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Risks and benefits of hormonal manipulation as monotherapy or adjuvant treatment in localized prostate cancer

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Abstract

A roundtable meeting was held to discuss the role of hormonal therapy in localised prostate cancer. The findings of the group were that immediate hormonal therapy does not provide an overall survival advantage in localised and locally advanced prostate cancer. A trend towards decreased survival with bicalutamide was observed in low risk patients such as those with localised disease. However, bicalutamide can prolong progression free survival in patients with locally advanced prostate cancer. In patients receiving bicalutamide, there were increased cardiovascular side-effects, in addition to the high incidence of gynaecomastia. Early hormonal therapy has to be balanced against such side-effects and the inevitable appearance of hormone refractory disease in patients who progress after hormonal therapy. Consequently, patients with localized, low risk disease are not considered appropriate candidates for hormonal therapy used either as monotherapy or in the adjuvant setting.

1. Introduction

The optimal use of hormonal therapy for prostate cancer is a topic that is hotly debated. The key issues are the use of early hormonal therapy after surgery or delayed therapy instituted when the disease progresses; the use of intermittent androgen ablation as opposed to continuous therapy, hormonal therapy in the neoadjuvant or adjuvant setting; MAB vs. luteinising hormone-releasing hormone (LHRH) analogue monotherapy or surgical castration; and antiandrogen monotherapy. What is known is that the development of hormonal resistance can be expected 3–5 years after the institution of hormonal therapy. Hormonal treatment is essentially palliative since patients dying from prostate cancer are hormone resistant.

In the era of prostate-specific antigen (PSA), more cancers are being identified at an early stage with 40–60% of them being localized at diagnosis, 30–40% being locally advanced and less than 5% with metastatic disease. While short-term adjuvant androgen deprivation has become standard care in conjunction with radiotherapy for localized disease because of its local synergistic effects, particularly if the local total radiation dose is relatively low, it remains to be seen at what stage hormonal therapy fits in the armamentarium after radical prostatectomy. Open to debate is whether hormonal therapy should be instigated as first line adjuvant therapy, when the PSA is rising or when metastases are documented. New strategies are needed to optimize the use of hormonal therapy in this setting.

This paper summarizes discussions on the role of hormonal therapy in localized prostate cancer that took place during a roundtable meeting at the 20th Congress of the European Association of Urology in Istanbul, Turkey 16–19 March 2005. The key issues under discussion were:

1. The role of hormonal treatment in the management of PSA relapse after local treatment with curative intent (radical prostatectomy, radiotherapy)
2. Which form of hormonal therapy should be used (orchiectomy, antiandrogen monotherapy); what is the optimal timing of such therapy (early vs. deferred); and which patients will benefit most from hormonal therapy taking into account its associated side-effects.

2. Side-effects of hormonal therapy

Hormonal therapy is not without side-effects and these can have a debilitating effect on the patient. Those commonly seen include erectile dysfunction, hot flushes, decreased libido, gynaecomastia and mental impairment. In addition, orchiectomy can be associated with

psychological trauma due to the nature of the surgery. However, we must also be aware of the study conducted by Potosky and associates who investigated the effect of primary androgen deprivation therapy (LHRH agonist or orchiectomy) on quality of life in 431 men with prostate cancer [1]. Results showed that sexual function outcomes were similar in the two treatment groups before and after the implementation of androgen deprivation therapy. More LHRH patients reported breast swelling, as well as more physical discomfort and worry about the cancer or its treatment than did orchiectomy patients. Overall health was assessed as fair or poor more frequently by LHRH patients than by orchiectomy patients and LHRH patients were also less likely to consider themselves free of prostate cancer after treatment.

Other side-effects of androgen suppression more recently identified are anaemia [2] and reduction of bone mineral density with an increased risk of fractures [3]. Green et al [4] described decreased cognitive function in a study involving 82 men with locally advanced prostate cancer treated with androgen suppression monotherapy. Androgen deprivation therapy can adversely affect the cardiovascular system and cardiovascular disease (CVD) is the most common cause of death in men with prostate cancer, more so than the cancer itself. CVD adverse events include alteration in lipid profile, hypertension, hypercoagulability, increased body mass index, glucose intolerance and increased QT interval [5]. The electrocardiographic (ECG) QT measures ventricular polarization and if increased may result in a predisposition to arrythmias and sudden death. Data reported in 2004 from three randomized controlled trials indicate an increase of 9 to 20 msec in ECG QT interval in men with prostate cancer subjected to androgen deprivation, involving leuprolide, leuprolide or goserelin plus bicalutamide, and the LHRH antagonist, abarelix [5]. These findings should be considered in the risk benefit assessment of hormonal therapy,

particularly in men with a baseline QT interval of > 450 msec or those taking class IA or III anti-arrythmics.

