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

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Summary

Background How best to treat rising prostate-specific antigen (PSA) concentration after radical prostatectomy is an urgent clinical question. Salvage radiotherapy delays the need for more aggressive treatment such as long-term androgen suppression, but fewer than half of patients benefit from it. We aimed to establish the effect of adding short-term androgen suppression at the time of salvage radiotherapy on biochemical outcome and overall survival in men with rising PSA following radical prostatectomy.

Methods This open-label, multicentre, phase 3, randomised controlled trial, was done in 43 French study centres. We enrolled men (aged ≥18 years) who had received previous treatment for a histologically confirmed adenocarcinoma of the prostate (but no previous androgen deprivation therapy or pelvic radiotherapy), and who had stage pT2, pT3, or pT4a (bladder neck involvement only) in patients who had rising PSA of 0·2 to less than 2·0 µg/L following radical prostatectomy, without evidence of clinical disease. Patients were randomly assigned (1:1) centrally via an interactive web response system to standard salvage radiotherapy (three-dimensional [3D] conformal radiotherapy or intensity modulated radiotherapy, of 66 Gy in 33 fractions 5 days a week for 7 weeks) or radiotherapy plus short-term androgen suppression using 10·8 mg goserelin by subcutaneous injection on the first day of irradiation and 3 months later. Randomisation was stratified using a permuted block method according to investigational site, radiotherapy modality, and prognosis. The primary endpoint was progression-free survival, analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number 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. Patients assigned to radiotherapy plus goserelin were significantly more likely than patients in the radiotherapy alone group to be free of biochemical progression or clinical progression at 5 years (80% [95% CI 75–84] *vs* 62% [57–67]; hazard ratio [HR] 0·50, 95% CI 0·38–0·66; p<0·0001). No additional late adverse events occurred in patients receiving short-term androgen suppression compared with those who received radiotherapy alone. The most frequently occuring acute adverse events related to goserelin were hot flushes, sweating, or both (30 [8%] of 366 patients had a grade 2 or worse event; 30 patients [8%] had hot flushes and five patients [1%] had sweating in the radiotherapy plus goserelin group *vs* none of 372 patients in the radiotherapy alone group). Three (8%) of 366 patients had grade 3 or worse hot flushes and one patient had grade 3 or worse sweating in the radiotherapy plus goserelin group versus none of 372 patients in the radiotherapy alone group. The most common late adverse events of grade 3 or worse were genitourinary events (29 [8%] in the radiotherapy alone group *vs* 26 [7%] in the radiotherapy plus goserelin group) and sexual disorders (20 [5%] *vs* 30 [8%]). No treatment-related deaths occurred.

Interpretation Adding short-term androgen suppression to salvage radiotherapy benefits men who have had radical prostatectomy and whose PSA rises after a postsurgical period when it is undetectable. Radiotherapy combined with short-term androgen suppression could be considered as a reasonable option in this population.

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Introduction

After radical prostatectomy a third of patients relapse with a rise in serum prostate-specific antigen (PSA) concentration without evidence of clinical or radiographic disease and, in the absence of salvage treatment, develop distant metastases.[1] Antonarakis and colleagues[2] reported metastasis-free survival rates of 67% at 5 years and 48% at 10 years in patients with PSA recurrence after radical prostatectomy without salvage treatment.

The standard treatment for most patients with biochemical recurrence after radical prostatectomy is salvage radiotherapy. Boorjian and colleagues[3] reported a decrease in the risk of distant metastasis of 75% with

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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, 2015. We took into account the consensus statement on radiation therapy of prostate cancer published in the *Journal of Clinical Oncology* (1999), the prescribing recommendations from the International Commission on Radiation Units (1993), the European Organisation for Research and Treatment of Cancer QLQ-C30 scoring manual, and the RTOG 9601 protocol even though this trial allowed the inclusion of patients with persistent PSA after radical prostatectomy. We found no randomised trials comparing hormone therapy and radiotherapy versus radiotherapy alone in patients with rising PSA concentrations after radical prostatectomy, that had excluded patients with sustained elevated PSA concentrations after surgery.

Added value of this study

Our study showed that progression-free survival was improved when goserelin treatment was added to salvage radiotherapy compared with salvage radiotherapy alone. Although no effect on overall survival has been found to date, combined treatment should be considered a reasonable option.

Implications of all the available evidence

Short-term androgen suppression combined with salvage radiotherapy should be considered as a reasonable treatment option, especially for high-risk patients. The improvement in progression-free survival could allow postponement of more aggressive treatment, such as long-term androgen suppression, and thus prevent a deleterious effect on quality of life and cardiovascular status. Comparison of this combined treatment with salvage radiotherapy plus abiraterone could be explored.

salvage therapy and a 20% reduction in the need of androgen ablation therapy compared with no salvage therapy in 2657 patients with PSA relapse after radical prostatectomy. However, fewer than 50% of patients are thought to be free of biochemical relapse 5 years after salvage radiotherapy alone.[4–9] Salvage radiotherapy delays the need for chronic, non-curative treatment, such as long-term androgen suppression, and is the only potentially curative treatment. Suggested risk factors for biochemical relapse following salvage radiotherapy after radical prostatectomy are time to relapse after surgery, PSA doubling time, PSA concentration at the time of salvage radiotherapy, Gleason score greater than 7, and positive surgical margins or seminal vesicle involvement.[8–10] Without treatment, risk of prostate cancer death at 10 years is estimated to be 99% for these high-risk subgroups, but retrospective data suggest an improvement in biochemical outcomes if short-term androgen suppression is added to salvage radiotherapy.[11] This combined modality approach has proved efficacious in randomised studies of patients with locally advanced prostate cancer who received radiotherapy. Results of the RTOG 9601 trial[12] showed a benefit for overall survival when 2 years of bicalutamide was combined with salvage radiotherapy. However, in this trial,[12] patients with persistently raised or recurrent PSA concentrations were included, and the benefit seemed to be higher for patients with a PSA concentration of greater than 1·5 µg/L than for those with a lower PSA concentration.

