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ORIGINAL REPORT

Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial

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ABSTRACT

Purpose

Retrospective studies suggest that metastasis-directed therapy (MDT) for oligorecurrent prostate cancer (PCa) improves progression-free survival. We aimed to assess the benefit of MDT in a randomized phase II trial.

Patients and Methods

In this multicenter, randomized, phase II study, patients with asymptomatic PCa were eligible if they had had a biochemical recurrence after primary PCa treatment with curative intent, three or fewer extracranial metastatic lesions on choline positron emission tomography–computed tomography, and serum testosterone levels > 50 ng/mL. Patients were randomly assigned (1:1) to either surveillance or MDT of all detected lesions (surgery or stereotactic body radiotherapy). Surveillance was performed with prostate-specific antigen (PSA) follow-up every 3 months, with repeated imaging at PSA progression or clinical suspicion for progression. Random assignment was balanced dynamically on the basis of two factors: PSA doubling time (≤ 3 *v* > 3 months) and nodal versus nonnodal metastases. The primary end point was androgen deprivation therapy (ADT)–free survival. ADT was started at symptomatic progression, progression to more than three metastases, or local progression of known metastases.

Results

Between August 2012 and August 2015, 62 patients were enrolled. At a median follow-up time of 3 years (interquartile range, 2.3-3.75 years), the median ADT-free survival was 13 months (80% CI, 12 to 17 months) for the surveillance group and 21 months (80% CI, 14 to 29 months) for the MDT group (hazard ratio, 0.60 [80% CI, 0.40 to 0.90]; log-rank $P = .11$). Quality of life was similar between arms at baseline and remained comparable at 3-month and 1-year follow-up. Six patients developed grade 1 toxicity in the MDT arm. No grade 2 to 5 toxicity was observed.

Conclusion

ADT-free survival was longer with MDT than with surveillance alone for oligorecurrent PCa, suggesting that MDT should be explored further in phase III trials.

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INTRODUCTION

Immediate or delayed androgen deprivation therapy (ADT) with initial surveillance is the preferred treatment strategy for biochemically recurrent prostate cancer (PCa) after radical prostatectomy and/or radiotherapy.[1,2] Analysis of the relapse patterns after primary PCa treatment suggests that most patients relapse with three or fewer metastases,[3-5] often termed oligorecurrences. In 1995, Hellman and Weichselbaum[6] hypothesized that eradicating oligorecurrences with metastasis-directed therapy (MDT) might prevent additional metastatic spread and improve survival.[7-8] Confirming this hypothesis could shift the paradigm for metastatic PCa from a palliative to a potentially curable disease in a subset of patients. Several retrospective, single-arm studies have supported the notion that MDT delays additional clinical progression and the start of subsequent palliative ADT, with minimal adverse events.[9,10] However, such an advantage has yet to be shown in well-controlled randomized studies. To address this, we compared the

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Data Supplements

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time to the start of ADT after MDT or surveillance (standard of care) for patients with oligorecurrent PCa with three or fewer metastases.

PATIENTS AND METHODS

Study Design and Participants

This multicenter, randomized, phase II trial was approved by the Ghent University Hospital ethics board, Ghent, Belgium. Patients were recruited in six Belgian institutions. Criteria met by eligible patients included pathologically confirmed PCa treated with curative intent (radical prostatectomy, primary radiotherapy, or a combination of both), followed by a prostate-specific antigen (PSA) relapse as defined by European Association of Urology criteria[2]; up to three extracranial metastases (any N1 or M1) diagnosed on choline positron emission tomography–computed tomography (PET-CT); a treated and controlled primary tumor; WHO performance status 0 to 1; and willingness to provide signed informed consent. Patients with testosterone levels < 50 ng/mL or with symptomatic metastases, and those who had had previous MDT, a PSA relapse while receiving an active systemic treatment (luteinizing hormone–releasing hormone agonist, luteinizing hormone–releasing hormone antagonist, anti-androgen, or estrogen), previous treatment with a cytotoxic agent for PCa, or treatment during the past month with products known to influence PSA levels (eg, fluconazole, finasteride, corticosteroids, and so forth) were considered ineligible. A negative multiparametric magnetic resonance imaging or negative biopsy of the prostate (bed) was mandatory even if choline PET-CT was negative at the level of the prostate (bed). Each metastatic lesion was counted separately and contributed to the total number of metastatic lesions. Mandatory laboratory values before random assignment included PSA and testosterone levels. This study was approved by the institutional review board at all participating sites; all patients were required to provide written approved consent before enrolment.

