Radical prostatectomy is the most commonly used treatment option in the United States for men with clinically localized prostate cancer. Up to 30% of these patients, particularly those with adverse pathological risk factors, will develop a biochemical recurrence within 10 years. Patients with a biochemical recurrence have a higher rate of local recurrence and cancer-specific mortality. Current accepted treatment options include salvage radiation therapy, hormone therapy, or a combination of both, depending on whether the disease recurrence is biochemical, local, or systemic. The role of adjuvant radiation therapy (ART) after prostatectomy in patients with adverse pathological risk factors prior to biochemical or clinical recurrence is unclear. Recent randomized trials have demonstrated that ART significantly improves multiple patient outcomes, including overall and cancer-specific survival, without major untoward effects. The evidence in support of using ART is evolving with the long-term follow-up of several long-term prospective trials. The decision to use ART should be based on the patient’s pathological characteristics, clinical status, side effects, and open communication between the patient and provider.

Introduction
For more than 20 years, radical prostatectomy has been the optimal approach to treat clinically localized prostate cancer (stage T1-T2) [1,2]. Despite well-accepted cancer control rates, a certain subset of patients will have unfavorable characteristics on pathology. These factors include seminal vesicle involvement, positive surgical margins, Gleason scores of 8 to 10, and extraprostatic disease. Patients with these findings are at a higher risk for developing biochemical recurrence; 20% to 40% will develop a rising prostate-specific antigen (PSA) postoperatively [3,4]. Of these patients, approximately 50% will have done so by 3 years, and 99% will have recurred by 10 years. In a study by Pound et al. [5] on patients with biochemical recurrence after prostatectomy (n = 304), median actuarial time to metastases was 8 years, and only 34% (103 of 304) of those patients went on to develop clinically apparent metastases. Cancer-specific mortality occurred in 43% (44 of 103), and the median time to death after the diagnosis of metastatic disease was slightly less than 5 years. This illustrates two conflicting points: 1) about one third of patients with biochemical recurrence will develop metastases and of those patients, about 15% will die due to prostate cancer—a possibly preventable outcome, and 2) a considerable percentage of patients with biochemical recurrence either will not clinically recur, or if they do, will not die from the disease. Thus, it becomes necessary to identify which patients would benefit from adjuvant radiation therapy (ART) after radical prostatectomy versus those who are overtreated.

Specific guidelines have been reported in order to establish what constitutes biochemical recurrence. In 2007, the American Urological Association Prostate Guidelines Update Panel published a review of the various definitions of biochemical recurrence. The panel recommended that biochemical recurrence after prostatectomy be defined as an initial (postoperative) serum PSA of ≥ 0.2 ng/mL, with a second confirmatory PSA level of greater than 0.2 ng/mL [6]. On the other hand, clinical recurrence is generally thought to mean the presence of objective disease (eg, biopsy-proven or palpable disease or new or growing lesions seen on imaging studies [visceral or osseous lesions]). Of course, in the case of adjuvant radiation, one treats a patient based on risk factors prior to the detection of a biochemical recurrence.

Risk Factors for Cancer Progression
The factors that most closely predict which postprostatectomy patients will develop clinical metastases and
cancer-specific mortality are not definitive, although there appears to be a general consensus among reportable findings. It should be noted that although the end outcomes are similar, patients will most commonly develop biochemical recurrence (elevated postprostatectomy PSA values) prior to developing local or systemic clinical recurrence. Commonly reported pathological predictive factors for biochemical recurrence are extraprostatic extension, seminal vesicle invasion, lymph node involvement, high Gleason score, and positive surgical margins [3,4,7–11]. The accuracy of positive surgical margins as a predictor for cancer progression has been questioned in the past [7–17]. However, recent studies seem to support its predictive value for cancer recurrence. In 2003, a study by Karakiewicz et al. [18] involving 5831 patients concluded that positive margins in prostatectomy specimens were associated with a 3.7-fold increased risk of cancer progression. Regarding risk factors for clinical recurrence, numerous studies have shown that PSA doubling time (PSADT) and prostatectomy Gleason score are reliable predictors for timing to metastatic progression and cancer-specific mortality following biochemical recurrence [5,19–22]. Typically, a PSADT of less than 6 to 12 months or a prostatectomy Gleason score of 8 or higher predicts higher rates of recurrence and mortality. The type and strength of association of these risk factors may have some variability in their predictability of cancer recurrence. However, many urologists would agree that these are the factors to include when discussing risks of prostate cancer recurrence.

