KCE REPORT 226S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

NATIONAL PRACTICE GUIDELINE ON THE TREATMENT OF LOCALISED PROSTATE CANCER – PART 2

APPENDIX

KCE REPORT 226S
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
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NATIONAL PRACTICE GUIDELINE ON THE TREATMENT OF LOCALISED PROSTATE CANCER – PART 2

APPENDIX

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COLOPHON

Title:	National practice guideline on the treatment of localised prostate cancer – part 2 – Appendix
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Stakeholders:	Filip Ameye (Maria Middelares Gent), Herlinde Dumez (UZ Leuven), Karin Haustermans (UZ Leuven), Nicolaas Lumen (UZ Gent), Ward Rommel (Vlaamse Liga tegen Kanker), Johan Govaerts (St Maarten ziekenhuis Mechelen), Bruno Mortelmans (Imelda ziekenhuis Bonheiden) Three patients participated at the stakeholders meeting. For the sake of privacy their names are not mentioned here.
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CEBAM validators:	Patrik Vankrunkelsven (president), Geert Goderis (general practitioner ACHG), Trudy Bekkering (methodological expert), Alex Breugelmans (urologist, H-H Leuven, user-validator)
Acknowledgements:	Leen Verleye (KCE), Joan Vlayen (KCE) The Guideline Development Group expresses its gratitude to the UK's National Collaborating Centre for Cancer (NCC-C) and National Institute for Health and Care Excellence (NICE). The evidence supporting the majority of the recommendations included in the present guideline is extracted from their source documents.
Other reported interests:	Membership of a stakeholder group on which the results of this report could have an impact: Axel Feyaerts Participation in scientific or experimental research as an initiator, principal investigator or researcher: Bertrand Tombal (president EORTC 60 Group), Dirk Schrijvers (studie Abiraterone acetaat en cabazitaxel), Gert De Meerleer (SBRT for oligo metastates prostae CA), Sandrine Rorive (study biomarkers prostate cancer), Nicolaas Lumen (PI Lomp trial) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Dirk Schrijvers (advisor Janssens Pharmaceuticals en Sanofi), Alain Servaes

	(Euromut) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Gert De Meerleer (Oncoforum), Nicolaas Lumen (Astra Zeneca, Ipsen, Amgen, Janssen)
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1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

1.1. Original list of potential GDG members proposed by the College for Oncology

Expert	Professional Association	Hospital	Email
Bertrand Tombal	GDG Group Chairman	Chef de Service - Service d'Urologie Cliniques universitaires Saint-Luc - 1200 Bruxelles	bertrand.tombal@uclouvain.be
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Van Velthoven Roland	Belgian Association of Urology (BAU-SBU)		rvanvelt@ulb.ac.be>
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Louis Libbrecht	Anatomo-Pathology	U Gent	louisj.libbrecht@ugent.Be
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Liesbet Van Eyken	Kankerregister		elizabeth.vaneycken@kankerregister.org
Nancy Van Damme	Kankerregister		

1.2. Composition of the Guideline Development Group

The GDG as defined in the present guideline consists of persons from the abovementioned “original” list who attended at least one GDG meeting. All of them were granted co-authorship.

Clinicians	Field of expertise, affiliations
Bertrand Tombal, President of the GDG	Urologist, Cliniques Universitaires Saint-Luc
Chris D’Hont	Urologist, ZNA
Gert Demeerleer	Radiotherapist, Belgische Vereniging voor Radiotherapie-Oncologie (BVRO), UZ Gent
Axel Feyaerts	Urologist, Belgian Association of Urology (BAU-SBU), Cliniques Universitaires Saint-Luc
Thierry Gil	Oncologist, Belgian Society of Medical Oncology (BSMO), Institut Jules Bordet
Laurette Renard	Radiotherapist, Association Belge de Radiothérapie-Oncologie (ABRO), Cliniques Universitaires Saint-Luc
Roland Van Velthoven	Urologist, Belgian Association of Urology (BAU-SBU)
Dirk Schrijvers	Oncologist, Belgian Society of Medical Oncology (BSMO), ZNA Middelheim
Sandrine Rorive	Pathologist, Belgian Society for Anatomo-Pathology, Erasme Hospital
Bram Spinnewijn	General Practitioner, Domus Medica
Alain Servaes	Patient representative, Wij Ook
Nancy Van Damme	Kankerregister

1.3. List of external experts

External experts as defined in the present guideline consists of persons from the abovementioned “original” list who did not attend any GDG meeting but provided feed-back by e-mail. Their comments were discussed at the GDG meetings and incorporated in the minutes of the meetings.

Clinicians	Field of expertise, affiliations
Steven Joniau	Urologist, UZ Leuven
Sara Junius	Radiotherapist, Belgische Vereniging voor Radiotherapie-Oncologie (BVRO), AZ Groeninge Moucron
Louis Denis	Patient, Wij ook
Denis Schallier	Oncologist, Belgian Society of Medical Oncology (BSMO), UZ Brussel

1.4. Composition of the KCE expert team

KCE member	Specific role
Kristel De Gauquier	Program Director
Marijke Eyssen	Principal Coordinator
Hans Van Brabandt	Principal Investigator
Anja Desomer	Scientific research
Pascale Jonckheer	Scientific research
Geneviève Veereman	Scientific research
Leen Verleye	Methodological support

1.5. List of stakeholders

Stakeholders in the present guideline are persons that were not involved in the guideline development and who were asked at the end of the guideline production process to provide their opinions on the clarity, completeness and acceptability of the recommendations, and on the potential barriers and facilitators related to the use of this guideline. A stakeholder can be a healthcare professional, a patient representative, a patient or his partner.

Clinicians	Field of expertise, affiliations
Filip Ameye	Urologist, Campus Maria Middelares Gent
Rik Cuypers	Patient and patient representative (Wij ook)
Philip Dejonghe	Patiënt
Herlinde Dumez	Oncologist, UZ Leuven
Karin Haustermans	Radiotherapist, UZ Leuven
Nicolaas Lumen	Urologist, UZ Gent
Ward Rommel	Patient representative, Vlaamse Liga tegen Kanker
Johan Govaerts	Urologist, St Maarten – Mechelen
Bruno Mortelmans	Urologist, Imelda ziekenhuis - Bonheiden

1.6. Acknowledgements

KCE is grateful to the following KCE experts who have contributed to the development of the guideline:

Clinicians	Field of expertise
Leen Verleye	Guideline development
Joan Vlayen	Guideline development

The Guideline Development Group acknowledges the UK's National Collaborating Centre for Cancer (NCC-C) and National Institute for Health and Care Excellence (NICE) for their massive preparatory work. The evidence supporting the majority of the recommendations included in the present guideline is based upon their research.

2. SEARCH STRATEGIES

2.1. Search strategy for guidelines

2.1.1. Searched guideline websites and websites of oncologic organizations

N Retrieved	Organisation	Website
0	Alberta Heritage Foundation For Medical Research (AHFMR)	http://www.ahfmr.ab.ca/
0	American Society of Clinical Oncology (ASCO)	http://www.asco.org/
0	American College of Surgeons (ACS)	http://www.facs.org/cancer/coc/
1[1]	CMA Infobase	http://mdm.ca/cpgsnew/cpgs/index.asp
1 (current KCE guideline in progress)	Guidelines International Network (GIN)	http://www.g-i-n.net/
1[2]	National Comprehensive Cancer Network (NCCN)	http://www.nccn.org/
7 [3-9]and 1 duplicate	National Guideline Clearinghouse	http://www.guideline.gov/
0	National Cancer Institute	http://www.cancer.gov/
2[10, 11]	Haute Autorité de Santé (HAS)	http://bfes.has-sante.fr/HTML/indexBFES_HAS.html
0	BC Cancer Agency	http://www.bccancer.bc.ca/delt.htm

0	Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/index.asp
0	National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/
0	Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/
0	New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
0	Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.fnclcc.fr
9 [12-20] and 1 duplicate [7]	National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/
1[21]	European Association of Urology (EAU)	http://www.uroweb.org
1[22]	Integraal Kankercentrum Nederland	http://www.oncoline.nl

2.1.2. Standardized search strategy for CPGs in Medline (Ovid)

Database	Search strategy
Medline	1. exp Prostatic Neoplasms/ 2. prostate cancer.mp. 3. therapy.mp. 4. 1 or 2 5. 4 and 3 6. Guideline/ 7. Practice Guideline/ 8. guideline.pt. 9. practice guideline.pt. 10. "recommendation*".ab,ti. 11. "standard*". ab,ti. 12. "guideline*". ab,ti. 13. “guidance*”. ab,ti.

	14. or/6-13 15. 5 and 14 16. limit 15 to yr="2005 –Current

2.2. Search strategies for other publications (systematic reviews, meta-analyses, individual studies)

2.2.1. Search strategies for HIFU

2.2.1.1. Search strategies for systematic reviews

Date	**15-05-2013**
Database	Medline
Search Strategy	1 High-Intensity Focused Ultrasound Ablation/ (370) 2 HIFU$.tw. (953) 3 (high and intens* and focus* and ultrasound*).tw. (1394) 4 (high and intens* and focus* and therap*).tw. (1575) 5 ((hemi* or focal or unifocal) adj3 ablat*).tw. (448) 6 "hemi-ablat*".tw. (9) 7 ablathermy.tw. (1) 8 sonablate.tw. (28) 9 ablatherm robotic HIFU.tw. (0) 10 (HIFU adj4 SUMO).tw. (0) 11 HIFU-2001.tw. (0) 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (2877) 13 Prostatic Neoplasms/ (86538) 14 (prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan*)).tw. (82971) 15 13 or 14 (99986) 16 12 and 15 (412) 17 exp Ultrasound, High-Intensity Focused, Transrectal/ (325) 18 16 or 17 (582)
Note	

Date	15-05-2013
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Search Strategy	1 High-Intensity Focused Ultrasound Ablation/ (0) 2 HIFU.tw. (132) 3 (high adj4 intens* adj4 focus* adj4 ultrasound*).tw. (168) 4 (high adj4 intens* adj4 focus* adj4 therap*).tw. (26) 5 ((hemi* or focal or unifocal) adj3 ablat*).tw. (29) 6 "hemi-ablat*".tw. (2) 7 ablathermy.tw. (0) 8 sonablate.tw. (0) 9 ablatherm robotic HIFU.tw. (0) 10 (HIFU adj4 SUMO).tw. (0) 11 HIFU-2001.tw. (0) 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (208) 13 Prostatic Neoplasms/ (4) 14 (prostat* adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$ or malignan$)).tw. (5437) 15 13 or 14 (5438) 16 12 and 15 (50) 17 exp Ultrasound, High-Intensity Focused, Transrectal/ (0) 18 16 or 17 (50)
Note	

Date	15-05-2013	
Database	Embase	
Search Strategy	#16. 'high intensity focused ultrasound'/de AND [embase]/lim OR hifu$:ab,ti OR (high:ab,ti AND intens*:ab,ti AND focus*:ab,ti AND ultrasound*:ab,ti) OR (high:ab,ti AND intens*:ab,ti AND focus*:ab,ti AND therap*:ab,ti) OR ((hemi* OR focal OR unifocal) NEAR/3 ablat*):ab,ti OR ablathermy:ab,ti OR sonablate:ab,ti OR (ablatherm AND robotic AND hifu:ab,ti) OR (hifu NEAR/4 sumo):ab,ti OR (hifu:ab,ti AND 2001:ab,ti) AND ('prostate cancer'/exp OR (prostat* NEAR/3 (neoplasm* OR cancer* OR carcinoma* OR adenocarcinoma* OR tumour* OR tumor* OR malignan*)):ab,ti) AND [embase]/lim	943
Note		

Date	15-05-2013	
Database	Cochrane Library	
Search Strategy	#1	HIFU$ (85)
	#2	MeSH descriptor: [High-Intensity Focused Ultrasound Ablation] explode all trees (41)
	#3	(high and intens* and focus* and ultrasound*) (361)
	#4	(high and intens* and focus* and therap*) (2079)
	#5	((hemi* or focal or unifocal) adj3 ablat*) (11)
	#6	"hemi-ablat*" (0)
	#7	ablathermy (0)
	#8	sonablate (1)

	#9	ablatherm robotic HIFU (0)
	#10	(HIFU adj4 SUMO) (0)
	#11	HIFU-2001 (0)
	#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 (2208)
	#13	(prostat* adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or tumour$ or tumor$ or malignan$)) (55)
	#14	MeSH descriptor: [Prostatic Neoplasms] explode all trees (2927)
	#15	#13 or #14 (2976)
	#16	#12 and #15 (51)
	#17	MeSH descriptor: [Ultrasound, High-Intensity Focused, Transrectal] explode all trees (28)
	#18	#16 or #17(61)
Note		

2.2.1.2. Search strategies for primary studies

No separate search strategies were used for the primary studies, but a manual date limit was added to the search strategy for systematic reviews (see above). This date limit was based on the selected systematic review of Warmuth 2010[23] (search date from 2000 until 2010) and only primary studies were included from 2010 onwards.

