

## Long-Term Neoadjuvant and Adjuvant Combined Androgen Blockade Is Needed for Efficacy in Localized Prostate Cancer

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### ABSTRACT

Even with screening, a large proportion of prostate cancers are not confined to the prostate at diagnosis, thus seriously limiting the possibility of a cure by radical prostatectomy, radiotherapy, or brachytherapy. The best hope for improving the success of therapy is the induction of apoptosis or cancer-cell death by androgen blockade before (neoadjuvant) or after (adjuvant) application of the above-indicated curative approaches. The most difficult remaining question is the duration of endocrine therapy. In this context, in a group of 26 previously untreated patients with Stage T2 cancers who received combined androgen blockade (CAB) for a median duration of 7.1 years, the first rise of serum prostate specific antigen (PSA) occurred in one patient only after 8 years and 4 months of treatment. Among the 17 patients who stopped CAB, a rise in PSA was seen in only three (18%) during a 2.2-year follow-up. Similarly, among 26 patients with Stage T3 disease who had undetectable PSA for a median of 9.9 years while receiving CAB, PSA rose in only four (15%) during a 1.8-year follow-up after cessation of CAB. Very different results were found when CAB was stopped after only 1 year in 11 patients with Stage T2 disease: in this group, PSA rose in all patients within 1 year after cessation of CAB. The present data show that CAB is highly efficient in controlling localized prostate cancer for many years. However, the present findings suggest that the treatment should be continued for approximately 5 years to achieve control of the cancer in the majority of patients after cessation of endocrine therapy.

### INTRODUCTION

PROSTATE CANCER is the second most frequent cause of cancer death in men in the Western world. In fact, in the United States alone, 41,800 men are expected to die from prostate cancer in 1997.<sup>1</sup> Prostate cancer has become a major health and social problem comparable to breast cancer.

Significant progress has been achieved during recent years in the field of diagnosis and therapy of prostate cancer, which has culminated in the first demonstration of better survival after treatment of localized disease with adjuvant endocrine therapy.<sup>2</sup> Although these very important findings do not answer the question of the best choice of therapy for early-stage prostate cancer,<sup>3</sup> they demonstrate that at least one treatment modality, namely androgen deprivation added to radiation therapy compared with radiotherapy alone, not only improves local control by 27% but also increases survival by 39% at 5 years.<sup>2</sup> These

data provide the long-awaited proof that treatment of localized prostate cancer is worthwhile, not only in terms of local control but, most importantly, on the duration of life. As will be discussed later, there are good reasons to believe that even better results will be achieved with combined androgen blockade. These important benefits demonstrated for the first time in localized disease are attributable to adjuvant androgen deprivation, similar to the survival advantages previously demonstrated in advanced disease by adding a pure antiandrogen to medical or surgical castration.<sup>4-9</sup>

As mentioned above, much progress has been made recently by several groups in the efficient use of prostate specific antigen (PSA) and transrectal ultrasonography (TRUS) of the prostate for earlier diagnosis of prostate cancer, while, simultaneously, more efficient and well-tolerated curative therapies have been developed.<sup>10-24</sup> In fact, a highly efficient, easily applied, and low-cost strategy for the detection of localized

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prostate cancer is now available.<sup>21-25</sup> Consequently, with the currently available diagnostic techniques, especially PSA coupled with TRUS of the prostate, more than 95% of prostate cancers can be diagnosed at a clinically localized stage, thus practically eliminating the diagnosis of advanced prostate cancer.<sup>25</sup>

Unfortunately, despite the marked improvement in diagnostic procedures,<sup>10,17,25</sup> a serious limitation to the curative therapy of prostate cancer remains that, in approximately 50% of cases, histopathologic examination of the surgical specimen shows that the cancer presumed to be localized at diagnosis has in fact migrated outside the prostate, thus seriously limiting the success of surgery as well as radiotherapy.<sup>26,27</sup> Thus, despite the improvements of radical prostatectomy, which have led to reduced blood loss, improved urinary continence, and better-preserved sexual potency,<sup>16,28</sup> the risk of incomplete removal of the cancer in approximately 50% of patients has a significant negative impact on the acceptability of radical prostatectomy or any other curative approach for the treatment of early-stage prostate cancer. In fact, the inaccuracy of staging of prostate cancer at diagnosis that leads to incomplete removal of cancer at surgery in an important proportion of patients is largely responsible for the controversies surrounding treatment and even diagnosis of early-stage prostate cancer.<sup>29-33</sup>

