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CLINICAL INVESTIGATION **Prostate**

HAZARDS OF DOSE ESCALATION IN PROSTATE CANCER RADIOTHERAPY

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Purpose: To assess the benefit of escalating the dose in definitive prostate cancer radiotherapy vs. the associated risk of complications.

Methods and Materials: Between 1987 and 1999, 1087 patients with clinical Stage T1b–T3 adenocarcinoma of the prostate were definitively irradiated without hormonal therapy and had a pretreatment serum prostate-specific antigen (PSA) and Gleason score recorded. The median follow-up was 65 months. Doses ranged from 64 to 78 Gy, with the treatment techniques corresponding to the year of therapy and the prescribed dose. A total of 301 patients were treated on a randomized protocol to either 70 or 78 Gy. Also, 163 patients were treated with three-dimensional conformal therapy and had dose–volume histograms available for review.

Results: Tumor stage, grade, pretreatment PSA level, and radiation dose were all independent predictors of PSA disease-free survival (PSA-DFS) in multivariate analysis. The hazard rate for biochemical failure peaked at 1.5–3 years after radiotherapy. Although a statistically significant dose effect on PSA-DFS was found in the pretreatment PSA levels of those with both ≤10 ng/mL and >10 ng/mL, in those with a pretreatment PSA ≤10 ng/mL, the improvement in outcome was only seen going from a dose level of 64–66 Gy to 68–70 Gy with a 5-year PSA-DFS rate of 66% vs. 81% ($p < 0.0001$). This was also confirmed by the data from the randomized patients who showed no difference in outcome whether treated to 70 Gy or 78 Gy. In patients with a pretreatment PSA level >10 ng/mL, a statistically significant improvement was found in disease-free outcome among the 64–66-Gy, 68–70-Gy, and 78-Gy levels. PSA-DFS was approximately 50% better at each higher dose level at 5 and 8 years after treatment. The dose had a statistically significant impact in both intermediate- and high-risk groups. Rectal morbidity was both dose and volume related. Although at 5 years after therapy, the Grade 2-3 rectal complication rate was twice as high for patients treated to 78 Gy than to 70 Gy, 26% vs. 12%, this risk could be markedly diminished by adhering to dose–volume constraints.

Conclusion: In intermediate- and high-risk prostate cancer patients, although it appears that radiation-dose escalation may improve PSA-DF outcome, the price paid in treatment morbidity can be high without adequate attention to dose–volume constraints of normal tissue. Care must be taken to consider not only the hazard of tumor recurrence but also that of complications.

Prostate cancer, Dose escalation, PSA-DFS, Complications.

INTRODUCTION

With the advent of prostate-specific antigen (PSA) testing as an early, objective measure of outcome in patients irradiated for prostate cancer, the results reported by many institutions were not as optimistic as we had become accustomed to with clinical end points (1–3). In an effort to improve local control with this modality, techniques were developed to allow dose escalation under the assumption that higher prostatic doses would reduce the risk of local failure and thereby increase the cure rate (4–7). Of great importance, however, is the price paid for this improvement in outcome (8–11). Thus, the double-edged sword: the hazards of failure vs. the hazards of complications. Long have we known that we must be mindful of the therapeutic ratio, and, especially now, in an era in which multiple options are available for treatment of this disease and quality-of-life issues have come to the forefront. In this study, we examined the balance between the hazard function for treatment failure and the risk of morbidity related to dose escalation in a large, single-institution cohort treated with radiotherapy (RT) alone.

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Table 1. Stage, Gleason score, PSA level, and dose characteristics

Stage	*n*	GS	*n*	PSA (ng/mL)	*n*	Dose (Gy)	*n*
T1b–c	397	2–6	650	0–4	164	64–66	362
T2a	189	7	307	4.1–10	509	68–70	492
T2b	197	8–10	130	10.1–20	304	78	233
T2c	75						
T3	229			>20	110		

Abbreviations: GS = Gleason score; PSA = prostate-specific antigen.

METHODS AND MATERIALS

Between 1987 and 1999, 1087 patients with clinical Stage T1b–T3, biopsy proven adenocarcinoma of the prostate were definitively irradiated without hormonal therapy at The University of Texas M. D. Anderson Cancer Center. All patients had pretreatment serum PSA (PT-PSA) levels recorded and were assigned a Gleason score. Doses to the isocenter ranged from 64 Gy in the earlier years to 78 Gy more recently, using techniques corresponding to the prescribed dose: four-field technique followed later by four-field with conformal six-field boost (5). For the dose–volume histogram calculation, the rectum was contoured for a distance of 11 cm from the inferiormost aspect of the ischial tuberosities and encompassing the entire rectal volume: rectal wall and internal contents. The bladder was defined within this same volume for consistency. The median follow-up was 65 months (range 1–164). Of the 1087 patients, 301 were treated on a randomized protocol comparing 70 and 78 Gy. The median follow-up for those patients was similar, 60 months. Patient characteristics are shown in Table 1. For dose comparisons, patients were divided into three groups: 64–66 Gy, 68–70 Gy, and 78 Gy. Risk groups were defined as low risk, Stage T1b, T1c, or T2a, Gleason score ≤6, and PSA ≤10 ng/mL; intermediate risk, Stage T2b or T2c, Gleason score ≤7, and PSA ≤20 ng/mL, or Stage T1b-T2a, Gleason score 7, and PSA ≤20 ng/mL, or Stage T1b-T2c, Gleason score ≤6, and PSA 10–20 ng/mL; and high risk, Stage T3 or PSA >20 ng/mL or Gleason score 8–10. Biochemical failure was defined according to the American Society for Therapeutic Radiology and Oncology definition: three consecutive rises in PSA level with backdating of the failure date to halfway between the last nonrising and first rising PSA value. Local, distant, and regional recurrence was a condition for clinical failure under this definition as well. A modified Radiation Therapy Oncology Group–Late Effects Normal Tissue Task Force complication grading system was used (5) (Table 2). Of the 163 patients with dose–volume histograms in whom complications were assessed, 128 were treated on the randomized protocol that included prospective complication reporting. In the remainder, ample information was attained from retrospective chart review. The life-table actuarial survival was calculated from the completion of RT, and the log–rank test was applied to compare groups. Cox proportional hazards regression analysis was used for multivariate analysis.

