VOLUME 25 · NUMBER 34 · DECEMBER 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Preliminary Results of GETUG-01

Pascal Pommier, Sylvie Chabaud, Jean Leon Lagrange, Pierre Richaud, François Lesaunier, Elisabeth Le Prise, Jean Philippe Wagner, Meng Huor Hay, Veronique Beckendorf, Jean Philippe Suchaud, Pierre Marie Pabot du Chatelard, Valerie Bernier, Nicolas Voirin, David Perol, and Christian Carrie

From the Centre Léon Bérard, Lyon; Hopital Henri Mondor, Creteil; Insitute Bergonie, Bordeaux; Centre Francois Baclesse, Caen; Centre Eugene Marquis, Rennes; Clinique de L'Orangerie, Strasbourg; Centre Val d'Aurelle, Montpellier; Centre Alexis Vautrin, Nancy; Hopital de Roanne, Roanne; and Centre Paul Papin, Angers, France.

Submitted January 25, 2007; accepted September 6, 2007.

Supported by the Groupe d'Etude des Tumeurs Uro-Genitales (French Genito-urinary Group) of the Fédération Nationale des Centres de Lutte Contre le Cancer, with a grant from the Ligue Nationale Contre le Cancer.

Presented in part at the 47th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, October 16-20, 2005, Denver, CO (Pommier P, Perol D, Lagrange J, et al: Does pelvis and prostate radiation therapy compared to prostate radiation therapy alone improve survival in patients with non metastatic prostate carcinoma? Preliminary results of the prospective randomized GETUG01 trial. Int J Radiat Oncol Biol Phys 63:S19-S20, 2005).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Pascal Pommier, MD, Centre Léon Bérard, Department of Radiotherapy, 28 rue Laennec, Lyon, 69008 France; e-mail: pommier@lyon.fnclcc.fr.

0732-183X/07/2534-5366/$20.00

DOI: 10.1200/JCO.2006.10.5171

ABSTRACT

Purpose
To assess the benefit and toxicity and quality-of-life (QOL) outcomes of pelvic nodes irradiation in nonmetastatic prostate carcinoma patients.

Patients and Methods
Between December 1998 and June 2004, 444 patients with T1b-T3, N0 pNx, M0 prostate carcinoma were randomly assigned to either pelvic and prostate radiotherapy or prostate radiotherapy only. Patients were stratified according to the prognostic factor of lymph node involvement (LNI). Short-term 6-month neoadjuvant and concomitant hormonal therapy was allowed only for patients in the high-risk group. The pelvic dose was 46 Gy. The total dose recommended to the prostate was changed during the course of the study from 66 Gy to 70 Gy. Criteria for progression-free survival (PFS) included biologic prostate-specific antigen recurrences or a local or metastatic evolution. Acute and late toxicities were recorded according to the Radiation Therapy Oncology Group and Late Effects in Normal Tissues Subjective, Objective, Management, and Analytic scales, respectively. The QOL outcome was recorded with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, the International Prostatic Symptom Score, and the Sexual Function Index scales.

Results
With a 42.1-month median follow-up time, the 5-year PFS and overall survival were similar in the two treatment arms for the whole series and for each stratified group. On multivariate analysis, low LNI risk and hormonal therapy were statistically associated with increased PFS. However, subgroup analyses based on these factors did not show any benefit for pelvic irradiation. There were no significant differences in acute and late digestive toxicities and in QOL outcomes.

Conclusion
Pelvic node irradiation was well tolerated but did not improve PFS.

J Clin Oncol 25:5366-5373. © 2007 by American Society of Clinical Oncology

INTRODUCTION

The publication in 2003 and the update in 2005 of the Radiation Therapy Oncology Group (RTOG) 9413 trial demonstrating the role of whole pelvic radiotherapy on progression-free survival (PFS) in intermediate-risk prostate carcinoma patients set a benchmark for daily radiotherapy practice.[1,2] However, this publication has led to much discussion about the therapeutic ratio of whole pelvic radiotherapy because of the lack of a demonstrated clinical benefit in terms of overall survival or distant metastasis and a slight increase in late grade 2 and 3 toxicities.[3-5]

In 1998, a prospective randomized study was initiated by the Genitourinary Study Group (Groupe d'Etude des Tumeurs Uro-Génitales) of the Fédération Nationale des Centres de Lutte Contre le Cancer with the objective of evaluating the therapeutic effect of pelvic and prostate radiotherapy compared with prostate irradiation alone in nonmetastatic prostate cancer patients (GETUG-01 study).

PATIENTS AND METHODS

Inclusion Criteria and Trial Design

Inclusion criteria included T1b-3c, pNx adenocarcinoma of the prostate according to the American Joint Committee on Cancer TNM staging system (fifth edition),[6] with a negative bone scan and pelvic computed tomography (CT) scan, all Gleason scores (GS), and all prostate-specific antigen (PSA) values. Patients who underwent a lymphadenectomy were excluded.

The trial used a randomized, multicenter, open phase III design in which patients were randomly assigned to receive either pelvis and prostate irradiation (arm 1) or prostate alone irradiation (arm 2; Fig 1). The major end point was PFS, including local progression, node or distant documented metastases, death from any cause, and/or biologic progression using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition because it was the standard at that time. The planned sample size was 450 patients to detect an absolute difference in PFS of 15% at 5 years with a power of 80% and a unilateral significance level of 5%. The study was powered to detect a hypothesized increase in PFS from 60% to 75% in favor of pelvic irradiation.[7,8]

Patients were stratified according to participating center and risk of nodal involvement with the use of a blocked method. Low risk of nodal involvement was defined as T1-2, GS ≤ 6, and PSA less than $3\times$ the upper normal limit of the laboratory, and high risk was defined as T3 and/or GS ≥ 7 and/or PSA $\geq 3\times$ the upper normal limit of the laboratory. The upper limit of normal for PSA in most of the laboratories was 4 ng/mL. The protocol was approved by an ethics committee, and written informed consent was obtained from all patients.

