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Trends in the Use of Androgen Deprivation in Prostate Cancer

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The aim of this study was to assess current management of prostate cancer patients with elevated prostate-specific antigen (PSA) among Finnish urologists and oncologists. Four case scenarios were presented: postprostatectomy PSA relapse, postradiotherapy (RT) relapse with a slowly or rapidly rising PSA, elderly patients prior to treatment. Management preferences and the use of androgen deprivation (AD) in prostate cancer were surveyed. Eighty-two informative replies, 60 from 90 practicing urologists (67%) and 22 from 70 practicing oncologists (31%) were received. For postprostatectomy relapse, salvage RT or follow-up until significant rise of PSA were the favored recommendations. For post RT with slowly or rapidly rising PSA and treatment of non-radical cases an active approach with even small PSA rises and immediate androgen deprivation were favored. For intervention, the recommended PSA border values ranged from 0.5 to >100 ng/mL. More research is needed focusing on criteria and timing of AD in the treatment of prostate cancer.

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Prostate cancer (PC) is the most common cancer among men in the Western world and also in the Nordic countries. The incidence is increasing due to the common use of PSA testing for detection and the increasing number of elderly in society. In the European Union the age-standardized incidence is 65/100 000 men and mortality 26/100 000 per year (1). Survival increases in prostate cancer in the 1990s in prostate cancer were due to both earlier diagnosis and improved therapeutic approaches, especially androgen deprivation therapy (ADT) (2). ADT is the standard option in the treatment of metastatic prostate cancer and is frequently used as an alternative to watchful waiting in cases with clinically localized prostate cancer calling for less aggressive management. It is used as a means of preventing progression if local therapies cannot be utilized for reasons of patient preference or poor general condition (3). In recent years it has become common practice to combine androgen deprivation with radical radiotherapy in a neo+adjuvant or adjuvant setting, since this approach has been shown to improve survival of poor-prognosis prostate cancer patients (4–6).

The use of ADT in the neo+adjuvant setting has increased rapidly during the last 10 years. At least 22 000 PC men each year in the USA have been estimated to receive hormonal therapy (7). However, the criteria for the use of androgen deprivation vary. Androgen deprivation for prostate cancer is known to affect the plasma concentration of several hormones (8, 9) and to be detrimental to the quality of life (10). ADT may be overused, since not all patients with rising PSA develop clinical relapse and identification of patients likely to progress rapidly is difficult (11). Latent subclinical PC is particularly common in men >80 years of age. Only 1/10 latent cancers will eventually become clinical cancers (1). The aim of the present study was to assess the use of ADT in prostate cancer among Finnish specialists in oncology and urology.

SUBJECTS AND METHODS

The prospective study included specialists in urology and oncology working in different hospitals in Finland. According to the Finnish Medical Association, in 2002 there were 90 urologists and 110 oncologists (covering both the specialities of medical and radiation oncology). The scenarios devised by Duchesne and colleagues (11) were translated into Finnish and sent to doctors listed in the societies' specialist network by e-mail (oncologists included in the e-mail list of the Finnish Society of Oncologists in 4/2003, n = 70) or by mail (urologists, n = 90). The respondents were asked to indicate their preferred treatment

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option in four clinical scenarios and also their favorite mode of using androgen deprivation and indications in neo+ adjuvant treatment of prostate cancer. The questionnaire was returned via e-mail or mail. The data were analyzed using a chi-squared test or Fisher's exact test. The difference in the timing of intervention between rapid rise and slow rise was examined using McNemar's test. The Mann-Whitney U-test was used to compare the PSA levels between specialist groups in the different scenarios. Statistical analysis was done using SAS system for Windows, release 8.02. A p-value of < 0.05 was considered statistically significant.

RESULTS

Responses

There were 82 informative responses, 60 from 90 practicing urologists (67%) and 22 from 70 practicing oncologists (31%). The reason for the low number of oncologists participating is that some replied 'this is taken care of by urologists in our hospital' and did not answer the queries.

Favored treatment options

Table 1 shows the treatment preferences for the different scenarios in the respective groups. In scenario 1, urologists were less likely than oncologists to recommend RT than ADT but the difference was not statistically significant. There were no statistically significant differences between the specialists when comparing the adoption of immediate vs. delayed use of ADT in scenarios 2 and 3 with rapid or slow PSA rise. Only in answers to scenario 4 was there a statistically significant difference between the oncologists and urologists, the latter favoring more frequently than oncologists immediate treatment with androgen ablation ($p = 0.003$).

Scenario 2, using PSA as the criterion for decision-making, can be interpreted with rapidly rising PSA as suggesting occult distant metastasis rather than local recurrence, which is more probable with a slow doubling time of PSA in scenario 3. With a rapid rise, early use of ADT was favored by 59% of oncologists vs. 40% of urologists. With a slow rise, 42% of oncologists vs. 25% of urologists favored immediate ADT. Combining the groups of specialists to compare the timing of intervention between rapid and slow rise, there was a significantly increased use of early ADT for the rapid risers ($p = 0.005$).

