The prostate-specific antigen (PSA) era has changed the pattern of prostate cancer at presentation. Patients now present with lower-stage, lower-risk disease. However, some patients continue to present with high-risk prostate cancer (high-risk PC), and the effect of PSA introduction on outcome is less clear. This review highlights the salient features of why radical prostatectomy should be considered in the management of men with high-risk PC (Gleason score 8–10, marked increase in PSA levels and advanced clinical T stage). Radical retropubic prostatectomy (RRP) can provide durable local control, long-term cancer-specific survival and accurate pathologic staging, and may guide further individualized treatment. For these reasons, RRP remains the best single treatment of high-risk PC in operable patients.

**Key words:** prostatectomy – prostate-specific antigen – prostatic neoplasms

**INTRODUCTION**

Prostate cancer is a worldwide health problem. Although there is no consensus as to what treatment has emerged as optimal for localized prostate cancer, radical prostatectomy has been associated with a lower risk of cancer recurrence and cancer-related death and with improved survival compared with watchful waiting (1). Numerous other studies, albeit non-randomized, have shown that radical prostatectomy provides durable local control and disease-free survival for localized prostate cancer. Radical retropubic prostatectomy (RRP) approached as an anatomical dissection continues to be refined and is the standard for surgical treatment of prostate cancer (2). Historically, RRP has been reserved for low-stage, low-risk prostate cancer, but it can be considered first-line therapy across all risk strata.

A common predictive model used in the management of prostate cancer is the risk-group stratification developed by D’Amico et al. (3). The value of this classification system lies, in part, with its basis on the pre-treatment prostate-specific antigen (PSA) level, biopsy Gleason score (GS) and clinical stage, variables that are readily available to the treating urologist. This risk-group stratification was originally derived to predict patient’s risk of biochemical recurrence (BCR) after RRP, external radiotherapy (RT) or brachytherapy for clinically localized disease (3). Subsequent to the study by D’Amico et al., a study that used the records of Mayo Clinic, including 7911 consecutive men, validated the ability of this risk-group stratification to predict not only BCR but also disease progression and survival after RRP (4). With a slight modification of the risk groups defined by D’Amico et al., high-risk prostate cancer (high-risk PC) was defined as a stage equal to or greater than cT2c (included cT3 which is not part of the D’Amico group), a pre-operative PSA value >20 ng/ml or a biopsy GS 8–10. The purpose of this review is to examine the role of RRP in cohorts of men with one or more of these features and those considered at higher risk.

Because the natural history of PSA recurrence is variable, and usually prolonged, BCR does not always translate into systemic progression and death from prostate cancer (5).
Therefore, predictive models that were designed to assess the risk of BCR must be tested for the ability to determine the risk of clinical progression and cancer-specific mortality; the latter is especially germane to high-risk PC.

In the Mayo Clinic validation study, data showed that in patients with high-risk PC according to the D’Amico risk-group model, the hazard ratio (95% confidence interval) was 3.3 (2.9–3.7) for BCR, 3.5 (2.6–4.6) for local recurrence, 10.7 (6.9–16.7) for systemic progression and 11.5 (5.9–22.3) for death from prostate cancer after RRP compared with patients in the low-risk group (cT1c or T2a disease, pre-operative PSA ≤ 10 ng/ml or biopsy GS ≤ 6). Moreover, although not highlighted by that study, the survival outcomes for the 1513 men who underwent RRP at Mayo Clinic for high-risk PC (as defined by the D’Amico criteria) underscore the importance of surgery in the management of the disease. The median duration of follow-up was 7.7 years, and ~25% of the patients received adjuvant hormonal therapy (AHT) and <10% received adjuvant RT. Also, ~60% had organ-confined disease (pT2) at the time of RRP. The 10-year survival outcomes were as follows: 55% BCR-free, 90% local recurrence-free, 89% systemic progression-free, 95% cancer-specific survival (CSS) and 80% overall survival.

In addition to the validation of the risk-group classification for predicting clinical progression and mortality after RRP, we found that the proportion of patients undergoing RRP for high-risk PC decreased from 34% (between 1987 and 1992) to 14% between 1999 and 2003. Simultaneously, the proportion of patients undergoing surgery for low-risk prostate cancer increased from 22% to 55%. Importantly, the risk-group model has remained predictive of outcome, despite these trends in tumor pathologic features over time.

