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# DEOXYRIBONUCLEIC ACID PLOIDY AND SERUM PROSTATE SPECIFIC ANTIGEN PREDICT OUTCOME FOLLOWING SALVAGE PROSTATECTOMY FOR RADIATION REFRACTORY PROSTATE CANCER

CHRISTOPHER L. AMLING, SETH E. LERNER, SANDRA K. MARTIN, JEFFREY M. SLEZAK, MICHAEL L. BLUTE AND HORST ZINCKE*

*From the Department of Urology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota*

ABSTRACT

Purpose: We assessed clinical and pathological variables for the ability to predict improved outcome following salvage prostatectomy for radiation refractory prostate cancer. We identify factors that might assist in selection of candidates for this procedure.

Materials and Methods: Between 1966 and 1996, 108 patients (mean age 64.7 years) underwent salvage radical retropubic prostatectomy for radiation refractory prostate cancer. Preoperative serum prostate specific antigen (PSA), available in 70 patients treated since 1987, was less than 4 in 19, 4 to 10 in 31 and greater than 10 ng./ml. in 20. Serum PSA before radiotherapy was available in 37 patients. Serum PSA before radiotherapy and salvage surgery, tumor grade, deoxyribonucleic acid (DNA) ploidy and margin status were analyzed for the ability to predict cancer specific and progression-free survival (local, systemic and PSA 0.2 ng./ml. or greater). Complication rates were compared between early (before 1990) and late (1990 to 1996) salvage prostatectomy groups.

Results: Overall cancer specific and progression-free survival at 10 years was 70 and 44%, respectively. The pathological stage was pT2N0 in 39%, pT3-4N0 in 42% and pTxN+ in 19% of cases. DNA ploidy was predominately nondiploid, that is diploid in 25%, tetraploid in 64% and aneuploid in 11% of tumors. Although preoperative serum PSA was not predictive of pathological stage, patients with preoperative PSA less than 10 ng./ml. had better progression-free survival than those with higher levels ($p = 0.05$). DNA ploidy was the strongest predictor of cancer specific ($p = 0.002$) and progression-free ($p = 0.002$) survival. Controlling for grade and PSA using the Cox proportional hazards model, DNA ploidy remained a significant predictor of prostate cancer death ($p < 0.001$) and disease progression ($p < 0.001$). Complication rates improved somewhat in more recently treated patients but incontinence and bladder neck contracture rates remained significant.

Conclusions: DNA ploidy and preoperative serum PSA appear to be the most important predictors of outcome following salvage prostatectomy for radiation refractory prostate cancer. Preoperative considerationof these factors may be helpful in selecting candidates for this procedure.

KEY WORDS: prostatic neoplasms, radiotherapy, prostatectomy

Radiation therapy continues to be a commonly used modality for the treatment of clinically localized prostate cancer. Recent statistics from the National Cancer Database and the National Prostate Cancer Detection Project indicate that approximately 25 to 30% of patients with clinically localized cancers are treated initially with radiation therapy.[1] Although many patients respond favorably to this treatment, a significant number have locally recurrent cancer. When increasing serum prostate specific antigen (PSA) is included as a marker of cancer relapse following definitive radiotherapy, biochemical failure rates exceeding 50% at 5 years have been reported in patients with clinically organ confined disease.[2,3] Before the era of widespread PSA use most local recurrences following radiotherapy were identified by a palpable or enlarging prostatic mass, or a positive transrectal needle biopsy. Radiation refractory cancer is now almost always identified by a progressive increase in serum PSA and often in the presence of a relatively unremarkable digital rectal examination. Since it is plausible that serum PSA monitoring after radiotherapy may detect recurrent disease much earlier in its course, many locally recurrent cancers may be found at an earlier stage when they are potentially more responsive to salvage therapies. This theory is supported by a recent study which suggested that decreased serum PSA before salvage prostatectomy was associated with an increased likelihood of organ confined disease.[4]

Although several options exist for the treatment of local recurrence after radiotherapy, each has limitations. While many cases are treated expectantly with deferred therapy at symptomatic progression, most progress rapidly with expectant treatment alone.[5] Androgen deprivation therapy alone may delay symptomatic progression but androgen insensitivity and subsequent disease progression inevitably occur.[6,7] Cryotherapy has been advocated by some for radiation refractory cancer but its safety has been questioned and the long-term benefit to cancer control is unproved.[8,9] Additional radiotherapy is also unlikely to be effective in tumors that have already demonstrated radiation resistance, and it has been associated with substantial additional risks.[10,11] Salvage radical prostatectomy has resulted in long-term disease-free survival of patients with radiation recurrent

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* Requests for reprints: Department of Urology, Mayo Clinic, 200 First St., S.W., Rochester, Minnesota 55905.

cancer[4, 12–21] but it has not gained widespread acceptance due to the technical difficulty, and the potential for significant operative and postoperative complications. In addition, the advanced local extent of many of these cancers makes complete tumor extirpation unlikely in a significant number of cases, which is reflected in the notably higher recurrence rates after salvage prostatectomy than after surgery for previously untreated prostate cancer.[4, 12–14]

Considering the significant morbidity and high recurrence rates associated with salvage surgical therapy, careful patient selection is important. Patients most likely to benefit from salvage prostatectomy are those with long life expectancy, and cancers potentially amenable to complete resection with the least possible morbidity and longest disease-free survival. Unfortunately, these patients are difficult to identify accurately before surgery since the extent of local disease and the biological potential of these cancers are often unpredictable. We investigate the relative importance of preoperative prognostic factors in predicting outcome following salvage prostatectomy with particular attention to serum PSA and deoxyribonucleic acid (DNA) ploidy. We identify better criteria that might assist in the selection of appropriate candidates for this procedure.

