

What is the best postoperative treatment for patients with pT3bN0M0 adenocarcinoma of the prostate?

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The purpose of this paper to identify the optimal therapy after radical prostatectomy (RP) for patients with adenocarcinoma of the prostate invading the seminal vesicles (pT3bN0M0 or SVI). A PubMed search using the keywords 'prostate', 'seminal vesicle', 'prostatectomy', 'radiotherapy', 'androgen blockade' was performed to identify literature regarding rates of disease failure in patients with SVI who are observed or treated with androgen blockade (AB), radiotherapy (RT) or RT + AB after RP. The outcome of 68 patients treated at Duke University with post-operative AB, RT or RT + AB for pT3bN0M0 is also presented. More than 70% of patients with SVI develop disease recurrence after surgery. For many, recurrence occurs within 2 y after RP. These patients have poor control rates with postoperative RT alone. While experience with AB and RT + AB is limited, control rates are generally superior to RT alone. At Duke University, after a median follow-up of nearly 4 y, patients treated with RT + AB or AB alone for pT3bN0M0 achieved better 5-y progression-free survival (PFS) compared with those who received RT alone (78 and 68 vs 30%, $P=0.03$ and 0.046 , respectively). There was no PFS difference between those who received AB alone or RT + AB (68 vs 78%, $P=0.5$). Seminal vesicle invasion confers a poor prognosis after RP. SVI is a consistent predictor of poor outcome after RT. The limited data available examining AB and RT + AB in pT3bN0M0 disease, including data from Duke University, are encouraging. Nonetheless, postoperative AB, RT and RT + AB for pT3bN0M0 disease require prospective evaluation, as RP alone is rarely curative. *Prostate Cancer and Prostatic Diseases* (2005) 8, 167–173. doi:10.1038/sj.pcan.4500789
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Introduction

Seminal vesicle invasion (SVI, pT3bN0M0) is found in 5–10% of men undergoing radical prostatectomy (RP) for prostate cancer. Numerous studies indicate that a majority of these patients will experience biochemical failure rapidly after surgery. The risk of metastatic disease and death from prostate cancer is higher in patients with short disease free intervals after surgery.

Thus, while little data exist regarding the optimal approach, adjuvant therapies including radiation (RT), androgen blockade (AB) or their combination (RT + AB) should be considered for patients with SVI.

Postoperative radiotherapy (RT), which provides excellent disease control for patients with extracapsular extension (pT3a) or positive surgical margins, is dramatically less effective in men found to have SVI. Some attribute poor response after local radiotherapy to subclinical distant metastases. Instead of RT alone, they argue that patients with SVI require adjuvant systemic therapies such as androgen blockade (AB) with or without local radiotherapy (RT + AB).

To provide better guidance on the postoperative management of patients with pT3b adenocarcinoma of

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the prostate, we performed a review of the existing literature regarding outcome with observation, AB, RT and RT + AB. We include data describing outcome with the above modalities for patients with SVI treated at Duke University.

Methods

A PubMed search using the keywords 'prostate', 'seminal vesicle', 'prostatectomy', 'radiotherapy' and 'androgen blockade' was performed. Articles were included in this review if the number of patients having pT3bN0M0 disease was clearly stated and their outcome after either observation, AB, RT or RT + AB was reported. Using this strategy, we found seven articles describing disease outcome with observation after surgery in patients with pT3bN0M0 disease.¹⁻⁷ Series that described outcome with SVI or found SVI as a predictor of failure were included even if patients without SVI were analyzed in the study.

The same search strategy was used to identify articles describing outcome with postprostatectomy AB, RT and RT + AB. While a number of articles evaluating outcome with RT with or without AB for patients with pT3-4 disease⁸⁻²² were found, there was only one article that described outcome with AB alone for pT3bN0M0 disease.²³ A single study was found that prospectively compared postoperative RT with postoperative RT + AB. This investigation included patients with high-grade disease, pT3-4 disease (including SVI) and those with lymph node involvement.^{24,25} Only one article reported outcome in patients with pT3bN0M0 disease treated with adjuvant or salvage RT.¹⁵

The outcome of 68 patients treated with AB, RT and RT + AB at Duke University for pT3bN0M0 disease from 1989 to 2001 was reviewed. Of these 68 patients, 20 received AB alone, 38 received RT alone and 10 received RT + AB. Adjuvant therapy, defined as treatment initiated with an undetectable PSA, was delivered with RT alone (eight patients) or AB alone (eight patients) in 16 patients. All 10 patients who received RT + AB had a detectable PSA at the time of therapy. No patients had overt local, regional or distant failure at the time of postoperative therapy. Details of the clinical and therapeutic characteristics of these patients are listed in Table 3.