Radiotherapy

Patients were treated with ≥ 8 MeV photon therapy using the International Commission on Radiation Units and Measurements recommendations. The pelvic irradiation technique consisted of a conventional four-field technique, including internal, external, and the first common iliac nodes with an upper limit defined as the level of the anterior portion of the junction between the first and second sacral vertebra. The shapes of the fields were designed using classical bony structure landmarks or using beam eye views after pelvic node delineation.

A three-dimensional treatment plan for prostate and seminal vesicles irradiation was mandatory. A 10-mm three-dimensional expansion of the clinical target volume was recommended for the planned target volume. A conventional four-field technique using shield blocks or a conformal approach with the use of a multileaf collimator was allowed for the prostate irradiation. Intensity-modulated radiotherapy (IMRT) was not performed.

Standard fractionated irradiation with 2 Gy per fraction and 5 fractions a week without any programmed split was recommended. The prescribed dose to the pelvis was 46 Gy. The total dose prescribed to the seminal vesicles was 46 Gy or up to 60 Gy in case of seminal involvement.

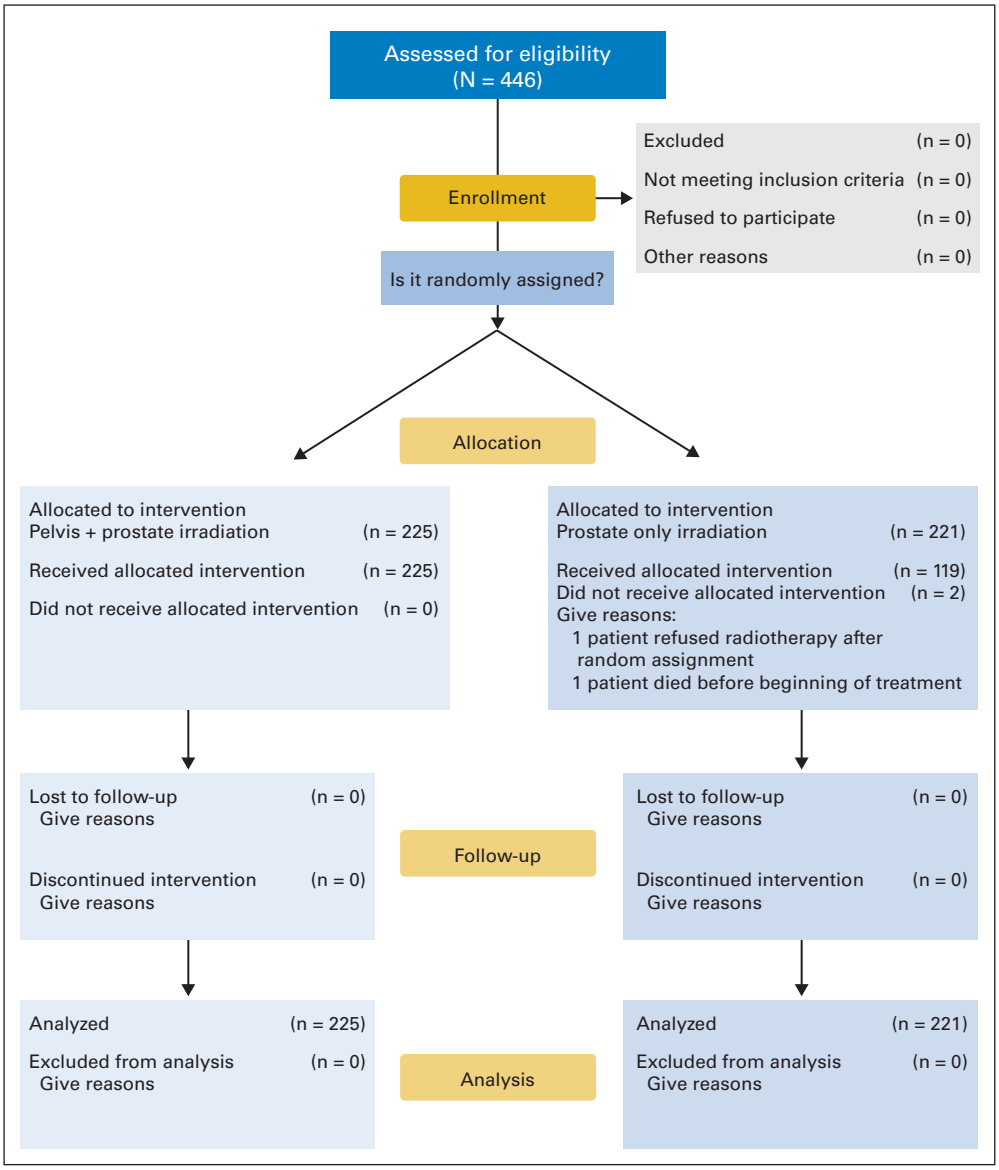

Fig 1. CONSORT diagram.

The total dose to the prostate increased from 66 Gy to a recommended dose of 70 Gy after March 2000, after the publications of dose-escalation studies.[9-12] Two others schemes were authorized, as follows: 1.8 Gy/session, five sessions a week, to total doses of 46.8 and 68.4 Gy (72 Gy after March 2000) for the pelvis and the prostate, respectively, and 2.25 Gy/session, four sessions a week, to total doses of 45 and 65.25 Gy (69.75 Gy after March 2000) for the pelvis and the prostate, respectively.