Furthermore, although the demographics of patients have changed during the PSA era (6), men nevertheless continue to present with high-risk PC, and although they have an increased risk of death from prostate cancer, classification of a patient as having high-risk PC should not preclude surgical treatment. To the contrary, the survival outcomes can be excellent at 10 years, as previously shown and as will be further highlighted in this review. Interestingly, in a review of the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database, a community-based disease registry of men with prostate cancer in the USA, Meng et al. (7) found that patients with high-risk PC were significantly less likely to be treated with RRP and more likely to receive RT or primary treatment with androgen deprivation. Because the outcome of patients with high-risk disease can be good, as outlined above, and has not changed significantly over time, as shown by others (8), continued investigation is needed of multimodal treatment strategies, including androgen deprivation, potentially with chemotherapeutic regimens in a neoadjuvant fashion (9).

RRP can achieve durable local control (90% local recurrence-free survival) and long-term CSS in a subset of patients with high-risk PC. Moreover, primary treatment of high-risk PC with RRP offers the ability to obtain accurate pathologic information, which may assist in the selection of patients for adjuvant therapies who might benefit the most from such treatments (10) and may avoid the application of these potentially harmful (11) therapies to patients not likely to benefit from them. For example, in the study by Meng et al. (7), patients with high-risk PC treated with primary RT were 3.5 times more likely to receive AHT than patients treated with RRP. This difference likely results from the additional information of surgical staging, which allows an improved prognostic assessment of risk of disease progression. For example, 31% of the patients with a biopsy GS of ≥8 have been shown to have a pathologic score of ≤7 at RRP (12,13), and nearly half of the patients treated with RRP for high-risk PC have been found to have organ-confined tumors (8). Similarly, a recent analysis of patients with high-risk PC from the Shared Equal Access Regional Cancer Hospital (SEARCH) database found that although PSA level at surgery was the lone independent predictor of post-operative BCR in a multivariate analysis that included only pre-operative features, when both pre-operative and post-operative variables were included, capsular penetration, a pathologic feature established at RRP, was the sole independent predictor of risk of progression (8).

Surgical staging allows identification of the strongest predictors of CSS, namely the presence of positive lymph nodes, positive surgical margins and pathologic tumor stage, all variables established at RRP. This last point is one of the most persuasive arguments for upfront RRP in the management of high-risk PC. This review addresses survival outcomes with RRP according to the three components of the stratification for high-risk PC developed by D’Amico et al. (3) modified to apply to cT3 disease (but not T2c disease), as in the original definition.

SURGICAL MANAGEMENT OF GS 8–10 IN THE PSA ERA

As known, the widespread use of PSA testing has affected the clinical and demographic characteristics of men with newly diagnosed prostate cancer. Specifically, patients now present at a younger age and with a lower serum PSA level and a higher proportion have organ-confined disease (6). However, men considered to have high-risk PC on the basis of a high GS continue to be seen in practice (8,14). In addition, a GS of 8–10 continues to be consistently identified as an independent risk factor for death from prostate cancer after RRP (5). Moreover, a recent multi-institutional study found that the outcome after RRP for patients with high-risk PC has not changed significantly during the PSA era (8).

Whether the clinical and pathologic outcomes of patients with a GS of 8–10 who have RRP have changed during the PSA era has been investigated (15). In addition, risk factors for disease progression in these cases have been identified to help optimize individualized treatment. Although the results of RRP in patients with a GS of 8–10 have been investigated
also limit the impact of PSA testing on the outcome. Recently, a series believed to be the largest to date reported the impact of a GS of 8–10 on systemic progression and CSS during a median follow-up of 8.3 years in 584 patients treated during the PSA era in a single center (15).

The median pre-operative PSA level decreased from 15 ng/ml in the early PSA era to 10 ng/ml in the late PSA era ($P < 0.001$). Additionally, an increased rate of organ-confined disease during the PSA era (35% of the patients who underwent RRP after 1993, compared with 23% between 1988 and 1993) supports the results from a previous study of patients with a GS of 8–10, in which organ-confined disease at RRP was found in 45% of the patients between 1995 and 1998 and in 19% between 1987 and 1994 (18).