The mode and duration of AB for those who received AB alone or concurrent RT + AB was at the discretion of the attending urologist or radiation oncologist. Either medical or surgical approaches were used. Drugs utilized included leuprolide, goserelin, bicalutamide and flutamide. One patient received diethylstilbestrol (DES). The median duration of medical therapy for AB alone was 48 months.

In the RT + AB group, patients began AB either a few weeks prior to RT or during RT. Agents used included leuprolide, goserelin, flutamide, and bicalutamide. The median duration of AB for these patients was 8 months.

Radiotherapy for the RT alone and RT + AB groups was delivered using 6–15 MV photons arranged in a four-field box to treat the prostatic bed without deliberate inclusion of the pelvic lymph nodes. The initial fields were treated to 4400–4600 cGy in 180–200 cGy fractions.

Patients with either a rising PSA or a persistently elevated PSA postoperatively were then boosted with smaller fields to a total dose of 6600 cGy while those with undetectable PSAs received 6000 cGy.

At 3–6-month follow-up visits, a history, physical examination and PSA were usually performed. Further testing, including CT scans, bone scans or X-rays was done if clinically indicated. Patients were followed for progression defined as (1) biochemical recurrence (three consecutive PSA rises from a nadir or a persistent rise), (2) local failure, (3) distant failure or (4) death. Wald tests from proportional hazards regression models were used to compare the progression-free survival (PFS) of the three treatment groups. Covariates in these models included age, race, margin status, Gleason score, and pretreatment PSA. Covariate-adjusted plots of estimated PFS for the three treatment groups were generated and 5-y PFS rates for the three treatment groups are presented.²⁶

SVI incidence in PSA era

The advent of PSA screening has seen a dramatic increase in the rates of clinically organ-confined disease from 25% in the 1990s to >50% in 2000. Nonetheless, between 1991 and 2000, the rates of seminal vesicle invasion identified at RP have remained relatively stable, accounting for 5–10% of patients who undergo RP.²⁷⁻²⁹ We can therefore expect that among the 70 000 RPs performed yearly, 3500–7000 patients will demonstrate invasion of the seminal vesicles (pT3b).

Recurrence rates after surgery alone

We identified seven studies that followed patients with pT3bN0M0 disease for disease recurrence using PSA or other clinical end points (Table 1).¹⁻⁷ No patient received postoperative therapy prior to disease recurrence. Failure was most commonly manifested as a PSA rise above 0.2 ng/ml. A majority of patients in these retrospective reviews had high Gleason scores (GS ≥ 7) and positive surgical margins. In fact, nearly 90% of those with SVI had either a GS ≥ 7 or positive surgical margins. It is not surprising, therefore that among the seven studies, the 5-y disease control rates ranged from 10 to 40%.

In five of the seven studies, the median time to disease recurrence was within 2 y of surgery. Pound *et al*³⁰ have shown that a short interval (≤ 2 y) between surgery and biochemical failure predicts for a high rate of distant metastasis and death from prostate cancer. In this series from Johns Hopkins University, nearly 2000 men with prostate cancer were followed for biochemical failure, distant failure and time to death after RP. While most had clinically organ-confined disease (98%) with preoperative PSA values ≤ 10 ng/ml (75%), more than half were upstaged at RP and pT3bN0 disease was found in 5% of patients. Nearly all of the 304 patients who were scored as having failure after surgery demonstrated a biochemical failure defined as a PSA > 0.2 ng/ml.