## MATERIALS AND METHODS

Between 1966 and 1996, 108 patients 51 to 78 years old (mean age 65) underwent salvage radical retropubic prostatectomy at our institution for local radiation failure. Of the patients 106 had received external beam radiotherapy (3,060 to 11,520 cGy., median 6,450) and 2 had undergone brachytherapy. The interval between radiation treatment and salvage prostatectomy ranged from 6 to 98 months (median 36). Surgical candidates included patients with low co-morbidity and at least a 10-year life expectancy. Histological confirmation of residual or recurrent cancer was established by transrectal needle biopsy in all cases. Patients were considered to have disease limited to the prostate or immediate periprostatic tissue, without extension to the pelvic side wall or involvement of the bladder base or trigone. There was no evidence of distant metastases on preoperative radiographic and radionuclide studies.

Serum PSA before salvage surgery available in 70 patients (65%) treated since 1987 ranged from 0.1 to 105 ng./ml. (median 6.2). In addition, serum PSA before radiation treatment (at cancer diagnosis) available in 37 patients ranged from 4.5 to 80 ng./ml. (median 17.2). Adjuvant androgen deprivation therapy was administered to 48 of 108 patients (44%) and 23 received hormonal therapy before surgery. In patients who received androgen ablation therapy prior to salvage prostatectomy only serum PSA before hormonal treatment was considered when evaluating the prognostic significance of preoperative serum PSA.

The radical prostatectomy specimens were examined by the pathologist immediately after resection using gross inspection as well as multiple frozen sections. Regional pelvic lymph nodes and all surgical margins, including the prostatic base, apex, urethra, bladder neck, periprostatic tissue and seminal vesicles, were examined by frozen section and later by routine paraffin fixed sections. Pathological tumor grade was determined using the Gleason (60 patients) or Mayo (48) grading system. Patients were considered to have high grade cancer if the Gleason grade was 7 or greater, or the Mayo grade was 3 or 4 (scale 1 to 4). Tumor DNA ploidy pattern was determined as previously described.[12]

Patients were followed at least 3 to 4 times during the first 2 years, semiannually for the following 2 to 3 years and subsequently at least once yearly. Early followup evaluation included digital rectal examination, bone scintigraphy and plain radiographs (when indicated) along with determination of enzymatic acid phosphatase. Since 1987 serum PSA testing has been performed and subsequently imaging studies have been used less often. Biochemical progression was considered in any patient with a PSA of greater than 0.2 ng./ml. according to the Hybritech* method.

The morbidity of salvage prostatectomy with regard to surgical complications and need for perioperative transfusions was assessed by comparing patients treated before (48) and after (60) 1990. Statistical analysis was performed for the end points of crude and cause specific survival as well as progression-free survival considering local, systemic and biochemical (PSA) recurrences using the Kaplan-Meier method. The log rank test was used for crude comparisons. The Cox proportional hazards model was used to control for the simultaneous effect of outcome related covariates of DNA ploidy, serum PSA and pathological tumor grade.

## RESULTS

*Stage and PSA.* The distribution of pathological stage, DNA ploidy and preoperative serum PSA is shown in table 1. Overall 39% of patients had organ confined disease (pathological stage T2a to T2c) on final pathological analysis. Cancer was pathological stage T3ab in 13% and T3c to T4 in 30% of patients, and 18% had metastases involving pelvic lymph nodes. Positive surgical resection margins were noted in 39 patients (36%). The pathological stage distribution of cases treated before and after 1990 is shown in table 2. Although there were fewer patients with lymph node positive cancer, in those more recently treated no significant difference in the percentage with organ confined disease was demonstrated. Preoperative serum PSA was less than 4 in 19 of 70 patients (27%), 4.1 to 10 in 31 (44%) and greater than 10 ng./ml. in 20 (29%). The relationship between preoperative serum PSA and pathological stage was not significant (table 3). Figure 1 shows the relationship between pre-radiotherapy PSA and pathological stage at salvage prostatectomy. Although this relationship did not reach statistical significance, increased pre-radiotherapy PSA was associated with an increased incidence of lymph node involvement and decreased likelihood of organ confined disease.

*DNA ploidy.* Tumor DNA ploidy was determined from the salvage prostatectomy specimen in 106 cases of which only 25% were diploid and 75% were nondiploid cancers. Tetraploid cancers accounted for 64% of all cases. The ploidy

* Hybritech, Inc., San Diego, California.