Table 2. Modified LENT–RTOG complication grading system: Late rectal toxicity

Grade	Symptoms
1	Excess bowel movements twice baseline Slight rectal discharge or blood
2	>2 antidiarrheals/wk; ≤2 coagulations; occasional steroids or dilatation; intermittent pad use; regular non-narcotics or occasional narcotics
3	>2 antidiarrheals/d; >2 coagulations; ≥1 transfusion; prolonged daily steroid enemas; hyperbaric oxygen; regular dilation; daily pads; regular narcotics
4	Dysfunction requiring surgery; perforation; life-threatening bleeding
5	Fatal toxicity

Abbreviations: LENT = Late Effects Normal Tissue Task Force; RTOG = Radiation Therapy Oncology Group.

RESULTS

Outcome

Tumor stage, tumor grade, PT-PSA, and radiation dose were all independent predictors of PSA disease-free survival (PSA-DFS) in multivariate analysis (Table 3). Subgrouping patients by initial PSA level showed a significant dose effect in patients with PSA levels of 4.1–10 ng/mL and 10.1–20 ng/mL (Fig. 1). No notable dose effect was found in patients with PT-PSA levels of ≤3 ng/mL. In patients with PT-PSA levels of 4–10 ng/mL, improvement in the PSA-DFS rate at 5 years was seen between doses of 64–66 Gy and 68–70 Gy, 54% vs. 80%, respectively. However, no additional improvement was seen with increasing the dose to 78 Gy. In patients with PT-PSA levels in the 10.1–20-ng/mL range, an incremental benefit in the 5-year PSA-DFS rate was seen between doses of 64–66 Gy (42%) and 68–70 Gy (55%) and 78 Gy (83%; $p = 0.0001$). Although the dose effect in the group with PSA levels >20 ng/mL was not statistically significant, this may have been a result of the small number of patients in this group, because the difference in outcome was quite large, 23% and 26% for the two lower dose levels vs. 51% for 78 Gy. As noted, this report included 301 patients treated on a randomized trial to 70 vs. 78 Gy. The 5-year PSA-DF outcome for these patients is seen in Fig. 2. The results are similar to those just discussed,

Table 3. Multivariate analysis for the end point PSA-DFS

Variable	Hazard ratio	Chi-square
Stage	1.527	<0.0001
Gleason	1.234	<0.0001
PT-PSA	1.023	<0.0001
Dose	0.886	<0.0001

Abbreviations: PSA = prostate-specific antigen; DFS = disease-free survival; PT = pretreatment.

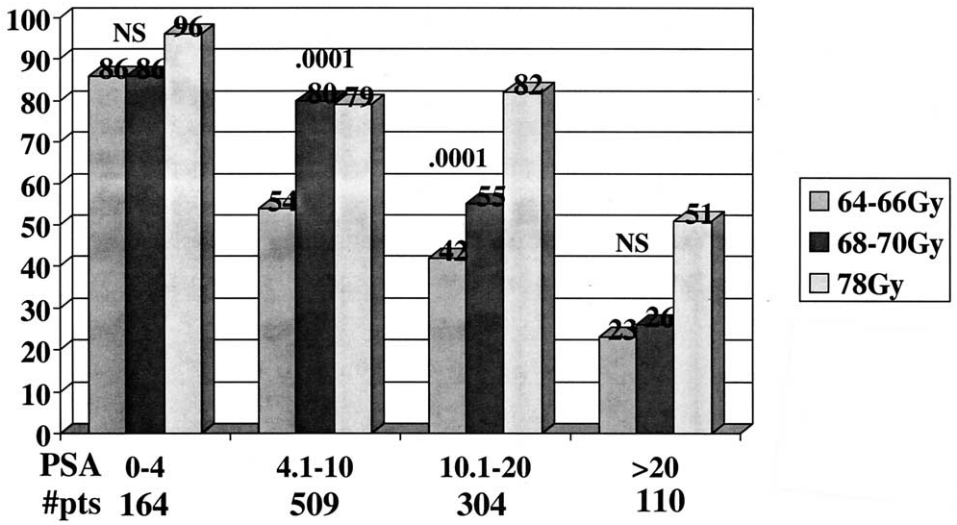

Fig. 1. Five-year PSA-DFS by PT-PSA level and dose for all patients. Mid-gray bars, 64–66 Gy; dark gray bars, 68–70 Gy; light gray bars, 78 Gy.

except that no significant dose advantage was seen in the 4.1–10-ng/mL PT-PSA group. This can be explained in that no patients in the randomized trial were treated to doses of <70 Gy and the statistically significant findings in the entire 1087 patient group for this PSA level were based on including patients treated to 64–66 Gy. At 8 years after RT, the same relationships held true, although the 78-Gy dose group could not be included because of insufficient follow-up time (Fig. 3).

