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CLINICAL INVESTIGATION **Prostate**

LATE MORBIDITY PROFILES IN PROSTATE CANCER PATIENTS TREATED TO 79–84 GY BY A SIMPLE FOUR-FIELD COPLANAR BEAM ARRANGEMENT

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Purpose: To describe the frequency and magnitude of late GI and GU morbidity in prostate cancer patients treated to high dose levels with a simple three-dimensional conformal technique.

Methods and Materials: A total of 156 intermediate- and high-risk patients were treated between January 1, 1992 and February 28, 1999 with a simple four-field three-dimensional conformal technique to 79–84 Gy. All patients were treated with a four-field conformal technique; the prostate received 82 Gy and the seminal vesicles and periprostatic tissue 46 Gy. GI and GU toxicity was scored according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Morbidity Grading Scale and compared using Kaplan-Meier estimates.

Results: The late Grade 2 GI complication rate was 9% and 38% at 3 years for patients treated with and without rectal blocking, respectively ($p = 0.0004$). No Grade 3 late GI complications developed. The rate of Grade 2 late GU complications was 5%, 8%, and 12% at 12, 24, and 36 months, respectively. The Grade 3 late GU complication rate was 2% at 36 months. These differences were not statistically significant.

Conclusion: The treatment method described is a simple four-field conformal technique that can be easily implemented in the general radiation community. A dose of 79–84 Gy can be safely delivered to the prostate, with a 9% rate of late Grade 2 GI, 12% rate of late Grade 2 GU, and 2% rate of late Grade 3 GU complications.

Prostate cancer, Three-dimensional conformal radiotherapy, Late morbidity.

INTRODUCTION

Results from multiple series of patients with prostate cancer have demonstrated improvements in biochemical control when radiation doses between 76 and 82 Gy are delivered compared with conventional doses <70 Gy. This benefit is most evident for patients with intermediate- and high-risk feature (1–5). With standard conventional techniques, it has been evident that with the increase in dose, normal tissue toxicity increases. The Patterns of Care Studies suggest that severe complication rates double when conventional techniques are used to treat at doses >70 Gy (6). The goal of delivering higher doses to tumor while minimizing the dose to normal tissue has been the driving force behind the development of three-dimensional conformal radiotherapy (3D-CRT). Additional strategies used in conjunction with conformal techniques to better localize the target while restricting the dose to adjacent normal tissues have used daily ultrasonography, fiducial markers, and daily CT scanning for improved organ localization (7). Although these later advances are vital to the future of radiation oncology, they are not yet widely available in the general community. To improve the treatment of patients receiving their care in the 1500 facilities across the United States, it is important to develop treatment techniques that can be used in the general radiation community. It is important that such a technique meet certain requirements: (*1*) sufficient dose delivery, (*2*) demonstrated cure rates, (*3*) tolerable side-effect profile, (*4*) easy implementation with standard treatment equipment, and (*5*) quality assurance with standard port films. This communication presents a 3D conformal treatment technique developed in 1989–1992 that we believe fits these criteria.

METHODS AND MATERIALS

A review of our prospectively maintained prostate cancer data base revealed 156 patients treated for prostate cancer with a four-field, 3D conformal technique to 79–84 Gy between January 1, 1992 and February 28, 1999. Patients treated during this period with more complex beam arrangements such as noncoplanar techniques were excluded. All patients were believed to be at increased risk of failure

