Adjuvant treatment to radiation: combined hormone therapy and external radiotherapy for locally advanced prostate cancer

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INTRODUCTION

Androgen suppression has been the primary treatment for locally advanced prostate cancer (LAPC); there is a response to androgen suppression in >80% of patients, but androgen suppression is not curative and has side-effects [1]. Oestrogen and castration have been replaced by LHRH analogues, with the same efficacy [2]. The long-term results of external beam irradiation are barely convincing, due to a high risk of local relapse or distant metastasis. The challenge is to improve local control by using innovative irradiation techniques and to reduce metastasis by combining irradiation with androgen deprivation, as has been done for locally advanced breast carcinoma [3]. The incidence of LAPC has declined as a result of screening, and we now face the challenge of high-risk prostate cancer, including LAPC and localized disease (T1/2 N0M0) with poor prognostic factors (Gleason score 8–10 or a PSA level of >20 ng/mL). Such cancers are associated with a significant risk of relapse within and outside the irradiated volume [4]. In this report we consider the methods, timing and results of the combined approach, without discussing its morbidity or impact on quality of life.

RATIONALE

The combined approach is used to:

- reduce the planning target volume of irradiation;
- reduce the risk of local relapse by inhibiting re-population during irradiation and, consequently, a second wave of metastases resulting from local relapse;
- decrease distant metastases occurring as a result of infra-clinical deposits present at the time of diagnosis;
- improve the effectiveness of radiation, as shown experimentally [5,6].

RANDOMIZED PHASE III TRIALS OF HORMONAL THERAPY (HT) ADJUVANT TO RADIOTHERAPY (RT)

The main phase III trials studying the benefit of HT using an LHRH analogue with or without antiandrogen were conducted by the Radiation Therapy Oncology Group (RTOG), the European Organization for Research and Treatment of Cancer (EORTC), and the Trans-Tasman Radiation Oncology Group (TTROG) (Table 1). In the Early Prostate Cancer (EPC) trial programme, the effect of antiandrogen adjuvant to RT was studied in patients receiving standard care, including those receiving RT.

RANDOMIZED PHASE III TRIALS OF LHRH ANALOGUES

Trials showing the benefit of androgen suppression using the LHRH analogue goserelin acetate were conducted by the RTOG, the EORTC and the TTROG.

CONCOMITANT AND ADJUVANT ANDROGEN SUPPRESSION

EORTC study 22863 compared RT and adjuvant HT with RT alone or RT with HT at relapse in 415 patients with prostate cancer of T1/2 WHO grade 3 or T3/4 N0/X M0 (T3 in 82% of patients; T4 in 10%; and N0 in 89%) [7]. The HT was cyproterone acetate, 50 mg three times daily for 1 month, beginning 1 week before RT, and s.c. goserelin, 3.6 mg every 4 weeks for 3 years, starting on the first day of RT. The planning target volume received 50 Gy and the prostatic target volume 20 Gy. At a median follow-up of 66 months, RT plus adjuvant HT and RT alone resulted in significantly different overall survival (OS) rates (78% vs 62%, respectively, $P = 0.001$; Fig. 1), survival without clinical relapse (78% vs 40%, respectively, $P < 0.001$), and 5-year survival with no clinical or biological failure (nadir PSA level 1.5 ng/mL; 81% vs 43%, respectively, $P < 0.001$) [7]. Three risk categories (low, intermediate, high) were formed according to prognostic index with respect to disease-free survival (DFS). The hazard ratio (HR, 95% CI) for combined treatment vs RT alone was 0.12 (0.01–1.01; $P = 0.05$) in the low-risk, 0.28 (0.18–0.46; $P < 0.001$) in the intermediate-risk, and 0.39 (0.24–0.63; $P < 0.001$) in the high-risk category. These values indicate that patients in each category benefit from concomitant and adjuvant HT.