Despite the decreased incidence of locally advanced and metastatic tumors, the adverse tumor pathologic variables of seminal vesicle invasion (pT3b) and lymph node metastases affected CSS. Overall, CSS was ~90% throughout the PSA era. In addition, other investigators have noted that pathologic tumor stage was the most significant predictor of disease recurrence after RRP in patients with a GS of 8–10 (18).

A study of RRP or RT, alone or in combination, for a GS of 8–10 found that a pre-treatment PSA level of $>20$ ng/ml and seminal vesicle invasion (pT3b) predicted BCR, although only seminal vesicle invasion predicted systemic failure (16). Other investigators have similarly reported the effect of the pre-operative PSA level on BCR after RRP (12,19,20), but an increased pre-operative PSA level was found to predict BCR but was not associated with systemic progression or CSS. In addition, surgical technique was found to affect the outcome of patients with a GS of 8–10 because positive surgical margins were also significantly associated with death from prostate cancer. This association had been previously noted in separate studies of patients with a GS of 8–10 (12,19).

Although the associated pathologic features of tumors with a GS of 8–10 were noted to have improved from the early (1988–93) to late (1998–2001) PSA era, the outcome for patients after RRP did not significantly change over time. Indeed, although there was a slight trend toward an improved rate of BCR (37% vs. 45%) ($P = 0.09$), there were no differences in the rates of systemic progression or death from prostate cancer. The lack of effect of PSA testing on survival after surgery may be due in part to the fact that a high GS reflects an inherent biologic aggressiveness of the cancer independent of other pathologic variables. In addition, an inverse relationship between the GS and the PSA content of prostate cancers has been found (21). This relationship may also limit the impact of PSA testing on the outcome. Although unpublished but presented and accepted for publication, Mayo Clinic data have also shown limited performance in the use of PSA doubling time when one limits its use in a GS of 8–10. A recent multi-institutional investigation similarly reported that the outcome of high-risk PC has not changed significantly during the PSA era, a further suggestion of the inability of surgery alone to treat the majority of patients with a GS of 8–10 in the community (8). Although this latter study finding could have many different explanations in this setting, a majority of GS 8–10 prostate cancers probably harbor occult metastasis. This last point highlights the need for protocols to be developed to prospectively evaluate the role of AHT or other systemic therapy as well as post-operative radiation in locally advanced prostate cancer.

The potential value of a multimodal approach in high-grade prostate cancer is suggested from the results of a study by Do et al. (16), who found improved 5-year rates of biochemical and clinical progression-free survival in patients with a GS of 8–10 treated with RRP plus post-operative RT (65% and 80%) compared with RRP (20% and 35%) or RT (30% and 60%) alone. Similarly, the addition of long-term AHT has been shown to improve overall survival and CSS in patients undergoing RT for locally advanced prostate cancer (22).

In a Mayo Clinic study in which ~40% of the patients received AHT (15), the additional therapy may be criticized as a confounder of the impact of RRP alone on high-grade prostate cancer; this practice is not uncommon among urologists today. In fact, Meng et al. (7) reported that a GS of 8–10 was a significant predictor for the receipt of AHT in a multivariate analysis. In the Mayo Clinic experience, AHT decreased the risk of BCR but did not significantly affect systemic progression or CSS (15). However, AHT was administered at the discretion of the treating physician. As such, patients who received AHT had significantly worse clinicopathologic features than those who did not receive AHT, a factor that limits the ability to assess the impact of immediate AHT in high-grade cancers. Nonetheless, if these men had received RT, the treatment strategy most likely would have included AHT for years. When patients have surgical treatment, perhaps AHT can be better individualized.

Comparison of the outcomes for patients with a GS of 8–10 after RRP in one study (15) with outcomes in other published series is made difficult by the varied patient populations, which have had different durations of post-operative follow-up and disparate definitions of failure. Nevertheless, the overall 7-year BCR-free rate of 42% in 584 patients with a GS of 8–10, of whom 122 (21%) had positive lymph nodes, can be compared with that in the study by Mian et al. (18), who noted a 55% 7-year disease-free rate in 188 patients with a GS of 8–10, of whom only 6% had positive nodes. Another investigation that included 54 patients with a pathologic GS of 8–10 who did not receive AHT reported a 41% rate of BCR at a median duration of follow-up of 49 months (12). Rioux-Leclercq et al. (17) reported a 33-month actuarial risk of disease progression of 32% in a study of 27 patients with a GS of 8–10. The Mayo Clinic 7-year overall CSS of 89% for patients with a GS of 8–10, of whom
Radical prostatectomy for high-risk cancer

65–77% from each PSA era (1988–93, 1994–97 and 1998–2001) had pT3 or T4 disease (15), compares favorably with the 69% 10-year CSS reported by Sciarra et al. (19) in 41 patients with a GS of 8–10 (pT3), none of whom received AHT.