2.2.2. Search strategies for hormones in mono-therapy

2.2.2.1. Search strategies for systematic reviews

Date	**7-11-2013**
Database	Medline
Search Strategy	1 exp Androgen Antagonists/ (12879) 2 ((androgen* or hormon*) adj3 (ablat* or block* or withdraw* or depriv* or suppress*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (13703) 3 Antineoplastic Agents, Hormonal/ (13492) 4 exp Cyproterone/ (2555) 5 Flutamide/ (2444) 6 exp Gonadotropin-Releasing Hormone/ (29776)

7 Buserelin/ (2087)

8 Goserelin/ (1499)

9 Leuprolide/ (2647)

10 Triptorelin Pamoate/ (1726)

11 exp Diethylstilbestrol/ (8316)

12 exp Estrogens/ (147635)

13 exp Megestrol/ (1548)

14 Progestins/ (8780)

15 (Abiraterone acetate or Zytiga or androsta*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (17146)

16 (Bicalutamide or Casodex or Cosudex or propanamide or propionanilide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1642)

17 (cyproterone acetate or Androcur or cyproplex or cyclopropa*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (8765)

18 (flutamide or Flutaplex or Niftolid* or Apo-flutamide or Chimax or Cytamid or Eulexin* or Drogenil or Euflex or Fluken or Flulem or Flumid or Flutacell or Fluta* or Flutamin or Flutandrona or Flutaplex or Flutexin or Fugerel or Grisetin or Novoflutamide or oncosal or Prostacur or Prostica or Prostogenat or Testotard or Apimid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (3217)

19 (nilutamide or imidazolidin* or nilandron or Anandron).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2872)

20 (Buserelin* or suprefact or suprecur or profact or bigonist or receptal or tiloryth).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2343)

21 (Goserelin* or Zoladex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1673)

22 (Histrelin* or vantas* or supprelin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (87)

23 (Leuprorelin* or leuprolide or eligard or lucrin or enantone or lupron).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary

concept, unique identifier] (3016)

24 (nafarelin* or synarel).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (350)

25 (triptorelin* or decapeptyl or gonapeptyl or salvacyl or trelstar).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1876)

26 (degarelix or firmagon or uglypeptide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (91)

27 (diethylstilbestrol or estrogen or stilbestrol or apstil or Tampovagan or Distilbene or agostilben).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (126011)

28 (megestrol or megace or megestat or megostat or maygace or megefren or mestrel or $megestrol or Borea).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1934)

29 (progestin or gestagen* or progesta* or progestogen).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (18803)

30 (MDV3100 or enzalutamide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (156)

31 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (290867)

32 Prostatic Neoplasms/ (95064)

33 (prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (110270)

34 32 or 33 (110270)

35 exp Androgen Antagonists/tu [Therapeutic Use] (6001)

36 Antineoplastic Agents, Hormonal/tu [Therapeutic Use] (8888)

37 exp Cyproterone/tu [Therapeutic Use] (1060)

38 Flutamide/tu [Therapeutic Use] (787)

39 exp Gonadotropin-Releasing Hormone/tu [Therapeutic Use] (5960)

40 Buserelin/tu [Therapeutic Use] (995)

41	Goserelin/tu [Therapeutic Use] (716)
42	Leuprolide/tu [Therapeutic Use] (1174)
43	Triptorelin Pamoate/tu [Therapeutic Use] (506)
44	exp Diethylstilbestrol/tu [Therapeutic Use] (1402)
45	exp Estrogens/tu [Therapeutic Use] (14479)
46	exp Megestrol/tu [Therapeutic Use] (627)
47	Progestins/tu [Therapeutic Use] (2303)
48	2 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (199411)
49	34 and 48 (15143)
50	Meta-Analysis/ (51544)
51	"meta analy*".tw. (57739)
52	"metaanaly*".tw. (1280)
53	meta analysis.pt. (51544)
54	(systematic adj (review* or overview*)).tw. (47003)
55	exp "Review"/ (1922276)
56	50 or 51 or 52 or 53 or 54 or 55 (1964760)
57	49 and 56 (3340)
58	limit 57 to yr="2008 -Current" (1103)

Note

Date	7-11-2013
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
Search Strategy	1 exp Androgen Antagonists/ (0) 2 ((androgen* or hormon*) adj3 (ablat* or block* or withdraw* or depriv* or suppress*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (763) 3 Antineoplastic Agents, Hormonal/ (0) 4 exp Cyproterone/ (0) 5 Flutamide/ (0) 6 exp Gonadotropin-Releasing Hormone/ (0) 7 Buserelin/ (0) 8 Goserelin/ (0) 9 Leuprolide/ (0) 10 Triptorelin Pamoate/ (0) 11 exp Diethylstilbestrol/ (0) 12 exp Estrogens/ (0) 13 exp Megestrol/ (0) 14 Progestins/ (0) 15 (Abiraterone acetate or Zytiga or androsta*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (177) 16 (Bicalutamide or Casodex or Cosudex or propanamide or propionanilide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (114) 17 (cyproterone acetate or Androcur or cyproplex or cyclopropa*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (919) 18 (flutamide or Flutaplex or Niftolid* or Apo-flutamide or Chimax or Cytamid or Eulexin* or Drogenil or Euflex or Fluken or Flulem or Flumid or Flutacell or Fluta* or Flutamin or Flutandrona or Flutaplex or Flutexin or Fugerel or Grisetin or Novoflutamide or oncosal or Prostacur or Prostica or Prostogenat or Testotard or Apimid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (65) 19 (nilutamide or imidazolidin* or nilandron or Anandron).mp. [mp=title, abstract, original title, name of substance word, subject

heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (243)

20 (Buserelin* or suprefact or suprecur or profact or bigonist or receptal or tiloryth).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (31)

21 (Goserelin* or Zoladex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (39)

22 (Histrelin* or vantas* or supprelin*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (6)

23 (Leuprorelin* or leuprolide or eligard or lucrin or enantone or lupron).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (67)

24 (nafarelin* or synarel).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4)

25 (triptorelin* or decapeptyl or gonapeptyl or salvacyl or trelstar).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (29)

26 (degarelix or firmagon or uglypeptide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (14)

27 (diethylstilbestrol or estrogen or stilbestrol or apstil or Tampovagan or Distilbene or agostilben).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (3722)

28 (megestrol or megace or megestat or megostat or maygace or megefren or mestrel or $megestrol or Borea).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (45)

29 (progestin or gestagen* or progesta* or progestogen).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (430)

30 (MDV3100 or enzalutamide).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (61)

31 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 (6292)

32 Prostatic Neoplasms/ (4)

33 (prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (5953)

34	32 or 33 (5953)
35	exp Androgen Antagonists/tu [Therapeutic Use] (0)
36	Antineoplastic Agents, Hormonal/tu [Therapeutic Use] (0)
37	exp Cyproterone/tu [Therapeutic Use] (0)
38	Flutamide/tu [Therapeutic Use] (0)
39	exp Gonadotropin-Releasing Hormone/tu [Therapeutic Use] (0)
40	Buserelin/tu [Therapeutic Use] (0)
41	Goserelin/tu [Therapeutic Use] (0)
42	Leuprolide/tu [Therapeutic Use] (0)
43	Triptorelin Pamoate/tu [Therapeutic Use] (0)
44	exp Diethylstilbestrol/tu [Therapeutic Use] (0)
45	exp Estrogens/tu [Therapeutic Use] (0)
46	exp Megestrol/tu [Therapeutic Use] (0)
47	Progestins/tu [Therapeutic Use] (0)
48	2 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (6292)
49	34 and 48 (695)
50	Meta-Analysis/ (36)
51	"meta analy*".tw. (6409)
52	"metaanaly*".tw. (100)
53	meta analysis.pt. (36)
54	(systematic adj (review* or overview*)).tw. (6875)
55	exp "Review"/ (837)
56	50 or 51 or 52 or 53 or 54 or 55 (12034)
57	49 and 56 (17)
58	limit 57 to yr="2008 -Current" (14)

Note

Date	7-11-2013
Database	Embase
Search Strategy	(('antiandrogen'/exp or 'androgen receptor antagonist'/exp or 'antineoplastic hormone agonists and antagonists'/exp or 'cyproterone'/exp or 'flutamide'/exp or 'gonadorelin'/exp or 'buserelin'/exp or 'goserelin'/exp or 'leuprorelin'/exp or 'triptorelin'/exp or 'diethylstilbestrol'/exp or 'estrogen'/exp or 'megestrol'/exp or 'gestagen'/exp and [embase]/lim) or (androgen* or hormon* and 'near3' and (ablat* or block* or withdraw* or depriv* or suppress*)) or ('abiraterone'/exp and 'acetate'/exp or 'zytiga'/exp or androsta*) or ('bicalutamide'/exp or 'casodex'/exp or 'cosudex'/exp or propa* or propiona*) or ('cyproterone'/exp and 'acetate'/exp or 'androcur'/exp or cypro* or cyclopropa*) or ('flutamide'/exp or niftolid* or 'apo flutamide' or chimax or 'cytamid'/exp or eulexin* or 'drogenil'/exp or 'euflex'/exp or 'fluken'/exp or 'flulem'/exp or 'flumid'/exp or flutacell or fluta* or 'flutamin'/exp or flutandrona or 'flutaplex'/exp or flutexin or 'fugerel'/exp or grisetin or novoflutamide or oncosal or prostacur or 'prostica'/exp or 'prostogenat'/exp or testotard or 'apimid'/exp) or ('flutamide'/exp or niftolid* or 'apo flutamide' or chimax or 'cytamid'/exp or eulexin* or 'drogenil'/exp or 'euflex'/exp or 'fluken'/exp or 'flulem'/exp or 'flumid'/exp or flutacell or fluta* or 'flutamin'/exp or flutandrona or 'flutaplex'/exp or flutexin or 'fugerel'/exp or grisetin or novoflutamide or oncosal or prostacur or 'prostica'/exp or 'prostogenat'/exp or testotard or 'apimid'/exp) or ('nilutamide'/exp or imidazolidin* or 'nilandron'/exp or 'anandron'/exp) or (buserelin* or 'suprefact'/exp or 'suprecur'/exp or profact or 'bigonist'/exp or 'receptal'/exp or tiloryth) or (goserelin* or 'zoladex'/exp) or (histrelin* or vantas* or supprelin*) or (leuprorelin* or 'leuprolide'/exp or 'eligard'/exp or 'lucrin'/exp or 'enantone'/exp or 'lupron'/exp) or (nafarelin* or 'synarel'/exp) or (triptorelin* or 'decapeptyl'/exp or 'gonapeptyl'/exp or salvacyl or 'trelstar'/exp) or ('degarelix'/exp or 'firmagon'/exp or uglypeptide) or ('diethylstilbestrol'/exp or 'estrogen'/exp or 'stilbestrol'/exp or apstil or tampovagan or 'distilbene'/exp or 'agostilben'/exp) or ('megestrol'/exp or 'megace'/exp or 'megestat'/exp or 'megostat'/exp or 'maygace'/exp or megefren or 'mestrel'/exp or $megestrol or borea) or ('progestin'/exp or gestagen* or progesta* or 'progestogen'/exp) or ('mdv3100'/exp or 'enzalutamide'/exp)) and ('prostate tumor'/exp or (prostat* near/3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan*)):ab,ti)) and ([cochrane review]/lim or [meta analysis]/lim or [systematic review]/lim) and [embase]/lim and [2008-2014]/py (141 hits)
Note	

Date	8-11-2013
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Androgen Antagonists] explode all trees #2 ((androgen* or hormon*) adj3 (ablat* or block* or withdraw* or depriv* or suppress*)) #3 MeSH descriptor: [Antineoplastic Agents, Hormonal] explode all trees #4 MeSH descriptor: [Cyproterone] explode all trees #5 MeSH descriptor: [Flutamide] explode all trees #6 MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees #7 MeSH descriptor: [Buserelin] explode all trees #8 MeSH descriptor: [Goserelin] explode all trees #9 MeSH descriptor: [Leuprolide] explode all trees #10 MeSH descriptor: [Triptorelin Pamoate] explode all trees #11 MeSH descriptor: [Diethylstilbestrol] explode all trees #12 MeSH descriptor: [Estrogens] explode all trees #13 MeSH descriptor: [Megestrol] explode all trees #14 MeSH descriptor: [Progestins] explode all trees #15 (Abiraterone acetate or Zytiga or androsta*) #16 (Bicalutamide or Casodex or Cosudex or propanamide or propionanilide) #17 (cyproterone acetate or Androcur or cyproplex or cyclopropa*) #18 (flutamide or Flutaplex or Niftolid* or Apo-flutamide or Chimax or Cytamid or Eulexin* or Drogenil or Euflex or Fluken or Flulem or Flumid or Flutacell or Fluta* or Flutamin or Flutandrona or Flutaplex or Flutexin or Fugerel or Grisetin or Novoflutamide or oncosal or Prostacur or Prostica or Prostogenat or Testotard or Apimid) #19 (nilutamide or imidazolidin* or nilandron or Anandron) #20 (Buserelin* or suprefact or suprecur or profact or bigonist or receptal or tiloryth) #21 (Goserelin* or Zoladex) #22 (Histrelin* or vantas* or supprelin*) #23 (Leuprorelin* or leuprolide or eligard or lucrin or enantone or lupron) #24 (nafarelin* or synarel) #25 (triptorelin* or decapeptyl or gonapeptyl or salvacyl or trelstar)

	#26 (degarelix or firmagon or uglypeptide) #27 (diethylstilbestrol or estrogen or stilbestrol or apstil or Tampovagan or Distilbene or agostilben) #28 (megestrol or megace or megestat or megostat or maygace or megefren or mestrel or $megestrol or Borea) #29 (progestin or gestagen* or progesta* or progestogen) #30 (MDV3100 or enzalutamide) #31 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 #32 MeSH descriptor: [Prostatic Neoplasms] explode all trees #33 (prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan*)) #34 #32 or #33 #35 #34 and #31
Note	