TABLE 1. *Pathological stage, DNA ploidy and preoperative serum PSA in patients undergoing salvage prostatectomy*

| | No. Pts. (%) |
|---|---|
| P stage (108 pts.): | |
| pT2a-c | 42 (39) |
| pT3ab | 14 (13) |
| pT3c | 30 (28) |
| pT4 | 2 (2) |
| pTxN+ | 20 (18) |
| DNA ploidy (103 pts.): | |
| Diploid | 26 (25) |
| Tetraploid | 66 (64) |
| Aneuploid | 11 (11) |
| Ng./ml. PSA (70 pts.): | |
| Less than 4 | 19 (27) |
| 4–10 | 31 (44) |
| Greater than 10 | 20 (29) |

TABLE 2. *Pathological stage in cases treated before and after 1990*

| Pathological Stage | No. 1966–1989 (%) | No. 1990–1996 (%) | Total No. |
|---|---|---|---|
| pT2N0 | 22 (45) | 20 (33) | 42 |
| pT34N0 | 15 (31) | 31 (52) | 46 |
| pTxN+ | 11 (25) | 9 (15) | 20 |
| Totals | 48 | 60 | 108 |

TABLE 3. *Pathological stage according to preoperative serum PSA in 70 patients undergoing salvage prostatectomy since 1987*

| PSA (ng./ml.) | No. pT2 (%) | No. pT3 (%) | No. pTxN+ (%) | Total No. |
|---|---|---|---|---|
| Less than 4 | 8 (42) | 9 (47) | 2 (11) | 19 |
| 4–10 | 9 (29) | 15 (48) | 7 (23) | 31 |
| Greater than 10 | 7 (35) | 10 (50) | 3 (15) | 20 |
| Totals | 24 | 34 | 12 | 70 |

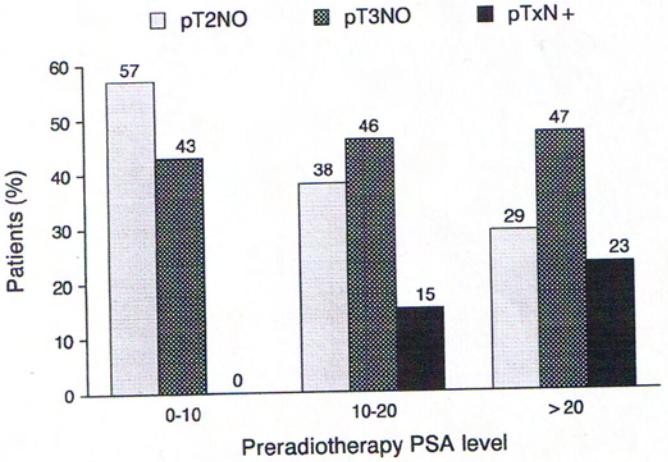


FIG. 1. Pathological stage according to PSA before radiotherapy in 37 patients undergoing salvage prostatectomy since 1987.

distribution of these radiation refractory cancers differed significantly from that in patients undergoing radical prostatectomy with no prior radiation treatment. DNA ploidy at de novo radical prostatectomy at our institution during the same period was diploid in 65%, tetraploid in 27% and aneuploid in 8% of tumors. There was a modest association between tumor grade and DNA ploidy ($p = 0.044$, chi-square 2 degrees of freedom 6.2). Cancer was high grade in 40% of patients with DNA diploid, 65% with tetraploid and 36% with aneuploid tumors.

*Survival.* Overall crude and cause specific survival at 10 years for all patients undergoing salvage prostatectomy was 60 and 70%, respectively (fig. 2). Survival free of local or systemic progression was 61% at 10 years (fig. 3). If biochemical recurrence (serum PSA 0.2 ng./ml. or greater) was included as evidence of disease progression, progression-free survival at 10 years decreased to 43%. The interval between

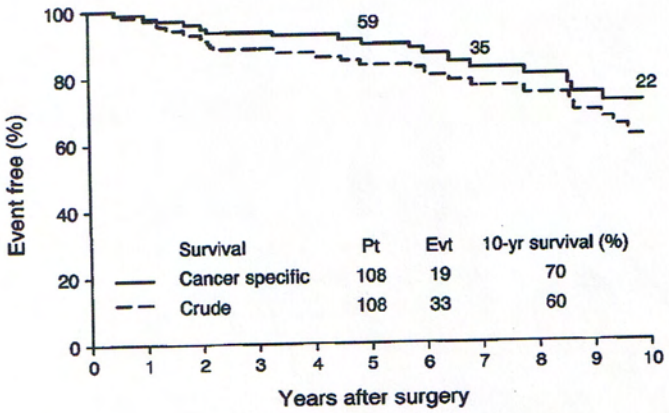


FIG. 2. Overall crude and cancer specific survival of 108 prostate cancer patients (*Pt*) undergoing salvage prostatectomy for local radiation failure. *Evt*, event.

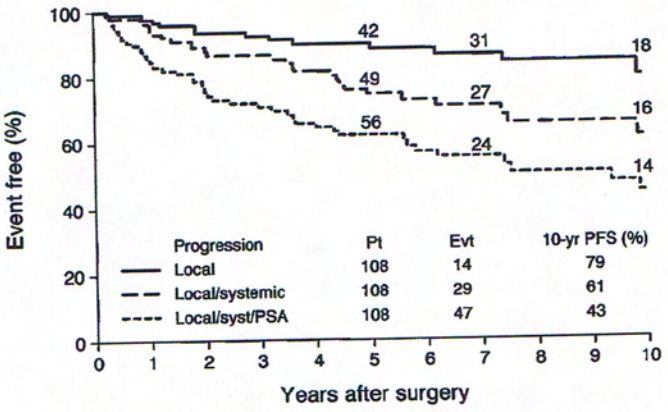


FIG. 3. Progression-free survival (*PFS*) (local, systemic or biochemical, PSA 0.2 ng./ml. or less) of 108 patients (*Pt*) undergoing salvage prostatectomy for local radiation failure. *Evt*, event.

radiation treatment and salvage prostatectomy (less than or greater than 36 months) did not significantly affect cancer specific or progression-free survival. Patients with well and moderately differentiated cancers demonstrated significantly better ($p = 0.025$) progression-free survival than those with high grade tumors (fig. 4). Cancer specific survival was better in patients with negative versus positive surgical margins (7-year survival 87 versus 67%, respectively, $p = 0.130$, not significant).

