Surgically managed lymph node-positive prostate cancer: does delaying hormonal therapy worsen the outcome?

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OBJECTIVES

To review our experience with the surgical management of lymph node-positive prostate cancer and to determine if there is a benefit to treating such patients with immediate rather than delayed hormonal therapy (HT).

PATIENTS AND METHODS

A retrospective analysis from January 1982 to January 2001 identified 100 patients treated by radical retropubic prostatectomy (RP) either alone (70, 23 later received delayed HT) or combined with adjuvant (immediate) HT (30), with the overall median follow-up being 5.2 years.

RESULTS

The median patient age at diagnosis was 58.7 years, with 20% having clinical T3 disease, and the median prostate specific antigen (PSA) level at presentation was 10 ng/mL. In 41% of patients the Gleason score on prostatic biopsy was ≥8. After RP, 30 patients received immediate HT used as an adjuvant after surgery in the absence of any evidence of disease progression, whereas 23 received delayed HT the use of which was provoked secondary to biochemical failure (PSA threshold of 0.2–5.0 ng/mL) with no evidence of metastatic disease. A comparison of the clinical variables between the groups showed a higher median PSA level at diagnosis ($P = 0.027$) and biopsy Gleason score ($P = 0.052$) in the delayed HT group. The immediate and delayed HT groups had similar metastatic-free ($P = 0.549$), disease-specific ($P = 0.843$) and overall survival ($P = 0.843$). Overall, biochemical failure developed in half the patients and distant metastasis in 13%, with only nine patients dying from disease.

CONCLUSIONS

Immediate and delayed HT provide similar treatment outcomes in patients with surgically managed lymph node-positive prostate cancer.

KEYWORDS

prostate cancer, lymph node positive, radical prostatectomy, survival

INTRODUCTION

The introduction of PSA screening has resulted in a significant stage migration of prostate cancer over the past two decades [1]. As a result, the incidence of nodal metastasis has decreased dramatically, from 20–40% in the 1980s to <5–10% at present [2–5]. Despite its infrequent clinical presentation, urologists are often faced with the dilemma of how to treat patients with lymph node-positive (LNP) prostate cancer. Previous studies from the European Organization for Research and Treatment of Cancer Genitourinary Group showed that symptomatic local progression can be expected in most patients with nodal metastasis at a median of 18–24 months [1,6,7]. Studies from the Mayo Clinic showed improved local control and disease-specific survival (DSS) rates when combining radical prostatectomy (RP) and adjuvant HT compared to HT alone (DSS at 10 years of 79% vs 39%, respectively) [1,8,9].

Traditionally, a significant proportion of surgically managed patients with LNP prostate cancer have received HT after surgery, but the indications for starting hormones vary among clinicians. These different approaches to HT include: (i) used immediately (adjuvant) after surgery; (ii) only on an early biochemical failure after surgery (the optimal PSA threshold for starting hormones is not clearly defined); (iii) only if a critical PSA doubling time (<10 months) or absolute serum PSA value (>40 ng/mL) is reached; (iv) only in the presence of asymptomatic metastatic disease; and (v) only if symptomatic metastatic disease develops. We have yet to define if and how HT should be used in the surgically managed patient with LNP prostate cancer. Messing *et al.* [10] provided some insight into the potential benefits of early HT in surgically managed patients with nodal metastases. In that study, 100 patients had retropubic RP and bilateral pelvic lymphadenectomy, after which they were randomly assigned to receive immediate hormonal ablative therapy or to be followed until there was evidence of disease progression, other than a newly detectable or increasing serum PSA level. Most of those receiving delayed HT had radiological or biopsy confirmed disease progression as the trigger for starting HT. However, biochemical failure might precede the development of systemic metastasis by 5–8 years [11]. Therefore, that study did not address the optimal use of HT after surgery.

Thus the aim of the present study was to evaluate our surgical experience in managing LNP prostate cancer and to compare the treatment-related outcomes of giving immediate HT as adjuvant therapy after RP or

delaying hormones until the development of biochemical failure.