We did a phase 3 trial (GETUG-AFU 16) to investigate whether the addition of short-term androgen suppression to salvage radiotherapy in men with rising PSA concentrations after radical prostatectomy would improve biochemical outcome and overall survival without jeopardising quality of life. To our knowledge, this is the first prospective controlled study of short-term androgen suppression combined with salvage radiotherapy in this clinical setting.

Methods

Study design and participants

In this open-label, multicentre, phase 3, randomised controlled trial, eligible patients were men aged 18 years or older, with histologically confirmed adenocarcinoma of the prostate, stage pT2, pT3, and pT4a (bladder neck involvement only), and pN0 or pNx, who had received radical prostatectomy. No systematic tests were done to assess testosterone recovery after hormonal treatment. Eligible patients had PSA concentrations of less than 0·1 µg/L for at least 6 months after surgery, which then began to rise (to between 0·2 µg/L and <2 µg/L, as confirmed by two consecutive tests) without evidence of clinical disease according to the international consensus guidelines.[13,14] Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0–1, life expectancy of 10 years or more, adequate cardiac function, including controlled hypertension, and no known pituitary adenoma. Patients were excluded if they had undergone previous androgen deprivation therapy or pelvic radiotherapy, if the initial status at the time of surgery was pN1, if histology findings showed cancer other than adenocarcinoma, if the patient had another invasive cancer in the previous 5 years, and if another antineoplasic treatment was in progress.

The study was done according to the Good Clinical Practice principles, as defined by the International Conference on Harmonization. The protocol was approved by the institutional review board of Centre Léon Bérard, Lyon, France, and the relevant authorities (South East IV Ethics Committee, Lyon, France; and the Agence Nationale de Sécurité du Medicament

[French Agency for the Safety of Health Care Products], Paris, France). Written informed consent was obtained from each patient before enrolment.

Randomisation and masking

Patients were randomly assigned (1:1) to receive radiotherapy alone or radiotherapy plus goserelin using a permuted block method of two and four patients. The randomisation list was generated by a statistician at the coordination centre who was not involved in the data analysis. Clinicians and patients were not masked to allocation of study treatment. Participants were enrolled by authorised clinicians, after obtaining patients' consent. Randomisation was done by use of an interactive web response system and was stratified according to investigational site, radiotherapy modality (intensity modulated radiotherapy *vs* conformational) and prognosis determined using GETUG group criteria and clinical trial data (high risk *vs* low risk). Patients and clinicians were unblinded to study treatment.

Procedures

All patients received three-dimensional (3D) conformal radiotherapy or intensity modulated radiotherapy, based on dosimetric CT scans. The planned target volume included the prostate operative bed. The dose given to the prostate bed was 66 Gy in 33 fractions, 5 days a week for 7 weeks, in both groups. The area of the seminal vesicles was included and received up to 50 Gy for pT3b disease only. According to the GETUG recommendation[15] for pelvic irradiation and other GETUG protocols (GETUG 01 and GETUG 18), the pelvis was irradiated only in patients who did not have node dissection during radical prostatectomy and only if the risk of nodal involvement was greater than 15% according to the Partin table.[16] If irradiated, the dose given to the pelvis was 46 Gy (2 Gy per fraction). Dose was prescribed according to the International Commission on Radiation Units.[17]

Patients in the radiotherapy plus goserelin group were given goserelin acetate 10·8 mg by subcutaneous injection on the first day of irradiation and again 3 months later.

Initial staging included measurement of PSA concentration and clinical examination. Bone scanning and CT or MRI of the pelvis was not mandatory since the upper limit of baseline PSA in eligible patients was 2 µg/L. Patients were clinically assessed and had their PSA concentration measured every 6 months for 5 years and every year thereafter. Patients had radiographical assessment only when clinical or biological progression was reported. In accordance with the ASTRO guidelines,[18] biochemical relapse had to be confirmed by two consecutive measurements at 2-month intervals. Biochemical relapse was defined as an increase in PSA concentration above the nadir of more than 0·5 µg/L (confirmed by a second PSA measurement) or clinical evidence of disease. Quality of life and functional dependence were evaluated at randomisation and at 1 year and 5 years after the end of radiotherapy using the quality-of-life questionnaire QLQ-C30 version 2.0 and QLQ-PR25 developed by the European Organisation for Research and Treatment of Cancer (EORTC), and by the Lawton Instrumental Activities of Daily Living (IADL) scale. The QLQ-C30 assesses 15 domains: a global health status scale, five functional scales (physical, role, emotional, cognitive, and social function), and nine symptom scales or single items (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The QLQ-PR25 assesses five domains: urinary symptoms, bowel symptoms, hormone treatment-related symptoms, sexual activity, and sexual function. We calculated absolute individual variations from baseline and used a threshold of 10 points over 100 on the global score to characterise a clinically significant difference.[19]

This study did not require confirmation of local or regional relapse by biopsy, and treatment after relapse was left to the discretion of participating physicians. Prostate specimens were not centrally reviewed.

Prognosis was determined using GETUG group criteria and based on data from randomised trials. Low risk was defined as patients with a Gleason score lower than 8, positive surgical margins, PSA doubling time at relapse of more than 6 months, and no seminal vesicle involvement.[20–23] High risk was defined as patients with Gleason score of 8 or higher, negative surgical margins, PSA doubling time at relapse of 6 months or less, and seminal vesicle involvement. The PSA doubling time was calculated by dividing the natural log of two (0·693) by the slope of the relation between the log of PSA and time of PSA measurement on three consecutive doses given with a gap of 2 months in between.[1]

Outcomes

The primary endpoint was progression-free survival defined as time from randomisation to documented biological progression or clinical progression (or both), death from any cause, or censoring at date of last follow-up. For biological progression, the date on which the first PSA increase was recorded was used. No central review of the progression status was planned. Secondary endpoints were overall survival, defined as time from randomisation to death from any cause or date of last follow-up; acute and late toxicities according to the Common Terminology Criteria for Adverse Events (version 3.0); time from randomisation to nadir PSA; metastasis-free survival defined as time from randomisation to documented metastasis; changes in quality of life measured by QLQ-C30 and QLQ-PR25 module questionnaire; and functional dependence in patients older than 75 years measured by the Lawton IADL scale.