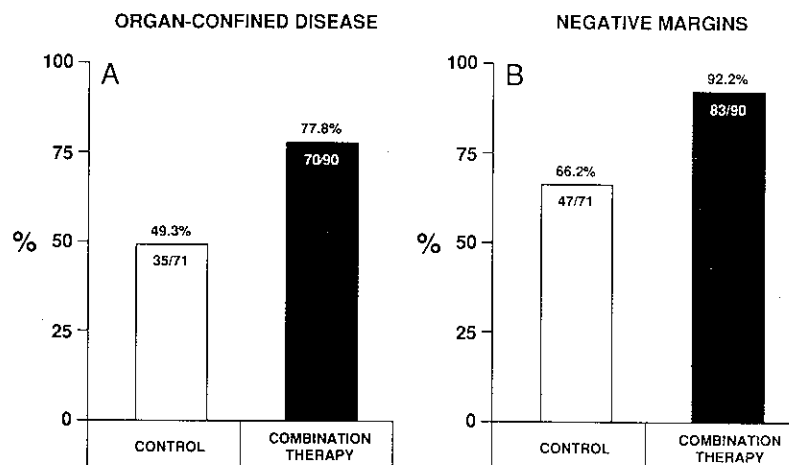
External-beam radiation therapy (EBRT) has also been widely used for curative treatment of early-stage prostate cancer.<sup>34,35</sup> In patients with small tumors, EBRT produces high locoregional control and survival rates, comparable to those achieved by radical prostatectomy.<sup>36</sup> However, the possibility of recurrence increases with the size of the primary tumor.<sup>37,38</sup> Since the introduction of serum PSA as indicator of efficacy during follow-up, the evaluation of the success of both radical prostatectomy and radiation therapy for localized prostate cancer has greatly decreased the earlier optimistic impressions about efficacy.<sup>39,40</sup>

A means of increasing the proportion of patients with organ-confined disease and cancer-negative margins at surgery, thus improving the success of surgery and radiotherapy, was suggested by the clinical observation that patients treated by combined androgen blockade (CAB) using a pure antiandrogen as-

sociated with medical or surgical castration for metastatic disease show a much more rapid and marked regression of their cancer in the prostatic area compared to distant metastatic sites.<sup>4,5,41</sup> Most importantly, it is well recognized that when the disease recurs in a patient with advanced prostate cancer given CAB, progression at the level of the prostate is a rare event, while the bones are the site of progression in at least 95% of cases. Because cancer localized in the prostatic area can be controlled so efficiently by androgen deprivation, it seemed logical to use CAB to downstage prostate cancer in men believed to have localized cancer before radical prostatectomy or radiotherapy and to use adjuvant endocrine therapy to cause further apoptosis or death of the micrometastases not under the control of surgery, radiotherapy, or brachytherapy.<sup>11,42-44</sup>

## RESULTS

A few randomized trials have studied the potential benefits of CAB using flutamide and an LHRH agonist administered for 3 months before radical prostatectomy.<sup>20,42,45-48</sup> The first randomized trial analyzed the rates of organ-confined and specimen-confined disease and compared the final stage at histopathologic examination of the surgical specimen with the clinical stage estimated at diagnosis.<sup>20,42</sup> In that study, neoadjuvant combination therapy before radical prostatectomy decreased cancer-positive surgical margins from 33.8% in the control group to only 7.8%, thus giving 92.2% of patients with negative margins at surgery (Fig. 1B). The most important endpoint, namely organ-confined disease, increased from 49.3% to 77.8% of patients after 3 months of CAB, for a 57.8% increase in the incidence of organ-confined disease (Fig. 1A). No cancer was found in six prostatectomy specimens from the treated group. Almost superimposable results have been obtained by Soloway et al<sup>46</sup> (1995) and Fair et al,<sup>47</sup> while Schulman and Wildschutz,<sup>48</sup> in a population of patients showing more advanced disease, have found comparable results. In fact, Soloway et al<sup>46</sup> reported that among 303 men with clinical Stage T2b prostate cancer, patients treated for 3 months with flutamide