PATIENTS AND METHODS

Before conducting this study, a retrospective chart-review protocol was designed and approved by the Institutional Review Board. All patients entered in this study were identified from our tumour registry. Between January 1982 and 2001, 219 patients with pelvic LNP prostate cancer were treated at our institution; of these, 123 had RP, of whom 100 had complete medical records available and constituted the present population assessed. Initial treatment was RP alone in 70 patients (23 later received delayed HT and 47 received no additional therapy as there was no biochemical failure) and 30 were treated with combined RP and adjuvant (immediate) HT. Evaluations before RP included a medical history, physical examination, laboratory investigations including serum PSA levels, and radiological imaging (radionuclide bone scan and pelvic CT). MRI or additional laboratory or radiological evaluations were used at the discretion of the treating physician. All patients had LNP prostate cancer confirmed by histopathology, with each patient having a staging pelvic lymphadenectomy, as previously described [12,13]. All RP and lymphadenectomy specimens were reviewed by two genitourinary pathologist (K.B., P.T.).

Variable	Value
Mean (SD) and median (range):	
Age at diagnosis, years	58.7 (7.1), 59.5 (40.0–72.0)
PSA at presentation, ng/mL	18.6 (24.7), 10.0 (2.3–133.0)
N and %:	
Clinical stage	
T1c	14
T2	66
T3a	9
T3b	11
Biopsy Gleason score	
≤6	10
7	49
≥8	41
Use of neoadjuvant treatment	
No	54
Yes	46
Primary treatment	
RP	70
RP + adjuvant HT	30
Pathological stage	
T2	9
T3a	25
T3b	66
Prostatectomy Gleason score	
Not available*	46
7	18
≥8	36
Surgical margin status	
Negative	63
Positive	37

TABLE 1
The characteristics of the 100 patients

**Patients receiving neoadjuvant therapy could not have a Gleason score assigned on the RP specimen.*

Patients were followed after RP with serum PSA measurements at regular intervals. The timing of the visits was determined by the physician, considering the pathological features of the tumour and the risk of progression. Thirty patients received immediate HT administered adjuvantly after RP in those having no evidence of biochemical or radiological progression; 23 received delayed HT with the indication for starting therapy being biochemical failure (with a threshold serum PSA level of 0.2–5.0 ng/mL) and in the absence of metastatic disease or local symptomatic progression.

The method of Kaplan and Meier [14] was used to estimate the median overall (OS), DSS and metastatic-free (MFS) survival. For the analysis of OS, death from any cause was the only event, and patients were censored at their date of last follow-up. For DSS, death from disease was the event, and those patients dying from other causes were censored at time of death or date of last follow-up. For the analysis of MFS, death from any cause and radiologically confirmed metastatic relapse were counted as events. Biochemical failure after RP was defined as a serum PSA level of >0.2 ng/mL and confirmed on a repeat measurement. The demographic and clinical characteristics of patients receiving immediate or delayed HT were compared using the rank sum, Fisher's exact, and chi-squared and log-rank tests, with significance indicated at $P < 0.05$. Treatment-related outcomes (MFS, DSS and OS) between the immediate and delayed HT groups were compared using the Kaplan–Meier method. The median follow-up of all patients from the date of RP to the date of the last follow-up or death was 5.2 years.

