Role of Androgen Deprivation in Patients Undergoing Radical Prostatectomy

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Abstract: Radical prostatectomy (RP) as a monotherapy is most likely to be curative only in patients with truly organ-confined PC. Several clinical and pathologic factors affect recurrence following RP. In an effort to improve the outcome Androgen deprivation therapy (ADT) has been evaluated in conjunction with RP. In this review we summarize the available evidence from prospective randomized studies concerning the use of ADT in both the preoperative and postoperative scenarios.

Keywords: Prostatectomy, androgen, deprivation, neoadjuvant, adjuvant.

INTRODUCTION

Androgen deprivation leads to inhibition of prostate cancer (PC) growth. In anticipation of an improved outcome, androgen deprivation therapy (ADT) has been evaluated in combination with the primary treatment modalities, such as radical prostatectomy (RP) and radiation therapy (RT). There is considerable evidence that a combination of ADT with RT leads to improved survival. However, in the setting of RP several controversies still exist. In this review we summarize the available evidence from prospective randomized studies concerning the use of ADT in both the preoperative and postoperative scenarios.

NEOADJUVANT ANDROGEN DEPRIVATION THERAPY PRIOR TO RP

RP as a monotherapy is most likely to be curative in patients with truly organ-confined PC. However, the inaccuracy of clinical staging is significant. Nearly 30% of clinical stage T1b, 60-65% of T2b-T2c, and 80% of T3a prostate cancer have extra prostatic extension [1]. 10%-40% have positive surgical margins following RP [2]. Under these circumstances, RP as a monotherapy is associated with significant recurrence rates prompting the evaluation of neoadjuvant ADT. The rationale for the use of neoadjuvant ADT is to induce adequate tumor regression, facilitate a complete surgical resection, and improve pathologic outcome and survival. Since the first report by Vallet in 1944, several investigators have reported their experience with neoadjuvant ADT [3-6]. From this early non-randomized experience it was clear that neoadjuvant ADT resulted in both clinical and pathologic down-staging including a reduction in positive surgical margin rates. However whether this down-staging with neoadjuvant ADT resulted in improved disease-free or overall survival was still unclear. Several randomized trials have been conducted to further address this controversy (Table **1**).

The significant findings from the randomized trials are as follows. The pathologic outcome is significantly improved following NADT. Specifically, the positive surgical margin rate was significantly lowered in the NADT group in all the trials. The proportion of pathologic organ confined disease [7-10] and negative lymph-node metastasis [7-9, 11, 12] was higher among the neoadjuvant ADT group in some trials. Although a longer duration of ADT (more than 3 months) showed better pathologic outcome in three trials, the data on recurrence and survival was not available from these studies [13-15]. Five trials reported the disease free survival (DFS) and none showed a significant difference in DFS [7, 8, 12, 16, 17]. Three trials reported the overall survival (OAS); two of them also reported disease specific survival (DSS) and none of them showed a difference in survival [7, 8, 16].

In summary, the available data does not support the use of neoadjuvant ADT with RP [18, 19].

ADJUVANT ANDROGEN DEPRIVATION THERAPY FOLLOWING RP

Several clinical and pathologic factors affect recurrence following RP. The risk of recurrence is higher in men with T3-4 disease, preoperative PSA more than 20 ng/ml, Gleason score of 8 or more, perineural invasion on biopsy, seminal vesicle invasion, lymph node metastases and positive surgical margins. Androgen deprivation has been extensively evaluated in an effort to improve the patient outcome in the presence of adverse prognostic factors. In this context the evidence from three randomized trials comparing immediate versus delayed adjuvant ADT following RP needs to be considered (Table **2**). It should be noted that each of the study had different selection criteria and the choice of ADT differed from one study to the other.

The overall survival (OAS) was reported by all the studies. The Eastern Cooperative Oncology Group (ECOG)

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1876-8229/10

Table 1. Summary of Randomized Trials Evaluating Neoadjuvant Hormone Therapy with Radical Prostatectomy

