Clinical Investigation

Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Update of the Long-Term Survival Results of the GETUG-01 Randomized Study

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Summary

With a median follow-up of 11.4 years, the randomized GETUG-01 study did not show any benefit in terms of overall survival and event-free survival (EFS) of pelvic nodes compared with prostate-only irradiation in nonmetastatic prostate cancer.

Purpose: To report the long-term results of the French Genitourinary Study Group (GETUG)-01 study in terms of event-free survival (EFS) and overall survival (OS) and assess the potential interaction between hormonotherapy and pelvic nodes irradiation.

Patients and Methods: Between December 1998 and June 2004, 446 patients with T1b-T3, N0pNx, M0 prostate carcinoma were randomly assigned to either pelvic nodes and prostate or prostate-only radiation therapy. Patients were stratified into 2 groups: “low risk” (T1-T2 and Gleason score ≤6 and prostate-specific antigen <3 × the upper normal limit of the laboratory) (92 patients) versus “high risk” (T3 or Gleason score >6 or prostate-specific antigen >3 × the upper normal limit of the laboratory). Short-term 6-month neoadjuvant and concomitant hormonal therapy was

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Introduction

The preliminary results of the French randomized study GETUG-01 conducted by the French Genitourinary Study Group (GETUG) addressing the role of pelvic nodes irradiation in nonmetastatic prostate carcinoma were published in 2007 (1). With a median follow-up of 42 months, the 5-year overall and progression-free survival rates were similar between pelvic nodes and prostate (pelvic) versus prostate-only (PO) irradiation. The other important issues of this analysis were (1) to show a similar outcome in terms of toxicity and quality of life in both arms; and (2) to demonstrate the prognostic impact of hormonal therapy (HT) and lymph node involvement risk in terms of progression-free survival.

The objective of this article is to report the final results of GETUG-01 in terms of overall and event-free survival, as well as to assess the potential interaction between HT and pelvic nodes irradiation observed by Lawton et al (2) in Radiation Therapy Oncology Group (RTOG) protocol 9413.

Patients and Methods

Patient characteristics

This study was designed in 1997 and randomized 446 patients between December 1998 and June 2004 within 21 French centers. Inclusion criteria were large, encompassing all T stage, prostate-specific antigen (PSA), and Gleason score (GS) values providing the absence of nodal and/or bone metastases on computed tomography and bone scan.

At the time of the randomization, patients were stratified according to 2 prognostic groups (high vs low) based on clinical T-stage (cT), PSA value, and GS. The “low risk” group included patients with all these criteria: cT1c or cT2 and a GS <6 and a PSA value <3× the upper normal value limit of the laboratory (usually 4 ng/mL), and the “high risk group” encompassed patients with cT3 and/or GS ≥7 and/or PSA value >3× the upper normal value limit of the laboratory.

After the results observed in the low-risk group, patients were also reclassified for a post hoc analysis on their risk of lymph node involvement (rLNI), using the Roach formula: 2/3 PSA + [(GS − 6) × 10] (3).

Radiation therapy modalities

Pelvic irradiation consisted of a conventional 4-field technique, including internal, external, and the first common iliac nodes with an upper limit as the level of the anterior portion of the junction between the first and second sacral vertebra. A 3-dimensional treatment plan for prostate and seminal vesicles irradiation was mandatory. A 10-mm 3-dimensional expansion of the clinical target volume (CTV) was recommended for the planned target volume. A conventional 4-field technique using shield blocks or a conformal approach with the use of a multileaf collimator was allowed for prostate irradiation.

Standard fractionated irradiation (2 Gy per fraction and 5 fractions per week) 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. The total dose to the prostate increased from 66 Gy to a recommended dose of 70 Gy after March 2000, after publication of dose-escalation studies. Two others schemes were authorized: 1.8 Gy per session, 5 sessions per week, to total a dose of 46.8 and 68.4 Gy (72 Gy after March 2000) for the pelvis and the prostate, respectively; and 2.25 Gy per session, 4 sessions per week, to a total dose 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 patients stratified in the “high-risk group” only but was left to the discretion of each institution (Table 1). It consisted of 4-8 months neo-adjvant and concomitant treatment using a luteinizing
hormone—releasing hormone agonist associated with initial short-term nonsteroidal antiandrogen administration.