**FIG. 1.** Effect of 3-month neoadjuvant combination therapy with flutamide and an LHRH agonist on organ-confined disease (A) and specimen-confined disease (B) in localized prostate cancer (T1/T2). (Data from reference 42).

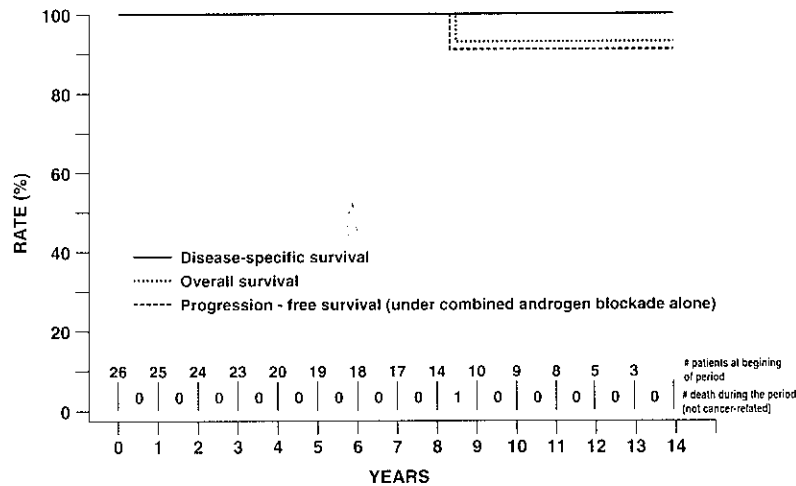


FIG. 2. Disease-specific, overall, and progression-free survival in 26 previously untreated patients with clinically localized prostate cancer who received as single treatment antiandrogen flutamide and LHRH agonist Tryptal for indicated time intervals (median 7.1 years).

and leuprolide showed an increase in the rate of organ-confined disease from 47% in those who had radical prostatectomy alone to 78% in patients who had neoadjuvant or primary CAB for only 3 months. Moreover, the rate of positive margins decreased from 48% to 18% in the same groups. Other studies also showed that combination endocrine therapy decreases the total volume of the prostate and of the cancer.<sup>11,22,45,49-52</sup> Several studies confirmed that neoadjuvant androgen deprivation dramatically reduces the incidence of positive margins.<sup>47,53-55</sup> Retrospectively, however, it is likely that the 3-month duration of neoadjuvant CAB is not sufficient to have a significant long-term impact on the disease. In this context, it is of special interest to review briefly some of our data, which provide pertinent information about the appropriate duration of CAB.

The present report summarizes the results obtained in 26 previously untreated patients with localized prostate cancer<sup>17,25</sup> who did not agree to be randomized in clinical trials including radical prostatectomy<sup>42</sup> or radiation therapy.<sup>44</sup> These patients received CAB alone, namely flutamide (250 mg t.i.d.) and the LHRH agonist [D-Trp<sup>6</sup>, des-Gly-NH<sub>2</sub><sup>10</sup>]LHRH ethylamide (Tryptal) for a median of 7.1 years.

