Prostate Cancer Clinical Trials of the Southwest Oncology Group

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The changing clinical dynamics of prostate cancer have resulted in a broadening of the research focus of the Genitourinary (GU) Cancer Committee of the Southwest Oncology Group (SWOG). Beginning with an emphasis on hormone-refractory disease in its early years, SWOG prostate cancer trials now cover the entire spectrum of the disease: localized, locally advanced, metastatic and hormone-refractory disease. As the world's largest GU cancer research group, the GU committee of SWOG has pioneered studies in combined androgen therapy for metastatic disease, quality-of-life (QOL) assessments for patients with localized and advanced disease, adjuvant therapy models, and prostate cancer chemoprevention. The committee has also formed the GU Global Group, whose purpose is to convene the chairs of the GU committees of all the major national and international oncology cooperative groups. Meeting semiannually, this group discusses activities within their respective organizations, plans collaborative strategies and protocols, and establishes global strategy in prostate cancer clinical research. The future directions of national and international prostate cancer trials will build on this broad foundation of well-conceived, logically sequenced studies. [ONCOLOGY 11(8):1155-1170, 1997]

Introduction

The Genitourinary (GU) Cancer Committee of the Southwest Oncology Group (SWOG) emerged in 1978 from a combined Gynecologic-Urologic Cancer Committee. Several phase II trials in hormone-refractory prostate cancer had been completed, but growing interest in prostate cancer led to the establishment of a separate and independent GU cancer committee. Hormone-refractory prostate cancer remained the primary focus of the newly formed committee in its early years, but in the mid-1980s the committee's focus broadened to encompass the evaluation of other therapeutic strategies for newly diagnosed metastatic disease.

The intergroup trial of leuprolide (Lupron) with or without flutamide (Eulexin) INT 0036 proved to be a landmark study of the efficacy of combined androgen blockade (CAB) for metastatic prostate cancer.[1] Recent SWOG trials for patients with metastatic prostate cancer have been designed in the shadow of this trial.[2] Controversy remains as to the universal, irrefutable benefit of CAB.[3,4] Nevertheless, this therapeutic approach provides the frame of reference from which clinical trials for metastatic prostate cancer are designed.[5-7]

Newly Diagnosed Metastatic Prostate Cancer

Bilateral Orchiectomy With or Without Flutamide in Stage D2 Disease

Following the initial study of total androgen deprivation, SWOG investigators deemed crucial the study of CAB in surgically castrated patients. SWOG-8894/INT 0105, which compared bilateral orchiectomy with or without flutamide in patients with histologically confirmed stage D2 prostate cancer, was designed to have adequate power to detect survival differences according to disease extent (minimal vs severe). It also evaluated various other potential prognostic factors, including PSA, site of disease, testosterone level, and comorbid conditions. This randomized, placebo-controlled trial was activated in 1989 and closed in September 1994, after an accrual of 1,387 patients. The objectives were: (1) to compare overall and progression-free survival in patients with histologically confirmed stage D2 adenocarcinoma of the prostate who were treated with either bilateral orchiectomy plus flutamide (250 mg tid) or bilateral orchiectomy plus placebo (2 capsules tid); and (2) to compare qualitative and quantitative toxicities associated with the addition of flutamide following bilateral orchiectomy. Like the INT 0036 protocol, SWOG 8894/INT 0105 stratified patients according to Eastern Oncology Group (ECOG) performance status of 0-2 vs 3 and extent of disease. Minimal disease was defined as pelvic plus axial skeleton and/or soft-tissue nodal metastases, and extensive disease was defined as appendicular (with or without axial)
skeleton and/or soft-tissue visceral involvement. Good-risk patients had performance status of 0-2 and minimal disease (Table 1).

The results of the trial in 1,371 eligible patients are shown in Table 2. The trial failed to demonstrate that the addition of flutamide to bilateral orchiectomy is associated with any therapeutic benefit, despite differences in prostate-specific antigen (PSA) response. Toxicity was modest. No treatment-related deaths occurred. The overall incidence of severe (grades 3-4) toxicity was low. The only significant differences between flutamide and placebo groups related to the incidences of diarrhea (3.3% vs 0.8%; \( P = .007 \)), elevation of aspartate transaminase/alanine transaminase (1.2% vs 0.8%; \( P = .027 \)), and anemia (3.0% vs 1.5%; \( P = .046 \)).