3. Early vs. delayed hormonal therapy

A number of studies have compared the benefits of immediate vs. deferred androgen therapy. One of the earliest studies was conducted by the Veterans Administration Cooperative Urological Research Group, who reported no difference in overall survival at 9 years in patients with advanced prostate cancer treated with immediate versus deferred orchiectomy [6]. The Medical Research Council initially reported a survival benefit with immediate hormonal treatment in a study of 938 M0/M1 prostate cancer patients [7]. However, on longer follow-up (up to 15 years), there was no significant difference in overall survival, with the survival curves coming together with time [8]. Another prospective, randomized trial has been conducted in Switzerland involving 197 patients treated either with immediate or deferred orchiectomy [2]. In terms of disease stage, 67% had T3−T4 tumours, 20% had lymph node metastases and 22% had distant metastases at randomization. Results showed that the time to onset of first pain, ureteric obstruction and/or documented metastases after randomization was significantly longer ($P < 0.01$) in patients treated with immediate therapy (Fig. 1). However, the time from randomisation to the first appearance of pain, ureteric obstruction or new bone metastases requiring additional treatment after immediate or deferred treatment were not significantly different (Fig. 2). No difference in the total pain free time (Fig. 3) or overall survival (Fig. 4) up to 14 years was evident between the two treatment groups. Overall, this study indicated that there was no major advantage for immediate therapy over deferred therapy and that many patients did not require it at all. In addition, patients in the deferred treatment arm still had

the possibility to respond to androgen deprivation when they progressed, unlike the patients who had immediate treatment.

The EORTC-GU group has conducted a prospective study in 985 patients with localized N0–2 prostate cancer comparing immediate androgen therapy involving orchiectomy or an LHRH analogue with deferred treatment initiated at the time of symptomatic disease progression or life-threatening complications (EORTC trial 30891) [9]. In terms of progression, patients on immediate therapy initially had a substantially longer symptom free period. However, the time to progression after initiation of deferred hormonal therapy was not different between the two groups. Results showed that overall survival was slightly greater with immediate treatment. However, mortality definitively or probably due to prostate cancer was not substantially increased with deferred therapy: 29.0% vs. 26.2% on deferred and immediate treatment, respectively. Overall only 20% of patients died as a result of prostate cancer and the difference in mortality between the two groups could be attributed to causes of death other than prostate cancer. Considering the advanced patient age of the study groups, it could not be concluded which competing cause of death accounted for the difference in overall survival.

In the same study, those patients who started deferred hormonal treatment did so at a median of 3.2 years after entry on study and 126 patients in the deferred therapy group died without needing treatment (44% of the deceased patients and 25% of all patients). Consequently, balanced against the small overall survival advantage in the immediate therapy group (apparently not caused by a difference in prostate cancer deaths), is the fact that the deferred approach may spare a substantial number of patients the burden of the treatment. Clearly, more research is needed to identify subgroups of patients who would profit from immediate treatment.

A retrospective study from the US has examined deferred versus immediate androgen therapy for PSA recurrence after radical prostatectomy using a risk stratified approach [10]. A total of 1352 men who underwent a radical prostatectomy between 1988 and 2002 and had a PSA level greater than 0.2 ng/ml after surgery were enrolled in the study. Time to bone metastases was similar for patients with immediate androgen therapy, which was started after PSA recurrence (n = 355), and for those with delayed therapy, which was given only after clinical metastasis developed (n = 997) (Fig. 5). In the overall study cohort, immediate androgen therapy had no impact on the development of clinical metastases. However, upon risk stratification, immediate therapy was associated with delayed bone metastasis in patients with a pathological Gleason sum > 7 or PSA doubling time of 12 months or less. These findings suggest that early hormonal therapy may be advantageous in high-risk cases but not in general for all patients.