RESULTS

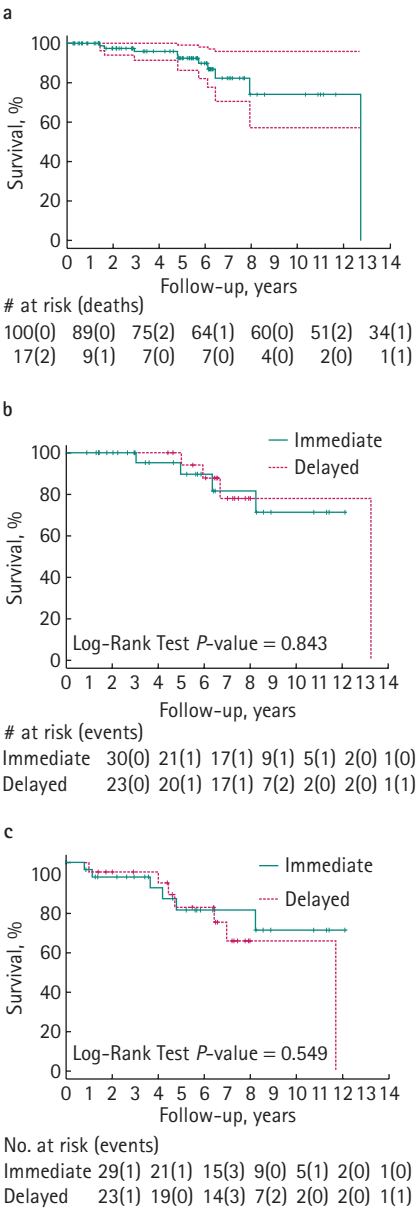
The patients' characteristics are summarized in Table 1; the median (range) age at the diagnosis of prostate cancer was 59.5 (40–72) years, with an equal distribution of patients aged <60 and ≥60 years. The mean and median serum PSA levels at diagnosis were 18.6 and 10.0 ng/mL, respectively. Most patients (80%) had clinical stage ≤T2 disease at diagnosis, with the biopsy Gleason score most commonly (49%) being 7, and 41% of patients having high-grade tumours (Gleason score ≥8). Neoadjuvant therapy was used before definitive surgery in 46 patients and consisted of HT in 11 (24%), chemotherapy in 17 (37%) or combined HT and chemotherapy in 18 (39%).

The pathological stage was pT3 in 91% of patients and the positive surgical margin rate was 37%. Seminal vesicle invasion was present in 66 patients. The RP Gleason score was ≥8 in 36 patients, but we were unable to assign a Gleason score in 46 due to previous neoadjuvant therapy. On pelvic lymphadenectomy, the median (range) number of lymph nodes removed per patient was 11 (3–32), with the median number of metastatic lymph nodes per patient being 1 (1–8). Lymph node extracapsular extension was identified in 26 patients.

Outcome	N (= %) or n/N (%)
Biochemical failure	
No	50
Yes	50
Local relapse	
None	98
Local	2
Distant metastasis	
No	87
Yes	13
Site of distal metastasis	
Bone	11/13
Liver	1/13
Lung	1/13
Salvage therapy	
No	67
Yes	33
Type of salvage therapy	
Hormones	23 (70)
Radiotherapy	2 (6)
Chemotherapy	2 (6)
Hormones and chemotherapy	6 (18)
Status	
Alive	90
Dead	10
Died from disease	
No	91
Yes	9

TABLE 2 Treatment-related outcomes of the 100 patients

FIG. 1. Kaplan–Meier analysis of: ***a,*** *OS, with 95% CI;* ***b,*** *DSS and* ***c,*** *MFS, of patients receiving immediate (30) and delayed (23) HT.*



At a median follow-up of 5.2 years, 50 patients had biochemical failure, with only two developing a local relapse (Table 2). Distant metastasis developed in 13 patients, with bony metastasis being the most common site (85%). The 5- and 10-year overall MFS rates were 84% and 69%, respectively. Salvage therapy was used in 33 patients, most of whom received HT (23, 70%). At the last follow-up, 10 patients had died, with nine of these deaths secondary to prostate cancer. The 5- and 10-year DSS rates were 94% and 75%, respectively, whereas the respective OS rates were 93% and 74%, respectively; the Kaplan–Meier analysis of OS is shown in Fig. 1a.

