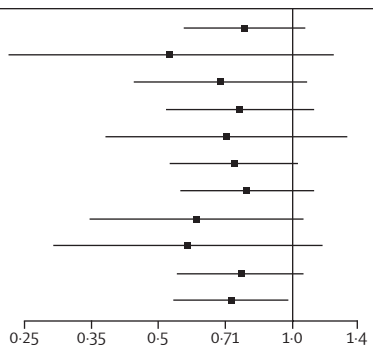

Figure 3: **Subgroup analysis of MFS**
MFS=metastasis-free survival

vs 62% [57–67] in the radiotherapy alone group; HR 0·50, 95% CI 0·38–0·66; p<0·0001).[12]

At data cutoff (March 12, 2019), the median duration of follow-up was 112 months (IQR 102–123) and 307 (41%) of 742 patients had progression or died: 120 (33%) of 369 patients in the radiotherapy plus goserelin group and 187 (50%) of 373 patients in the radiotherapy alone group. The 120-month progression-free survival was 64% (95% CI 58–69) for patients in the radiotherapy plus goserelin group and 49% (43–54) for patients in the radiotherapy alone group (HR 0·54, 0·43–0·68; stratified log-rank test p<0·0001; figure 2A).

See Online for appendix

A post-hoc subgroup analysis found a 120-month progression-free survival of 61% (95% CI 51–70) in the radiotherapy alone group versus 74% (63–83) in the radiotherapy plus goserelin group for patients in the low-risk subgroup, and of 43% (37–50) versus 60% (53–66) for patients in the high-risk subgroup (figures 2B, 2C).

Metastasis-free survival events were diagnosed in 77 (21%) of 369 patients in the radiotherapy plus goserelin group versus 106 (28%) of 373 patients of radiotherapy alone group. 120-month metastasis-free survival was 75% (95% CI 70–80) in patients assigned to the radiotherapy plus goserelin group versus 69% (63–74) in patients assigned to the radiotherapy alone group (HR 0·73, 0·54–0·98; stratified log-rank test p=0·0339; figure 2D).

No difference in metastasis-free survival was observed between treatment groups for patients in the low-risk subgroup or high-risk subgroup (figures 2E, 2F).

Post-hoc subgroup analysis of metastasis-free survival showed no difference between treatment groups (figure 3).

97 (13%) of 742 patients died, 46 (12%) of 369 patients in the radiotherapy plus goserelin group and 51 (14%) of 373 patients in the radiotherapy alone group. Deaths were due to prostate cancer (n=30; n=12 in the radiotherapy plus goserelin group versus n=18 in the radiotherapy alone group), any other cancer (n=19; n=9 *vs* n=10), cardiac causes (n=9; n=3 *vs* n=6), other causes (n=25; n=14 *vs* n=11), or unknown causes (n=14; n=8 *vs* n=6). No treatment-related deaths occurred.

120-month overall survival was 86% (95% CI 81–89) for patients assigned to the radiotherapy plus goserelin group and 85% (80–89) for patients assigned to the radiotherapy alone group (HR 0·93, 0·63–1·39; two-sided p=0·73; appendix).

Mortality due to cancer was similar in the two groups (18 [5%] of 369 patients died in the radiotherapy plus goserelin group *vs* 12 [3%] of 373 patients in the radiotherapy alone group), as was the proportion of patients diagnosed with the onset of a secondary cancer (ten [3%] of 369 *vs* nine [2%] of 373).

Two cases of secondary cancers have been reported since the primary analysis[12] but were not considered to be treatment related. Tolerance data for serious adverse events were updated. No differences in the newly reported serious adverse events were observed. Only one grade 3 treatment-related serious adverse event was reported of all grade 3 or worse genitourinary events (n=55). No aggravation of urinary incontinence was observed with the addition of 6-month androgen deprivation therapy to radiotherapy (15 [4%] of 369 patients in the radiotherapy plus goserelin group *vs* 20 [5%] of 373 in the radiotherapy alone group reported late grade 3–4 adverse events of urinary incontinence).

At 120 months, the number of patients needed to treat to prevent one event (metastasis or death) when adding androgen suppression to radiotherapy was 14 (calculated on the basis of the prevalence of events of 19·2% in the radiotherapy plus goserelin group *vs* 26·3% in the radiotherapy alone group).

Discussion

The final results of the multicentre, open-label, randomised, controlled, phase 3 trial GETUG-AFU 16 confirm that the addition of 6-month goserelin to salvage

radiotherapy leads to an increased metastasis-free survival in patients with biochemical relapse after radical prostatectomy.

