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Long-Term Followup of 3-Month Neoadjuvant Hormone Therapy Before Radical Prostatectomy in a Randomized Trial

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Abstract

Objective—Neoadjuvant hormone therapy (NHT) prior to radical prostatectomy results in pathologic downstaging, but generally no reduction in biochemical recurrence (BCR) on early followup. In an institutional randomized prospective trial of radical prostatectomy with or without a 3-month course of NHT, we observed no reduction in BCR at 3 years. We report our long-term followup of this cohort.

Patients and Methods—From December 1992 to June 1996, 148 patients with clinically localized prostate cancer were randomized to radical prostatectomy only or 3 months of goserelin acetate and flutamide before radical prostatectomy. BCR was defined as a detectable serum prostate specific antigen (greater than 0.1 ng/mL) at least 6 weeks after surgery with a confirmatory rise.

Results—The median followup for recurrence-free patients was 8 years. There was no significant difference in recurrence-free probabilities between groups ($p = 0.7$). The BCR-free probability at 7 years was 78% for patients undergoing RP only and 80% for patients undergoing NHT and RP (difference of 2%; 95% CI, 12%–16%). A Cox regression showed no significant relationship between NHT and BCR (HR 1.16; 95% CI, 0.56–2.39, $p = 0.7$). Overall, 2 patients had local recurrence and 6 patients developed metastases, and were evenly split among the RP only and NHT groups.

Conclusion—Although our study was not originally powered to detect differences in BCR, we did not demonstrate an overall benefit in BCR-free probability, local recurrence or metastasis with 3 months of NHT at 8 years of followup. Pending evidence of improvement in patient outcomes, NHT before radical prostatectomy appears unjustified outside of clinical trials.

Keywords

prostate; prostatic neoplasms; prostatectomy; neoadjuvant therapy; hormones

INTRODUCTION

The rationale for neoadjuvant hormone therapy (NHT) prior to radical prostatectomy (RP) is to reduce the positive surgical margin (PSM) rate, and therefore improve patient outcomes after RP. Potential mechanisms of NHT include increased apoptosis and decreased proliferation of carcinoma cells to induce tumor regression.[1,2] Vallet first described NHT in 1944.[3] During that decade, other investigators reported their results with castration and/or

diethylstilbestrol given before RP.[4,5] In 1969, Scott and Boyd reported 5, 10 and 15-year survival rates in patients treated with NHT before radical perineal prostatectomy.[6]

The introduction of less toxic and reversible androgen deprivation led to renewed interest in NHT. Initial prospective randomized studies of NHT demonstrated decreased extraprostatic extension and reduced PSM rates. However, these findings have not generally translated into improved BCR-free rates on early followup.[7–10]

Only 8 randomized prospective NHT studies have been published to date.[8,11–17] In 1992, we began a prospective randomized study comparing the effects of RP only versus 3 months of NHT before RP. Although the NHT group had decreased positive margin rates,[18] there was no significant difference in BCR at almost 3 years of followup.[8] In this report, we present the long-term effects of NHT on BCR in this same group of patients with a median followup of 8 years.

PATIENTS AND METHODS

Patient Population

Between December 1992 and June 1996, 148 patients with clinically localized prostate cancer were randomized to RP only versus 3 months of NHT before RP in a phase III trial at Memorial Sloan-Kettering Cancer Center. None of the patients had received previous hormonal, radiotherapy, or chemotherapy. Patients were randomized to the treatment group with stratification by clinical stage using central telephone randomization, which ensured allocation concealment. NHT patients received 3.6 mg of goserelin acetate subcutaneously once a month and 250 mg flutamide three times daily for 3 months prior to RP.

Of the 74 patients randomized to the NHT before RP group, 2 patients did not undergo RP due to lymph node metastasis at surgery or unresectable prostatic disease. Of the 74 patients randomized to the RP only group, 1 patient had nodal metastasis and underwent lymphadenectomy alone, 1 had no followup, and 8 withdrew from the study. The remaining 136 patients were followed for BCR after surgery and were included in the current analysis (fig. 1). Pathological specimen processing was performed as previously described.⁸

Patients were followed at 3-month intervals for the first 2 years, at 6-month intervals for the next 3 years, and annually thereafter with digital rectal examinations and serum PSA measurements. BCR was defined as a serum prostate-specific antigen (PSA) > 0.1 ng/ml at least 6 weeks after surgery with a confirmatory rise. Patients who received adjuvant therapy before BCR (n = 1) were not considered to have disease recurrence until they met the criteria above.

Statistical Analysis

The primary endpoint of the original study was to determine whether NHT reduced the rate of non-organ confined disease. The study was designed to detect a difference in the rate of non-organ confined disease of approximately 50% in the control arm versus approximately 25% in the treatment arm. A sample size of 68 patients per treatment arm was required to give an 80% power at the 5% significance level. In total, 74 patients were recruited to each arm to allow for drop out.