Statistical analysis

We initially designed the trial to detect an improvement in biochemical or clinical progression-free survival at 5 years from 45% with radiotherapy alone to 60% with radiotherapy plus androgen deprivation (hazard ratio [HR] of 0·64), with a 5% two-sided α risk and 90% power. With an estimated recruitment period of 5 years and a minimum follow-up of 30 months, 221 events were required and 466 patients were needed for randomisation. With this number of patients, we could also detect an overall survival difference at 10 years of 10% (from 75% to 85%) with a power of 60%. The prespecified number of patients was reached after only 26 months of recruitment. Because of this unexpectedly rapid accrual, to gain power for overall survival, the sample size was enlarged by a protocol amendment (Dec 13, 2011), so that the study would have 80% power to detect a gain of 10% (from 75% to 85%) in overall survival (HR 0·58). This increase in sample size ensured a 98% power for the primary endpoint (progression-free survival). 349 cases of progression or death were expected among the 738 patients required.

An interim analysis for efficacy was planned for 1 year after the inclusion of 94 patients or after the 64 documented progression events, whichever occurred first. The corresponding p value for early stopping of the trial was defined as 0·001, according to Peto rules. Only three progression events had been recorded 1 year after inclusion of the 94th patient, therefore the interim analysis was done on Dec 18, 2012, after a median follow-up of 27 months (IQR 17–38) and 95 progression events. The independent data monitoring committee concluded that the safety profile of the intervention was acceptable and, even though an improvement in progression-free survival had been observed in the radiotherapy plus goserelin group, recommended continued follow-up of patients to increase the power to detect a benefit for overall survival.

See Online for appendix

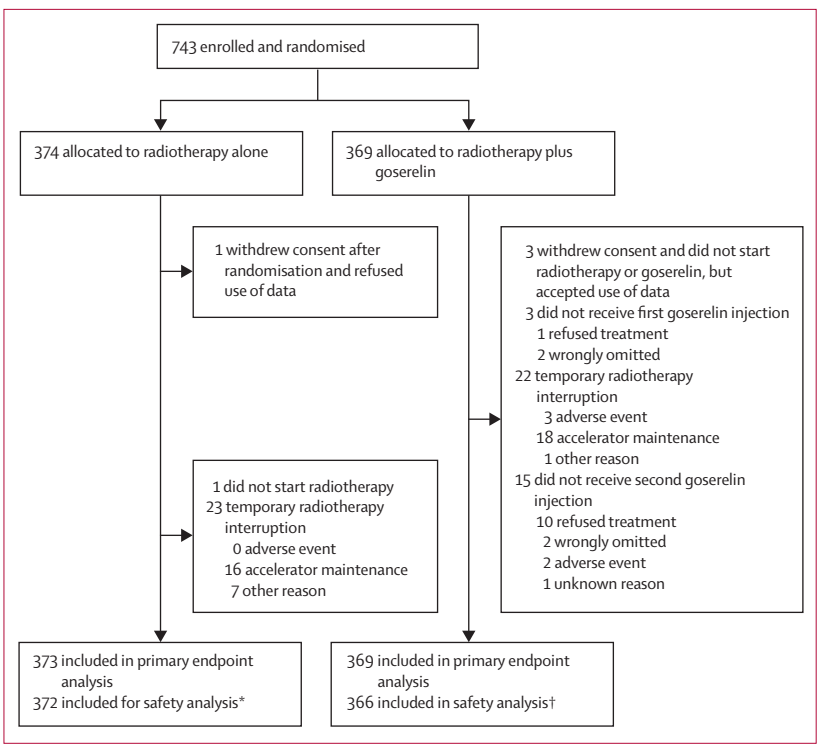

Figure 1: **Trial profile**
*Only patients who received at least one dose of radiotherapy were analysed. †Only patients who received at least one dose of radiotherapy or one injection of goserelin were analysed.

We analysed efficacy endpoints in the intention-to-treat population. We used the Kaplan-Meier method to estimate time-to-event endpoints, and used two-sided log-rank tests stratified for the stratification factors for between-group comparisons of progression-free survival and overall survival. We used a Cox proportional hazards model to investigate and adjust progression-free survival for the following prespecified factors: PSA concentration at the time of radiotherapy (at baseline), Gleason score (<8 or ≥8), positive surgical margins (yes or no), PSA doubling time at relapse of more than 6 months (yes or no), and seminal vesicle involvement (yes or no). We also analysed the following post-hoc factors: age, presurgical PSA concentration, and delay between prostatectomy and recurrence of longer than 30 months (yes or no). All parameters significant at or below p=0·2 in the univariate analysis were used in a backward selection procedure to build the final model. We calculated median follow-up using a reverse Kaplan-Meier estimate. Between-group comparisons used a χ^2 or Fisher's exact test for categorical data, and *t* test or non-parametric Wilcoxon's test for continuous data.

We included all patients who received at least one dose of radiotherapy or at least one dose of goserelin in the safety analysis. Global and summary quality-of-life scores were calculated according to the scoring manual.[19] We did not use an imputation method for missing data. We calculated absolute individual variations from baseline and used a threshold of 10 points over 100 on the global score to characterise a clinically significant difference.[24]

We did the statistical analyses using SAS software (version 9.3). This trial is registered with ClinicalTrials.gov, number NCT00423475.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The funder was involved in data monitoring and pharmacovigilance. CC, SD, and CF 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 Oct 19, 2006, and March 30, 2010, 743 patients were enrolled patients were enrolled from 43 French study centres (appendix); 374 were randomly assigned to radiotherapy alone and 369 to radiotherapy plus

goserelin. One patient, randomly assigned to the radiotherapy alone group, subsequently withdrew consent and refused the use of his data, leaving 742 patients in the intention-to-treat analysis (figure 1). Four additional patients (three in the radiotherapy plus goserelin group and one in the radiotherapy alone group) did not start study treatment and were not included in the safety analysis. Baseline characteristics were well balanced between groups (table 1). At randomisation, 691 (94%) of 738 patients had a PSA concentration of less than 1 µg/L (345 in the radiotherapy alone group and 346 in the radiotherapy plus goserelin group) and 589 (80%) of patients had a concentration of less than 0·5 µg/L (305 in the radiotherapy alone group and 284 in the radiotherapy plus goserelin group).