**Objectives and statistical methodology**

The GETUG-01 study was powered to detect a 15% improvement (60%-75%) of 5-year progression-free survival (PFS) in favor of pelvic nodes irradiation. Progression-free survival included local progression, node or distant documented metastases, death from any cause, and/or biologic progression using the American Society for Radiation Oncology definition that was the standard at that time. Patients were stratified according to participating center and risk of nodal involvement (low vs high risk) using a blocked method.

Event-free survival (EFS) including only progression events was preferred to PFS for this long-term update, because no systematic long-term monitoring was initially planned in the study beyond the analysis carried out in 2007. A one-shot update performed 8 years after the end of the study would have overestimated the PFS because no earlier progressive disease notification in the deceased patients would have been searched. This decision also aimed to focus on the role of pelvic irradiation on prostate cancer recurrence excluding deaths unrelated to prostate cancer. Subgroup analyses were performed to assess the potential interaction between HT and pelvic irradiation.

The analysis was performed according to the intent-to-treat principle and using SAS software (version 9.3; SAS Institute, Cary, NC). Overall survival (OS) was defined as the time from randomization to death from any cause or censored at the last follow-up. Survival functions were calculated using the Kaplan-Meier method (4). Survival distributions were compared between the 2 arms using a log–rank test (5). Event-free survival was defined from random assignment to the date of disease progression or censored at last follow-up. Event-free survival was analyzed using a competing risk method (considering deaths unrelated to prostate cancer as a competing risk event). The cumulative incidence function developed by

### Table 1  Patient and treatment characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pelvis + prostate (n=225)</th>
<th>Prostate only (n=221)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic group (stratification), n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low-risk</td>
<td>48 (21.3)</td>
<td>44 (19.9)</td>
<td>.727</td>
</tr>
<tr>
<td>High-risk</td>
<td>177 (78.7)</td>
<td>177 (80.1)</td>
<td></td>
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<tr>
<td>Age at diagnosis (y)</td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>68.8 (5.0)</td>
<td>68.9 (4.9)</td>
<td>.812</td>
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<tr>
<td>Median (range)</td>
<td>69.8 (52.6-75.6)</td>
<td>69.9 (49.2-75.8)</td>
<td></td>
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<tr>
<td>Stage T, n (%)</td>
<td></td>
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<tr>
<td>1</td>
<td>56 (25.1)</td>
<td>48 (21.9)</td>
<td>.648</td>
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<tr>
<td>2</td>
<td>113 (50.7)</td>
<td>111 (50.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>54 (24.2)</td>
<td>60 (27.4)</td>
<td></td>
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<tr>
<td>PSA (µg/L)</td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>16.3 (16.5)</td>
<td>15.0 (14.7)</td>
<td>.359</td>
</tr>
<tr>
<td>Median (range)</td>
<td>12.0 (0.2-144)</td>
<td>11.0 (1.3-150)</td>
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<tr>
<td>Gleason score (GS), n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤6</td>
<td>114 (50.9)</td>
<td>106 (48.6)</td>
<td>.432</td>
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<tr>
<td>7</td>
<td>82 (36.6)</td>
<td>91 (41.7)</td>
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<tr>
<td>8-10</td>
<td>28 (12.5)</td>
<td>21 (9.6)</td>
<td></td>
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<tr>
<td>RT dose to prostate/pelvis (Gy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>22.32 (1.8)/46.14 (1.1)</td>
<td>68.08 (5.8)</td>
<td>.369</td>
</tr>
<tr>
<td>Median (range)</td>
<td>22 (18-28)/46 (44-50)</td>
<td>68.4 (4-76)</td>
<td></td>
</tr>
<tr>
<td>RT dose to pelvis + prostate (Gy)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>68.45 (2.0)</td>
<td>68.08 (5.8)</td>
<td>.369</td>
</tr>
<tr>
<td>Median (range)</td>
<td>68.4 (63/74)</td>
<td>68.4 (4/76)</td>
<td></td>
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<tr>
<td>RT dose to the prostate* (Gy)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;70</td>
<td>138 (61.6)</td>
<td>121 (56.3)</td>
<td>.286</td>
</tr>
<tr>
<td>≥70</td>
<td>86 (38.4)</td>
<td>94 (43.7)</td>
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<tr>
<td>LNI risk† (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>115 (51.3)</td>
<td>124 (56.8)</td>
<td>.364</td>
</tr>
<tr>
<td>15-35</td>
<td>83 (37.1)</td>
<td>76 (34.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;35</td>
<td>26 (11.6)</td>
<td>18 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Concomitant HT in patients stratified as high risk</td>
<td>97 (57.5)</td>
<td>102 (59.7)</td>
<td>.261</td>
</tr>
</tbody>
</table>

