Success and Failure of Single-Modality Treatment for Early Prostate Cancer

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Many men who undergo radical prostatectomy or radiotherapy for early prostate cancer have an excellent outcome; however, a significant proportion subsequently experience disease recurrence and/or cancer-related death. Adjuvant hormonal therapy after treatment of curative intent is given with the aim of eradicating undetected cancer cells outside the surgical margins or radiation field and/or micrometastatic disease. In the analogous setting of early breast cancer, adjuvant hormonal therapy is already established as standard care. Efficacy and tolerability data from the ongoing bicalutamide ('Casodex') Early Prostate Cancer program are expected to determine the role of adjuvant hormonal therapy with antiandrogens in early prostate cancer.
[Rev Urol. *2004;6(suppl 2):S13-S19*]

Key words: Adjuvant hormonal therapy • Radical prostatectomy • Radiotherapy

Wider use of prostate-specific antigen (PSA) screening, improved diagnostic techniques, and increased awareness have led to prostate cancer diagnoses at an earlier stage of disease and in younger men than in the past.[1,2] For example, recent data from the United States collected by the National Cancer Data Base indicate that nearly 80% of prostate cancers are localized at diagnosis and that almost 17% of reported cases occur in men aged under 60 years.[3]

'Casodex' and 'Nolvadex' are trademarks of the AstraZeneca group of companies.

Table 1
Actuarial Risk of Progression Following Radical Prostatectomy

Finding at Radical Prostatectomy	Progression-Free* Survival at 10 years (%)
Organ confined	85
Focal capsular penetration	68
Established capsular penetration	58
Negative margins	79
Positive margins	55
Gleason score	
2–4	96
5–6	82
7	52
8–9	35

* Biochemical, local, and/or systemic progression.
Reproduced with permission from Epstein et al.[14]

Traditionally, men with clinically localized prostate cancer and a life expectancy of 10 years or more have been offered potentially curative treatment with either radical prostatectomy or radiotherapy; ongoing improvements in both these techniques have been evident in recent years. New treatment options are also becoming available, including various forms of hormonal therapy, cryotherapy, interstitial seed implantation, and laser therapy. In addition to these potentially curative treatments, "watchful waiting" (often referred to as conservative management) is an option for men with shorter life expectancies and/or comorbid conditions, especially those with low-grade and early-stage tumors.

Many men who undergo radical prostatectomy or radiotherapy for early prostate cancer have an excellent outcome; however, a significant proportion subsequently experience disease recurrence and/or cancer-related death. This article reviews the success and failure of single-modality treatment for early prostate cancer and discusses the potential role of antiandrogens as adjuvant hormonal therapy by drawing parallels with tamoxifen (Nolvadex) in the analogous setting of breast cancer.

Radical Prostatectomy

Radical prostatectomy has become increasingly common in the United States and Europe.[4–7] This is due in part to the increased use of PSA testing and the resulting rise in the number of patients diagnosed with early disease, who are potentially curable with radical strategies. In 1989, 78 patients per 100,000 received radical prostatectomy in the United States as their initial treatment, compared with 146 per 100,000 in 1995.[6] In contrast, more patients diagnosed in the pre-PSA era had advanced, incurable disease and therefore received either immediate or deferred hormonal therapy.

Radical prostatectomy involves the removal of the entire prostate gland, attached seminal vesicles, and some nearby tissue, either by the open retropubic or perineal approach or, more recently, by using laparoscopic techniques. Overall, the outcome following surgery is favorable, with disease-specific survival rates of 90% or more at 10 years.[8–10] For example, Lai and colleagues[10] reported 10-year disease-specific survival rates of between 94% and 98% following radical prostatectomy for 11,429 patients from the nine geographic regions of the U. S. Surveillance, Epidemiology, and End Results (SEER) program. However, a substantial proportion of patients treated with radical prostatectomy subsequently experience local, systemic, and/or biochemical recurrence.[8,11–13] In a series involving 2782 men who underwent radical prostatectomy for clinically localized prostate cancer, the overall biochemical progression-free survival rate at 10 years was 59%.[13]

Outcome after radical prostatectomy tends to reflect prostate cancer stage, and men in whom the disease has spread beyond the prostate capsule at surgery generally have a poorer outcome than those with truly organ-confined disease.[9,12–14] Epstein and colleagues[14] analyzed data for 721 men with clinically localized disease who underwent radical prostatectomy by a single surgeon over an 8-year period. They found that 85% of men with pathologically confirmed, organ-confined disease remained progression-free 10 years after surgery, compared with only 68% of those with focal capsular penetration and 58% of those with established capsular penetration (Table 1).