2.2.2.2. Search strategies for primary studies

Date	**22-01-2014**
Database	Medline
Search Strategy	1 exp Prostatic Neoplasms/ 88597 2 (prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor* or malignan* or sarcoma*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 108700 3 1 or 2 108700 4 exp Androgen Antagonists/ 12221 5 Antineoplastic Agents, Hormonal/ 12206 6 exp Cyproterone/ 2524 7 Flutamide/ 2321 8 exp Gonadotropin-Releasing Hormone/ 28209 9 Buserelin/ 2039 10 Goserelin/ 1437 11 Leuprolide/ 2491 12 Triptorelin Pamoate/ 1615 13 exp Diethylstilbestrol/ 8162

14	exp Estrogens/ 140403
15	exp Megestrol/ 1519
16	Progestins/ 8431
17	(Abiraterone acetate or Zytiga or androsta*).mp. 15961
18	(Bicalutamide or Casodex or Cosudex or propanamide or propionanilide).mp. 1617
19	(cyproterone acetate or Androcur or cyproplex or cyclopropa*).mp. 9310
20	(flutamide or Flutaplex or Niftolid* or Apo-flutamide or Chimax or Cytamid or Eulexin* or Drogenil or Euflex or Fluken or Flulem or Flumid or Flutacell or Fluta* or Flutamin or Flutandrona or Flutaplex or Flutexin or Fugerel or Grisetin or Novoflutamide or oncosal or Prostacur or Prostica or Prostogenat or Testotard or Apimid).mp. 3118
21	(nilutamide or imidazolidin* or nilandron or Anandron).mp. 3003
22	(Buserelin* or suprefact or suprecur or profact or bigonist or receptal or tiloryth).mp. 2318
23	(Goserelin* or Zoladex).mp. 1643
24	(Histrelin* or vantas* or supprelin*).mp. 94
25	(Leuprorelin* or leuprolide or eligard or lucrin or enantone or lupron).mp. 2911
26	(nafarelin* or synarel).mp. 348
27	(triptorelin* or decapeptyl or gonapeptyl or salvacyl or trelstar).mp. 1773
28	(degarelix or firmagon or uglypeptide).mp. 95
29	(megestrol or megace or megestat or megostat or maygace or megefren or mestrel or $megestrol or Borea).mp. 1934
30	(progestin or gestagen* or progesta* or progestogen).mp. 18622
31	(MDV3100 or enzalutamide).mp. 211
32	exp Androgens/ai 529
33	((androgen* or hormon*) adj3 (ablat* or block* or withdraw* or depriv* or suppress*)).mp. 13470
34	(hormonotherapy or hormonotherapies).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 621
35	((androgen* or hormon*) adj3 inhibit*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 8431
36	randomized controlled trial.pt. 359559
37	controlled clinical trial.pt. 86972
38	randomized.ti,ab. 299973
39	placebo.ti,ab. 152701
40	clinical trials as topic/ 166454
41	randomly.ti,ab. 204482

42	trial.ti.	119514
43	36 or 37 or 38 or 39 or 40 or 41 or 42	875054
44	animals/ not humans/	3772468
45	43 not 44	807689
46	or/4-35	233086
47	3 and 46	15861
48	47 and 45	2411
49	limit 47 to systematic reviews	352
50	Chemoradiotherapy, Adjuvant/	652
51	Chemotherapy, Adjuvant/	28541
52	Radiotherapy, Adjuvant/	16357
53	48 not (50 or 52 or 51)	2160
54	((32 or 35) and 3) not (50 or 51 or 52)	955
55	limit 54 to systematic reviews	13
56	53 not 49	2053
57	56 or 55	2066

Note

Date	22-01-2014
Database	Embase
Search Strategy	(('prostate tumor'/exp OR prostat* NEAR/3 (neoplasm* OR cancer* OR carcinoma* OR adenocarcinoma* OR tumour* OR tumor* OR malignan* OR sarcoma*)) AND ('antiandrogen'/exp OR 'antiandrogen therapy'/exp OR 'antineoplastic hormone agonists and antagonists'/exp OR 'cyproterone'/exp OR 'flutamide'/exp OR 'gonadorelin'/exp OR 'buserelin'/exp OR 'goserelin'/exp OR 'diethylstilbestrol'/exp OR 'estrogen'/exp OR 'megestrol'/exp OR 'gestagen'/exp OR 'cancer hormone therapy'/exp OR hormonotherapy OR hormonotherapies OR (androgen* OR hormon*) NEAR/3 (ablat* OR block* OR withdraw* OR depriv* OR suppress* OR inhibit*) OR mdv3100 OR enzalutamide OR progestin OR gestagen* OR progesta* OR progestogen OR megestrol OR megace OR megestat OR megostat OR maygace OR megefren OR mestrel OR borea OR degarelix OR firmagon OR uglypeptide OR triptorelin* OR decapeptyl OR gonapeptyl OR salvacyl OR trelstar OR nafarelin* OR synarel OR leuprorelin* OR leuprolide OR eligard OR lucrin OR enantone OR lupron OR histrelin* OR vantas* OR supprelin* OR goserelin* OR zoladex OR buserelin* OR suprefact OR suprecur OR profact OR bigonist OR receptal OR tiloryth OR nilutamide OR imidazolidin* OR nilandron OR anandron OR flutamide OR niftolid* OR 'apo flutamide' OR chimax OR cytamid OR eulexin* OR drogenil OR euflex OR fluken OR flulem OR flumid OR flutacell OR fluta* OR flutamin OR flutandrona OR flutaplex OR flutexin OR fugerel OR grisetin OR novoflutamide OR oncosal OR prostacur OR prostica OR prostogenat OR testotard OR apimid OR 'cyproterone acetate' OR androcur OR cyproplex OR cyclopropa* OR bicalutamide OR casodex OR cosudex OR propanamide OR propionanilide OR 'abiraterone acetate' OR zytiga OR androsta* OR 'cyproterone acetate'/exp OR 'hydroxyflutamide'/exp OR 'gonadorelin agonist'/exp OR 'gonadorelin acetate'/exp OR 'gonadorelin antagonist'/exp OR 'gonadorelin derivative'/exp OR 'dalarelin'/exp OR 'triptorelin'/exp OR 'buserelin acetate'/exp OR 'fosfestrol'/exp OR 'diethylstilbestrol dipropionate'/exp OR 'diethylstilbestrol phosphate'/exp OR 'estrogen derivative'/exp OR 'megestrol acetate'/exp)) NOT (('adjuvant chemoradiotherapy'/exp OR 'adjuvant chemotherapy'/exp OR 'cancer adjuvant therapy'/exp OR 'adjuvant therapy'/exp) OR ('animal'/exp NOT 'human'/exp)) AND ([embase]/lim NOT [medline]/lim) AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference review]/lim OR [erratum]/lim OR [review]/lim OR [short survey]/lim OR [note]/lim) AND ('crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR (cross NEXT/1 over*):de,ab,ti OR placebo*:de,ab,ti OR (doubl* NEAR/1 blind*):de,ab,ti OR (singl* NEAR/1 blind*):de,ab,ti OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti)
Note	

3. SEARCH RESULTS

3.1. Quality appraisal tools

3.1.1. Guidelines

The AGREE II evaluation score was used to critically appraise guidelines retrieved (Table 1).

Table 1 – AGREE II instrument

Critical appraisal of clinical practice guidelines - AGREE II
Domain 1. Scope and Purpose
1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Domain 2. Stakeholder Involvement
4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
Domain 3. Rigour of Development
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
Domain 4. Clarity of Presentation
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.

Critical appraisal of clinical practice guidelines - AGREE II
17. Key recommendations are easily identifiable.
Domain 5. Applicability
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.
Domain 6. Editorial Independence
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

3.1.2. Systematic reviews

AMSTAR criteria were used to assess systematic reviews (Table 2).

Table 2 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

3.1.3. Primary studies for therapeutic interventions

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool (Table 3).

Table 3 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment	Describe all measures used, if any, to blind outcome	Detection bias due to knowledge of the allocated

Domain	Support for judgement	Review authors' judgement
Assessments should be made for each main outcome (or class of outcomes)	assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	interventions by outcome assessors
Attrition bias		
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

3.2. Guidelines selection and quality appraisal

The screening of the **guidelines** was performed on title and abstract by a group of two researchers (GV and AD) based on the P.I.C.O. in- and exclusion criteria. This evaluation was done in two steps. First, only 3 questions in the topic on the rigour of development were assessed (Q7, Q8, Q10) by the two researchers. If the global assessment of this dimension was too low (score ≤ 3 for each criterion), the evaluation process stopped and the guideline was excluded. A comprehensive evaluation was only performed in the included guidelines after this first selection on rigour of development. After removal of duplicate guidelines, 24 guidelines were selected based on title and abstract and retained for full-text evaluation. Of these, 16 guidelines were selected after appraisal with Agree II.

Table 4 – Rapid appraisal of guidelines: overview of results

General treatment approach		App1 Q7	App1 Q8	App1 Q10	App2 Q7	App2 Q8	App2 Q10	Total	Inclusion/ Exclusion	Remarks
2012	EAU[21]	7	7	7	6	5	6	39/42	Inclusion	
2012	Horwich A et al: ESMO Consensus[24]	1	1	6	2	3	2	15/42	Exclusion	No systematic search
2012	Arranz Arija JA et al. SEOM clinical guidelines[25]	1	1	1	1	1	1	6/42	Exclusion	
2012	HAS. Cancer de la prostate. Guide - affection de longue duree.[11]	1	1	1	1	1	1	6/42	Exclusion	
2011	Oncology NCCN. Prostate Cancer.[2]	1	1	5	1	1	6	15/42	Exclusion	
2010	Droz Jp International Society of Geriatric Oncology.[26]	4	2	5	3	2	5	21/42	Exclusion	Specific population
2010	Salomon L, Recommandations en Onco-Urologie [27]	1	1	1	1	1	2	7/42	Exclusion	
2008	NICE.Prostate cancer. Diagnosis and	7	7	7	7	7	7	42/42	Inclusion	

General treatment approach		App1 Q7	App1 Q8	App1 Q10	App2 Q7	App2 Q8	App2 Q10	Total	Inclusion/ Exclusion	Remarks
	treatment.[7]									
2008	Madrid: Aragon Institute of Health Sciences[3]	5	7	7	6	4	6	35/42	Inclusion	
2007	AUA Panel [4].	7	7	7	5	5	6	37/42	Inclusion	
2007	IKNL [22]	5	6	6	6	6	6	35/42	Inclusion	
Surgery										
2012	Montorsi F Robotic prostatectomy - Pasadena Consensus Panel.[28]	6	6	6	6	6	6	36/42	Inclusion	
2010	German S3 guideline[29]	3	2	5	2	2	5	19/42	Exclusion	
2006	NICE. Laparoscopic radical prostatectomy. London (UK): IPG193[18]	7	7	3	7	7	3	34/42	Inclusion	No grading of recommendations
Radiation therapy										
2008	Sidhom MA, Post-prostatectomy radiation therapy: consensus GL[30]	3	2	5	2	2	6	20/42	Exclusion	
IMRT										
2006	Maceira Rozas Recommendations for treatment with IMRT for prostate and head-neck cancer.[31]	5	2	2	2	1	3	15/42	Excluded	

General treatment approach		App1 Q7	App1 Q8	App1 Q10	App2 Q7	App2 Q8	App2 Q10	Total	Inclusion/ Exclusion	Remarks
External beam radiation therapy										
2010	Hayden AJ, consensus GL [32]	5	2	5	2	3	5	22/42	Exclusion	No systematic search
2010	ACR Appropriateness Criteria®[5]	6	7	7	4	6	6	36/42	Inclusion	
2006	NICE. IPG 174 [19]	7	7	3	7	7	3	34/42	Inclusion	No grading of recommendations
Brachytherapy										
2012	Yamada Y - American Brachytherapy Society consensus GL [33]	4	1	2	2	1	5	15/42	exclusion	Summarizes recent litt but no systematic search or search criteria
2012	Langley S,. Report of a consensus meeting [34]	1	1	3	1	1	4	11/42	Exclusion	
2010	American College of Radiology (ACR) ASfROA. ACR–ASTRO practice guideline for transperineal permanent brachytherapy of prostate cancer.[8]	5	2	6	4	1	4	22/42	Exclusion	
2010	ACR Appropriateness Criteria® permanent source brachytherapy for prostate cancer.[9]	6	7	7	4	6	6	36/42	Inclusion	

General treatment approach		App1 Q7	App1 Q8	App1 Q10	App2 Q7	App2 Q8	App2 Q10	Total	Inclusion/ Exclusion	Remarks
2005	Kovacs G, GEC/ESTRO-EAU [35]	1	1	1	2	1	4	10/42	Exclusion	
2005	NICE. Low dose rate brachytherapy ICP 132 [15]	7	7	3	7	7	3	34/42	Inclusion	No grading of recommendations
HIFU										
2012	NICE. Focal therapy using high-intensity focused ultrasound for localised prostate cancer.[13]	7	7	3	7	7	3	34/42	Inclusion	No grading of recommendations
2010	HAS. High Intensity Focalized Ultrasound for the treatment of localized prostate cancer.[10]	5	2	2	4	4	5	22/42	Exclusion	No grading of recommendations
2010	Lukka H -High-intensity focused ultrasound for prostate cancer: a practice guideline.[36]	7	6	2	4	3	6	28/42	Inclusion	No grading of recommendations
Cryosurgery										
2012	NICE. Focal therapy using cryoablation for localised prostate cancer.[14]	7	7	3	7	7	3	34/42	Inclusion	No grading of recommendations
2008	AUA [6]	6	5	6	5	4	5	31/42	Inclusion	

