Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy

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Summary

Background **Appropriate timing of androgen deprivation treatment (ADT) for prostate cancer is controversial. Our aim was to determine whether immediate ADT extends survival in men with node-positive prostate cancer who have undergone radical prostatectomy and pelvic lymphadenectomy compared with those who received ADT only once disease progressed.**

Methods **Eligible patients from 36 institutes in the USA were randomly assigned in 1988–93 to receive immediate ADT (n=47) or to be observed (n=51), with ADT to be given on detection of distant metastases or symptomatic recurrences. Patients were followed up every 3 months for the first year and every 6 months thereafter. The primary endpoint was progression-free survival; secondary endpoints were overall and disease-specific survival. Analysis was by intention to treat. To ensure that the treatment groups were comparable, we did a retrospective central pathology review of slides and regraded the Gleason scores for available samples. This trial predates the requirement for clinical trial registration.**

Findings **At median follow-up of 11·9 years (range 9·7–14·5 for surviving patients), men assigned immediate ADT had a significant improvement in overall survival (hazard ratio 1·84 [95% CI 1·01–3·35], p=0·04), prostate-cancer-specific survival (4·09 [1·76–9·49], p=0·0004), and progression-free survival (3·42 [1·96–5·98], p<0·0001). Of 49 histopathology slides received (19 immediate ADT, 30 observation), 16 were downgraded from the original Gleason score (between groups ≤6, 7, and ≥8) and five were upgraded. We recorded similar proportions of score changes in each group (p=0·68), and no difference in score distribution by treatment (p=0·38). After adjustment for score, associations were still significant between treatment and survival (overall, p=0·02; disease-specific, p=0·002; progression-free survival, p<0·0001).**

Interpretation **Early ADT benefits patients with nodal metastases who have undergone prostatectomy and lymphadenectomy, compared with those who receive deferred treatment. The beneficial effects of early ADT, rather than an imbalance in risk factors, are likely to explain the differences in outcomes between treatments.**

Introduction

The appropriate timing of androgen deprivation treatment (ADT) for prostate cancer has been debated. For patients with symptomatic metastases, ADT remains the standard treatment with very good short-term efficacy, but no curative promise. Since the publication of the first Veterans Administration Cooperative study in 1967,[1] traditional oncological dogma has stated that because delayed use of ADT does not adversely affect survival, such treatment can be withheld until late in the disease process, when symptoms demand its use. However, with the development of new forms of ADT, this issue of appropriate timing to use ADT has been revisited.

Five randomised prospective trials have shown that early use of long-term ADT extends survival, compared with treatment that is delayed until mandated by progressive disease. Three of these trials[2–4] combined long-term ADT with external-beam radiotherapy for locally advanced and regional prostate cancer, and, although improved survival was seen, these changes were modest in patients treated with radiotherapy and deferred ADT. Furthermore, whether ADT suppressed or cured micrometastases or improved local tumour control achieved by radiotherapy is unclear. Even 6 months of ADT combined with radiation has been shown to significantly improve cause-specific[5,6] and overall[5] survival compared with radiotherapy alone in men with intermediate-risk[5,6] or high-risk,[6] localised[5,6] or locally advanced[6] prostate cancer. In a trial[7,8] of early ADT as the sole treatment for patients with advanced (localised or metastatic) prostate cancer, researchers saw a significant, but modest, improvement in survival in patients without distant metastases, and prevention of serious symptomatic sequelae of progressive disease (eg, paraplegia and pathological fractures) in patients with metastases. The conclusion of this study has been questioned because the timing of ADT use in deferred patients was not rigidly prescribed, and in some patients never given.[9]

The fifth study, by contrast with the other four, investigated the timing of ADT in men with very small quantities of cancer (ie, no clinical evidence of disease and in most instances, undetectable prostate-specific antigen [PSA] in serum); however, the participants had aggressive disease, with nodal metastases found after radical prostatectomy and pelvic lymphadenectomy. An initial

report[10] showed improved survival with early ADT. This study has also been criticised because it had a small sample size; a purportedly poorer prognosis in observed patients than in single-institution, retrospective series of radical prostatectomy in patients with nodal metastases; and concerns about the absence of a centralised histological review, resulting in a possible imbalance between treatment groups in the distribution of Gleason scores.[9] We have addressed the first two criticisms in editorial replies.[11] Here, we present the study with mature data with a centralised histological review, at a time when observed patients have exceeded 50% mortality and pathology materials have been requested for all participants and received for half.