Many men who undergo radical prostatectomy or radiotherapy for early prostate cancer have an excellent outcome.

Unfortunately, current clinical staging methods are often unreliable,

Table 2
Actuarial Recurrence-Free Rate at 5 and 10 Years after Radical Prostatectomy by Preoperative PSA Level

	Actuarial Recurrence-Free Rate (%)	
Preoperative PSA Level (ng/mL)	5 Years	10 Years
0–4	94	87
4.1–10	82	75
10.1–20	72	30
> 20	54	28

Reproduced with permission from Pound et al.[12]

and when the disease is staged pathologically after surgery, up to 50% of men with clinically staged localized disease are found to have more advanced disease, with positive surgical margins, extracapsular extension, or seminal vesicle invasion.[9,13,14] For example, in Epstein and colleagues,[14] only 42% of men with clinically staged T1 or T2 disease actually had organ-confined disease on pathologic review. Of the remaining men, 24% had focal capsular penetration and 33% had established capsular penetration.

Even when the cancer appears to be confined to the prostate gland, a substantial proportion of patients experience disease recurrence after surgery. For example, Amling and colleagues[13] reported that nearly one quarter (22%) of 1904 men with pathologically staged T2 disease had biochemical failure, local recurrence, or distant metastases within 10 years of radical prostatectomy.

Gleason score is also an independent predictor of disease progression following radical prostatectomy.[12,14,15] In the study by Epstein and colleagues,[14] the percentage of men remaining progression-free 10 years after surgery was only 35% for those with a Gleason score of 8 to 9 compared with 82% for men with a score of 5 to 6 (Table 1). Preoperative PSA level is also predictive of disease-free survival following radical prostatectomy.[15] Pound and colleagues[12] reported that patients with a preoperative PSA level of 0–4 ng/mL had an 87% likelihood of disease-free survival at 10 years, compared with 30% or less for patients with a preoperative PSA level of 10 ng/mL or above (Table 2).

Radiotherapy

Radiotherapy, either by external beam or brachytherapy, is an alternative radical approach widely used for the treatment of prostate cancer. Candidates for radiotherapy tend to be patients with locally advanced disease, a life expectancy of 10 years or more, and for whom surgery is not suitable or desired. As with radical prostatectomy, there has been an increase in the number of patients diagnosed with prostate cancer in the United States who have received radiotherapy as their initial treatment: 30% in 1993 compared with only 6% in 1973.[7]

Radiotherapy appears to provide a similar outcome in terms of disease-specific survival when compared with surgery.[16–19] For example, using data from the SEER program, Lu-Yao and Yao[16] reported a 10-year disease-specific survival rate of 74% for nearly 17,000 men with clinically localized prostate cancer who had received radiotherapy as initial treatment; this compares with a value of 89% for over 21,000 men who had received radical prostatectomy.

As with radical prostatectomy, outcome after radiotherapy is dependent on the disease stage at diagnosis. In a review of several studies, Roach[20] found that approximately two thirds of patients with localized prostate cancer (clinical stage T1–T2) were disease-free 5 years after radiotherapy, compared with only one third of patients with locally advanced disease (clinical stage T3–T4). A meta-analysis of four Radiation Therapy Oncology Group trials has identified four distinct prognostic groups based on clinical stage and Gleason score for patients treated with radiotherapy (Table 3).[21] There were differences between the prognostic groups in terms of both overall and disease-specific survival at 5, 10, and 15 years. For example, the risk of dying from prostate cancer 10 years after radiotherapy was 14% for patients with clinical stage T1–T2, NX disease and a Gleason score of 2–6, but 66% for those with clinical stage T3, NX or N+ disease, and a Gleason score of 8–10 (Table 3).

Other studies have shown that the outcome of radiotherapy is also dependent on PSA level at diagnosis. In a retrospective analysis of 1765 men with localized (clinical stage T1b/c–T2) prostate cancer treated with radiotherapy at 6 medical centers in the United States, the overall 5-year estimate of freedom from biochemical failure was 66%.[18] However, the 5-year estimates ranged from 81% for patients with a PSA level of below 9.2 ng/mL at diagnosis to 29% for patients with a PSA level of 19.7 ng/mL or more and a Gleason score of 7–10 (Figure 1).