3.3. Selection of studies and quality appraisal for HIFU

3.3.1. Selection and quality appraisal of systematic reviews

Selection of systematic reviews

Table 5 – Included systematic reviews (n=12)

Reference	Title
Anonymous 2012[37]	Management of localised prostate cancer
Ahmed 2008[38]	Active surveillance and radical therapy in prostate cancer: can focal therapy offer the middle way?
Cordeiro 2012[39]	High-intensity focused ultrasound (HIFU) for definitive treatment of prostate cancer
Iberti 2011[40]	A review of focal therapy techniques in prostate cancer: clinical results for high-intensity focused ultrasound and focal cryoablation
Lukka 2010[41]	High-intensity focused ultrasound for prostate cancer: a systematic review
Ranjan 2008[42]	High intensity focused ultrasound vs cryotherapy as primary treatment for prostate cancer
Rebillard 2008[43]	High intensity focused ultrasound; a systematic literature review of the French Association of Urology
Tsakiris 2008[44]	Transrectal high-intensity focused ultrasound devices: a critical appraisal of the available evidence
Uchida 2012[45]	High-intensity focused ultrasound therapy for prostate cancer
Warmuth 2010[23]	Systematic review of the efficacy and safety of high-intensity focused ultrasound for the primary and salvage treatment of prostate cancer
Wilt 2008[46]	Systematic review: comparative effectiveness and harms of treatment for clinically localized prostate cancer
Yu 2011[47]	Adverse events of extracorporeal ultrasound-guided high intensity focused ultrasound therapy

Table 6 – Excluded systematic reviews after full text evaluation (n=102)

Reasons for exclusion	Number of references	References
Population	4	Alongi 2011[48], Chaussy 2010[49], Chaussy 2010[50], Mallick 2009[51]
Intervention	4	Bomers 2012[52], Sanseverino 2011[53], Thueroff 2009[54], Warmuth 2012[55]
Outcome	0	/
Design	85	Anonymous 2013[56], Abdel-Wahab 2010[57], Ahmed 2010[58], Ahmed 2009[59], Al-Bataineh 2012[60], Andreoiu 2010[61], Avances 2008[62], Barqawi 2008[63], Bastian 2010[64], Bastian 2010[65], Blana 2009[66], Borofsky 2011[67], Bozzini 2013[68], Carter 2011[69], Chaussy 2010[49], Chaussy 2009[70], Chaussy 2011[71], Cheng 2011[72], China 2011[73], Chopra 2008[74], Chopra 2010[75], Christian 2011[76], Coakley 2013[77], Coleman 2013[78], Crehange 2012[79], Crouzet 2010[80], Eggener 2010[81], Ganzer 2010[82], Gomella 2009[83], Gonzalgo 2008[84], Haddad 2009[85], Hoang 2012[86], Hou 2009[87], Hsu 2010[88], Hurwitz 2010[89], Jamal 2008[90], Jolesz 2008[91], Klotz 2011[92], Lam 2008[93], Lazzeri 2012[94], Lecornet 2010[95], Lecornet 2010[96], Legramanti 2013[97], Lindner 2010[98], Macbeth 2008[99], Mearini 2010[100], Migliore 2011[101], Mouraviev 2011[102], Mundy 2012[103], Muto 2011[104], Nemade 2011[105], Nguyen 2011[106], Nomura 2012[107], Ong 2012[108], Orovan 2008[109], Orsola 2009[110], Patel 2010[111], Pfeiffer 2009[112], Pichon-Riviere 2008[113], Popert 2011[114], Ray 2011[115], Rove 2010[116], Sanchez Salas2011[117], Seki 2011[118], Siomos 2011[119], Skolarus 2008[120], So 2011[121], Solovov 2012[122], Sullivan 2009[123], Sumimoto 2009[124], Tempany 2011[125], Thueroff 2009[126], Thuroff 2008[127], Tsivian 2012[128], Turkbey 2009[129], Veda Padma Priya 2011[130], Ward 2010[131], Ward 2010[131], Ward 2011[132], Warde 2010[133], Warmuth 2010[134], Zini 2012[135]
Language	0	/
Duplicate	2	Netsch 2009[136], Obyn 2009[137]
Date	2	Dussault 2008[138], Obyn 2009[139]
Not found by librarian	5	Benedict 2011[140], Clyne 2013[141], de la Rosette 2009[142], Hayes 2009[143], Manea 2011[144]

Quality appraisal of selected systematic reviews

Table 7 shows the results of the risk of bias assessment for the 12 included systematic reviews, using AMSTAR criteria. Based on the Amstar scores only two systematic reviews of good quality were found. The most recent systematic review of Warmuth 2010[23] was used to update these results with more recent primary studies.

Table 7 – Methodological quality of the included systematic review (AMSTAR) (example of presentation)

	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Anonymous 2012[37]	No	Yes	Yes	Yes	No	No	No	No	NA	No	Review No Studies No
Ahmed 2008[38]	No	CA	No	No	No	No	No	No	NA	No	Review :Yes Studies :No
Cordeiro 2012[39]	Yes	CA	Yes	Yes	No	Yes	No	No	NA	No	Review :Yes Studies :No
Iberti 2011[40]	Yes	CA	CA	CA	No	Yes	No	No	CA	No	Review :Yes Studies :No
Lukka 2010[41]	No	Yes	Yes	No	No	Yes	No	No	NA	No	Review :Yes Studies :No
Ranjan 2008[42]	CA	Yes	No	No	No	No	No	No	NA	No	Review : Yes Studies :No
Rebillard 2008[43]	No	No	Yes	Yes	No	Yes	No	No	NA	No	Review :Yes Studies :No
Tsakiris 2008[44]	CA	CA	No	CA	No	Yes	Yes	No	NA	No	Review :No Studies :No
Uchida 2012[45]	No	CA	No	No	No	Yes	No	No	NA	No	Review :Yes Studies :No

	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusion	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Warmuth 2010[23]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	yes	Review :Yes Studies :No
Wilt 2008[46]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Review :Yes Studies :No
Yu 2011[47]	Yes	CA	No	No	No	No	No	No	CA	No	Review :Yes Studies :No

3.3.2. Selection and quality appraisal of primary studies

Selection of RCTs

Due to the lack of RCTs, the selection of primary studies included only observational studies (mostly case series). The selection process of these primary studies is described in “selection of observational studies”.

Selection of observational studies

Table 8 – Included observational studies (n=18)

Interventions	References
Ablatherm	Blana 2012[145], Boutier 2011[146], Callea 2010[147], Crouzet 2010[148], Crouzet 2011[149], Crouzet 2013[150], Ganzer 2013{Ganzer, 2013 #1012}, Maestroni 2012[151], Netsch 2010[152], Netsch 2011[153], Pfeiffer 2012[154], Pinthus 2012[155], Ripert 2011[156], Sung 2012[157]
Sonoblate	Eltermann 2011[158], Inoue 2011[159], Komura 2011[160], Shoji 2010[161]

Table 9 – Excluded primary studies after full text evaluation (n=119)

Reasons for exclusion	Number of references	References
Population	8	Solovov 2011[162], Stefan 2011[163], Thueroff 2012[164], Uchida 2011[165], Uchida 2011[166], Uchida 2010[167], Uchida 2009[168], Van Velthoven 2009[169]
Intervention	5	Grimm 2012[170], Haddad 2012[171], Pinthus 2009[172], Sanseverino 2010[173], Thueroff 2009[174]
Outcome	3	Inamoto 2011[175], Li 2010[176], Sumimoto 2010[177]
Design	54	Ahmed 2009[178], Ahmed 2010[179], Barret 2009[180], Barret 2012[181], Barret 2011[182], Barret 2012[183], Barua 2009[184], Bastide 2008[185], Benchikh 2009[186], Blana 2012[187], Blana 2009[188], Blana 2010[189], Blana 2009[190], Chaussy 2012[191], Chaussy 2012[192], Crouzet 2013[193], Crouzet 2010[194], Crouzet 2010[148], Crouzet 2011[149], Crouzet 2012[195], Dickinson 2011[196], Dickinson 2012[197], Dickinson 2013[198], Dickinson 2011[199], Dickinson 2011[200], Dickinson 2012[201], Droz 2010[202], Dudderidge 2009[203], Eduard 2013[204], Fiaschetti 2012[205], Ganzer 2012[206], Ganzer 2011[207], Ganzer 2011[208], Gelet 2012[209], Heinrich 2011[210], Inamoto 2012[211], Kim 2012[212], Leslie 2010[213], Manea 2010[214], Napoli 2013[215], Petrucci 2012[216], Pisanti 2012[217], Ripert 2009[218], Robertson 2011[219], Shayegan 2011[220], Sung 2012[157], Thueroff 2011[221], Thuroff 2011[222], Thuroff 2012[164], Traficante 2012[223], Uchida 2012[224], Van Velthoven 2011[225], Ward 2013[226], Widmark 2011[227]
Language	0	/
Duplicate	6	Ganzer 2012[228], Pinthus 2009[229], Sangez-Salas 2011[230], Stefan 2011[231], Thueroff 2011[232], Thuroff 2011[222]
Date	37	Ahmed 2009[233], Blana 2009[234], Blana 2008[235], Blana 2008[236], Blana 2008[237], Boudrant 2009[238], Carlo 2009[239], Cellarius 2009[240], Challacombe 2009[241], Chaussy 2009[242], D'Urso 2009[243], Finazzi 2008[244], Ganzer 2009[245], Goto 2009[246], Illing 2009[247], Li 2009[248], Maestroni 2008[249], Mearini 2009[250], Misrai 2008[251], Moul 2009[252], Murat 2009[253], Murat 2008[254], Murphy 2009[255], Muto 2008[256], Neumayr 2009[257], Pfeifer 2009[258], Realfonso 2008[259], Robertson 2009[260], Sahu 2009[261], Sahu 2009[262], Sahu 2009[263], Sahu 2009[264], Sanseverino 2009[265], Satoh 2009[266], Thueroff 2009[54], Thueroff 2009[126], Uchida 2009[267]
Not found by librarian	6	Da Rosa 2011[268], Lecornet 2010[269], Pisanti 2010[270], Ripert 2010[271], Robertson 2012[272], Zhao 2008[273]

Quality appraisal of selected observational studies

See last column of evidence tables.

3.4. Selection of studies and quality appraisal for hormone therapy in mono-therapy

3.4.1. Selection and quality appraisal of selected systematic reviews

Selection of systematic reviews

The references of all found systematic reviews are available on request. The results of the quick quality appraisal for the 83 relevant systematic reviews are shown is the table below.

Table 10 - Quick quality appraisal of relevant systematic reviews

Topic	Reference	Quick QA	comments
Effectiveness: general/mix	Akaza 2010[274]	No method mentioned	• Focus exactly on our scope • No overview of the studies • Also info on evolution use and adverse event. • No same reference as Prescrire (no Lu-Yao)
	Akaza 2011[275]	No method mentioned	• Advanced PCa mainly • Focus on CAB and bicalutamide • Also info on adverse event.
	Anonymous 2012[276] (Prescrire Localised PCa)	Search date mentioned (2 January 2012), >3 database, QA but search of guideline and SR	• No overview of included studies • No reference to Akaza • Broader than hormonotherapy
	Anonymous 2013[277] (Prescrire Locally advanced PCa)	Search date mentioned (5 June 2012), >3 database, QA but search of guideline and SR	• No overview of included studies • No reference to Akaza • Broader than hormonotherapy
	Bourke 2013[278]	No methods mentioned	• No overview of included studies • 2 interesting references (Cochrane 2002 & Studer 2011) • Also info on adverse event and cost-effectiveness
	Connolly 2012[279]	No methods mentioned	• Overview of Phase III trials supporting the ADT use • ADT alone in 1 § with 3 references (Lu-Yao 2008, Schroder 2004 & Widmark 2009)
	Corona 2012[280]	Search date mentioned (September	• Advantage of ADT

		2011), 1 database (Medline), no QA mentioned	• Combined vs alone; immediate vs delayed… • Adverse events (not only sexual effects)
	Dean 2009[281]	No methods mentioned	• Overview of included studies in metastatic or locally advanced PCa
	Droz 2010[282]	No methods mentioned	• 1 § on ADT with 2 references (Studer 2006, Studer 2008) • Description of side effects
	Falci 2009[283]	No search date mentioned, 1 database (PubMed), no QA mentioned	• Focus on unfit senior patients • No overview of included studies
	Gaztanaga 2012[284]	No methods mentioned	• No overview of included studies except for high risk PCa • In low risk, quote Lu-Yao 2008 • A lot of studies with radiotherapy
	Isbarn 2009[285]	No search date, 1 database (Medline), Highest evidence (but on what)?	• 2 studies for localised PCA (Iversen 2004 & Wirth 2007) • More studies for locally advanced & metastatic PCa. • Side effects • No overview of included studies
	Martin 2011[286]	No search date mentioned, >2 databases, no QA	• Focus on locally advanced cancer • Also info on adverse events • Overview of different hormones and types of therapy • No comparison with watchful waiting (only with other therapies)
	Namiki 2008[287]	No methods mentioned	• Only based on own (Japanese) data • Narrative review
	Namiki 2012[288]	No methods mentioned	• Only based on Japanese data • Also info on adverse events
	Nguyen 2011[289, 290]	Search date mentioned (11 April 2011), >2 databases, QA	• Focus on cardiovascular mortality • 11 studies for PC-specific mortality and all-cause mortality • 8 studies on cardiovascular mortality • In some studies also T4 included • Mostly comparison with other therapies
	Niraula 2012[291]	No methods mentioned	• Narrative overview on CYP17 inhibitors, AR-targeting agents (MDV3100)
	Pagliarulo 2012[292]	Search date mentioned (2008), 2 databases, no QA but level of evidence	• Section on ADT alone compared to observation (2 population-based studies Wong 2009, Lu-Yao 2008) and 1 study on bicalutamide (McLeod 2006)
	Pfitzenmaier	Search date mentioned (2000-2011), 2	• Focus on patients over age 70

