Strategies for Improving the Outcome of Patients with Poor Prognosis Prostate Cancers*

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Prostate cancer patients who present with pretreatment PSA levels >10 ng/ml, Gleason sums of 7–10 or palpation stage T2C/T3 cancer all show a relatively poor prognosis after treatment with any single modality. Freedom from failure rates at 5 years after radiation or prostatectomy for patients with one or more of these indicators ranges from 10 to 40% depending on the specific individual combination of these prognostic factors (1–4).

There is an intermediate group of patients with pretreatment PSA levels of 10–19.9 ng/ml combined with T1, 2AB Gleason 2–6 tumors where the 5-year freedom of failure rate is 66% and those patients do not qualify for this discussion (1). However, when intermediate PSA levels of 10–19.9 ng/ml are combined with Gleason 7–10 or T2C, T3 tumors, the 5-year failure rate exceeds 50% and those patients should be considered for implementation of these strategies (1).

Several strategies have emerged directed at improving the outcome for these patients based in part on a better understanding of their patterns of failure (5). They include 1) increasing dose with 3D conformal treatment technique (3DCRT) to improve local control, 2) reducing treatment morbidity by more accurate targeting and by reduced margins of normal tissue with 3DCRT, 3) evaluating the role of adjuvant androgen deprivation combined with radiation therapy, and 4) multi-modal treatments, including chemotherapy, radiation and hormonal therapy (6–10). This communication reviews some of the progress in these areas.

PATTERNS OF FAILURE: PRETREATMENT PSA >20 ng/ml

We have previously reported the patterns of failure in patients with pretreatment PSA levels >20 ng/ml, and this is summarized and updated in this section (5). Table 1 records freedom from metastasis (FDM) and biochemical and clinical freedom from failure (bNED) for various PSA groupings above 20 ng/ml. Our expression bNED failure is a rising PSA on two consecutive values exceeding 1.5 ng/ml. There is no difference in failure pattern by PSA grouping above 20 ng/ml. PSA values represent the Hybritech technique with normals 0–4.0 ng/ml.

Fig. 1 plots FDM and bNED for the total group and shows 76% overall failure at 5 years with 20% by metastasis. This illustrates that there are two problems in the management of these patients; one of improving local or regional failure that occurs in 56% of patients and the other reducing metastatic disease which accounts for first failure in 20% of patients in 5 years.

PATTERNS OF FAILURE: GLEASON 7–10

The patterns of failure for a less well-differentiated prostate cancer is shown in Fig. 2. We have previously shown that the bNED outcome of patients with Gleason 7 tumors is significantly different from Gleason 5–6 tumors so that Gleason 7 is pooled together with Gleason 8–10 tumors (11). The overall failure at 5 years is 65% with 20% due to metastasis and 45% due to local regional failure or occult metastasis. Again, failure patterns in this group indicate that two strategies are needed: one approaching local regional disease and the other metastasis.

PATTERNS OF FAILURE: T2C, T3

Patterns of failure for palpation T2C, T3 tumors are shown in Fig. 3. We include T2C patients in this grouping

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Table 1

Outcome by PSA grouping above 20 ng/ml

PSA group (ng/ml)	n	5 year	
		FDM	bNED
20–29.9	55	84%	26%
30–49.9	39	71%	18%
50+	35	78%	23%
		p = 0.25	p = 0.12

as their failure rate is similar to T3 patients in our experience. At 5 years, the total failure rate is 59% with 23% due to metastasis and 36% due to local regional disease and/or occult metastasis. Again, two patterns of failure are evident.

There is, however, one exception to this patient grouping. We have previously reported the outcome for T2C-T3 tumors treated with 3DCRT (1). For the subgroup with pretreatment PSA levels < 10 ng/ml, 70% are free of failure at 5 years' follow-up. This low pretreatment PSA group with locally advanced cancers should be excluded from consideration as a poor prognosis subset.