Radiotherapy was given to 738 patients; 119 (16%) of 737 patients had irradiation of pelvic nodes (56 [15%] of 372 in the radiotherapy alone group and 63 [17%] of 365 in the radiotherapy plus goserelin group). 3D conformal radiotherapy was used in 709 (96%) of 738 patients (355 in the radiotherapy alone group and 354 in the radiotherapy plus goserelin group) and intensity modulated radiotherapy in 29 (4%) of 738 patients (17 in the radiotherapy alone group and 12 in the radiotherapy plus goserelin group). The median dose given to the prostate bed was 66 Gy (IQR 66–66) and the median duration was 7 weeks (6·7–7·3; 7 weeks [6·7–7·3] in radiotherapy alone group and 7 weeks [6·7–7·3] in radiotherapy plus goserelin group). The total duration of radiotherapy was more than 10 weeks for three patients because of acute urinary retention in one patient in the radiotherapy plus goserelin group, intercurrent disease in one patient in the radiotherapy alone group, and an unknown reason in one patient in the radiotherapy alone group. The first injection of goserelin was given to all but three patients in the radiotherapy plus goserelin group (figure 1). The second injection was given to 351 (96%) of 366 patients (figure 1). The median duration from randomisation 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 the time of data cutoff (Dec 12, 2014) and final analysis, the median duration of follow-up was 63 months (IQR 56–75). 138 progression events or deaths had occurred in the radiotherapy alone group compared with 78 in the radiotherapy plus goserelin group. Disease progression was recorded in 124 (33%) of 373 patients in the radiotherapy alone group versus 66 (18%) of 369 patients in the radiotherapy and goserelin group, with median duration between randomisation and relapse of 22 months (IQR 14–38) in the radiotherapy alone group versus 32 months (26–44) in the radiotherapy plus goserelin group (p=0·0001). 5-year progression-free survival was 62% (95% CI 57–67) in the radiotherapy alone group and 80% (75–84) in the radiotherapy plus goserelin group (HR 0·50, 95% CI 0·38–0·66; p<0·0001; figure 2).

Of 190 patients who had disease progression, 157 (83%) had a local progression event with or without biochemical progression as their first progression event (104 [84%] of 124 patients in the radiotherapy alone group *vs* 53 [80%] of 66 patients in the radiotherapy plus goserelin group). Metastatic progression data were not available for these patients because metastatic data were only recorded at first progression. At first recorded relapse, 26 (7%) of 373 patients in the radiotherapy alone group had a clinical progression event (metastatic or local) associated with biochemical relapse (seven had local and biochemical progression, one had metastatic progression, and 18 had metastatic and biochemical progression) versus 16 (4%) of 369 patients in the radiotherapy plus goserelin group (three had local and biochemical progression, three had metastatic progression, nine had metastatic and biochemical progression, and one had local, metastatic, and biochemical progression). In the

	Radiotherapy alone (n=373)	Radiotherapy and goserelin (n=369)
Age (years)	67 (52–85)	67 (49–80)
Gleason score		
<8	332 (89%)	329 (89%)
≥8	41 (11%)	40 (11%)
Pathological tumour stage (TNM 2005)		
pT2a	37 (10%)	29 (8%)
pT2b	76 (20%)	75 (20%)
pT2c	88 (24%)	92 (25%)
pT3a	121 (32%)	127 (34%)
pT3b	50 (13%)	44 (12%)
pT4 bladder neck involvement	0	1 (<1%)
Missing	1 (<1%)	1 (<1%)
Pathological node involvement (TNM 2005)		
pN0	274 (74%)	273 (74%)
pNX	99 (27%)	96 (26%)
Positive surgical margins	196 (53%)	175 (47%)
Seminal vesicle involvement	318 (85%)	312 (85%)
PSA doubling time >6 months	276 (74%)	270 (73%)
ECOG performance status		
0	345 (92%)	329 (89%)
1	13 (4%)	22 (6%)
Missing	15 (4%)	18 (5%)
PSA at baseline randomisation (µg/L), median (IQR)*	0·30 (0·20–0·50)	0·30 (0·20–0·50)
Time between surgery and relapse (months), median (IQR)*	29·99 (19–52)	33·98 (21–53)
Presurgery PSA (µg/L), median (IQR)†	8·10 (6–12)	8·35 (6–12)

Date are n (%) or median (range) unless otherwise noted. PSA=prostate-specific antigen. ECOG=Eastern Cooperative Oncology Group. TNM=TNM Classification of Malignant Tumours. Percentages might not sum to 100 because of rounding. *Four missing values. †169 missing values.