	2009[293]	databases, no QA but level of evidence	• Search in databases + ASCO 2007 and EAU 2008 guidelines • Section on hormonal therapy vs watchful waiting (ref 4-7, 13-19) • Also studies on intermittent vs continuous
	Rozet 2011[294]	Search date mentioned (1995-2011), 1 database, no QA	• Only 3 studies on ADT+RT vs ADT alone (Widmark 2009, Warde 2010, Mottet 2010)
	Sharifi 2010[295]	Search date mentioned (2010), >2 databases, QA	• Also info on adverse events (7 trials), intermittent vs continuous ADT (4 trials) • No overview of included studies, only narrative
	Tareen 2010[296]	No methods mentioned	• No overview of included studies • 5 studies on monotherapy (Kawakami 2006, Lu-Yao 2008, Widmark 2009, Klotz 1986, Bong 2008)
	Taylor 2009[297]	Search date mentioned (2008), >2 databases, no QA but pooling + test for homogeneity	• Outcomes: fracture risk, osteoporosis, diabetes, cardiovascular mortality • Overview of included studies
	Wilt 2008[298]	Search date mentioned (2007), >2 databases, QA	• Also info on adverse events • Comparison hormone therapy vs watchful waiting (Wirth 2004)
Drug class effect	Gonzalez 2010[299, 300]	no search data, 1 database (PubMed), QA accordng to SIGN?	• No overview of included studies • Adjuvant, neoadjuvant but also comparison between LHRH analogues
Effectiveness: intermittent ADT	Abrahamson 2010[301]	Search date not mentioned, 1 database (Medline) + abstract conference, no QA mentioned	• Overview of included studies • Also tolerability • Mix of cancer stage • Interesting for IAD vs CAD
	Buchan 2010[302]	Search date not mentioned, 1 database (PubMed) + abstract conference, No QA mentioned	• Overview of included studies • Locally advanced and metastatic PCa
	Lopez 2012[303]	Search date mentioned (2002-2012), 2 databases, no QA	• Spanish • Only metastatic cancer?
	Niraula 2013[304]	Search date mentioned (2012), >2 databases, QA	• Mix of cancer stages • Useful source of primary studies • 9 studies included (5 locally advanced cancer) • Results on overall survival, time to progression, QoL, adverse effects, cost

	Schulman 2012[305]	No methods mentioned	• Overview of included studies • Ref to review on IADT (Abrahamsson 2010)
	Shaw 2009[306]	No methods mentioned	• Overview of included studies • Ref to Cochrane review (Conti 2007)
	Thelen 2012[307]	No methods mentioned	• German • No overview of included studies
	Tsai 2013[308]	Search date mentioned (2012), >2 databases, no QA but pooling + test for heterogeneity	• Meta-analysis • Only focus on metastatic PC
	Zhu 2012[309]	Search date mentioned, >2 databases, QA	• Meta-analysis • No overview of included studies • Focus on advanced PA without clear definition
Effectiveness: degarelix	HTA 2012[310]	No search date & no database mentioned, no QA	• No overview of included studies • Overview of clinical trials comparing Degarelix with other homonotherapy • Also safety and cost-effectiveness
	Doehn (Clin Inter) 2009[311]	No methods mentioned	• Overview of Phase II & III trials (3 studies: (Gittelman 2008, van Poppel 2008 & Klotz 2008) • Efficacy & safety
	Doehn (Exp Opinion) 2009[312]	No methods mentioned	• No overview of included study • Efficacy & safety
	Klotz 2009[313]	No methods mentioned	• No table with characteristics included studies • No info on cancer stage • No list of included studies
Effectiveness: GnRH antagonists	Shore 2013[314]	No search date mentioned, 1 database, no QA mentioned	• Studies on Degarelix vs leuprolide and Abarelix vs leuprolide vs bicalutamide • No overview of included studies
	Steinberg 2009[315]	Search date mentioned (2009), >2 databases, no QA	• No overview of included studies • Background?
Effectiveness: 5-AR-inhibitors	Azzouni 2012[316]	No methods mentioned	• No overview of included studies • Prevention and treatment • Not alone (adjuvant or with IAD)

	Margel 2012[317]	No methods mentioned	• Comparison to active surveillance • 2 studies: 1 cohort (Finelli 2011) and 1 RCT (Fleshner 2012)
	Montorsi 2009[318]	No methods mentioned	• Mostly studies on benign hypertrophy • Useful source of primary studies
	Vis 2009[319]	No search date mentioned, 1 database, no QA	• No overview of included studies, but clear description per study
Effectiveness: histone deacetylase inhibitors	Qiu 2013[320]	Search date mentioned (2011), >2 databases, no QA	• Only 2 studies on PC (metastatic)
Effectiveness: leuprorelin	Sethi 2009[321]	No methods mentioned	• No overview of included studies
Effectiveness: oestrogens	Norman 2008[322]	Search date mentioned (2007), >2databases, QA	• 17 included studies • Mix of cancer stages • Refers for details on studies to Dean 2006 • Focus on PEP (polyoestradiol phosphate) • Outcomes: overall mortality, PC mortality, CVS mortality, CVS morbidity
Effectiveness of abitarone	Iqwi 2011[323]		• German
Effectiveness of glucocorticoids	Keith 2008[324]	Search date mentioned, > 3 databases, QA mentioned	• Broader than PCa • Overview of included studies
Adverse events	Casey 2012[325]	No methods mentioned	• QoL: overview of several AE • 96 references! • No overview of included studies
	Choong 2010[326]	No methods mentioned	• Body composition, metabolic & cardiovascular effects • Overview of included studies without QA
	Collins (Asian J) 2012[327]	No methods mentioned	• Metabolic & cardiovascular • No overview of included studies
	Collins (Endocrino J) 2012[328]	No search date mentioned, 1 database (Medline), no QA mentioned	• Metabolic & cardiovascular • No overview of included studies

	Conteduca 2013[329]	No search date mentioned, 1 database (Medline), no QA mentioned	• Cardiovascular effects • Overview of included studies
	Corona 2011[330]	No methods mentioned	• Metabolic & Cardiovascular effects • Physiological explanation • Overview of included studies on CV
	Deepinder 2012[331]	No date search mentioned, 3 databases (Medline, Embase, BIOSIS), level of evidence (3-point scale defined by authors)	• Gynecomastia • Far away from PCa
	Faris 2010[332]	No methods mentioned	• Metabolic effects • Some overview of included studies
	Fizpatrick 2008[333]	No methods mentioned	• 1 & on hormonotherapy (p 19-20) • 1 reference for efficacy (Studer 2006) + references for adverse events
	Grossmann (Endocrin) 2012[334]	Search date (February 2012), 1 database (PubMed), no QA	• Metabolic effects • Overview of included studies
	Grossmann (MJA)2011[335]	Search date (30 November 2009), 1 database (PubMed), grade according to NHMRC	• Bone & Metabolic effects • Focus mainly on management of adverse effects • No overview of included studies
	Grossmann (Asian) 2012[336]	Search date (June 2011), 1 database (PubMed), no QA mentioned	• Hematological effects • Overview of some included studies
	Gruca 2012[337]	Search date mentioned, > 3 databases, no QA mentioned	• Overview of included studies • Safety and tolerability
	Hakimian 2008[338]	No search date, 1 database (Medline), no QA	• Metabolic and cardiovascular effects • No overview of included studies
	Hara 2012[339]	Search date (November 2011), 2 databases? (PubMed & Medline), Level of evidence (but on what?)	• Diabetes • No overview of included studies
	Haseen 2010[340]	Search date (January 2009), 3 databases (Medline, Embase & Web of Science), no	• Body composition • Overview of included studies

		QA	
	Jamadar 2012[341]	No search date, 1 database (PubMed), no QA	• Cognitive measures • Overview of included studies
	Kintzel 2008[342]	Search date mentioned (2008), only 1 database, no QA	• No overview with included studies • No info on cancer stage • Focus on metabolic syndrome, diabetes, cardiovascular disease
	Levine 2010[343]	No methods mentioned	• Table with characteristics included studies • Useful as source of primary studies • Focus on cardiovascular risk
	Martin 2011[286]	No search date mentioned, >2 databases, no QA	• Focus on locally advanced cancer • Also info on effectiveness
	Namiki 2012[288]	No methods mentioned	• Only based on Japanese data • Also info on adverse events
	Nelson 2008[344]	No search date mentioned, >2 databases, no QA	• Focus on cognitive effects • Incomplete info on cancer stage • Useful source of primary studies • No overview of included studies
	Nguyen 2011[289]	Search date mentioned (2011), >2 databases, QA	• Focus on cardiovascular mortality • 11 studies for PC-specific mortality and all-cause mortality • 8 studies on cardiovascular mortality • In some studies also T4 included • Mostly comparison with other therapies
	Nobes 2009[345]	Search date mentioned (2008), >2 databases, no QA	• Focus on metabolic syndrome • Mainly focus on (neo)adjuvant therapies • Useful studies: Saigal 2007, D'Amico 2007
	Philips 2012[346]	Search date mentioned (1999-2010), >2 databases, no QA	• Focus on association between pharmaceutical industry and reporting of LHRH agonists side effects • No overview of included studies • No info on cancer stage
	Saylor 2013[347]	No search date mentioned, 1 database, no QA	• No clear methods section • No overview of included studies • No info on cancer stage • Tables with RCTs, on clinical endpoints, metabolic changes

	Serpa Neto 2010[348]	Search date mentioned (2009), >2 databases, no QA but pooling + test for homogeneity	• Focus on bone metabolism • No info on cancer stage • Meta-analysis
	Shahani 2008[349]	Search date mentioned (1988- 2008), 1 database, no QA	• Focus on metabolic syndrome • Overview of included studies • Outcomes: body composition, glycemic control, lipoprotein profile
	Taylor 2009[297]	Search date mentioned (2008), >2 databases, no QA but pooling + test for homogeneity	• Outcomes: fracture risk, osteoporosis, diabetes, cardiovascular mortality • Overview of included studies
	Terrier 2013[350]	No search date mentioned, 1 database, QA	• Overview of included studies • Focus on metabolic syndrome and insulin resistance
	Trost 2013[351]	No search date mentioned, 1 database, no QA	• Summaries of effect but no overview of included studies • No info on cancer stage

3.4.2. Selection and quality appraisal of primary studies

Selection of RCTs

Table 11 – Included RCTs (n=51)

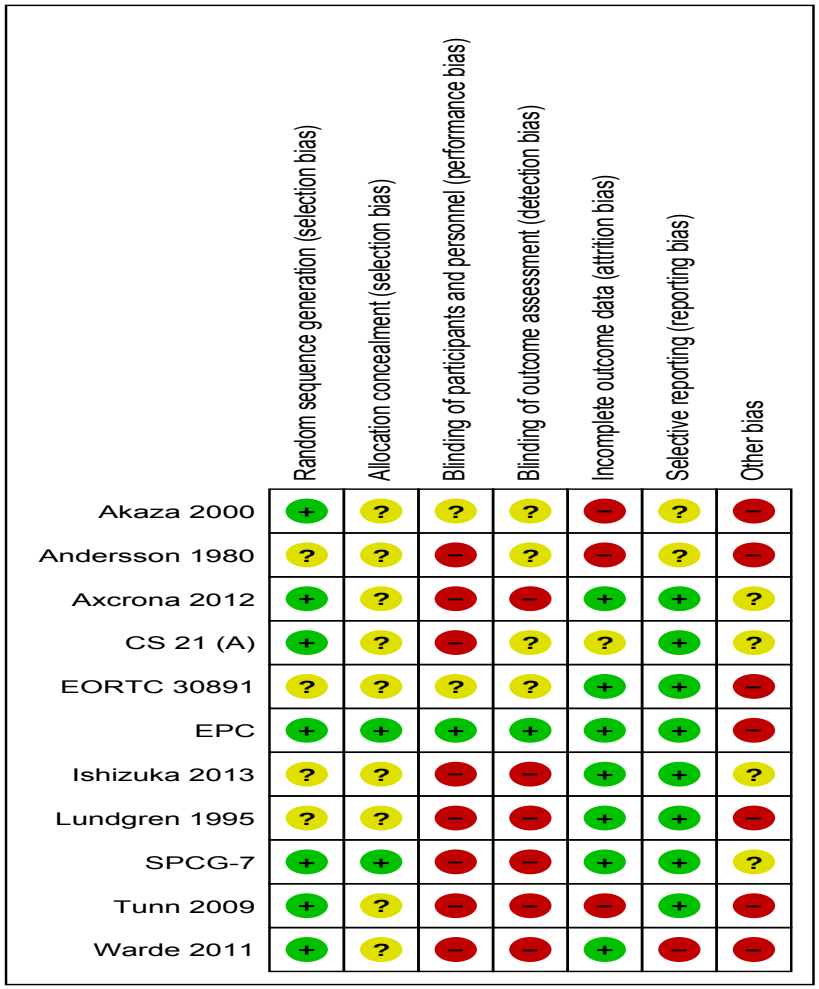
Interventions	References
Hormone vs placebo (n=14)	results of the three RCTs[352-359] trial 25 (SPCG-6)[360-362] trial 24[363-365]
Immediate vs deferred (n=5)	EORTC 30891[366-369] trial of Lundgren 1995[370]
Hormone A vs hormone B (n=26)	trial of Akaza 2006[371-373] CS 21 (A) trial[374-392] trial of Axcrona 2012[393, 394] trial of Anderson 1980[395] trial of Lundgren 1995[370]
Hormone Dose A vs same hormone Dose B (n=2)	trial of Ishizuka[396] trial of Tunn[397]
Hormone vs other monotherapy (n=5)	NCIC CTG UK PRO7[398-400] SPCG-7[401, 402]