ADJUVANT ANDROGEN SUPPRESSION

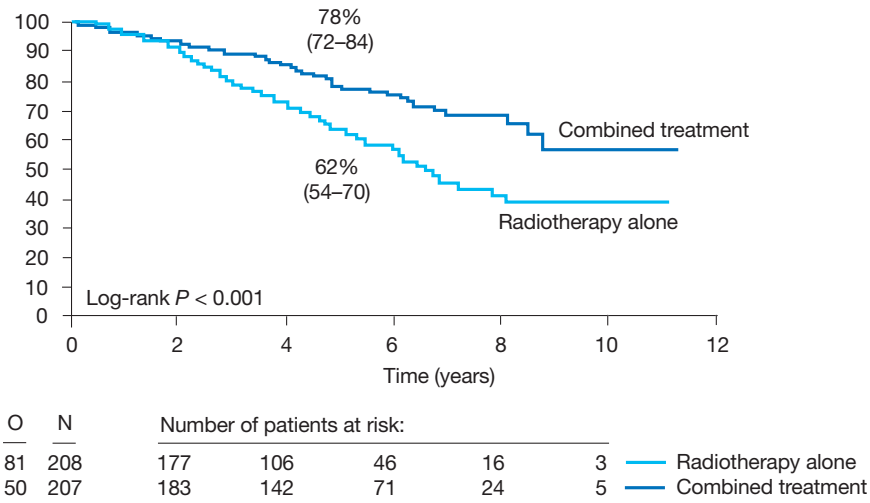
RTOG trial 85–31 evaluated the effectiveness of goserelin adjuvant to RT in 977 patients with stage T3/4 M0 (with or without lymph node involvement) or pT3 after radical prostatectomy because of capsule invasion, positive margins, or seminal vesicle involvement [8]. Monthly administration of goserelin began during the last week of RT and continued indefinitely or until relapse (arm 1, adjuvant HT) or began at relapse (arm 2). To inhibit the initial rise of LH and then testosterone, no antiandrogen was given at the start of goserelin treatment. Radical prostatectomy had been performed in 15% of patients in arm 1 and in 14% in arm 2; 29% of arm 1 and 26% of arm 2 patients had lymph node involvement. The pelvic target volume received 45 Gy and the prostatic target volume 65–70 Gy. Patients with a pT3 tumour received 60–65 Gy to the postoperative target volume.

At a median follow-up of 5.6 years, the 8-year local failure rate was 23% in arm 1 (adjuvant HT) and 37% in arm 2 (HT at relapse; $P < 0.001$). The distant metastasis rate was also lower in arm 1 than in arm 2 (27% vs 37%; $P < 0.001$). DFS and survival with no evidence of disease and a PSA level of ≤ 1.5 ng/mL were significantly better in arm 1 than arm 2 ($P < 0.001$), but the OS was similar in each arm (49% vs 47%; $P = 0.36$). However, interestingly, for centrally reviewed patients with Gleason 8–10 tumours who had not had radical prostatectomy, subset analysis by Gleason score revealed a statistically

Trial	Neoadjuvant	Concomitant	Adjuvant
EORTC 22863 [7]		+	+
RTOG 85–31 [9–10]			+
EPC [15]			+
RTOG 92–02 [13]	+	+	+
RTOG 86–10 [11]	+	+	
RTOG 94–13 [14]	+	+	
TTROG 96–01 [12]	+	+	

TABLE 1
Trials indicating the benefit of HT when given neoadjuvantly, concomitantly, or adjuvantly to RT

FIG. 1. Kaplan–Meier estimates of OS by treatment group (RT with androgen ablation or RT alone) in EORTC trial 22863. N, number of patients; O, number of deaths. (Adapted from Bolla et al. *[7] Copyright 2002, with permission from Elsevier.)*



significant difference in OS ($P = 0.036$) and cause-specific survival ($P = 0.019$) in favour of the adjuvant HT arm [8]. At a median follow-up of 7.6 years, the estimated 10-year OS was significantly higher after adjuvant HT (49%) than after HT at relapse (39%; $P = 0.002$) [9]. In this trial, of 173 patients who had pN1 lymph nodes, 98 received RT plus adjuvant HT. These 98 patients had a significantly better 5-year progression-free survival (PFS) with a PSA level of <1.5 ng/mL ($P < 0.001$) and metastasis-free survival ($P = 0.02$) than did those who received HT at relapse [10].