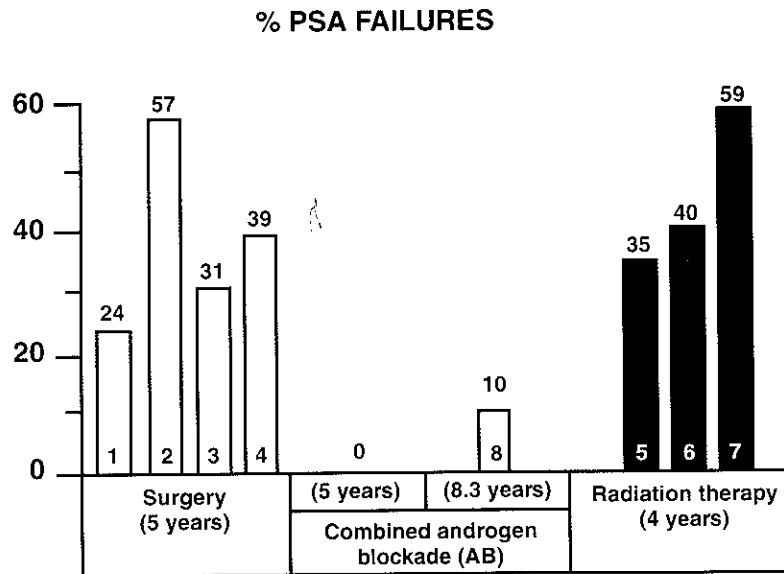
As illustrated in Figure 2, of 26 patients treated for a median of 7.1 years (ranging from 2.8 to 11.8 years), only 1 has shown an elevation of serum PSA, the first event being observed after 8.3 years of treatment. This patient then received radiotherapy to the prostatic area, and his cancer is under control with no clinical sign of recurrence after 2 years. At 8.3 years of CAB (N = 9), the estimated response rate is thus 89% with a 95% confidence interval of 68% to 100%. The side effects of CAB are well tolerated, namely hot flushes, usually confined to a few months at start of therapy, impotence, and loss of libido.<sup>5-7</sup> Unlike estrogens, the combination of flutamide and an LHRH agonist leads to a better lipid profile than orchiectomy.<sup>56</sup>

The present data clearly indicate that androgen deprivation is highly efficient for the treatment of clinically localized prostate cancer, its ability to control the disease in 26 patients as long as 8.3 years possibly being superior to that of radical prostatectomy and radiation therapy alone (Fig. 3). Although a 15-year follow-up is required to assess the long-term effect of

treatment of localized prostate cancer, it is recognized that local recurrence, and especially serum PSA, can be used as an interim measure to evaluate efficacy.<sup>40</sup> Without a randomized study, however, it is not possible to compare one clinical series strictly with another. Despite these limitations, it is of interest to see in Figure 3 that the 5-year actuarial rate of recurrence in a similar category of patients who had radical prostatectomy was 24% at the Johns Hopkins Hospital,<sup>57</sup> while it was 57% at the Boston University Medical Center<sup>58</sup> and 31% in a comparable series at the UCLA Medical Center.<sup>59</sup> In a series of Stage T1-2 prostate cancers at the Cleveland Clinic Foundation, the 5-year recurrence rate was calculated at 39%.<sup>60</sup> Similarly, PSA failure after radiation therapy has identified a high level of cancer recurrence. Thus, after radical irradiation for T1 and T2 disease, the 4-year actuarial rate of recurrence has been reported as 35% at the Boston University Hospital<sup>40</sup> and 59% at Baylor University.<sup>61</sup> The 5-year rate of disease-free survival has been calculated as 40% at the M.D. Anderson Hospital.<sup>63</sup>

Because serum PSA had remained undetectable during treatment for as long as 11.8 years (median 7.1 years) in all other patients, treatment has been stopped in 17 patients, who have now been followed for a median of 2.0 years. As can be seen in Figure 4A, only three patients have shown progression as indicated by rising serum PSA. Including the median post-treatment follow-up of 2.4 years (up to 4.2 years) in the 17 patients who stopped CAB, the median overall follow-up is 8.9 years (range 2.8-14.1 years). One patient died at 8.4 years from a noncancer-related cause.