Hormonal Therapy

Hormonal therapy was authorized in the high-risk group only. It consisted of 4 to 8 months of neoadjuvant and concomitant treatment using a luteinizing hormone–releasing hormone agonist associated with initial short-term nonsteroidal antiandrogen administration.

Follow-Up and Assessment of Toxicity and Quality of Life

Systematic follow-up consisted of PSA, a digital rectal examination, and an assessment of acute and then late toxicity using the RTOG and Late Effects in Normal Tissues Subjective, Objective, Management, and Analytic scales, respectively, 2 and 6 months after the treatment completion and then every 6 months until progression or death. CT scan (or magnetic resonance imaging) and bone scan were mandatory on PSA progression or when symptoms were suspicious for tumor progression.

Quality of life (QOL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30,[13] the International Prostatic Symptom Score,[14] and the Sexual Function Index.[15] Patients were asked to complete the questionnaires before the onset of the radiotherapy and then every year.

Statistical Analysis

The analysis was performed according to the intent-to-treat principle and using the SAS software (version 8.02; SAS Institute, Cary, NC). PFS was defined from random assignment to the date of disease progression or death or censored at last follow-up. Survival functions were calculated using the Kaplan-Meier method.[16] Survival distributions were compared between the two arms or other variables using a log-rank test.[17] According to the protocol, a one-sided log-rank test was used for the primary end point; all other tests were two sided. A multivariate analysis to adjust the treatment effect was tested by the introduction of prognostic factors in a Cox proportional hazards model.[18] A backward selection procedure has been used to build the final model. Candidate variables for the selection procedure were those statistically significant at the $P = .1$ level in the univariate analysis. Median follow-up time was calculated using a reverse Kaplan-Meier estimate.[19]

Secondary end points were overall survival, toxicity profiles tested using the χ^2 test, and QOL assessed according to the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 scoring manual.[20] Baseline QOL scores were compared between treatment arms for each of the QOL domains, and the variations from baseline were calculated for each patient and compared between arms after stratification into three categoric levels on the assumption that a 10-point disparity in score represented a clinically pertinent differential.[21] Analysis of International Prostatic Symptom Score was expressed as worsened, stable, or improved according to the evolution of the score within the three classes (score: 0 to 7 = mild, 8 to 19 = moderate, and 20 to 35 = severe symptoms).[14] Regarding the Sexual Function Index, mean and median absolute variations at 12 and 24 months were compared.

RESULTS

Patients

From December 1998 to June 2004, 446 patients were enrolled by 21 centers. The majority of the patients (78.7%) were stratified in the high-risk group. The risk of lymph node involvement (LNI) was retrospectively calculated using the formula described by Roach et al[22]: (2/3 PSA) + [(GS – 6) × 10]. No substantial difference between the two arms was found (Table 1). Use of concomitant hormonal therapy was well balanced between arms.

Survival

With a 42.1-month median follow-up time, there was no difference in 5-year PFS, with rates of 66.0% (95% CI, 58.0% to 74.0%) and

Table 1. Patients Characteristics

Characteristic	Pelvis + Prostate (n = 225)	Prostate Only (n = 221)	*P*
Prognostic group, % of patients			.727
Low risk	21.3	19.9	
High risk	78.7	80.1	
Age at diagnosis, years			.812
Mean	68.8	68.9	
SD	5.0	4.9	
Median	69.8	69.9	
Range	52.6-75.6	49.2-75.8	
Tumor stage, % of patients			.648
T1	25.1	21.9	
T2	50.7	50.7	
T3	24.2	27.4	
PSA, μg/L			.359
Mean	16.3	15.0	
SD	16.5	14.7	
Median	12.0	11.0	
Range	0.2-144.0	1.3-150.0	
Gleason score, % of patients			.432
≤ 6	50.9	48.6	
7	36.6	41.7	
8-10	12.5	9.6	
RT dose to pelvis			
Mean	46.14		
SD	1.1		
Median	46		
Range	44-50		
RT dose to prostate			
Mean	22.32	68.08	
SD	1.8	5.8	
Median	22	68.4	
Range	18-28	4-76	
RT dose to pelvis + prostate			.369
Mean	68.45	68.08	
SD	2.0	5.8	
Median	68.4	68.4	
Range	63-74	4-76	
RT dose to the prostate, % of patients			.286
< 70 Gy	61.6	56.3	
≥ 70 Gy	38.4	43.7	
RT dose/fraction, % of patients			.148
2 Gy	53.8	62.3	
1.8 Gy	44	34.9	
2.25 Gy	2.2	2.8	
LNI risk,* % of patients			.364
< 15%	51.3	56.8	
15%-35%	37.1	34.9	
> 35%	11.6	8.3	
Concomitant hormonal therapy,† % of patients	57.5	59.7	.261

Abbreviations: SD, standard deviation; PSA, prostate-specific antigen; RT, radiotherapy; LNI, lymph node involvement.
*LNI risk was calculated using the Roach formula: (2/3 PSA) + [(GS – 6) × 10].
†In patients stratified as high risk.

65.3% (95% CI, 57.5% to 73.1%) for the pelvis + prostate and prostate alone arms, respectively ($P = .34$). Five-year PFS rates were also similar for patients stratified in the high-risk or low-risk groups, with 63.4% (95% CI, 53.8% to 73.0%) versus 59.8% (95% CI, 50.5% to 69.1%; $P = .20$) and 75.1% (95% CI, 59.6% to 90.6%) versus 83.9% (95% CI, 71.9% to 95.9%; $P = .21$) for the prostate alone and the pelvis + prostate arms, respectively (Fig 2).