MULTIVARIATE ANALYSIS OF OUTCOME PREDICTORS

Table 2 shows a multivariate analysis of pretreatment outcome predictors including pretreatment PSA levels, Gleason sum 7–10 and T2C, T3 tumors. Outcomes evaluated are bNED, distant metastasis (DM) and cause-specific survival (CSS). This table shows that pretreatment PSA levels predicts for bNED outcome but not CSS or DM, that T2C-T3 predicts for bNED CSS and DM, and that Gleason 7–10 predicts for only bNED. Dose is also an independent variable for bNED outcome and our previous work has shown that one Gy equals an 8% change in 5-year bNED rate.

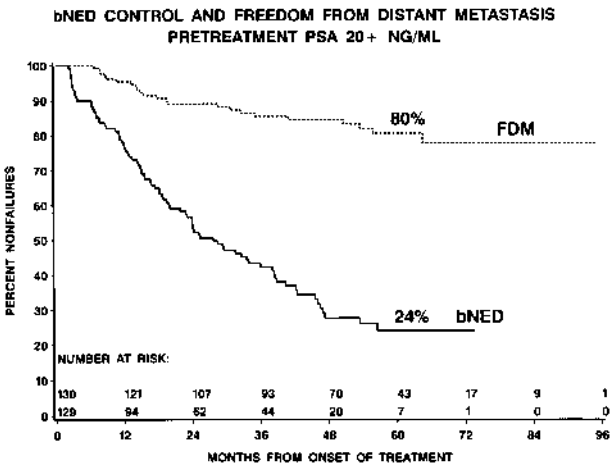

Fig. 1. Patterns of failure for pretreatment PSA 20 + ng/ml.

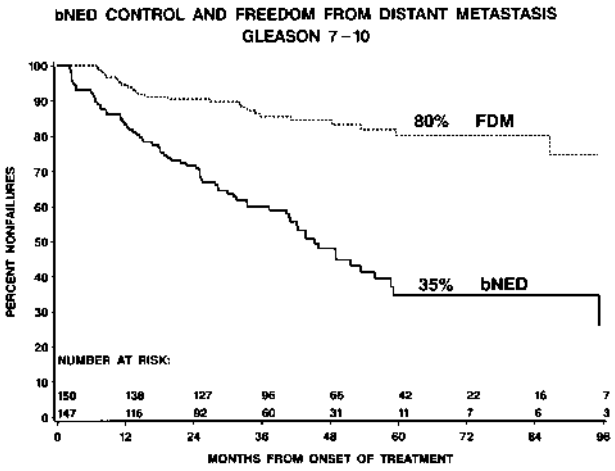

Fig. 2. Patterns of failure for Gleason 7–10 tumors.

3D CONFORMAL RADIATION TECHNIQUE—MORBIDITY

3D CRT allows the use of higher doses of radiation with less morbidity than observed with conventional technique. For example, using the RTOG morbidity scale, we have observed $< 1\%$ late grade 3 or 4, GI morbidity at 5 years in sharp contrast to the 4.5–5.5% reported for the USA national average and to the 8–10% reported from older RTOG studies (12, 13). Our low rates are similar to those obtained at Memorial Sloan Kettering with 3DCRT (7).

Serious genitourinary morbidity has been similarly infrequent. For patients without a previous TURP, we have no patients wearing a pad everyday for incontinence and only 1% intermittently wearing a pad for incontinence. Prior TURP, however, is associated with a 2% rate of serious incontinence (14).

Fig. 4 shows our dose responses for morbidity assessed by the Late Effects on Normal Tissue scale for grade 2 GI, grade 2 GU, and grade 3, 4 GI, based on 4-year actuarial results (14, 15). The grade 3, 4 GI scale is a Fox Chase

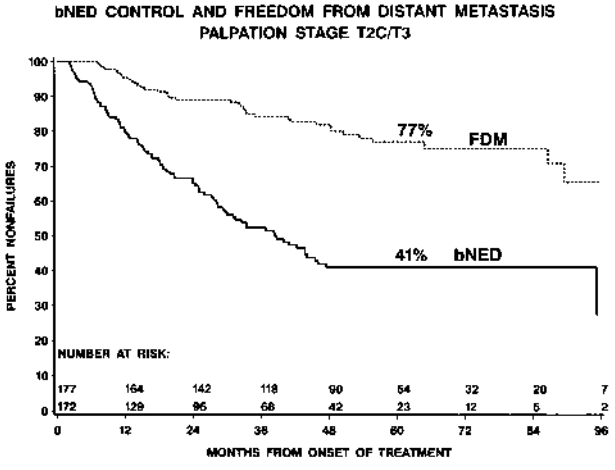

Fig. 3. Patterns of failure for palpation T2C, T3 tumors.