DNA ploidy was the strongest predictor of cancer specific and progression-free survival (fig. 5). The 10-year cancer specific survival for patients with DNA diploid, tetraploid and aneuploid tumors was 100, 71 and 32%, respectively ($p = 0.002$). Of the 26 patients with diploid cancers 3 had progression and only 2 died of prostate cancer (neither within 10 years). In contrast, of the 11 patients with aneuploid tumors 9 had progression and 6 died of prostate cancer within 10 years of salvage prostatectomy. We also compared outcomes between patients with preoperative PSA less than 10 and those with PSA 10 ng./ml. or greater. Although preoperative serum PSA was not predictive of pathological stage, it was associated with disease progression (fig. 6). The 5-year progression-free survival was 70% for patients with PSA less than 10 compared to 47% for those with serum PSA 10 ng./ml. or greater ($p = 0.057$).

When analyzing grade and serum PSA using the Cox proportional hazards model, DNA ploidy remained a significant predictor of prostate cancer death ($p < 0.001$) and disease

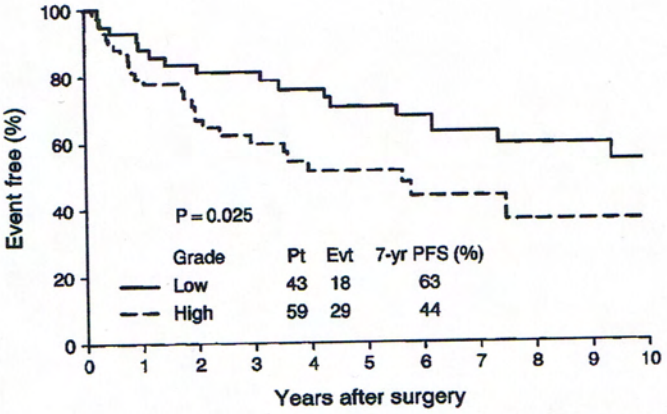


FIG. 4. Impact of tumor grade on progression-free survival (*PFS*) (local, systemic or biochemical, PSA 0.2 ng./ml. or less) of patients (*Pt*) undergoing salvage prostatectomy for local radiation failure. *Evt*, event.

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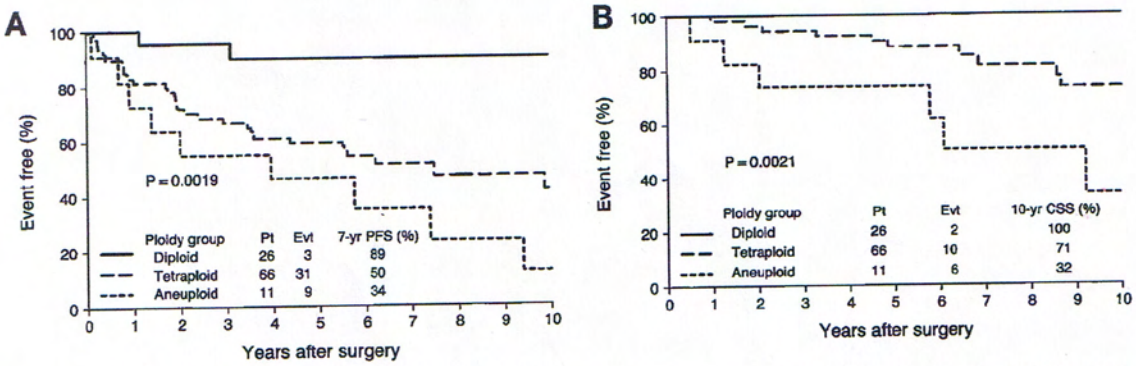


FIG. 5. Impact of DNA ploidy on survival of prostate cancer patients (*Pt*) undergoing salvage prostatectomy for local radiation failure. *A*, progression-free survival (*PFS*) (local, systemic or biochemical, PSA 0.2 ng./ml. or less). *B*, cause specific survival (*CSS*). *Evt*, event.

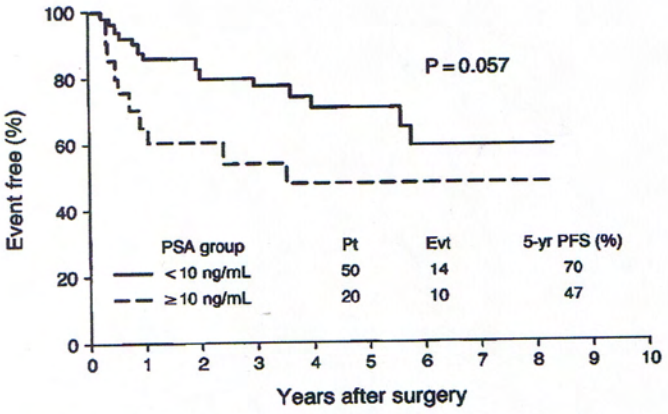


FIG. 6. Impact of preoperative serum PSA on progression-free survival (*PFS*) (local, systemic or biochemical, PSA 0.2 ng./ml. or less) of patients (*Pt*) undergoing salvage prostatectomy for local radiation failure. *Evt*, event.

