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DOI

[10.1056/NEJM199707313370502](https://doi.org/10.1056/NEJM199707313370502)

Publication date

1997

Published in

The New England journal of medicine

[Link to publication](#)

Citation for published version (APA):

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<https://doi.org/10.1056/NEJM199707313370502>

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IMPROVED SURVIVAL IN PATIENTS WITH LOCALLY ADVANCED PROSTATE CANCER TREATED WITH RADIOTHERAPY AND GOSERELIN

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ABSTRACT

Background We conducted a randomized, prospective trial comparing external irradiation with external irradiation plus goserelin (an agonist analogue of gonadotropin-releasing hormone that reduces testosterone secretion) in patients with locally advanced prostate cancer.

Methods From 1987 to 1995, 415 patients with locally advanced prostate cancer were randomly assigned to receive radiotherapy alone or radiotherapy plus immediate treatment with goserelin. The patients had a median age of 71 years (range, 51 to 80). Patients in both groups received 50 Gy of radiation to the pelvis over a period of five weeks and an additional 20 Gy over an additional two weeks as a prostatic boost. Patients in the combined-treatment group received 3.6 mg of goserelin (Zoladex) subcutaneously every four weeks starting on the first day of irradiation and continuing for three years; those patients also received cyproterone acetate (150 mg orally per day) during the first month of treatment to inhibit the transient rise in testosterone associated with the administration of goserelin.

Results Data were available for analysis on 401 patients. The median follow-up was 45 months. Kaplan-Meier estimates of overall survival at five years were 79 percent (95 percent confidence interval, 72 to 86 percent) in the combined-treatment group and 62 percent (95 percent confidence interval, 52 to 72 percent) in the radiotherapy group ($P=0.001$). The proportion of surviving patients who were free of disease at five years was 85 percent (95 percent confidence interval, 78 to 92 percent) in the combined-treatment group and 48 percent (95 percent confidence interval, 38 to 58 percent) in the radiotherapy group ($P<0.001$).

Conclusions Adjuvant treatment with goserelin, when started simultaneously with external irradiation, improves local control and survival in patients with locally advanced prostate cancer. (N Engl J Med 1997;337:295-300.)

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THE role of external irradiation in patients with locally advanced prostate cancer is controversial.^{1,2} At this stage of the disease the tumor extends beyond the capsule of the prostate; it may infiltrate neighboring structures and involve regional lymph nodes, but there are no distant metastases (stage T3-4, N0-2, M0, accord-

ing to the tumor-node-metastasis [TNM] classification system of the International Union against Cancer). In a study begun in 1973, the overall survival after 15 years for 287 patients with locally advanced prostate cancer who were treated with conventional external irradiation was 23 percent.³ Achieving local control after radiotherapy improved the prognosis; among patients who did not have involvement of regional lymph nodes at the time of diagnosis, 70 percent of those who attained local control survived for 20 years free of distant metastases, as compared with 13 percent of those who had a local relapse ($P<0.001$).⁴

Hormonal therapy often prolongs the suppression of the primary tumor by radiotherapy,⁵ but the question remains whether hormonal therapy should be reserved for relapse or used early in asymptomatic patients with locally advanced disease who are receiving external radiation treatment. Three controlled clinical trials have failed to demonstrate the value of prophylactic therapy with diethylstilbestrol, orchiectomy, or both in patients treated with external radiotherapy.⁶⁻⁸ A study of 277 patients found no differences among those undergoing orchiectomy, radiotherapy, or combined treatment; orchiectomy, however, whether alone or combined with radiotherapy, significantly delayed metastases as compared with radiotherapy alone.⁹

Goserelin is an agonist analogue of gonadotropin-releasing hormone that induces hypogonadism by reducing the secretion of gonadotropin and therefore testosterone. The purpose of this trial was to determine whether treatment with goserelin, when initiated during the first week of irradiation, increases disease-free survival and prolongs overall survival in patients at high risk for metastatic prostate cancer.