4. Antiandrogen monotherapy

The role of antiandrogen monotherapy has been evaluated in three large-scale studies which, in combined analysis, involved over 8000 patients with localized or locally advanced prostate cancer (T1b-T4, M0, any N [N0 in one study]) [11]. Patients were randomized to receive bicalutamide 150 mg/day or placebo in addition to standard care consisting of radical prostatectomy, radiotherapy or watchful waiting. Results indicated, as expected, that bicalutamide significantly prolonged progression free survival in the overall population at a median follow-up of 5.4 years (Fig. 6). The greatest difference was seen in patients with locally advanced disease. There was no difference, however, in overall survival between the bicalutamide and placebo groups. Among the watchful waiting patients bicalutamide appeared to improve survival in those with locally advanced disease, whereas it appeared to reduce survival in those with localized disease.

These findings were further examined in a sub-cohort of the study involving 1218 patients with localized or locally advanced prostate cancer from 62 Scandinavian centres [12]. Again, bicalutamide was shown to significantly prolong progression-free survival, decreasing the risk of disease progression by 43% compared with placebo (HR 0.57, 95% CI 0.48 to 0.68, $p < 0.0001$). Again, there was a distinction between patients with localized and locally advanced prostate cancer. At a median follow-up of 5.3 years patients with locally advanced disease had improved survival with bicalutamide (HR 0.68, 95% CI 0.50 to 0.92), while those with localized disease had decreased survival (HR 1.47, 95% CI 1.06 to 2.03) (Fig. 7). The possible reasons for this phenomenon are not clearly known, but an increase in cardiovascular death was observed with bicalutamide [11].

Although these data suggest that patients with locally advanced prostate cancer may benefit from early bicalutamide, an earlier comparative study reported by Tyrell et al showed that orchiectomy provides a greater benefit in these patients [13]. Two identical, multicentre, randomised studies compared bicalutamide 150 mg/day with castration in 1453 patients with either confirmed metastatic disease (M1), or T3/T4 non-metastatic disease with elevated PSA (M0). At a median follow-up of 100 weeks, combined analysis of both studies indicated that bicalutamide was less effective than castration in patients with metastatic disease (M1) at entry with a difference in median survival of 6 weeks (Fig. 8). Based on these findings bicalutamide is not the treatment of choice or a true alternative to standard androgen deprivation in patients with metastatic disease. It maintains a role as short-term treatment in preventing tumour flare associated with the use of LHRH analogues at risk of rapid progression (spinal compression, bone pain).

It should be noted that patients who progress after hormonal therapy invariably have hormone refractory disease. Patients given immediate therapy will develop hormone refractory disease at an earlier time point than those on deferred therapy.

Hormone refractory prostate cancers express high levels of androgen receptor (AR) and androgen receptor (AR)-regulated genes [14], although the mechanism of AR activation in these clinically androgen-independent tumours is not clear. An *in vitro* study by Masiello et al [15] involving androgen-independent cell lines showed that the antiandrogen bicalutamide stimulated the assembly of a transcriptionally inactive AR on DNA. Other findings from the study support the expression of altered coactivator (or corepressor) as a possible mechanism of bicalutamide-resistant androgen-independent prostate cancers. A recently published report by Chen et al [16] confirm these findings and, in addition, showed that androgen receptor antagonists show agonistic (stimulatory) activity in cells with increased AR levels. This conversion from antagonist to agonist was associated with alterations in the recruitment of coactivators and corepressors to the promoters of AR target genes. These findings have also been reported by Culig and co-workers [17–19]. A recent publication has reported on the x-ray crystal structure of a mutant on the AR ligand binding domain which confers agonist activity to bicalutamide [20]. This group has also shown conformational changes in the bicalutamide molecule that could result in agonistic activity. A detailed review of the possible steps in the development of hormone refractory prostate cancer can also be found in an article published by de la Taille et al [21]. Clearly, these findings caution the use of nonsteroidal anti-androgens as a therapeutic option for prostate cancer.