Methods

Patients

From 1988 to 1993, participating urologists and oncologists (including EMM, DC, GW) enrolled 100 men from 36 US institutions who had undergone radical prostatectomy and bilateral pelvic lymphadenectomy for clinically localised (tumour [T] stage T1b or T2) prostate cancer and were found to have histologically confirmed nodal metastases. Operative reports indicated that at a minimum, a complete bilateral dissection of external iliac and obdurator chains had been undertaken. Men were randomly assigned to receive immediate, continuous ADT (3·6 mg goserelin monthly or bilateral orchiectomy, by choice of the patient) or to be followed up and receive ADT when clinical recurrence was detected (not counting events with only detectable or rising concentrations of PSA). No patient showed evidence of metastases from preoperative nuclear bone scans and chest radiographs, and none had palpable (or other) evidence of extraprostatic disease. No patient received any form of ADT before randomisation. The institutional review board of every participating institution had approved the study, and written informed consent was obtained from all patients before their entry.

Procedures

Patients were randomly assigned within 12 weeks after surgery by use of a permuted blocks algorithm that was balanced by institution and stratified by choice of type of ADT. Randomisation was done centrally by telephone by personnel at the central randomisation desk of the Eastern Cooperative Oncology Group (ECOG), who had no further role in the trial. Treatment assignments were not revealed to study personnel or participants until the end of the randomisation and registration process. No placebo group was used in the trial. Participating study personnel and physicians (who gave treatment and assessed disease status) were not blinded to the allocated treatment group.

Patients were followed up every 3 months for the first year, and underwent physical examinations, and tests to measure serum concentrations of prostatic acid phosphatase (changed to PSA during the study), and had bone scans every 6 months. After the first year, follow-up, physical examinations, and PSA testing were done every 6 months, and bone scans done yearly. We diagnosed metastases by bone scan and other imaging when deemed clinically appropriate. To be regarded as local progression, newly palpable prostatic-bed nodules had to be confirmed with a second examination and by a detectable and rising concentration of PSA (≥0·4 μg/L) between two visits, but did not need a positive biopsy sample. If only a local recurrence was suspected in observed patients, the protocol strongly recommended physicians to withhold ADT and, if clinically indicated, to treat with local modality treatment such as radiotherapy.

We investigated deaths by using clinical records, physician reports, study forms, and by other means (ie, obituary) in the one patient lost to follow-up. Overall survival included all men who had not died at the time of investigation. Causes of death were determined by treating physicians and confirmed by study records, death certificates, and autopsies, if available. Patients who died from prostate cancer were defined as having progressive, symptomatic metastatic disease at the time of death or, if unknown at death, less than 6 months before death.

Of the enrolled men, 52 were randomly assigned to receive expectant management and 48 to immediate ADT. Two men were found to be ineligible, resulting in 51 observed and 47 immediate ADT patients eligible for follow-up (figure 1). We did not achieve the sample size of 220 patients initially planned, mainly because the study was conceived and begun before the usefulness of serum PSA concentrations was recognised to monitor, stage, and detect prostate cancer. With the change in clinical practice created by generalised PSA testing, fewer men with nodal metastases underwent prostatectomy. Moreover, both patients and physicians were reluctant to ignore postoperative concentrations of PSA in management decision-making. These factors reduced the number of patients available for study participation; thus an independent committee of ECOG decided that further accrual was not feasible, and the study was closed.