That long-term treatment with CAB is required is well supported by the data shown in Figure 4B and 4C. It is in fact quite remarkable to see in Figure 4B that of 26 patients with Stage T3 prostate cancer who had undetectable serum PSA for a median of 9.9 years, serum PSA increased in only 4 (15%) during a median follow-up of 1.8 years. Serum PSA has thus far remained undetectable in 25 of them (85%). It is of interest that serum PSA returned to undetectable concentrations in the two patients when combined androgen blockade was reinstated after secondary elevation of serum PSA. Very different results

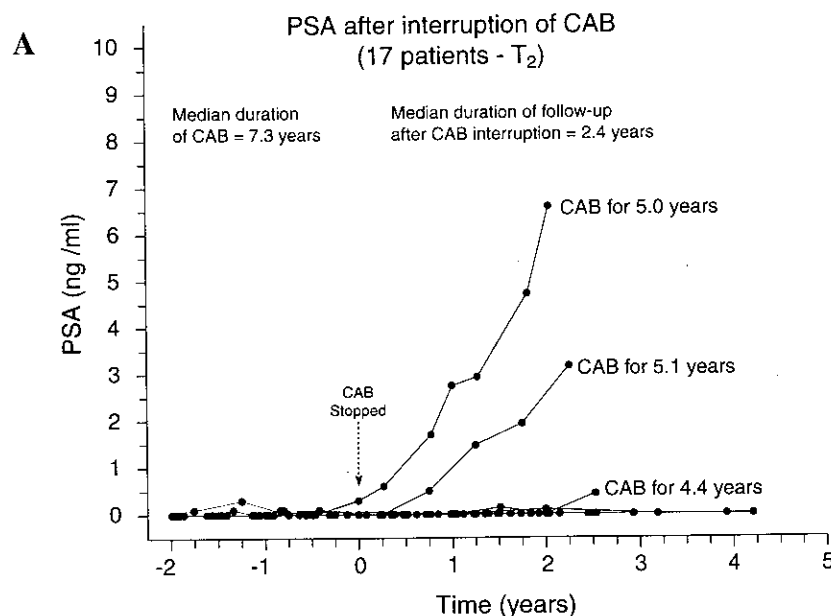


**FIG. 3.** Comparison of PSA failure rate (%) after combined androgen blockade (first failure at 8.3 years in this study v failure rates of 24%, 57%, 31% and 39% at 5 years after radical prostatectomy and 35%, 40%, and 59% 4 years after the start of radiation therapy. 1 = Morton et al, 1991;<sup>57</sup> 2 = Zietman et al, 1994;<sup>58</sup> 3 = Trapasso et al, 1994;<sup>59</sup> 5 = Kupelian et al, 1996;<sup>60</sup> 5 = Zietman et al, 1994;<sup>40</sup> 6 = Kaplan et al, 1993;<sup>62</sup> 7 = Goad et al, 1993;<sup>61</sup> 8 = present study.

can be seen in Figure 4C, where among 11 patients with Stage T2 prostate cancer who received the same CAB for a median of only 1.0 year, serum PSA has risen in all within 1 year of follow-up.

As summarized in Figure 5, the present data show a dramatic

effect of the duration of CAB on the PSA failure rate after cessation of endocrine therapy. In fact, whereas serum PSA did not remain undetectable for 1 year in any of the 11 patients when CAB was stopped, 82% of the same category of patients who had received CAB for a median of 7.3 years continued to



**FIG. 4.** Change in serum PSA after cessation of combined androgen blockade (LHRH agonist + flutamide) (CAB). A. Seventeen patients with Stage T2 disease, who received CAB for median of 7.2 years. Serum PSA increased in only three patients during median follow-up of 2.2 years. B. Twenty-six patients with Stage T3 disease, who received CAB for median 9.9 years. Serum PSA increased in only four patients during median follow-up of 1.8 years. C. Eleven patients with Stage T2 disease, who received CAB for median duration of 1 year. Serum PSA increased within 1 year in all patients.