5. Conclusions

Although clinical studies have shown that immediate hormonal therapy can provide a degree of delay in disease progression, there is no evidence to suggest it increases overall survival. Based on the evidence from clinical trials, patients who are followed expectantly can benefit from androgen deprivation once they become symptomatic or when

metastases are documented. Any benefits of early hormonal therapy have to be balanced against the not insignificant side-effects of therapy and the knowledge that patients who progress after hormonal therapy invariably have hormone refractory disease and limited subsequent treatment options. The group conclude that initiation of hormonal therapy for minimal disease or any biochemical disease progression after local treatment with curative intent is not warranted. A possible benefit may be expected in patients with poorly differentiated aggressive disease. In this case, medical or surgical castration is preferable to bicalutamide monotherapy.

Fig. 1. Time from randomisation to first pain, ureteric obstruction and/or documented new metastases in patients treated with immediate or deferred orchiectomy. Reproduced with permission from the American Society of Clinical Oncology: Studer et al. J Clin Oncol 2004;22:4109–18.

Fig. 2. Time from randomisation to the first appearance of pain, ureteric obstruction or new bone metastases requiring additional treatment after immediate or deferred orchiectomy. Reproduce with permission from the American Society of Clinical Oncology: Studer et al. J Clin Oncol 2004;22:4109–18.

Fig. 3 Overall symptom free interval up to 14 years in patients treated with immediate or deferred orchiectomy. Reproduced with permission from the American Society of Clinical Oncology: Studer et al. J Clin Oncol 2004;22:4109–18.

Fig. 4. Overall survival up to 14 years in patients treated with immediate or deferred orchiectomy. Reproduced with permission from the American Society of Clinical Oncology: Studer et al. J Clin Oncol 2004;22:4109–18.

Fig. 5. Time to development of bone metastasis following immediate or deferred androgen therapy. Reproduced with permission from Moul et al. J Urol 2004;171:1141–7.

Fig. 6. Kaplan Meier curves of progression-free survival at a median follow-up of 5.4 years in patients treated with bicalutamide or placebo in addition to standard care. Reproduced with permission from Wirth et al. J Urol 2004;172:1865–70.

Fig. 7. Kaplan-Meier curve of overall survival in patients with localized disease receiving bicalutamide 150 mg/day in addition to standard care or standard care alone. Reproduced with permission from Iversen et al. J Urol 2004;172:1871–6.

Fig. 8. Survival rates in patients with metastatic disease or T3/T4 non-metastatic disease with elevated PSA at study entry treated with castration or antiandrogen monotherapy. Reproduced with permission from Tyrrell et al. Eur Urol 1998;33:447–56.