If patients were grouped according to a PT-PSA level of <10 or >10 ng/mL, a significant, dose-dependent difference in PSA-DFS at 5 years after treatment was seen in all patients with a PSA level >10 ng/mL, as well as in the randomized study patients (Fig 4). In patients with PT-PSA levels ≤10 ng/mL, a statistically significant difference according to dose was seen for patients treated to 64–66 Gy vs. those treated to both 68–70 Gy and 78 Gy, with no difference between the latter two groups (Fig. 5). The randomized study patients, treated to 70 and 78 Gy, had similar PSA-DF outcomes, 80% at 5 years after RT. For the 786 patients who were not randomized, for PT-PSA levels of ≤10 and >10 ng/mL, the outcome was not different from that for all 1087 patients, and therefore, the same comparisons hold true.

When patients were divided into risk groups, low-risk patients showed a benefit in going from doses of 64–66 Gy to 68–70 Gy, with no improvement beyond that point (Fig. 6). Intermediate- and high-risk patients showed incremental improvement in outcome at each dose level.

Another way to analyze failure is by using a yearly

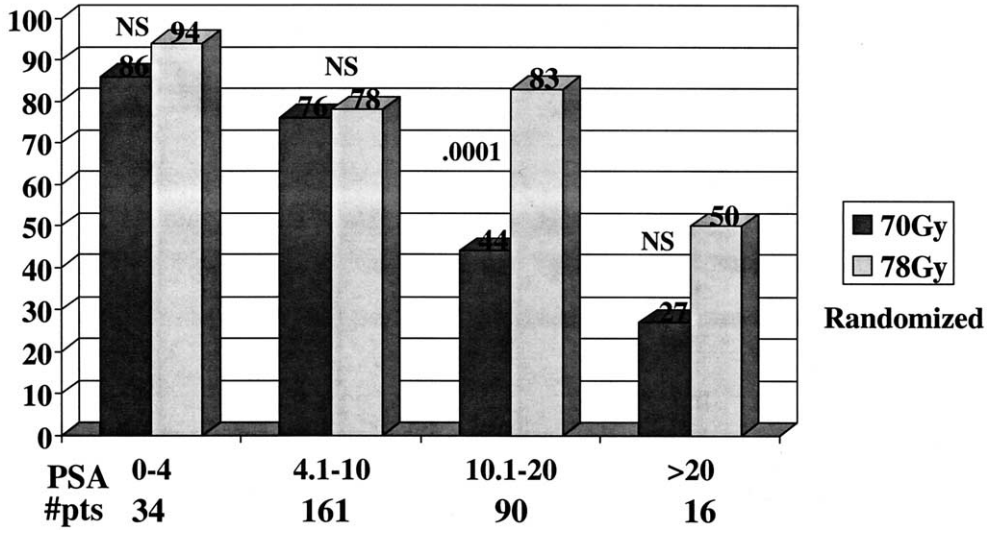

Fig. 2. Five-year PSA-DFS by PT-PSA level and dose for 301 randomized patients. Dark gray bars, 70 Gy; light gray bars, 78 Gy.

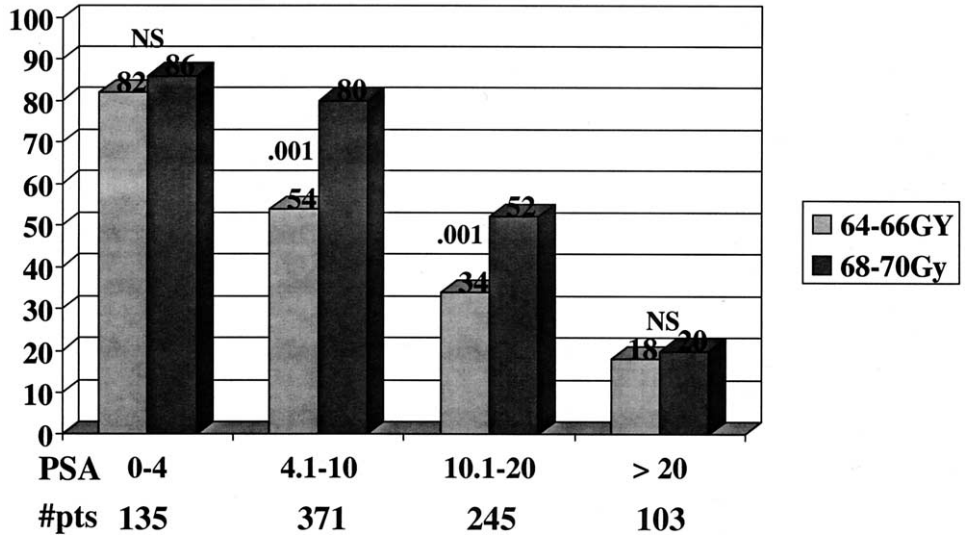

Fig. 3. Eight-year PSA-DFS by PT-PSA and dose for all patients. Light gray bars, 64–66 Gy; dark gray bars, 68–70 Gy.

hazard method. This was done by risk group in Fig. 7. In general, the greatest risk of failure occurred from 1.5 to 3 years after RT. However, for patients in the low- and intermediate-risk groups who were treated to 78 Gy, the failure rate appeared to peak later, at 4.5 to 5.5 years after treatment. Longer follow-up of this pattern is necessary, however, because this observation was based on a small number of patients. Overall, the risk of failure was greater for patients treated to lower doses and with poorer prognostic factors.