Table 12 – Excluded RCTs after full text evaluation (n=47)

Reasons for exclusion	Number of references	References
Population	10	Ozono 2011, Sommerauer 2009, Alfthan 1983, Aro 1989, Blackard 1970, Carvalho 1989, Hedlund 2000, Irani 2008, Labrie 1989, Pavone-Macaluso 1989[403-412]
Intervention	12	De Domenico 2012, Kanayama 2010, Maffezzini 2010, Mirhadi 2013, Smith 2009, Smith 2010, Stein 2012, Bailar 1970, Hainsworth 2006, Kuriyama 2001, Muller 2012, Ono 1999[413-424]
Outcome	12	Efstathiou 2012, Hamilton-Reeves 2013, Eriksson 1988, Eriksson 1995, Gittelman 2008, Kuhn 1997, Kumar 2007, McLeod 2001, Nabors 1990, Noguchi 2001, Ozono 2012, Van Poppel 2008[425-436]
Design	11	Albertsen 2004, Black 2013, Klotz 2014, Olson 2010, Saad 2009, Tombal 2013, Akaza 1996, Bischoff 1990, Homma 2004, Raina 2007, Schelhammer 2001[437-447]
Language	0	/
Duplicate	2	Ishizuka 2013, Studer 2011
Date	0	/
Not found by librarian	0	/

Quality appraisal of selected RCTs

Figure 1 – Quality appraisal of included RCTs



4. EVIDENCE TABLES BY CLINICAL QUESTION

4.1. HIFU

4.1.1. Evidence tables of systematic reviews on HIFU

Table 13 – Evidence table of SR on HIFU

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results outcome:efficacy	VI Results outcome: safety	VII Critical appraisal of review quality
Warmuth, 2010 [23] **Note:limited to treatment of localised or locally advanced cancer**	1. Systematic review 2. Sources of funding: none 3. Search date:2000-2010 4. Searched databases: Medline,Embase, Cochrane,CRD York databases (DARE,NHS EED,HTA) 5. Included study designs: observational case series with over 50 inclusions 6. Number of included studies:18, 2794 patients	1. Eligibility criteria:Local (T1-T2,N0-Nx,M0) and locally advanced (T3-T4,N0-Nx,M0) prostate cancer 2. *A priori* patient characteristics: age 45-88 yrs, some patients received adjuvant hormonal therapy or TURP	1. Intervention(s) HIFU with Ablatherm (A) or Sonoblate (S) (separate analysis) 2. Comparator(s) : none	**1.Overall survival:** no evidence (A & S) only one study (40 patients): 90% at 5 yrs, 83% at 8 yrs **2.Prostate-cancer specific survival rate:** no evidence (A & S) only one study(40 patients) 100% at 5 yrs, 98% at 8 yrs **3.Biochemical disease free survival rate (%):** 66–77% at 5 yr,69% at 7 yr (A), 78–84% at 1 yr, 0–91% at 2 yr, 20–86% at 3 yr,45– 84% at 5 yr (S) **2.Negative biopsy rate**: 80% at 15 mo, 78–80% (point in time not specified**)** (A), 19–89% at 6 mo, 77–84% at 12 mo (S)	• Urinary tract: 2-58%(A),1-30%(S) • Potency: 18-0% (A),1-39% (S) • Rectum: 0-15%(A)0-2%(S) • Pain:1-6%(A), No evidence (S) • QOL: Small or controversial differences (A)	• Level of evidence :very low • Results critical appraisal: all case series, serious methodological limitations and publication bias • Outcomes based on small number of studies

4.1.2. Evidence tables of primary studies on HIFU

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
Blana 2012[145] **Europe**	**Objective**: To-determine if complete HIFU provides a good oncologic outcome. **Design**: Retrospective analysis of a voluntary HIFU user database (@-Registry) **Funding**: **Unrestricted educational grant from EDAP**. **Setting**: 9 European Centres **Sample size**:356 patients **Recruitment duration**: February 1993 –October 2010 **Follow-up:** median 2.8 y	**Eligibility criteria:** • ≤T2 • Prostate ant-post length ≤24 mm • Treated volume > 120% of the protate volume. • Possible TURP at the time of HIFU (within 2 days) **Exclusion criteria:** Specific prior treatment (non steroidal antiandrogens, luteinizing hormone-releasing hormone agonist, radiation therapy or cryotherapy) **Characteristic of the sample** • Low risk (44.9%) Intermediate risk (39.6%) or high risk (14.6%) • Mean age 69.6y (SD 7.2) • Gleason score:	**Complete (whole gland)**: ablation: treated vol > 120% and ant-post diameter ≤24 mm Ablatherm (EDAP-TMS) TURP at the time of HIFU (57.6%) .	**3.Biochemical Outcomes** ***PSA nadir*** Median PSA nadir=0.11 ng/ml (mean 0.78, SD 3.6) achieved at a mean of 14.4 (SD 11.6) weeks after HIFU. The 5- and 7-year BDFRS rates reported using the Phoenix definition were 85% and 79%, respectively. BDFRS rates were higher In low risk patients but the differences between risk groups were not statistically significant **4.Biopsy** Negative biopsy was reported in 80.5% (182/226) patients overall; Number of patients and rates for low-, intermediate- and high-risk groups = 86 (86.0%), 73 (78.5%)	Level of evidence: Very low **Selection:** consecutive patients with inclusion criteria **Drop out:** 226/356 for who follow-up biopsy was available (63.5%) • Voluntary registry and reflective of clinical practice variability by site • Definition of complete HIFU based on consensus not on a community standards aggreed • TRUS measurements of AP diameter are more accurate in small glands (<30 ml) than in large (> 50ml)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		76.1% ≤6; 22.5%=7 and 1.4%=8-10. • T1c (39.9%), T2a (23.3%), T2b (14.9%) T2c (10.4%) • Mean PSA= 6.8 ng/ml (0.12-58.0) • Prostate vol: 18 ml (4-38)		and 23 (74.2%), respectively. There was no statisticaliy significant difference between the risk groups (p = 0.228). The disease-free survival at 5 years and at 7 years = 64% and 54%. **Morbidity in another paper**	
Boutier 2011[146] **France**	**Objective**: To evaluate whether the location (apex/midgland/base) of prostate cancer influences the risk of incomplete transrectal HIFU ablation. **Design**: Retrospective Case series **Funding**: **?** **Setting**: **Sample size**:99 patients **Recruitment duration**: limited to the biopsy procedures performed after July 2005 **Follow-up:** 6 months	**Eligibility criteria:** • Clinically localized PCa. • Post-HIFU biopsies performed 3-6 months after the treatment. **Exclusion criteria:** • HIFU as salvage treatment for local recurrence after radiation therapy • Biopises performed for PSA elevation	Ablatherm (EDAP-TMS) With a 6-mm safety margin at the apex . All transrectal biopsies were performed by 1 of 4 experienced radiologists according to a standardized procedure (with random and colour Doppler guided cores)	**4.Biopsy** <u>Before treatment</u> All patients had at least one positive pre-HIFU biopsies. 215/594 sextants (36.2%) were positive: 55 (25.6%) positive sextants were in the apex, 86 (40%) in the midgland and 75 (34.4%) in the base. <u>After treatment</u> Prostate volume at inclusion: 11.3 ml (DS 5.5) PSA at inclusion 1.1	Level of evidence: Very low **Selection** – **Drop out**: - • Retrospective case-series • Lack of information o the HIFU procedure • No assessment of the ant-posr position of residual cancers, even if the anterior part of the prostate is another possibily undertreated area.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		Characteristic of the sample • Mean age (at inclusion in the study) 71.3y (SD 5.7) • Gleason score: before HIFU 6.5 (SD 0.8) • Mean PSA before HIFU= 8.8 ng/ml (SD 5.7) • Prostate vol before HIFU: 24 ml (SD 7.5) Delay from HIFU treatment to biopsy: 5.7 months (SD 2)	All biopsies were analyzed by a single uropathologists.	ng/ml (SD 1.8)• Residual cancer at 3-6 mo: 36 patients (36.4%) and 50 sextants (8.4%); 30 (60%) positive sextants were in the apex, 12 (24%) in the midgland and 8 (16%) in the base. Both statistical analyses found that the locations of the positive sextants before and after HIFU ablation were significantly different (p<0.001), with a higher proportion of positive apical sextants after treatment.	• Transrectal biopsy is not a perfect means of mapping cancer within the prostate.
Callea 2010[147] **Italy**	**Objective**: To evaluate whether the location (apex/midgland/base) of prostate cancer influences the risk of incomplete transrectal HIFU ablation. **Design**: Retrospective Case series **Funding**: ? **Setting**: ? **Sample size**:171 patients	**Eligibility criteria** • patients choice or not eligible to radical prostatectomy because • age (> 75 years) • or high anaesthesiological risk • or PSA > 20 ng/ml • or clinical stage ≥	Spinal anesthesia SPC Debulking TUR of the transition zone of the prostate Ablatherm 197 HIFU treatments for 171 patients; 22	**3.Biochemical success rate** (PSA constantly < 0.5 ng/ml) was obtained in 84.2% of low and intermediate risk patients and in 43.1% of high risk patients; **4.Biopsy** Post-treatment biopsies	Level of evidence: Very low **Selection:** consecutive patients with inclusion criteria **Drop out: -** • Mix of first and salvage HIFU

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
	Recruitment duration: May 2002 – June 2010 **Follow-up:** mean 67.9 months	T3. **Characteristic of the sample** • Low risk (16.9%) Intermediate risk (27.5%) or high risk (55.6%) • Mean age 74.7y (44-86) • Mean Gleason score: 6.3 (range 3-9) • Mean PSA = 27.9 (range 0.1-143) • Mean prostate vol: 38.5 ml (range 9-172 ml)	patients needed a second treatment as the first was incomplets (4 patients) or because of recurrence (18 patients). The patients received a mean of 1.15 HIFU sessions.	(6 months after treatment) revealed no residual tumour in 93.4% of low or intermediate risk patients and in 63.1% of high rish patients. **5.Adverse events** No severe side-effects (except 1 rectourethral fistula 0.6%) were observed in this population: • Asymptomatic urinary tract infections (17.5%), haematuria (3.5%), prostatitis (2.9%), epididymorchitis (1.8%), hemorrhoidal pain (0.6%), strictures of urethra (7.6%) and bladder neck sclerosis (12.2%). • Light stress incontinence occurred in 4.0% of the patients • Erectile dysfunction in 77.7%.	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				These outcomes certainly temper the enthusiasm for HIFU as a minimally invasive treatment alternative.	
Crouzet 2010[448] **France**	**Objective**: report the outcome of 803 consecutive patients who underwent HIFU as primary care option for localized PCa in 6 institutions and to determine the factors influencing the outcome **Design**: prospective case series **Funding**: none **Setting**: 6 centers **Sample size**:803 patients/1457 **Recruitment duration**: 1993-2007 **Follow-up:** mean 42±33 mo	**Eligibility criteria** • Stage T1-T2, N0,M0 • No previous therapy or adjuvant therapy • Not suited for RP • ≥ 2 yr follow-up **Characteristic of the sample** • Low risk (40.2%) Intermediate risk (46.3%) High risk (13.5%) • Mean age 70.8 ±5.6 yr • Gleason score: ≤ 6 (63.5% • T1 (59.9%); T2 (40.1%) • Mean PSA = 9.1 ± 5.9 , median PSA 7.7 • Mean prostate vol: 24.5 ml ±10 ,	**Intervention:** Ablatherm prototypes in 80, Maxis in 446 and Ablatherm Integrated Imaging in 277 patients. In the 2 last subgroups, combined with TURP. mean number of HIFU sessions:1.4 ± 0.6	**1. Overall survival:** 89% at 8 yr **2. Prostate-cancer specific survival rate:** 99% at 8 yr **3.Biochemical disease free survival rate:** 5-yr and 7-yr BFSR (Phoenix criteria) for low-, intermediate-, and high-risk patients were, respectively, 83–75%, 72–63%, and 68–62% (p = 0.03) **4. Negative biopsy rate**: in 459 patients 77.9% - for low-, intermediate-, and high-risk patients were, respectively, 84.9%, 73.5%, and 72.0% (p = 0.003). **5. Adverse events** reported in separate publication	Very low **Selection:** **Drop out**