Random Assignment and Masking

Patients were randomly assigned (1:1) to either surveillance or MDT of all detected lesions, according to pregenerated sequences produced on the principle of randomly permuted blocks with variable block sizes of two and four. The random assignment was not masked, so both the patient and the provider were aware of the random assignment. The data managers and data analysts were also not masked to the treatment groups. Patients were stratified at random assignment by PSA doubling time (≤ 3 *v* > 3 months) and location of metastases (nodal *v* non-nodal). After the responsible physician or research nurse enrolled each patient and entered that variable, random assignment was performed by a physicist not involved in any other aspect of the trial.

Procedures

Patients randomly assigned to surveillance underwent every-3-months clinical examination and serum PSA measurement. Patients randomly assigned to the MDT group were treated with the intent to eradicate all visible metastatic deposits with metastasectomy or stereotactic body radiotherapy (SBRT). After MDT, their follow-up was identical to that of the surveillance group. The choice of MDT was determined in consultation with the multidisciplinary team and the patient. The surgical technique to be used was at the discretion and expertise of the surgeon but had to be in accordance with the best surgical practice available. A minimally invasive technique was preferred but was not obligatory. For pelvic nodal metastases, in the case of a previous extended pelvic lymph node dissection (PLND) or pelvic radiotherapy, only the suspicious lymph nodes were removed. If no extended PLND had been performed at initial PCa treatment, a bilateral salvage PLND (sPLND) of the true pelvis, with removal of all nodal and fibrofatty tissue at the external and internal iliac regions and the obturator fossa region, was preferred.[11] For all other regions, a metastasectomy was preferred. In the case of SBRT, the gross tumor volume was defined as all visible tumor by combining iconographic and metabolic information. No additional margin was added for microscopic spread of disease. The gross tumor volume was expanded by 2 to 5 mm to the planning target volume to account for organ

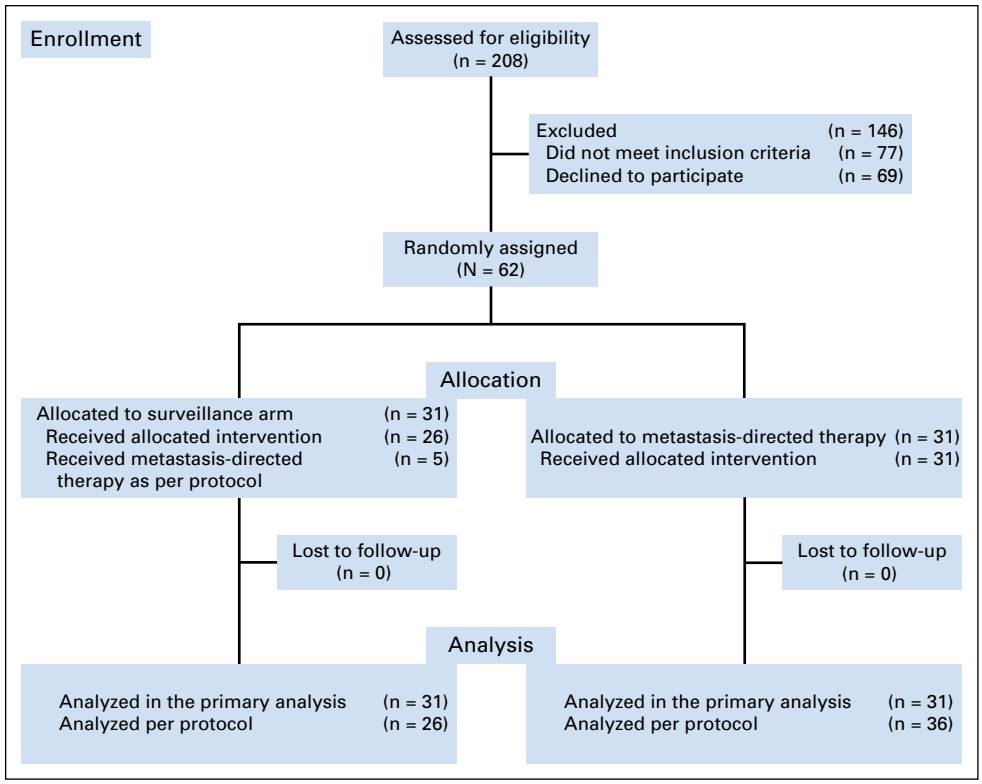

Fig 1. CONSORT diagram.

motion and setup error. Margins depend on the site irradiated, with 2-mm margins for bony lesions, 3-mm margins for nodes, and 5-mm margins for other sites. A total dose of 30 Gy (80% of the maximal dose) was delivered in three fractions; fractions were separated into > 48 hours and < 96 hours. Treatment was prescribed to the periphery of the target (80% of the dose [30 Gy]), covering 90% of the planning target volume. Dose constraints for organs at risk were in accordance with the recommendations of American Association of Physicists in Medicine Task Group 101.[12] At each fraction, a cone-beam CT was used for patient setup and target verification before treatment. All plans were verified using the Delta(4) diode array phantom (Scandidos, Uppsala, Sweden) before treatment delivery.[13]

Patients in both groups were observed for toxicity and PSA progression every 3 months after random assignment, until the primary end point was met, and according to the European Association of Urology guidelines thereafter.[2] Choline PET-CT was repeated at PSA or symptomatic progression. Patient-reported health-related quality of life (HRQOL) was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)–C30 and QLQ-PR25 at baseline, at month 3, and yearly.