To date, radical prostatectomy is one of the most established treatments for localised prostate cancer in men younger than 70 years. However, the rate of biochemical recurrence at 5 years is 30–70%, depending on the initial staging. Studies have suggested a potential benefit of salvage radiotherapy, following which half of relapsing patients achieved complete biochemical response.[11,17] One prospective study and other retrospective analyses strongly suggest a benefit of androgen suppression combined with salvage radiotherapy.[18–21] Although guidelines show high-grade recommendations in favour of salvage radiotherapy, salvage treatment has not been precisely defined yet.

Current prognostic tools include the determination of PSA concentration, and its increase over time has long been the sole proof of a disease progressing in the absence of clinical symptoms; however, offering salvage therapy in response to rising PSA concentrations has never been shown to correlate with overall survival except in one randomised trial.[13] Shipley and colleagues showed a benefit in overall survival at 13 years in patients with rising PSA concentration or persistently elevated PSA concentration after radical prostatectomy who were treated with a 2-year androgen deprivation therapy and salvage radiotherapy.[13] Although we had a median follow-up of nearly 10 years in this study, a longer follow-up would be necessary to achieve the required number of events and high enough power to obtain significant results in subgroup and overall survival analyses. Improvements in the efficacy of second-line treatments has resulted in prolonged survival, even in patients with advanced, castration-resistant disease.[22,23] The resulting reduced number of prostate cancer-related deaths means a longer-term follow-up (over 10 years) is required before an improvement in overall survival can be observed. Hence, in this specific context, metastasis-free survival appears to be particularly appropriate outcome and has been described as a strong surrogate of overall survival in patients with localised prostate cancer.[16]

This trial reports a significant benefit in metastasis-free survival in the patients assigned to the radiotherapy plus goserelin group compared with those assigned to the radiotherapy alone group.

On the basis of Xie and collaborators' results reporting metastasis-free survival as a strong surrogate for overall survival,[16] our results for metastasis-free survival showing a HR 0·73 (95% CI 0·54–0·98), should translate into a predictive estimated HR of 0·77 (0·62–0·96) for overall survival. This projection is close to that calculated on the basis of the correlation between progression-free survival and overall survival (HR 0·71 [0·62–0·82]).[16] The results of our trial support other published results.[12,13] However, some important differences were observed. Patients in the RTOG 9601 trial[13] had persistently detectable PSA, received androgen deprivation therapy for longer, and reported more side-effects (such as gynecomastia). Moreover, half of the patients had a PSA concentration greater than 0·7 ng/mL at trial inclusion, whereas 80% of the patients in the GETUG-AFU 16 trial had PSA concentration less than 0·5 ng/mL; hence, the GETUG-AFU 16 confirmed the potentially positive effect of adding androgen suppression to radiotherapy even in the most favourable group.[12] The RTOG 9601 trial[13] showed that 20 patients had to be treated by a combined approach to prevent one death from prostate cancer. We found that 14 patients should be treated by adding 6-month goserelin to radiotherapy to prevent one patient from developing one event (metastatic disease or death) in the 10 years after salvage radiotherapy.[12]

Pelvic irradiation treatment did not improve survival in our trial contrary to what was discussed in the SPPORT trial.[24] Pelvis irradiation, PSA concentration doubling time less than 3 months, and the time to biological recurrence after surgery was not associated with survival, as reported by Freedland and colleagues.[7,17]

Limitations of the GETUG-AFU 16 trial include that baseline scans to rule out metastatic disease and follow-up scans to define metastatic events were not centrally reviewed. In addition, CT and bone scans were done only in case of relapse and no CT scan was required for follow-up, which might introduce a bias since pain tolerance threshold varies between individuals. However, we assume that this difference was equally balanced in the two groups.

Another limitation is the still controversial use of Partin tables for the assessment of seminal vescicle involvement status, as the risk associated with seminal vescicle involvement. However, we chose these criteria in order to ensure consistency in the decision to deliver pelvic irradiation across participating centres. We used a dose of 66 Gy, which was the standard recommended dose at the time of trial design.[9,17,25] Thus far, no randomised study has reported that an increased dose would be more appropriate.[26,27]

Regarding tolerance data, we exclusively updated serious adverse events in the present follow-up. However, only 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 androgen suppression to radiotherapy does not aggravate urinary incontinence.[12,28] The rate of toxic effects at 5 years was low and did not increase with an extended follow-up[12] However, only long-term data collection would allow accurate conclusions to be drawn. Current prognostic criteria are not definitively validated. Further harmonisation on stratification according to prognostic factors would be helpful in interpreting data. The criteria used for classification according to European Association of Urology guidelines and those used by the GETUG group are different and current results are not comparable.[10]

GETUG-AFU 16 enrolled patients more likely to have a favourable outcome than those included in the

