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Platinum Priority – Prostate Cancer

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Addition of Radiotherapy to Long-Term Androgen Deprivation in Locally Advanced Prostate Cancer: An Open Randomised Phase 3 Trial

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Abstract

Background: Radiotherapy combined with androgen-deprivation therapy (ADT) is superior to radiotherapy alone in localised prostate cancer; however, data comparing ADT alone are somewhat limited.
Objective: To compare 3-yr ADT plus radiotherapy with ADT alone in locally advanced prostate cancer patients.
Design, setting, and participants: A multicentre randomised open controlled phase 3 trial in 264 histologically confirmed T3–4 or pT3N0M0 prostate cancer patients randomised from March 2000 to December 2003.
Intervention: ADT (11.25 mg subcutaneous depot injection of leuprorelin every 3 mo for 3 yr) plus external-beam radiotherapy or ADT alone. Flutamide (750 g/d) was administered for 1 mo.
Outcome measurements and statistical analysis: The primary objective was 5 yr progression-free survival (PFS) according to clinical or biologic criteria, using the American Society for Therapeutic Radiology and Oncology (ASTRO) and the newer (Phoenix) definition (nadir plus 2 ng/ml), by intention to treat. Secondary objectives included time to locoregional recurrence and distant metastases, and overall and disease-specific survival. Our Analyses: intent-to-treat analysis, multivariate analyses using a Cox model with a 5% threshold from univariate analysis, and Kaplan-Meier estimates.
Results and limitations: ADT alone was administered to 130 patients and combined therapy to 133. With a median follow-up of 67 mo, 5-yr PFS was 60.9% for combined therapy versus 8.5% with ADT alone (ASTRO; $p < 0.0001$), and 64.7% versus 15.4%, respectively, for Phoenix ($p < 0.0011$). Locoregional progression was reported in 9.8% of combined-therapy patients versus 29.2% with ADT alone ($p < 0.0001$) and metastatic progression in 3.0% versus 10.8%, respectively ($p < 0.018$). Overall survival was 71.4% with combined therapy versus 71.5% with ADT alone; disease-specific survival was 93.2% versus 86.2%. Limitations included the relatively small population and a relatively short follow-up period.
Conclusions: Combined therapy strongly favoured improved PFS, locoregional control, and metastasis-free survival. Longer follow-up is needed to assess the potential survival impact.

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1. Introduction

The benefit of the addition of long-term adjuvant androgen-deprivation therapy (ADT) to local radiotherapy in patients with locally advanced prostate cancer was first demonstrated in 1997 [1,2]. Results from the European Organisation for Research and Treatment of Cancer (EORTC) 22863 and the Radiation Therapy Oncology Group (RTOG) 85-31 trials demonstrated significant improvements in disease control (biochemical, local, and distant) with combination therapy [1,2]; a benefit in 10-yr overall and disease-specific survival was later confirmed [3,4]. The RTOG 92-02 study reported improved 10-yr prostate-specific and progression-free survival (PFS) comparing 28-mo androgen suppression with 4 mo [5]; in the EORTC 22961 study, 6-mo androgen suppression was inferior to 3-yr suppression for prostate-specific and overall survival at 5 yr [6]. Two recent meta-analyses confirmed these results [7,8]. The aim of the current study was to assess the possible benefits of the combined treatment on PFS.

2. Patients and methods

A prospective open-label randomised multicentre study was conducted in 40 centres in France (239 patients) and Tunisia (25 patients). Enrolment took place between March 2000 and December 2003. Men with histologically confirmed, locally advanced (T3–4N0) or pathologic pT3 prostate adenocarcinoma without documented nodes or metastases were eligible. Patients included had no prior treatment for prostate cancer, were <80 yr of age, with a Karnofsky performance status of $\geq$70%, a life expectancy of $\geq$7 yr, and adequate haematological and hepatic function. Written informed consent prior to enrolment was received.