From University Hospital, Grenoble, France (M.B.); Akademisch Medisch Centrum, Amsterdam, the Netherlands (D.G.); Princess Margaret Hospital, Toronto (P.W.); Centre Régional de Lutte contre le Cancer Val d'Aurelle, Montpellier, France (J.B.D.); Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland (R.-O.M.); Oncologisch Centrum, Brussels (G.S.); Ospedale San Giovanni, Bellinzona, Switzerland (J.B.); Rambam Medical Center, Haifa, Israel (A.K.); Ufficio Sternberg & Pansadoro, Rome (C.S.); and the European Organization for Research and Treatment of Cancer Data Center, Brussels (T.G., L.C., M.P.). Address reprint requests to Dr. Bolla at the Radiotherapy Department, University Hospital, B.P. 217 38043 Grenoble CEDEX 9, France.

METHODS

Eligibility Criteria

Patients were eligible if they were under 80 years of age, with histologically proved prostatic adenocarcinoma that was intracapsular (T1) or confined to the gland (T2), without detectable involvement of regional lymph nodes (N0-X), and of World Health Organization (WHO) histologic grade 3; or if they had prostate cancer of any histologic grade that extended beyond the capsule (T3) or infiltrated neighboring structures (T4) without involving regional lymph nodes. The clinical evaluation included bone scanning, chest radiography, and ultrasonography or computed tomography (CT) of the liver. Lymph nodes were evaluated by CT, bipedal lymphangiography, or extraperitoneal lymphadenectomy. Laboratory studies included complete blood counts and measurements of creatinine, serum prostatic acid phosphatase, serum testosterone, and prostate-specific antigen (PSA), as assessed by radioimmunoassay or immunoenzyme assays. Eligible patients had had no previous treatment for prostate cancer and gave written informed consent. Patients with a previous malignant disease, except for treated basal-cell carcinoma of the skin, and those with evidence of distant metastases, including metastases to common iliac or paraaortic lymph nodes, were excluded. Pathological specimens were reviewed centrally.

Techniques of Treatment

Radiotherapy

Photons of 10 MV and above were recommended; when they were not available, the use of cobalt-60 was acceptable provided the skin-to-source distance was more than 80 cm and patients had a maximal anterior–posterior pelvic diameter of less than 22 cm. Planning target volume I was the whole pelvis, and planning target volume II the prostate and seminal vesicles. The whole pelvis was irradiated with a four-field technique, with one anterior–posterior field, one posterior–anterior field, and two parallel opposed lateral fields. In the craniocaudal direction the upper limit was the L5–S1 interspace, the lower limit was the ischial tuberosities, and the lateral margins were 1 cm beyond the maximal width of the bony pelvis; some centers preferred to irradiate a smaller target volume by using anterior–posterior fields averaging 12 by 12 cm and lateral fields averaging 12 by 10 cm. Planning target volume II was irradiated with either the same technique or with three fields: one anterior–posterior and two lateral fields with wedge filters. The anterior and posterior security margins on the lateral fields were at least 2 cm. The specification of the dose was given at the intersection of the beam axes according to Report 29 of the International Commission on Radiation Units and Measurements.¹⁰ The dose per fraction was 2 Gy. Patients were treated once a day, five days a week, for seven weeks; planning target volume I was irradiated during a five-week period with up to 50 Gy, and planning target volume II was treated during the last two weeks with an additional 20 Gy.

Hormonal Treatment

Goserelin (Zoladex, Zeneca-Pharma) was supplied by the manufacturer in a disposable syringe loaded with 3.6 mg of the drug and fitted with a 16-gauge needle. The drug was administered subcutaneously every four weeks, starting on the first day of pelvic irradiation and continuing for three years; 150 mg of a steroidal antiandrogen, cyproterone acetate (Androcur, Schering), was given orally for one month, starting one week before the first dose of goserelin, to inhibit the transient rise of testosterone caused by goserelin.

Toxicity

Acute side effects of radiotherapy were scored according to the WHO scale.¹¹ Late toxicity was scored according to the Radiotherapy Oncology Group scale: 0, no symptoms; 1, minor tran-

sient symptoms; 2, distressing, persistent, or recurring symptoms requiring occasional prolonged medical treatment; 3, symptoms requiring prolonged medical treatment, surgical intervention, or both; or 4, fatal complications. For patients receiving goserelin, adverse reactions were registered as hot flashes and gynecomastia. There was no quality-of-life study.

Assessment of Progression

Local failure was defined as an increase of more than 50 percent in the product of the two maximal perpendicular diameters of the primary lesion as measured digitally, by CT or transabdominal ultrasonography; in case of doubt, biopsy was highly recommended. Local progression was defined as the recurrence of a palpable tumor after initial regression. Regional failure, in the pelvic or paraaortic lymph-node areas, was demonstrated by ultrasonography or CT and was confirmed by biopsy. Distant metastases in bones, parenchymal organs, or soft tissues were identified radiologically and then by biopsy if deemed necessary.