In univariate analysis, LNI risk, PSA, GS, and stratified prognostic group were significant. Because these variables were highly correlated, only LNI was included in the multivariate model. The final multivariate model showed that LNI risk using the Roach formula and hormonal therapy were highly significant, whereas dose per fraction and random assignment arm were not (Table 2). The principal type of recurrence was biologic progression (20%), whereas clinical progression (local, nodal, and/or metastatic) was reported in only 8% of patients, without significant differences between the two arms ($P = .224$). A total of 36 deaths was noted during the study (5-year overall survival, 86.5% *v* 88.3% with or without pelvic radiotherapy, respectively; $P = .62$).

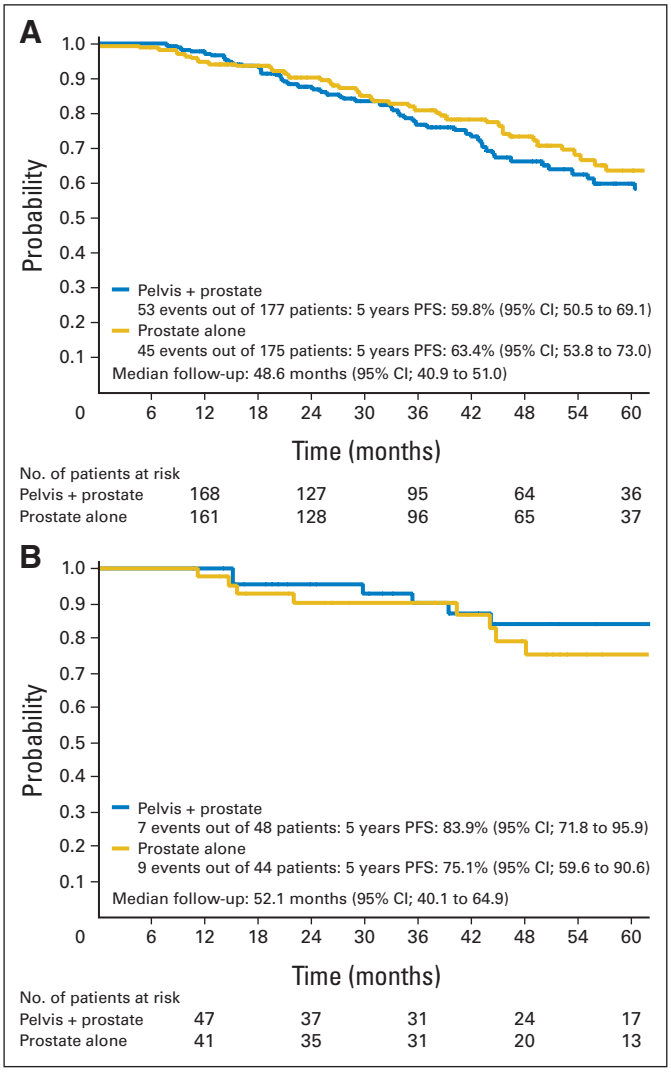

Fig 2. Progression-free survival (PFS) according to the stratified groups. (A) High-risk group. (B) Low-risk group.

Acute and Late Toxicities

We observed a small but insignificant increase in mild lower digestive tract acute toxicity with pelvic irradiation. Urinary acute grade ≥ 2 toxicity was similar in both arms. Grade 3 to 4 acute urinary toxicity was significantly higher in the prostate-only radiotherapy arm. The two grade 4 notified events were in the prostate-only arm (urinary obstructions; Table 3). Pelvic irradiation was associated with a small but nonsignificant increase in digestive tract late toxicity of grade ≥ 2 according to the Late Effects in Normal Tissues Subjective, Objective, Management, and Analytic scale (Table 4).

QOL Assessment

Because baseline scores were not similar in both arms, comparative QOL outcomes between the two groups were assessed on the modification of the scores at 12 and 24 months after the completion of radiotherapy compared with baseline data for each individual with available data.[14,15,21] No statistically detectable differences were observed between the two arms for each tested scale (Table 5).

DISCUSSION

In this trial, pelvic irradiation did not lead to any improvement in PFS. With a median follow-up time of 12 years, the first randomized trial assessing pelvic irradiation (RTOG 7706) did not demonstrate any significant benefit for pelvic irradiation on clinical end points.[23,24] This trial has been criticized for including men with low risk of nodal involvement and for its use of relatively low radiation doses and no hormonal therapy. RTOG 9413 addressed the same question for patients at highest risk of nodal disease (> 15%) using hormonal therapy. With a 59.5-month median follow-up time, a significant benefit for whole pelvis irradiation was seen in terms of 4-year PFS. The most important benefit for whole pelvis irradiation was reported when hormonal treatment was used in a neoadjuvant and concomitant setting. These later results were confirmed in a subsequent subset analysis with a 70.8-month median follow-up time.[1]

The retrospective data have also been confusing. Two recent retrospective comparative studies of patients with a high risk of positive lymph nodes using the same criteria as defined in the RTOG 9413 trial also failed to demonstrate any advantages for pelvic irradiation.[5,25] Conversely, in 2002, Pan et al[26] reported a significant increase in 5-year biochemical freedom from progression (60.2% *v* 47.9% for pelvic *v* prostate-only radiotherapy, respectively; $P = .02$) and in median duration to biochemical recurrence (107 *v* 53 months for pelvic *v* prostate-only radiotherapy, respectively) in patients with intermediate LNI risk (> 5% to 15%, Partin tables). It is likely that patients stratified as intermediate LNI risk in the Pan et al study using Partin tables are likely to be similar to the patients included in the RTOG 9413 study with a 15% to 35% LNI risk using the Roach formula.[22,26,27]

At the time of the study design, there was no consensus about the criteria to use for biochemical relapse definition after radiotherapy associated with short-term hormonal therapy. The ASTRO criteria were finally chosen rather than the criteria defined for the RTOG 9413 study that were more in agreement with the new ASTRO/RTOG definition.[2,28] However, in that trial, both definitions led to the same

Table 2. Univariate and Multivariate Survival Analysis Testing Factors on Progression-Free Survival.