Complications

One hundred sixty-three patients were treated with three-dimensional conformal therapy and had dose–volume histo-

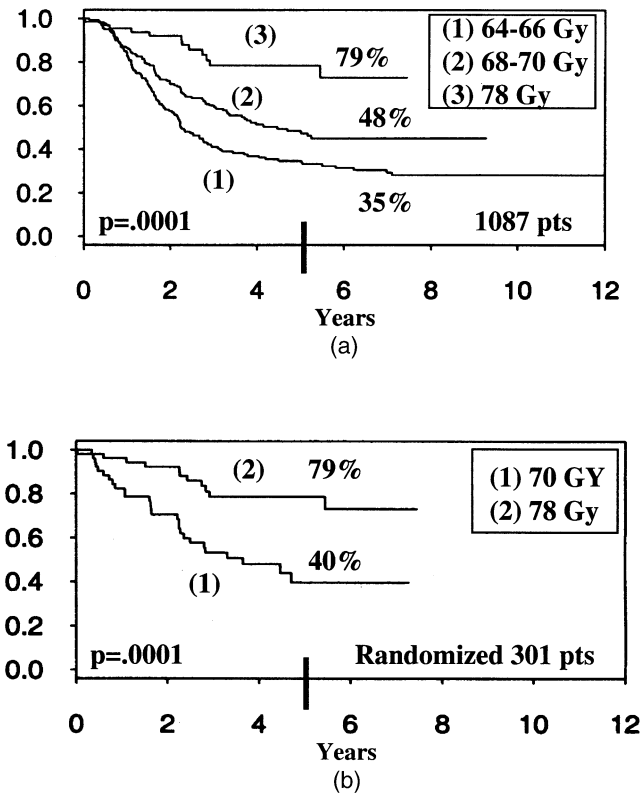

Fig. 4. PSA-DFS by dose level for patients with PT-PSA >10 ng/mL. (a) All patients. (b) Randomized patients.

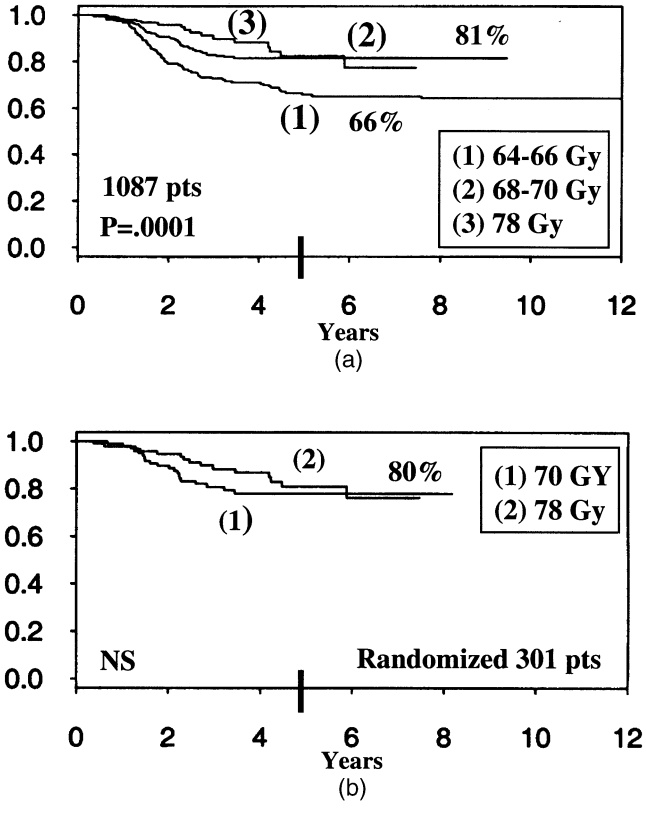

Fig. 5. PSA-DFS by dose level for patients with PT-PSA ≤10 ng/mL. (a) All patients. (b) Randomized patients.

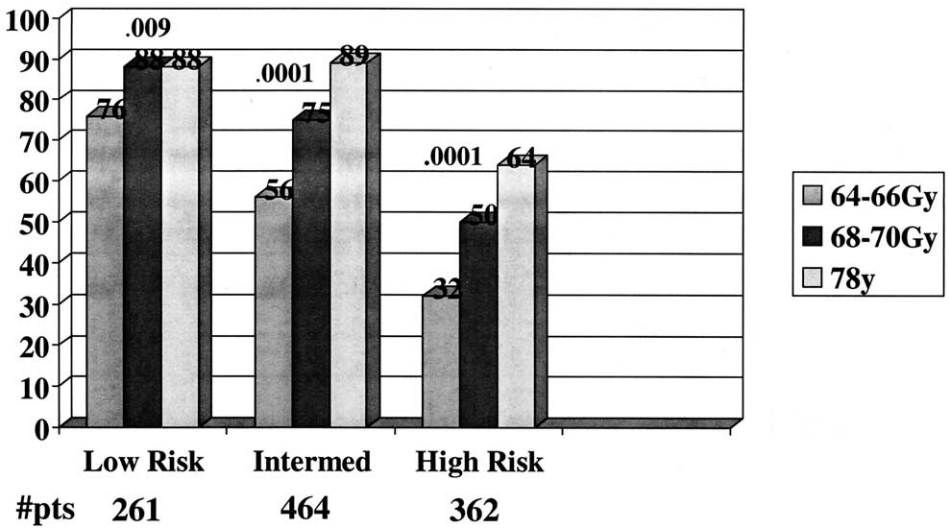

Fig. 6. Five-year PSA-DFS by risk group and dose level.