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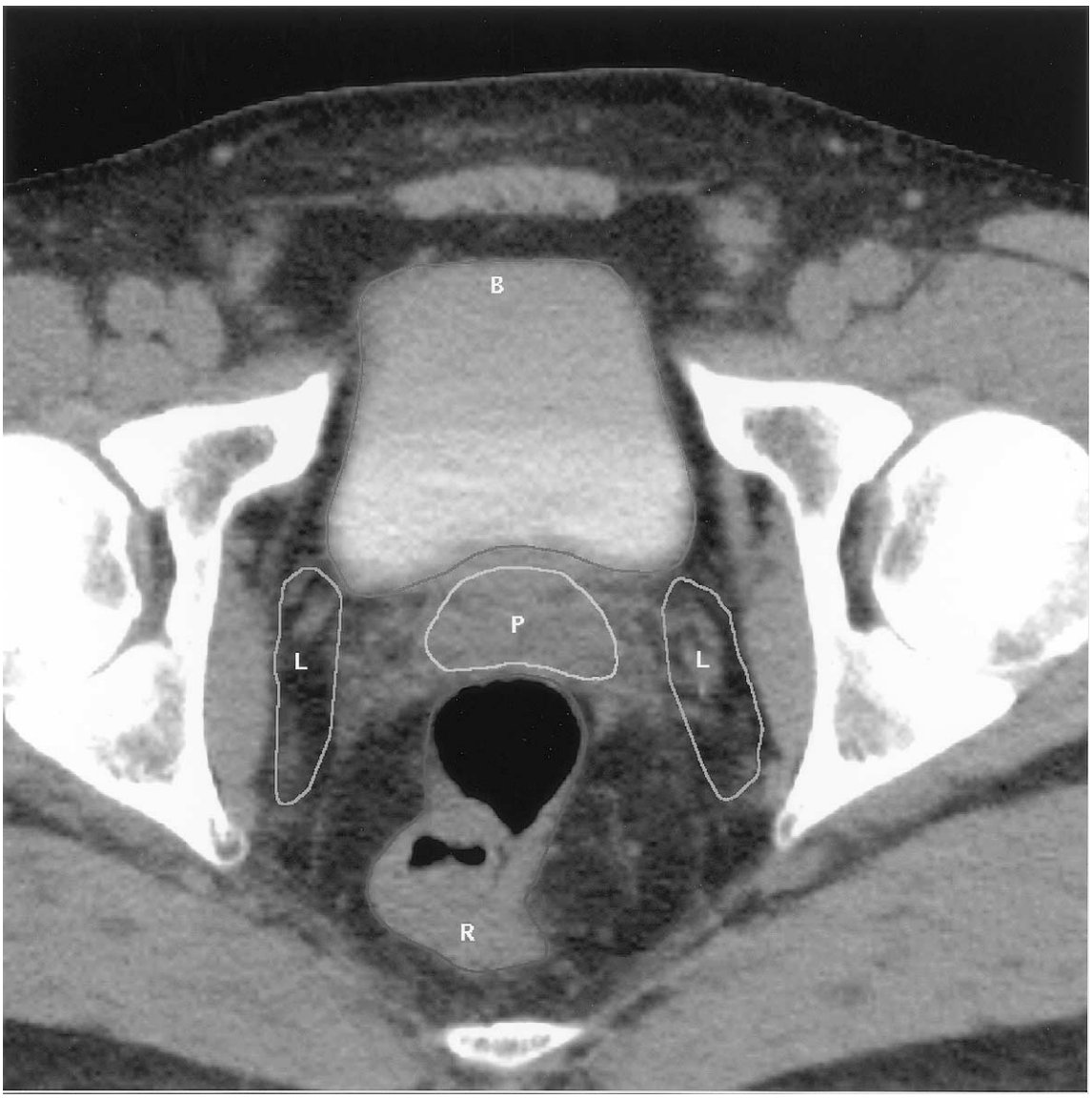

Fig. 1. Typical axial slice demonstrating prostate (P), periprostatic tissue (L), bladder (B), and rectum (R).

because of the presence of at least one of the following presenting characteristics: T2b-T3 tumor, Gleason score 7–10, pretreatment prostate-specific antigen >10 ng/mL, or the presence of perineural invasion. Two cohorts of patients were identified. The first group (24 patients) was treated in 1990–1993 at the initiation of our original dose-escalation study. This cohort was included for the purpose of comparison; we do not recommend the treatment. These patients were treated in a similar manner to the technique described, with the only exception the presence of anterior rectal wall shielding on the lateral fields for the last 9–11 fractions of treatment in the more contemporary cohort. The second group (136 patients) was treated between January 1, 1999 and February 28, 1999 and serves as the cohort of interest.

Simulation and dosimetry

All patients underwent CT simulation in the treatment position. The prostate, seminal vesicles, bladder, rectum (on prostate-containing slices), femoral heads, and periprostatic tissue were contoured using AQSim virtual simulation software. A sample axial slice demonstrating these structures is shown in Fig. 1. We have previously reported our techniques. In brief, a shrinking field technique was used with a standard AP–PA, right lateral, and left lateral beam arrangement. The initial planning target volume (PTV) was defined as 1 cm around the prostate, seminal vesicles, and periprostatic lymph nodes. The first cone down, PTV 2, was defined as 1 cm around the prostate alone. At 5600 cGy, the posterior border was changed to 2.5 mm posterior to the prostate. The final cone down volume (PTV 3) was defined as 0.7 cm around the prostate, except for the posterior border, which remained 0 mm. To account for penumbra, 5 mm were added to all stated borders. All four beams received equal weighting. Three-dimensional dose calculations were performed, and the dose was normalized to ensure coverage of the PTV by the 95% isodose line according to Interna-