Factor	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Arm: pelvis + prostate *v* prostate alone	1.08	0.75 to 1.56	.680	0.96	0.64 to 1.43	.821
Prognostic group: high *v* low risk	1.92	1.13 to 3.26	.016	—		—
Age at diagnosis	0.99	0.96 to 1.03	.645	—		—
Tumor stage						
T2 *v* T1	1.18	0.72 to 1.93	.44	—		—
T3 *v* T1	1.41	0.83 to 2.41				
PSA	1.02	1.01 to 1.03	< .0001	—		—
Gleason score						
7 *v* ≤ 6	2.01	1.32 to 3.07	< .0001	—		—
≥ 8 *v* ≤ 6	2.22	1.57 to 3.16				
Dose: < 70 *v* ≥ 70 Gy	1.33	0.87 to 2.04	.188	—		—
Dose/fraction: 2 *v* 1.8 Gy	0.70	0.48 to 1.03	.071			NS
HT: yes *v* no	0.69	0.48 to 1.01	.058	0.58	0.39 to 0.88	.009
LNI*						
15%-35% *v* < 15%	2.99	1.84 to 4.87	< .0001	3.06	1.86 to 5.04	< .0001
> 35% *v* < 15%	5.29	2.98 to 9.39		6.39	3.55 to 11.52	

Abbreviations: HR, hazard ratio; PSA, prostate-specific antigen; HT, hormonal therapy; LNI, lymph node involvement.
*LNI risk was calculated using the Roach formula: (2/3 PSA) + [(GS – 6) × 10].

conclusion regarding the role of pelvic irradiation. Differences in the study design and patient recruitment may explain the lack of pelvis benefit in the GETUG-01 series compared with RTOG 9413.

In our series, the high-risk group consisted of a heterogeneous population including patients with widely varying estimates of LNI. These selection criteria are likely to explain a much more favorable outcome in the GETUG-01 study compared with the RTOG 9314 data, especially in the GETUG-01 high-risk group.

Neither the group stratified as low risk in the GETUG-01 study nor the subgroup of patients with a less than 15% LNI risk using the

Table 3. Acute Toxicity According to Radiation Therapy Oncology Group Scale

Toxicity and Grade	Pelvis + Prostate (n = 225)		Prostate Only (n = 221)		
	No. of Patients	%	No. of Patients	%	*P**
Upper digestive					.999
0	188	83.9	195	91.1	
1	26	11.6	11	5.1	
2	9	4.0	7	3.3	
3	1†	0.4	0	0.0	
4	0	0.0	1‡	0.5	
Lower digestive					.747
0	71	31.7	73	34.0	
1	80	35.7	84	39.1	
2	69	30.8	53	24.7	
3	4	1.8	4	1.9	
4	0	0.0	1§	0.5	
Urinary					.022
0	61	27.2	45	21.0	
1	104	46.4	101	47.2	
2	52	23.2	50	23.4	
3	7	3.1	16	7.5	
4	0	0.0	2‖	0.9	

*Grade 0 to 2 *v* grade 3 to 4.
†Abdominal pain.
‡Upper digestive tract occlusion.
§Sigmoiditis.
‖Urinary retention.

Table 4. Late Toxicity According to the Late Effects in Normal Tissues Subjective, Objective, Management, and Analytic Scale

Toxicity and Grade	Pelvis + Prostate (n = 225)		Prostate Only (n = 221)		
	No. of Patients	%	No. of Patients	%	*P**
Upper digestive tract					.332
0	113	50.4	112	52.3	
1	47	21.0	49	22.9	
2	56	25.0	40	18.7	
3	6	2.7	9	4.2	
4	2	0.9	3	1.4	
Lower digestive tract					.208
0	92	41.1	92	43.0	
1	61	27.2	66	30.8	
2	51	22.8	42	19.6	
3	13	5.8	10	4.7	
4	7	3.1	4	1.9	
Digestive tract, all					.173
0	78	34.4	74	34.6	
1	50	22.3	60	28.0	
2	73	32.6	56	26.2	
3	16	7.1	17	7.9	
4	8	3.6	6	2.8	
Genitourinary					.379
0	56	25.1	54	25.2	
1	83	37.2	70	32.7	
2	50	22.4	55	25.7	
3	24	10.8	27	12.6	
4	10	4.5	8	3.7	

*χ^2 *P* value comparing grade 0 to 1 *v* grade 2 to 4.