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		median 23 ml			
Crouzet 2011[449] **France**	**Objective**: To report the functional and oncological outcomes of HIFU for PCa **Design**: Retrospective Case series ICS, IPSS, IIEF-5 et EORTC QLQ-30 **Funding**: ? **Setting**: ? **Sample size**:297 patients **Recruitment duration**: January 2005 – June 2009 **Follow-up:** mean 27 months, median 17 (3-64 mo)	**Eligibility criteria** • Stage T1-T2 • PSA ≤ 15 • Gleason ≤7 **Characteristic of the sample** • Low risk (50.2%) Intermediate risk (49.8%) • Mean age 71.4y (5.10) • Gleason score: ≤ 6 (64%) and 7 (36%) • T1 (57.9%); T2 (42.1%) • Mean PSA = 6.49 (3.43) • Mean prostate vol: 23.5 ml (10.76 ml) • Hormonotherapy (30.3%)	TURP, immediatly before HIFU, during the same anesthesia (Patient with a ant-post length > 26 mm received a hormonal treatment during 3 to 6 months or a TURP 2-3 months before the HIFU) SPC Ablatherm Integrate Imaging® (allowiing a real time control of the intervention) Whole gland abltion (120%) with a 4-mm safety margin at the apex The patients received a mean of 1.2 HIFU sessions.	**2.Specific survival** The 5 year **specific survival and metastase free survival** = 100 and 97% **The disease free survival rate (DSFR)** at 40 months was 79% for low risk group and 62% for intermediate risk group. **3.Biochemical Outcomes** ***PSA nadir*** The mean PSA nadir was 0.64 (1.54) ng/ml and the median PSA nadir was 0.12ng/mt with 65% of patients reaching a nadir less than 0.3 ng/ml. **4.Biopsy** Mean prostate volume after HIFU = 17.1 (12) Systematic control biopsies were performed if sign in PSA nadir on 175	Level of evidence Very low **Selection:** consecutive patients with inclusion criteria **Drop out:?**

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				patients with 89% of negative biopsies. **5.Adverse events** Two urethrorectal fistula after a second HIFU were observed. **6.QoL** The pre and post-HIFU treatment International Prostate Symptoms Score (IPSS) score and quality of Life questionnaire were not statistically different. However, the pre and post-HIFU erection function and continence status were significantly different: IIEF-5 >15 in 37.7% vs 7.7% in pre and post HIFU; a grade 2 or 3 incontinence post-HIFU concerned 5% of patients.	
Crouzet 2013[150] **France**	**Objective**: To report the cancer control and morbidity outcomes for all patients treated with HIFU as primary therapy **Design**: prospective, single arm, single institution cohort **Funding**: none	**Eligibility criteria** • Stage T1-T2 M0 • PSA ≤ 30 • No previous radical therapy • No candidates for surgery	**Intervention:** Ablatherm prototypes in 63, Maxis in 652 and Ablatherm Integrated Imaging in 287 patients.	**1. Overall survival:** 80% at 10 yrs **2. Prostate-cancer specific survival rate:** 97% at 10 yr 99% for low-risk patients, 98% for intermediate-risk patients, and 92% for	Population probably overlaps with other reports Low evidence level

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
	Setting: community hospital **Sample size:** 1002 patients **Recruitment duration**: 1997-2009 **Follow-up:** mean 6.4 yr (0.2–13.9).	**Characteristic of the sample** • Low risk 357 (35.6%) Intermediate risk 452 (45.1%) High risk 174 (17.4%) • Median age 71 (48-87) • Gleason score: ≤ 6 (55.4%);7 (34.7%); ≥ 8 (8.4%) • T1 (51.7%); T2 (44.8%) (T3 2.8%° • Median PSA :7 (0-30) • Median prostate vol: 23 ml (5-78 ml) • Previous ADT 39.1%	TURP.in 93.7%) median number of HIFU sessions:1(1-3)	high- risk patients; **PCa metastasis–free survival** rate was 94% and was 99%, 95%, and 86% for low-, intermediate-, and high-risk patients, respectively **3.Biochemical disease free survival rate:** 5- and 8-yr biochemical-free survival rates (BFSRs) for low-, intermediate-, and high-risk patients were 86–76%, 78–63%, and 68–57%, respectively ($p < 0.001$) overall 10 yr BFSR was 60%. The 8-yr BFSRs in patients with and without previous ADT were 70% and 66%, respectively ($p = 0.992$). 5-yr BFSR progressively increased over time: 66% in patients treated before 2000, 80% in patients treated from 2000 to 2004, and 83% in patients treated from 2005 onward ($p = 0.010$).	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				4.Negative biopsy rate: Available for 774 patients (77%) according to PSA nadir: negative in 485 (63%) **5. Adverse events** differ according to technique **Urinary tract:** overall**:** stress incontinence 1 18.7%-2 or 3: 5%, UTI overall 3.9% but improved overtime p<0.001, Acute retention: 7.6%, bladder obstruction overall 16.6% improved overtime p<0.001 Hematuria:5.5%, stenosis 9 % improved overtime p<0.001, fistula 0.4% **Potency:** evaluated after 2005 preserved (IIEF≥17) in the 42.3% of patients with a baseline IIEF score ≥17 (<70 yr: 55.6%; >70 yr: 25.6%; p < 0.001) without pharmacologic aid **Rectum:** 4 fistula after repeated HIFU	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				Pain: NA **6.QOL:** NA	
Elterman 2011[158] **Canada**	**Objective**: report early single center experience **Design**: retrospective case series **Funding**: none **Setting**: university hospital **Sample size:** 95 patients **Recruitment duration**:March 2006-December 2007 **Follow-up:** 24 mo	**Eligibility criteria** • localized prostate cancer • prostate volume < 40 ml • Self elected • Primary and salvage **Characteristic of the sample** • Based on Gleason : Low risk: 55.8%, Intermediate risk 36.8 % High risk 7.3 %, of these 42.9% (n=7) were salvage therapy after previous • Mean age 64 yr (46-91) • Median PSA :5.33 (0.19-14.5) • Mean prostate vol: 30.5 ml (14.4-73 ml) • Previous ADT	**Intervention:** Sonoblate 500 (Focus surgery Indianapolis,IN, US), TURP was not performed	**3.Biochemical disease free survival rate**: (Stuttgart definition) overall BCFailure in 14/95 patients (15 %) at 24 mo **4.Negative biopsy rate**: Not systematic **5. Adverse events** Differ according to technique **Urinary tract:** acute urinary retention 17%, urosepsis in 1/95, need for cystoscopy 28%, retained necrotic tissue necessitating TURP:6%, urinary stricture 9%, bladder neck stricture 4% Urinary function evaluated with self report and EPIC questionnaire: 51% any leakage at 6 mo – with 7/41 (17%) clinically significant incontinence **Potency:** evaluated with IIEF : 10/52 (19%) moderate to severe ED (IIEF ≤ 11) at 6 mo	Very low evidence level

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		10.5 %		however 6/10 had scores < 11 pre-treatment **Rectum:** NA **Pain:** NA **QoL**	
Ganzer 2013[450] **Germany**	**Objective**: To assess the safety, functional and oncological long-term outcomes of HIFU as a primary treatment option for localized prostate cancer **Design**: retrospective single center case series **Funding**: senior author paid consultant for EDAP **Setting**: university hospital **Sample size:** 538 patients **Recruitment duration** November 1997-September 2009 **Follow-up:** mean 8.1 (2.9 SD, 2.1-14.0) yr	**Eligibility criteria** • Localized prostate cancer • Self elected or unsuitable for surgery • Primary or at least 2 yrs post prior HIFU **Characteristic of the sample** • Low risk: 42.6%, Intermediate risk 339.2 % High risk 16.9 % • Mean age 67.7 ± 7 yr • Mean PSA :11.2 ± 19.7 ng/ml • Mean prostate vol: 20.9 ± 9.2 ml • **Previous ADT** 36.4 %	Intervention: Ablatherm 2nd prototype in 43 (8%), Maxis in 355 (66%) and Ablatherm Integrated Imaging in 140 (26%) patients. TURP.for all; on same day in 39.6 % Number of HIFU sessions:1 in 78.6%, 2 in 20.6%, 3 in 0.8% Whole gland?	**1. Overall survival:** 86.1% (75 patients died) **2. Prostate-cancer specific survival rate:** PCa-specific death occurred in 18 (3.3%) patients which included none, eight (3.8%) and 10 (11%) patients within the low-, intermediate- and high-risk group, respectively (p <0.001). progression to metastatic disease based on bone scan and CT data occurred in 1/229 (0.4%) patients in the low-risk group, 12/211 (5.7%) in the intermediate- and 14/91 (15.4%) in the high-risk groups (*P* >0.001). **3.Biochemical disease free survival rate**: (Phoenix definition) BDFS rates	low evidence level Selection: all consecutive patients without pre-selection

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				at 5 and 10 yrs overall were 81% and 61%. The 5-yr BDFS rates for the low-, intermediate- and high-risk groups were 88, 83 and 48%, respectively- the 10-yr BDFS rates were 71, 63 and 32%, respectively - 5-yr BDFS rates for patients with a PSA nadir <0.2 ng/mL,0.21–1 ng/mL and >1 ng/mL were 91, 67 and 27%,respectively (*P* <0.001). **4.Negative biopsy rate**: 297 (55.2%) patients underwent at least one follow-up biopsy (random or PSA 3-6 mo): 76 (25.6%) had histological evidence of cancer; incidence in the low-risk group was 20/125 (16%), in the intermediate-risk group 35/122 (28.7%) and in the high-risk group 20/50 (40%). **5. Adverse events**	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				Urinary tract: BOO 28.3% decreasing overtime p <0.03, UTI 10.2%, recto urethral fistula 0.7% , incontinence grade 1 in 2.8%, grade 2 in 2.8%, grade 3 in 0.7 and 83,1% were pad free **Potency:** Of 202 patients with unimpaired pre-treatment potency outcome data were provided by 169 (83.7%) patients. 12 mo after HIFU, 43 (25.4%) were potent (intercourse without medical assistance), 67 (39.6%) were able to perform intercourse with medical assistance and 59 (35%) patients were impotent. **Rectum:** NA **Pain:** NA **6.QOL:** NA	
Inoue Japan **2011**[159]	**Objective**: assess long –term outcome **Design**: retrospective case series **Funding**: no mention **Setting**: community hospital	**Eligibility criteria** • Localized prostate cancer T1,2 N0M0 • At least 12 mo FU	**Intervention:** Sonoblate 500 and 500 version 4 (Focus surgery Indianapolis,IN, US)	**1. Overall survival**: 96.4% 5/137 died of other causes **2. Prostate-cancer specific survival rate:** 100%	low evidence level

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
	Sample size: 137 patients **Recruitment duration**:May 2003-April 2010 **Follow-up:** 36 mo (12-84)	• Consecutive case enrolment **Characteristic of the sample** • Low risk: 21%, Intermediate risk 50 % High risk 29 % • Mean age 70 yr (50-82) • Mean prostate vol: 20 ml (8-52 ml) • Previous ADT 23 %, TURP 13%, HIFU 8%		**3. Biochemical disease free survival rate**: (Phoenix definition and negative biopsy and no local and distant metastase): 3 yr overall DFS 83,6 %; 96.7 % for low risk, 83.9% for intermediate risk and 73.5 % for high risk - 5 yr overall DFS 77.8 %; 91.3 % for low risk, 80.7 % for intermediate risk and 61.7 % for high risk p<0.05 difference low and high risk **4. Negative biopsy rate**: 121/133 patients after first HIFU (91%) **5. Adverse events** **Urinary tract:** urethral stricture 10%, urinary difficulty 22%, urgency 11% **Potency:** evaluated with IIEF : ED (IIEF < 7 post and > 7 pre) in 22/59 (37%) of patients **Rectum:** NA **Pain:** NA **6.QOL:** NA	
Komura 2011[160]	**Objective**: to assess	**Eligibility criteria**	**Intervention:**	**1. Overall survival:**	low evidence level

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
Japan	association urethral stricture and DFS **Design**: retrospective case series **Funding**: no mention **Setting**: community hospital **Sample size:** 144 patients **Recruitment duration**:2004-2008 **Follow-up:** 47 mo (2-70)	• Localized prostate cancer T1,2 N0M0 • Prostate volume < 40 ml • Primary therapy **Characteristic of the sample** • Low risk: 31.9%, Intermediate risk 29.9 % High risk 38.2 % • Mean age 68.4±7.3 yr • Median PSA :5.33 (0.19-14.5) • Previous ADT 43.8%, TURP 29.9%	Sonoblate 500 before december 2007 and 500 version 4 thereafter (Focus surgery Indianapolis,IN, US)	98.6% 2/144 died of other causes **2. Prostate-cancer specific survival rate:** 100% **3. Biochemical disease free survival rate**: (Phoenix definition) 5 yr BFSR 67.8% - in patients with US 76.7% and 55.8% in patients without US (p=0.004) – DFSR (combination of biochemical and histological parameters) 61.2% at 5yr – 78.2 in patients with US and 47.8% in patients without US (p<0.001) **4. Negative biopsy rate**:48/66 (72.7%)- in 16/19 patients with US (84.2%) **5. Adverse events** **Urinary tract:** (subclinical) urethral stricture : 58/144 (40.3%) **Potency:** NA **Rectum:** NA **Pain:** NA **6. QOL:** NA	a complication is positive prognostic factor for DFS (more complete ablation of the apex)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
Maestroni 2012[151] **Italy**	**Objective**: To report experience in first 100 patients **Design**: Retrospective case series **Funding**: No mention **Setting**: University hospital **Sample size:** 74 patients **Recruitment duration**: April 2006 – December 2011 **Follow-up:** 29.9 (9-40)mo	**Eligibility criteria** • Localized prostate cancer T1,2 N0M0 • Primary and salvage • Age over 70 yr • 1 yr follow-up • No anal stenosis or coxofemoral anchilosis • Prostate diameter anteroposterior < 25 mm **Characteristic of the sample** • Low risk: 13.5%, Intermediate risk 16.2 % High risk 70% • Mean age 72.7 yr (65-80) • Mean PSA :8.07±8.17 ng/ml(0.19-14.5) • Previous ADT 28.3%, TURP 9.4% at the same time + 59.5 2 mo	**Intervention:** Ablatherm (EDAP, Lyon, France) under supervision of EDAP No sparing series TURP before or combined	**3. Biochemical disease free survival rate**: (Phoenix definition) failure in 26.6% - 16.6% low risk, 20% intermediate risk, 87.5% high risk – mean time to failure: 12.5 mo (3-40) **4. Negative biopsy rate**:45/74 had biopsies- 84.5% negative **5. Adverse events** **Urinary tract:** Stress incontinence gr1: 5-11%,gr 2 :4%, dysuria 10%, bladder outlet obstruction 4%, 1 fistula **Potency:**impotence 90% but 75 % when comparing pre and post **Rectum:** NA **Pain:** NA **6.QOL:** NA	Very low evidence level selected patients