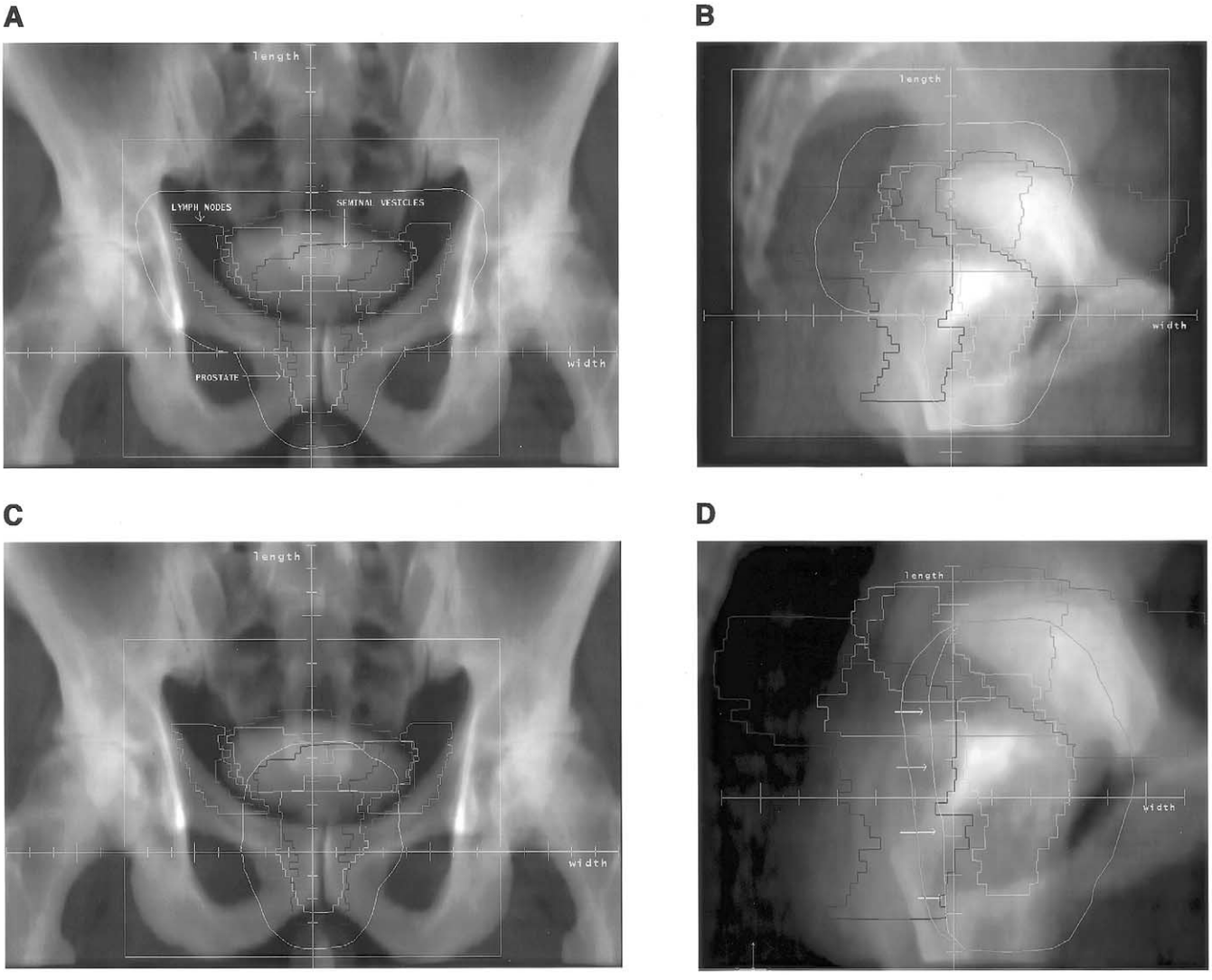

Fig. 2. (A,B) Typical AP and right lateral fields for initial treatment volume. (C,D) Typical AP and right lateral fields for first cone-down volume. Arrows indicate anterior rectal wall shield placed at 5600 cGy.

tional Commission on Radiation Units and Measurements (ICRU) criteria for dose reporting (8). Figure 2 demonstrates digitally reconstructed radiographs of typical anterior and right lateral fields for each PTV 1 and PTV 2. Figure 3 demonstrates a sample dose–volume histogram. During the study period, no set criteria were used to define the total rectal volume, thus the ability to analyze dose–volume histogram characteristics is limited. No set dose–volume histogram criteria were used to accept or reject a plan.