While pathological stage was not found to be an important predictor of metastasis-free survival (MFS), nearly half of the patients with pT3bN0 disease devel-

Table 1 Outcome with observation after surgery for pT3bN0M0 disease

Study	# pts with SVI	% +margins	% GS \geq 7	% 5-y DFS	Median DFS (months)
Salomon <i>et al</i> ¹	137	45	45	35	20
Freedland <i>et al</i> ²	152	52	76	40	30
Bloom <i>et al</i> ³	113	55	92	30 (3-y)	<24*
Epstein <i>et al</i> ⁴	60	52	93	36	30*
Tefilli <i>et al</i> ⁵	93	63	91	40 (3-y)	20
D'Amico <i>et al</i> ⁶	35	NG	NG	10	10
Sofer <i>et al</i> ⁷	66	52	85	35	12

pT3b = SVI: seminal vesicle involvement, +margins: positive surgical margins; GS = Gleason score; DFS = disease-free survival: usually defined as PSA <0.2 ng/ml; NG = not given.

*GS = 7, +margins.

oped disease recurrence and they accounted for 17% of all patients who developed biochemical failure. The authors identified several important predictors of MFS and subsequent death from prostate cancer in patients who experienced biochemical failure.

Significant predictors of MFS included pathological Gleason score (5–7 vs 8–10) and timing of PSA failure after surgery (\leq 2 y or >2 y). Patients with a GS 5–7 who experienced biochemical failure within 2 y of surgery had a 5-y MFS of 62% compared with 82% for those with failure after 2 y. A 5-y MFS rate of only 30% was predicted for patients with a GS 8–10 who had biochemical failure within 2 y of prostatectomy. The median time to death in patients who developed distant metastases within 5–7 y after surgery was only 5 y.

As we have already shown, a majority of patients with SVI have high-grade tumors (GS \geq 7) and many develop biochemical failure within 2 y of surgery (Table 1).^{1–7} These patients can expect to have a 5-y MFS of 30–62% after biochemical recurrence. Thus, a 55-y-old man with pT3bN0 disease will likely experience biochemical failure within 2 y of surgery, distant metastasis 7 y postoperatively and subsequent death from prostate cancer at the age of 67.

Not all patients with SVI are destined to develop biochemical failure. Bloom *et al* and Freedland *et al* found disease-free survival rates of 67–100% at 3–5 y among patients observed after surgery with GS \leq 6 and negative surgical margins. However, these favorable features were found in <10% of patients with SVI.^{2,3} Thus, with observation alone after surgery, patients with SVI are at a very high risk of early biochemical recurrence, metastasis and death from prostate cancer.

Postoperative AB

Despite the apparent high risk of distant failure and death from prostate cancer in patients with SVI, there are little data regarding the efficacy of adjuvant systemic hormonal therapies. Zincke *et al*²³ performed a retrospective review of outcome with immediate versus delayed androgen blockade in 707 patients with pT3bN0M0 disease treated from 1966 to 1994. In this investigation, 157 patients received adjuvant androgen blockade within 90 days of surgery while 550 patients began treatment at the time of clinical or biochemical failure. Androgen blockade consisted of an oral antiandrogen or orchiectomy. Margin status was the primary determinant of who received adjuvant therapy. Nearly

2/3 of patients treated with adjuvant AB had positive margins compared with 1/3 of those who received salvage therapy.

After a median follow-up of 8 y, biochemical failure, MFS and rate of death from prostate cancer was significantly lower in patients who received adjuvant compared with salvage androgen blockade²³ (Table 2).

Surprisingly, we were unable to find other articles describing outcome with adjuvant AB alone in patients with pT3bN0M0 disease. Nonetheless, a growing body of literature supports early over delayed AB in patients at high risk of systemic relapse. A recent prospective trial compared outcome with immediate or delayed goserelin therapy in 98 men with positive lymph nodes detected after RP and nodal dissection. At a median follow-up of 7 y, there was a significant improvement in overall survival in those patients treated with immediate rather than delayed goserelin therapy (7 y OS: 85 vs 64%, $P = 0.02$).³¹

