Pergamon

European Journal of Cancer Vol. 33, No. 4, pp. 555 559, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(96)00442-X

Clinical Oncology Update: Prostate Cancer

Progress in the Management of T3-4 Adenocarcinoma of the Prostate

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INTRODUCTION—CONVENTIONAL EXTERNAL BEAM RADIATION THERAPY

OVER THE last three decades, the U.S. and European standard for the curative treatment of locoregionally confined prostate cancer (clinical stages T1-4NxM0) has been radical irradiation [1]. The radical prostatectomy has, more recently, become a widely used alternative, but is limited to younger men with no significant comorbid conditions and only the earlier stages of the disease (T1-2N0) [2]. Clinical T3 disease is treated by surgery at only a few institutions, and then usually in conjunction with androgen suppression as cure rates are low [3].

The ability of radiation to cure, when used as the sole treatment modality, is limited by two main factors. The first is the bulk of the primary tumour, large tumours having a lower likelihood of eradication [4]. The second is the possibility that occult micrometastatic disease may exist undetected at the time of local treatment. Although T3-4NxM0 disease is judged clinically to be locoregionally confined, the probability of this decreases with increasing tumour bulk, Gleason grade and pretreatment prostate specific antigen (PSA) level [5].

Radiation treatment results were, until the late 1980s, usually expressed in terms of clinical local control (i.e. the absence of local regrowth) [6–8]. For T1 and T2 tumours, clinical control rates exceeding 80% at 10 years have been repeatedly observed. Values of between 50 and 70% are usually seen for T3 and T4 tumours. Fuks and colleagues demonstrated that, for T2-4 tumours treated by radioiodine implantation, clinical local control was associated with a better overall prognosis, and palpable local recurrence was followed by a second wave of metastases [9]. In a randomised multicentre study reported in 1988 by Griffin and associates stage T3-4 tumours when treated by mixed photon and neutron beams showed better clinical local control than when treated by photons alone [10]. This translated into better disease-free and overall survival. The Baylor group have also documented the substantial morbidity associated with local recurrence following radiation [11]. The average patient required two or three subsequent surgical procedures to palliate the morbid consequences of regrowth. Even if there were no survival gains, the quest to improve local control would still be worthwhile to alleviate these unpleasant consequences of failure.

The assumption common to all the previously mentioned studies of local control has been that a clinically negative gland rarely harbours tumour. In recent years, this assumption has come under significant challenge by the use of more stringent criteria of local control and relapse-free existence. A number of series have been published in which palpably normal prostate glands were rebiopsied 18 months or more after irradiation [12, 13, 15]. It is disquieting that in all series anything from 14–91% of rebiopsies showed viable tumour. The likelihood of obtaining a positive rebiopsy was higher for patients whose tumours were initially large (T2b-3) and in patients with an elevated serum PSA level at the time of rebiopsy. A positive rebiopsy predicts strongly for both local and distant failure, and for decreased overall survival compared with histologically negative patients [12, 15]. Thus, clinical local control is no longer an adequate measure of the efficacy of radiation as a local treatment. Pathological control is the new yardstick of local success.

A second parameter now widely used to detect persistent or recurrent disease is the serum PSA [16, 17]. A rise in serum PSA almost invariably precedes clinical recurrence, although sometimes years may pass between the two. Studies in which freedom from PSA elevation has been included in the definition of disease-free existence are now being reported. These show recurrence-free survival figures approximately 20% lower than those obtained historically using a purely clinical endpoint [18–21]. This is the case for both early stage and locally advanced tumours and suggests that there is room for improvement at both ends of the spectrum. Rising postirradiation PSA may be due to occult metastatic disease, but the positive rebiopsy data from patients with clinically normal glands suggests that, in a proportion, it must also come from occult uncontrolled primary

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disease. Indeed, Dugan and associates reported that 38% of rebiopsies performed on palpably normal glands 2 or more years after irradiation for T3-4 disease were positive [14]. When the PSA was elevated at greater than 1.0 ng/ml, 63% of rebiopsies were positive.