Improving the Outcome of Early Prostate Cancer

The results of several studies[22,23] indicate that men who undergo single-

Table 3
Overall and Disease-Specific Survival by Risk Group in Men with Early Prostate Cancer Treated with Radiotherapy

	Overall Survival (%)			Disease-Free Survival (%)		
Risk Group*	5 Years	10 Years	15 Years	5 Years	10 Years	15 Years
1	85	59	39	96	86	72
2	82	50	24	94	75	61
3	68	32	16	83	62	39
4	52	19	12	64	34	27

*Risk group 1: Gleason score 2–6, T1–T2, NX
Risk group 2: Gleason score 2–6, T3, NX
Gleason score 2–6, N+
Gleason score 7, T1–T2, NX
Risk group 3: Gleason score 7, T3, NX
Gleason score 7, N+
Gleason score 8–10, T1–T2, NX
Risk group 4: Gleason score 8–10, T3, NX
Gleason score 8–10, N+
Data from Roach et al.[21]

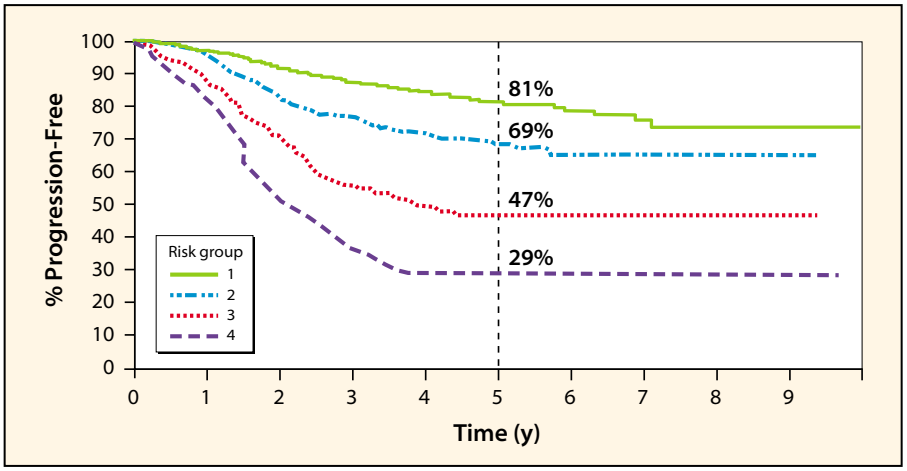
modality treatment for early prostate cancer have a favorable outcome in terms of disease-specific survival. However, a significant proportion of men subsequently face disease progression and/or death from prostate cancer following radical prostatectomy or radiotherapy. Indeed, approximately 17%–35% of patients with early-stage prostate cancer require secondary treatment within 5 years of initial therapy.[22,23] In view of the limitations of current treatments for early prostate cancer—particularly for patients with locally advanced disease, those with a Gleason score of 8–10, and those with a high pretreatment PSA level—there would appear to be a need for new treatment options.

Adjuvant Hormonal Therapy

The unfavorable outcome for some men after radical therapy is thought to be due to the growth of undetected cancer cells outside the surgical margins or radiation field, or to the presence of micrometastatic disease. A number of new treatment approaches are being developed to improve the outcome for patients with early prostate cancer, including improved surgical techniques to reduce the incidence of positive surgical margins and conformal radiotherapy, which enables higher doses of radiation to be delivered. Another potential treatment option is adjuvant hormonal therapy, which is aimed at controlling undetected cancer cells as well as targeting any cancer cells in tissue that remains outside the surgical margins or radiation field.

Prostate cancer is androgen-dependent, and when systemic therapy is indicated, androgen deprivation therapy is considered first-line treatment. Androgen deprivation has generally been achieved by surgical castration (bilateral orchiectomy), medical castration using a luteinizing hormone-releasing hormone analog, or medical or surgical castration in combination with an antiandrogen (known as maximum androgen blockade). The benefits of castration as adjuvant hormonal therapy in early prostate cancer have been demonstrated in both the radiotherapy[24–27] and surgical[28,29] settings. However, surgical and medical castration are both associated with loss of libido, impotence, fatigue, and hot flashes. Furthermore, as men may potentially receive adjuvant hormonal therapy for many years, the long-term complications of castration, such as osteoporosis and anemia, are also of concern. With the recent trend toward earlier diagnosis, many men face treatment choices when they are still physically and sexually active, and

Figure 1. *Estimated rate of biochemical failure by risk group in men with early prostate cancer treated by radiotherapy. Risk group 1: PSA < 9.2 ng/mL; risk group 2: PSA 9.2–19.6 ng/mL; risk group 3: PSA ≥ 19.7 ng/mL and Gleason score 2–6; risk group 4: PSA ≥ 19.7 ng/mL and Gleason score 7–10. Reproduced with permission from Shipley et al.[18]*



so the effect of treatment on quality of life is an important issue. The availability of a well-tolerated hormonal agent that could be offered as adjuvant to therapy of curative intent would be a useful development.