In patients who receive definitive local radiotherapy rather than surgery, two major prospective trials show superior outcome in locally advanced prostate cancer treated with adjuvant, long-term AB compared to salvage AB. Pilepich *et al* evaluated outcome in 770 patients with locally advanced or high-grade disease, which included a cohort of post-prostatectomy patients with extraprostatic disease or positive lymph nodes. In all groups, including patients treated postoperatively, the biochemical relapse-free survival was greater for patients receiving immediate compared with delayed AB. Patients with high-grade tumors (GS 8–10), excluding those receiving postoperative therapy, enjoyed an overall survival benefit when treated with early compared with delayed AB.^{24,25}

Unfortunately, the above prospective trials looking at adjuvant long-term AB do not specifically evaluate the outcome in patients with clinical or pathologic SVI.

We identified 20 patients with pT3bN0M0 disease treated with AB alone from 1989 to 2001 at Duke University. After a median follow-up of nearly 4 y, the

Table 2 Outcome with adjuvant vs salvage AB²³

Timing of AB	# pts	10-y biochemical failure (%)	10-y systemic failure (%)	10-y death from prostate cancer (%)
Adjuvant	157	73	10	5
Salvage	550	33*	27*	13**

* $P < 0.001$; ** $P = 0.046$. AB = androgen blockade; Adjuvant = AB begun immediately postoperatively; Salvage = AB begun at the time of disease recurrence.

5-y PFS was 65% (Table 3). Of particular interest was the finding that no patient treated with adjuvant AB immediately after surgery has experienced progression. This is similar to the benefit of adjuvant compared with salvage AB found by Zincke *et al*.

A number of questions remain regarding postoperative AB therapy including the optimal agents, duration of therapy and impact on quality of life. There are ongoing studies comparing oral antiandrogens, such as bicalutamide with GnRH agonist therapy. Trials showing a survival benefit with adjuvant AB employed a GnRH agonist, sometimes with an oral antiandrogen for a period of at least 3 y.^{23–25,31–33} The potential detriment in quality of life as well as the risk of osteoporosis from long-term testosterone suppression needs to be discussed with patients. However, the above data support the need to further investigate adjuvant, long-term AB after RP for pT3bN0M0 disease.

Postoperative RT

Systemic failure is likely the main determinant of survival in prostate cancer but local recurrence after

surgery can produce significant morbidity and possibly even mortality. Anscher *et al*⁸ demonstrated a 5-y actuarial rate of local recurrence of nearly 40% in patients with SVI. Since patients with SVI typically have extracapsular extension and positive surgical margins, it is not surprising that local recurrence rates would be high.

Radiotherapy delivered to the surgical bed, either immediately after RP (adjuvant therapy) or at the time of PSA rise (salvage therapy), provides durable biochemical control in most patients with positive surgical margins or extracapsular extension (T3a).^{9–19} This is not the case, however, in patients with SVI. In fact, SVI is a consistent poor predictor of disease control after postoperative RT with 5-y biochemical control rates of only 11–60% compared with 45–100% in patients without SVI (Table 4).^{9–12,14,18,19}

The preponderance of data favors adjuvant compared with salvage RT in optimizing biochemical control in patients with pT3 disease or those with positive surgical margins. Adjuvant RT yields 5-y biochemical control rates of 67–100% compared with 11–65% for salvage therapy (Table 5).^{9–19} Adjuvant RT, however, seems to be more effective in pT3a compared with pT3b disease. Shetty and co-workers⁹ compared adjuvant and salvage

Table 3 Duke University experience with RT, AB and RT+AB for pT3b disease

Characteristics (range)	RT	AB	RT+AB
# patients	38	20	10
Age (y)	63 (48–68)	70 (57–79)	66 (58–69)
Median preoperative PSA (ng/ml)	17.4 (3.9–200)	17.6 (3.9–79)	16.8 (6.1–44)
Median Gleason Score	7 (5–10)	8 (5–10)	7 (3–9)
% Extracapsular extension	86	83	78
% Positive margins	86	80	80
Median pretherapy PSA (ng/ml)	1.00 (<0.1–15.9)	0.35 (<0.1–95)	0.8 (<0.1–17.7)
Adjuvant therapy (#pts)	8	8	0
Median time to post-op therapy (days)	174 (0–2918)	108 (0–2344)	139 (26–802)
Median follow-up (y)	3.4	3.4	3.4
Median PFS (y)	3*	7.5	8
5-y PFS (%)	30*	69	78

pT3b = pathological seminal vesicle involvement; RT = radiotherapy alone; AB = androgen blockade alone; RT+AB = radiation and androgen blockade; PFS = progression-free survival; adjuvant therapy = postoperative treatment with PSA ≤ 0.1 ng/ml.