progression ($p < 0.001$). Although the risk ratios were large, high tumor grade was not an independent predictor of prostate cancer death ($p = 0.18$, risk ratio 2.0) or progression ($p = 0.063$, risk ratio 1.9), and serum PSA 10 ng./ml. or greater was significant only for the disease progression end point ($p = 0.049$, risk ratio 2.2). No significant interactions between ploidy and grade or serum PSA were found for prostate cancer death or progression ($p > 0.10$).

*Morbidity.* There were no treatment related deaths. We compared morbidity of salvage retropubic prostatectomy between the patients undergoing surgery before (48, early group) and after (60, late group) 1990 (table 4). The percentage of patients requiring operative or perioperative blood transfusion decreased from 75% in the early group to 17% in the late group. The incidence of rectal injury (6%) remained the same in both groups. The bladder neck contracture rate increased (overall 21%) and continence rates were no better in the late group. Overall approximately 50% of patients were completely continent (requiring no pads) and 25% required 1 to 2 pads daily.

TABLE 4. *Complications in 108 patients undergoing salvage prostatectomy before and after 1990*

| | No. 1966–1989 (%) | No. 1990–1996 (%) | Total No. (%) |
|---|---|---|---|
| No. pts. | 48 | 60 | 108 |
| Blood transfusion | 36 (75) | 10 (17) | 46 (43) |
| Rectal injury | 3 (6) | 3 (5) | 6 (6) |
| Bladder neck contracture | 7 (15) | 16 (27) | 23 (21) |
| Deep vein thrombosis | 3 (6) | 2 (3) | 5 (5) |
| Pulmonary embolus | 1 (2) | 0 (0) | 1 (1) |
| Continence (No. pads): | | | |
| 0 | 20 (47) | 30 (50) | 50 (49) |
| 1–2 | 10 (23) | 14 (23) | 24 (23) |
| 3 or More | 13 (30) | 16 (27) | 29 (28) |
| Unknown | 5 | 0 | 5 |

## DISCUSSION

There are several treatment options to consider for patients with radiation refractory prostate cancer. Patients who are asymptomatic and have multiple co-morbidities may be best treated with observation alone, although this strategy is inevitably associated with progressive disease. When PSA is increased after radiotherapy at least 75% of patients will have clinically evident recurrent disease and 24% will die of prostate cancer within 5 years.[5] While most patients with radiation refractory prostate cancer are treated with androgen deprivation monotherapy, its efficacy is unproved and it may be associated with significant morbidity.[6,7] Schellhammer et al reported that patients treated with early or delayed hormonal therapy following external beam radiation failure had a median cancer specific survival of only 70 months and 60% required transurethral resection of the prostate for symptoms associated with local disease progression.[6] More recently cryosurgical ablation has been used in patients with radiation resistant prostate cancer.[8,9] However, experience with this treatment is limited and long-term cancer control has not been established. The morbidity of cryotherapy for radiation refractory tumors can also be significant. Pisters et al reported urinary incontinence in 73%, obstructive symptoms in 67%, impotence in 72% and severe perineal pain in 8% of patients treated with salvage cryotherapy in this setting.[8] Additional radiation treatment (boost radiation therapy) with prostate brachytherapy has also been reported with significant urinary and rectal complications, and disease progression was not altered.[10,11]

While the benefits of most treatment options for patients with radiation refractory prostate cancer have not been well established, the efficacy of salvage surgery has been demonstrated by several investigators.[4,12–21] In a recent report of 40 patients undergoing salvage prostatectomy at Baylor College of Medicine the 5 and 8-year cancer specific survival rates were 95 and 87%, respectively.[4] Others have reported similar survival rates.[13,14,18] In our large series 10-year crude and cancer specific survival rates were 60 and 70%, respectively, although many cancers were locally advanced and nondiploid at salvage surgery. Of our patients 18% had positive pelvic lymph nodes and an additional 30% had pathological stage T3c or T4 disease. The 10-year disease-free survival rate of 43% (biochemical failure inclusive) parallels the 43 and 33% rates in series from Duke University and Baylor College of Medicine, respectively.[4,14]

Of our patients 79% had no clinical evidence of local failure at 10-year followup. Since locally persistent disease after

radiation therapy has been correlated with subsequent distant spread and survival, obtaining local tumor control may be a primary advantage of salvage prostatectomy.[22,23] However, while 39% of our patients had organ confined disease at salvage surgery, suggesting that a significant number of these tumors could have been completely resected, many were locally advanced at radiation failure, making complete surgical extirpation unlikely. The potential for incomplete tumor resection and the fact that salvage surgery is associated with significant complication rates have limited the widespread acceptance of salvage prostatectomy for patients with radioresistant cancers. Patients most likely to benefit from salvage surgery are those with completely resectable tumors and good long-term disease-free outcomes. Unfortunately, it has been difficult to identify these patients accurately preoperatively.