Antiandrogens block the effects of androgens and offer a therapeutic alternative to medical or surgical castration. Moreover, nonsteroidal antiandrogens, such as bicalutamide (Casodex,® AstraZeneca LP, Wilmington, DE) do not suppress testosterone production and so may provide quality-of-life advantages over castration.

The Breast Cancer Experience

The use of adjuvant hormonal therapy after surgery or radiotherapy is already established as standard care in the treatment of early breast cancer. Like prostate cancer, breast cancer is hormone-responsive, though not all tumors express detectable levels of estrogen receptors. Antiestrogens such as tamoxifen bind to the estrogen receptor, thereby blocking the effects of estrogens. Tamoxifen was first approved for the treatment of advanced breast cancer in the United States in 1978 and has since become the treatment of choice for advanced disease.

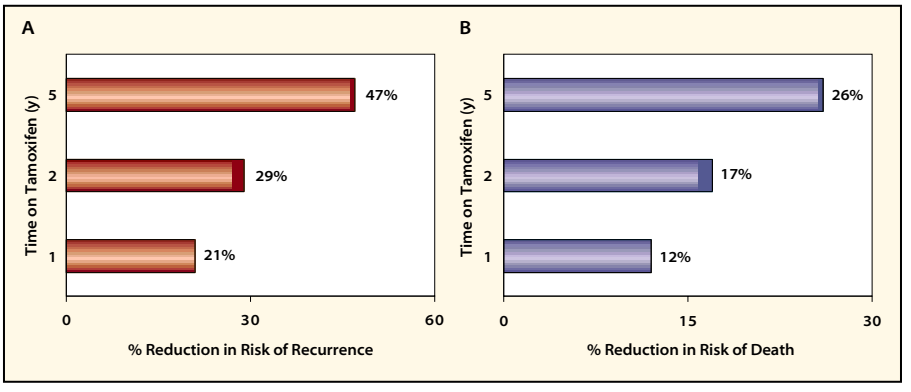
In 1980, the National Institutes of Health Consensus-Development Panel stated that there was insufficient evidence to support the use of adjuvant hormonal therapy in early breast cancer.[30] As a result, a number of studies were initiated to determine the effectiveness of tamoxifen in this setting. One study, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial, compared tamoxifen with placebo in women with node-negative, estrogen-receptor–positive, invasive breast cancer.[31] The first results of the NSABP B-14 trial were reported in 1989 and showed a significant increase in disease-free survival in the tamoxifen group compared with the placebo group (83% vs 77%; $P < .00001$). Tamoxifen treatment was also associated with a significant reduction in the risk of developing tumors in the contralateral breast and in the incidence of tumor recurrence after lumpectomy and breast irradiation. Based on these results, the U.S. Food and Drug Administration approved the use of adjuvant tamoxifen to prevent recurrence of early breast cancer even in the absence of mature survival data.

Many large trials of tamoxifen as adjuvant to standard care in early-stage breast cancer have since been conducted. The Early Breast Cancer Trialists' Collaborative Group has undertaken meta-analyses of randomized trials that explored adjuvant tamoxifen in this setting. The most recent meta-analysis, published in 1998, is based on the results of 55 randomized trials involving nearly 37,000 women.[32] In this analysis, conducted after a median follow-up of 10 years, adjuvant tamoxifen was associated with a significant delay in disease recurrence and an improvement in survival in women with estrogen-receptor–positive tumors or in whom estrogen receptor status was unknown. In these women there was a 47% reduction in the risk of recurrence and a 26% reduction in the risk of death following adjuvant tamoxifen treatment for 5 years (Figure 2). These benefits were apparent irrespective of other prognostic factors such as age, menopausal status, and nodal status. There was also a small benefit in women with confirmed estrogen-receptor–negative tumors; however, further research is needed before adjuvant tamoxifen use can be advocated in these women. Tamoxifen treatment was also associated with an approximately 50% reduction in the risk of contralateral breast cancer, irrespective of estrogen receptor status.