grams available for review. Of these, 150 patients received 78 Gy, and 13 received 74–76 Gy; 128 of these were treated on the 78-Gy arm of the randomized protocol. Most patients, 77%, had minimal or no late rectal toxicity, and no patient had Grade 4 or 5 toxicity (Table 4). The actuarial incidence of Grade 2 and 3 rectal toxicity was 21% and 6%, respectively, at 5 years after RT. All patients had at least 2 years of follow-up, and 80% of the complications had developed by that point. When compared by dose level to the 150 randomized study patients treated to 70 Gy, the 150 patients treated to 78 Gy had twice the rate of Grade 2 and 3 rectal complications, 26% vs. 12% at 5 years after treatment (Fig. 8). However, additional investigation showed that the complication rate could be reduced if the amount of rectum treated to the 70-Gy dose level was limited to not >26% (Fig. 9). When this criterion was met (116 patients), the rectal complication rate (Grade 2 or greater) was 13% at 5 years after therapy compared with 51% when it was not (47 patients). When these patients were treated, this dose constraint had not yet been defined and analyzed, and therefore, no attempt was made to meet this particular parameter. The risk of bladder complications, Grade 2 or 3, was moderate, with no statistically significant difference found according to RT dose. Seven percent of patients treated to 70 Gy experienced Grade 2 complications, and in 1% the morbidity was Grade 3. At the 78-Gy dose level, the Grade 2 and Grade 3 bladder complication rate was 10% and 3%, respectively.

DISCUSSION

Dose benefit

Because RT is a local therapeutic modality, the emphasis has long been on developing methods to affect better local control. In the case of prostate cancer, the current prevailing hypothesis centers on delivering higher doses to the gland. The necessary technology for treatment planning, delivery, and target localization to support this has recently become available. As with any new technology, care must be taken to define the particular group of patients who would benefit and what would be the associated risk of complications and adverse effects on quality of life.

Studies to date seem to agree that a positive effect exists by increasing the radiation dose in the intermediate-risk group of prostate cancer patients, similar to the findings of this report (4–6, 12). The effect thus far has largely been demonstrated by improvement in PSA-DFS, although Hanks and colleagues (4) have recently published a report with longer term follow-up that also showed a significant impact on the distant metastasis rate. That study demonstrated an increase in the 8-year PSA-DFS in patients with a PT-PSA of 10–20 ng/mL in going from a dose of <71.5 Gy (19%) to 71.5–75.5 Gy (31%) to >75.5 Gy (84%). Although in other studies, the difference in outcome was not quite so profound, nevertheless, improvement in the 15–20% range (absolute) has been seen (5, 6).

The conclusions to date on the effect of radiation dose in the low-risk subgroup have been mixed. Hanks and colleagues (4) saw a dose–response relation in multivariate analysis in patients with a PT-PSA level of <10 ng/mL only if they also had unfavorable features such as T stage greater than T2a, Gleason score >6, or perineural invasion. In most series, these patients would not be considered to be at low risk of failure. Even then, in the patients with a PT-PSA level <10 ng/mL but with other unfavorable characteristics, the PSA-DF outcome was improved by 20% at 8 years after treatment, 64% vs. 44%, in patients receiving a higher dose (>72 Gy vs. <70 Gy), but the difference in outcome was not statistically significant. Similarly, the randomized study reported by Pollack *et al.* (5) showed no statistically significant effect of doses >70 Gy in patients with a PT-PSA level <10 ng/mL, as did the retrospective analysis from the same institution reported here, 80% 5-year PSA-DFS rate for both 70 and 78 Gy. Hurwitz and colleagues (15) did not see improvement in biochemical outcome at 5 years after therapy in low-risk patients (Stage T1-