As mentioned previously, further studies, ideally in the setting of clinical trials, are needed to better define the role of AHT, potentially used with chemotherapeutic regimens, in men with a GS of 8–10. A future challenge will be to individualize the timing and selection of systemic treatments in patients with high-risk PC by assessing an individual patient’s risk for progression and likelihood of treatment response. For example, a potential predictor of response to AHT is DNA tumor ploidy (23). Patients with non-diploid tumors, and therefore at increased risk of systemic progression and death from prostate cancer, may benefit from additional systemic treatments such as chemotherapy or investigational agents.

Although Mayo Clinic data represent a retrospective, single-center experience in which the treatment after RRP was not standardized (15), the relative infrequency of a GS of 8–10 and the heterogeneity of associated pathologic variables make prospective randomized trials difficult. Therefore, large retrospective series with long-term follow-up remain an important tool for risk stratification and assessment of treatment outcomes.

HIGH SERUM PSA LEVELS

Of the various clinicopathologic features that characterize high-risk PC, the serum PSA level is arguably one of the most robust. Men with a high pre-operative serum PSA (≥50 ng/ml) who have RRP are undoubtedly a high-risk cohort. Although high-risk PC has been studied by several groups, the outcomes of men with a very high PSA level treated with radical prostatectomy are not well known. In fact, in creation of the D’Amico risk groups, the landmark study that defined prostate cancer risk groups on the basis of PSA level, biopsy GS and clinical stage (3), the analysis did not include any men with a pre-therapy PSA value of ≥50 ng/ml. Recently, a study found that roughly 25% of the patients with PSA values of ≥50 ng/ml can be expected to present with a GS of 8–10 (24). Additionally, nearly half of such men will have extraprostatic extension of their cancer and a third will have pelvic lymph node involvement. Patients with a serum PSA level of ≥50 ng/ml might be expected to have poor outcomes after attempted curative treatment as was expected for a GS of 8–10. When a serum PSA level of ≥50 ng/ml is used as the cornerstone of an aggressive multimodal treatment regimen, patients may not do as poorly as initially suspected.

At 10 years, a Mayo Clinic study found that the PSA recurrence-free survival was 40% in men with a serum PSA level of 50–99 ng/ml and 36% in those with a PSA level of ≥100 ng/ml (24). Although a study by D’Amico et al. (25) did not include men with a PSA value >50 ng/ml, the authors found that men with a PSA level >20 ng/ml have a >50% risk of PSA failure at 5 years, a rate that is worse than that in the Mayo Clinic study (24). In the study by Han et al. (26), 120 men with palpable disease (cT2a-cT3a) and a pre-operative PSA value >15 ng/ml had an overall PSA recurrence-free survival rate of 56% at 5 years and of 40% at 10 years. These results are similar to those of the Mayo Clinic study (24), even though the cohort of Han et al. did have lower PSA values.

Prior studies did not address the more clinically meaningful endpoints of metastasis-free survival and CSS. In the Mayo Clinic series (24), patients with a PSA value between 50 and 99 mg/dl experienced a 10-year metastasis-free survival rate of 83% and a CSS rate of 90%. For patients with a PSA level ≥100 ng/ml, the 10-year metastasis-free survival rate was 74% and the CSS rate was 79%. Recent surgical series have found 10-year CSS rates between 72% and 92% for men with high-risk PC. These results further support our assertion that men with high-risk PC, including those with a very high PSA level, stand to benefit from radical prostatectomy (27–29). In fact, when one considers that in 2004, the average life expectancy for a 65-year-old man in the USA was 17 years (30), it becomes apparent that the high-risk patients in the Mayo Clinic series (24) had a surprisingly modest reduction in survival compared with their normal peers. At 15 years of follow-up, the median survival of the cohort (mean age at treatment was 65 years) has still not been achieved, thereby providing clear evidence that with appropriate treatment, many men with high-risk PC can have very prolonged survival. This study provided additional information for counseling a man with a new diagnosis of high-risk PC, whether based on a marked increase in the PSA level or other components.