Outcomes

The primary outcome measure was ADT-free survival, defined as the time between random assignment and the start of palliative ADT or death as a result of any cause. The indication to start ADT was symptomatic progression, progression to more than three metastases, or local progression of baseline-detected metastases. Patients who did not start ADT at the time of last follow-up were censored at that time point. The type of ADT was left to the discretion of the treating physician. In the case of a nonlocal, metastatic recurrence after MDT, a re-treatment with MDT was allowed if there were three or fewer new metastases. Secondary outcomes for the study were PSA progression, defined as a PSA increase of ≥ 25% and ≥ 2 ng/mL if PSA was ≥ 2 ng/mL from baseline, or a PSA increase of ≥ 25% if PSA was < 2 ng/mL at random assignment. PSA progression only was not an indication to start ADT. Local progression of a soft tissue metastatic lesion was defined as an increase of ≥ 20% in the largest tumor dimension with a minimum absolute increase of 5 mm. All lesions were considered target lesions, irrespective of size, if they were suspicious on choline PET-CT. Local progression of bone metastases was assessed using MD Anderson Cancer Center–criteria,[14] with a ≥ 25% increase in the size of a measurable lesion on CT or a ≥ 25% increase in the size of ill-defined lesions on CT considered to be progression.

Quality-of-life scoring was performed using the EORTC QLQ-C30 supplemented with the QLQ-PR25.[15] The questions on both measures were scaled and scored using the recommended EORTC procedures.[16] Toxicity was assessed in the MDT group using Common Terminology Criteria for Adverse Events version 4.0 and the Clavien-Dindo classification in the case of patients who underwent surgery.[17]

Statistical Analysis

This study used a randomized phase II design to determine which arm was justified to be tested in a subsequent phase III trial, with an α and β of 0.20,[18,19] to detect an improvement in ADT-free survival from 12 months in the surveillance group to 24 months in the MDT group. The effect size was based on retrospective studies in the same type of patients.[9,20,21] This corresponds to a hazard ratio (HR) of 0.50. In view of these assumptions, the trial required 62 patients randomly assigned over 36 months, with an additional follow-up of 12 months (assuming a 5% dropout rate).

Descriptive statistics were used to summarize patient characteristics by treatment group. ADT-free survival was compared between the surveillance group and the MDT group using the log-rank test. Kaplan-Meier estimates of ADT-free survival were provided for each group and as a subgroup analysis on the basis of the initial stratification factors. The median follow-up time was derived using both complete and incomplete follow-up times. Cox proportional hazard regression was used to provide HR estimates when assessing ADT-free survival. Weighted Schoenfeld residuals were used to check the proportional hazards assumption of the fitted models. We found no substantial time trend in the proportional covariate effects on the hazards. PSA-based outcomes were reported in agreement with the Prostate Cancer Clinical Trials Working Group recommendations.[22] The percentage change in PSA from baseline to 12 weeks, and the maximum decline in PSA that occurred at any point after treatment, were reported for each patient using a waterfall plot. Time to PSA progression was calculated from the time of random assignment to the time of progression. We calculated the mean and standard deviation of the EORTC QLQ-C30 and QLQ-PR25 scores at baseline and at the 3-month