*Abbreviations: HT = hormonal therapy; LNI = lymph node involvement; PSA = prostate-specific antigen; RT = radiation therapy; SD = standard deviation.*

* Total dose.
† LNI risk = risk of LNI using the Roach formula: 2/3 PSA + [(GS – 6) × 10].
Kalbfleisch and Prentice (6) and nonparametric Gray’s test (7) were used to estimate and compare cumulative incidence function between the 2 arms. Event-free survival probabilities were reported as \((1 - \text{cumulative incidence probability})\). A proportional subdistribution hazard model (8) was performed to adjust the treatment effect to the stratification risk factor (high vs low risk). A subgroup analysis in patients stratified as “high risk” adjusted on concomitant HT was performed using the same method. Median follow-up time was calculated using a reverse Kaplan-Meier estimate (9).

**Results**

The characteristics of the patients and treatments are detailed in Table 1. Baseline data, as well as treatment, toxicity, and quality of life data were not updated for this article but can be seen in the original report (1).

Ninety-two patients (21%) were stratified in the “low-risk” group. Of note, 6 patients received HT in this group (4 and 2 patients in the pelvic and PO arms, respectively). According to the Roach formula, distribution of the rLNI was similar within the 2 arms, with 54% of the population \((n=239)\) classified in the <15% rLNI class (Table 1).

The updated median follow-up was 11.4 years (range, 0.01-15.7 years). One patient was lost to follow-up, and relapse could not be dated precisely in 4 patients.

**OS and EFS**

At the time of the analysis, 135 deaths (30.3%) (66 vs 69 for the pelvic and PO arms, respectively) and 187 recurrences (95 vs 92 for pelvic and PO, respectively) were notified. Among the 135 deaths, 69 patients died of an intercurrent cause without beforehand notification of disease progression (34 and 35 patients for pelvic and PO, respectively).

There was no difference between pelvic and PO irradiation in OS for the whole series or within the 2 stratified subgroups (10-year OS: respectively, 74.9% vs 73.6%, 87.7% vs 84%, and 71.2% vs 71% for the whole population, low-risk, and high-risk groups) (Fig. 1).

As for EFS, there were no statistically significant differences for the whole series or for patients stratified in the high-risk group (respectively, 57.6 vs 55.6 and 52 vs 54.2 at 10 years) (Fig. 2). However, for the patients stratified as “low risk,” we observed an unexpected either non-statistically significant long-term difference in favor of pelvic irradiation for EFS (77.2%, (95% confidence interval [CI] 63.8-88.4%) versus 62.5% (95% CI 47.0-78.1%) at 10 years; \(P= .1778\).

Adjusted analysis of stratification factor did not show a significant effect of treatment arms (hazard ratio 0.97 [95% CI 0.73-1.31] and 1.81 [95% CI 1.23-2.69] for pelvic arm and high-risk group, respectively). A post hoc subgroup analysis was performed according to rLNI patients (<15% vs ≥15%) according to the Roach formula (Fig. 3). Patients with the lowest rLNI seemed to benefit from pelvic irradiation in terms of EFS (82.2% vs 60.7% at 10 years; \(P= .0058\)), whereas those with a ≥15% risk did not.

**Interaction between radiation therapy and HT (high-risk group)**

A subgroup analysis was performed in patients stratified to the high-risk group to assess a potential interaction between pelvic nodes irradiation and concomitant HT (Fig. 4). Long-term EFS was similar in patients treated with HT with or without pelvic irradiation, whereas a nonsignificantly higher EFS was observed in favor of the pelvic irradiation arm when radiation therapy was delivered alone. Analysis of the study treatment adjusted for concomitant HT showed a nonsignificant hazard ratio of 0.94 (95% CI 0.68-1.29), whereas the use of concomitant HT showed a strongly significant hazard ratio of 0.68 (95% CI 0.49-0.93).