Radiation dose and volume

All patients were treated with megavoltage energies (10–18 MV). Daily fractions of 2.0 Gy were used to deliver 46 Gy prescribed to the 95% isodose line, which was designed to encompass PTV 1. This equates to an ICRU dose of 48.3 Gy to the 100% isodose line. The prostate and base of the seminal vesicles were then treated to 58 Gy in 2.0-Gy fractions (with rectal shielding added at 56 Gy) prescribed to the 95% isodose line for an ICRU dose of 61.0 Gy. The prostate alone was then treated in 2-Gy fractions prescribed to the 95% isodose line for a median total dose of 78 Gy (range 75–80) or an ICRU median total dose of 82 Gy (range 79–84).

Biochemical and clinical end points

The identified patients were evaluated for biochemical control status, late GI toxicity, and late GU toxicity. After each follow-up visit, an independent nonphysician data manager updated the patient's data file. The study author then verified all pertinent data on patients identified within this prospective database. GI and GU toxicity was scored according to the Radiation Therapy Oncology Group (RTOG)/European Organization on Research and Treatment of Cancer (EORTC) Late Morbidity Grading Scale (Table 1). We have previously reported our morbidity results according to the RTOG, Late Effects Normal Tissue Task Force (LENT), and the Fox Chase modified LENT scales. We believe that the LENT and Fox Chase modified

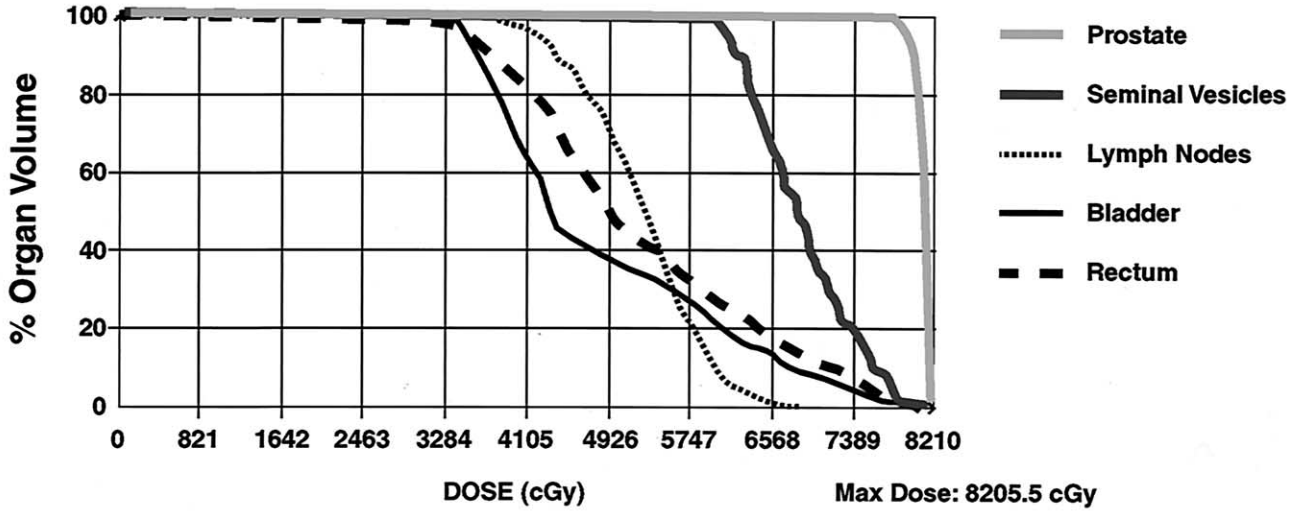

Fig. 3. Sample composite dose–volume histogram.

LENT scales are more conservative for reporting GI complications and more accurately assess the impact of morbidity on a patient's quality of life (9). To more easily allow data comparisons with other reported series, we have reported our results according to the RTOG scale.