Table 1. Patient and Tumor Characteristics

Characteristic	Surveillance (n = 31)	Metastasis-Directed Therapy (n = 31)
Age at PCa diagnosis, years		
Mean (range)	63.3 (47-79)	60.8 (43-75)
Median (IQR)	64.0 (58-69)	62 (57-66)
PSA at PCa diagnosis, ng/mL		
Mean (range)	12.1 (2.5-36.2)	22.0 (3.5-114.0)
Median (IQR)	10.5 (7.3-15.3)	14.4 (8.6-27.3)
Gleason score		
≤ 6	10 (32.3)	4 (12.9)
7	11 (32.3)	17 (54.8)
≥ 8	10 (32.3)	10 (32.3)
Primary tumor classification		
p/c T1	4 (12.9)	2 (6.5)
p/c T2	13 (41.9)	9 (29.0)
p/c T3 or T4	14 (45.2)	20 (64.5)
Nodal status at PCa diagnosis		
pNx/cN0	5 (16.1)	2 (6.5)
pN0	24 (77.4)	25 (80.6)
pN1	2 (6.5)	4 (12.9)
Type of treatment at PCa diagnosis		
RP	5 (16.1)	2 (6.5)
RT	8 (25.8)	7 (22.6)
RP and RT	18 (58.1)	22 (70.9)
ADT at PCa diagnosis		
No	16 (51.6)	19 (61.3)
Yes	15 (48.4)	12 (38.7)
Time between PCa diagnosis and inclusion, years		
Mean (range)	6.3 (0.5-22.9)	5.9 (0.6-14.2)
Median (IQR)	4.9 (3.3-8.0)	5.3 (3.5-8.3)
PSA at inclusion, ng/mL		
Mean (range)	6.9 (0.3-31.0)	9 (0.7-44.5)
Median (IQR)	3.8 (0.8-9.6)	5.3 (2.8-12)
PSA-DT at inclusion		
≤ 3 months	10 (32.3)	10 (32.3)
> 3 months	21 (67.7)	21 (67.7)
No. of metastases		
1	9 (29.0)	18 (58.1)
2	10 (32.3)	6 (19.3)
3	12 (38.7)	7 (22.6)
Location of metastases		
Nodal	17 (54.8)	17 (54.8)
N1	8 (25.8)	13 (41.9)
M1a	5 (16.2)	4 (12.9)
Combination of N1 and M1a	4 (12.9)	0 (0.0)
Non-nodal	14 (45.2)	14 (45.2)
M1b	11 (35.5)	13 (41.9)
Combination of N1/M1a and M1b	3 (9.7)	0 (0.0)
M1c	0 (0.0)	1 (3.3)

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: ADT, androgen deprivation therapy; DT, doubling time; IQR, interquartile range; PCa, prostate cancer; PSA, prostate specific antigen; RP, radical prostatectomy; RT, radiotherapy.

and 1-year follow-up. All analysis was performed as per intention to treat (ITT) and per protocol (PP). Tests were performed two sided; *P* values < .20 were deemed significant. Data were analyzed with R (www.R-project.org).

RESULTS

Between August 1, 2012, and August 31, 2015, 62 patients were randomly assigned (Fig 1). Patient characteristics are listed in Table 1. The median follow-up time for the whole cohort was 3 years (interquartile range [IQR], 2.3-3.8 years). The type of MDT used was SBRT (n = 25), surgery in 6 patients (sPLND in 5 and lung metastasectomy in 1).

For the ITT analysis, the median ADT-free survival was 13 months (80% CI, 12 to 17 months) for the surveillance group and 21 months (80% CI, 14 to 29 months) for the MDT group (HR, 0.60 [80% CI, 0.40 to 0.90], log-rank *P* = .11; Fig 2A). Table 2 lists the reasons for starting ADT, with polymetastatic progression being the main reason in both groups. No symptomatic or local progression was observed in the MDT group, as compared with three and six occurrences, respectively, in the surveillance group. In the MDT group, 11 patients were treated with a repeated course of MDT because of oligometastatic progression at the time of first radiographic progression, and two patients received two additional courses of MDT for oligometastatic progression. In the subgroup analysis (Fig 3A), no significant interaction was observed between the effect of MDT and PSA doubling time or the location of metastases (*P* value of interaction, .35 and .31, respectively). Because of the difference in the number of lesions between the surveillance and the MDT arm (Table 1), a post hoc analysis was performed, with stratification on the number of metastases. The corresponding HR was 0.64 (80% CI, 0.42 to 0.96); log-rank *P* = .16. This is in line with the findings stratified on the location of metastases and PSA doubling time. Eleven patients developed castration-resistant PCa, six in the surveillance arm and five in the MDT arm. In total, four patients died, three from other cancers and one from cardiac failure.

For the PP analysis, the median ADT-free survival was 12 months (80% CI, 7 to 17 months) for the surveillance group and 21 months (80% CI, 16 to 28 months) for the MDT group (HR, 0.55 [80% CI, 0.36 to 0.85]; log-rank *P* = .08; Fig 2B). In the subgroup analysis (Fig 3B), no significant interaction was observed between the effect of MDT and the location of the metastases (*P* value of interaction, .95). We did observe a larger magnitude of association between MDT and improved ADT-free survival in patients with a PSA doubling time of ≤ 3 months as compared with > 3 months (*P* value for interaction, .01).

The PSA change is depicted as a waterfall plot at 3 months after random assignment and as the largest change in PSA (Figs 4A and 4B). In total, 74% of patients treated with MDT had a PSA decline, as compared with 42% in the surveillance arm. The median time until PSA progression for the ITT was 6 months (80% CI, 4 to 7 months) for the surveillance group, as compared with 10 months (80% CI, 8 to 13 months) for the MDT group (HR, 0.53 [80% CI, 0.37 to 077]; *P* = .03; Fig 4C). For the PP analysis, the HR was 0.52 (80% CI, 0.36 to 0.76); *P* = .02. Seventy-five percent of patients treated with MDT experienced a PSA decline, as compared with 35% in the surveillance arm.