**Need for Novel Therapeutic Approaches**

Fifty years have elapsed since the landmark discoveries of Huggins et al of the effect of castration on advanced prostate carcinoma.[8-10] Despite improvements in the treatment of metastatic prostate cancer during that half-century, there have been remarkably few significant advances showing an impact on survival.

Prognostic differences among patients with metastatic prostatic carcinoma and their differing treatment responses have led researchers to conceptualize and design therapeutic protocols accordingly. Thus, patients with a superior clinical response to androgen ablation have been targeted with trials that seek to enhance such a response. Patients either unlikely to have such a response or who initially show an unsatisfactory response may be targeted for more aggressive chemohormonal approaches. These observations, together with growing scientific data on the potential mechanisms of progression to androgen independence, guided the design of the next series of SWOG trials for untreated patients with stage D2 disease.

**Interruption Androgen Deprivation (Good-Risk Patients)**

No existing therapy for metastatic prostatic carcinoma prevents progression to a hormone-refractory condition. Progression to such an androgen-independent state appears to be linked to the loss of apoptotic potential in stem cells. This results in the survival and cloning of androgen-insensitive cells. Research has investigated methods by which the regeneration of apoptotic potential could be continued or restored.[11] Intermittent androgen deprivation (IAD) seems to induce multiple apoptotic regressions of prostatic tumors, resulting in a threefold prolongation in the duration of androgen dependence.[11] However, the cyclic effects of such treatment on prostate cancer can be followed efficiently only by sequentially measuring serum PSA levels. Only patients whose PSA values have initially fallen to nadir levels following the institution of hormonal ablation therapy—an indication of androgen dependence—are appropriate candidates for IAD.

In 1995, SWOG activated a trial to test this therapeutic approach (SWOG 9346). Patients who achieve a PSA nadir within the normal range (0 to 4.0 ng/mL) after an induction period are randomized to either continuous or intermittent androgen therapy. In addition to the prospect of lengthening response by IAD, quality of life (QOL) and cost-effectiveness may also be positively influenced. The trial will use survival and QOL as primary end point measures. The utility of IAD may be greatest in the long-term management of patients with a PSA-only relapse after local therapy or as a primary treatment for selected patients with less than advanced disease.

**Suramin and CAB (Poor-Risk Patients)**

Despite the poor response of metastatic prostatic carcinoma to chemotherapeutic agents, a greater understanding of apoptosis and the establishment of hormone resistance have led to renewed enthusiasm for chemohormonal therapy.[12] The identification of potentially more active chemotherapeutic agents and combinations provides an attractive opportunity for evaluating chemohormonal therapy. A phase II SWOG pilot study of Suramin plus CAB (SWOG 9343) has recently completed accrual. This trial was implemented as preparation for a phase III randomized intergroup study of CAB with or without Suramin to be coordinated by ECOG.

Suramin is a polysulfonated naphtylurea that has been used for many years for the treatment of parasitic diseases. The drug has shown activity in hormone-refractory prostate cancer.[12] While not completely elucidated, Suramin's mechanism of action appears to involve inhibition of growth factor binding. Toxicity is manageable if serum levels are maintained between narrowly defined limits. SWOG 9343 will study the efficacy of attempting to eradicate stem cells by means of chemotherapy in conjunction with CAB in newly diagnosed stage D2 patients. Interesting observations have been reported in this regard by the National Prostatic Cancer Project.[13]
From 1978 through the present, a total of 13 phase II clinical trials have been completed in hormone-refractory prostate cancer (stage D3). These studies evaluated promising new therapeutic agents, combination therapy, and biologics. Unfortunately, none of the agents studied had sufficient activity to warrant testing in phase III clinical trials.[14] A recent reexamination of the methods of developing phase II and III studies for hormone-refractory disease discusses the persistent conundrums of making progress in end-stage prostate cancer.[15]

The conventional approach to treating "hormone-refractory" prostate cancer has been palliative. This judgement has been influenced by the fact that these patients tend to be older and have comorbid conditions and, most importantly, that no effective systemic therapy has been found. From a clinical trials perspective, progress in treating this disease has been hindered by the paucity of active agents and the difficulty in assessing response in patients with end-stage disease.