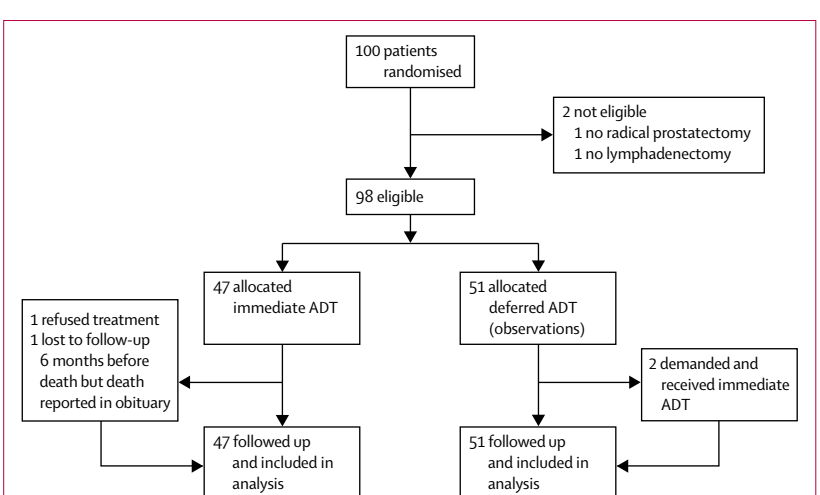

Figure 1: **Trial profile**

For all patients, we requested haematoxylin and eosin-stained slides of formalin-fixed representative portions of the primary tumour and nodal metastases, as well as unstained slides or tissue blocks of these regions. Financial incentives that exceeded the expenses of preparing and shipping materials and other incidental costs were provided to institutions. We received materials for 49 (50%) of the 98 patients from 1995 to 2004, despite contacting participating pathology departments and investigators at least twice more, and raising financial incentives. Received slides were reviewed by two pathologists (PAdS, JY), who were unaware of each other's review, the original pathology report, the original Gleason scores assigned, the allocated treatment, or clinical outcomes. We recorded no major discrepancies between the two pathology reviewers that would affect the assigned Gleason scores (ie, ≤6, 7, and 8–10). Here, we present Gleason scores from the central pathology review, unless no materials were received—in which case the originally reported Gleason score was used. In nine patients, no materials were received for review and the Gleason system was not used by the original pathologist. Gleason scores were classified for analysis into groups of low risk (score ≤6), intermediate risk (score 7), and high risk (score 8–10).

We defined survival as the time from randomisation to death. Patients still alive at analysis were censored at the date last known alive. Progression-free survival was the primary outcome and was defined as the time from randomisation to the first evidence of recorded clinical progression or death from any cause. We censored patients who were alive with no recorded progression at the date they were last known to be progression-free. Overall and disease-specific survival were secondary outcomes.

Statistical analysis

The sample size of 220 patients allowed a probability of 0·79 or greater of detecting an increase from 40% to 60% in recurrence-free survival at 5 years (not including detectable or rising concentrations of PSA only). The study was designed with one-sided type I error (alpha) of 0·05.

	Immediate ADT (n=47)	Deferred ADT (n=51)
Surgical margins		
Positive	32 (70%)	31 (61%)
Unknown	1	0
Seminal vesicles		
Positive	27 (59%)	32 (62%)
Unknown	1	0
Nodal status		
Number assessed (median, range)	11 (3–36)	14 (2–39)
Number positive (median, range)	2 (1–19)	2 (1–20)
Postoperative serum PSA		
Range	<0·2–87·4 μg/L	<0·2–48·7 μg/L
Undetectable	35 (78%)	39 (81%)
Not known	2	3

Table 1: Baseline characteristics

For observed men with node-positive disease who had undergone lymphadenectomy and localised treatment to the prostate, we used an estimate of progression-free survival of 40% on the basis of reports published in the early 1980s.[12–15] The improvement to 60% was actually lower than the results of the one contemporary series[15] published (n=22, with only nine patients assessable at 5 years), but was judged by the ECOG genitourinary committee as the minimum improvement meaningful enough to justify the morbidity and expense of immediate ADT. Analysis was by intention to treat.

We used the Wilcoxon rank sum test to test for differences in age and nodal status (number of positive nodes) between groups at baseline. Mehta's exact test for ordered categorical data was used to examine the distribution and changes in Gleason scores. We estimated the survival and time to clinical progression with Kaplan-Meier method. A two-sided log-rank test measured differences in overall survival, prostate-cancer-specific survival, and progression-free survival. Methods developed by Gray and colleagues were used to estimate and compare competing risks of death between treatment groups. The interaction between Gleason score and treatment group with respect to overall survival, prostate-cancer-specific survival, and progression-free survival were examined by Cox proportional hazards models. This trial predates the requirement for clinical trial registration.

Role of the funding source

The sponsor of the study approved the study design, but had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

All 98 patients had clinical stage T1b (immediate ADT, three; observation, four) or T2 (44; 47) prostatic adenocarcinoma with no evidence of distant metastases. The 80 men who underwent preoperative pelvic CT scans had no nodal metastases reported. The median age of all participants was 65·6 years (immediate ADT, 65·1 [range 52–75] years; observation, 66·6 [45–78] years). Pathological and clinical postoperative characteristics of tumours were well matched between groups (table 1). These characteristics included positive surgical margins, positive seminal vesicles, number of nodes examined, number of positive nodes, undetectable serum concentrations of PSA after surgery, and Gleason scores assigned by institutional pathologists. Although requested, the tumour mass was not measured in every node in most pathology reports in each group, and therefore no meaningful or reliable information can be presented here.