Study	N(RP / NADT+RP)	Regimen	T-stage	Results (RP+NADT VS RP)*			FU (Yr)
				Positive SM	5-yr PFS	5-yr OAS	
Dalkin *et al.* [9]	56 (28/28)	3 m G	T1c-T2b	18% vs. 14%	--	--	--
Labrie *et al.* [10]	161 (90/71)	3 m L+F	B0-C2	7.8% vs. 33.8%*	--	--	--
Van Der Kwast *et al.* [14]	40 (0/18/22)	3/6 L+F	T1-T3	27.8%(3m) vs. 9.1%(6m)*	--	--	--
Schulman *et al.* [7]	402 (210/192)	3 m G+F	T2-T3	13% vs. 37%* T2 42% vs. 61% T3	74% vs. 67%	No difference at 4 yr (5 vs 3 deaths)	4
Gleave *et al.* [15]	547 (0/273/274)	3/8 L+F	T1b-T2c	23%(3m) vs. 12%(8m)*	__	--	--
Aus *et al.* [16]	126 (55/57)	3 m T	T1b-T3a	23.6% vs. 45.5%*	49.8% vs. 51.5%	No difference	6.85
Selli *et al.* [13]	393 (128/143/122)	3/6m G+B	T2–T3	18.7%(6m) vs. 46.5%* 26 % (3m)vs. 46.5%*	--	--	--
Soloway *et al.* [12]	303 (144/138)	3 m L+F	T2b	18% vs. 48%*	64.8% vs. 67.6%	--	5
Klotz *et al.* [8]	213 (110/112)	3 m C	T1b-T2c	28% vs. 65%*	68.2% vs. 60.2 Benefit if PSA>20ng/ml	88.4% vs 93.9	6
Prezioso *et al.* [11]	167 (75/70)	3m L+C	T1a-T2b	39% vs. 60%*	--	--	--
Yee *et al.* [17]	148 (64/72)	3 m G+F	T1b-T3a	19% vs. 38% *	80% vs. 78%	--	8

G= Goserelin acetate (3.6 mg SC depot each month)
F= Flutamide (250 mg TID)
T= Triptorelin (3.75 mg IM)
C= Cyproterone acetate (100 mg TID)
L=Leuprolide (7.5 mg. IM monthly)
B = Bicalutamide (50 mg/ day orally)
SM: Surgical margin, PFS:Progression-free Survival,OAS: Overall Survival.
* Significant difference.

Table 2: Summary of Randomized Trials Evaluating Immediate Versus Delayed Adjuvant Hormone Therapy Following Radical Prostatectomy

Study	N (Immediate / Delayed)	Patient Selection Criteria	Regimen	Results	HR(CI)#			FU (Yr)
					PFS	DSS	OAS	
Messing *et al.* [20]	98(47/51)	RP+BPLND for ≤ cT2. Postoperatively pN+	G or BO	Improved PFS,DSS and OAS	3.42 (1.96-5.98)#	4.09 (1.76-9.49)#	1.84 (1.01-3.35)#	11.9
Wirth *et al.* [22]	309(152/157)	pT3-4, N0	F	Improved PFS	0.51 (0.32-0.81)#	-	1.04 (0.53-2.02)	6.1
McLeod *et al.* [21]	4454(?)	T1-4,any N,M0	B/Placebo	Improved PFS in locally advanced				7.4
		Localized			1.00 (0.76-1.15) 0.75		1.00 (0.76-1.25) 1.09	
		Locally advanced			(0.61 -0.91)#		(0.85-1.39)	

Significant and favors immediate treatment.

study [20] which enrolled patients with lymph node metastases reported significant improvement in both the overall and disease-specific survival for the immediate ADT group. It must be pointed out that a significant number of patients in this study had gross nodal disease, 70% also had positive margins and 60% had seminal vesicle invasion. Bicalutamide Early Prostate Cancer (EPC) trial program [21] which studied both localized and locally advanced PC did not report

improvement in OAS in either group. Another study by Wirth *et al*. [22] which studied locally advanced yet lymph node negative PC did not report improvement in OAS. The disease free survival (DFS) was significantly improved in the immediate treatment group in all the three studies. However, in the EPC study improvement in DFS was mainly seen in the locally advanced group.

In summary, the use of early adjuvant ADT has important clinical benefits. The DFS is significantly better; the benefit in OAS is still unclear although one study reported significant improvement in the presence of lymph node metastases. In view of the toxicity associated with the use of ADT and prolonged treatment duration, the benefits must be carefully assessed in each patient, his clinical status and pathologic characteristics must be considered before advocating immediate ADT.

CONCLUSION

The available data does not support the use of neoadjuvant ADT with RP. Early adjuvant ADT has important clinical benefits which must be carefully assessed in each patient.

ABBREVIATIONS

RP	=	Radical prostatectomy
BPLND	=	Bilateral pelvic lymph node dissection
G	=	Goserelin 3.6 mg sc every 28 days until progression
BO	=	Bilateral orchidectomy
F	=	Flutamide 250 mg TID
B	=	Bicalutamide 150mg OD
PFS	=	Progression free survival
DSS	=	Disease specific
OAS	=	Overall survival

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Received: September 25, 2009 Revised: December 19, 2009 Accepted: December 19, 2009