The use of rebiopsy and serum PSA as tumour control endpoints has made it evident that radiation therapy as a single modality is considerably less effective in managing locoregionally confined disease than was previously presumed. This is particularly true for locally advanced tumours (T2b-4) and for those of high grade (Gleason grade 4 and 5) and high initial serum PSA (>15 ng/ml; Hybritech Assay). At the Massachusetts General Hospital, Massachusetts, U.S.A., over 500 T3-4 patients were treated with conventional external beam radiation to tumour doses of 68–72 Gy during the 1980s. Actuarial disease-free survival at 10 years, using the new strict criteria, show that only 20% remain disease-free (Figure 1a,b). The true value may actually be lower than this as some men died apparently disease-free prior to the introduction of PSA into routine use at our institution in 1988. Strategies to improve local control will both decrease the morbidity of local recurrence and improve metastasis-free survival. A systemic therapy effective against the small volume occult metastatic disease commonly present at diagnosis offers the potential for further survival gains.

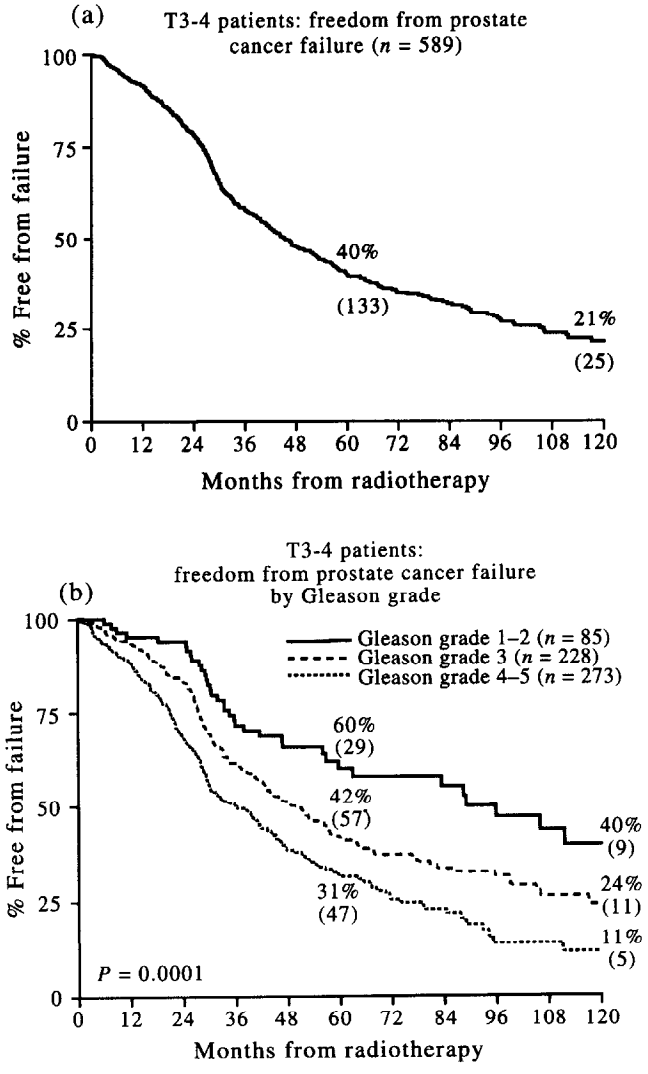

Figure 1. (a) Disease-free survival for 589 men with T3-4 Nx M0 adenocarcinoma of the prostate treated at the Massachusetts General Hospital between 1978 and 1993. The criteria for failure include the requirement that serum PSA be below 1 ng/ml 2 or more years after radiation therapy, (b) disease-free survival for the same 589 men divided according to biopsy Gleason grade (grade 1–2, well differentiated; grade 3, moderately differentiated; grade 4–5, poorly differentiated).

NEW RADIATION STRATEGIES TO IMPROVE OUTCOME

Local control may be improved by one of two strategies: (i) Dose escalation: increasing the delivered radiation dose to increase the probability of tumour eradication. This requires conformal delivery and planning systems in order to avoid a parallel increase in morbidity; and (ii) neoadjuvant cytoreduction: to improve local control without the necessity for increased dose.