**Objectives of SWOG Trials**[16] SWOG clinical trials in hormone-refractory disease have had two major objectives. The short-term objective is to identify active agents/combinations that can be of immediate benefit in terms of palliation while potentially improving survival. The long-term objective is based on the recognition that a significant impact on survival is more likely to occur if active agents are used in earlier stages of the disease.

The current SWOG focus is the evaluation of non-hormonal agents, whether cytotoxic or non-cytotoxic, in patients with minimal prior hormonal therapy and no prior chemotherapy exposure. Since biochemical progression (ie, a rising PSA) presages objective progression by about 6 months in stage D2 patients treated with first-line androgen deprivation, it provides an early opportunity to recruit these patients into trials of novel agents aimed at retarding progression.[16]

Response definition in this disease is evolving. Current PSA response criteria remain arbitrary and have not been prospectively defined and validated. The SWOG approach to this issue has been to avoid the use of declining PSA as a primary response end point until validation of this criterion is established. While conservative, this approach is justified by the lack of controlled validated data characterizing the true clinical significance of a "PSA response" and the reported effects of certain agents, such as Suramin, on PSA expression in the absence of a significant antitumor effect.[5,14-15]

**Second-Line Antiandrogen Therapy**[17] A recently completed SWOG trial (SWOG 9235) tested the efficacy of second-line antiandrogen therapy with bicalutamide (Casodex) in patients with advanced prostatic carcinoma who relapsed or progressed after conventional hormonal manipulation (ie, bilateral orchiectomy, a luteinizing hormone-releasing hormone (LHRH) agonist, or diethylstilbestrol [DES]) and who had not previously received therapy with flutamide or another antiandrogen. The trial assessed the tolerance and toxicity of bicalutamide through a combination of physician and patient reporting. A total of 54 patients were registered. Enrolled patients were classified according to: (1) disease type—measurable (16%) vs evaluable (84%) disease only; (2) prior hormone therapy—bilateral orchiectomy (51%) vs an LHRH analog or DES (22%) or both (27%); (3) performance status—ECOG 0-1 (94%) vs 2 (6%); and (4) metastases—bone (69%) vs soft tissue (12%) vs both (18%). The regimen was found to be ineffective.[17]

**Estramustine Plus Etoposide**[18] A recently completed study of estramustine (Emcyt) plus etoposide (Vepesid)[19] SWOG 9407 was designed to validate previous encouraging observations regarding the activity of oral etoposide (50 mg/m²/d) in combination with estramustine (15 mg/kg/d) for 21 days in a 28-day cycle. In a preclinical model, these drugs were found to be synergistic in inhibiting DNA synthesis at the level of the nuclear matrix.[18] In the initial clinical report, an overall 36% response rate was observed, with 9 out of 18 patients with measurable soft-tissue disease experiencing complete or partial responses. The SWOG 9407 study has completed its accrual of 54 patients and is awaiting analysis.

**Flutamide Withdrawal**[20, 21] Several studies have reported that withdrawal of flutamide results in a significant decline in PSA, as well as symptomatic relief.[19-22] In two of the studies,[20, 21] flutamide was stopped when patients who had initially responded to CAB (an LHRH agonist or bilateral orchiectomy and flutamide) began to show disease progression. Sartor et al.[22] have hypothesized that prolonged exposure to flutamide results in the selective proliferation of cancer cells containing a mutant androgen receptor that aberrantly recognizes flutamide metabolites and non-androgenic steroids as androgenic stimuli. An ongoing phase II prospective study (SWOG 9426) was designed to characterize the biologic significance of this phenomenon. Eligible patients are those who received flutamide as their initial hormonal therapy but who showed objective or biochemical (rising PSA) evidence of progression.