In addition, only patients with <15% rLNI and receiving exclusive radiation therapy seemed to benefit from pelvic irradiation (Fig. 5).

**Discussion**

The GETUG-01 study is the third randomized trial published addressing the role of pelvic nodes irradiation in nonmetastatic (M0) prostate cancer (1, 2, 10).

The RTOG 77-7 protocol enrolled T1B and T2 patients, treated with external beam radiation therapy (associated with HT in 5%), classified as N0 either with lymphangiography (74%) or lymph node dissection (26%) (10). The GS was 8 to 10 in 20%. Doses delivered to the prostate (mainly 65 Gy, up to 72 Gy) and pelvic nodes (45-50 Gy) were similar to the ones recommended in GETUG-01. Despite a very long-term follow-up, no difference was observed between PO or prostate plus pelvis irradiation in terms of OS, cause-specific survival, no evidence of disease survival, local/regional failure, and distant metastases rates. However, the authors demonstrated the impact of laparotomy for nodes staging compared with lymphangiography.

Likewise, the 4-arm randomized RTOG 9413 study did not demonstrate a benefit for pelvic irradiation in the whole population. However a significant difference in terms of PFS was observed in favor of pelvic irradiation in patients receiving neoadjuvant and concomitant hormonotherapy (2).

**Limitations of the GETUG-01 study**

The low dose delivered to the prostate and its heterogeneity, as well as the absence of a strict recommendation for the use of HT in the high-risk group, may limit the applicability of the GETUG-01 findings to contemporary patients. In addition, this study was designed in 1997, before the publication of the D’Amico classification of 3 risk groups,
Fig. 1. Overall survival (OS) according to the whole population (A), the stratified low-risk group (B), and the high-risk group (C). Abbreviations: IC95% = 95% confidence interval; RT = radiation therapy.
Fig. 2. Event-free survival (EFS) according to the whole population (A), the stratified low-risk group (B), and the high-risk group (C). Abbreviations: IC95% = 95% confidence interval; RT = radiation therapy.
Fig. 3. Event-free survival (EFS) according to lymph node involvement risk <15% (A) and ≥15% (B). Abbreviations: IC95% = 95% confidence interval; RT = radiation therapy.
actually considered as a standard, and did not allow us
to report specific results in intermediate- and high-risk
groups.

The low dose level delivered to the prostate may explain
the relatively low EFS results, especially in patients strat-
ified as “low risk.” The administration of a higher dose to

Fig. 4. Event-free survival (EFS) in high-risk patients according to concomitant hormonal therapy (A) or not (B). Ab-
breviations: IC95% = 95% confidence interval; RT = radiation therapy.
**Fig. 5.** Event-free survival (EFS) according to lymph node involvement (LNI) risk <15% without hormonal therapy (HT) (A), LNI risk <15% with HT (B), LNI risk ≥15% without HT (C), and LNI risk ≥15% with HT (D). *Abbreviations:* IC95% = 95% confidence interval; RT = radiation therapy.
the prostate may certainly have reduced the occurrence of local recurrence and delayed (“second wave”) distant recurrences in this population. This could explain the absence of benefit from pelvic nodes irradiation in our series. Note that the dose level delivered to the pelvic nodes was homogeneous in that study, 46 Gy being the still-recommended dose.

The nearly 15% observed difference of 10-years EFS in favor of pelvic radiation therapy in patients stratified as “low risk” was not significant, possibly related to the limited effective size. The highly significant benefit observed for <15% rLNI patients was based on a post hoc subgroup analysis and has therefore to be considered with caution.

### Pelvic nodes volume definition

Another potential explanation for the lack of benefit of pelvic irradiation may come from an inadequate coverage of metastatic lymph nodes when limiting the nodes target volume to internal and external iliac nodes. Indeed several publications based on lymph node dissection and sentinel lymph node techniques have shown “atypical” drainage to presacral, pararectal, and/or peribladder areas in 10% to 20% of cases (12-15). In addition, functional imaging studies performed at the time of biological recurrence after surgery or radiation therapy have also shown a high rate of recurrence sites (para-aortic, proximal common iliac, pararectal, and inguinal) outside the nodal CTV recommended by cooperative groups (15-17).