With 11·9 years' median follow-up (range 9·7–14·5 for living patients), 17 (36%) immediately treated and 28 (55%) observed patients died (immediate ADT, median survival

13·9 years [range 2·1–14·5]; observation, 11·3 years [1·3–14·2]; figure 2A). Disease-specific survival and progression-free survival apart from biochemical failure also showed significant differences between treatments (figure 2B, C).

Seven (15%) patients assigned immediate treatment and 25 (49%) assigned observation had died from prostate cancer. Although the median disease-specific survival was not reached in immediately treated men (range 2·1–14·5 years), a median of 12·3 years was recorded in observed men (1·3–14·2; log-rank test, p=0·0004). 22 (47%) men in the immediate group and 44 (86%) in the observation group had at least PSA recurrence (median progression-free survival: immediate ADT, 13·9 years [range 0·9–14·0]; observation, 2·4 years [0·1–13·2]; log-rank test, p<0·0001). 19 (40%) immediately treated men and 38 (75%) observed men had had some clinical evidence of recurrence apart from PSA detectability (13·9 years [0·9–14·5] for immediately treated men; 4·1 years [0·2–14·2] for observed men; p<0·0001).

22 (47%) men allocated immediate ADT were alive without detectable disease, including serum concentrations of PSA, whereas eight (17%) were alive with recurrent disease (four with metastases, four with local disease). Seven (15%) men died of prostate cancer, and ten (21%) died of non-disease-specific causes, including three with no recurrences of prostate cancer before death; three who had detectable PSA without clinical recurrences; and four without metastases (but with rising concentrations of PSA and suspected local recurrences). One man in the immediate treatment group initially refused ADT, but received it when symptomatic metastases developed 24 months later. He died 17 months after ADT and was regarded as a death due to prostate cancer in the immediate treatment group.

In the observation group, seven (14%) men did not have recurrence, all of whom were alive at last follow-up. Six (12%) men had PSA recurrence only, of whom five were alive at last follow-up. Four of the six men who did not receive ADT were still alive; another who did not receive treatment died from causes other than prostate cancer; and one demanded immediate ADT, refused further follow-up, but was still alive and had a rising concentration of PSA. Three (6%) had had a suspected local recurrence, of whom two received ADT in response (one received radiotherapy and ADT) and one received no treatment; they all survived. Two (4%) demanded immediate ADT; one (mentioned above) survived but refused further follow-up and one progressed to metastatic disease. 35 (69%) had distant metastases: 33 (65%) initiated ADT when metastases were diagnosed, one initiated ADT 4 months after metastases were found on further PSA progression, and one (mentioned above) demanded and received ADT immediately after randomisation and subsequently progressed to metastatic disease. Almost all these patients were receiving ADT before the initial results of the study were presented in 1999; to our knowledge, no patient in the observation group started early ADT thereafter.

Thus, 36 (71%) men in the observation group received ADT for clinically progressive disease (34 metastatic,