Our data suggest that DNA ploidy status and serum PSA are the most important factors to consider when selecting patients for salvage surgery. Previous reports from our institution have demonstrated the importance of tumor DNA ploidy in patients with pathologically organ confined and advanced cancers.[24,25] The prognostic importance of DNA ploidy is evident in patients with radiation refractory cancers as well, and it serves as a strong predictor of outcome independent of serum PSA and tumor grade. Our patients with DNA diploid tumors had good outcomes following salvage surgery and fared as well as those undergoing de novo radical prostatectomy for clinically localized disease at our institution. In contrast, patients with aneuploid cancers fare poorly regardless of other factors and salvage prostatectomy probably does not impact the ultimate disease outcome, which is characterized by early recurrence and high prostate cancer death rates. The majority of our patients had nondiploid tumors with a particularly high proportion of tetraploid cancers. In patients undergoing de novo radical prostatectomy at our institution tetraploid cancers account for only 27% of tumors compared to 64% in the present series. Like patients undergoing de novo radical prostatectomy, those with tetraploid cancers undergoing salvage prostatectomy had cancer specific and progression-free survival rates between those of diploid and aneuploid cancers. While patients with tetraploid tumors appear to fare somewhat worse than those with diploid cancers, many do well following salvage surgery. If DNA ploidy is used as a selection criterion for salvage prostatectomy, our data suggest that patients with nonaneuploid cancers are more likely to benefit than those with aneuploid tumors. Although salvage prostatectomy may be beneficial to alleviate the potential for local complications in aneuploid cancers which have the potential to be locally aggressive, surgical therapy is unlikely to impact the ultimate prostate cancer death rates in these patients. Since DNA ploidy can now be determined preoperatively from core prostate biopsies, tumor ploidy status can be determined before considering salvage prostatectomy.[26–28]

Serum PSA has become an important marker for defining radiation failure as most cases of recurrent disease after radiotherapy are now detected by increasing serum PSA.[2,3] It has been suggested that this increase might identify cancers earlier in their course while still organ confined and potentially at a more curable stage. Rogers et al reported that pre-salvage surgery serum PSA was predictive of pathological stage, and improved progression-free survival was noted in patients undergoing salvage prostatectomy before serum PSA reached 10 ng./ml.[4] Although our patients with PSA greater than 10 ng./ml. also had significantly higher biochemical progression rates than those with lower PSA levels, PSA was unrelated to pathological stage. Serum PSA before radiotherapy appeared to correlate more closely to pathological stage. Patients with pre-radiotherapy PSA less than 4 ng./ml. had a much higher likelihood of organ confined disease than those with progressively higher PSA levels, which suggests that the initial serum PSA at diagnosis is probably more closely related to pathological stage than the PSA level induced by the effect of radiotherapy. These findings have important implications in selecting patients for salvage prostatectomy. Patients with serum PSA less than 10 ng./ml. at diagnosis and before radiation therapy are more likely to have organ confined disease at salvage prostatectomy. Similarly, patients with pre-salvage serum PSA less than 10 ng./ml. appear to have improved progression-free outcomes compared to those with higher PSA levels. If serum PSA data are going to be used to assist in selection of patients for salvage surgery, our data suggest that those with PSA less than 10 ng./ml. before radiotherapy and salvage surgery are most likely to benefit with extended disease-free outcomes.

Although salvage surgery has been associated with good long-term disease-free status in radiation refractory disease, the technical difficulty of this procedure has limited its widespread use. However, the degree of technical difficulty is variable. In some patients no significant tissue reaction is observed, while in others significant obliteration of surgical planes by tissue fibrosis is apparent. Salvage prostatectomy is more difficult, particularly in patients who have previously undergone pelvic lymphadenectomy or radioactive seed implantation, while tissue planes may be surprisingly normal in those treated with external beam therapy alone. Unfortunately, it is difficult to predict the degree of tissue fibrosis preoperatively. Like other published series, our data confirm the relatively high morbidity of this procedure.[4,14–20] Although the requirement for blood transfusion has decreased significantly in our more recently treated patients, approximately 50% require absorbent pads for urinary incontinence and bladder neck contracture rates remain high. While the use of serum PSA may detect radiation failure at an earlier stage, it appears that the effect of radiation on the tissues of the bladder neck and sphincter is constant, and likely accounts for these high incontinence and bladder neck contracture rates. These potential complications should be considered when selecting patients for salvage surgery, especially older patients with multiple co-morbidities and locally advanced tumors, in whom surgery is unlikely to affect the ultimate disease outcome.

## CONCLUSIONS

It has been suggested that when patient age and pre-radiation clinical stage are considered, only 2 to 5% of patients treated with radiation modalities are ultimately candidates for salvage surgery.[6] However, in the younger patient with radiation refractory disease and long life expectancy salvage prostatectomy may offer the best chance of long-term disease control. We believe that salvage prostatectomy should only be considered for patients in good general health with life expectancy longer than 10 years who would have been considered candidates for de novo radical prostatectomy. In addition, candidates should have biopsy proved recurrent cancer 1 year or longer after completion of radiotherapy with an initially low (T1 to T2) clinical stage before radiotherapy. Ideally serum PSA initially (before radiotherapy) and before salvage surgery should be less than 10 ng./ml. Preoperative determination of tumor ploidy may also assist in the selection of candidates most likely to benefit from salvage surgery.