Statistical analysis

All patients were followed at 3–6-month intervals, and the length of follow-up was calculated from the first day of RT. Biochemical failure was defined as three consecutive rises in prostate-specific antigen according to the American Society for Therapeutic Radiology and Oncology consensus definition (10). The Kaplan-Meier method was used to estimate the time-adjusted morbidity and biochemical rates (11); comparisons were made by the log–rank statistic (12). $p < 0.05$ was considered statically significant.

RESULTS

GI complications

The median follow-up was 26 months for the cohort of interest and 86 months for the comparison group. The 5-year actuarial rate of Grade 2 GI complications was 9% in patients treated with lateral rectal shielding and 38% in patients treated without rectal blocking ($p = 0.0004$; Fig. 4). Late Grade 2 GI complications consisted primarily of rectal bleeding. Of the 132 patients treated with rectal blocking, 10 experienced late Grade 2 GI complications; 9 experienced rectal bleeding and 1 bowel frequency. Of the 24 patients treated without lateral rectal shielding, all 8 with Grade 2 GI morbidity experienced rectal bleeding. Rectal bleeding in the cohort of interest was treated effectively with steroid enemas or suppositories in 6 patients, laser fulguration was required in 2 patients, and blood transfusion was required for 1 patient. The 1 patient with bowel frequency was treated effectively with Imodium. Of the patients treated without rectal blocking, 3 were treated effectively with steroid enemas, 3 required laser fulguration, and 2 required blood transfusions for bleeding refractory to other treatment. No patient experienced Grade 3 GI morbidity, and no patient required surgery.

Table 1. RTOG/EORTC scale for late GU morbidity

Grade	Description
1	Mild diarrhea, mild cramping, bowel movements 5 times daily, slight rectal discharge/bleeding
2	Moderate diarrhea, moderate cramping, >5 bowel movements daily, excessive mucous or intermittent bleeding
3	Obstruction or bleeding requiring surgery
4	Necrosis, perforation, fistula

Abbreviation: RTOG/EORTC = Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

GU morbidity

No statistically significant difference was found in either Grade 2 or Grade 3 GU morbidity according to the use of lateral rectal shielding. The rate of Grade 2 GU morbidity was 12% at 5 years (Fig. 5). Ten patients experienced urinary frequency, two experienced hematuria, and two experienced cystitis. The 5-year actuarial rate of Grade 3 GU complications was 2% (Fig. 5). All events occurred within 25 months. Three patients experienced Grade 3 GU toxicity; one experienced urethral stricture, one experienced Grade 3 cystitis, and one with a history of transurethral resection of the prostate experienced incontinence requiring a sphincter implant.

Biochemical control status

The overall 3-year actuarial biochemical control rate was 94% for the 134 patients treated with rectal shielding. Because the follow-up period for these patients was short, this result should be viewed with caution. Differences in the