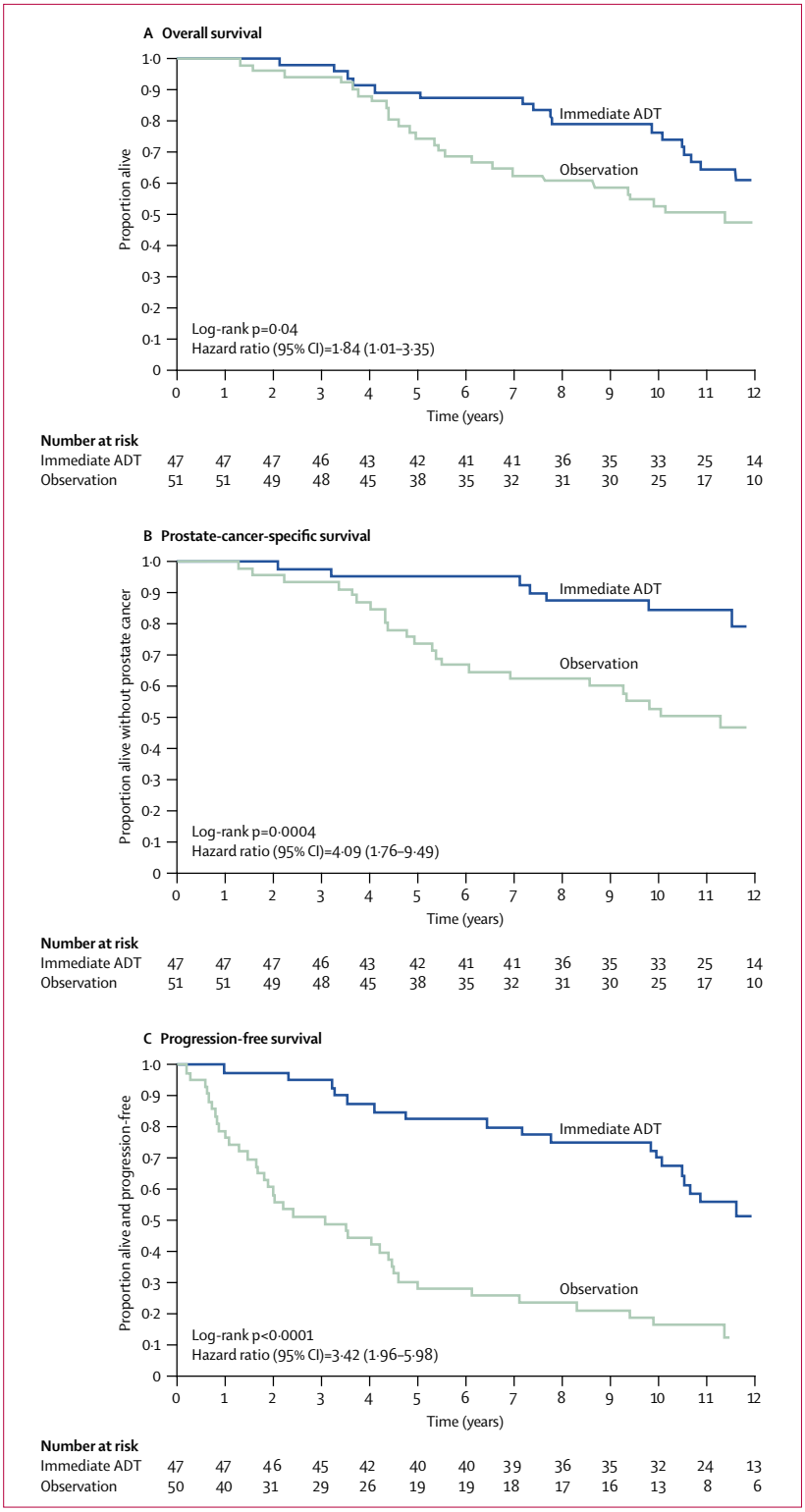

Figure 2: **Kaplan-Meier curves for (A) overall, (B) prostate-cancer-specific, and (C) progression-free (other than PSA recurrence) survival by intention-to-treat analysis**

	Immediate ADT (n=47)	Observation (n=51)	Hazard ratio (95% CI)	p
Number of deaths	17	28	1·84 (1·01–3·35)	0·04
From prostate cancer	7	25	4·09 (1·76–9·49)	0·0004
From other causes	10	3	..	..
Number of recurrences*	22†	44‡	3·42 (1·96–5·98)	<0·0001
Number of patients alive	30	23	..	..
Without recurrence	22	7	..	..
With recurrence	8	16	..	..

*Including PSA recurrence only. †Sites of recurrence at last follow-up or death: three PSA only, eight local only, 11 metastatic. ‡Sites of recurrence at last follow-up or death: six PSA only, three local only, 35 metastatic.

Table 2: **Vital and disease status after median follow-up of 11·9 years**

two local). 19 had remissions lasting more than 12 months, of whom 11 were alive at last follow-up (median survival 144 months [range 12–172]) after initiating ADT. 25 (49%) observed men died after starting ADT, 23 (45%) died from progression of prostate cancer, with a median survival of 36 months (range 10–144 months) after starting ADT. Table 2 shows the disease status of patients at last follow-up or death.

Of patients assigned to the immediate ADT group, 13 underwent bilateral orchiectomy and 33 received goserelin (remaining on the drug continually). Types of ADT for patients assigned to the observed group were medical or surgical castrative treatments, most receiving a depot agonist for luteinising hormone-releasing hormone (not necessarily goserelin, which was available at no cost from the study). No patient received oestrogens, anti-androgens alone, or 5-alpha reductase inhibitors (alone or with anti-androgens). Only one man in the observed group received salvage radiotherapy (with ADT) for a suspected local recurrence, and none in either group underwent adjuvant radiotherapy to the prostatic bed.

	Sample (n=49)	No sample (n=49)	Two-sided p value
Treatment group			
Immediate ADT	19	28	0·11
Observation	30	21	..
Age			
≤65 years	21	24	0·36
>65 years	28	25	..
Median (range)	66 (52–76)	65 (45–77)	..
Nodal status			
Nodes examined (median [range])	10·5 (2–36)	14 (3–37)	0·12
Node-positive status (median [range])	2 (1–20)	2·5 (1–19)	0·74
Gleason score (original)			
3–6	12	12	0·41
7	9	25	..
8–10	9	3	..
Not scored by Gleason system	19	9	..