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

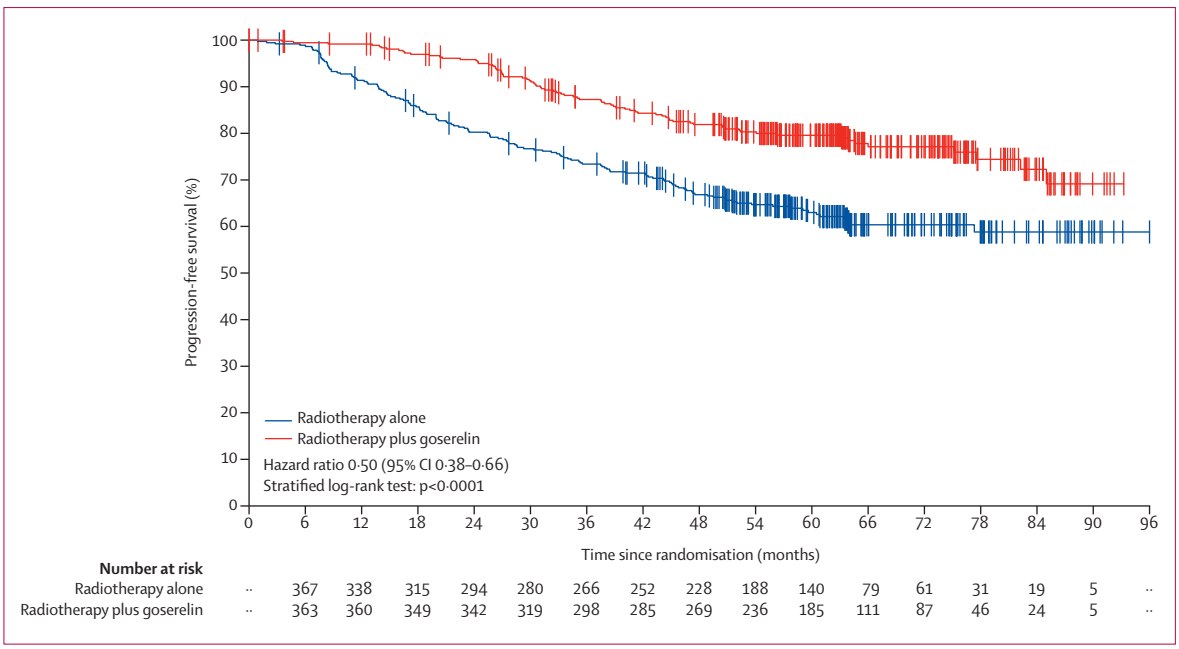

Figure 2: **Kaplan-Meier estimates of progression-free survival**

	n	Univariate analysis		Multivariate analysis*	
		HR (95% CI)	p value†	HR (95% CI)	p value†
Age at randomisation			0·166		NS‡
≤65 years	283	Reference		Reference	
>65 years	459	0·83 (0·6–1·1)		..	
Gleason score			0·001		NS‡
<8	661	Reference		Reference	
≥8	81	1·81 (1·6–2·6)		..	
PSA at relapse (baseline)			<0·0001		<0·0001
≤0·5 µg/L	589	Reference		Reference	
0·5–1 µg/L	86	1·97 (1·4–2·8)		2·05 (1·4–3·0)	
≥1 µg/L	63	2·40 (1·6–3·6)		2·30 (1·5–3·4)	
Seminal vesicle			0·001		<0·0001
Non-involvement	630	Reference		Reference	
Involvement	112	1·88 (1·4–2·6)		1·93 (1·4–2·7)	
Surgical margins			0·003		0·010
Positive	371	Reference		Reference	
Negative	371	1·52 (1·2–1·99)		1·44 (1·1–1·9)	
PSA doubling time at relapse			0·002		0·007
≥6 months	546	Reference		Reference	
<6 months	196	1·57 (1·2–2·1)		1·48 (1·1–2·0)	
Delay between prostatectomy and recurrence			0·045		NS‡
>30 months	390	Reference		Reference	
≤30 months	348	1·32 (1·0–1·7)		..	

HR=hazard ratio. NS=non-significant. PSA=prostate-specific antigen. *Multivariate model including significant parameters at 20% significance level in the univariate procedure. †p value for overall trend on multiple categories of the predictor in the regression model. ‡Parameter not kept in the final model because of non-significant p value in the backward procedure.

Table 2: **Prognostic factors for relapse**

radiotherapy alone group, 97 (26%) of 373 patients (one patient with missing data for the type of progression) had biochemical progression only versus 50 (14%) of 369 patients in the radiotherapy plus goserelin group.

In the multivariate analysis, prognostic factors for disease progression were PSA concentration at the time of radiotherapy (PSA at relapse [baseline]), surgical margin status, PSA doubling time at relapse, and seminal vesicle status (table 2). Age, Gleason score, and time between prostatectomy and recurrence were not prognostic.

Subgroup analysis of progression-free survival is consistent with the overall progression-free survival result (figure 3). 5-year progression-free survival for low-risk versus high-risk patients was 75% (95% CI 66–82) versus 58% (51–64) in the radiotherapy alone group (HR 1·8, 95% CI 1·2–2·6; p=0·0066) and 87% (79–93) versus 77% (71–82) in the radiotherapy plus goserelin group (HR 2·3, 95% CI 1·2–4·2, p=0·0088).

At the time of final analysis, 26 (7%) of 374 patients in the radiotherapy alone group had died compared with 17 (5%) of 369 in the radiotherapy plus goserelin group. The median overall survival was 58 months (IQR 53–64): 56 months (51–62) in the radiotherapy alone group and 58 months (57–79) in the radiotherapy plus goserelin group. 5-year overall survival was 95% (95% CI 92–97) in the radiotherapy alone group and 96% (93–98) in the radiotherapy plus goserelin group (HR 0·7, 95% CI 0·4–1·2, p=0·18; appendix). The cause of death was cancer progression in eight (2%) patients in the radiotherapy alone group versus three (1%) in the radiotherapy plus goserelin group. The median age of the 11 patients who died from disease progression was