The results of comparing the demographic and clinical variables of patients receiving immediate or delayed HT are shown in Table 3. There was no statistically significant difference in age ($P = 0.637$) or clinical stage of disease ($P = 0.207$) between the groups; however, the delayed HT group had a higher median PSA level at diagnosis ($P = 0.027$) and a higher proportion of patients with poorly differentiated tumours ($P = 0.052$). The delayed HT group also had a higher incidence of previous neoadjuvant therapy ($P < 0.001$). Despite the more adverse clinical variables in the delayed HT group, the groups had comparable rates of distant metastasis ($P = 0.235$), DSS ($P = 0.683$), and OS ($P = 0.683$), with comparable median lengths of follow-up. The 5-year DSS rates for the immediate and delayed HT groups were 90% and 94%, respectively, whereas their 5-year MFS rates were 77% and 63%, respectively. The range of serum PSA levels at which delayed HT was initiated was 0.2–5 ng/mL, but we were unable to determine a specific PSA value above which there was a higher risk of metastatic progression or disease-specific mortality. The Kaplan–Meier survival curves for the immediate and delayed groups were similar in terms of DSS ($P = 0.843$, Fig. 1b) and MFS ($P = 0.549$, Fig. 1c).

DISCUSSION

LNP prostate cancer has traditionally been considered a systemic disease best treated with early hormonal ablative therapy [10]. However, several centres have evaluated RP alone or combined with HT as a treatment for LNP prostate cancer. A previous study by Zwergel *et al.* [15] showed a 73.7% DSS rate at 10 years for patients treated by RP with or without HT. Several other studies showed that the surgical management of LNP prostate cancer offers a survival benefit over HT alone [1,16]. Consequently, controversy remains as to what constitutes the optimum treatment for this disease. In a retrospective study by Moul *et al.* [17], 355 patients with a rising PSA level after RP were started on HT, in most cases before reaching a PSA level of >5 ng/mL, with no overall better outcome than

in patients for whom HT was initiated on evidence of clinical metastases. Similarly, in the present surgically managed patients with LNP disease, the disease-related outcomes of immediate vs delayed HT revealed no reported differences in MFS, DSS and OS.

At a median follow-up of 5.2 years, only half of the patients developed biochemical failure, 15% had disease relapse (either local in 2% or distant relapse in 13%) with the reported disease-specific mortality being 9%. Most of the patients had clinical stage T2 prostate cancer, with a median serum PSA level at presentation of 10 ng/mL. In addition, the tumour grade on prostatic biopsy was most frequently Gleason pattern 7 (49%). As such, a substantial proportion of the patients had low- to intermediate-risk prostate cancer based on the prostate cancer risk stratification groups of D'Amico *et al.* [18]. We caution clinicians not to conclude from our findings that LNP disease occurs frequently in patients with low-risk prostate cancer. Nevertheless, the study shows that nodal metastasis can present even in these patients, suggesting that pelvic lymphadenectomy might be a valuable diagnostic and potentially therapeutic method in most surgically managed patients with prostate cancer. A previous study by Bader *et al.* [19] supports our findings, suggesting that up to 25% of patients with clinically suspected organ-confined prostate cancer can harbour nodal metastasis on meticulous lymph node dissection.

TABLE 3 Comparison of immediate and delayed HT groups

Variable	Immediate HT	Delayed HT	P
Number of men	30	23	
n (%):			
Neoadjuvant treatment			
No	26 (87)	4 (17)	<0.001*
Yes	4 (13)	19 (83)	
Age at diagnosis, years			
<60	15 (50)	13 (57)	0.637*
≥60	15 (50)	10 (44)	
Clinical stage			
T1c	5 (17)	1 (4)	0.246†
T2	21 (70)	14 (61)	
T3a	2 (7)	4 (17)	
T3b	2 (7)	4 (17)	
PSA level at presentation, ng/mL			
Mean (SD)	15.1 (18.6)	34.7 (40.1)	
Median (range)	9.4 (3.1–102)	19.5 (2.5–133)	0.027‡
n (%):			
Biopsy Gleason score			
<8	21 (70)	10 (44)	0.052*
≥8	9 (30)	13 (57)	
Distant metastasis			
No	25 (83)	16 (70)	0.235*
Yes	5 (17)	7 (30)	
Died from disease			
No	26 (87)	19 (83)	0.683*
Yes	4 (13)	4 (17)	
Status			
Alive	26 (87)	19 (83)	0.683*
Dead	4 (13)	4 (17)	
Median: follow-up, years	5.4	6.3	0.080¶