The median (range) levels of intervention PSA values (ng/mL) adopted by the specialist groups are given in Table 2.

Figures 1, 2, and 3 show the percentages of specialists recommending ADT at specific PSA range values in scenarios 1, 2, and 3, respectively. PSA levels were not significantly different between specialist groups in these scenarios.

Figure 4 presents the cumulative number of responders by PSA level in scenarios 1, 2, and 3.

Use of neo+adjuvant androgen deprivation

In this indication recommendations for the duration of treatment diverged widely, ranging from 1 month to lifetime. Opinions differed on T-stage, grade, and Gleason criteria for use of ADT, this indicating common use but no uniformity in clinical practice criteria. Opinions on modes of ADT were more uniform, 53% of urologists (U) and 50% of oncologists (O) recommending a subcutaneously admi-

Table 1

Treatment preferences according to clinical scenario by oncologists and urologists[1]

	Option				
	Radiotherapy	Immediate AD	Delayed AD	Treatment when symptoms	Other
Scenario 1					
Oncologist	10 (50)	0 (0)	8 (40)	–	2 (10)
Urologist	16 (29)	5 (9)	29 (53)	–	5 (9)
Scenario 2					
Oncologist	–	13 (59)	3 (14)	4 (18)	2 (9)
Urologist	–	23 (40)	20 (34)	10 (17)	5 (9)
Scenario 3					
Oncologist	–	8 (42)	5 (26)	4 (21)	2 (11)
Urologist	–	15 (25)	26 (44)	14 (24)	4 (7)
Scenario 4[2]					
Oncologist	–	3 (17)	0 (0)	2 (11)	13 (72)
Urologist	–	33 (59)	2 (4)	5 (9)	16 (29)

[1] Values are presented as the number of respondents, with the percentage in parentheses.
[2] The difference between groups; Fisher's exact test, $p = 0.003$.

Table 2

Median (range) of PSA values (ng/mL) range favored by oncologists and urologists to activate treatment with androgen ablation

Question	Oncologist n	Oncologist Median (range)	Urologist n	Urologist Median (range)
Scenario 1	5	4.0 (1.0–112)	30	4.0 (0.5–20)
Scenario 2	4	7.5 (5.0–20)	20	5.0 (2.0–10)
Scenario 3	6	15.0 (5.0–20)	24	8.0 (2.0–30)

nistered LHRH analogue, 72% (U)/59% (O) an implant LHRH analogue, 55% (U)/50% (O) per oral bicalutamide. Orchidectomy was mentioned by only 45% of urologists as a possible approach, but by none of the oncologists ($p < 0.001$).

About half of the respondents, 53% of urologists and 43% of oncologists, indicated an interest in participating in clinical studies on the use of ADT. Most urologists wished this to take place within the Finnprostata group's research activities.

DISCUSSION

Prostate cancer is the most common cancer among men and second most common cause of male cancer death in most Western countries. In Finland 3 114 new cases were diagnosed in 1999 and 773 patients died of prostate cancer (12). Among those with clinically diagnosed prostate cancer, the likelihood of death from prostate cancer is about 32%. Although no consensus recommendations exist for the use of ADT in prostate cancer the treatment mode is commonly applied. This calls for research to clarify indications in specific clinical situations. Individual dosing is not used in AD, although the castrate testosterone duration has proved dependent on body mass index, pretreatment testosterone level, and AD duration (13). Many patients may thus become unnecessarily exposed to ADT and its adverse effects. There are also suggestions from the MRC study (14) that early rather than delayed intervention in some clinical circumstances may lead to later increases rather than decreases in mortality.

PSA has become a marker of response and progression keenly followed by both doctors and patients for the clinical monitoring of PC. PSA doubling time may be a better predictor of biologic behavior than traditional parameters reflecting only a static picture of a given malignancy at a single point in its natural history (15). In most studies searching for a correlation between PSA doubling time and Gleason score none was found (15) and the wide variation in PSA doubling time reflects the heterogeneity of prostate cancer as a disease (15). Taylor and coworkers (16) have suggested criteria for PSA failure, the requirement of two rises involving a climb over 1.5. These criteria have a slightly decreased specificity compared with ASTRO-s definition of three consecutive rises (17) but a substantially increased sensitivity (16). Another claim is that requiring a rise in PSA above 1.5 may improve the quality of life of the patients by reducing the anxiety associated with small PSA fluctuations in the range of 0.5–1.5 (18). The increasing use of androgen deprivation in prostate cancer indicates a need for consensus recommendations to assist clinical practice. Even in a small country like Finland with five university hospitals responsible for specialist education there is heterogeneity in clinical practice, as seen in this example of the use of androgen deprivation for prostate cancer patients.