NEOADJUVANT AND CONCOMITANT ANDROGEN SUPPRESSION

RTOG trial 86–10 [11] tested combined androgen blockade (CAB) with goserelin and flutamide before (2 months) and during RT (2 months); this therapy was compared with RT alone. The trial included 471 patients with stage T2b/c (tumours at least 5 × 5 cm on rectal examination), T3 and T4M0. Patients with regional lymph-node involvement were eligible provided the involved nodes were below the common iliac chain; 7% had positive nodes in the CAB arm, vs 9% in the RT-alone arm. Overall, 30% of patients had T2 tumours and 70% T3/4; 91% of tumours were node negative. The HT comprised oral flutamide, 250 mg three times daily, and s.c. goserelin, 3.6 mg every 4 weeks. The pelvis received 45 Gy and the prostatic target volume 65–70 Gy.

With a median follow-up of 6.7 years, at 8 years androgen ablation was associated with

- improved local control (42% vs 30%; $P = 0.016$);
- reduced incidence of distant metastases (34% vs 45%; $P = 0.04$);
- improved DFS (33% vs 21%; $P = 0.004$) and biochemical DFS with a PSA nadir of 1.5 ng/mL (24% vs 10%; $P < 0.001$);
- reduced cause-specific mortality (23% vs 31%; $P = 0.05$).

Subset analysis showed that patients with Gleason score 2–6 had a significantly better OS than did those with Gleason score ≥7 (70% vs 52%; $P = 0.015$) [11].

The TTROG trial 96–01 was implemented to determine whether outcomes after 3 or 6 months of CAB given before and during RT are better than those after RT alone. It included 818 patients with prostate cancer of stage T2b/c N0 or T3/4 N0M0. The tumour was T2 in 61% of patients and T3/4 in 39%. The HT comprised oral flutamide, 250 mg three times daily, and s.c. goserelin, 3.6 mg every 4 weeks, starting 2 months before RT for a total of 3 months or starting 5 months before RT and continuing for a total of 6 months. Patients assigned to the control group received no androgen-deprivation therapy. During 6.5–7 weeks, 66 Gy was delivered to the prostate and seminal vesicles in 33 fractions of 2 Gy/day. With a median follow-up of 5.9 years, 6 months of androgen deprivation reduced local failure ($P < 0.001$) and distant failure ($P = 0.046$) and increased biochemical failure-free survival ($P < 0.001$), DFS ($P < 0.001$), and cancer-specific survival ($P = 0.04$) [12].

NEOADJUVANT AND CONCOMITANT CAB WITH AND WITHOUT ADJUVANT LHRH ANALOGUE

RTOG protocol 92–02, for patients with tumours classified as T2c–4 N0, assessed long-term androgen suppression (LTAS) after short-term androgen suppression (STAS) according to protocol 86–10. All patients received 2 months of CAB before RT, and the prostate received a radiation dose of 65–70 Gy. Patients were then randomly assigned to receive no additional therapy or 24 months of goserelin. This trial was closed after accruing 1554 patients, sufficient to show a 6% potential survival advantage. At a median follow-up of 5.8 years, all endpoints except 5-year OS were better in the LTAS arm than in the STAS arm (80% vs 78.5%; $P = 0.73$). In a subset of patients with Gleason scores 8–10 who were not part of the original study, those in the LTAS arm had a significantly better OS than did those in the STAS arm (81% vs 70.7%; $P = 0.04$) [13].