**Promising New Agents**[23] A new phase II study (SWOG 9510) activated in late 1996 is evaluating topotecan (Hycamtin) in hormone-refractory prostate cancer. Topotecan is a semisynthetic analog of...
camptothecin and a specific reversible inhibitor of topoisomerase I.[23] Topoisomerases cause transient protein-bridged DNA strand breaks that relieve torsional strain ahead of replication forks during DNA replication. Topoisomerase I is responsible for single-strand breaks, permitting the intact strand to pass through the break and then rejoin the nicked strand.[24] Therefore, treatment with topoisomerase I inhibitors prevents repair of single-strand breaks.

In the only published phase II trial to date, topotecan, given as a 30-minute infusion daily for 5 days in a 21-day cycle, was found to have modest activity against prostate cancer.[25] However, considering the mechanism of action of this drug and the slow growth rate of prostate cancer, prolonged exposure to this agent may be more likely to demonstrate activity. A 21-day infusional schedule of 0.5 mg/m²/d of topotecan is being tested.

Another trial, SWOG 9452, is an intergroup collaborative effort with the Cancer and Leukemia Group B (CALGB) to study Suramin dosing levels for hormone-refractory prostate cancer.[13] Patients will be randomized to receive Suramin at one of the following dose levels: 3,000, 5,000, or 7,000 mg/m².

**Locally Advanced Prostate Cancer**

In the mid- to late 1980s, when the seminal study of leuprolide and flutamide was conducted, the incidence of metastatic prostate cancer was considerable; men presenting clinically with this stage of the disease represented 25% to 30% of all men diagnosed with prostate cancer.[26] Ten years later, however, the clinical dynamics of the disease have changed considerably. Today, the majority of cases diagnosed are localized or locally advanced prostate cancer.

In 1996, locally advanced prostate cancer (T3) will likely be the most commonly diagnosed form of the disease. In 1995, an estimated 244,000 men were diagnosed with prostate cancer, and in 1996, that estimate increased to 317,000.[27,28] Over half of these cases will likely be T3 disease despite the fact that in prostate cancer screening and early detection programs, only 10% to 15% of diagnosed cases are clinical stage T3 (cT3).[29]

An estimated 100,000 radical prostatectomies were performed with curative intent in 1995. However, reviews of large prostatectomy series indicate that 20% to 50% of patients who undergo prostatectomy for clinically localized disease are pathologically upstaged to T3 (pT3).[30-31] In addition, upon careful review, as many as 37% of T1c tumors clinically staged by elevated PSA only are shown to have extracapsular extension.[32-34] Some 100,000 men undergoing radiation therapy are likely to have similar, if not higher rates of extracapsular disease. Previously, more cT3 tumors than pT3 tumors were reported, because of the upstaging to N1-3 and M1 disease. Now, many more pT3 than cT3 tumors are being reported. Cumulatively, T3 disease (cT3 and pT3) probably accounts for over 150,000 cases annually.

The major emphasis of SWOG in T3, N0, M0 prostate cancer has been the implementation of a series of innovative strategies designed to build on the knowledge gained in preceding studies. A phase II trial of pelvic irradiation plus a prolonged venous infusion of 5-FU (SWOG-9024) was recently completed. The objective of the study was to evaluate the likelihood of complete response of T3-4, N0, M0 prostate cancer to this combined therapy. Patients had to have histologic documentation of adenocarcinoma with clinical evidence of extension to seminal vesicles or invasion of prostatic capsule without nodal involvement or distant metastases. No prior radiation therapy, hormonal therapy, or chemotherapy was allowed.

A total of 50 patients were accrued, and 28 have been evaluated for toxicity. Of the 6 patients with a maximum toxicity grade of 3 to 4, none required the discontinuation of treatment due to toxicity. This pilot study is currently undergoing evaluation.

**Neoadjuvant Hormonal Therapy**

For nearly 3 decades, neoadjuvant hormonal therapy has been given in an effort to shrink the volume and lower the stage of locally advanced prostate cancer. Pathologic downstaging remains an elusive dream. Whether positive tumor margins are eradicated by such therapy remains controversial, but results from large randomized trials are hard to ignore.