Table 5. QOL Assessment

QOL Measure	Pelvis + Prostate	Prostate Only	*P*
EORTC QLQ-C30			
Baseline score, n = 327			.173
Mean	70.3	67.4	
SD	19.7	19.9	
Median	66.7	66.7	
Range	16.7-100.0	8.3-100.0	
12-month score, n = 145			.561
Mean	72.6	74.4	
SD	19.6	18.9	
Median	79.2	83.3	
Range	16.7-100.0	16.7-100.0	
24-month score, n = 122			.170
Mean	74.1	69.4	
SD	19.9	17.8	
Median	75.0	66.7	
Range	16.7-100.0	0.0-100.0	
Evolution at 12 months compared with baseline,* n = 116, % of patients			.904
Worsened	20.6	17.0	
Stable	57.1	60.4	
Improved	22.2	22.6	
Evolution at 24 months compared with baseline,* n = 92, % of patients			.364
Worsened	15.6	25.5	
Stable	58.8	57.5	
Improved	26.7	17.0	
IPSS			
Baseline score, n = 330			.057
Mean	9.0	10.6	
SD	7.2	7.5	
Median	7	9	
Range	0-33	0-35	
12-month score, n = 138			.634
Mean	6.4	6.8	
SD	5.3	5.6	
Median	5	5	
Range	0-25	0-27	
24-month score, n = 126			.783
Mean	7.0	7.3	
SD	5.5	5.5	
Median	5	6	
Range	0-24	0-37	
Evolution at 12 months compared with baseline,† n = 110, % of patients			.709
Worsened	6.9	12.0	
Stable	56.9	54.0	
Improved	36.2	34.0	
Evolution at 24 months compared with baseline,† n = 95, % of patients			.117
Worsened	15.6	12.0	
Stable	62.2	46.0	
Improved	22.2	42.0	
SFI			
Baseline score, n = 311			.018
Mean	27.3	24.6	
SD	10.5	9.6	
Median	27	24	
Range	4-50	3-51	
12-month score, n = 135			.873
Mean	24.5	24.7	
SD	9.3	8.0	
Median	25	24	
Range	6-48	7-44	
24-month score, n = 117			.359
Mean	27.0	25.6	
SD	10.0	6.7	
Median	27	24	
Range	11-50	13-44	
Evolution at 12 months compared with baseline,‡ n = 110			.157
Mean	−3.2	−0.3	
SD	11.0	9.0	
Median	−1	0	
Range	−9-15	0-19	
Evolution at 24 months compared with baseline,‡ n = 95			.919
Mean	0.0	−0.2	
SD	12.9	9.1	
Median	−1	−1	
Range	−22-25	−23-19	

Abbreviations: QOL, quality of life; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; SD, standard deviation; IPSS, International Prostatic Symptom Score; SFI, Sexual Function Index.

*An absolute variation of 10 points was considered as clinically pertinent.

†Evolution during time according to three classes (0 to 7, 8 to 19, and 20 to 35).

‡Absolute variation.

Roach formula benefited from pelvic irradiation. Similar results were reported in the RTOG 7706 study and in retrospective studies.[23,29] In the series by Roach et al,[2] the sample size was too low for the low-risk group (GS of 2 to 6 and PSA < 30 μg/L) and the highest risk group (GS of 7 to 10 and PSA > 30 μg/L) to draw any definitive conclusions.

Pan et al[26] Seawards et al,[30] in nonrandomized comparative studies, did not demonstrate a significant benefit for this selected highest risk subgroup of patients. Interestingly, although no benefit was reported for patients with an LNI risk of more than 15%, Vargas et al[5] observed a significant reduction of PSA failure for a selected subgroup of 368 patients with stage $\geq$ T3 or GS $\geq$ 8 (respectively, 40.3% *v* 32.9% at 8 years with and without pelvic radiotherapy; $P = .002$).

One of the major conclusions of the RTOG 9413 study was to demonstrate the interaction between the volume irradiated and hormone timing, combining neoadjuvant and concomitant hormonal therapy with 50 Gy of pelvic node irradiation, in terms of PFS.[4] Interestingly, whole pelvic irradiation and neoadjuvant and concomitant hormonal therapy were associated with a highly significant 10% improvement in 5-year PFS ($P = .005$) when compared with whole pelvic irradiation and adjuvant hormonal treatment. The use of hormonal therapy was a significant factor for PFS in our series (Table 2). Despite similar modalities to the best treatment arm of the RTOG 9413, subgroup comparative analysis for patients receiving hormonal therapy did not reveal any significant differences or a trend for prostate plus pelvis compared with prostate-only irradiation.

Differences in radiotherapy modalities may also explain the lack of pelvic irradiation benefit in the GETUG-01 study. The necessity to

deliver a dose greater than 66 Gy has been demonstrated by Valicenti et al[11] in a series of 1,465 patients included in four RTOG randomized studies and in several dose-escalation studies.[12,31] Therefore, the low dose (66 Gy) delivered to the prostate during the first period of the study could have masked the benefit of the pelvic irradiation. However, the subgroup analysis of patients receiving at least 70 Gy to the prostate did not demonstrate any differences or a trend for a benefit of pelvic irradiation, but the shorter follow-up time for this subgroup has to be taken into account (Table 2). A potential benefit of whole pelvis irradiation for this group of patients may still exist if a higher tumor control in the prostate can be achieved.

To date, there is no consensus about the dose to be delivered to the pelvic node. The dose prescribed in GETUG-01 was slightly lower than the RTOG 9413 recommendation (50.4 with a 1.8-Gy daily fractionation). In a retrospective study, Perez et al[32] reported a significant decrease in pelvic failure in stage T3 poorly differentiated tumors with a pelvic dose of $\geq$ 50 Gy, but pelvic dose was not significant in multivariate analysis for the whole series.