**Chi-squared test; †rank sum test; ‡Fisher's exact test; ¶log-rank test.*

Other than a higher median PSA level at diagnosis, elevated biopsy Gleason score, and more frequent use of previous neoadjuvant therapy in the delayed group, patients receiving immediate and delayed HT had similar patient and clinical characteristics. To exclude the confounding effect that neoadjuvant hormones could have had on treatment outcome, a subgroups analysis was conducted among those patients not receiving neoadjuvant hormones in the immediate and delayed HT groups, with no differences in DSS and MFS (both $P = 0.333$), although there were only a few patients in both subgroups.

Overall, the immediate and delayed HT groups had similar disease-related outcomes with similar lengths of follow-up, suggesting that both hormonal ablative therapy strategies are feasible choices in this patient population. Messing *et al.* [10] conducted a randomized study in which immediate HT was considered to improve survival and reduce the risk of recurrence in LNP prostate cancer; however, 97% of the patients who received delayed HT did so only on detection of metastatic disease. In the present study, biochemical progression served as a trigger to initiate delayed HT, and the PSA value was never >5 ng/mL. Therefore, we feel that if patients are vigilantly followed with regular visits and serum PSA measurements after RP, HT can only be initiated on biochemical progression without imparting a worse outcome. This practice pattern would have several advantages including: (i) a substantial reduction in the proportion of surgically managed node-positive patients receiving HT, as treatment would be limited only to patients with disease progression; (ii) the morbidity and side-effects of long-term HT would be limited; and (iii) a significant cost-saving benefit to the healthcare system. In the present study we estimate that delaying HT to those men developing biochemical failure would avoid a median of 1.2 years of HT compared with the immediate HT group. If we estimate the cost of monthly hormonal ablative therapy using an antiandrogen and LHRH agonist to be ≈US$1200/month, the cost saving of delayed HT would be $16 800/patient. Furthermore, significant side-effects are associated with hormonal ablative therapy, including osteoporosis, hot flashes, gynaecomastia, depressed mood, and muscle loss. Consequently, any significant period off HT might have a dramatic effect on the patients' quality of life.

We have yet to define the specific serum PSA level at which delayed HT should be

initiated, although we caution physicians in starting delayed HT with a serum PSA level of >5 ng/mL.

There are several limitations to the present study. First, this was a retrospective study, and thus there is an inherent selection bias, which is common to most surgical series of LNP prostate cancer, because of the infrequent clinical presentation of pathology confirmed LNP disease. Second, the median follow-up was only 5.2 years, which helps to explain why there were only a few disease-related events. It is possible that with a more extensive follow-up we would detect an advantage to either immediate or delayed HT. Furthermore, we cannot exclude that the differences in neoadjuvant therapy use between the immediate and delayed HT groups might have affected treatment outcome. As such, we feel that the present comparable disease-related outcomes with both hormonal ablative strategies require corroboration from others, and a more extensive follow-up.

In conclusion, this study shows the oncological outcomes with the surgical management of LNP prostate cancer. The surgical management of LNP prostate cancer either alone or combined with systemic therapy can provide effective treatment-related outcomes at a follow-up of 5 years. Immediate and delayed hormonal ablation therapies appear to be equally effective in surgically managed patients with LNP prostate cancer. We favour the delayed HT approach as it might reduce a significant healthcare cost and avoid many unnecessary side-effects of long-term hormonal ablative therapy.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **HT**, hormonal therapy; **RP**, radical retropubic prostatectomy; **LNP**, lymph-node positive; **(O)(DS)(MF)S**, (overall) (disease-specific) (metastasis-free) survival.