Six (17%) of the 36 patients treated with MDT experienced grade 1 toxicity. No grade 2 or higher toxicity was observed. The toxicities observed after SBRT were temporary looser stools (n = 1) and temporary muscle soreness (n = 1). One patient who underwent a video-assisted thoracoscopic lung metastasectomy developed thoracic wall pain requiring nonopioid analgesics for 6 months. After sPLND, toxicities observed included hypoesthesia of the genitofemoral nerve (n = 1), lymphorrhea (n = 1), and scrotal and penile edema (n = 1).

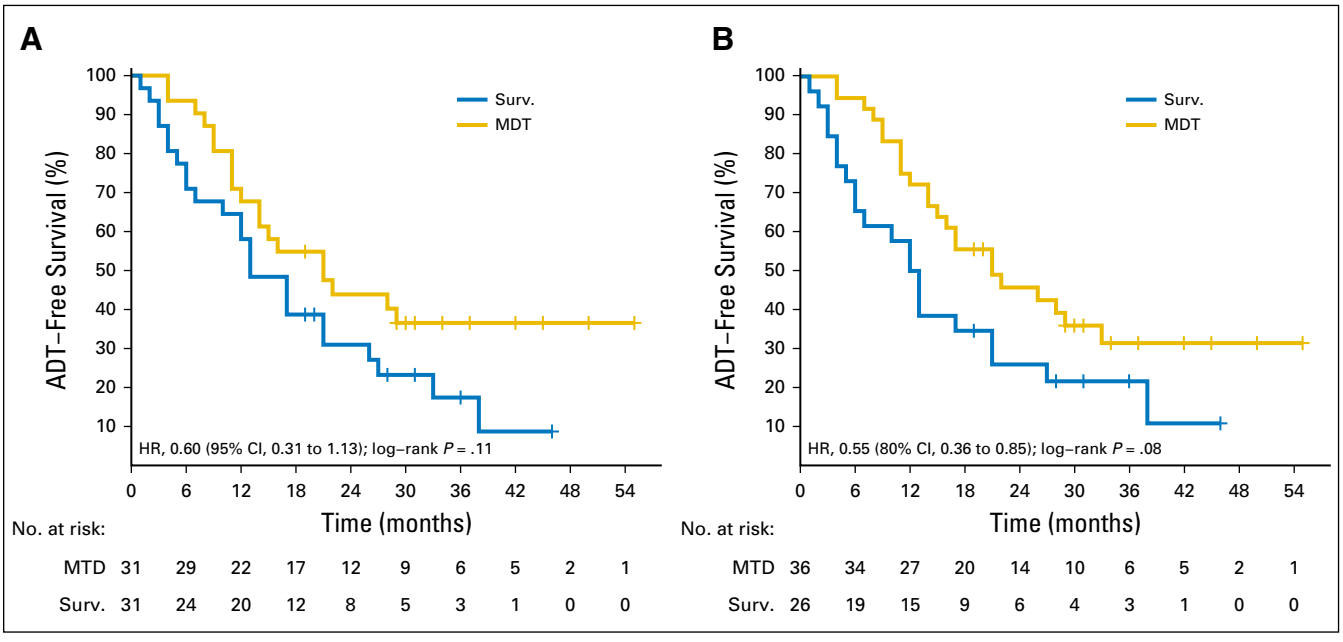

Fig 2. Kaplan-Meier plot comparing androgen deprivation therapy (ADT)–free survival of surveillance versus metastasis-directed therapy (MDT) for (A) the intention-to-treat analysis and (B) the per-protocol analysis. HR, hazard ratio; Surv., surveillance.

Table 2. Indications for Starting Androgen Deprivation Therapy

Indication	Surveillance (n = 31)	Metastasis-Directed Therapy (n = 31)
Not started yet	6 (19)	12 (39)
Polymetastatic progression	16 (55)	19 (61)
Local progression	6 (23)	0 (0)
Symptomatic progression	3 (10)*	0 (0)

NOTE. Data are presented as No. (%).
*Two patients with symptomatic progression also showed local and polymetastatic progression.

In total, 60 (97%) of 62 patients completed the baseline QLQs, 55 (89%) completed them at 3 months, and 52 (84%) completed them at 1 year. Figure 5 depicts the global health score for both arms at the three time points for the ITT group. We did not observe clinically relevant changes in HRQOL scores between the two study arms (across all visits; Data Supplement). Overall, HRQOL scores remained stable for both groups at baseline, 3 months, and 1 year (Data Supplement).