There is no consensus about the extent of the nodal irradiation for prostate carcinoma. The upper limit of the pelvic fields in GETUG-01 was S1/S2, which is slightly lower than the minimal unblocked field size of 16 $\times$ 16 recommended in the RTOG study. In a subset analysis of the patients treated with concomitant and adjuvant hormonal therapy, Roach et al[33] dichotomized the prostate-only group into two subgroups according to the field sizes; these were less than or equal to the median field sizes (10 $\times$ 11 cm; prostate only) and superior to the median field sizes (mini-pelvis). The authors demonstrated a statistically significant volume effect between whole pelvis, mini-pelvis, and prostate only irradiation for PFS.

Jacob et al[25] did not find any significant differences between prostate only and two pelvic volumes, partial pelvis (limited to periprostatic and obturator nodes; typical size, 10 $\times$ 14 cm), and whole pelvic irradiation (upper margin at the inferior sacroiliac joints). However, the limited volume for whole pelvis irradiation compared with the RTOG 9413 could have contributed to the absence of benefit for pelvic irradiation in this series.[25] Using lymphotropic nanoparticle-enhanced magnetic resonance imaging, Shih et al[34] demonstrated that 80% of the metastatic nodes were located only in the pelvis, with a superior border of 2 cm superior to the common iliac bifurcation. Then, the S1/S2 higher limit in the GETUG-01 study for the pelvic field could have missed more than 20% of involved nodes. Comparative dosimetric studies have also demonstrated that a traditional four-field technique, lateral rectal shielding to respect the dose constraints to the rectal wall, resulted in an underdosage of the pelvic lymph nodes draining the prostate.[35,36] This could also be an explanation for the therapeutic gain of pelvic radiotherapy observed in the series by Pan et al,[26] using conformal radiotherapy. It has also been demonstrated that using an IMRT technique results in better pelvic node coverage.[37]

Using the same scales, acute digestive grade $\geq$ 2 toxicities were significantly increased (+16.3%) in the pelvis + prostate arm in the RTOG study, whereas an insignificant +6.9% increase was observed in the GETUG-01 study. These differences are likely to be linked to different radiotherapy features, especially the lower pelvic volume, the lower dose, and the use of three-dimensional CT data in the GETUG-01 design.

A significant unexpected increase of grade $\geq$ 2 urinary acute toxicities in the prostate-only group was observed in our study, possibly explained by the more frequent use of $\geq$ 2 Gy per fraction in the prostate only-group and 1.80 Gy per fraction in the pelvic + prostate group (P = .051). Using different late toxicity scales, a small but nonsignificant increase in late grade $\geq$ 2 digestive and urinary toxicities was observed between treatment arms in both studies with pelvic irradiation. The use of IMRT should reduce this toxicity.[38] Despite the small increase in acute and late digestive toxicity in the pelvic arm, there was no significant difference and no trend of QOL impairment with pelvic irradiation with the modalities defined in the GETUG-01 study.

In conclusion, the GETUG-01 trial did not support the observations seen in the RTOG 9413 study for PFS. Long-term results and the demonstration of a clinical end point benefit will be of major importance for decision making and shared choice with the patient. One of the major contributions of the GETUG-01 study was to demonstrate that the pelvic irradiation with the radiotherapy modalities used in this study did not impair patients' QOL.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Pascal Pommier, Nicolas Voirin, David Perol, Christian Carrie
Provision of study materials or patients: Pascal Pommier, Jean Leon Lagrange, Pierre Richaud, François Lesaunier, Elisabeth Le Prise, Jean Philippe Wagner, Meng Huor Hay, Veronique Beckendorf, Jean Philippe Suchaud, Pierre Marie Pabot du Chatelard, Valerie Bernier, Christian Carrie
Collection and assembly of data: Sylvie Chabaud, Nicolas Voirin, David Perol
Data analysis and interpretation: Sylvie Chabaud, David Perol
Manuscript writing: Pascal Pommier
Final approval of manuscript: Pascal Pommier, Jean Leon Lagrange, Pierre Richaud, Elisabeth Le Prise, Jean Philippe Wagner, Meng Huor Hay, Veronique Beckendorf, Jean Philippe Suchaud, Pierre Marie Pabot du Chatelard, Valerie Bernier, David Perol, Christian Carrie

REFERENCES

1. Lawton CA, DeSilvio M, Roach M, et al: An update of the phase III trial comparing whole-pelvic (WP) to prostate only (PO) radiotherapy and neoadjuvant to adjuvant total androgen suppression (TAS): Updated analysis of RTOG 94-13. Int J Radiat Oncol Biol Phys 63:S19-S19, 2005 (suppl)
2. Roach M III, DeSilvio M, Lawton C, et al: Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 21:1904-1911, 2003
3. Ennis RD: Uncertainties regarding pelvic radiotherapy for prostate cancer. J Clin Oncol 22: 2254-2255, 2004
4. Pollack A: A call for more with a desire for less: Pelvic radiotherapy with androgen deprivation in the treatment of prostate cancer. J Clin Oncol 21:1899-1901, 2003
5. Vargas CE, Galalae R, Demanes J, et al: Lack of benefit of pelvic radiation in prostate cancer patients with a high risk of positive pelvic lymph nodes treated with high-dose radiation. Int J Radiat Oncol Biol Phys 63:1474-1482, 2005
6. Fleming ID, Cooper JS, Henson DE: American Joint Committee on Cancer Staging Manual (ed 5). Philadelphia, PA, J.B. Lippincott, 1997, pp 219-222
7. Collett D: Survival Data in Medical Research. London, United Kingdom, Chapmann & Hall, 1994