At times, RRP might not be adequate as monotherapy for patients with high-risk disease. A multimodal treatment approach with RT or AHT or both will be needed to achieve the long-term success rates that we have reported. In the latest Mayo Clinic study of treatment with RRP for high-risk PC in which the PSA level was ≥50 ng/ml (24), early AHT was used in ~60% of the patients and late or salvage AHT in 34%. Men could have received both if the hormonal therapy was discontinued and then reinstituted later. Similarly, but obviously not allowing reintroduction, adjuvant RT was provided to 17% and late or salvage AHT to 21%. Mayo Clinic data show that immediate AHT after RRP can improve survival in patients with locally advanced disease (31). As described above, a randomized trial has also shown a survival advantage to immediate AHT compared with delayed AHT in men with lymph node-positive disease undergoing RRP (10). Also, the International Early Prostate Cancer study found that 150 mg of bicalutamide daily may be beneficial when given after radical prostatectomy to patients with high-risk PC (32). Adjuvant RT is also of benefit in patients with extraprostatic disease and positive...
margins whose risk of local failure is higher (33). In summary, adjuvant RT and early AHT can offer benefit in high-risk PC.

Opponents of surgery in patients with high-risk PC have argued for a lack of benefit if the prostate cancer is not completely excised, that is, if there are micrometastases. This argument does not consider the importance of local pelvic control, despite micrometastatic disease. In the Mayo Clinic experience, RRP provides excellent local control in high-risk PC, as evidenced by a local recurrence rate of only 13% in the current series (24). The same cannot be said of primary RT. Zagars et al. (34) found that RT provided a 10-year metastasis-free survival rate of only 41% and a local recurrence-free survival rate of only 64%. Furthermore, biopsy studies after RT have shown persistent prostate cancer in 14–91% of the patients (35). Coen et al. (36) found an independent association between delayed metastasis and the local persistence of cancer on biopsy and an increasing hazard rate in men treated with RT for prostate cancer. They postulated that a biologically altered prostate cancer after RT resulted in a late wave of metastatic seeding. In favor of this argument, D’Amico et al. (37) showed a significantly lower 10-year prostate cancer-specific mortality rate in men treated with surgery (10%) than in those who received RT (25%). Also, data from a large population study and a randomized trial suggest that RT is inferior to surgery as the primary therapy for high-risk PC (38,39). The authors acknowledge that prior primary RT used less than modern dosages and did not always provide hormonal therapy which is now considered standard. Thus, larger randomized trials are certainly needed to clarify this issue. However, we suspect such trials comparing radiation protocols to radical prostatectomy as upfront treatment for high-risk PC will never be conducted and we will continue to be left with analysis of large datasets to draw conclusions.

As also discussed above, the low number of patients who have metastases develop and die of prostate cancer (24), a testament to the value of an aggressive multimodal approach to treating high-risk PC, also presents limitations for statistical modeling. Specifically, because the number of metastases and deaths are low, the multivariate Cox model may be overfitted for these endpoints, despite having been pre-specified at the design phase of the study. Although the median duration of follow-up is almost 13 years, more patients will probably have development of metastases and die during the next 5–10 years and thus model estimates will change somewhat. We look forward to publishing an update after another 5 years of follow-up.

**ADVANCED CLINICAL T STAGE**

Historically, high-risk PC was defined primarily from digital rectal examination indicating some element of prostate fixation and a sense of extraprostatic extension or from overt metastases on radiography and later bone scintigraphy. However, refined pathologic grading and measurement of the PSA level changed the perception about high-risk PC, as shown in the more recent work described above. At Mayo Clinic, during the PSA era beginning in 1987, with its ensuing stage migration, the percentage of cT3 disease (extraprostatic extension) decreased from 25% in 1987 to 3% in 2003, and non-palpable cT1c disease increased from 2% to 56% (28). Currently, 1–2% of the RRP done yearly at Mayo Clinic are for cT3 disease or higher. This difference reflects stage migration rather than selection by surgeons. Currently, this variable reflects a smaller proportion of Mayo Clinic patients undergoing RRP than those with a GS of 8–10.