SHORT-TERM NEOADJUVANT VS SHORT-TERM ADJUVANT COMBINED ANDROGEN SUPPRESSION WITH WHOLE-PELVIS OR PROSTATE-ONLY RT

The RTOG 94–13 study [14] is a four-arm trial for patients with T1c–4 N0M0 tumours, a PSA level of <100 ng/mL, and an estimated 15%

risk of lymph node involvement. Patients were randomly selected to receive neoadjuvant concurrent HT (NCHT; 2 months before and 2 months during RT) or adjuvant HT 4 months after RT, then to undergo whole-pelvis RT followed by a boost to the prostate or prostate-only RT. The trial accrued 1323 patients; with a median follow-up of 59.5 months, whole-pelvis RT plus NCHT improved the 4-year PFS (61%) compared with prostate-only RT plus NCHT (45%), prostate-only RT plus adjuvant HT (49%), and whole-pelvis RT plus adjuvant HT (47%; $P = 0.008$). A longer follow-up is needed to address the issue of specific survival and OS. These results are not surprising, because we know that there is an enhanced biological interaction when short-term HT is given before and during whole-pelvis RT (RTOG trial 86–10), whereas adjuvant HT needs to be given over a long period to have a positive effect on OS in patients with Gleason scores 8–10 (RTOG trials 85–31, 92–02) [8–10,13].

EPC TRIAL PROGRAMME

In three randomized double-blind trials (trial 23 in North America, 24 in Europe and 25 in Scandinavia), 8113 men with localized prostate cancer (T1/2 N0/x) or LAPC (T3/4, any N or any T N+) were given bicalutamide, 150 mg per day, or placebo in addition to radical prostatectomy, RT or watchful waiting; the primary endpoints were PFS and OS. The investigators analysed subsets of patients, separating those with localized disease from those with LAPC; 1370 patients with T1–4 any N M0 tumours received RT, and of these, 305 were classified with LAPC. Overall, 13 patients from trial 23 took bicalutamide for 2 years, 249 from trial 24 took bicalutamide for 5 years, and 43 from trial 25 took bicalutamide until progression. After a median follow-up of 7.4 years, a pooled analysis merging these three cohorts showed a 44% reduction in the risk of progression (PFS: HR 0.56; 0.40–0.78; $P < 0.001$) and a 35% increase in OS (HR 0.65; 0.44–0.95; $P < 0.03$) [15].

CONCLUSION

For high-risk prostate cancer, long-term androgen suppression is recommended. To determine the best adjuvant hormonal scheme to associate with external irradiation, EORTC equivalence trial 22961 has randomized 966 patients to undergo external irradiation and CAB for 6 months followed by surveillance only (483 patients) or HT with an LHRH analogue, triptorelin, 11.25 mg (483 patients) for 30 months [16].

Whether LTAS alone is as effective as LTAS plus RT remains controversial, and the National Cancer Institute of Canada has launched a randomized trial comparing CAB plus RT with the same HT to determine whether the combined approach is more effective than HT alone [17]. For bulky tumours the value of dose escalation has to be considered, taking into account the results of a randomized study by the University of Texas M.D. Anderson Cancer Center, which showed a significant increase in survival with no biochemical relapse ($P = 0.01$) in patients with a pretreatment PSA level of >10 ng/mL who received the higher of two radiation doses [18].

To summarize, HT prescribed with external irradiation increases clinical and biochemical relapse-free survival in patients with prostate cancer of stage T2c–4 N0/1 M0. Moreover, there was a significant improvement in OS in

- patients with poorly differentiated tumours who receive LHRH analogue alone in the last week of irradiation and until relapse ($P = 0.03$) (RTOG trial 85–31) or CAB, before and during irradiation, followed by 2 years of LHRH analogue ($P = 0.04$) (RTOG trial 92–02);
- patients with Gleason score 2–6 ($P = 0.015$) who receive CAB 2 months before and during RT (RTOG trial 86–10);
- patients with tumours of any histological grade who receive LHRH analogue during and after irradiation for a total of 3 years ($P = 0.001$) (EORTC trial 22863).

The TTROG trial showed a gain in prostate cancer-specific survival ($P = 0.04$) resulting from androgen deprivation, and in the EPC trial programme, a pooled analysis showed an improvement in OS in patients who received bicalutamide.

CONFLICTS OF INTERESTS

The authors have declared no conflicts of interests.