2.1. Treatment

Patients were randomised to treatment with the luteinising hormone-releasing hormone (LHRH) agonist leuprorelin (11.25 mg subcutaneous depot injection every 3 mo) for 3 yr or to LHRH agonist plus external-beam radiation therapy. Oral flutamide (750 mg/d) was administered during month 1. ADT could be resumed during follow-up. Radiation therapy was initiated within 3 mo of randomisation and delivered with a four-field technique for the pelvic volume and a four- or six-field technique for the prostatic volume using high-energy photons (>10 Mv) and three-dimensional computed tomography (CT) planning. All patients received 46 ± 2 Gy given in 25 fractions over 5 wk to the whole pelvis and 22 ± 2 Gy given in 10–12 fractions over 2–2.5 wk in a volume encompassing the prostate gland and periprostatic tumour extension. In May 2011, the protocol was amended to increase the dose to the prostate from 68 ± 2 Gy to 70 ± 4 Gy. Delivery of radiation therapy was centrally reviewed (technique, target volumes, dose, and portals imaging) for all patients by four independent radiotherapists.

2.2. Evaluations

Pretreatment evaluations included medical history, physical examination, complete blood counts, biochemistry tests, prostate-specific antigen (PSA), performance status, and a complete radiologic assessment. A follow-up visit was performed 1 mo after the end of radiation (combined arm only) and every 6 mo for 5 yr. Thereafter, patients were followed annually for progression and survival. Follow-up assessments included a digital rectal examination and serum PSA. A transrectal ultrasound was recommended at 6 mo, 1, 3, and 5 yr. CT and bone scans were systematically performed in case of clinical or biologic progression. Adverse events were recorded throughout. Acute radiation toxicity was evaluated at the end of radiotherapy and after 6 mo according to the RTOG scale. Late radiation toxicity was evaluated throughout according to the Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic scale.

2.3. Study end points

The primary end point was 5-yr PFS (biochemical or clinical) defined as the interval between randomisation and disease progression or death from any cause. Two definitions for the time of biochemical progression were evaluated. According to standard practices at the time of study initiation, the initial American Society for Therapeutic Radiology and Oncology (ASTRO) guidelines, published in 1997 [9], were used, defined as an increase in PSA after nadir on two consecutive measurements, with a minimum interval of 3 mo between two determinations. Following revision of the ASTRO definition to an increase of $\geq$2 ng/ml above the PSA nadir at the ASTRO-RTOG consensus meeting in Phoenix, Arizona, in 2005 [10], an additional analysis of the primary end point was performed using the revised ASTRO-Phoenix definition. Locoregional clinical progression was defined as >50% increase in prostate volume compared with the lowest value by ultrasound, the appearance of a new palpable prostate lesion in the event of previous complete clinical normalisation, and identification of new regional lymph nodes by CT scan. Metastatic progression was defined by CT or bone scan. Secondary end points were disease-specific and overall survival, time to locoregional recurrence, time to distant metastases, and tolerance. Adverse events were classified according to MedDRA, v.11.1.

2.4. Statistical analysis

Statistical analyses were performed using SAS, v.8.2. Analyses were performed in the intent-to-treat population, defined as all randomised patients receiving at least one dose of study treatment (excluding

Table 1 – Baseline patient and disease characteristics

	ADT $n = 131$	ADT plus radiotherapy $n = 133$
Age, yr, median (range)	71 (53–79)	72 (53–80)
Karnofsky performance status, %, median (range)	100 (70–100)	100 (80–100)
Clinical tumour stage, no. of patients (%)*		
T3N0M0	122 (93)	123 (93)
T4N0M0	3 (2)	5 (4)
Biopsy pT3	5 (4)	5 (4)
Local Gleason score, no. of patients (%)		
4–6	68 (52)	61 (46)
7	41 (31.3)	40 (30.1)
8–10	22 (16.8)	32 (24.1)
PSA, ng/ml, mean (SD)	51.8 (129.3)	41.5 (45.9)
PSA level, no. of patients (%)		
<20 ng/ml	50 (38)	47 (35)
20–50 ng/ml	52 (40)	55 (41)
≥50 ng/ml	29 (22)	31 (23)
Pelvic lymph node dissection	10 (7.6)	14 (10.5)
Pathologically positive nodes	1 (0.8)	1 (0.8)
Metastatic disease	0 (0.0)	0 (0.0)

ADT = androgen-deprivation therapy; PSA = prostate-specific antigen; SD = standard deviation.
* All patients were N0M0 (clinical and computed tomography criteria).