*RT vs AB: *P* = 0.046; RT vs RT+AB: *P* = 0.03.

Table 4 Comparison of results of RT after RP in patients with or without SVI

Study	# Patients	Stage (pts)	RT dose (Gy)	5-y bNED (–SVI vs +SVI)	Median DFS
Shetty and co-workers ⁹	35 (A)	T3a: 59	60	100 vs 60%	NG
	41 (S)	T3b: 17	65		
Schild <i>et al</i> ¹⁰	60 (A)	T3b: 44	62	81 vs 36%	2.5 y
	27 (n-AB)				
Shipley <i>et al</i> ¹¹	54 (S)	T3a: 40	65	45 vs 11%	3.5 y
		T3b: 14			
Anscher <i>et al</i> ¹²	89 (S)	T3a: 56	65	NG	1.9 y
		T3b: 30			
Choo <i>et al</i> ¹⁴	73 (A)	T3a: 63	60	NG	HR = 2.0 worse
	52 (no A)	T3b: 26			
Mayer <i>et al</i> ¹⁸	29 (A)	T3a: 25	70	85 vs 36%	HR = 16.0 worse
	37 (S)	T3b-4: 32			
Stephenson <i>et al</i> ¹⁹	501 (S)	T3a: 282	65	52 vs 18%	HR = 1.4 worse
		T3b: 139			

RT = radiotherapy; RP = radical prostatectomy; +SVI = seminal vesicle involvement; –SVI = no seminal vesicle involvement; T3a = extracapsular extension; T3b = seminal vesicle involvement; A = adjuvant therapy—PSA < 0.1 ng/ml prior to postprostatectomy therapy; S = salvage therapy—PSA > 0.1 ng/ml prior to postprostatectomy therapy; bNED = no biochemical evidence of disease; usually defined as PSA < 0.2 ng/ml; DFS (disease-free survival) = usually defined as no PSA < 0.2 ng/ml, no local failure, no distant failure or death from prostate cancer. NG = not given, HR = hazard ratio; n-AB = number of patients receiving AB only; no A = number of patients treated with RP only.

Table 5 Comparison of adjuvant *vs* salvage RT in patients with pT3-4 disease

Study	# Patients	Median follow-up (months)	Median pre-RT PSA (ng/ml)	Stage (#pts)	RT dose (Gy)	Adjuvant bNED (%)	Salvage bNED (%)
Shetty and co-workers ⁹	35 (A) 41 (S)	60	0.5	T3a: 59 T3b: 17	60 (A) 65 (S)	86	57
Schild <i>et al</i> ¹⁰	60 (A) 27 (n-AB)	35	0.1	T3b: 44	62	NA	57
Shipley <i>et al</i> ¹¹	54 (S)	45	1.3	T3a: 40 T3b: 14	65	NA	35
Anscher <i>et al</i> ¹²	89 (S)	48	1.4	T3a: 56 T3b: 30	65	NA	50
Pollack and co-workers ¹³	75 (A)	65	0.4–0.8	T3a (NG)	60 (A)	88	65
Choo <i>et al</i> ¹⁴	71 (S) 73 (A)	60	<0.20	T3b: 29 T3a: 63 T3b: 26	70 (S) 60	88	NA
Valicenti <i>et al</i> ¹⁵	15 (A) 18 (S)	38	1.0	T3b: 33	65	86	32
Vicini <i>et al</i> ¹⁶	38 (A) 23 (S)	48	NG	T3a (NG) T3b (NG)	59 (A) 61 (S)	67	16
Catton <i>et al</i> ¹⁷	51 (A) 43 (S)	44	2.8	T3a: 36 T3b: 36	60	81	18
Mayer <i>et al</i> ¹⁸	29 (A) 37 (S)	54	1.3	T3a: 25 T3b: 32	70	85	34
Stephenson <i>et al</i> ¹⁹	501 (S)	45	0.72	T3a: 282 T3b: 139	59–70	NA	45