REFERENCES

1 **Schröder FH.** What is new in endocrine therapy of prostatic cancer? In Newling DW, Jones WG eds, *EORTC Genitourinary Group monograph 7: Prostate Cancer and Testicular Cancer*. New York: Wiley-Liss, 1990: 45–52

2 **Parmar H, Philipps RH, Lightman SL, Edwards L, Allen L, Schally AV.** Randomised controlled study of orchidectomy vs long-acting D-Trp-6-LHRH microcapsules in advanced prostatic carcinoma. *Lancet* 1985; **2**: 1201–5

3 **Overgaard M, Jensen MB, Overgaard J *et al.*** Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999; **353**: 1641–8

4 **D'Amico AV, Whittington R, Malkowicz SB *et al.*** Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; **280**: 969–74

5 **Zietman AL, Prince EA, Nakfoor BM, Park JJ.** Androgen deprivation and radiation therapy: sequencing studies using the Shionogi *in vivo* tumor system. *Int J Radiat Oncol Biol Phys* 1997; **38**: 1067–70

6 **Joon DL, Hasegawa M, Sikes C *et al.*** Supraadditive apototic response of R3327-G rat prostate tumors to androgen ablation and radiation. *Int J Radiat Oncol Biol Phys* 1997; **38**: 1071–7

7 **Bolla M, Collette L, Blank L *et al.*** Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002; **360**: 103–6

8 **Lawton CA, Winter K, Murray K *et al.*** Updated results of the phase III radiation therapy oncology group (RTOG) trial 85–31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001; **49**: 937–46

9 **Pilepich MV, Winter K, Lawton CA *et al.*** Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma – long-term results of phase III RTOG 85–31. *Int J Radiat Oncol Biol Phys* 2005; **61**: 1285–90

10 **Lawton CA, Winter K, Byhardt R *et al.*** Androgen suppression plus radiation versus radiation alone for patients with D1 (pN+) adenocarcinoma of the prostate (results based on a national prospective

randomized trial, RTOG 85–31). Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1997; **38**: 931–9

11 **Pilepich MV, Winter K, John MJ *et al.*** Phase III radiation therapy oncology group (RTOG) trial 86–10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001; **50**: 1243–52

12 **Denham JW, Steigler A, Lamb DS *et al.*** Short-term androgen deprivation and radiotherapy for locally advanced prostate cancer: results from the Trans-Tasman Radiation Oncology Group 96.01 randomised controlled trial. *Lancet Oncol* 2005; **6**: 841–50

13 **Hanks GE, Pajak TF, Porter A *et al.*** Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the radiation therapy oncology group protocol 92–02. *J Clin Oncol* 2003; **21**: 3972–8

14 **Roach M 3rd, DeSilvio M, Lawton C *et al.*** Phase III trial comparing whole-pelvis versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003; **21**: 1904–11

15 **McLeod DG, Iversen P, See WA *et al.*; Casodex Early Prostate Cancer Trialists' Group.** Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. *BJU Int* 2006; **97**: 247–54

16 **Bolla M, de Reijke TM, Zurlo A, Collette L.** Adjuvant hormone therapy in locally advanced and localized prostate cancer: three EORTC trials. *Front Radiat Ther Oncol* 2002; **36**: 81–6

17 **Warde P, Whittington R, Vijayakumar S, Lillis-Hearne P, Mason M.** Phase III randomized trial comparing total androgen blockade versus total androgen blockade plus pelvic irradiation in clinical stage T3–4, N0, M0 adenocarcinoma of the prostate trial NCT00002633. National Cancer Institute, US National Institutes of Health 1995

18 **Pollack A, Zagars GK, Smith LG *et al.*** Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. *J Clin Oncol* 2000; **18**: 3904–11

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Abbreviations: **HT**, hormonal therapy; **CAB**, combined androgen blockade; **DFS**, disease-free survival; **EORTC**, European Organization for Research and Treatment of Cancer; **EPC**, Early Prostate Cancer; **HR**, hazard ratio; **LAPC**, locally advanced prostate cancer; **LTAS**, long-term androgen suppression; **NCHT**, neoadjuvant concurrent HT; **OS**, overall survival; **PFS**, progression-free survival; **RT**, radiotherapy; **RTOG**, Radiation Therapy Oncology Group; **STAS**, short-term androgen suppression; **TTROG**, Trans-Tasman Radiation Oncology Group.