DOSE ESCALATION

The relationship between delivered radiation dose and tumour control probability is central to the practice of modern radiotherapy. The Patterns of Care Studies have shown an apparent dose response for T3-4 tumours over the range 60–70 Gy with clinical local control as the endpoint [1]. It seems reasonable to assume that this can be extrapolated to pathological local control. Dose escalation above 70 Gy in the pelvis can only be safely achieved by the use of conformal techniques with or without three-dimensional planning.

Leibel and associates presented interesting early results from a phase I dose escalation study [22]. 324 patients received doses ranging from 65 to 81 Gy with 237 being treated to at least 70 Gy. The 3-year actuarial probability of surviving with a normal PSA was 97% for stages T1c-2a, 86% for T2b, 60% for T2c and 43% for T3. Encouraging as these results are for early disease, those obtained for T3 patients leave much to be desired. They are likely to decline considerably further with the passage of more years. In addition, a normal PSA after irradiation was defined as being $\leqslant 4$ ng/ml. This may well be too high and, if so, results in an underestimation of biochemical failure [21].

The only randomised study to address comprehensively dose escalation was reported by Shipley and associates [23]. 202 T3-4NxM0 patients were given 50.4 Gy by conventional 4-field external beam photons and were then randomised to receive either a photon boost to 67.2 Gy or a conformal boost using a perineal proton field to 75.6 Cobalt Gray Equivalent (CGE). The results with a median of 5 years follow-up are shown in Table 1. No significant differences were seen between the treatment arms in terms of local control, disease-free survival or overall survival. There was a trend towards an improvement in local control for those receiving high dose and subset analysis showed this resulted from a significant difference in local control amongst those with poorly differentiated tumours. The rate of positive rebiopsy in patients whose digital rectal examination had normalised following treatment and who underwent prostate rebiopsy was lower for the high-dose than the low-dose ram (28% versus 45%) but this did not reach a level of significance.

Table 1. Results of a Massachusetts General Hospital randomised trial comparing conventional external beam photon radiation therapy to external beam photons with a high dose proton boost in T3-4NxM0 adenocarcinoma of the prostate

Radiation dose	*n*	8-year local control†	8-year disease-free survival‡
67.2 Gy	99	59%	16%
75.6 Gy*	103	73%	20%

*50.4 Gy using photons, and 25.2 Cobalt Gray Equivalent using a perineal proton boost; †Includes rebiopsy data from 32 patients with no clinical evidence of regrowth; ‡Disease-free defined as no clinical evidence of disease and serum PSA below 4 ng/ml.

The fact that this trial was largely negative should not necessarily deter us from a further exploration of dose escalation. It is possible that the dose tested was not high enough. It is also probable that a large number of men with occult metastatic disease with nothing to gain from dose escalation were included in the trial. Future studies will exclude those who are known to be node positive and those with exceedingly high serum PSA values. The latter was not available at the initiation of this study to discriminate the highest risk subgroups.

It has been suggested that dose escalation can be achieved with minimal rectal toxicity when conformal techniques are employed [21, 24, 25]. A note of warning, however, has been sounded by the Massachusetts General Hospital randomised trial. This study, with considerably longer follow-up than any other reported, showed a 27% level of grade 1–2 late rectal bleeding when 75.6 Gy was given in a randomised trial as compared with only 9% when the dose was 67.2 Gy [26]. The vast majority of the bleeding was only grade 1 or 2 and temporary and may not be a high price to pay for a higher likelihood of cure if it exists.

Recent work by Corn and associates with only short follow-up seems to show an advantage, in terms of early biochemical control, to conformal radiation over conventional technique without any increase in total given dose [27]. This raises the possibility that more cures may be achieved simply by improved targeting.