Table 2

Factors associated with bNED, cause specific survival and distant metastasis with 3DCRT. Stepwise multivariate analysis

Factor	bNED	CSS	DM
Dose (continuum)	0.0096	NS	NS
PSA (continuum)	0.0001	NS	NS
T2C, T3 vs T1, 2AB	0.025	0.0047	0.0003
Gleason 7–10 vs 2–6	0.0001	NS	NS

CSS = cause specific survival; DM = distant metastasis; Median follow-up 54 months.

modification of the LENT scale where any transfusion for rectal bleeding or >2 fulgurations for bleeding becomes a grade 3 event (16).

With our original 3DCRT technique, which included a 1 cm CTV to PTV interval around the prostate, including the rectal side, at 76 Gy, grade 2 GI morbidity was 32%, grade 2 GU was 11% and grade 3–4 GI was 8% (14, 15). Our further studies have demonstrated that by restricting the dose to the anterior rectal wall to 71–72 Gy by appropriate shielding, the grade 2 and grade 3, 4 GI sequelae are reduced to 11% and 2% respectively, at 76 Gy to the ICRU reporting point (17).

3D CONFORMAL RADIATION TECHNIQUE—bNED DOSE RESPONSE

Fig. 5 shows the dose response for bNED for patients in our dose escalation study based on 4-year actuarial results with a median follow-up of 60 months. There was no dose response for patients with pretreatment PSA <10 ng/ml and we currently treat them to 71 Gy to the ICRU recording point with a 5% various across the target with a four-field conformal technique.

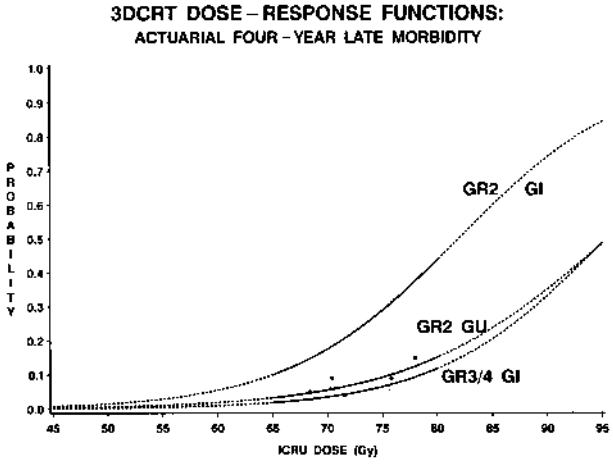

Fig. 4. Logit response model (based on LENT grade 2 GI and GU morbidity and Fox Chase modification of LENT grade 3, 4 scale.

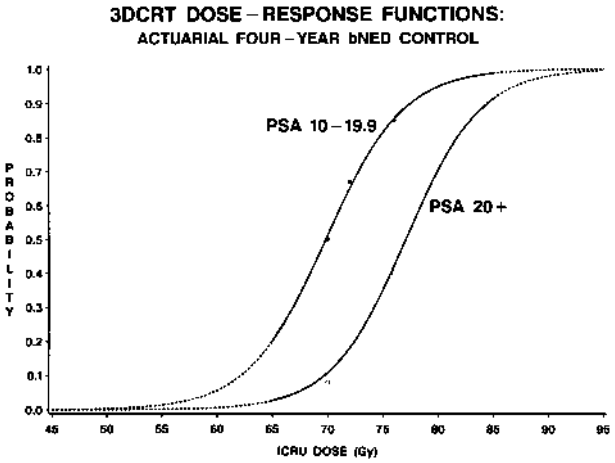

Fig. 5. Logit response model based on 4-year bNED by PSA level.