In the USA, RRP for cT3 disease is used with greatest frequency for the younger man and its use progressively declines with increasing patient age. RT dominates as definitive therapy in the age groups from 50–54 through 70–74 years, after which active surveillance becomes increasingly dominant because co-morbidity is progressively factored into treatment decisions (40).

With respect to treatment of cT3 disease and high-risk PC in general, the failure of RRP or RT alone (monotherapy) is well recognized, and multimodal therapy may need to be used. We argue that RRP is the most successful as a single method. A multimodal treatment approach was introduced >60 years ago. Neoadjuvant hormonal therapy followed by radical prostatectomy was first reported by Vallett (41). In 1977, Tomlinson et al. (42) addressed the local control issue and found that radical prostatectomy was superior to ‘conservative measures’ for producing improved quality of life and reduced morbidity (urethral and ureteral obstruction), requiring repeated local treatment. In selecting patients, they stressed ‘surgically removable prostate glands’.

Primary prostate cancers have been estimated to contain up to $10^8$ malignant cells per cubic centimeter (43). Thus, RRP for large tumor volumes instantly debulks cancer cells and thereby sets the stage for possibly improved therapeutic efficacy against residual locoregional or micrometastatic disease, whether RT, AHT or other therapy is used. Moreover, as mentioned previously, early RRP or potentially other forms of definitive localized therapy removes the prostate as a future source of metastatic cells and identifies 19–37% of the patients with node-positive disease (28,29), who may then experience improved CSS if given immediate androgen-deprivation therapy (10).

In the Mayo Clinic study of RRP for patients with stage cT3 disease (28) ($n = 842$, median follow-up 10.3 years), the CSS rate was 90% at 10 years and 79% at 15 years, but 78% of the patients received adjuvant AHT or salvage RT. One of the most important findings in that study was that 27% of the patients had overstaging of their disease as T3 in that, on pathologic analysis, they had organ-confined disease (pT2N0M0). This finding indicated that use of surgery as a first-line treatment prevented some of these patients from automatic entry into immediate therapy with long-term androgen ablation (up to 2–3 years in various reports or
protocols) and external-beam radiation or combined high-dose radiation. The average duration of freedom from AHT was 4.0 years in that study.

A considerable period of freedom from androgen deprivation or adjuvant RT is most certainly laudable. AHT is not inconsequential (11,44–46) and can be associated with metabolic syndrome, depression, loss of libido, hot flashes, diabetes, potential cardiovascular morbidity and mortality, osteoporosis and bone fracture. Adjuvant RT is associated with fatigue and variable acute or late skin, rectal, or vesical irritability or toxicity (47). In some carefully selected patients who do not receive androgen deprivation after RRP, a CSS rate of 85% at 10 years has been possible (29), an outcome approaching that with external-beam RT and long-term (2 years) AHT (47). Salvage RT was used in only 10%.

CURRENT TREATMENT GUIDELINES

All stages of adenocarcinoma of the prostate are problematic with respect to treatment options, especially stage T3. For stage T3, the National Comprehensive Cancer Network (21 US institutions with international affiliation, including Japan and China) emphasizes RT (inverting either three-dimensional conformal, intensity-modulated, image-guided external-beam RT or brachytherapy) as first-line, standard-of-care approach (48). The Network’s 2009 recommendations are the following: (i) long-term androgen deprivation (2–3 years) plus RT for high-risk PC (three risk factors: T3a disease, GS of 8–10 or PSA value >20 ng/ml), (ii) short-term androgen deprivation (4–6 months) plus RT for one risk factor, or (iii) radical prostatectomy plus extended bilateral pelvic lymph node dissection in select patients (low-volume cancer, no fixation).

CONCLUSION

RRP provides accurate pathologic staging. More than 25% of the patients with cT3 tumors will have pathologic organ-confined disease (pT2) (4). Approximately half of all patients with high-risk PC according to the D’Amico stratification will have pT2 cancers (28). In addition, a recent report indicates that more than one-third of the patients with a GS of 8–10 on biopsy will have a GS of ≤7 in the RRP specimen (12,13). RRP may also indicate pathologically advanced disease (pT3a or b or node-positive), information that allows better stratification and potential use of adjuvant therapy. Furthermore, RRP, either as a single approach or part of a multimodal regimen, can provide excellent local control that is durable and provides excellent CSS.

Conflict of interest statement

None declared.

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