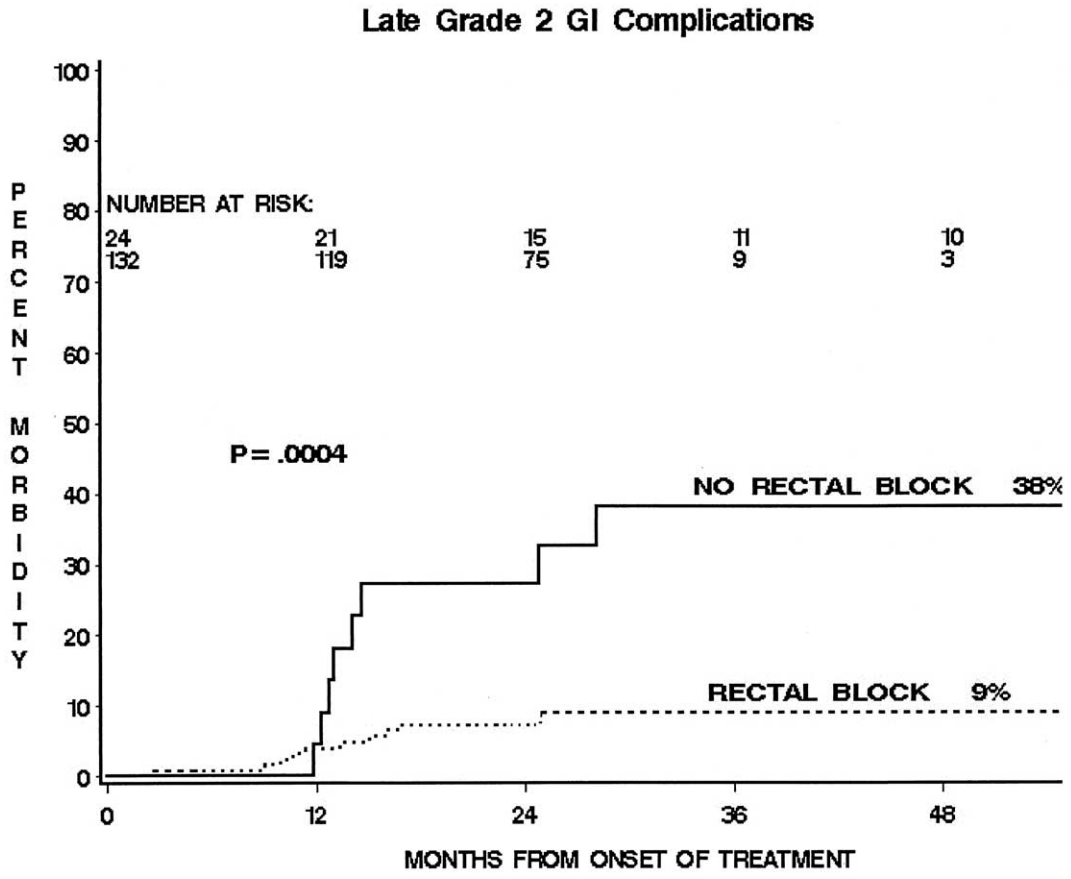

Fig. 4. Kaplan-Meier curves for late Grade 2 GI morbidity by treatment group.

length of follow-up and presenting characteristics between the patients treated with and without a rectal block prohibit a comparison between these two groups.

DISCUSSION

This communication reports our observations on late GI and GU morbidity in patients with prostate cancer treated with 3D-CRT. We demonstrate that a dose that has been previously described to be associated with higher biochemical control rates can be safely delivered to the prostate with a four-field technique. A late Grade 2 GI morbidity rate of 9%, late Grade 2 GU morbidity rate of 12%, and a late Grade 3 GU morbidity rate of 2% were found. This is comparable to the morbidity rates for 3D-CRT reported by other institutions (3, 13). One concern was that blocking the rectum on the lateral fields would lead to a decrease in the dose delivered to the cancer-containing posterior portion of the peripheral zone, and thus a decrease in cancer control. Our previously published experience and the experience of others, however, do not support this concern (1, 3). Longer follow-up is required before meaningful conclusions regarding biochemical control can be made from this patient cohort.

The goal of 3D-CRT is to deliver a high dose of radiation to the target and at the same time limit the dose to the surrounding normal tissue. This results in an improvement in the therapeutic index by improving the biochemical and clinical outcomes and restricting or reducing complications. Several institutions have found a dose–response curve from dose escalation in the treatment of prostate cancer (1–5). It is clear that dose escalation must be attempted with care, because higher radiation doses to normal tissue result in increased morbidity (6).

We believe it is important to view these results in the context of the morbidity profiles reported for other prostate treatment modalities, such as brachytherapy and intensity-modulated RT (IMRT). Brachytherapy is a popular treatment option for patients with low-risk disease. A recent study found a 10% rate of Grade 2 proctitis after brachytherapy for low-risk disease. The bleeding rates were found to be as high as 23% when doses to various cutoff volumes were exceeded (14). Recently, a report of toxicity after treatment with IMRT suggested an improvement in late Grade 2 GI morbidity from 10% with 3D-CRT (delivered to the prostate alone) to 3% using IMRT (3). The technique we described treats approximately one-half of the pelvis to 45 Gy. Concerns have been raised over the morbidity associated with pelvic irradiation. The late Grade 2 GI morbidity rate reported here suggests this rate is low. In fact, it is the same as the GU morbidity rate after 3D-CRT to the prostate alone reported from the Memorial Sloan-Kettering Cancer