In one nonrandomized study of 34 patients with clinical stage T2c or T3 prostate cancer who underwent androgen deprivation therapy before radical prostatectomy at the University of Colorado, PSA levels dropped by 98% and tumor volume was reduced by 50%, but all patients (except one with disputed initial biopsy findings) had pathologic T3 disease.[35] In a Canadian randomized trial, Labrie et al[36] reported that, among cT2-3 patients, neoadjuvant combination therapy (an LHRH agonist plus an antiandrogen) significantly decreased positive margins to 7.8% in the treatment arm, as compared with 33.8% in the nontreatment arm. A multi-institutional randomized trial in the United States reported that T2 patients who received preoperative androgen deprivation had a significantly
lower rate of capsule penetration than those who did not receive this therapy (47% vs 78%; \( P < .001 \)),
as well as lower rates of positive surgical margins (18% vs 48%; \( P < .001 \)) and tumor at the urethral
margin (6% vs 17%; \( P < .01 \)).\[37\]
Moreover, the Radiation Therapy Oncology Group (RTOG) recently reported on a study (RTOG 86-10)
in which patients with stage T3 prostate cancer were randomized to receive either (1) neoadjuvant
therapy with goserelin (Zoladex, 3.6 mg q4wk) and flutamide (250 mg tid) for 3 months, followed by
radiation therapy (≥ 6,500 cGy); or (2) radical radiotherapy alone.\[38\] A 3-year interim analysis of
255 eligible patients showed a significantly higher rate of digitally evaluated local control in the
group receiving neoadjuvant therapy than in the group receiving radiotherapy alone (84% vs 71%; \( P
= .003 \)). The patients treated with androgen ablation prior to radiotherapy also showed significant
improvements in disease-free survival. Rates of disease-free survival, without taking PSA into
account, were 61% and 43%, respectively, in the neoadjuvant-therapy and radiotherapy-alone
groups (\( P = .0014 \)). When taking PSA into account (and accepting a value of more than 4.0 ng/mL as
being evidence of disease progression), disease-free survival rates in the two groups were 46% and
26%, respectively (\( P = .0001 \)).\[38\]

**SWOG Studies**

To initiate a comprehensive strategy in T3 disease, SWOG recently completed a
phase II trial of neoadjuvant hormonal therapy (goserelin and flutamide) in bulky and nonbulky
clinical stage C prostate cancer (SWOG 9109). The objectives of the study were to evaluate: (1) the
resectability rate following 16 weeks of neoadjuvant hormonal therapy; (2) the likelihood of clinical
response to this hormonal regimen; and (3) time to progression. Patients were classified by
extraprostatic disease (verified by imaging only), existence of bulky disease, method used to rule out
nodal involvement, and stage (T3 or T4). Sixty patients were accrued, and toxicities have been
consistent with prior experience with these hormonal modalities.

Through the GU Global Group (see discussion below), SWOG will also be participating in a
neoadjuvant study of the National Cancer Institute of Canada (INT 194-0110) to assess the relative
contributions of radiotherapy vs hormonal therapy in stage T3-4 prostate cancer. Patients will be
randomized to receive either hormonal therapy or hormonal therapy plus radiotherapy.

**Adjuvant Therapy Following Radical Prostatectomy**

Adjuvant radiotherapy and/or various methods of androgen deprivation are available for patients
thought to have organ-confined disease but who, on pathologic examination of excised specimens,
are found to have positive surgical margins, seminal vesicle involvement, or confirmed
organ-positive, surgical margin-negative disease. A Mayo Clinic study found that the 5-year local
recurrence-free survival rate was more than 95% among prostatectomy patients who received either
adjuvant radiation or orchietomy, as compared with 84% for patients who received no adjuvant
therapy.\[39\]

**Adjuvant Radiotherapy vs Observation**

A major accomplishment of SWOG in T3 prostate cancer
has been to achieve complete patient accrual to a phase III randomized trial of adjuvant
radiotherapy vs observation following radical prostatectomy (SWOG-8794/INT 0086). The objectives
of the study are to compare disease-free survival in completely resected patients with pathologic T3,
N0, M0 prostate cancer treated with adjuvant radiotherapy to those who receive no adjuvant therapy
and to assess radiotherapy-related toxicities in patients randomized to the adjuvant therapy arm.
Patients are stratified according to the extent of tumor and whether preprostatectomy hormonal
therapy was given.