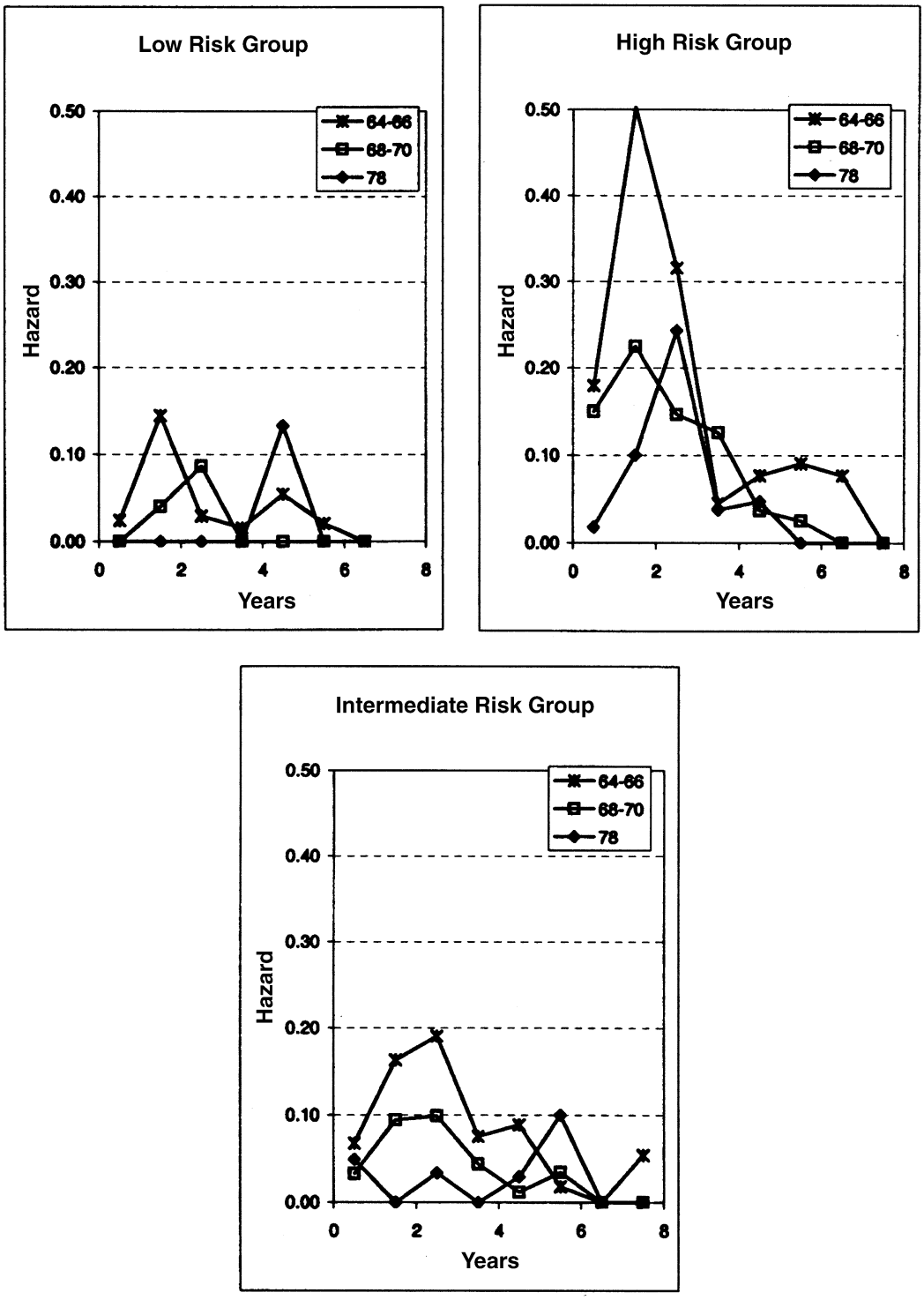

Fig. 7. Yearly hazard rates of PSA failure by risk group and dose level.

T2a, Gleason score ≤6, and PSA ≤10 ng/mL) based on higher radiation doses. However, the study by Hurwitz *et al.* showed no difference in comparing doses of <66.6 Gy to 66.6 Gy to >66.6 Gy, with a 5-year biochemical failure free rate of 79%, 78%, and 84%, respectively. In comparison, our data did show an advantage in PSA-DF outcome at both 5 and 8 years in going from a dose range of 64–66 Gy to 68–70 Gy. Because the prescription was largely to the isocenter in our study and to a volume normalized to 95% in the Hurwitz report, our 64–66-Gy and 68–70 Gy range was quite comparable to the <66.6-Gy and 66.6-Gy group of Hurwitz *et al.* (15). Even when comparing the extremes of dose, ≤65 Gy and ≥68 Gy, Hurwitz and colleagues (15) did not show a dose effect in this favorable group of patients. As admitted by these authors, other reasons such as a narrow dose range (61–73 Gy by International Commission on Radiation Units and Measure-

Table 4. Incidence of late rectal toxicity

	Patients		
Grade	*n*	%	% at 5 y
0	73	45	
1	52	32	
2	29	18	21
3	9	5	6
4–5	0	0	

ments reference point) and relatively small patient numbers (78–89 in each dose group) lacking statistical power may have influenced their findings. Also, they had a relatively short median follow-up time of 35 months, although this likely would have favorably biased the outcome for the high-dose patients who were probably treated more recently. The 5-year PSA-DFS rate was still only 5–6% greater for the >66.6 Gy group and not statistically different. Lyons *et al.* (13) drew the conclusion that doses of ≥72 Gy led to better biochemical relapse-free survival in their favorable (Stage T1-T2, PSA ≤10 ng/mL, and Gleason score ≤6) group of prostate cancer patients. However, 36% of patients in that study received doses <68 Gy. It was this group of patients that did worse than the 68–70-Gy group in our study, but our 68–70-Gy patients had the same PSA-DF outcome as those treated to 78 Gy. Therefore, it is possible that it is this mixture of low doses that accounts for the comparative improvement in the study by Lyons *et al.* Also, the patients treated to <72 Gy had a median follow-up of 51 months compared with 25 months for patients treated to ≥72 Gy. As clearly illustrated by Thames *et al.* (14), when using the American Society for Therapeutic Radiology and Oncology failure definition, this, in itself, could introduce enough bias to produce a difference in outcome between groups. Zelefsky and colleagues (6) also reported improved PSA relapse-free survival with doses of 75.6–86.4 Gy compared with 64.8–70.2 Gy in favorable patients (Stage T1-T2, Gleason score ≤6, and PSA ≤10 ng/mL). In contrast to the study by Lyons *et al.* (13), only 9% of patients received <70 Gy; therefore, this was not likely the source of the dose effect. The same follow-up bias was present, however, because the median follow-up was 95 months for patients treated to ≤70.2 Gy vs. 69 months for the 75.6–81-Gy group. The absolute difference in the 5-year PSA-DFS was approximately 10% ($p = 0.04$). This dose advantage was not seen in a previous analysis from the same institution (16). Perhaps this suggests that data sets must mature further before conclusions are drawn. Unfortunately, the Radiation Therapy Oncology Group randomized dose escalation study, P-0126, does not address this group of patients. On subset analysis, Zelefsky *et al.* (6) did find that biochemical outcome was not improved by increasing the dose to >75.6 Gy in either favorable or intermediate-risk patients.