Data are number of patients unless stated otherwise.

Table 3: **Patients' characteristics by availability of samples**

We received histopathology slides for central pathological review taken from 49 patients. Table 3 shows demographics, original pathology characteristics, and treatment group of patients whose samples underwent central review. Of the 49 patients reviewed, we recorded reductions in Gleason score risk category in 16 patients (five immediate ADT, 11 observation), and increases in five (one immediate ADT, four observation). 19 patients with missing Gleason scores in the original analysis had scores assigned in the central review. Nine samples (three immediate ADT, six observation) did not have an original Gleason score assigned, and no pathology materials were received for these patients for central review. Table 4 shows the original and regraded Gleason scores that were assigned, including 49 centrally reviewed samples and 40 samples for which a Gleason score was given by an institutional pathologist and for which no materials were received for central pathology review. The distribution of Gleason categories did not differ significantly between the treatment groups, although not every sample could have a Gleason score assigned (p=0·22 for 49 new reviews; p=0·38 for 89 original and regraded reviews). Furthermore, proportions of score changes did not differ between groups (p=0·68).

For the 45 (88%) observed men who had Gleason score assigned, median progression-free survival (local, regional, or metastatic—not PSA failure alone) was 5·0 years (range 0·5–13·2) for men with Gleason 3–6 cancers, 4·3 years (0·2–14·2) for Gleason 7 cancers, and 1·8 years for Gleason 8–10 cancers (0·3–10·9). Outcomes did not differ between men with higher Gleason scores (≥8) and those with lower scores (≤7; p=0·18 and p=0·40 for pairwise comparisons of the three Gleason groups). We used proportional hazards models (table 5) to assess the effect of treatment on overall survival, cause-specific survival, and progression-free survival, adjusting for Gleason score. 89 men provided information to contribute to the model (excluding the nine for whom score could not be assigned). After adjusting for Gleason category, we noted a significant association between treatment and survival (overall, p=0·02; cause-specific, p=0·002; progression-free, p<0·0001).

Morbidities of ADT in this trial have been described previously.[10] Apart from expected side-effects such as hot flushes, treatment was generally well-tolerated, and no patient assigned to immediate ADT discontinued treatment because of toxic effects. However, many long-term toxic effects of ADT, including a deleterious effect on bone density,[16,17] were not widely recognised in 1986 when the trial was conceived and approved, or throughout the early years of the study. Thus specific information about skeletal complications of ADT was not expressly monitored, although major medical events, admissions, and surgeries were often reported. In view of this drawback, no patient in the immediate treatment group was reported to have had an osteoporotic fracture. Data are too incomplete to assess their bone-wasting status, or the fracture status of individuals in the observation group.

Ten men assigned to the immediate ADT group had attributed causes of death (based on autopsy, death certificate, clinical records, and data forms) not believed to be due to prostate cancer. These events included three caused by malignant disease (two colon cancer, one lung cancer), two by vascular disease (one ischaemic bowel, one peripheral and cardiovascular), one each by chronic pulmonary disease, myelodysplasia, Alzheimer's disease, pulmonary embolism, and unknown reasons (the patient had recently moved from the follow-up centre with his death discovered by study personnel in an obituary). Of the three men in the observation group who died from non-prostate-cancer causes, one each had cerebral vascular disease, amyotropic lateral sclerosis, and melanoma; one patient had a rising concentration of PSA and two had metastatic prostate cancer, both of whom were receiving ADT at the time of their deaths. Table 6 shows cumulative incidence of the probability of death from prostate cancer and other causes. Although more men assigned immediate treatment died of non-prostate cancer causes, the prevention of death from prostate cancer had a stronger effect in this group than in the observation group.

Discussion

Our findings indicate that in men with clinically localised prostate cancer who undergo radical prostatectomy and lymphadenectomy, have nodal metastases, and have very low or undetectable residual cancer after surgery, immediate ADT significantly improves overall, disease-specific, and progression-free survival compared with the withholding of ADT until disease progression takes place. Whether this benefit of early ADT also occurs with less aggressive prostate cancers or if given with larger tumour masses is unknown.

When we first presented our data nearly 5 years ago (7·1 years median follow-up), about a third of men assigned to the observation group had died. More than 50% of patients in the observed group have since died—all but three from prostate cancer. Overall survival and prostate-cancer-specific survival was significantly better in men assigned immediate ADT than in those assigned observation. One criticism of our initial publication was that, because of small numbers, the risks could have been imbalanced between the two groups.[9] Gleason score was postulated as a possible example of such an imbalance, because it was neither prospectively stratified for nor centrally reviewed, and based on original institutional assignment, did not significantly predict outcome in either treatment group. Despite randomisation, an imbalance is always possible.