Despite initial concerns that this study would not remain relevant several years after its inception,
the growing numbers of patients with localized prostate cancer initially managed with surgery and
the continuing 30% to 50% rate of positive margins, capsular involvement, or seminal vesicle
invasion appear to validate the original design. The results of this study should significantly influence
treatment decisions in the future. The effect of other surrogate markers, such as local control and
PSA recurrence, on survival end points will also be of clinical importance.

This trial also features a companion study of QOL, an area in which SWOG investigators have made
important contributions.\[40-43\] The companion study will compare three primary and three
secondary aspects of QOL according to treatment assignment. Primary assessments will include
treatment-specific symptoms, physical functioning, and emotional functioning, while secondary
assessments will consist of general symptoms, global perception of QOL, and social functioning.

**Biologic Studies**

Two SWOG trials that involve radiation therapy (SWOG 9024 and 8794) also feature a companion
biologic protocol (SWOG 9428) to evaluate DNA ploidy and the cancer-suppressor gene p53. This
biology study will evaluate the clinical utility of DNA ploidy data gained from prostate biopsy by
comparing it to prostatectomy specimens from the adjuvant radiotherapy trial and by evaluating the
predictive value of ploidy with regard to outcome in both studies. The GU Committee established an Applied Basic Science Subcommittee specifically to develop such studies. The goals were to take advantage of the availability of tissue from participating centers, maximize the productivity of clinical trials, and tighten the link between basic and clinical research.[44]

Localized Prostate Cancer

Several years ago when the debate raged over the superioriety of surgery vs radiation therapy for localized prostate cancer, a SWOG randomized trial of prostatectomy vs external-beam radiotherapy was halted because of difficulties in recruiting patients. Since that time, three distinctive priorities for localized disease have emerged: neoadjuvant hormonal therapy, chemoprevention, and surgery vs observation.

Neoadjuvant Hormonal Therapy

Following the above-mentioned report[37] of successful outcomes with neoadjuvant hormonal therapy in stage T2 prostate cancer, SWOG activated a large phase III randomized trial (SWOG 9615) to determine whether neoadjuvant hormonal therapy prior to radical prostatectomy had an impact on long-term end points in localized (stages T1 and T2) disease. Secondary objectives of the trial include comparisons of distant metastasis-free survival, disease-free survival, PSA failure-free survival, and pathologic extraprostatic disease. Although neoadjuvant therapy for localized disease had been addressed previously in several small trials, none of these trials had sufficient power to assess survival end points, relying instead on such surrogate end points as local or PSA recurrence.[45-47]

The accrual goal of SWOG 9615 is 1,740 eligible patients. An elaborate, well-conceived specimen procurement and analysis component of the trial should add important scientific data about this therapeutic option.

Chemoprevention

Two major national policy priorities in prostate cancer have been implemented following the dramatic rise in prostate cancer incidence seen in the 1990s. SWOG took the lead in the design and implementation of the Prostate Cancer Prevention Trial (PCPT), which has met its target randomization of 18,000 in just 3 years. This double-blind, placebo-controlled trial will test whether finasteride (Proscar) reduces the prevalence of histologically proven prostate cancer in healthy men.[48,49] After 7 years on the study drug or placebo, all participants will undergo biopsy. A serum and tissue repository will add important information about the natural history of the disease.

Surgery vs Observation

A substantial federal effort has been undertaken to investigate whether maximal intervention for the treatment of prostate cancer (radical prostatectomy) significantly reduces all-cause mortality compared with palliative therapy. The Prostate Intervention Versus Observation Trial (PIVOT) is centered in the Veterans Affairs medical system and has become a priority of the National Cancer Institute (NCI).[50] A number of SWOG institutions are participating in PIVOT, and several GU Committee investigators have provided senior leadership for the study. This trial randomizes men to either surgery or watchful waiting/expectant management, with palliative therapy initiated only if symptoms appear. The study will enroll 2,000 men over a 3-year period, following them for an additional 12 years.

