The case for dose escalation versus adjuvant androgen deprivation therapy for intermediate risk prostate cancer

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Patients with intermediate-risk prostate cancer have a significant risk of biochemical failure after treatment with external beam radiation therapy. Two strategies to improve outcomes are radiation dose escalation and androgen deprivation therapy (ADT). This article discusses the evidence in favor of dose escalation.

The case for radiation dose escalation has been established by several randomized studies, which show improved biochemical control (bNED) rates. Although late toxicity was also increased, it remains at clinically acceptable levels. The use of more focal methods of radiation, such as proton therapy and intensity modulated radiation therapy (IMRT), allows safe dose escalation to 80 Gy. The role of adjuvant ADT is most clearly established in high-risk disease. Advantages in the intermediate-risk group are less pronounced. It is probable that therapeutic gain seen from dose escalation in intermediate-risk patients might allow them to be spared the toxicity of ADT and yet achieve good PSA and clinical control rates. Further randomized trials comparing and or combining the two treatment strategies are required.

Key Words: prostate neoplasms, radiation therapy, radiotherapy dosage, antineoplastic agents, hormonal, adjuvant therapy

Introduction

Risk grouping schema have identified the intermediate risk group to be at significant risk of biochemical failure.[1,2] While retrospective dose-escalation studies have indicated that outcomes are better with increasing radiation dose, such trials are confounded by more recent cohorts of patients having better outcomes. This results from the earlier diagnosis by PSA screening, as well as Gleason score migration.[3] Additionally the American Society for Therapeutic Radiation Oncology (ASTRO) PSA relapse definition (bNED) favors more recently treated patients because of the bias of backdating, a problem that does not occur with the new 'Phoenix' (nadir + 2) relapse definition.[4]

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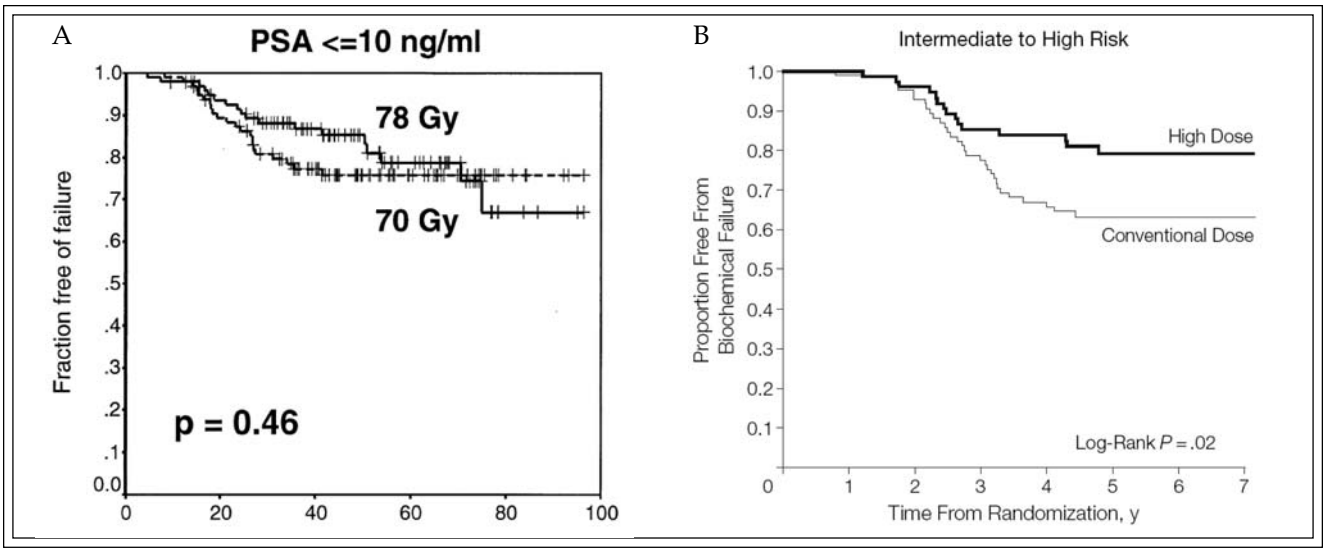

Figure 1. PSA control rates with dose escalation
A) Intermediate risk group, Pollack et al.[6] Reprinted with permission from Elsevier ©2002
B) Intermediate-High risk group. Proton boost dose escalation from 70.2 to 79.2 GyE.[7] Reprinted with permission from American Medical Association ©2005. All rights reserved.

The case for dose escalation

Phase 2 dose escalation trials suggest a possible benefit in the intermediate risk group. For example the RTOG 9406 trial showed 5-year bNED rates of 62% with 68.4 Gy (1.8 Gy/#), rising to 67% with 79.2 Gy (1.8 Gy/#) and 71% with 74 Gy (2 Gy/#).[5]

Randomized trials of dose escalation have now been published. The MD Anderson trial[6] compared 70 Gy with 78 Gy, and showed a significant improvement in the 6-year bNED rate with 78 Gy of 62% versus 53% for the intermediate risk group with a PSA>10ng/ml (p=0.012), Figure 1a.