Outcome assessment in high-risk patients is confounded by

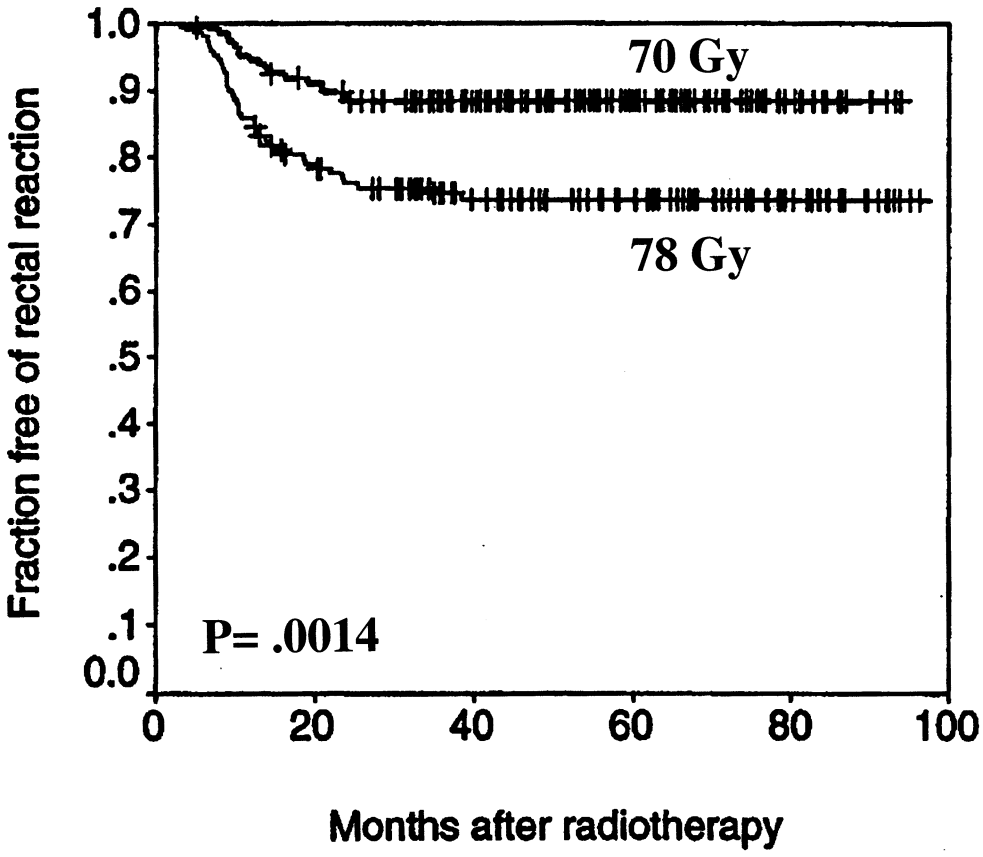

Fig. 8. Actuarial incidence of Grade 2 or greater rectal complications by dose level.