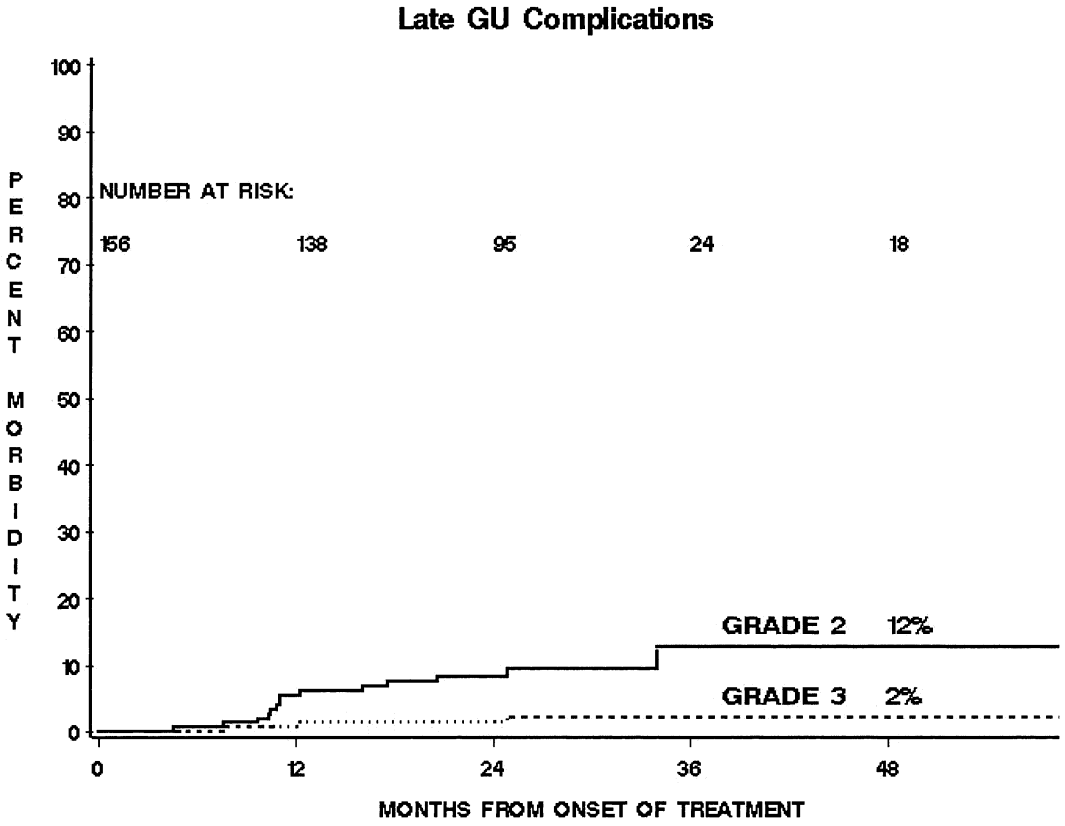

Fig. 5. Kaplan-Meier curves for late GU morbidity by treatment group.

Center (3). Our finding is consistent with the morbidity profiles previously published. Hanlon *et al.* (15) found no difference in rectal bleeding or bowel control rates between patients treated to the pelvis vs. the prostate alone. The differences found were modest, with patients treated to the pelvis more likely to experience rectal urgency (40% vs. 22%), less satisfied with bowel function (72% vs. 88%), and more likely to have bother from nocturia (7% vs. 3%) (15).

We believe that this 3D conformal treatment technique can be used to deliver high-dose radiation safely. The doses reported here have previously been shown to be associated with improved biochemical control compared with lower doses (1–3). Because of the simple nature of its design, this technique could be safely implemented in the general radiation oncology setting without undue burden. As technology advances, we will continue to witness improvements in dose distribution, cure rates, and morbidity profiles. These technologies will, however, require time before they are adopted in the general radiation oncology community. Because of the complexity of implementation and the costs associated with necessary auxiliary equipment, it will be some time before IMRT, ultrasound localization, fiducial markers, or in-room CT simulators are widely available outside of select institutions. Additionally, it is important for clinicians to make incremental changes in their practice to adjust to the details of applying new techniques and technology. We believe this technique will provide the future-looking radiation oncologist with an appropriate initial step in dose escalation and will serve as a stepping stone toward future techniques. We are not suggesting that this treatment should take the place of further technological developments, but rather that the safe implementation of high-dose treatment strategies need not be delayed.

CONCLUSION

The treatment method described is a simple four-field conformal technique that can be easily implemented in the general radiation community. A dose of 79–84 Gy can be safely delivered to the prostate, with a 9% rate of late Grade 2 GI, 12% rate of late Grade 2 GU, and 2% rate of late Grade 3 GU complications.

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