Despite concerted efforts to obtain all histological material, 14 of the 36 institutions that contributed patients did not comply with our requests, even when informed of our need for their assistance. Because half the samples were never reviewed centrally, a meaningful imbalance of Gleason scores might still have existed. However, neither the original nor regraded Gleason score assignments showed any imbalance. Gleason scores also indicated a non-significant tendency (especially for scores ≤7 *vs* ≥8) to predict disease progression in observed men, indicating that the score assigned by central reviewers and (if not available) institutional pathologists was indicative of the overall biological aggressiveness of disease. We thus think that the distribution of Gleason scores between treatment groups was not sufficiently different to account for, or even contribute to, the differences in outcome. However, other inequities could exist between the groups (but what these might be is not apparent). Many pathological and clinical criteria were similar between groups, including pathological stage, tumour volume,[10] extent of lymphadenectomy, lymph-node density, and burden of residual disease (as determined by postoperative PSA concentrations, which were undetectable in 80% of participants).

	Immediate ADT		Observation	
	Original	Regraded	Original	Regraded
Gleason score				
3–6	11 (23%)	9 (19%)	13 (25%)	11 (22%)
7	20 (43%)	26 (55%)	14 (27%)	29 (57%)
8–10	5 (11%)	9 (19%)	7 (14%)	5 (10%)
Not graded	11 (23%)	3 (6%)	17 (33%)	6 (12%)

Data are number (%) of patients.

Table 4: **Original and regraded Gleason scores**

	Multivariable models	
	Hazard ratio (95% CI)	p
Overall survival		
Immediate *vs* observation group	2·14 (1·12–4·09)	0·02
Gleason score 3–6 *vs* 7	0·95 (0·44–2·04)	0·89
Gleason score 3–6 *vs* 8–10	1·05 (0·37–2·97)	0·93
Cause-specific survival		
Immediate *vs* observation group	3·63 (1·60–8·24)	0·002
Gleason score 3–6 *vs* 7	1·06 (0·42–2·68)	0·90
Gleason score 3–6 *vs* 8–10	1·42 (0·43–4·68)	0·57
Progression-free survival		
Immediate *vs* observation group	4·11 (2·21–7·66)	<0·0001
Gleason score 3–6 *vs* 7	1·02 (0·51–2·04)	0·96
Gleason score 3–6 *vs* 8–10	2·07 (0·84–5·12)	0·12

Table 5: **Effect of treatment on outcome, adjusted for Gleason score**

	Immediate ADT	Observation	p
Prostate cancer			
Deaths within 5 years	2 (4%, 3·4–5·1)	12 (24%, 21·9–25·2)	0·0003
Deaths within 10 years	6 (13%, 11·6–14·4)	21 (41%, 39·3–43·2)	..
Not prostate cancer			
Deaths within 5 years	3 (6%, 5·4–7·4)	1 (2%, 1·4–2·5)	0·03
Deaths within 10 years	5 (11%, 9·4–12·0)	3 (6%, 4·9–6·8)	..

Data are number of events (%, 95% CI) unless stated otherwise.

Table 6: **Competing risk analysis of causes of death**

Furthermore, the outcomes of men in the observation group were much the same as those in patients with a node-positive status from single-institution series[11] who had undergone prostatectomy and were managed expectantly. Four publications or presentations[18–21] have since reported outcomes of their single-institution retrospective series. Three reported similar (or worsened) PSA recurrence to that for men in the observed group in our study.[18–20] One[21] reported fewer PSA failures (ie, recurrence events as assessed by PSA concentration) at 12 years than in men in the observed group in our study, no plateau in PSA recurrence, and by 16 years, a higher proportion of men had PSA failures than in our study. Thus, although extensive and meticulous lymphadenectomy and reduced extent of disease could cure a few patients with nodal metastases treated by surgery alone, most would not be cured by this method alone.