NEOADJUVANT CYTOREDUCTION

The probability of local tumour eradication by radiation may be increased by an initial volume reduction assuming this comes from a reduction in the number of tumour clonogens [4]. The relationship between decreasing tumour volume and increasing tumour control is well established in both the clinic and the laboratory. We have performed a series of experiments using two androgen dependent murine adenocarcinomas: Shionogi SC-115 and Dunning R3327 [28]. When implanted into male athymic nude mice, The Shionogi tumour grows in a predictable manner only to regress to less than 10% of its original volume 12–12 days after the animals are castrated. One week later an androgen independent tumour regrows. If radiation is given at the time of maximal regression, the TCD_{50} (radiation dose required to eradicate 50% of tumours) is reduced substantially and significantly (Table 2). The Dunning tumour does not regress after orchiectomy like the Shionogi tumour but instead displays a period of clinical growth arrest. When orchectomy and radiation were combined the same enhancement was seen. The mechanism for this effect is unclear although many possibilities exist: (i) cytoreduction with a straightforward diminution in the number of clonogens that the radiation is required to eradicate; (ii) synergism through a common mechanism of cell death such as apoptosis; (iii) volume reduction improving the nutritional status and oxygenation of the tumour, thus enhancing radiation kill; and (iv) the removal of cells from active cycle and into a resting phase. This could reduce the rate of accelerated repopulation during a long course of fractionated irradiation but would not be expected to impact, except negatively, on a single dose experiment.

Table 2. Combined radiation and orchiectomy in the treatment of androgen sensitive rodent tumours grown in athymic nude mice

Tumour	Androgen status of host animal	TCD_{50}*
Shionogi SC-115	Intact	>89.0 Gy
	Castrate	42.1 Gy
Dunning R3327	Intact	47.0 Gy
	Castrate	28.7 Gy

*TCD_{50} is the radiation dose required to control, on average, 50% of irradiated tumours.
Shionogi tumours irradiated at 6 mm diameter in intact mice. In the second group, orchiectomy was performed on mice with 6 mm tumours and irradiation given at the time of maximal tumour regression 10–12 days later. Dunning tumours irradiated at 8 mm diameter in intact mice. In the second group, orchiectomy was performed on mice with 8 mm tumours and irradiation given the following day. Irradiation was performed using a 137 Cs small animal irradiator with 3 cm circular portals. Mice were observed for greater than 3 months for evidence of tumour regrowth. Over 40 mice were used to obtain each TCD_{50} value [28].

Rodent tumours obey the same basic radiobiological principles as human tumours and thus this experimental model holds out the hope for successful clinical application of neoadjuvant androgen deprivation.

When dicthylstilbestrol (DES) is administered orally for 3–6 months prior to radical surgery in stage T3-4 prostate cancer, clinical downstaging is observed in 80% [29]. A recent Dutch study, utilising transrectal ultrasound to monitor volume changes in prostatic tumours treated by various androgen suppressing strategies, demonstrated a mean volume reduction of 37% at 3 months [30]. Ninety-seven per cent of patients had a documented volume reduction. Little further reduction was seen after 3 months. In 1974, Green reported the use of neoadjuvant DES prior to radical radiation therapy in patients with locally advanced tumours [31]. Clinical local control rates of 72% were observed compared with 55% for those treated with radiation alone.

The most compelling data currently available on the use of radiation in combination with total androgen suppression come from RTOG protocol 8610 [32]. This study evaluated the efficacy and the safety of the combination of goserelin acetate (3.6 mg subcutaneous (s.c.) 4 weekly) and flutamide (250 mg three times daily, orally) administered prior to and during radiation in patients with bulky, locally advanced

Table 3. Combined neoadjuvant androgen suppression and radiation: 5-year results from a comparative randomised trial by the Radiation Therapy Oncology Group (RTOG-8610)

Treatment arm	Local control	Metastasis-free survival	Disease-free survival*
Radiation alone	29%	59%	15%
	($P < 0.001$)	($P < 0.09$)	($P < 0.001$)
NAS plus radiation	54%	66%	36%

*Including PSA.
NAS, neoadjuvant androgen suppression with goserelin acetate and flutamide; 2 months prior to irradiation and 2 months during.