There is a clear and dramatic dose response for both the intermediate and higher pretreatment PSA groupings. The relative ineffectiveness of conventional dose (65–70 Gy) treatment compared with easily achieved 3DCRT doses of 76 Gy is apparent and detailed in Table 3. For the PSA grouping 10–19.9 ng/ml, the bNED difference is 40% and a difference of 22% is observed for patients with pretreatment PSA levels >20 ng/ml. Any strategy designed to improve outcome of high PSA levels in patients must include an appropriate increase in dose.

ADJUVANT ANDROGEN DEPRIVATION

The RTOG has made important contributions to this area of investigation and they are summarized in Table 4 (8, 9). The RTOG trials show a prolongation of time to failure with short-term (4 months) total androgen deprivation and with long-term (2 years) androgen deprivation with LHRH agonist alone. There is no survival advantage in either RTOG-8610 or RTOG-8531. A subset analysis of RTOG-8531, however, demonstrates a survival advantage for centrally reviewed Gleason 8–10 tumors receiving long-term LHRH agonist treatment where 66% 5-year survival was observed for the adjuvant group and 55% for the radiation only group ($p = 0.03$) (9).

The EORTC has completed and important trial in patients with T1 and T2 tumors with WHO grade 3 histology and all T3–T4 tumors (10). Goserelin was begun with

Table 3

Importance of increasing dose 5-year bNED

	PSA group	
	10–19.9 ng/ml	20+ ng/ml
Conventional dose, 70 Gy	30%	10%
3DCRT dose, 76 Gy	75%	32%
Improvement	40%	22%

Table 4

RTOG trials with androgen deprivation and radiation

Trial	Entered	Result	Survival difference
86–10 4-mo. TAD	5×5 tumors	Delays failure	No
85–31 2 y LHRH	N+ and local advanced	Delays failure	No
85–31 subset	Gleason 8–10	Delays failure	Yes

TAD = LHRH and androgen blocker; LHRH = Goserelin.

radiation therapy, delivered in standard doses (< 70 Gy) and continued for 3 years in the experimental arm. The survival difference at 5 years was 79% vs 62%, a 17% difference ($p = 0.001$). The adjuvant arm noted a reduction in metastasis. This study will change the treatment of advanced prostate cancer and one wonders what might have been achieved in either treatment arm with a higher radiation dose.

MULTI-MODAL TRIALS

Phase 2 trials are underway in a number of institutions testing estramustine, taxol, VP16 and other active chemotherapy agents in combination with radiation. There are no reports at present indicating the efficacy of these combinations.

SUMMARY

It is clear that we can identify groups of patients with a poor outcome when treated with radiation therapy alone. Patterns of failure indicate the problem in these patients, including both excessive local regional failure and metastatic disease (5). The latter is probably present in 30–60% of these patients at the time of treatment but is not detectable by present diagnostic means.

There is a clear dose response for 4-year bNED and dose is an independent variable on multivariate analysis (14, 15). The relative ineffectiveness of conventional dose level radiation (< 70 Gy) vs 76 Gy is clearly demonstrated. If possible, despite the technological requirements of 3DCRT, future trials of adjuvant treatments should be combined with radiation-delivering doses of 75–80 Gy by 3DCRT. The reduction in the late morbidity associated with 3DCRT is impressive and on its own justifies adopting this technology (1, 6, 7).

Adjuvant androgen deprivation with radiation in prostate cancer was originally thought to perhaps be similar to the addition of tamoxifen to breast cancer management with an opportunity for eliminating micro-metastasis. With the Bolla et al. (10) trial, it appears that this result may have been achieved in prostate cancer, but the magnitude of effect (17%) is much more than one would expect and this trial needs to be confirmed.

It is worth noting from both a cost and morbidity viewpoint that LHRH agonist used alone with radiation is the only adjuvant hormone manipulation associated with a survival advantage. The addition of androgen blockers with their cost, GI, liver and other toxicities has yet to be proven in the adjuvant setting.

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