Quality Assurance

The calibration of every linear accelerator was obtained by mailed thermoluminescence dosimetry checks. Individual clinical, biologic, pathological, and follow-up procedures for the main participating centers were reviewed individually to reconcile discrepancies between local data and data registered at the European Organization for Research and Treatment of Cancer (EORTC) Data Center. Protocol compliance was checked by a dummy-run procedure to evaluate differences in the definition of target volume, in treatment technique, and in dose specification and homogeneity.¹²

End Points and Statistical Analysis

Overall survival was measured from the date of randomization to the date of death or the most recent follow-up. The disease-free interval was measured from the date of randomization to the date of local or regional failure, the first appearance of distant metastases, or the last follow-up, whichever occurred first. The time until the first treatment failure after a biologic response was measured from the date of randomization to the date of clinically determined progression, PSA-determined progression, or the most recent follow-up; PSA-determined progression was defined as a PSA level greater than 1.5 ng per milliliter and increasing on two consecutive measurements.

The protocol was designed to detect a minimal increase from 40 percent to 55 percent in the 5-year disease-free rate, corresponding to an increase from 3.8 to 5.8 years in the median disease-free interval (assuming exponential distribution). To detect this difference, 75 patients in each treatment group had to be followed until relapse ($\alpha=0.05$, $\beta=0.2$). Survival curves were estimated by using the Kaplan–Meier technique.¹³ All comparisons were made by means of a two-sided log-rank test with a 0.05 significance level.¹⁴ Data were analyzed according to the intention-to-treat principle.

Randomization

Randomization was centralized at the EORTC Data Center. Patients were stratified according to institution, the clinical stage of the disease, the results of extraperitoneal pelvic lymph-node biopsy, and the irradiation technique. The randomization was performed by the minimization technique.¹⁵

RESULTS

Characteristics of the Patients

From May 1987 through September 1995, 415 patients entered the study — 208 in the pelvic radiotherapy group and 207 in the combined-treat-

ment group. The median duration of follow-up was 45 months. At the time of analysis, all but 14 patients had been evaluated. For the analysis, these 14 patients were considered eligible. Ten patients — six in the radiotherapy group and four in the combined-treatment group — were ineligible because of bone metastases (two patients), paraaortic lymph-node metastases (one), thrombocytopenia (one), inappropriate clinical stages (T1G1, one; T2G1, one; and T2G2, three; and T2 without mention of grade, one). The two groups of patients were well balanced with regard to age, WHO performance status, clinical stage, presence or absence of pelvic lymph-node metastases, WHO histologic grade, Gleason grade, serum acid phosphatase level, and base-line PSA level (Table 1). Cardiovascular disease was present in 29 percent of the patients in the radiotherapy group and 24 percent of those in the combined-treatment group; no chronic disease was mentioned for 48 percent of the patients in the radiotherapy group as compared with 53 percent in the combined-treatment group.

Compliance

Information about treatment was available for 401 patients — 198 in the radiotherapy group and 203 in the combined-treatment group. Of the patients in the radiotherapy group, 99 percent received external irradiation; 80 percent of these patients received large-field and 20 percent small-field radiotherapy. Three of the 198 patients refused the treatment.

Of the 203 patients in the combined-treatment group, 2 refused any treatment and 6 refused hormonal therapy. At the time of analysis, not all the patients in this group had completed the three-year treatment with goserelin, but 15 patients continued that treatment for more than three years (Table 2). Eighty-one percent of the patients in this group received large-field and 19 percent small-field radiotherapy.

Toxicity

Of the acute toxic effects listed in Table 3, none with a grade of 3 or 4 affected more than 5 percent of either group except for diarrhea. With a median follow-up of 45 months, not more than 1 percent of either group had grade 3 late toxic effects, including hematuria, chronic diarrhea, proctitis, cystitis, small-bowel obstruction, incontinence, and urethral stricture. Data on erectile function were not collected systematically. Among the patients receiving goserelin, 62 percent had hot flashes, but only 34 percent had more than three per day. During follow-up, more patients in the combined-treatment group than in the radiotherapy group had late grade 1–3 incontinence (29 percent vs. 16 percent, $P=0.002$); the proportions of patients with late

TABLE 1. AGE, PERFORMANCE STATUS, WHO GRADE, GLEASON SCORE, AND TUMOR AND NODE CLASSIFICATION AMONG PATIENTS ELIGIBLE FOR THE TRIAL.