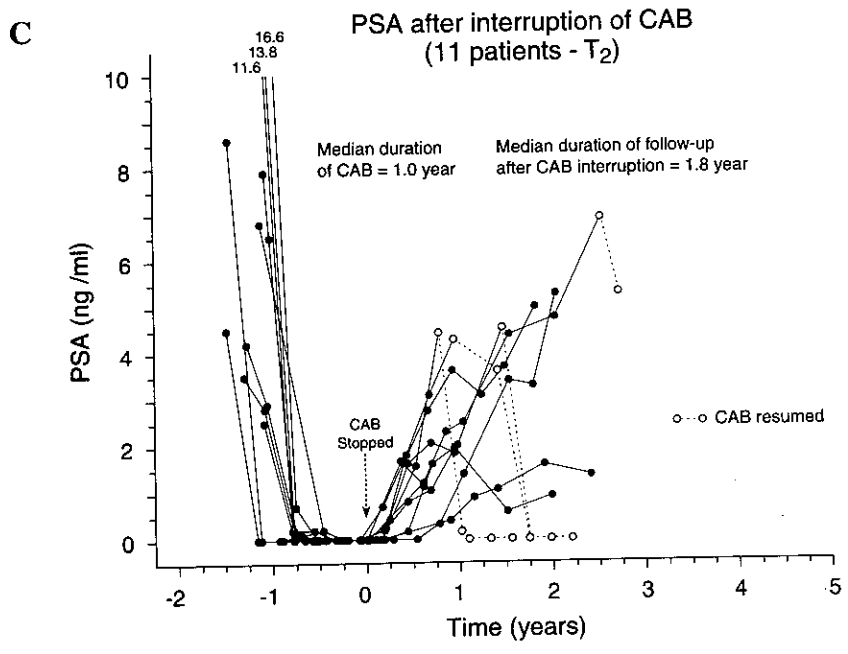
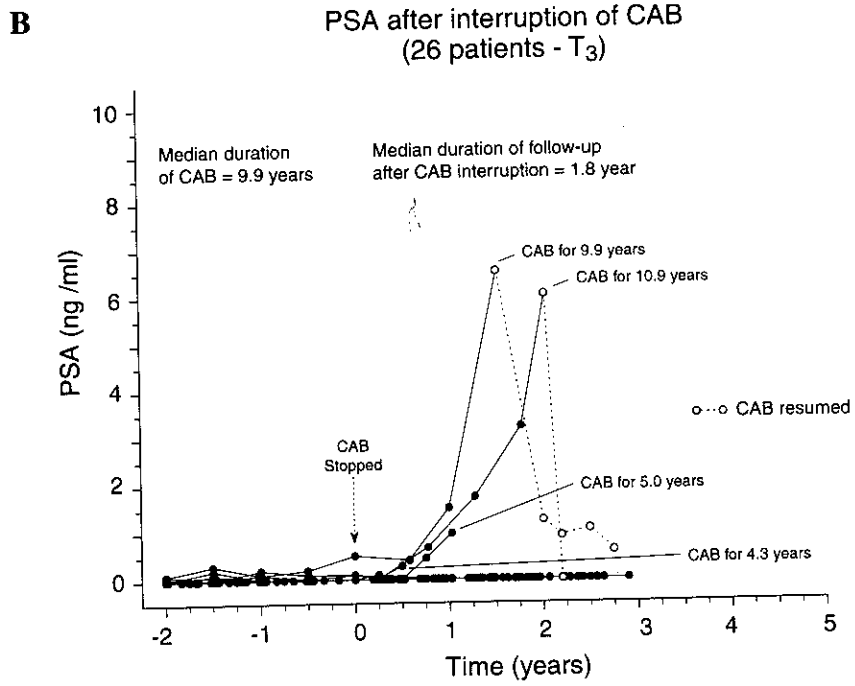
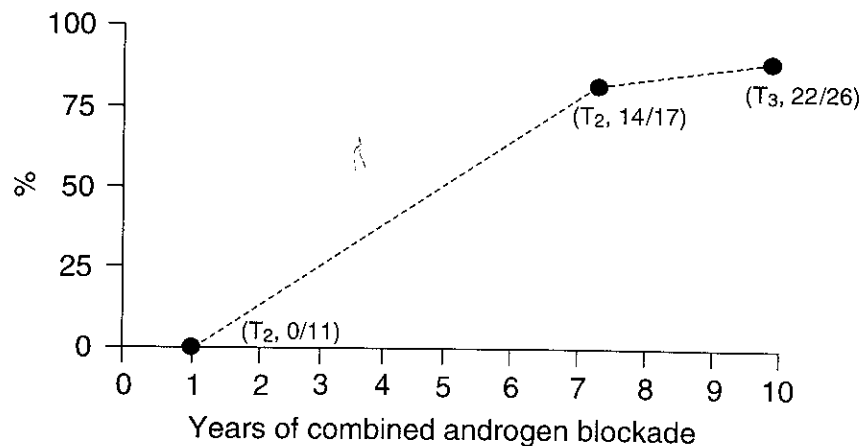