A = adjuvant (PSA undetectable); S = salvage (Detectable PSA); NA = not applicable; RT = radiotherapy; n-AB = neoadjuvant androgen blockade alone; Pre-RT PSA = PSA prior to initiating radiotherapy; T3a = extracapsular extension; T3b = seminal vesicle involvement; bNED = no biochemical evidence of disease; usually defined as PSA <0.2 ng/ml; NA = not applicable; NG = not given.

RT in pT3N0 disease and found that patients who received adjuvant RT for pT3a disease had a 100% disease free survival at 5 y compared with 60% for those with pT3b disease. Similarly, Pollack and co-workers¹³ showed a 65% 5-y bNED for patients with SVI after adjuvant RT compared with 94% for patients without SVI.

We identified a single retrospective review exclusively examining postoperative RT in patients with seminal vesicle involvement. In this series, Valicenti *et al*¹⁵ showed that adjuvant RT provided superior biochemical control compared with salvage therapy in 33 patients with pT3bN0M0 disease. Actuarial biochemical control at 3 y was 86% for adjuvant RT compared with 32% for salvage therapy ($P = 0.01$).

There have been 38 patients with pT3bN0M0 disease treated with RT alone at Duke University from 1989 to 2001. After a median follow-up of nearly 4 y, the 5-y PFS with RT alone was a disappointing 30% (Table 3). Not all patients fared poorly, however. The eight patients who received adjuvant RT had a 5-y PFS of 78%. This favorable outcome with adjuvant therapy is similar to the results obtained by Valicenti *et al*.¹⁵ Unfortunately, patient numbers were too small to detect a statistically significant difference in PFS among patients who received salvage *vs* adjuvant RT.

Both groups enjoyed excellent 5-y survival rates, which is not surprising given the long natural history of prostate cancer. Longer follow-up, however, is likely to reveal higher cause-specific mortality from prostate cancer in patients with PSA progression after salvage RT. Thus, by providing better PFS, adjuvant RT may eventually lead to a survival improvement *vs* salvage RT in pT3bN0M0 disease.

Despite some encouraging data with adjuvant RT, most series indicate local radiotherapy after surgery will not provide durable disease control for patients with SVI.

There is likely some element of local control benefit with RT but optimal postoperative therapy for SVI needs to address the high likelihood of systemic failure.

Combined RT + AB

The rapid rate of disease failure with observation and the poor response rates with RT lend credence to the hypothesis that SVI predicts for subclinical distant metastases. Given the high risk of systemic failure with SVI, it is not surprising that further local therapy after surgery is not curative. However, RT likely enhances local control leading some to support combined RT + AB as the optimal postoperative therapy in patients with SVI.

In fact, androgen blockade given prior to or during postprostatectomy radiotherapy has been shown to improve biochemical disease-free survival compared with RT alone (Table 6).^{20–22,24,25} Katz *et al* treated 115 patients after prostatectomy with RT alone (70 patients) or RT with neo-adjuvant AB (45 patients). There were 27 patients with SVI but the number in each arm was not given. In patients with either SVI, extracapsular extension or close margins, neo-adjuvant AB improved outcome compared with RT alone (4-y RFS of 43 *vs* 20%, $P = 0.03$). Similarly, both Pilepich and Eulau show improved biochemical control rates with RT + AB compared with RT alone in patients found to have locally advanced disease after surgery.^{21,24,25} These investigations did not specifically indicate whether SVI predicted for worse outcome after RT + AB. Also, none address the issue of adjuvant compared with salvage RT + AB.