The BCR-free probability was estimated using Kaplan-Meier methods and compared between those with and without NHT using the log rank test. The time to recurrence was calculated from the surgery date instead of the randomization date, as patients are not at risk of recurrence until they have had their prostate removed. Percentile based bootstrap confidence intervals were obtained for the difference in BCR-free probabilities between groups with 2000

replications. Multivariable Cox regression analysis was used to estimate the hazard ratio and 95% confidence interval for NHT, with adjustment for clinical stage as this was a stratifying variable at randomization. Three patients in the control arm received NHT but were analyzed based on intention to treat.

Some investigators have hypothesized that the reduction in positive margin rates associated with NHT is artifactual, resulting from an inability to recognize cells and architecture after androgen deprivation.[10,19] If this is true, then some patients in the NHT group classified as having negative surgical margins could truly have had PSMs; as a result, we would observe a lower recurrence-free probabilities for patients with negative surgical margins receiving NHT prior to RP compared to patients with RP only. To explore this hypothesis, we summarized BCR-free probabilities stratified by both surgical margin status and treatment group. All p values are 2-sided; $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the Stata software package 10 (Stata Corp., College Station, TX).

RESULTS

Clinical features are given in Table 1. As reported previously, the PSM rate was significantly reduced in patients given NHT than without (19% versus 38%; $p = 0.022$, Fisher's exact test; table 2).⁸ There were no other obvious differences between treatment groups in pathological characteristics, including organ confined disease, extracapsular extension, seminal vesicle invasion, and lymph node metastasis.

The median followup for BCR-free patients was 8.0 years (IQR: 5.2, 10.7; range 0.1 to 15.3). In total, 30 patients experienced BCR (13 with RP only and 17 with NHT and RP). BCR-free probability was similar between groups (fig. 2, $p = 0.7$). The 7-year BCR-free probability was 80% for those with NHT compared to 78% for those without NHT (difference of 2%; 95% CI, 12% – 16%).

NHT was not significantly associated with BCR after RP with adjustment for clinical stage (HR 1.16; 95% CI, 0.56 – 2.39; $p = 0.7$). A multivariable Cox regression model also controlling for biopsy Gleason score had similar results (HR 1.19; 95% CI, 0.57 – 2.48; $p = 0.6$). One patient in the NHT group had adjuvant radiation therapy prior to a documented BCR. A sensitivity analysis censoring this patient at the time of adjuvant therapy did not change our results (data not shown).

The time from randomization to surgery was approximately 3 months longer for the NHT group than the RP only group given those patients needed to complete NHT before having surgery. A sensitivity analysis adding 3 months to the recurrence-free time for patients who received NHT did not make a significant difference in our results (HR 1.13; 95% CI, 0.55 – 2.33; $p = 0.7$). Moreover, Figure 2 demonstrates that the BCR-free probabilities virtually overlap at approximately 2 years after surgery, and therefore a 3 month difference in survival time would not impact the long-term results.

Overall, 2 patients developed local recurrences, one each in the RP only group and the NHT group (table 2). Six patients developed metastases, of which 3 received NHT and 3 did not. There was 1 death from prostate cancer, which was in the NHT group. In total, 14 deaths occurred from other causes, 5 in the RP only group and 9 in the NHT group.

Recurrence-free probabilities stratified by both treatment group and surgical margin status are given in Table 3. The 7-year BCR-free probabilities among patients with negative surgical margins were very similar between treatment groups: 84% for RP only and 82% for NHT and RP (difference of 2%; 95% CI, 17% – 15%). Therefore, we found no evidence to suggest that the reduction in positive margin rates with NHT is artifactual.

DISCUSSION

A PSM is well established as an independent predictor for BCR.[20] Pathologic downstaging and a reduction in positive margins should be associated with reduced BCR and improved disease-specific survival. However, despite the decreased positive margin rate demonstrated in our initial study,[18] we continue to see no BCR benefit from NHT after a median followup of 8 years.

Our findings are consistent with previous randomized prospective studies that demonstrate a reduction in positive margin rates, but no difference in overall BCR-free survival (table 4). [7–10,19] Soloway *et al.* reported no difference in BCR rates between cT2b patients in the RP only and 3-month NHT (leuprolide and flutamide) groups at 5 years followup.[10] Similarly, at a median followup of almost 7 years, Aus *et al.* found no improvement in BCR-free rates in clinically localized prostate cancer patients given 3 months of NHT (triptorelin and cyproterone acetate).[7] Furthermore, Klotz *et al.* showed no BCR benefit in the 3-month NHT (cyproterone acetate) group overall, though improved BCR-free survival was seen in the highest risk PSA group (PSA > 20 ng/mL) on subgroup analyses.[19]