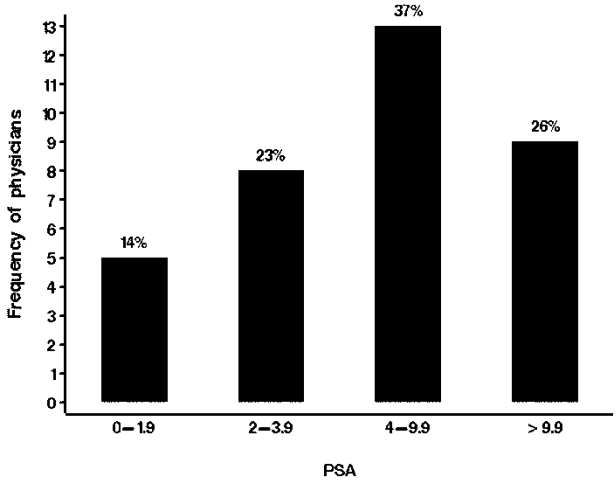

Fig. 1. Percentage of respondents recommending androgen deprivation therapy in scenario 1 by PSA values (specialists combined).

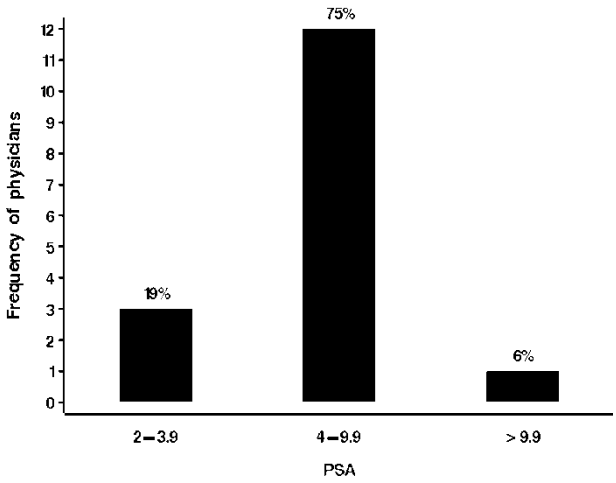

Fig. 2. Percentage of respondents recommending androgen deprivation therapy in scenario 2 by PSA values (specialists combined).

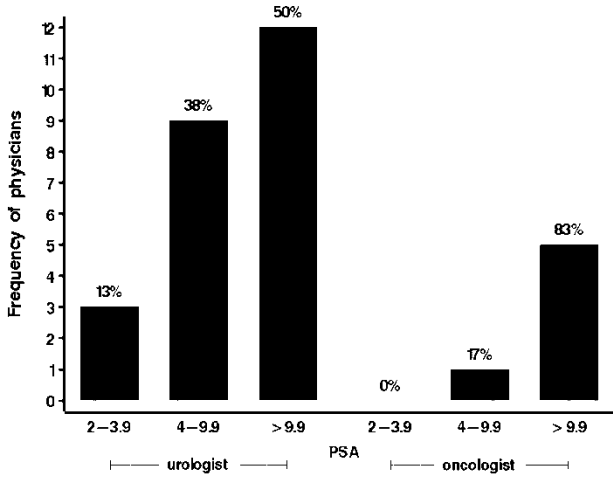

Fig. 3. Percentage of respondents recommending androgen deprivation therapy in scenario 3 by PSA values and by specialty.

The reliability of PSA as a treatment guide is confounded by the phenomenon of bouncing PSA, a temporary post-treatment elevation of PSA values. Recovery of s-testosterone after treatment may cause a temporary rise in PSA without clinical progression (19). The recommendations on the importance of repeated measurements of PSA therefore include three consecutive rises before progression should be diagnosed (17). Alternative criteria have been introduced with the Vancouver and Houston precepts (20). The need to await confirmative repeated PSA values was rarely noted in the recommendations by the Finnish specialists.

Recently published Australian survey results (11) are compared with the present findings in Table 3. Some interesting observations may be made. In scenario 1, postoperative RT was significantly more often recommended by Australian than Finnish specialists. This may be due to differences in the availability of RT services and educational collaboration between specialists. In relapse after radiotherapy more Finnish specialists tended to recommend early AD compared with Australian practice, indicating different treatment philosophies.