DISCUSSION

To our knowledge, this is the first randomized trial of MDT to all lesions versus surveillance alone for patients with oligorecurrent PCa after primary treatment with curative intent. Patients treated with MDT experienced a longer time to start of palliative ADT than did those who underwent surveillance alone. Time to ADT is a composite end point chosen because of the effect of the start of ADT on health care costs and HRQOL.[23] Recently the Intermediate Clinical Endpoints in Cancer of the Prostate working group identified metastasis-free survival as a surrogate for overall survival.[24] Unfortunately, this end point is valid only for localized PCa and, as such, cannot be extrapolated to patients with metastatic disease.

Many retrospective case series with promising results have been reported. However, because of the absence of comparative or randomized trials, the overall low number and heterogeneity of patients treated, a recent systematic review concluded that MDT should not be considered the standard of care.[9] Nevertheless, approximately two thirds of experts at the 2017 Advanced Prostate

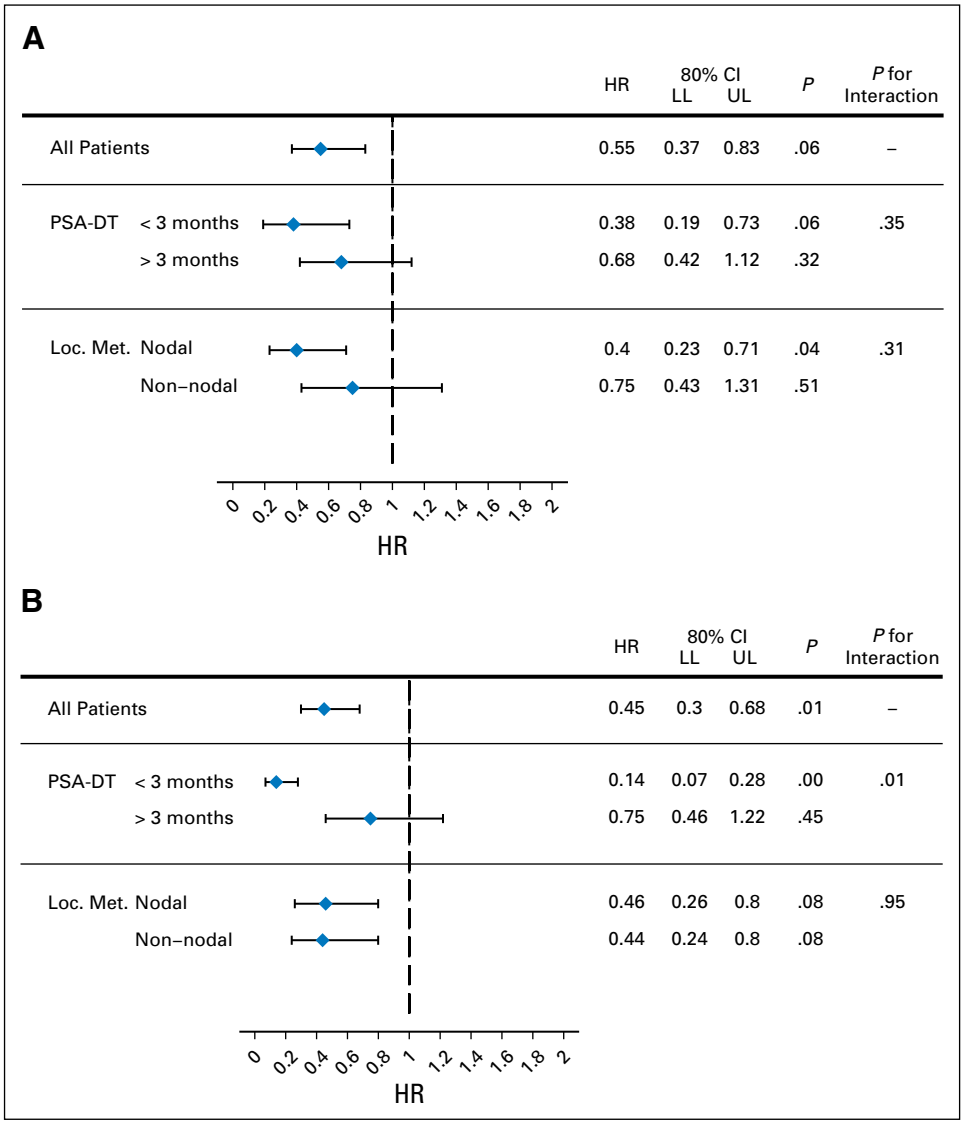

Fig 3. Forest plots of the association between metastasis-directed therapy and androgen deprivation therapy–free survival by subgroup for (A) the intention-to-treat analysis and (B) the per-protocol analysis. Hazard ratio for all patients was based on a Cox proportional hazard model containing only main effects. For the interactions, only those specific interactions were added. HR, unadjusted hazard ratio associated with metastasis-directed therapy (surveillance is the reference [HR, 1]); LL, lower limit of the 80% CI; Loc. Met., location of metastases; PSA-DT, prostate-specific antigen doubling time; UL, upper limit of the 80% CI.