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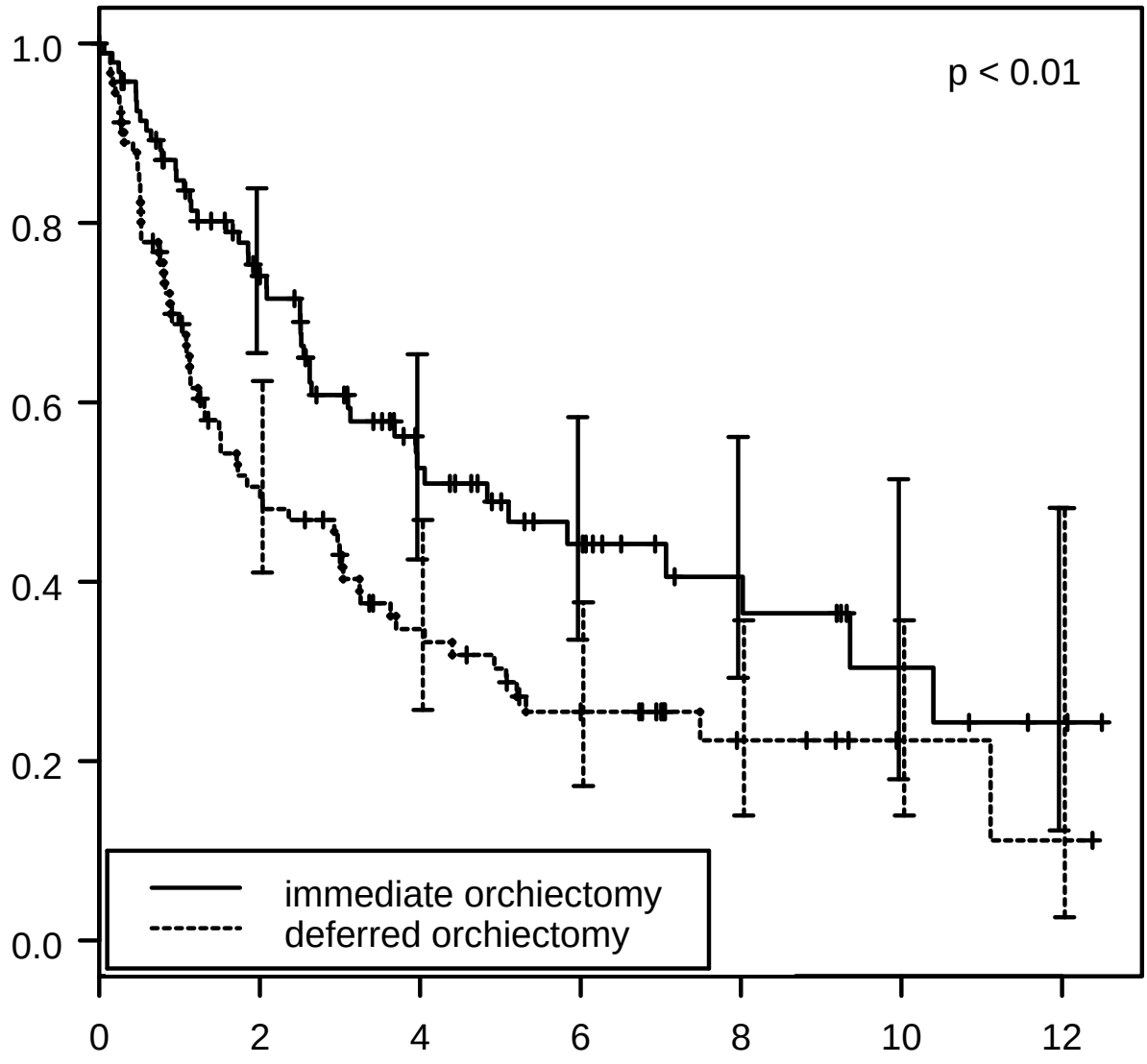
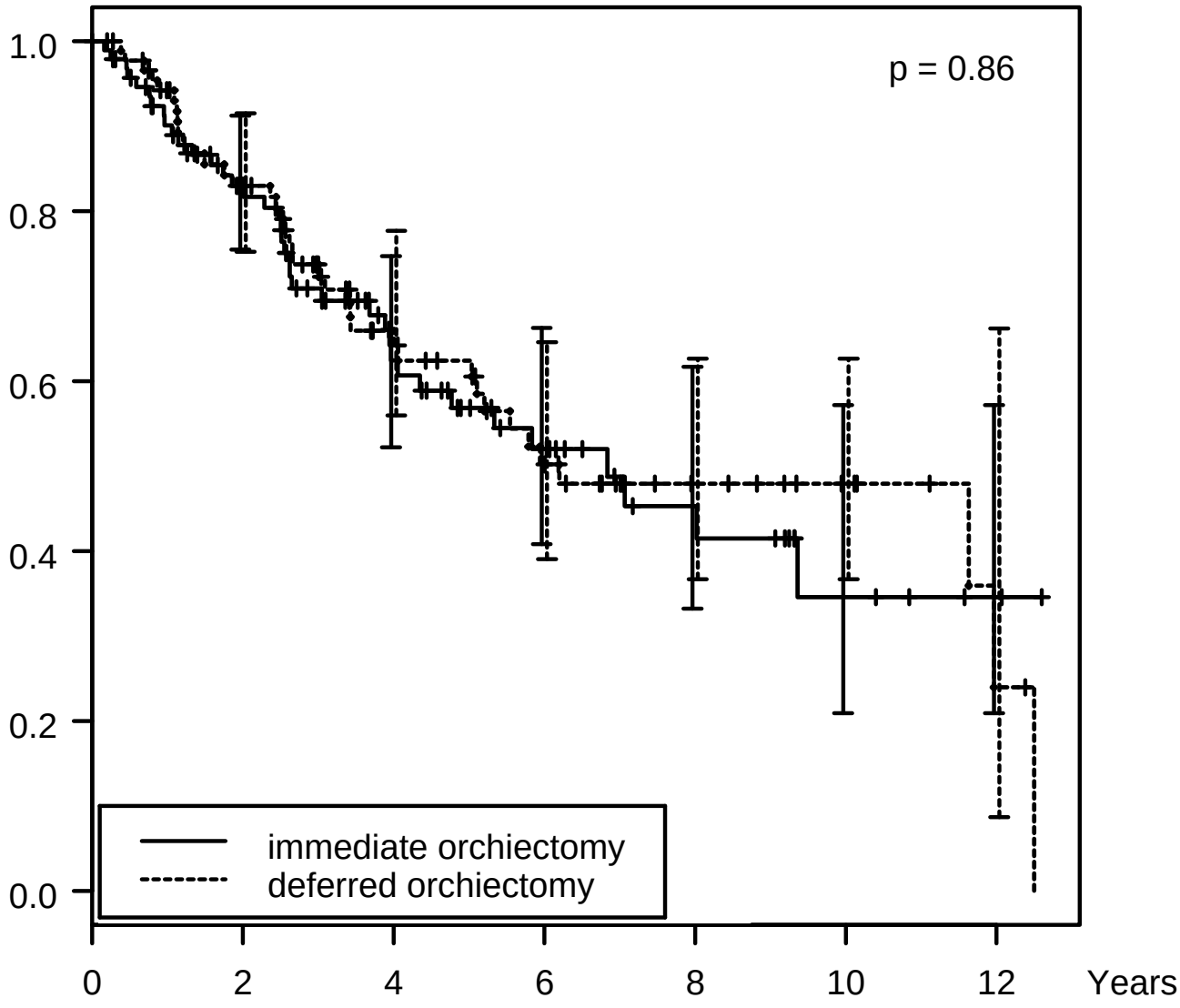
Time to first Pain, Ureteric Obstruction and/or documented new Metastases after Randomisation