We identified 10 patients with pT3bN0M0 disease treated with combined RT + AB at Duke University from 1989 to 2001. After a median follow-up of 4 y, the 5-y PFS

Table 6 Outcome with postprostatectomy RT with or without AB

Study	Groups: # pts	pT3b (# pts)	Pre-RT PSA (ng/ml)	5-y Biochemical DFS: RT+AB vs RT
Pilepich <i>et al</i> ^{24,25}	RT: 68 RT+AB: 71	74	2.4	65 vs 42%, $P = 0.002$
Katz <i>et al</i> ²⁰	RT: 70 nAB+RT: 45	27	0.87	43 vs 20%*, $P = 0.04$
Eulau <i>et al</i> ²¹	RT: 74 RT+AB: 29	42	5.86	56 vs 27%, $P = 0.004$
Tiguert <i>et al</i> ²²	nAB+RT: 81	13	0.8	50%
Zincke <i>et al</i> ²³	Adjuvant AB: 157	157	NA	73% (10-y DFS)

RT = radiotherapy; nAB = neoadjuvant androgen blockade; AB = androgen blockade; RT+AB = combined therapy; pre-RT = prior to radiotherapy; SVI = seminal vesicle involvement; NA = not available; DFS = disease-free survival—usually defined as PSA <0.2 ng/ml, no local failure, distant failure or death from any cause

*4-y DFS.

was 78% for combined RT + AB (Table 3). The differences in PFS for patients receiving RT, AB and RT + AB were compared using Wald tests from proportional hazards regression models. Patients who received RT alone had a markedly inferior 5-y PFS compared with those who received AB (30 vs 68%, $P = 0.046$) or RT + AB (30 vs 78%, $P = 0.03$, Table 3). PFS with RT + AB was not significantly better than AB alone (78 vs 68%, $P = 0.50$, Table 3).

The lack of additional benefit with combined RT + AB vs AB alone could be due to differences in the timing of RT for the two arms. None of the patients in the RT + AB group had the benefit of receiving adjuvant therapy compared with nearly half of those who received AB alone. Also, patients treated with AB alone received sustained therapy (median duration AB = 4 y) compared with a relatively short duration of AB in the combined RT + AB group (median duration AB = 8 months). The benefit of RT given concurrent with AB may be realized if AB therapy is sustained for 2–3 y and if patients are treated in the adjuvant, rather than salvage setting.

Although we were unable to identify a difference in PFS between RT + AB vs AB alone, both offered superior PFS compared with RT alone (78 and 68 vs 30%, $P = 0.03$ and 0.046, Table 3). With time, the benefit in PFS offered by a treatment regimen employing some form of AB will likely lead to better local control, distant control and survival for patients with pT3bN0M0 disease.

Conclusions

Patients found to have seminal vesicle invasion at RP usually have positive surgical margins and poorly differentiated tumors ($GS \geq 7$) placing them at high risk of local failure, distant failure and ultimate death from prostate cancer. The short disease-free interval after surgery among those with SVI and poor control with local RT alone suggests that subclinical distant metastases are likely present at diagnosis. A growing body of literature supports adjuvant systemic AB in patients at high risk of systemic failure, such as those with node-positive disease or poorly differentiated tumors. Similarly, systemic AB for patients with SVI appears to provide superior disease control compared with observation or local RT alone in the retrospective data presented by both Zincke *et al* and our experience at Duke University.

Since combined RT + AB improves disease-free survival compared to RT alone in patients treated definitively for locally advanced or high-grade disease,^{24,25,32,33} we expect a similar improvement in outcome with postoperative RT + AB vs RT alone in patients with SVI. The ongoing RTOG P-0011 trial comparing adjuvant RT to RT + AB for pT2b–4 disease should provide further guidance regarding the efficacy of postoperative combined modality therapy compared with RT alone. However, this trial lacks an AB alone arm, which, based on the data presented here, should be compared prospectively with RT + AB.

At DUMC we do not routinely recommend RT alone for patients with SVI. Instead, for patients treated ‘off protocol’, we typically employ combined RT + AB in the adjuvant setting. AB alone is also an acceptable approach in the absence of an available research study, as it appears to provide excellent PFS.

In conclusion, patients with SVI have a poor prognosis after RP. While the optimal postoperative therapeutic approach is unknown, growing evidence suggests treatment should be initiated immediately after surgery. A randomized, prospective comparison between adjuvant AB, RT and combined RT + AB after RP in patients with pT3bN0M0 disease should be performed.

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