Several limitations and factors may account for the lack of difference in BCR rates despite improved positive margin rates. Approximately 40% of the patients in this study had “low risk” tumors (PSA < 10 ng/mL, biopsy Gleason score ≤6; n=50) with an associated low risk of BCR after RP alone; such patients may derive little benefit from the addition of NHT. Similar to prior studies, this trial was also initially designed to identify differences in pathologic stage and not powered to detect differences in BCR. Thus, the lack of a demonstrable BCR benefit for NHT on long-term followup may be due to insufficient sample size. However, even in a recent meta-analysis combining several studies on 1,129 men, NHT did not improve BCR rates (OR 1.20, 95% CI, 0.95 – 1.52; p = 0.13).[21]

Another factor in the failure of 3-month NHT to reduce BCR rates may result from insufficient duration of NHT. In an early pilot study, Gleave *et al.* showed that serum PSA does not reach nadir or undetectable levels in most patients during this period. While serum PSA decreased by 84% after 1 month of NHT, significant reductions continued to occur between 3 and 8 months of treatment. PSA decreased to nadir or undetectable levels in 22% of patients after 3 months, 42% at 5 months, and 84% after 8 months of therapy.[1] In another study of 156 patients treated with 8 months of NHT, Gleave *et al.* reported low positive margin (6%) and BCR (12.2%) rates at a mean postoperative followup of 54 months.[22] These observations suggest that the optimal duration of NHT may be longer than 3 months.[1,22–24]

In a prospective cohort study of 756 men, Meyer *et al.* reported a BCR survival advantage seen in patients treated with NHT > 3 months compared with those treated by RP only or with those who received a similar treatment for ≤3 months.[25] This benefit of longer NHT became statistically significant after year 3, reached its greatest magnitude in year 4 and was still present 8 years after RP. Concerns with this study’s findings include the lack of randomization and the differences in baseline BCR risk between the RP only and NHT groups.

These data led to the Canadian Urologic Oncology Group P95A study, a prospective randomized trial of 547 men comparing 3 versus 8 months of NHT (leuprolide and flutamide). On preliminary analysis, Gleave *et al.* reported significantly lower positive margin rates in the 8-month group compared to the 3-month group (12% versus 23%).[23] Analyzing BCR outcomes among all patients at 3 years showed no significant difference in outcome between the 2 treatment groups.[26] However, when stratified by surgical volume, BCR rates in high-volume centers were significantly lower in the 8-month group (16%) compared to the 3-month group (25%). In addition, patients who received surgery at high-volume centers did better than those at low-volume centers regardless of NHT duration. Thus, surgical site proved a strong

independent predictor of BCR. Now that we better understand the optimal duration of NHT and patient selection, an ideal trial might include intermediate and high risk patients randomized to no NHT versus 8 months of NHT and stratified by surgeon volume.

Another reason for the lack of apparent difference in BCR rates may be that the reduction in positive margin status is artifactual. The decrease in margin positivity may partially result from an inability to recognize cells and architecture after androgen deprivation, as morphological changes include loss of glandular architecture, cytoplasmic vacuolization, and nuclear pyknosis. Pathologists unaware of these changes may have difficulty in identifying residual disease. In addition, Gleason grading by conventional methods may be misleading and is discouraged.[27]

Bazinet *et al.* compared routine hematoxylin and eosin staining with cytokeratin immunohistochemistry in 22 whole mount prostatectomy specimens from patients treated with 3 months of NHT.[28] Hematoxylin and eosin staining compared to cytokeratin immunohistochemistry overestimated organ confinement (46% versus 27%) and underestimated capsular penetration (45% versus 68%) and PSMs (14% versus 23%). Standard histology also identified as tumor-free 2 specimens for which cytokeratin staining later confirmed adenocarcinoma. Thus, morphological tissue changes by NHT may obscure tumor cells and cause underreporting of positive margins. In the current series, the 7-year BCR-free probabilities for those with negative surgical margins were similar by treatment group (84% for no NHT versus 82% for NHT).

Even if improvement in positive margin rates with NHT is real, it may not produce the same effect in contemporary RP series. In the randomized prospective studies that showed a significant difference in positive margin rates, positive margins in the RP only group occurred in 34% to 65% of patients.[12–17] These values are high compared with those in contemporary RP series, which report positive margin rates of 9% to 13%.[20,29] This marked decrease in positive margin rates in current RP series may greatly reduce any possible BCR benefit of NHT.