Number at risk (immediate/deferred):

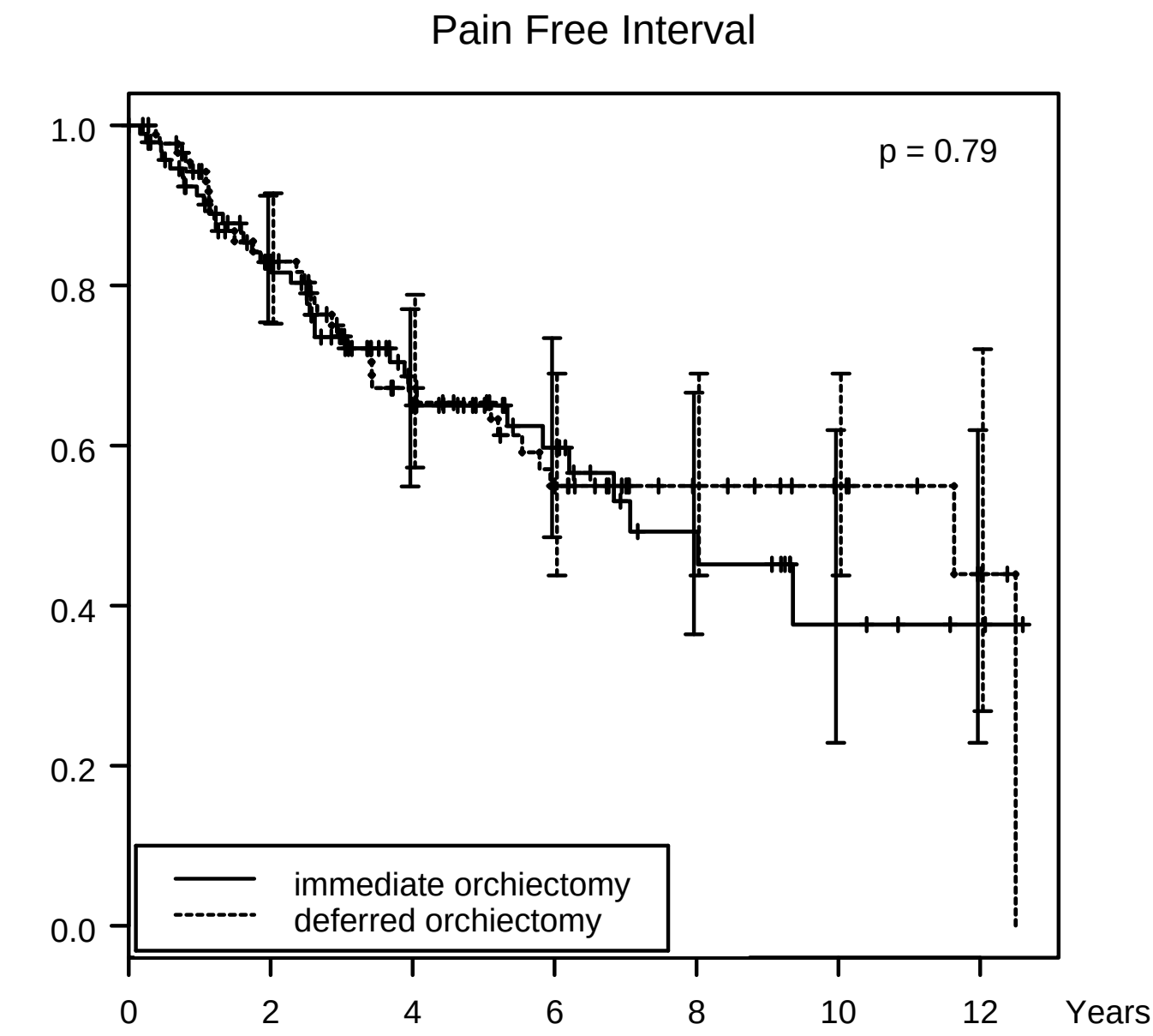
i:	96	59	30	18	10	5	2
d:	92	41	24	15	6	2	1