CHARACTERISTIC*	RADIOTHERAPY (N=198)	COMBINED TREATMENT (N=203)
Age (yr)		
Median	70	71
Range	51–80	54–80
	number (percent)	
Performance status		
0	157 (79)	158 (78)
1	37 (19)	38 (19)
2	4 (2)	7 (3)
WHO grade		
1	37 (19)	44 (22)
2	90 (45)	96 (47)
3	67 (34)	62 (31)
X	4 (2)	1 (<1)
Gleason score		
2–4	16 (8)	10 (5)
5–6	38 (19)	49 (24)
7–10	71 (36)	66 (33)
Unknown	73 (37)	78 (38)
T classification		
T1	0	2 (1)
T2	17 (9)	15 (7)
T3	163 (82)	167 (82)
T4	18 (9)	19 (9)
T according to grade		
T1–T2, G3	17 (9)	17 (8)
T3–T4, any G	181 (91)	186 (92)
N classification		
N0	175 (88)	181 (89)
N+	6 (3)	8 (4)
Unknown	17 (9)	14 (7)
PSA (no. of times the upper limit of normal)		
<1	10 (5)	15 (7)
1–2	11 (6)	12 (6)
>2–5	46 (23)	40 (20)
>5–10	48 (24)	47 (23)
>10	62 (31)	72 (35)
Unknown	21 (11)	17 (8)

*T denotes tumor and N node, according to the TNM (tumor–node–metastasis) classification system; PSA denotes prostate-specific antigen.

grade 1–3 urethral stricture (20 percent in the combined-treatment group vs. 13 percent in the radiotherapy group) were not significantly different ($P=0.09$). Thirty-eight patients (19 percent) had adverse reactions to the gonadotropin-releasing hormone analogue: hot flashes (22 patients), gynecomastia (4), mastodynia (1), breast pain and galactorrhea (1), sweating (2), weakness (2), depression (1), deep venous thrombosis (1), and unspecified reactions (4).

Efficacy

The Kaplan–Meier estimate of overall survival at five years in the combined-treatment group was 79

TABLE 2. COMPLIANCE WITH THE GOSERELIN REGIMEN AMONG 195 PATIENTS IN THE COMBINED-TREATMENT GROUP.

COMPLIANCE	No. (%)
Continued goserelin for >3 yr	15 (8)
Received goserelin for 3 yr	93 (48)
Received goserelin until progression or death	21 (11)
Stopped in <3 yr because of toxicity*	8 (4)
Stopped in <3 yr for other reasons†	5 (3)
In study for <3 yr, still receiving treatment	53 (27)

*Five patients declined further treatment because of hot flashes (after 3, 8, 11, 14, and 16 months). Two patients had their treatment stopped because of depression (after 3 and 19 months). One patient stopped because of mastodynia and galactorrhea (after 4 months).

†One patient underwent orchiectomy because of poor compliance with goserelin treatment (after 20 months). One patient stopped taking goserelin to undergo urethrotomy because of recurrent strictures (after 4 months). One patient was lost to follow-up (after 15 months). Two patients stopped the radiotherapy and goserelin treatment for reasons unrelated to the potential side effects of the drug.

TABLE 3. GRADE 3 OR 4 TOXIC EFFECTS REPORTED DURING RADIOTHERAPY AMONG ALL ELIGIBLE PATIENTS WHO UNDERWENT RADIOTHERAPY.