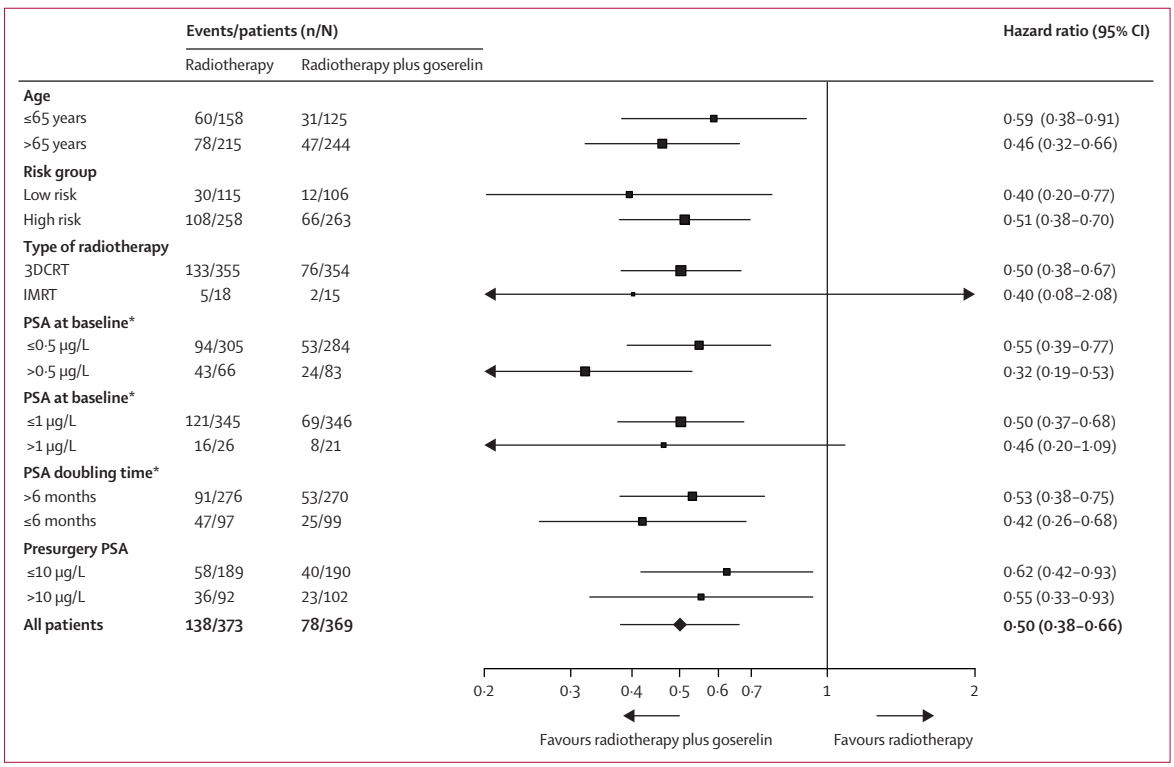

Figure 3: **Subgroup analysis of progression-free survival**
3D CRT=three-dimensional conformal radiotherapy. IMRT=intensity modulated radiotherapy. PSA=prostate-specific antigen. *Before starting radiotherapy.

62 years (IQR 60–72) compared with 67 (62–72) for the population as a whole. Five deaths from other cancers occurred in each group and cardiac disease was the cause of five deaths in the radiotherapy alone group and three in the radiotherapy plus goserelin group. The eight other deaths in the radiotherapy alone group were due to pulmonary embolism (n=1), chronic obstructive pulmonary disease (n=1), septic shock (n=1), vascular cerebral accident (n=1), vascular dementia (n=1), accident (n=1), suicide (n=1), and an unknown reason (n=1), versus vascular dementia (n=1), Alzheimer's diseases (n=2), accident (n=1), suicide (n=1), and an unknown reason (n=1) for the six other deaths in the radiotherapy plus goserelin group. No treatment-related deaths occurred.

The most frequently occurring acute adverse events related to goserelin were hot flushes, sweating, or both. 30 [8%] of 366 patients had a grade 2 or worse event (30 [8%] patients had hot flushes and five [1%] had sweating in the radiotherapy plus goserelin group *vs* none of 372 in the radiotherapy alone group) and grade 2 or worse hypertension (six [2%] *vs* one [<1%]; table 3). Late adverse events related to goserelin are shown in the appendix.

Acute genitourinary adverse events that were grade 2 or worse were noted in 39 (11%) of 372 patients in the radiotherapy alone group versus 46 (13%) of 366 in the radiotherapy plus goserelin group. Acute gastrointestinal adverse events that were grade 2 or worse were noted in 52 (14%) versus 42 (12%). For late adverse events, genitourinary events of all grades were reported in 261 (70%) of 372 patients in the radiotherapy alone group and 246 (67%) of 366 patients in the radiotherapy plus goserelin group; grade 3 or worse genitourinary events were reported in 29 (8%) and 26 (7%). Any grade sexual disorder was reported in 91 (25%) in the

	Radiotherapy alone (n=372)		Radiotherapy plus goserelin (n=366)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Gynaecomastia	0	0	4 (1%)	0
Hot flushes	1 (<1%)	0	163 (45%)	3 (1%)
Breast pain	0	0	5 (1%)	0
Sweating	0	0	47 (13%)	1 (<1%)
Paraesthesia	0	0	0	0
Spinal-cord compression	0	0	0	0
Hypertension	1 (<1%)	0	21 (6%)	0
Muscular weakness	0	0	6 (2%)	0
Arthralgia	1 (<1%)	0	7 (2%)	0
Osteoarticular and muscular pain	6 (2%)	0	6 (2%)	0
Sexual disorders	4 (1%)	1 (<1%)	3 (1%)	0

Data are number of patients with at least one episode of that event (% of patients). No grade 4 or 5 events were reported.

Table 3: **Acute adverse events previously associated with hormone therapy**

	Radiotherapy alone (n=373)			Radiotherapy and goserelin (n=369)		
	Inclusion	1 year after treatment	5 years after treatment	Inclusion	1 year after treatment	5 years after treatment
QLQ-C30 global quality-of-life scores	83 (83–83)	83 (75–83)	83 (67–83)	83 (83–83)	83 (75–83)	83 (67–83)
Number of respondents	313	204	80	302	199	83
QLQ-PR25 urinary symptoms	12 (8–13)	13 (13–17)	15 (13–21)	11 (8–13)	17 (13–17)	17 (13–21)
Number of respondents	302	185	75	301	183	78
QLQ-PR25 bowel symptoms	0 (0–0)	0 (0–8)	0 (0–8)	0 (0–0)	8 (0–8)	0 (0–8)
Number of respondents	283	173	72	289	167	72
QLQ-PR25 treatment-related symptoms	11 (8–11)	11 (11–11)	13 (11–17)	11 (6–11)	22 (17–22)	11 (6–17)
Number of respondents	301	186	75	300	183	79
QLQ-PR25 sexual activity	33 (33–33)	33 (17–33)	33 (33–33)	33 (17–33)	8 (0–17)	33 (17–33)
Number of respondents	289	177	68	289	172	76
QLQ-PR25 sexual function	44 (42–56)	50 (42–58)	33 (25–50)	50 (44–58)	33 (25–50)	33 (22–50)
Number of respondents	153	101	41	149	66	34

Data are median (95% CI).