Current Treatment

Currently, there is no single optimal treatment for patients with biochemical recurrence after prostatectomy. Current options include salvage radiation therapy, salvage hormone therapy, or a combination of both. It is important to establish the difference between adjuvant and salvage treatment, which is the timing. In adjuvant therapy, patients are treated postoperatively once adverse risk factors are identified but before biochemical or clinical disease recurrence. On the other hand, salvage therapy begins after the physician discovers a biochemical recurrence, palpable, biopsy-proven, or radiological evidence of disease. Outcomes after salvage therapy vary with patient characteristics, timing of therapy, and type of therapy. A 2008 study comparing salvage radiotherapy, salvage radiotherapy plus hormone therapy, and observation for patients with recurrent disease after prostatectomy reported a significant increase in prostate cancer-specific survival following salvage radiotherapy if started within 2 years of biochemical recurrence when compared with no salvage therapy [23]. The addition of hormone therapy did not improve cancer-specific survival. Trying to identify which factors could predict response to salvage radiation, Stephenson et al. [24] in 2004 reported improved prostate cancer progression-free probability based on Gleason score, preradiotherapy PSA level, surgical margins, PSADT, and seminal vesicle invasion. In this series the overall salvage rate of patients treated with radiotherapy for a biochemical recurrence was 45%. One important feature of salvage radiation for a biochemical recurrence appears to be at what level of PSA the radiation is administered to give the greatest chance of a successful outcome. The initial study suggested that patients with a biochemical recurrence after radical prostatectomy be treated with salvage radiation at or below a PSA level of 2.0 ng/mL [24]. However, a more recent update suggests that patients be treated at a level below 0.5 ng/mL [25]. Clearly, what studies seem to indicate is that the earlier you treat, the better patients respond.

Adjuvant Radiation Therapy After Prostatectomy

Although ART has been used in the past, solid evidence to support its use and identify its specific indications has been limited until recently. Two randomized clinical trials (RCTs) recently have been published specifically looking at outcomes for ART after prostatectomy [26,27]. Results from these trials argue in favor of ART despite an initial lack of benefit with regard to overall and cancer-specific survival. However, a recent update of the studies revealed that there were significant increases in overall and cancer-specific survival after adjuvant radiotherapy. In addition, to further investigate which patients benefit from ART, authors from a third study used data from one of these trials to report on some of the specific indications and prognostic factors for using ART [28].

The European Organisation for Research and Treatment of Cancer (EORTC) 22911 study published in 2005 randomly assigned 1005 men with positive surgical margins or pT3 prostate cancer to either a “wait-and-see” arm (n = 503) or an ART arm (n = 502) [26]. The median follow-up was 5 years. The radiation dose was 60 Gy given over 5 weeks. The median start time for ART was 90 days from surgery. Radiation was limited to the periprostatic area. Significant findings in favor of the radiation arm included a higher biochemical progression-free survival rate (53% vs 74%; HR, 0.48; P < 0.0001), a longer time to biochemical failure (P < 0.0001), and a higher clinical progression-free survival. In addition, the cumulative incidences of locoregional failure at 5 years were significantly lower in the ART group than in the wait-and-see arm (5.4% vs 15.4%; P < 0.0001). However, there were no differences between these groups regarding overall survival and cancer-specific survival. The conclusion was that longer follow-up was needed to determine any significant difference in these end points. In other words, it was unclear in this study how ART would affect these patients in the long run despite an apparent delay to biochemical and local progression.

A second study published in 2006, the Southwest Oncology Group (SWOG) trial 8794, also has provided