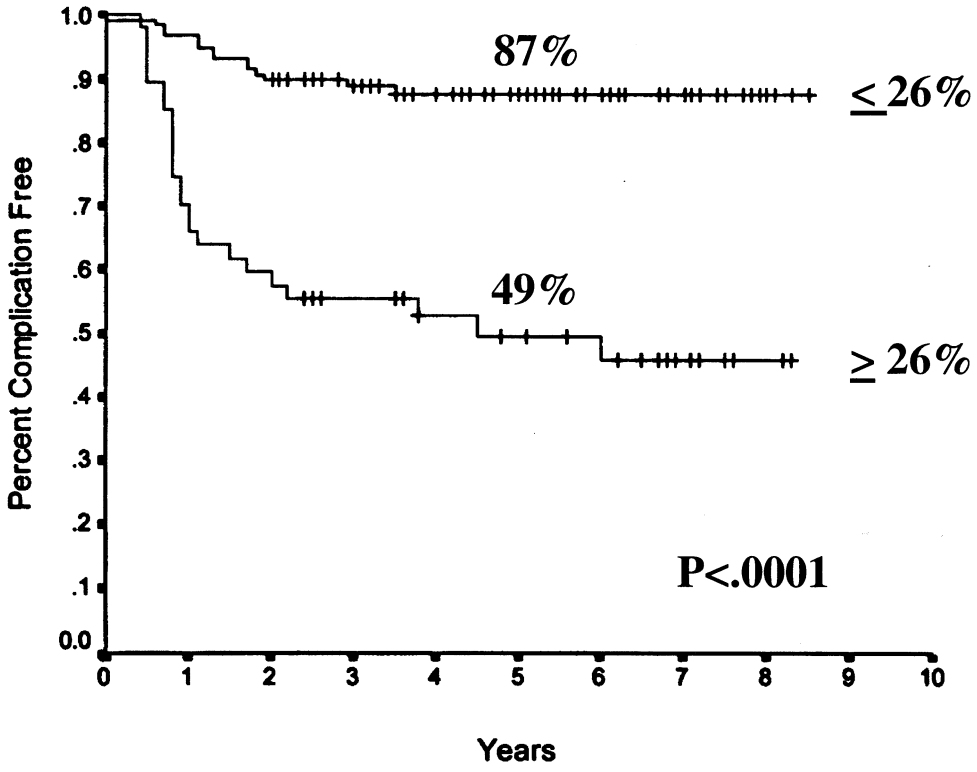

Fig. 9. Actuarial incidence of Grade 2 or greater rectal complications by percentage of rectum receiving dose of at least 70 Gy.

the relatively high risk of systemic failure and that patients are no longer routinely treated with RT alone. The high-risk patients in the study reported here did show a dose–response effect as did patients in the randomized subset. Zelefsky *et al.* (6) showed an incremental benefit in the 5-year PSA relapse-free survival of at least 20% in going from doses of 64.8–70.2 Gy (21%) to 75.6 Gy (43%) to 81 Gy (67%). Lyons and colleagues (13) reported a difference of >30% in 5-year PSA-DFS, 75% vs. 41%, in unfavorable patients (Stage T3, Gleason score ≥7, or PSA >10 ng/mL) treated to ≥72 or <72 Gy. Hanks and colleagues (4), in contrast, failed to show a dose–response effect in patients with a PT-PSA of >20 ng/mL. Although only 65 patients were in the group reported by Hanks *et al.*, all patients were treated at least 8 years before analysis. Furthermore, in multivariate analysis, dose did not have a significant effect on the incidence of distant metastasis in these patients. Therefore, it would appear that there are unsettled issues regarding the benefit of an increasing radiation dose in high-risk patients as well. The length of follow-up and definition of patient characteristics may be playing a significant role.

Complication risk

As the benefit of dose escalation has been analyzed, so too has the risk of induced complications been assessed. As seen in our study, as well as other studies, increasing the dose without changing the technique will invariably lead to greater complication rates (6, 8–9, 11, 17). Zelefsky and colleagues (6) reported a 5% rate of Grade 2 or greater rectal complications at 5 years after treatment in patients who were treated by conformal techniques to conventional doses of 64.8–70.2 Gy. Raising the dose level to 75.6 Gy with the same technique increased the rectal complication rate to 17%. In the analysis by Lee *et al.* (8), in patients treated to doses of 71–76 Gy, adding a rectal block to the lateral boost fields for the last 10 Gy decreased the Grade 2 or greater rectal toxicity rate from 22% to 7%.

In the present study, maintaining the amount of rectum treated to 70 Gy at ≤26% kept the Grade 2 or greater complication rate at 13% at 5 years after therapy compared with 51% if this dose constraint was not met. Several other dose–volume cutpoints ranging from 35 to 81 Gy have been shown to be significant in predicting rectal complications (9, 11, 18). Although the debate is considerable regarding whether lower vs. higher dose regions of the dose–volume histogram are most important in predicting complications (19, 20), modern treatment planning systems can easily provide information to assess all of these dose points. As shown by Zelefsky *et al.* (6, 10) the next generation treatment techniques such as intensity-modulated RT can significantly reduce complication rates even with doses as high as 81–86 Gy. In a recent report on 772 patients treated to this dose range using intensity-modulate RT, the incidence of Grade 2 or greater rectal toxicity at 3 years after therapy was only 4% (10).

As noted in this and other reports, the rate of Grade 2 or greater late bladder complications is quite moderate, 10–13% at 5 years after treatment, but the dose–volume relationship has not been nearly so well documented (5, 10).

This may be because dose–volume analysis is confounded by changes in bladder volume throughout therapy that are difficult to overcome and are not accounted for in the analysis of complication rates. Additional study of this issue is underway at our institution through use of a CT scanner in the treatment room and a protocol to better assess organ motion and volume changes. Moreover, a certain proportion of late genitourinary effects are a result of the location of the urethra within the tumor volume.

CONCLUSION

As a prevalent malignancy, often presenting with localized disease and, therefore, lending itself to RT during the past 40 years, prostate cancer has presented the opportunity to improve directed therapy by addressing the therapeutic ratio: the benefit in disease outcome vs. the risk of morbidity. Because this is also a malignancy for which multiple effective treatment methods are available and the option of no therapy is still considered to be a reasonable alternative for at least some patients, it is all the more critical that the hazards of RT, both in terms of tumor recurrence and complications, be seriously considered. Recent technological improvements in treatment planning and delivery systems have given us the tools to improve targeting and, thereby, increase the dose. Our challenge now is in determining who will benefit, by how much, and at what price. The analysis reported here is offered as one more piece of a growing body of information necessary to answer these questions.

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