Table 4: **Quality-of-life scores**

radiotherapy alone group and 102 (28%) in the radiotherapy plus goserelin group; grade 3 or worse sexual disorder events were reported in 20 (5%) and 30 (8%). Gastrointestinal events of all grades were reported in 190 (51%) of 372 in the radiotherapy alone group and 174 (48%) of 366 patients in the radiotherapy plus goserelin group, and grade 3 or worse gastrointestinal events were noted in five (1%) and six (2%) patients.

Compliance with health-related quality-of-life surveys (QLQ-C30) was 615 (83%) of 738 patients at inclusion, 403 (55%) of 738 patients 1 year after treatment, and 163 (22%) of 738 patients 5 years after treatment. Quality-of-life results for QLQ-C30 and QLQ-PR25 are shown in table 4 and the appendix. Between inclusion and 1 year after treatment, global quality-of-life score was stable (no variation from baseline) in 103 (56%) of 184 patients in the radiotherapy alone group versus 83 (48%) of 173 in the radiotherapy plus goserelin group, improved in 34 (19%) versus 30 (17%), and was worse in 47 (26%) versus 60 (35%). Between inclusion and 5 years after treatment, global quality-of-life score was stable in 35 (50%) of 70 patients in the radiotherapy alone group versus 38 (51%) of 74 in the radiotherapy plus goserelin group, improved in 14 (20%) versus 13 patients (18%), and was worse in 21 (30%) versus 23 patients (31%). 603 (82%) of 738 patients answered to PR25 questionnaires, which contain questions related to sexual activity (302 [41%] in the radiotherapy alone group and 301 [41%] in the radiotherapy plus goserelin group at inclusion), which dropped to 368 (50%) at 1 year after treatment (185 [25%] in the radiotherapy alone group and 183 [25%] in the radiotherapy plus goserelin group), and 153 (21%) at 5 years (75 [10%] in the radiotherapy alone group and 78 [11%] in the radiotherapy plus goserelin group). In patients who responded, 144 (51%) of 283 in the radiotherapy alone group and 130 (46%) of 285 in the radiotherapy plus goserelin group were sexually active at inclusion, 84 (48%) of 175 and 51 (30%) of 172 were sexually active 1 year after treatment, and 35 (52%) of 68 and 35 (46%) of 77 were sexually active 5 years after treatment. 603 completed PR25 questionnaires were received, but 35 questionnaires did not have an answer to the sexual activity question. The median scores of sexual function were 50 (IQR 25–67) at inclusion, 42 (22–67) at 1-year follow-up, and 33 (22–58) at 5 years' follow-up, with no differences between groups (table 4).

In our study, 71 patients were aged 75 years and older and were assessed with the Lawton IADL scale, which studies functional dependence in patients aged 75 years and older. We received 44 (62%) auto-questionnaires at inclusion, 16 (23%) at 1 year after treatment, and 13 (18%) at 5 years after treatment of these 71 patients. Therefore, the numbers were too small to be analysed.

Discussion

In the GETUG-AFU 16 multicentre, open-label, randomised phase 3 trial, we assessed whether adding 6 months of androgen suppression using goserelin to standard salvage radiotherapy is superior to salvage therapy alone in patients with rising PSA concentrations after radical prostatectomy. 5-year progression-free survival in the radiotherapy plus goserelin group was significantly higher than in the radiotherapy alone group.

To date, radical prostatectomy remains one of the standard treatments for localised prostate cancer in men younger than 70 years. However, 30–70% of men have biochemical relapse at 5 years, depending on their initial prognosis.[10] Although no standard salvage treatment has been defined, retrospective studies have suggested a potential benefit from salvage radiotherapy with a biochemical complete response seen in half of relapsing

patients.[6,8,25,26] A potential role for adjuvant androgen suppression has been investigated and a higher response rate was reported for patients treated with androgen suppression than for those not treated, but only an uncertain effect on time to biochemical relapse was reported and there was no effect on overall survival.[27]

The RTOG 9601 study, updated results of which were presented during the 2015 American Society for Radiation Oncology meeting, is a phase 3 trial of radiotherapy and atypical anti-androgen therapy (150 mg of bicalutamide during and after radiotherapy for 2 years) versus radiotherapy alone. An improvement in overall survival in the combination group compared with the radiotherapy alone group after a median follow-up of 12·6 years was reported.[12] However, this trial included both patients with persistently elevated PSA concentrations after radical prostatectomy and patients with rising PSA concentrations after a period of biochemical complete response. Moreover, the upper limit of PSA concentration accepted was 4 µg/L, compared with 2 µg/L in our trial. The reported benefit in the RTOG 9601 study is more substantial in patients with a PSA concentration of more than 1·5 µg/L than in patients with a PSA concentration of less than 1·5 µg/L, which probably explains why prolonged hormone therapy would have had a greater effect on overall survival than with radiotherapy alone. GETUG-AFU 16 is the first phase 3 trial to our knowledge that specifically studied patients who had undetectable PSA after surgery (<0·01 µg/L) that subsequently began to rise, and that explores the potential benefit of androgen suppression when added to salvage radiotherapy. After 5 years of follow-up, the combined modality approach had improved the time to biochemical progression or clinical progression compared with salvage radiotherapy alone, with an HR of 0·50 (95% CI 0·38–0·66). Combined treatment benefited all relevant subgroups.

In relation to previously published risk factors for relapse after salvage radiotherapy, we confirmed the negative prognostic effect of PSA doubling time, surgical margins, seminal vesicle status, and PSA concentration at the time of radiotherapy.[28] Gleason score was not prognostic on multivariate analysis, but no central review was done and only 11% of patients had a Gleason score of 8 or higher. However, more than 90% of patients had a PSA concentration of less than 1 µg/L, which has been considered an upper limit by some clinicians and could explain the absence of histological factors as prognostic indicators.[8,28]

Few deaths were reported at the time of the main analysis for progression-free survival, which could explain the absence of an effect of goserelin treatment on overall survival to date. Longer follow-up is needed to ascertain the effect of our intervention on the overall survival of patients in whom PSA concentrations rise after a period of non-detectability after radical prostatectomy. These outcome data will provide important new information to add to results already recorded (eg, in RTOG 9601) in patients with persistently elevated PSA concentrations.