8. Lakatos E, Lan KK: A comparison of sample size methods for the logrank statistic. Stat Med 11:179-191, 1992

9. Hanks GE, Hanlon AL, Schultheiss TE, et al: Dose escalation with 3D conformal treatment: Five year outcomes, treatment optimization, and future directions. Int J Radiat Oncol Biol Phys 41:501-510, 1998

10. Pollack A, Zagars GK, Smith LG, et al: Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. J Clin Oncol 18:3904-3911, 2000

11. Valicenti R, Lu J, Pilepich M, et al: Survival advantage from higher-dose radiation therapy for clinically localized prostate cancer treated on the Radiation Therapy Oncology Group trials. J Clin Oncol 18:2740-2746, 2000

12. Zelefsky MJ, Leibel SA, Gaudin PB, et al: Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 41:491-500, 1998

13. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993

14. Barry MJ, Fowler FJ Jr, O'Leary MP, et al: The American Urological Association symptom index for benign prostatic hyperplasia: The Measurement Committee of the American Urological Association. J Urol 148:1549-1557, 1992

15. O'Leary MP, Fowler FJ, Lenderking WR, et al: A brief male sexual function inventory for urology. Urology 46:697-706, 1995

16. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

17. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. Br J Cancer 35:1-39, 1977

18. Cox DR: Regression models and life tables. J R Stat Soc B 34:187-220, 1972

19. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. Control Clin Trials 17:343-346, 1996

20. European Organisation for Research and Treatment of Cancer Quality of Life Study Group.E-ORTC QLQ-C30 Scoring Manual (ed 2). Brussels, Belgium, European Organisation for Research and Treatment of Cancer, 1999

21. Osoba D, Bezjak A, Brundage M, et al: 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 41:280-287, 2005

22. Roach M III, Marquez C, Yuo HS, et al: Predicting the risk of lymph node involvement using the pre-treatment prostate specific antigen and Gleason score in men with clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 28:33-37, 1994

23. Asbell SO, Krall JM, Pilepich MV, et al: Elective pelvic irradiation in stage A2, B carcinoma of the prostate: Analysis of RTOG 77-06. Int J Radiat Oncol Biol Phys 15:1307-1316, 1988

24. Asbell SO, Martz KL, Shin KH, et al: Impact of surgical staging in evaluating the radiotherapeutic outcome in RTOG #77-06, a phase III study for T1BN0M0 (A2) and T2N0M0 (B) prostate carcinoma. Int J Radiat Oncol Biol Phys 40:769-782, 1998

25. Jacob R, Hanlon AL, Horwitz EM, et al: Role of prostate dose escalation in patients with greater than 15% risk of pelvic lymph node involvement. Int J Radiat Oncol Biol Phys 61:695-701, 2005

26. Pan CC, Kim KY, Taylor JM, et al: Influence of 3D-CRT pelvic irradiation on outcome in prostate cancer treated with external beam radiotherapy. Int J Radiat Oncol Biol Phys 53:1139-1145, 2002

27. Partin AW, Kattan MW, Subong EN, et al: Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: A multi-institutional update. JAMA 277:1445-1451, 1997

28. Roach M III, Hanks G, Thames H Jr, et al: Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 65:965-974, 2006

29. Seaward SA, Weinberg V, Lewis P, et al: Improved freedom from PSA failure with whole pelvic irradiation for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 42:1055-1062, 1998

30. Seaward SA, Weinberg V, Lewis P, et al: Identification of a high-risk clinically localized prostate cancer subgroup receiving maximum benefit from whole-pelvic irradiation. Cancer J Sci Am 4:370-377, 1998

31. Hanks GE, Hanlon AL, Epstein B, et al: Dose response in prostate cancer with 8-12 years' follow-up. Int J Radiat Oncol Biol Phys 54:427-435, 2002

32. Perez CA, Michalski J, Brown KC, et al: Non-randomized evaluation of pelvic lymph node irradiation in localized carcinoma of the prostate. Int J Radiat Oncol Biol Phys 36:573-584, 1996

33. Roach M III, DeSilvio M, Valicenti R, et al: Whole-pelvis, "mini-pelvis," or prostate-only external beam radiotherapy after neoadjuvant and concurrent hormonal therapy in patients treated in the Radiation Therapy Oncology Group 9413 trial. Int J Radiat Oncol Biol Phys 66:647-653, 2006

34. Shih HA, Harisinghani M, Zietman AL, et al: Mapping of nodal disease in locally advanced prostate cancer: Rethinking the clinical target volume for pelvic nodal irradiation based on vascular rather than bony anatomy. Int J Radiat Oncol Biol Phys 63:1262-1269, 2005

35. Sanguineti G, Cavey ML, Endres EJ, et al: Is IMRT needed to spare the rectum when pelvic lymph nodes are part of the initial treatment volume for prostate cancer? Int J Radiat Oncol Biol Phys 64:151-160, 2006

36. Wang-Chesebro A, Coleman J, Xia P, et al: IMRT improves pelvic lymph node (PLN) coverage and dose to critical structures compared with standard four field (4F) whole pelvis (WP) radiation therapy (RT) in prostate cancer (PC). Int J Radiat Oncol Biol Phys 63:S194, 2005 (suppl)

37. Wang-Chesebro A, Xia P, Coleman J, et al: Intensity-modulated radiotherapy improves lymph node coverage and dose to critical structures compared with three-dimensional conformal radiation therapy in clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 66:654-662, 2006

38. Ashman JB, Zelefsky MJ, Hunt MS, et al: Whole pelvic radiotherapy for prostate cancer using 3D conformal and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 63:765-771, 2005

Acknowledgment

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).