External radiotherapy with or without hormonal ablation therapy

The value of either hormonal therapy in combination with moderate dose, conventionally fractionated radiotherapy (total dose ≤70 Gy) (table 1), or of dose escalation with exclusive radiotherapy up to 78 Gy total dose [1, 2] have both been addressed in numerous randomised clinical trials on locally advanced adenocarcinoma of the prostate. To summarise the results it became obvious that both strategies are able to improve local tumour control, recurrence free and cancer-specific survival.

Against the background of those trials, the present retrospective evaluation of Miralbel et al. [3] indicates a superiority even in overall survival of a mean 6-months endocrine treatment plus slightly escalated radiation therapy (mean total dose ≈72 Gy) compared with radiotherapy alone. Of course, this is a retrospective evaluation, and might be influenced by several factors: unequal distribution of pelvic irradiation, and change in policy of hormonal therapy, treatment planning and target volumes over time. These previous problems could explain the missing effect of hormonal therapy on overall survival in the multivariate analysis, but this is speculative.

Therefore, it seems reasonable to compare the data with previous published data from randomised clinical trials on the effect of hormonal therapy (table 1). In most prospective trials, the parameters defining high risk groups and radiation treatment portals including pelvic lymph nodes have been very similar as in the present concept of Miralbel et al. In combination with moderate radiation doses (≤70 Gy), which is less than in the present trial, overall survival benefit in locally advanced prostate cancer depends mostly on the duration of the hormonal ablation. It has been reported predominantly in studies with androgen deprivation of long duration (at least 3 years). Endocrine treatment includes either orchiectomy, single or complete hormonal therapy, the latter being more toxic without its superiority ever having been proven. All those trials could demonstrate improvements of 10–23% in overall survival at 5–10 years by adding hormonal therapy to radiation therapy. Very recently, Widmark

Table 1

Results from randomised clinical trials with external radiotherapy plus/minus hormonal ablation: significant improvement in overall survival in locally advanced prostate cancer by long-term hormonal therapy.

Author	Year	Pats.	Clinical stage	Therapy	Survival (%)	Significance (p)
Granfors [8]	2006	91	T 1–4 pN 0–3 M0	RT RT + Orchiectomy	39% OS (9-Y) 62% OS (9-Y)	0.02
Roach [7] (RTOG 94-13)	2006	1323	T 2c–4 N x M0 or PSA >10 or GS >7	Pelvic-RT + HT neo. No Pelvic-RT/no HT	61% DFS (4-Y) 45–49% DFS (4-Y)	0.005
Pilepich [9] (RTOG 85-31)	2005	945	T 2 N + T 3 N x pT 3 postop.	RT RT + HT adjuvant until progression	39% OS (10-Y) 49% OS (10-Y)	0.002
Horwitz (Subgroup of RTOG 85-31 and 86-10) [10]	2001	993	T 2b–4 N 0 M0	RT RT + HT neo 4 months RT + HT adjuvant	14% DFS (8-Y) 27% DFS (8-Y) 52% DFS (8-Y)	<0.0001
Bolla (EORTC 22863) [11]	2002	412	T 1–2 G 3 N x T 3–4 G x N x	RT RT + HT adjuvant (3 years)	62% OS (5-Y) 78% OS (5-Y)	0.0002
D'Amico [12]	2004	206	T 1–2 G 3 N x T 3–4 G x N x	RT RT + HT adjuvant (6 months)	78% OS (5-Y) 88% OS (5-Y)	0.04
McLeod et al.[1)] [13]	2006	1370	T 1–2 N 0-x T 3–4 N x or T x N +	RT RT + HT adjuvant (5 years or until progression)	DFS-/OS-improv. in advanced stages	<0.0001
Horwitz (RTOG 92-02) [14]	2008	1554	T 2c–4 N 0–1 M0 PSA <150 ng/ml	RT + HT adjuvant 4 months vs 28 months	13.2% DFS (10-Y) 22.5% DFS (10-Y)	<0.0001
D'Amico[2)] [6]	2007	412	T 3–4 G x N 0 T 1–2 G 3 N 0	RT + HT adjuvant 6 months vs 3 years	No difference in overall survival	0.7
Widmark [4]	2009	875	T 2–4 N 0 M0, PSA <70	HT until progress HT until progress + RT	60.6% OS (10-Y) 70.4% OS (10-Y)	0.004

OS = overall survival; DFS = disease-free survival; RT = radiotherapy; HT = hormonal therapy; HT adjuvant = start of hormonal therapy during or after radiotherapy; HT neo = start/end of hormonal therapy before/during radiotherapy; [1)]: several arms modified form risk factor and therapy; [2)]: subgroup analysis from 3 randomised trials.

et al. [4] have proven also the value of radiotherapy in very advanced but not clinically metastasised high risk prostate cancer when added to long-term hormonal therapy. By a total radiation dose of 70 Gy to the prostate only, overall survival at 10 years was absolutely improved by 9.8%. Although quality of life was reduced in social function for patients with combined treatment in the study of Fransson et al. [5], it was not significantly different in any other aspect. On the other hand, the improvement even in overall mortality by adding radiotherapy was profound, although pelvic lymph nodes were not included and mean total dose was 70 Gy only.

In contrast to all those trials, in the study of Miralbel et al. dose was slightly increased to about 72 Gy in mean (89% of patients >70 Gy), but still there remains an improvement in overall survival by short-term hormonal therapy. To support this strategy of 6-months hormonal therapy, there has also been one randomised trial with short term hormonal therapy that was able to achieve a significant improvement in overall survival at 5 years [6]. Interpreting the latter together with the present study of Miralbel et al. and a retrospective evaluation of D'Amico et al., analysing three randomised trials (3 years vs 6 months androgen ablation) with prostate cancer carrying at least one major risk factor (either G3 or T 3–4) in 2007, it might be an option to individually offer short term androgen ablation when longer hormonal therapy will not be tolerated by the individual patient. It is known that acute as well as long-term side-effects are increased with both hormonal therapy and higher radiation doses, but remain in a tolerable range regarding severe late toxicity. There might, however, be some patients suffering severely under hormonal therapy, and might ask for cessation of androgen ablation after some months of treatment.

Actual trials of combination of both concepts as well as hypofractionated RT schedules will bring further information on the best type of radiation fractionation and total dose. But until further reliable data, conventional fractionated radiotherapy including the pelvic lymph nodes [7] and in combination with at least 3 years of single hormonal therapy might be the choice of treatment in locally advanced adenocarcinoma of the prostate at least for patients in good general health. Thereby, a perfect treatment planning with an optimal shielding or protection of both rectum and urogenital tract is a prerequisite, to avoid an unacceptable increase in severe toxicity. In contrast, the value of the most modern techniques such as image-guided radiation therapy, proton therapy and tomotherapy in the treatment of prostate cancer is still open. Nevertheless, treatment can and should be altered individually when planning parameters can not be fulfilled due to individual local anatomy, or when severe acute toxicity during radiotherapy or hormonal therapy occurs. The data of Miralbel et al. support this decision.

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