The potential benefit of adding androgen deprivation to radiotherapy could be due to an effect on subclinical metastatic disease, but this remains to be established. We only recorded first progression and, because most patients initially have local progression, with or without biochemical progression, we were not able to estimate metastasis-free survival, which is a limitation of our study. In-vitro data suggest a supra-additive response when androgen deprivation and radiotherapy are combined.[29,30] These findings could explain the improved local control observed when radiotherapy was combined with androgen deprivation;[30,31] in our study, three patients had local and biochemical progression in the androgen therapy group compared with seven in the control group. However, the number of local relapses is probably underestimated in most reports because local biopsy is not routinely done in isolated cases of biochemical relapse.

With a median of follow-up of 63 months, we found no additional serious acute or late genitourinary, gastrointestinal, or cardiovascular toxicities in the combined modality group. Short-term anti-androgen therapy in our trial was not associated with a high incidence of gynaecomastia, in contrast with the 70% rate observed in the RTOG 9601 trial. We observed more acute adverse events in the radiotherapy plus goserelin group than in the radiotherapy alone group, but most of these were grade 1–2. The fact that there was no difference in radiation-related late adverse events between treatment groups supports the observation that no difference in health-related quality of life was seen between the two groups. However, quality of life was not measured 6 months after start of goserelin treatment, when side-effects were most likely to be observed, but at 1 year, when most side-effects of goserelin would have resolved, which is another limitation of our study.

In our study, salvage radiotherapy combined with short-term androgen suppression significantly improved 5-year progression-free survival compared with salvage radiotherapy alone and can delay the need for more aggressive therapy. Longer follow-up is needed to establish the effect of this therapeutic strategy on overall survival; however, when considered in the context of results from RTOG 9601, even if the two populations are not strictly identical, the data from this trial suggest that combined treatment could be a reasonable option.

Contributors

CC and SD contributed to the trial concept and design. All authors contributed to data collection. CF did the statistical analysis and CF, CC, and SD analysed and interpreted the data. CC, SD, and MH supervised the study. All authors reviewed the manuscript, provided comments, and gave final approval for publication.

Declaration of interests

J-LL has received personal fees from Takeda. MH has received grants from AstraZeneca, La Ligue Contre le Cancer, and the French Health Ministry through Unicancer. All other authors declare no competing interests.

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References

1 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.

2 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.

3 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.

4 Briganti A, Wiegel T, Joniau S, et al. Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. *Eur Urol* 2012; **62:** 472–87.

5 Choo R. Salvage radiotherapy for patients with PSA relapse following radical prostatectomy: issues and challenges. *Cancer Res Treat* 2010; **42:** 1–11.

6 Geinitz H, Riegel MG, Thamm R, et al. Outcome after conformal salvage radiotherapy in patients with rising prostate-specific antigen levels after radical prostatectomy. *Int J Radiat Oncol Biol Phys* 2012; **82:** 1930–37.

7 Moul JW, Banez LL, Freedland SJ. Rising PSA in nonmetastatic prostate cancer. *Oncology (Williston Park)* 2007; **21:** 1436–45.

8 Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007; **25:** 2035–41.

9 Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005; **294:** 433–39.

10 Siegmann A, Bottke D, Faehndrich J, et al. Salvage radiotherapy after prostatectomy—what is the best time to treat? *Radiother Oncol* 2012; **103:** 239–43.

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 Shipley WU, Seiferheld W, Lukka H, et al. Report of NRG Oncology/RTOG 9601, a phase 3 trial in prostate cancer: anti-androgen therapy (AAT) with bicalutamide during and after radiation therapy (RT) in patients following radical prostatectomy (RP) with pT2–3pN0 disease and an elevated PSA. *Int J Radiat Oncol Biol Phys* 2016; **94:** 3 (abstr).

13 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.

14 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.

15 Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol* 2007; **25:** 5366–73.

16 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.

17 International Commission on Radiation Units and Measurements. Prescribing, recording and reporting photon beam therapy recording and reporting photon beam therapy. Report 50. Bethesda, MD: International Commission on Radiation Units and Measurements, 1993.

18 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.

19 Fayers P, Aaronson NK, Bjordal K, Curran D, Groenvold M, for the European Organisation for Research and Treatment of Cancer Quality of Life Study Group. EORTC QLQ-C30 scoring manual: 2nd edn. Brussels: European Organisation for Research and Treatment of Cancer, 1999.

20 Wiegel T, Lohm G, Bottke D, et al. Achieving an undetectable PSA after radiotherapy for biochemical progression after radical prostatectomy is an independent predictor of biochemical outcome—results of a retrospective study. *Int J Radiat Oncol Biol Phys* 2009; **73:** 1009–16.

21 Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009; **181:** 956–62.

22 Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol* 2007; **25:** 2225–29.

23 Bolla M, Van PH, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005; **366:** 572–78.

24 Osoba D, Bezjak A, Brundage M, Zee B, Tu D, Pater J. Analysis and interpretation of health-related quality-of-life data from clinical trials: basic approach of The National Cancer Institute of Canada Clinical Trials Group. *Eur J Cancer* 2005; **41:** 280–87.

25 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.

26 Bartkowiak D, Schrader AJ, Wiegel T. Adjuvant vs. salvage radiotherapy after radical prostatectomy. *Aktuelle Urol* 2015; **46:** 52–58.

27 Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. *JAMA* 2008; **299:** 2760–69.

28 Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004; **291:** 1325–32.

29 Joon DL, Hasegawa M, Sikes C, et al. Supraadditive apoptotic response of R3327-G rat prostate tumors to androgen ablation and radiation. *Int J Radiat Oncol Biol Phys* 1997; **38:** 1071–77.

30 Zietman AL, Shipley WU. Androgen deprivation and radiation therapy in prostate cancer: the evolving case for combination therapy. *Int J Radiat Oncol Biol Phys* 1997; **37:** 245–46.

31 Bolla M, de Reijke TM, Van TG, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009; **360:** 2516–27.