(T2c, T3 and T4) prostate cancer. Androgen suppression began 8 weeks prior to irradiation and continued through it for a total of 16 weeks. Radiation was administered in a manner that is standard for both the U.S.A. and Western Europe.

A total of 471 patients were enrolled and randomised with a median follow-up of 4.5 years. The results demonstrated some remarkable differences between the two treatment arms (Table 3). The estimated cumulative incidence of local failure at 5 years was 71% of control patients but only 54% of experimental patients ($P < 0.001$). Interestingly, the two cumulative incidence curves appear to be diverging suggesting that this advantage to the experimental arm may increase with the passage of further time. This study is the first convincing demonstration that eradication of prostatic tumour is enhanced by prior cytoreduction. It also answers the theoretical criticism that androgen suppression might put tumour cells into a more resistant phase of the cell cycle and thus render them more radiation resistant. The limited rebiopsy data is also supportive of these contentions.

It is of note that the local failure rates are higher in the control arm than in many other series reporting results with radiation alone for similar staged tumours [1, 33]. This most probably reflects the use of more rigorous failure criteria, in particular the presumption that those with biochemical failure and no clinical evidence of distant metastases have local failure. This may well overestimate the incidence of local failure.

There was also a strong trend towards a reduction in the cumulative incidence of distant metastases at 5 years between the treatment and control groups (34% and 41%, $P = 0.09$). It is not clear whether this results from the improved local control or whether it is the result of the systemic action of the androgen suppression on occult micrometastases. An examination of the curves shows them to be parallel up to 5 years suggesting the latter. A divergence of the curves might be expected with further follow-up if the improvement in local control proves durable.

The disease-free survival curves that incorporate PSA criteria are the most informative. As PSA failure predicts clinical failure by months to years, the use of this biochemical endpoint provides a window into the clinical future. The estimated incidence of disease-free survival at 5 years was only 15% in the control group but 36% for the experimental group ($P < 0.001$). It is likely that the clinical disease-free survival figures with approximately 6–10 years of follow-up will reflect these numbers. The 21% gain in biochemical disease-free survival mirrors the gain in local control (25%) suggesting that it is here that, to date, most of the advantage of the addition of androgen suppression has been felt. It is of concern that the disease-free survival curves for both arms do not seem to have reached an asymptote and more failure is likely over the next few years perhaps reducing the differences ultimately achieved. Even if the ultimate disease-free survival figures were identical, the median disease-free survival time will have been extended from 1.5 to 2.7 years. This represents a considerable gain from the therapeutic addition of only 4 months of reversible androgen blockade. Subgroup analysis is not yet available to determine whether one particular TN-stage or tumour grade benefits more than another.

Despite the differences in disease-free survival, overall survival is identical in both arms to 5 years. This is not surprising as deaths from locoregionally confined prostate cancer take many years to accumulate and deaths from competing comorbidities should be the same in both groups. The median time to death after the development of metastatic disease is 2–3 years and only 47 experimental and 62 control patients of a total of 455 evaluable patients had developed distant metastases at the time of analysis. An overall survival gain may yet emerge with the passage of more time.

The RTOG have recently closed a subsequent randomised study in which all men received radiation and neoadjuvant androgen suppression as in the experimental arm of RTOG 8610 and half were given 2 further years of supplementary suppression. Over 1600 patients were accrued and the first analysis will be performed in 1997.

CONCLUSION

Conventional external beam radiation may provide durable clinical local control for the majority of patients with T3-4 prostate carcinoma, but is very unlikely to cure them when cure is judged by strict biochemical and pathological criteria. Dose escalation offers the hope of increased local control, but long-term data are lacking. The only randomised trial to date [23] reports a gain only for the poorly differentiated subgroup. It also reported a significant increase in late rectal morbidity. Neoadjuvant androgen suppression offers the hope of increased local control and, perhaps, systemic control without the need for potentially morbid radiation dose increases. The first report of RTOG 8610, a randomised trial with 5 years of follow-up, supports this contention [32].

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