More recently Zietman and colleagues[7] showed significant improvements in the bNED rate with 79.2 GyE compared to 70.2 GyE in a trial of proton boost following conformal photon radiation. The improvement was seen in both low and intermediate groups, where the bNED rate improved from 63% to 79.5%, Figure 1b. A third trial in the Netherlands of 68 Gy versus 78 Gy has been completed and shows a 10% improvement in PSA control at 5 years.[8] The improvement was slightly greater in the intermediate group than the high risk group. The summary message from these trials is that the benefits are most pronounced for intermediate risk cases, and modestly beneficial in low and high-risk tumors.

Toxicity is a potential concern where doses are escalated. The MDACC trial did show increased late rectal toxicity (26% grade 2+ compared with 12% in the low dose arm, p=0.0001). Further analysis however revealed that this was closely related to the V_{70} of the rectum. When <25% of the rectum had received 70 Gy the late toxicity incidence was 16%, rising to 54% where the V_{70} was above 25%. There was no significant difference in late urinary toxicity. The Dutch randomized trial generally showed similar rates of late toxicity between the 68 Gy and 78 Gy arms, with late grade 3 incidence rising from 2.3% to 4.7%.[9] The proton dose escalation trial showed a doubling of the late GI toxicity from 8% to 17% (p=0.005), but very low rates of grade 3 toxicity (<2%). Other studies have shown that rectal toxicity can be reduced by the use of three-dimensional conformal radiation therapy, IMRT, and by restricting the exposure of rectal mucosa by utilizing dose-volume histogram-based planning.[10]

The role of adjuvant androgen deprivation therapy (ADT)

Randomized trials have also shown benefit from the use of adjuvant androgen deprivation (ADT) when used in combination with radiation therapy. Generally these benefits have been most in the high-risk group utilizing long durations of adjuvant therapy.[11,12] In the intermediate risk group benefit has also been shown with shorter durations of *neoadjuvant* ADT.[13-15] All three showed a reduction in cause specific mortality and in the D'Amico analysis an overall survival benefit

was seen. The D'Amico study[15] requires replication as the difference in death rate that was observed resulted from only six deaths, and the relatively early emergence of a difference in survival for this good prognosis group is unexpected and not readily explicable.

It has been suggested that patients who relapse after such therapy might have faster PSA doubling time kinetics than patients who did not receive neoadjuvant therapy but this has not been borne out in clinical practice,[16,17] and there is even experimental evidence that it may be slower.[18] The degree of improvement in bNED rates with such approaches in intermediate cases approximates to the improvement seen with dose escalation.

Androgen deprivation has the potential for serious toxicity including sporadic reports of increased non-prostate death.[19] Less serious toxicity includes weight gain, hot flashes, mood disturbance, decreased libido, muscle weakness and the potential for cognitive dysfunction.

The important question then arises whether the decreased toxicity profile of dose escalation in comparison with the toxicity of ADT might support dose escalation as the preferred method to improve outcomes. However, there is no reason to suppose that the benefits of dose escalation and adjuvant ADT might not be additive. A recent study by the Italian GICOR study group[20] used a risk-adapted approach whereby men with low risk cancer received radiation alone, intermediate risk cancers received 4-6 months of neoadjuvant ADT and the high risk group an additional 2 years of ADT. Two dose levels were used; <72 Gy in 55% of patients and >72 Gy in the remainder. There was no significant difference in bNED rates according to risk group and multivariate analysis revealed that higher radiation dose improved outcome for both low and high-risk cancer and was of borderline benefit in the intermediate group. This suggests that there is still a place for dose escalation in those high-risk cases that also receive long term ADT. Increased rectal toxicity was seen in those receiving pelvic radiotherapy and was of borderline significance in the higher dose groups. Randomized trials comparing dose escalation versus adjuvant ADT are required to further examine the relative benefits.

Conclusion

Dose escalation has been established to improve bNED rates in several randomized studies. Although late toxicity has also increased, it remains at clinically acceptable levels. The use of more focal methods of radiation such as proton therapy and IMRT has allowed safe dose escalation to 80 Gy. The only randomized trial to have reported other clinical endpoints to date is the MSKCC trial which also showed a significant reduction in metastasis rate. Whether or not this will translate into a survival benefit with more mature follow-up is uncertain.

The role of adjuvant ADT is most clearly established in high-risk disease, and advantages in the intermediate risk group are less pronounced, although a survival benefit has been realized in some studies. It is probable that therapeutic gain seen from dose escalation in this patient subgroup may allow patients to be spared the toxicity of ADT and yet achieve good PSA and clinical control rates. □

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