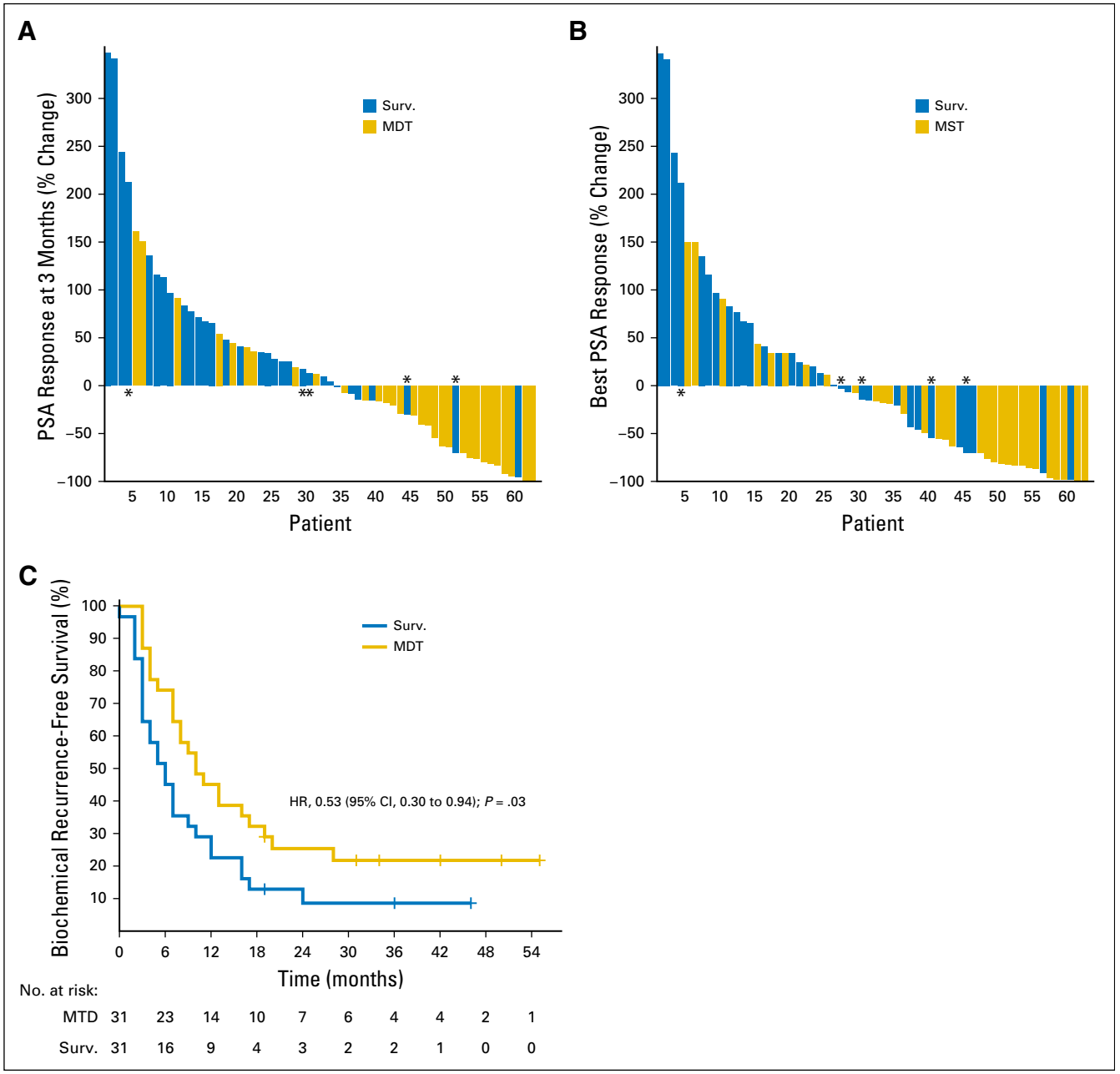

Fig 4. Waterfall plot of (A) the percentage change in prostate-specific antigen (PSA) after 3 months and (B) the best response. (C) Kaplan-Meier plot comparing biochemical recurrence-free survival of Surv versus MDT in the intention-to-treat analysis. (*) Indicates patients who were randomly assigned to the surveillance (Surv) arm but who were treated with metastasis-directed therapy (MDT). HR, hazard ratio.