FIG. 4. Continued.



**FIG. 5.** Percentage of patients in whom serum PSA remains undetectable after cessation of treatment for 54 Stage T2 or T3 prostate cancer. Patients received CAB for median of 1 year (0/11 T2), 7.1 years (82.4%; 17 T2), or 9.9 years (84.6%, 26 T3).

have undetectable PSA for a median follow-up of 2.4 years. Moreover, 85% of patients with Stage T3 cancer treated for a median of 9.9 years had undetectable PSA during a 1.8-year follow-up. Although the maintenance of serum PSA at undetectable concentrations after cessation of CAB cannot be considered equivalent to cure or complete apoptosis of the tumors, it certainly indicates a significant impact on the viability of the cancer.

A duration of treatment much longer than 3 months is also supported by our recent data obtained on serum PSA and positive biopsies performed 12 and 24 months after radiation therapy associated with neoadjuvant and adjuvant combination therapy for a total of 3 or 10.5 months, respectively. Much better results, although not yet reaching 100% negative biopsies, were obtained with 10.5 months compared with 3 months of combination therapy as judged by both the rate of positive biopsies and normal PSA.<sup>44</sup>

As a main control endpoint, TRUS-guided needle biopsies were performed 12 and 24 months (when there was sufficient follow-up) after the end of radiotherapy for the three groups of patients. Ninety-two and sixty-eight patients had control biopsies at 12 and 24 months, respectively. The biopsy findings, shown in Table I, were reported as no cancer, suspicious, and

presence of cancer. Whereas 62% of the control patients disclosed residual cancer, only 30% and 4% showed residual neoplasm in Groups 2 and 3, respectively, at 12 months. When looking at 24 months, 65%, 28%, and 5% of patients showed residual cancer. The differences between the three groups are statistically highly significant at both 12 and 24 months.

## DISCUSSION

Prostate cancer is now diagnosed at a clinically localized stage in the majority of patients. Because no randomized study has compared the potential benefits of radical prostatectomy and radiation therapy or any other form of therapy,<sup>3</sup> the development and choice of therapy for localized disease becomes a priority. As mentioned above, the problem with both surgery and radiation therapy alone is the relatively high rate of failure attributable to extension of the cancer outside the prostate before diagnosis can be made.<sup>26,27,64</sup>

The potential complications of radical prostatectomy, namely urinary incontinence, urethral stricture, impotence, and morbidity associated with anesthesia and a major surgical proce-

TABLE I. NUMBER (%) OF POSITIVE BIOPSY RESULTS AT 12 AND 24 MONTHS AFTER EBRT

	Group 1		Group 2		Group 3	
	12	24	12	24	12	24
Absence of cancer	10 (29)	5 (22)	17 (52)	18 (72)	22 (88)	18 (90)
Suspicious	3 (9)	3 (13)	6 (18)	0 ( )	2 (8)	1 (5)
Presence of cancer	21 (62)	15 (65)	10 (30)	7 (28)	1 (4)	1 (5)

Chi-square statistics:

12 months:  $P < 0.001$ ; group 1 v 2  $P = 0.033$ ; group 1 v 3  $P < 0.001$ ; group 2 v 3  $P < 0.006$ .

24 months:  $P < 0.001$ ; group 1 v 2  $P = 0.001$ ; group 1 v 3  $P < 0.001$ ; group 2 v 3 NS.