Our results were also criticised because of European Organisation for Treatment of Cancer (EORTC) trial 30846,[21] which randomly assigned men with positive nodes who had undergone pelvic lymphadenectomy without definitive treatment to the prostate to receive immediate ADT or deferred management. This study found no significant difference in survival between the two groups (hazard ratio 1·24 [95% CI 0·87–1·7]). However, as the investigators pointed out, patients in this trial probably had at least 12·5 cm^3 of cancer tissue (the mean volume of local tumour in our patients)[10] remaining after lymphadenectomy at the time of ADT use in the immediate treatment group. As discussed by the EORTC 30846 researchers[22] and by ourselves,[10,11] ADT is probably most effective against very small quantities of tumour, as has been shown in several experimental systems.[23–25]

Another European study[26] of early versus deferred ADT as primary treatment for non-metastatic prostate cancer has been reported. In this trial, men not regarded as candidates (on the basis of comorbidities) for immediate or deferred ADT, or who refused curative local treatment were randomly assigned to immediate or deferred ADT. Again, disease-specific survival did not differ between groups (p=0·09), but notably, 42% of men in the deferred group died without ever needing to receive ADT. This finding probably indicates that the comorbidities of the trial's participants were much greater than those for men in our trial or EORTC 30846.

Although our study and several others support the benefits of early ADT in patients with aggressive prostate cancer without distant metastases, other trials[1,22,26,27] have not shown such survival advantages. Importantly, a meta-analysis of all available trials of early versus deferred ADT for more than 3000 men without distant metastases, excluding those using oestrogen treatment (eg, diethylstilbestrol) or steroid-containing antiandrogens (eg, cyproterone acetate), which are both known to have pronounced cardiovascular toxic effects,[1,28] also confirms substantial benefits in overall and disease-specific survival for early ADT.[29] This meta-analysis[29] included some trials in which early versus deferred ADT was combined with radiotherapy, which might have attributed the benefits of ADT partly to local tumour control by radiotherapy. But if early ADT is most effective against small tumours, the exclusion of studies that used radiotherapy (some of which began ADT only after completion of radiotherapy)[4] would be inappropriate.

However, these data do not indicate that all men with non-metastatic prostate cancer should receive immediate ADT. Morbidities and expenses of such treatments are not trivial,[16,17] and almost all the men in the meta-analysis[29] had very high-risk prostate cancer. The men in our study fit that criterion because more than 85% of the patients in the observed group were not cured by surgery, despite 80% having undetectable concentrations of PSA after prostatectomy. Use of immediate ADT as a long-term adjuvant, as primary treatment, or for early salvage (eg, on PSA recurrence) for low-risk disease has not yet been shown to have any survival advantage and could provide additional risk.

In view of this disadvantage, we recorded more deaths from causes other than prostate cancer in men receiving immediate ADT than in those receiving deferred ADT. This negative effect was outweighed by the benefit of immediate ADT in reducing deaths from prostate cancer, and no obvious explanation for ADT-associated mortality was noted. Moreover, in EORTC 30846[22] and the meta-analysis of castrative treatments,[29] no additional non-prostate-cancer mortality was seen in men treated with immediate ADT. However, this effect could not be stated for ADT containing oestrogens, progestins, cyproterone acetate,[1,28] or for long-term use of high-dose bicalutamide, a non-steroidal antiandrogen.[30] Thus, any type of long-term hormonal treatment in men at low risk for serious disease sequelae should be viewed with great caution. Furthermore, if comorbidities seem to be more life-threatening than prostate cancer, early ADT might not be needed.[26]

Our trial withheld ADT for men in the observation group until bony metastases occurred, a practice rarely followed now. We do not know whether such patients received ADT when their PSA concentration became detectable or began to rise, or whether their outcomes would have been similar to those of our immediately treated patients. In view of the change in practice at diagnosis that informal PSA screening has caused, node-positive disease is now seen much less often than when we began our study in 1988, and it would be impractical to address these issues in a randomised prospective trial. We also do not know whether men at high risk, but who do not have as advanced disease as our trial participants (eg, seminal vesicle involvement, positive surgical margins, cancers with Gleason score 8–10),[31,32] would benefit as much as our trial participants who received immediate ADT. Although no randomised trial has been completed in this group of patients to address these issues, some are underway in Europe.[33,34] Unfortunately, these trials might be too small and might not have restricted entry to sufficiently high-risk patients

to be definitive. The role of immediate ADT remains uncertain in high-risk patients with node (N) 0 status.

Conflicts of interest

We declare no conflicts of interest.

Contributors

E Messing developed the study design, oversaw the conduct of study, analysed data, and decided on the time of publication. J Manola did the statistical analysis of data. J Yao and A diSant'Agnese provided central histology review and supervision. M Kiernan assisted with data collection and archiving. G Wilding and D Trump coordinated participation in the trial by investigators at the Eastern Cooperative Oncology Group (ECOG); and D Crawford did the same for the Southwest Oncology Group (SWOG).

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