In the Early Breast Cancer Trialists' Collaborative Group meta-analysis,[32] the magnitude of benefit in terms of disease recurrence and overall survival in women with unknown estrogen receptor status or estrogen-receptor–positive status tumors was related to the duration of adjuvant tamoxifen therapy (Figure 2). For example, the risk of death in these women was reduced by 12%, 17%, and 26% following 1, 2, and 5 years of tamoxifen treatment, respectively.

Results from the NSABP B-14 study indicate no advantage for continuation of tamoxifen treatment beyond 5 years in women with node-

Figure 2. *Duration of adjuvant tamoxifen therapy and reduction in risk of* (A) *disease recurrence and* (B) *death in women with early breast cancer (estrogen-receptor–positive tumors and tumors of unknown estrogen receptor status). Significant trend for greater effect with longer duration of therapy observed, for both disease recurrence* ($P < .00001$) *and death* ($P = .003$). *Data from Early Breast Cancer Trialists' Collaborative Group.*[32]



negative, estrogen-receptor–positive breast cancer.[33] In contrast, the optimum duration of tamoxifen treatment in node-positive women remains a controversial issue.

The Bicalutamide Early Prostate Cancer (EPC) Program

The experience with adjuvant tamoxifen therapy in early breast cancer provides a rationale for examining adjuvant antiandrogen therapy in early prostate cancer. The bicalutamide EPC program is an international trial program initiated to explore the benefits of bicalutamide (150 mg) once daily as adjuvant therapy to standard care of radical prostatectomy, radiotherapy, or "watchful waiting" in patients with early prostate cancer.[34] The program comprises three ongoing, randomized, double-blind, placebo-controlled clinical trials and involves over 8000 men; the primary endpoints are time to objective progression and overall survival. Approximately 55% of the patients in the program received radical prostatectomy as primary therapy, whereas about 18% received radiotherapy.[34] It is hoped that the results of this trial program, the largest to date in prostate cancer treatment, will determine the role of adjuvant therapy with antiandrogens in early prostate cancer.

Conclusions

Single-modality treatment with radical prostatectomy or radiotherapy does not always achieve a cure in patients with early prostate cancer, and a significant proportion of men may benefit from further therapy. Adjuvant hormonal therapy given immediately after treatment of curative intent with the aim of eradicating undetected cancer cells outside the surgical margins or radiation field and/or micrometastatic disease is accepted as standard care in early breast cancer. Evidence from both the radiotherapy and surgical settings supports the use of adjuvant hormonal therapy in early prostate cancer. The ongoing results of the bicalutamide EPC program are expected to provide valuable information on the role of antiandrogens as adjuvant to treatment of curative intent in early nonmetastatic prostate cancer. ■

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Main Points

- Men in whom prostate cancer has spread beyond the prostate capsule at surgery generally have a poorer outcome than those with truly organ-confined disease.
- Radiotherapy appears to provide a favorable outcome in terms of disease-specific survival when compared with surgery; outcome after radiotherapy is dependent on the disease stage at diagnosis.
- Approximately 17%–35% of patients with early-stage prostate cancer require secondary treatment within 5 years of initial therapy, perhaps because of growth of undetected cancer cells outside the surgical margins or radiation field, or the presence of micrometastatic disease.
- Prostate cancer is androgen-dependent; androgen deprivation has generally been achieved by surgical castration (bilateral orchiectomy), medical castration using a luteinizing hormone-releasing hormone analog, or medical or surgical castration in combination with an antiandrogen (known as maximum androgen blockade).
- The benefits of castration as adjuvant hormonal therapy in early prostate cancer have been demonstrated, but surgical and medical castration are both associated with loss of libido, impotence, fatigue, and hot flashes, as well as long-term complications such as osteoporosis and anemia.
- Nonsteroidal antiandrogens such as bicalutamide do not suppress testosterone production and so may provide quality-of-life advantages over castration.
- The experience with adjuvant tamoxifen therapy in early breast cancer provides a rationale for examining adjuvant antiandrogen therapy in early prostate cancer.
- The bicalutamide Early Prostate Cancer program is expected to provide valuable information on the role of antiandrogens as adjuvant to treatment of curative intent in early prostate cancer.

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