Time to Pain, Ureteric Obstruction or Risk of Pathological Fracture after Immediate or Deferred Treatment



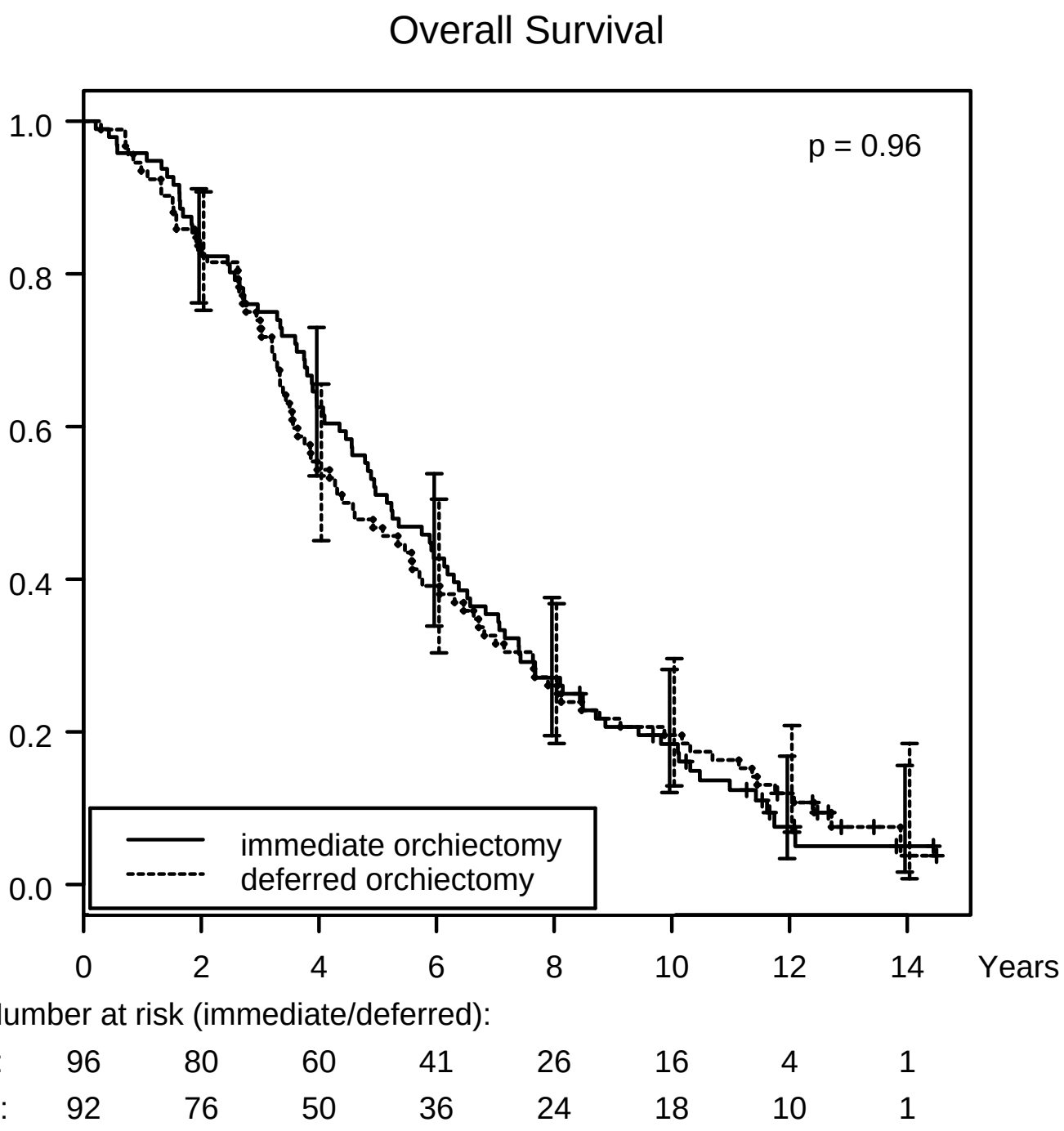
Number at risk (immediate/deferred):