Data from reference 44.

ture, as well as the risks of prostatitis, enteritis, cystitis, urethral structure, and impotence associated with radiation therapy, add to the controversy surrounding treatment of localized prostate cancer.<sup>3,33,65,66</sup> The lack of convincing data on the benefits of treatment of localized prostate cancer has led some authors to suggest deferred treatment<sup>33</sup> (for review, see Labrie et al<sup>65</sup>). However, the evidence demonstrates that although prostate cancer grows at various rates in different patients, it grows exponentially and will kill all those who live long enough.<sup>65,67</sup>

By analogy with breast cancer,<sup>68</sup> a major hope appears to reside in the induction of apoptosis of the micrometastases by endocrine therapy.<sup>38,43,44</sup> In fact, short-term neoadjuvant CAB has recently produced encouraging results: three studies where combination therapy with flutamide and an LHRH agonist was administered for only 3 months before surgery increased organ-confined disease from 50% to approximately 75% of patients.<sup>42,46,47</sup> Most importantly, no histopathologic sign of growth of androgen-independent tumor clones has been observed when patients were receiving androgen blockade,<sup>69-71</sup> thus indicating the very low (if any) risk that some androgen-independent cancer clones could grow during CAB. As strong support for these short-term histopathologic data, the present study shows that the first rise in PSA was observed after 8.3 years of treatment of 26 patients with localized prostate cancer. In fact, no sign of proliferation of cancer cells has been seen in any of the studies where androgen blockade has been used before surgery<sup>69,70,72</sup> (DG Bostwick, personal communication). Such data demonstrate that localized prostate cancer does not contain androgen-insensitive clones. In addition to the histopathologic findings mentioned above, the absence of the androgen-sensitive cells is well illustrated by the observation summarized in Figure 2: of 26 patients with Stage T2 prostate cancer who received CAB alone for as long as 12 years, the first and only rise in serum PSA occurred after 8.3 years of treatment.

The present data indicate that it is unlikely that 3 months of androgen blockade will translate into a significant survival advantage, especially with the small number of patients enrolled in all radical prostatectomy studies. The previous choice of 3 months of neoadjuvant therapy<sup>11</sup> was motivated by the possibility of growth of prostate cancer under neoadjuvant combination therapy before proceeding to the removal of the prostate by radical prostatectomy. However, the data that have accumulated convincingly show that localized prostate cancer does not progress for many years while the patient receives combination therapy alone.<sup>69-72</sup>

It is important to mention that the best results are expected with CAB using a pure antiandrogen associated with an LHRH agonist: monotherapy or a lower degree of androgen blockade should achieve a lower degree of apoptosis, with the added risk of development of androgen-insensitive clones. It is also well known that suboptimal androgen blockade induces the development of tumors that are unresponsive to additional androgen blockade or CAB applied later, at the time of progression.<sup>5,73</sup>

In addition to potential survival benefits, CAB alone in older men could prevent, or at least delay for many years, the complications of local recurrence, including urinary obstruction and other signs and symptoms related to enlargement of the tumor in the prostate, thus improving the quality of life. For patients

having a life expectancy longer than 10 years and those unwilling to receive continuous CAB for such a long time, the present data clearly support the long-term (up to 5 years) use of neoadjuvant and adjuvant CAB in association with radical prostatectomy or radiotherapy to control extraprostatic micrometastatic disease and thus improve the success of surgery and radiotherapy.

It is hoped that randomized studies will compare the relative efficacy of CAB associated with surgery and radiation therapy vs CAB alone in order to obtain a final answer about the relative merits of each approach. The recent demonstration of survival benefits in patients who received androgen ablation combined with radiation therapy compared with radiation therapy alone strongly suggests that radiation therapy alone (and most likely surgery alone) is not the optimal therapy, at least in Stage T3 disease and in the majority of patients with localized prostate cancer. The present data strongly suggest, as mentioned earlier,<sup>65</sup> that for men aged 70 years or more, as well as those having a life expectancy of less than 10 years, CAB alone can efficiently control the disease for many years and should prevent death from prostate cancer.

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