Cancer Consensus Conference had already considered MDT a treatment option for patients with oligorecurrent PCa despite only retrospective evidence of its value.[25] A multi-institutional case series tried to overcome some of the shortcomings of the reported retrospective studies by using fixed inclusion and exclusion criteria, resulting in an ADT-free survival of 28 months (95% CI, 16.2 to 69.7 months) after SBRT oligorecurrent PCa.[26]

Nevertheless, important limitations were still present because a comparator arm was missing and 50% of these patients received a temporary course of adjuvant ADT at the time of SBRT. This temporary course of ADT is probably responsible for the better ADT-free survival than that of the current trial, because the addition of temporary ADT to radiotherapy is known to prolong progression-free survival and overall survival in both high-risk and biochemical recurrent PCa.[2] Consequently, we believe it is worthwhile to investigate the addition of a temporary systemic drug to MDT in future trials. The synergistic approach might improve the therapeutic ratio by eradicating microscopic disease, which is still often missed by choline PET-CT. This is demonstrated clearly by the current trial—30% of patients treated with MDT progressed to polymetastatic disease within the first year. Advances in imaging, such as ^{68}Ga prostate-specific membrane antigen (PSMA) PET-CT, might also improve patient selection for MDT.[27] PSMA-PET, which is widely available and has a better sensitivity and specificity than does

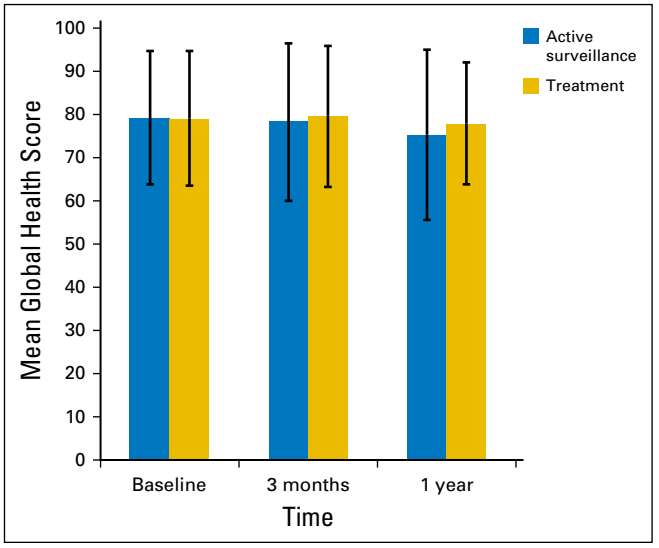

Fig 5. Mean global health status as measured with European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 per treatment arm at baseline, at month 3, and at 1 year for the intention-to-treat population. Bars represent means and error bars, the standard deviation.

choline PET-CT,[27] holds great promise in this field. The Advanced Prostate Cancer Consensus Conference consensus panel agreed, with 78% of the panelists voting for one of the next-generation imaging methods to restage biochemically recurrent PCa (PET-CT and/or whole-body magnetic resonance imaging), with 76% preferring PSMA over fluciclovine (10%) or choline (6%).[25] In the case of nodal recurrences, one might also consider opting for salvage lymph node dissection or whole pelvis radiotherapy to consider microscopic disease.[28,29]

To our knowledge, this randomized trial provides the first evidence of the effect of MDT compared with surveillance with delayed ADT. We demonstrated that MDT results in a PSA response in three out of four patients. A remarkable observation was the fact that 35% of patients undergoing surveillance experienced spontaneous PSA declines without receiving any therapy (Figs 4A and 4B). However, these declines were not durable, as demonstrated by the fact that only approximately 20% of men were free from PSA progression at 1-year follow-up and approximately 10% at 2-year follow-up. Nevertheless, these data support the Hellman and Weichselbaum[6] concept of oligometastases—that certain tumors have not fully developed their metastatic potential and show a slow natural history.

Our subgroup analysis showed a comparable benefit with MDT for patients with nodal and non-nodal metastases. Retrospective data suggested that patients with a PSA doubling time < 3 months had a shorter time to progression-free survival with MDT than did patients with a longer doubling time. From our PP data, it seems that the magnitude of benefit with MDT as compared with surveillance is greater for those patients with a shorter PSA doubling time. Consequently, there is no rationale to decline MDT for patients with a short PSA doubling time.

The global health status of men with biochemically recurrent PCa was high in our study and was comparable to that of other studies that included patients with biochemically recurrent PCa.[30] It is not surprising that no benefit of MDT was seen in terms of HRQOL at month 3 and year 1 because the difference in patients who started with ADT in the first year was comparable (Fig 2A). The safety of MDT was excellent, with no grade 2 or higher events and only 17% grade 1 toxicity.

In conclusion, MDT for patients with oligorecurrent PCa is safe and improves ADT-free survival when compared with surveillance. We recommend testing MDT in larger phase III studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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