TOXIC EFFECT	RADIOTHERAPY	COMBINED
	(N=195)	TREATMENT (N=201)
	no. of patients (%)	
Leukopenia*	1 (1)	0
Thrombocytopenia*	1 (1)	0
Anemia*	0	3 (1)
Nausea or vomiting*	0	1 (<1)
Diarrhea*	22 (11)	11 (5)
Urinary frequency	10 (5)	10 (5)
Dysuria	6 (3)	4 (2)
Radiation dermatitis*	4 (2)	1 (<1)
Hematuria*	1 (1)	0
Performance status	3 (2)	3 (1)

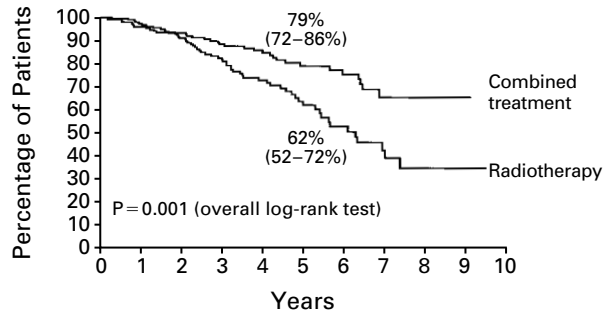
*Only grade 3 toxic effects were observed.

percent (95 percent confidence interval, 72 to 86 percent), as compared with 62 percent (95 percent confidence interval, 52 to 72 percent) in the radiotherapy group ($P=0.001$) (Fig. 1). For overall survival, the hazard ratio was 0.50 (95 percent confidence interval, 0.33 to 0.76). There were 58 deaths in the radiotherapy group and 35 in the combined-

treatment group. Of these deaths, 26 in the radiotherapy group and 6 in the combined-treatment group were due to prostate cancer. Among the patients who survived for five years, the disease-free rate was 85 percent (95 percent confidence interval, 78 to 92 percent) in the combined-treatment group and 48 percent (95 percent confidence interval, 38 to 58 percent) in the radiotherapy group (hazard ratio=0.22; 95 percent confidence interval, 0.15 to 0.32; $P<0.001$) (Fig. 2). Seventy-eight patients had disease progression in the radiotherapy group, as compared with 20 in the combined-treatment group. Table 4 shows the sites of progression. In the radiotherapy group, the treatment given after progression included goserelin in 56 cases (72 percent) and another hormonal treatment in 17 cases and was unspecified in 5 cases. The 17 other treatments were orchiectomy (eight patients), another hormonal treatment (two), delayed treatment (five), and no treatment, because of intercurrent death (one) and the patient's refusal (one). The five-year local-control rate was 97 percent in the combined-treatment group and 77 percent in the radiotherapy group (hazard ratio=0.19; 95 percent confidence interval, 0.10 to 0.37; $P<0.001$). The combined-treatment group had a longer time until the first treatment failure after a biologic response than the radiotherapy group (6.6 years [95 percent confidence interval, 3.5 to 5.3] vs. 4.4 years [95 percent confidence interval, 5.8 to 9.0]; hazard ratio=0.17; 95 percent confidence interval, 0.11 to 0.48; $P<0.001$). The five-year failure-free rate after biologic response was 81 percent for the combined-treatment group and 43 percent for the radiotherapy group.

DISCUSSION

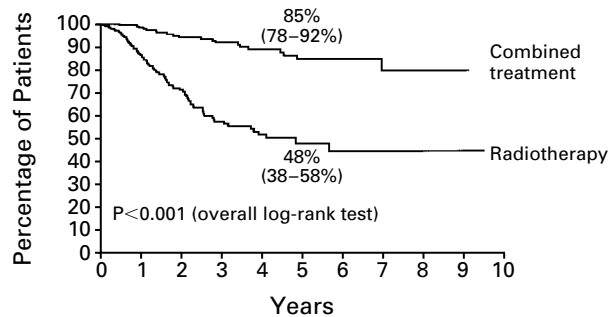
We found that adjuvant therapy with an analogue of gonadotropin-releasing hormone (goserelin), started at the beginning of external irradiation treatment and continuing for three years, can improve the five-year overall survival of patients with locally advanced prostate cancer. Two previous studies have compared short-term hormonal therapy before and during external irradiation, or long-term hormonal therapy after external irradiation, with radiation therapy alone for locally advanced prostatic carcinoma. The hormonal therapy included flutamide and goserelin for the former and goserelin alone for the latter; both protocols showed advantages over radiotherapy alone in terms of local control, the incidence of distant metastases, and progression-free survival.^{16,17} However, it is difficult to compare these three trials, since the eligibility criteria, the timing and duration of administration of goserelin, the definition of local control, and the results in the radiotherapy groups are not quite comparable. In our study, we assessed local control by endorectal examination; a second bi-



	NO. OF PATIENTS AT RISK										No. WHO DIED
Radiotherapy	208	183	139	96	67	39	23	10	6	1	58
Combined treatment	207	190	144	111	82	55	39	19	7	0	35

Figure 1. Kaplan–Meier Estimate of Overall Survival.