RTOG 9601 trial[13] or other retrospective trials.[6,17] Therefore, the probability of showing a benefit in overall survival with a combined treatment of radiotherapy and 6-month androgen suppression after a nearly 10-year median follow-up was reduced. GETUG-AFU 16 and RTOG 9601 use two complementary approaches and we propose the definition of two groups of patients. The first group comprises patients with high-risk of cancer-related death, who should benefit from long-term administration of androgen suppression combined with radiotherapy.[13] The risk–benefit balance could be acceptable with regards to related side effects (gynecomastia, osteoporosis, or cardiovascular injury) and overall-survival benefit. The second group, including patients at lower-risk of cancer-related death, should have a shorter duration of androgen deprivation therapy, as defined by the GETUG-AFU 16 trial and in accordance with D'Amico and colleagues[29] to prevent the onset of serious deleterious side effects.[30]

The GETUG-AFU 16 trial was designed in 2006 and since study initiation there have been substantial improvements in the fields of medical physics and oncology (eg, improved staging and characterisation of metastatic disease) and in radiotherapy treatments. In the near future, patients with biological relapse will have MRI examinations and access to higher resolution technologies with PET imaging; recent publications emphasised the importance of prostate-specific membrane antigen PET for radiotherapy planning. GETUG clinical trials required local CT scans 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 an extended follow-up of the GETUG-AFU 16 trial would be required to show a benefit in overall survival. The use of metastasis-free survival is especially appropriate in this population of patients with fewer prostate cancer-related deaths, even after relapse. Aside from the effect of treatment on overall survival, the time without additional treatment, which affects the patient's the quality of life, should be carefully considered.

In conclusion, the results of the GETUG-AFU 16 trial confirmed the efficacy of androgen deprivation therapy plus radiotherapy as salvage treatment in patients with rising PSA concentrations after radical prostatectomy, as evidenced in the RTOG trial[13] for patients with more aggressive relapse.

Contributors

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

Declaration of interests

The sponsor, Unicancer, has received grants from Astra Zeneca, La Ligue Contre le Cancer, French Health Ministry (PHRC 2005), and La Ligue de Haute-Savoie. DP reports personal fees from Astellas Pharma, Sanofi Aventis France, Janssen Cilag, Takeda, outside of the submitted work. SS reports grants from Janssen, Astellas, Ferring, and AstraZeneca; personal fees from Janssen, Ipsen, Takeda, Astellas, and AstraZeneca; and non-financial support from Janssen, Ipsen, Takeda, Astellas, Ferring, and AstraZeneca, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Unicancer will share de-identified individual data that underlie the results reported 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 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, from 6 months to 5 years after the publication of this article.

Acknowledgments

The authors thank the local investigators who enrolled patients, all the patients who participated in the study, and the clinical and research staff at all the participating sites from the French GETUG-AFU group. The authors thank Sophie Darnis for medical editorial assistance with this manuscript.

References

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; **182:** 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; **19:** 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; **34:** 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; **281:** 1591–97.

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; **109:** 32–39.

6 Choo R. Salvage radiotherapy for patients with PSA relapse following radical prostatectomy: issues and challenges. *Cancer Res Treat* 2010; **42:** 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 27; **294:** 433–39.

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; **32:** 3892–98.

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; **24:** 3973–78.

10 Van den Broeck T, van den Bergh RCN, Arfi N, et al. Prognostic value of biochemical recurrence following treatment with curative intent for prostate cancer: a systematic review. *Eur Urol* 2019; **75:** 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; **83:** 1493–99.

12 Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol* 2016; **17:** 747–56.

13 Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Engl J Med* 2017; **376:** 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; **58:** 843–48.

15 International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy (report 50). Bethesda, MD: International Commission on Radiation Units and Measurements. 1993.

16 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; **35:** 3097–104.

17 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; **48:** 369–75.

18 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; **59:** 341–47.

19 Cheung R, Kamat AM, de Crevoisier R, et al. Outcome of salvage radiotherapy for biochemical failure after radical prostatectomy with or without hormonal therapy. *Int J Radiat Oncol Biol Phys* 2005; **63:** 134–40.

20 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; **21:** 483–89.

21 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; **82:** 1227–32.

22 Mateo J, Carreira S, Sandhu S, et al. DNA-Repair defects and olaparib in metastatic prostate cancer. *N Engl J Med* 2015; **373:** 1697–708.

23 Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in mtastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017; **377:** 352–60.

24 A Pollack, TG Karrison, AG 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. *Int J Radiat Oncol Biol Phys* 2018; **102:** 1605.

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; **17:** 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; **71:** 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; **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; **71:** 330–36.

29 D'Amico AV. Can short-term hormone therapy for rising PSA prolong survival? *Lancet Oncol* 2016; **17:** 687–88.

30 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; **34:** 3781–86.

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; **99:** 701–09.

32 Calais J, Kishan AU, Cao M, et al. Potential impact of GA-PSMA-11 PET/CT on the planning of definitive radiation therapy for prostate cancer. *J Nucl Med* 2018; **59:** 1714–21.