## REFERENCES

1. Mettlin, C.: The American Cancer Society National Prostate Cancer Detection Project and national patterns of prostate cancer detection and treatment. CA Cancer J. Clin., **47:** 265, 1997.
2. Zeitman, A. L., Coen, J. J., Shipley, W. U., Willett, C. G. and

Efird, J. T.: Radical radiation in the management of prostatic adenocarcinoma: the initial prostate specific antigen as a predictor of treatment outcome. J. Urol., **151:** 640, 1994.
3. Kaplan, I. D., Cox, R. S. and Bagshaw, M. A.: Prostate specific antigen after external beam radiotherapy for prostate cancer: followup. J. Urol., **149:** 519, 1993.
4. Rogers, E., Ohori, M., Kassabian, V. S., Wheeler, T. M. and Scardino, P. T.: Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. J. Urol., **153:** 104, 1995.
5. Lee, W. R., Hanks, G. E. and Hanlon, A.: Increasing prostate-specific antigen profile following definitive radiation therapy for localized prostate cancer: clinical observations. J. Clin. Oncol., **15:** 230, 1997.
6. Schellhammer, P. F., Kuban, D. A. and El-Mahdi, A. M.: Treatment of clinical local failure after radiation therapy for prostate carcinoma. J. Urol., **150:** 1851, 1993.
7. Kuban, D. A., El-Mahdi, A. M. and Schellhammer, P. F.: Prognostic significance of post-irradiation biopsies. Oncology, **7:** 29, 1993.
8. Pisters, L. L., von Eschenbach, A. C., Scott, S. M., Swanson, D. A., Dinney, C. P. N., Pettaway, C. A. and Babaian, R. J.: The efficacy and complications of salvage cryotherapy of the prostate. J. Urol., **157:** 921, 1997.
9. Bales, G. T., Williams, M. J., Sinner, M., Thisted, R. A. and Chodak, G. W.: Short-term outcomes after cryosurgical ablation of the prostate in men with recurrent prostate carcinoma following radiation therapy. Urology, **46:** 676, 1995.
10. Wallner, K. E., Nori, K., Morse, M. J., Sogani, P. C., Whitmore, W. F. and Fuks, Z.: 125Iodine reimplantation for locally progressive prostatic carcinoma. J. Urol., **144:** 704, 1990.
11. Cumes, D. M., Gogginet, D. R., Martinez, A. and Stamey, T.: Complications of 125Iodine implantation and pelvic lymphadenectomy for prostate cancer with special reference to patients who had failed external beam therapy as their initial mode of therapy. J. Urol., **126:** 620, 1981.
12. Rainwater, L. M. and Zincke, H.: Radical prostatectomy after radiation therapy for cancer of the prostate: feasibility and prognosis. J. Urol., **140:** 1455, 1988.
13. Lerner, S. E., Blute, M. L. and Zincke, H.: Critical evaluation of salvage surgery for radio-recurrent/resistant prostate cancer. J. Urol., **154:** 1103, 1995.
14. Moul, J. W. and Paulson, D. F.: The role of radical surgery in the management of radiation recurrent and large volume prostate cancer. Cancer, **68:** 1265, 1991.
15. Thompson, I. M., Rounder, J. B., Spence, R. and Rodriguez, F. R.: Salvage radical prostatectomy for adenocarcinoma of the prostate. Cancer, **61:** 1464, 1988.
16. Link, P. and Freiha, F. S.: Radical prostatectomy for radiorecurrent adenocarcinoma of the prostate. J. Urol., **140:** 544, 1988.
17. Zincke, H.: Radical prostatectomy and exenterative procedures for local failure after radiotherapy with curative intent: comparison of outcome. J. Urol., **147:** 894, 1992.
18. Ahlering, T. E., Lieskovsky, G. and Skinner, D. G.: Salvage surgery plus androgen deprivation for radioresistant prostatic adenocarcinoma. J. Urol., **147:** 900, 1992.
19. Stein, A., Smith, R. B. and deKernion, J. B.: Salvage radical prostatectomy after failure of curative radiotherapy for adenocarcinoma of prostate cancer. Urology, **40:** 197, 1992.
20. Pontes, J. E., Montie, J., Klein, E. and Huben, R.: Salvage surgery for radiation failure in prostate cancer. Cancer, **71:** 976, 1993.
21. Garzotte, M. and Wajsman, Z.: Androgen deprivation with salvage surgery for radiorecurrent prostate cancer: results at 5-year followup. J. Urol., **159:** 950, 1998.
22. Fuks, Z., Leibel, S. A., Wallner, K. E., Begg, C. B., Fair, W. R., Anderson, L. L., Hilaris, B. S. and Whitmore, W. F.: The effect of local control on metastatic dissemination in carcinoma of the prostate: long term results in patients treated with 125I implantation. Int. J. Rad. Oncol. Biol. Phys., **21:** 537, 1991.
23. Zagars, G. K., von Eschenbach, A. C. and Ayala, A. G.: Prognostic factors in prostate cancer: analysis of 874 patients treated with radiation therapy. Cancer, **72:** 1709, 1993.
24. Lerner, S. E., Blute, M. L., Bergstralh, E. J., Bostwick, D. G., Eickholt, J. T. and Zincke, H.: Analysis of risk factors for progression in patients with pathologically confined prostate-cancers after radical retropubic prostatectomy. J. Urol., **156:** 137, 1996.
25. Zincke, H., Bergstralh, E. J., Larson-Keller, J. J., Farrow, G. M., Myers, R. P., Lieber, M. M., Barrett, D. M., Rife, C. C. and Gonchoroff, N. J.: Stage D1 prostate cancer treated by radical prostatectomy and adjuvant hormonal treatment: evidence for favorable survival in patients with DNA diploid tumors. Cancer, **70:** 311, 1992.
26. Ross, J. S., Figge, H., Bui, H. X., del Rosario, A. D., Jennings, T. A., Rifkin, M. D. and Fisher, H. A.: Prediction of pathologic stage and postprostatectomy disease recurrence by analysis of initial needle biopsy specimens of prostate cancer. Cancer, **74:** 2811, 1994.
27. Lo, J., Kerns, B. J., Amling, C. L., Robertson, C. N. and Layfield, L. J.: Correlation of DNA ploidy and histologic diagnosis from prostate core-needle biopsies: is DNA ploidy more sensitive than histology for the diagnosis of carcinoma in small specimens? J. Surg. Oncol., **63:** 41, 1996.
28. Sweat, S. D., Sebo, J. J. and Zincke, H.: Prostate cancer DNA ploidy concordance rates between needle biopsy and radical prostatectomy specimens. J. Urol., part 2, **157:** 230, abstract 898, 1997.