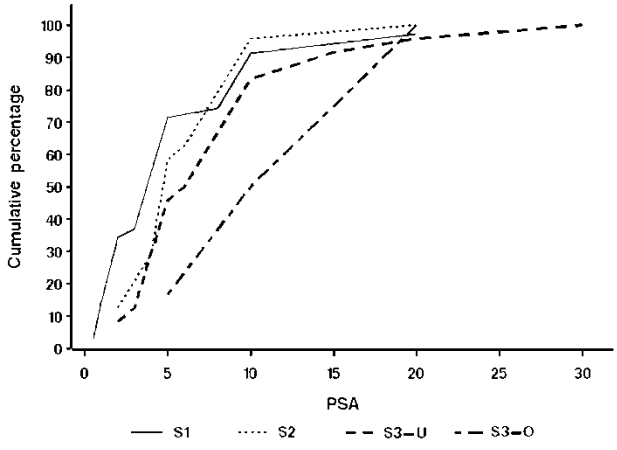

Fig. 4. Cumulative percentage of physicians recommending androgen deprivation therapy by PSA values in scenarios 1 (S-1), 2 (S-2), and 3 (S3-U: urologists in scenario 3, S3-O: oncologists in scenario 3).

Table 3

Comparison between Australian (Aus) and Finnish (Fin) practices in the use of androgen deprivation (ADT) in four clinical scenarios (appendix 1) in the management of prostate cancer[1]

			p-value
Scenario 1	RT	Delayed ADT	<0.001
Aus	67 (69)	30 (31)	
Fin	26 (41)	37 (59)	
Scenario 2	Immediate ADT	Delayed ADT	0.04
Aus	36 (44)	46 (56)	
Fin	36 (61)	23 (39)	
Scenario 3	Immediate ADT	Delayed ADT	0.02
Aus	16 (23)	53 (77)	
Fin	23 (43)	31 (57)	
Scenario 4	RT	Other	0.001
Aus	21 (20)	83 (80)	
Fin	0 (0)	45 (100)	

[1]Values are presented as the number of respondents (%).
Other = immediate AD, delayed AD, or treatment when symptoms occur.

The message of this study highlights the importance of education, collaboration, and the development of treatment guidelines in the use of AD in prostate cancer. The ease of this mode makes its use common, although for each patient its use should be tailored, taking into consideration the rapidity of the progression, adverse effects and overall prognostic situation, if it is not used in the context of a clinical study. Significant cost saving could be obtained when treatment with LH-RH analogues is tailored following individual testosterone values (13).

CONCLUSION

Early treatment with AD was favored in the management of prostate cancer regardless of the possibility of silent progression or falsely interpreted PSA. This contrasts with the practice reported in Australia. The diversity of practice amongst specialists and between different communities is a reflection of the complexities attending the use of PSA to monitor disease, and of the lack of available evidence to guide practice. More research is needed focusing on the timing of ADT to provide this evidence.

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Appendix 1

Scenarios used in the survey study

1) A 67-year-old man undergoes radical prostatectomy for organ-confined prostate cancer; his PSA is undetectable postoperatively but rises progressively in 18 months to 0.4 ug/L. Biopsy and restaging show no overt disease, so this is a PSA relapse only.
   Would you:
   (a) offer radiotherapy to the prostate bed ( )
   (b) start androgen ablation immediately ( )
   (c) observe the PSA, with delayed androgen ablation ( ). If so, at what PSA level would you start the therapy?____ug/L
   (d) other ( ) please specify?:

2) A 70-year-old man undergoes radical radiotherapy for an intermediate risk prostate carcinoma. After a nadir, his PSA rises on 3 successive occasions, with a doubling time of 8 months. Restaging is negative, so this is a PSA relapse only. Would you:
   (a) start androgen ablation immediately ( )
   (b) observe, with delayed androgen ablation ( ). If so, at what PSA level would you start the therapy?____ ug/L
   (c) observe for symptoms, then start androgen ablation ( )
   (d) other ( ), please specify?:

3) A 70-year-old man undergoes radical radiotherapy for an intermediate risk prostate carcinoma. After a nadir, his PSA rises on 3 successive occasions, with a doubling time of 24 months. Restaging is negative, so this is a PSA relapse only. Would you:
   (a) start androgen ablation immediately ( )
   (b) observe, with delayed androgen ablation ( ). If so, at what PSA level would you start the therapy?____ ug/L
   (c) observe for symptoms, then start androgen ablation ( )
   (d) other ( ), please specify?:

4) A 74-year-old asymptomatic man is found to have a PSA of 30 ug/L on routine examination. Staging confirms localized Gleason 2+3 adeno ca of the prostate.
   Would you:
   (a) start androgen ablation immediately ( )
   (b) observe the PSA, with delayed androgen ablation? If so, at what PSA level would you start the therapy _____( ) ug/L
   (c) observe for symptoms, then start androgen ablation ( )
   (d) other ( ), please specify?:

5) Please specify your criteria for neo+/adjuvant androgen ablation in curative radiotherapy:
   TNM:
   Grade:
   Gleason:
   PSA:
   Neo/adjuvant treatment duration: (months)

6) Your favored treatment for androgen ablation?