i:	96	65	35	21	12	5	2
d:	92	65	38	24	12	7	2



Number at risk (immediate/deferred):

i:	96	65	35	22	12	5	2
d:	92	65	38	26	13	8	3



Number at risk (immediate/deferred):

i:	96	80	60	41	26	16	4	1
d:	92	76	50	36	24	18	10	1

Fig. 6. Kaplan-Meier curve of overall survival in patients with localized disease receiving bicalutamide 150 mg/day in addition to standard care or standard care alone. Reproduced with permission from Iversen et al. J Urol 2004;172:1871–1876.

Fig to be redrawn and permission sought (Fig. 2)

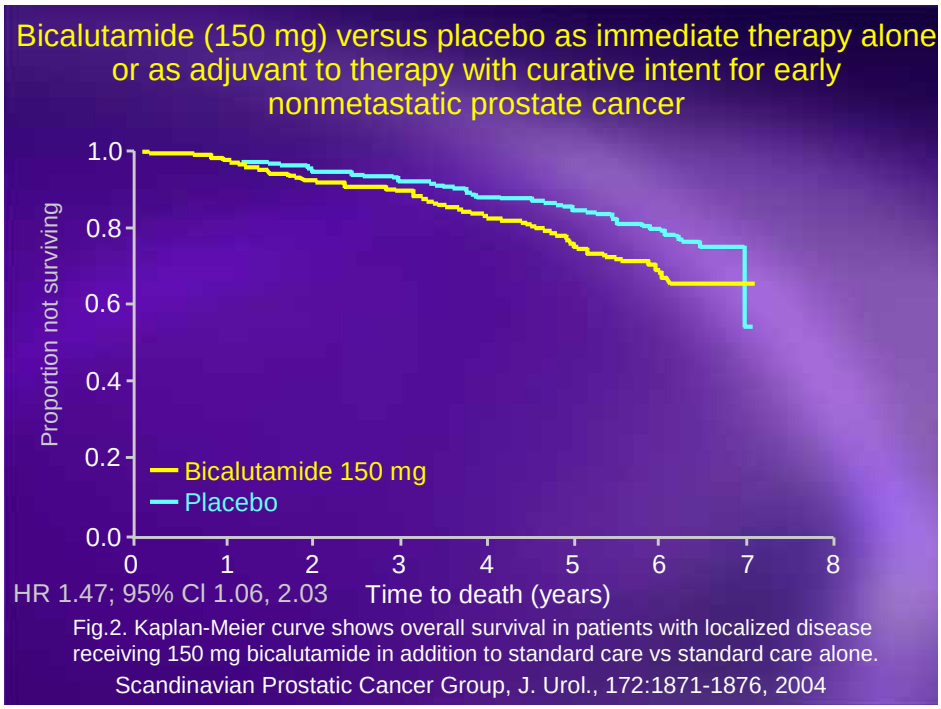


Fig. 7. Survival rates in patients with metastatic disease or T3/T4 non-metastatic disease with elevated PSA at study entry treated with castration or antiandrogen monotherapy. Reproduced with permission from Tyrrell et al. Eur Urol 1998;33:447–456. **Need to get permission from journal. Fig to be redrawn**