The importance of this trial cannot be overstated, and despite the natural recruitment difficulties in today's environment, it is crucial that PIVOT be completed. Not only will major issues be addressed, but also critical economic analyses will contribute important findings.[51]

Future Directions

Advanced Metastatic Disease

Treatments that have had a minimal impact in men with objectively defined chemohormonally "resistant" tumors may yield different results if administered earlier. Therefore, in addition to continued evaluation of promising agents in phase II trials, phase III studies should focus on establishing the clinical utility of early intervention compared with observation (control) in patients with PSA-only progression. In this regard, trials of second-line hormonal manipulations, as well as novel chemohormonal agents to retard progression, are under consideration. Phase III studies are also being considered for patients with objective evidence of progression to determine the impact of chemotherapy on the natural history of this disease and on patients' QOL. Research focusing on the biology of hormone-refractory prostate cancer is critical for the
development of new therapeutics. Thus, elucidating the mechanisms of tumor progression to androgen independence and the mechanisms of chemoresistance would be of particular relevance to hormone-refractory prostate cancer.[52-54]

**Localized and Locally Advanced Prostate Cancer**

With the recent approval of a labeled antibody scan (Prostascint), the possibility of preoperatively identifying patients with extraprostatic disease may become a reality. At present, a follow-up protocol to the trial of adjuvant radiotherapy vs observation after prostatectomy (SWOG 8794) is being considered. This follow-up study would assess how these newer staging methods may affect treatment.

Many investigators have proposed that adjuvant therapy for localized disease should be an important research priority. Others believe that such an initiative may dilute and/or compromise the perceived benefits of PIVOT. At the present time, it is difficult to predict the future of this controversy.

**The GU Global Group**

The GU Global Group was formed by the SWOG GU Committee chair in 1992 and is comprised of the chairs of the GU Committees of all the major national and international cooperative groups with ex officio NCI representation. The global group meets twice a year in conjunction with the SWOG group meeting. The GU Global Group discusses activities within their respective committees, plans for collaborative interactions, and establishes global strategy in GU cancer clinical research. A major challenge in international trials, which is currently being addressed, is implementing uniform data monitoring standards.

Various important issues are being targeted by the GU Global Group for possible clinical study:

- An area of international interest, collaboration, and planning is the issue of a rising PSA after failed local therapy. The GU Global Group has preliminary designs to study this issue.
- Another critical issue is early vs delayed (hormonal) therapy. Such a study would be very difficult to do in the United States and Canada because of patient fixation on PSA values. The European Organization for Research and Treatment of Cancer (EORTC) will conduct an important clinical trial comparing early vs delayed hormonal therapy for a rising PSA.
- The RTOG, SWOG, and ECOG will examine radiation, with or without hormonal therapy, for a rising PSA after radical prostatectomy.
- The NCI-Canada will evaluate intermittent hormonal therapy for a rising PSA after failed radiation therapy.
- An industry-sponsored randomized clinical trial will address adjuvant hormonal therapy in patients at high risk of failing radical prostatectomy. SWOG, ECOG, and NCI-Canada are completing a protocol of adjuvant radiation vs observation for pT3 disease following radical prostatectomy.

**Conclusions**

The relentless course of metastatic prostatic carcinoma compels a more timely integration of "translational research" into clinical trials for the disease. As this article indicates, gains made in the laboratory are being considered more quickly for implementation as phase I and II trials, so that efficacious phase III studies can follow without undue delay.

The efficacy of CAB may be significantly enhanced as scientific knowledge moves more quickly into the multicenter clinical trials network. The hope of the SWOG GU committee is that while prevention and alternative responses to the early detection of clinically localized prostate cancer are being studied, valuable therapeutic advances can be made for the majority of men with prostate cancer diagnosed and treated in the United States and abroad.

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