In GETUG-01, the upper limit of the pelvic CTV was defined as the S1/S2 level, thus omitting most of the common iliac nodes area. Because of the conventional 4-field technique applied at that time, the presacral nodes and anterior external iliac nodes were probably not adequately treated.

The superior border in RTOG 9413 was at the level of L5-S1, with a minimum unblocked field size of 16 × 16 cm (11, 18). A post hoc subgroup analysis was performed to assess the impact of the size of pelvic fields in patients stratified to receive neoadjuvant and concomitant HT (18). Patients randomized to the prostate-only group were dichotomized according to the radiation field size, less (PO) versus greater (MP) than the median (10 cm × 11 cm). The field sizes were significantly correlated with the median and 7-year PFS (40%, 31%, and 27% for whole pelvis, MP, and PO, respectively). However, the difference was not significant between MP and PO fields (P = .76), which advocates the treatment of a larger nodal CTV.

### Patient selection

Several prospective and retrospective analyses have shown that intermediate and favorable high-risk patients would benefit the most from pelvic irradiation. On the basis of the Roach formula, Seaward et al reported that patients with a 15% to 35% rLNI may be the best candidates for pelvic irradiation in terms of improved freedom from PSA failure (19, 20). Similarly, in a subset analysis of RTOG 9413, Roach et al (18) identified in their series 2 high-risk subgroups that benefited the most from pelvic irradiation (PSA <30 ng/ml and GS 7-10) or (PSA >30 ng/ml and GS 2-6).

Conversely, Vargas et al (21) did not observed any benefit of pelvic nodes irradiation for 15-35% rLNI patients treated with external beam radiation therapy and a boost with brachytherapy. Unfortunately, the authors did not report their results in <15% rLNI patients. Using the Partin tables and based on a matched paired analysis, Pan et al (22) reported a higher 2-year freedom from biochemical recurrence with pelvic irradiation, but this exclusively benefited the 5% to 15% rLNI patients. In addition, the very large retrospective series recently published by Amini et al and a subgroup analysis of the GETUG-12 randomized study also failed to demonstrate any added value of pelvic irradiation in high-risk patients (23, 24).

Even though the definitive results of GETUG-01 failed to demonstrate a benefit of the irradiation of pelvic nodes within the whole population, an unexpected (although nonsignificant) 15% benefit for EFS was observed for patients stratified into a low-risk group. This so-defined group encompassed both patients considered as “low risk” in the D’Amico classification as well as favorable intermediate-risk patients according to Zumsteg et al (25). However, according to a post hoc analysis only patients with a <15% rLNI using the Roach formula seemed to benefit from node irradiation in GETUG-01, which is consistent with the observation from Pan et al.

### Potential interaction between HT and pelvic nodes irradiation

Conversely to RTOG 9413, the short course of HT in our series seemed to mask the potential benefit of pelvic nodes irradiation. No benefit or trend for pelvic irradiation in patients treated with concomitant HT and RT was observed in our trial.

In high-risk patients with a large burden of disease, the risk of atypical lymph nodes involvement (outside the treated pelvic volume) and the presence of occult distant metastases at the time of diagnosis may have masked any benefit from pelvic irradiation. Indeed, the efficacy of radiation therapy in pelvic involved nodes was strongly suggested in the recent Surveillance, Epidemiology, and End Results survey addressing the role of local therapy in cN+ and pN+ (26).

The GETUG-01 data may indicate that short-course HT and pelvic nodes irradiation may both be able to sterilize micrometastatic lymph nodes in relatively low-risk patients. Similar results were recently published by Braunstein et al in a very large multiple-institution cohort (27). In that series, even if whole pelvic irradiation or use of concomitant HT were associated with a decreased risk of all-cause mortality, the combination of both did not further improve this benefit.
Conclusion

The GETUG-01 study did not demonstrate any benefit from pelvic nodes irradiation in terms of OS and EFS. Added value of pelvic irradiation with advanced radiation therapy techniques and more accurate nodal CTV definition and doses is currently being explored in at least 2 randomized trials combining radiation and HT (RTOG 0924 for intermediate-risk and favorable high-risk patients and GETUG-AFU-23 for unfavorable high-risk patients). On the basis of our results, pelvic irradiation in selected “intermediate-risk” patients who do not require HT should also be prospectively addressed.

References

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