The overall survival rate at five years was 79 percent (95 percent confidence interval, 72 to 86 percent) for the combined-treatment group and 62 percent (95 percent confidence interval, 52 to 72 percent) for the group treated only with radiotherapy.



	NO. OF PATIENTS AT RISK										No. WITH DISEASE PROGRESSION
Radiotherapy	208	163	107	59	38	19	11	5	3	1	78
Combined treatment	207	189	138	108	78	51	36	16	5	0	20

Figure 2. Kaplan–Meier Estimate of the Disease-free Interval.

This curve shows the proportion of surviving patients who were free of disease at each time point. The method takes the censoring process into account. The number of patients who are at risk for the event at each time point is the total number of patients minus the number in whom disease progressed or who were lost to follow-up.

opsy of the prostate was not mandatory if the endorectal examination was normal, even if the serum PSA level was elevated. This aspect of assessment has been addressed previously, and one year after the completion of external irradiation the rate of positive biopsy results has been found to reach a plateau of 35 percent.¹⁸ The clinical results in our control group are in keeping with those of a retrospective analysis of 397 patients, with stage T3–T4 disease, who were treated only by external irradiation in 19

French institutes from 1983 to 1987. The rate of local control at five years was 79 percent, as compared with 77 percent (95 percent confidence interval, 68 to 86 percent) in the EORTC trial.¹⁹ The time until the first treatment failure after a biologic response is a surrogate end point that represents the time from randomization to the date of clinically determined progression or PSA-determined progression. Analysis using this end point showed a significant difference between combined treatment and radiotherapy alone

TABLE 4. SITES OF DISEASE PROGRESSION.

TYPE OF PROGRESSION	RADIO-	COMBINED
	THERAPY	TREATMENT
	no. of patients	
Any clinical progression	78	20
Local progression	8	3
Locoregional progression	5	0
Distant metastases	48	15
Distant and local metastases	15	2
Distant and locoregional metastases	2	0

(hazard ratio = 0.17; 95 percent confidence interval, 0.11 to 0.48; $P < 0.001$).

We are indebted to Zeneca-Pharma for providing Zoladex and to F.W.J. Ten Kate, M.D., J. Mattelaer, M.D., J. Lopez Torrecilla, M.D., J.R. Pfeffer, M.D., C.L. Cutajar, M.D., T. Roberts, M.D., S. Fossa, M.D., J.C. Horiot, M.D., H. Hamers, M.D., J.F. Bossett, M.D., F. Kovner, M.D., H. Van Poppel, M.D., J. Jager, M.D., V. Svoboda, M.D., J.J. Zambon, M.D., J.J. Wijndaele, M.D., O. Koriakine, M.D., and C. Boekenkruger, M.D., for their collaboration.

APPENDIX

The following EORTC Radiotherapy Cooperative Group institutions participated in this study: Grenoble, Hôpital Albert Michallon; Montpellier, Centre Val d'Aurelle; Dijon, Centre Georges-François Leclerc; Besançon, Hôpital Jean Minjot; Amsterdam, Akademisch Medisch Centrum; Heerlen, Radiotherapeutisch Instituut Limburg; Tilburg, B. Verbeeten Instituut; Lausanne, Centre Hospitalier Universitaire Vaudois; Bellinzona, Ospedale San Giovanni; Toronto, Princess Margaret Hospital; Haifa, Rambam Medical Hospital; Jerusalem, Hadassah University Hospital; Tel Aviv, Tel Aviv Medical Center–Ichilov Hospital; Valencia, Instituto Valenciano de Oncología; and Portsmouth, St. Mary's Hospital.

The following EORTC Genitourinary Group institutions participated in this study: Maastricht, Akademisch Ziekenhuis; Rotterdam, Zuiderziekenhuis; Brussels, Akademisch Ziekenhuis; Kortrijk, St. Maarten Hospital; Leuven, Universitair Ziekenhuis Sint Rafael; Antwerp, Universitair Ziekenhuis; Rome, Ufficio Sternberg & Pansadoro; Malta, St. Luke's Hospital; Newcastle-upon-Tyne, Freeman Hospital; Obninsk, Medical Radiological Research Center; and Oslo, Norwegian Radium Hospital.

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