## EDITORIAL COMMENT

The authors attempt to describe clinical features to be considered in selecting patients for salvage radical prostatectomy after radiation therapy failure. They observe that pre-radiation therapy and pre-radical prostatectomy PSA values are important, and suggest that DNA ploidy is the most important criterion. The report potentially has a major hypothetical problem. From an institution with an extremely high prostate cancer experience only 108 patients were selected for salvage radical prostatectomy during a 30-year period. In my opinion many selection biases must have been used, and it would be interesting and instructive to analyze them. One must presume that thousands of patients with radiation refractory prostate cancer have been referred to the Mayo Clinic during this period but how were these 108 patients selected from them? Age alone is not a criterion. Although the authors claim that a 10-year life expectancy is a criterion, the patients ranged from 51 to 78 years old. Additionally, there is a wide post-radiotherapy interval from time of recurrence (6 to 98 months) and, therefore, the length of this interval to failure cannot be a criterion.

An added concern regarding the data involves the fact that 48 of the 108 patients received hormone therapy before surgery and many might have received hormone treatment after surgery as well. Relative to other studies of neoadjuvant endocrine manipulation, the pathological stage at surgery might have been altered, particularly with regard to margin positive status. The lack of comment on postoperative maintenance of endocrine therapy is a problem in this report as well.

DNA ploidy was more powerful than tumor grade in this series. However, 2 separate grading systems were used. It would have been helpful to review the tumor grade of resected specimens by a single pathological grading system to compare accurately tumor grade with ploidy status.

In conclusion, DNA ploidy status and PSA were important in selecting patients for salvage radical prostatectomy. However, the small number of patients from an institution with such a large experience in prostate cancer potentially belies the observations that are made. For example, what would have been the outcome if all patients referred to this institution during this study period were treated with salvage prostatectomy when PSA and DNA ploidy status criteria were appropriate? It is clear to this reviewer that many other criteria have been used in selecting these 108 patients for salvage prostatectomy, and patient bias towards treatment, surgeon bias and many other features might be involved in the selection of this relatively small number from a presumed higher number of radiation refractory referrals. It would be of great interest to the urological oncologist to examine the other variables not mentioned.

*Carl A. Olsson*
*Department of Urology*
*Allen Pavillion Presbyterian Hospital*
*New York, New York*

## REPLY BY AUTHORS

The criteria for patient selection have been clearly outlined in the Materials and Methods section and we delineated the hormonal treatment patients received, usually in an adjuvant setting. Patient

selection was based on potential for curability and/or alleviation of possible morbidity from local disease progression. Except for what was stated in our report, no other criteria for patient selection were used. The paucity of reports in the literature speaks for itself and our series corresponds to the entire experience reported in the literature. This fact supports our contention that patients who are candidates for salvage prostatectomy are rare. In our series only 108 patients underwent radical prostatectomy during a time when 10,000 radical prostatectomies were performed at Mayo Clinic, Rochester, which corresponds to about 1% of salvage prostatectomies performed in all patients. We would not be surprised if other institutions have similar data. Unfortunately, most of these patients are being kept too long under observation by the radiation oncologist, who follows continuous increases in PSA waiting for an event that will not occur, namely a miraculous stoppage of the relentless PSA increase. It is imperative that our colleagues in radiation oncology understand the problem of local failure and that they refer these patients for early salvage surgery since this is the only treatment in our opinion which might impact favorably quality of life as well as progression and survival.

The take home message of our report is that preoperative PSA values are related to outcome but not to p stage which, however, is clearly related to pre-radiation PSA. DNA ploidy status of the specimen is the most important pathological variable for disease outcome. It seems that patients with PSA below 10 before radiation and surgical therapy are ideal candidates for salvage surgery when they are younger than 70 years and disease is clinically organ confined. Furthermore, the incidence of vesical neck contracture continues to be high (20%) as does that of urinary incontinence, with only half of the patients entirely pad-free. The latter data support the long held impression that we will not be able to improve these numbers with surgical technique since radiation therapy has caused irrevocable damage to the tissues and left them not amenable to a better technique.