If NHT increases prostate cancer cell death or decreases the progression rate, its effects should also be seen on the seminal vesicles and lymph nodes.[30] However, none of the randomized prospective studies which examined this aspect showed an advantage for NHT with respect to seminal vesicle invasion rate.[11,12,15] Similarly, the rate of lymph node metastases was decreased with NHT in only 1 of the 3 randomized prospective studies reporting this aspect. [12,13,15]

The cost of NHT is not insignificant, particularly when randomized prospective studies have not shown a clear survival advantage. Scolieri *et al.* reported the 3-month cost of a luteinizing hormone-releasing hormone agonist and antiandrogen at \$2,131.[30] Additional costs associated with NHT include additional preoperative office visits and PSA measurements. Another disadvantage to NHT may be increased patient anxiety due to delaying definitive cancer treatment. Patients may also suffer from common adverse effects of androgen deprivation, including decreased libido, impotence, vasomotor symptoms, impairment of cognitive function, and risk of osteoporosis. NHT may also increase operative difficulty by inducing a desmoplastic reaction.[13,15] Furthermore, a potential disadvantage is the theoretical continued proliferation of androgen resistant cells.[30]

Although our study was not originally powered to detect differences in BCR, 3 months of NHT did not show a benefit in BCR-free probability, local recurrence, and metastasis with 8 years of followup. The side effects and added cost of NHT, patient anxiety from delay of definitive therapy, and theoretical risk of androgen resistant cell proliferation makes its use difficult to justify. A prospective randomized trial of intermediate and high risk patients randomized to 0

versus 8 months of NHT stratified by surgeon volume may shed further light into its utility. Pending evidence of improvement in patient outcomes, NHT before RP appears unjustified outside of clinical trials.

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FIG. 1.
Flow of patients through the study

Number at risk												
no NHT	64	58	55	51	45	40	35	30	26	23	17	
NHT	72	69	63	54	50	47	40	35	29	23	18	

FIG. 2. Biochemical recurrence-free probability stratified by whether patients received (dashed line) or did not receive (solid line) neoadjuvant hormone therapy

TABLE 1

Clinical characteristics of 136 patients treated with radical prostatectomy in the MSKCC phase III trial

	RP only	NHT and RP
No. pts	64	72
Age, median, years (IQR)	61 (57, 65)	61 (57, 66)
Preoperative PSA, ng/mL, n (%)		
< 10	44 (69)	45 (63)
10 – 20	15 (23)	19 (26)
≥ 20	5 (8)	8 (11)
Biopsy Gleason score, n (%)		
2 – 6	33 (52)	34 (47)
7	10 (16)	23 (32)
8 – 10	21 (33)	15 (21)
Clinical stage, n (%)		
T1b/c	27 (42)	30 (42)
T2a	8 (13)	12 (17)
T2b	20 (31)	25 (35)
T2c	8 (13)	5 (7)
T3	1 (2)	0 (0)

RP, radical prostatectomy; NHT, neoadjuvant hormone therapy; IQR, interquartile range; PSA, prostate specific antigen

TABLE 2

Pathological characteristics and long-term followup of 136 patients treated with radical prostatectomy in the MSKCC phase III trial

	RP only (n = 64)	NHT and RP (n = 72)
Organ confined disease, * n (%)	51 (80)	61 (85)
Extracapsular extension, n (%)	13 (20)	10 (14)
Seminal vesicle invasion, n (%)	4 (6)	3 (4)
Lymph node metastasis, n (%)	2 (3)	1 (1)
Positive surgical margin, n (%)	24 (38)	14 (19)
Local recurrence	1	1
Metastases	3	3
Death from prostate cancer	0	1
Death from unknown causes	5	9

* Defined as the absence of extracapsular extension, seminal vesicle invasion, or lymph node metastasis.

RP, radical prostatectomy; NHT, neoadjuvant hormone therapy

TABLE 3

The 7-year biochemical recurrence-free probability stratified by surgical margin status

	RP only (n = 64)	NHT and RP (n = 72)	Difference between groups (95% Confidence Interval)
Surgical margin status			
Positive	69%	71%	2% (-31%, 32%)
Negative	84%	82%	-2% (-17%, 15%)

RP, radical prostatectomy; NHT, neoadjuvant hormone therapy

Literature review of prospective randomized trials on biochemical recurrence free rates in patients treated with and without 3 months of neoadjuvant hormone therapy before radical prostatectomy

TABLE 4

References	N	Clinical Stage	Followup (months)	% BCR-free in RP only group	% BCR-free in NHT and RP group	Significant
Fair[8]	137	cT1-3	35	NR	NR	No
Schulman[9]	402	cT2-3	48	67	74	No
Aus[7]	126	cT1b-T3a	82	52	50	No
Soloway[10]	282	cT2b	60	68	65	No
Klotz[19]	213	cT1-2	72	66	62	No*

* Improved biochemical recurrence in highest risk PSA group (PSA > 20 ng/mL).

RP, radical prostatectomy; NHT, neoadjuvant hormone therapy; NR, not recorded; PSA, prostate specific antigen