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		before			
Netsch 2010[152] **Germany**	**Objective:** To investigate the occurrence of bladder outlet obstruction (BOO) after HIFU **Design:** Retrospective analysis **Funding**: No declared **Setting**: 1 hospital **Sample size:** 226/277 patients **Recruitment duration**: December 2002- September 2007. **Follow-up:** Mean = 50 mo (range 24–80).	**Eligibility criteria** Patients with localized PCa as diagnosed by prostate biopsies or TURP (pT1a-1b) The decision for HIFU the prostate based on the patient's age, comorbidity, and the decline of any kind of surgery. **Exclusion criteria:** Lost to follow-up (2); death in the first year of follow-up (5); primary RT (19); primary RP(1); secondary RT (3); secondary RP (3); development of rectourethral fistula (6); repeated HIFU sessions (12). **Characteristics of the sample:** • Low risk: 37.6%, intermediate: 32.3% and high risk: 30.1% • Mean age =	Ablatherm Maxis device until February 2006 added with the Integrated imaging HIFU device after. All men underwent a single HIFU treatment; 93 men received antihormonal pretreatment. TURP before treatment	**5. Adverse events** **Urinary tract** BOO developed in 58 (25.66%) patients. Actuarial cumulative incidences of BOO after HIFU at 1, 2, and 3 years were 20.8%, 23.89%, and 24.34%. Stratifying by risk group, BOO after HIFU developed in 23.5%, 32.9% and 20.6% at low, intermediate, and high risk, respectively. Repeated BOO episodes were observed in 27 (11.94%), three to seven episodes in 13 (5.75%) patients. Patients with repeated BOO were older than patients with singular BOO (71.75 +- 4.97 vs 68.18 +- 5.03; P = 0.024). In primary BOO, multiple sites of obstruction were more often involved than in	**Selection:**Consecutive patients **Patient flow:** 2 lost to FU

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		70.06 +- 5.8 years		repeated BOO (25/58 vs 8/27). Conversely, isolated bladder neck stenosis was predominantly found in patients with ≤two episodes of BOO. The rate of primary BOO was significantly different between patients who had undergone TURP the same day as HIFU or within 2 days of HIFU (33/96; 34.38%) and patients with TURP more than 1 month (16/89; 17.98%) before HIFU (P = 0.032). BOO occurred in 21.95% (9/41) of the patients who were treated with HIFU only. Combining HIFU with TURP decreases the perioperative urinary retention time but may lead to delayed development of BOO (25.66%) after HIFU, particularly affecting the bladder neck.	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				A longer interval between TURP and HIFU (>1 month) might reduce this risk.	
Netsch 2011[153] **Germany**	**Objective:**To report 8 cases of rectourethral fistula (RUF) in patients treated with (HIFU) for either localized or locally recurrent prostate cancer (PCa). **Design:** Retrospective analysis of 363 consecutive patients with PCa. **Funding**: No mention **Setting**: 1 hospital **Sample size:** 341 patients **Recruitment duration**: December 2002- January 2010. **Follow-up:** Mean = 50.45 mo (range 25 to 84)	**Eligibility criteria** For those with localized stage pT1 PCa, the decision for HIFU of the prostate was determined by patient age and the presence of co-morbidities, as well as patient choice and refusal of surgery. **Characteristic of the sample** One HIFU session was performed in 341 patients with localized PCa. Two HIFU sessions were performed in 22 patients. Salvage HIFU was performed in 22 patients after radiotherapy.	Ablatherm Maxis device until February 2006 added with the Integrated imaging HIFU device after. . TURP before HIFU .	**5. Adverse events** **Rectourethral fistula (RUF)** occurred in 8 (2.2%) of the 363 patients. The mean interval between HIFU and the development of RUF was 3 weeks (range 1-4). The mean fistula size was 9 mm (range 3-25). RUF was developed after 1 HIFU session in 4 patients (1.17%), after 2 sessions in 3 patients (13.63%) and after salvage HIFU in 1 patient. No differences in the manifestation of RUF were observed between the 2 HIFU devices used (Ablatherm Maxis and Integrated imaging HIFU device).	**Selection:**Consecutive patients

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				Conservative treatment failed in all patients with RUF.	
Pfeiffer 2012[154] **Germany**	**Objective:** To report cancer control results after a single application of HIFU in patients with localized prostate cancer (PCa), stratified by tumour recurrence risk according to D 'Amico risk classification. **Design:** Retrospective case series **Funding**: Dietrich Pfeiffer acted as a Trainer for EDAP-TMS. **Setting**: One hospital **Sample size:** 189/191 patients **Recruitment duration**: December 2002 and October 2006 **Follow-up:** Median = 52.8 (0.2 – 79.8) mo.	**Eligibility criteria** Elderly patients or patients with significant medical co-morbidities diagnosed with clinically localized PCa. All the patients were unsuitable candidates for RP and unwilling to undergo RT. **Exclusion criteria** Nodal extension or metastatic disease. **Characteristic of the sample** • Low- (38%), intermediate- (34%) and high-risk (28%) groups • Median patient age = 69.7 (51 – 82) years, • 75 patients (39.3%) had an elevated perioperative risk	Ablatherm Maxis ® or (after February 2006) Ablatherm Integrated Imaging ® HIFU device TURP or adenomectomy before HIFU to downsize large prostate glands (49%). Androgen deprivation therapy (42%) was discontinued at the time of HIFU.	1. **Overall survival** at 5 years = 86.3% 2. **Specific survival** rates at 5 years = 98.4%. Three men died from PCa at 2, 3 and 4 years after HIFU treatment. **3. Biochemical** The biochemical failure-free survival rate (BFSR) at 5 years was 69.2%, and was significant higher in the low-risk group (84.8%) than the intermediate-risk (64.9%; P < 0.002) and high-risk (54.9%; P < 0.001) groups. **4. Biopsy** Control biopsies of the prostate were available for 152 patients (after 6 mo and in case of PSA increase). The median (range) interval between HIFU and biopsy was 8.1 (2 – 72) months.	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		(ASA III – IV).		Of the entire sample, control biopsies were negative in 110 (72.4%) patients, and negative biopsy rates of 84.2, 63.6, and 67.5% were found in patients in the low-, intermediate-, and high-risk groups, respectively (P = 0.033) Metastases were detected in seven (3.7%) patients after PSA relapse, including 2 patients with intermediate-risk tumours and 5 with high-risk tumours. Bone metastases were detected in 4 patients and lymph node involvement in the remainder. 5-year disease-free survival rates were 62.8 for all and 81.7%, 53.2% and 51.2% (p< 0.01), by risk level respectively.	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				5. Adverse events **Urinary tract** In 99 (51.5%) patients BOO was found within 12 months of single-session HIFU, Transient urinary incontinence was reported in 75 (39.0%) patients, including grade I (safety pad during the day) in 51 (26.5%), grade II (2 – 3 pads daily, dry at night) in 12 (6.3%), and grade III (> 3 pads daily and/or wet at night) in 2 (1.6%) patients. Recurrent UTIs occurred in 51 (26.5%) patients, **Rectum** Three (1.6%) patients experienced rectourethral fistulas. **Potency** Preservation of erectile function was not a treatment goal in this sample of elderly patients or patients with co-morbidities.	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
Pinthus 2012 [155] **Canada**	**Objective:** To assess 4-year biochemical failure (BCF) rates in patients after HIFU using the Horwitz and Stuttgart definition **Design:** Retrospective analysis of the **l**argest North American prospective cohort of primary HIFU for PCa with mid-term oncological outcome data **Funding**: None declared **Setting**: One centre **Sample size:** 402/447 patients **Recruitment duration**: May 2005 and December 2010 **Follow-up:** Median = 24 (6 – 48) mo.	**Eligibility criteria:** Clinical stage of T1 and T2, Gleason score of = 7 and serum PSA of < 20 ng/mL **Exclusion criteria** Previous radiation, androgen deprivation or HIFU therapy, and patients with < 2 consecutive PSA measurements; Prostate volume of > 40 ml (based on their pre-treatment TRUS at the time of the diagnostic prostate biopsy) **Characteristics of the sample:** • Low risk 45.5% and intermediate risk= 54.5% • Mean age= 62.7 (SD 7.5)	**Single session with** Ablatherm ® integrated imaging model system under spinal anaesthesia and i.v. sedation. **No peri-HIFU TURP** **No ADT**	**3.Biochemical** Overall 4-year mean (range) BCF-free rates were 68% (61 – 75) and 72% (68 – 77) according to the Stuttgart and Horwitz definitions According to the Stuttgart definition, BCF-free survival rates were 75% (95% CI: 67 – 84%) for low-risk patients and 62% (95% CI: 52 – 71%) for intermediate-risk patients at 4 years (Fig. 1A), with a statistically significant difference (log-rank P = 0.047). Using the Horwitz definition, BCF-free survival rates were 76% (95% CI: 69 – 83%) for low-risk patients and 69.5% (95% CI: 63 – 76%) for intermediate-risk patients at 4 years with no statistically signifi cant differences (log-rank P = 0.258). Mean (range) BCF-free rates were significantly	**Selection**: Consecutive patients **Patients flow**: 1 died of unrelated cause; none died of PCa

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				higher for a PSA nadir ≤ 0.5 ng/mL and prostate volume ≤ 30 mL for both definitions at 4-year follow-up [Stuttgart: 79% (72 – 86) vs. 25% (13 – 38); Horwitz: 82% (77 – 87) vs. 33% (21 – 44)] and [Stuttgart: 72% (64 – 79) vs. 56% (42 – 69); Horwitz: 75% (69 – 80) vs. 63% (53 – 74)], respectively.	
Ripert 2011[156] **France**	**Objective:** To determine oncological outcomes after HIFU in patients with localized prostate cancer using a new, more accurate, definition ('Stuttgart' definition) of biochemical failure. **Design:** Retrospective analysis of all patients who received HIFU for localized PCa. **Funding**: None declared **Setting**: One centre **Sample size:** 53 patients **Recruitment duration**: April 2004 - February 2010 **Follow-up:** Mean = 45.4 mo (range 16–71).	**Eligibility criteria** Files with complete oncological data and at least 1 year of follow-up. Only low- and intermediate-risk patients. Patients who did not qualify for or refused surgery. Account was taken of life expectancy. Prostate < 50 ml. **Exclusion criteria** Patients in whom HIFU treatment was incomplete because of a technical incident,	First-line treatment with a second-generation AblathermTM device and, from March 2005 onwards, one that was robot-assisted with real-time integrated imaging. General anaesthesia No nerve-sparing surgery was performed TURP, when	**3.Biochemical** Overall, 36 patients (67.9%) experienced oncological failure during the FU. These included 33 cases (62.2%) of biochemical failure according to Stuttgart. A PSA nadir of ≤0.2, 0.21–1.0 and >1 ng/ml was reached in 20.8%, 30.2% and 49% of patients, respectively, and was associated with biochemical failure in 9.1%, 30.3% and 60.6%, respectively.	**Patient flow**: no died of PCa, no lost Not all patients underwent routine post-HIFU biopsies. Routine biopsies do not form part of the French Association of Urology's guidelines for HIFU treatment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		excessive rectal wall thickness or ultrasonography detection problems, and who were not offered a second HIFU session. A follow-up of □□1 year Positive criteria for high-risk prostate cancer HIFU as second-line treatment were also excluded. **Characterisitic of the sample** • Low risk(28/53) and intermediate risk (25/53) • Mean age = 72.5 years, (range 60–79 years)	performed, was carried out during the 3 months before the HIFU procedure and not concomitantly with the procedure. None have received neoadjuvant androgen deprivation therapy (ADT).	In total, 19 (35.8%) patients according to the Phoenix definition, and 29 (54.7%) patients according to the ASTRO definition, experienced biochemical failure during follow-up. Clinical stage category was significantly associated with biochemical failure (P = 0.04) and not oncological failure (P = 0.06). (17 low-risk and 16 intermediate-risk cases for biochemical failure, and 18 low-risk and 18 intermediate risk cases for oncological failure.) The 5-year biochemical-free survival rate according to Stuttgart and disease free survival rate were 21.7% and 13.5%, respectively.	
Shoji 2010[161] **Japan**	**Objective:** To report our health-related quality of life (QOL) and functional	**Characteristic of the sample** Mean age =68 years	Single HIFU therapy with Sonoblate	**3.Biochemical** BDFR after HIFU therapy for localized	Lack of several information

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
	outcomes following HIFU for localized prostate cancer. **Design:** Analysis of prospective database; use of IPSS, theJapanese version of FACT-G and FACT-P anduroflowmetry. **Funding**: No mention **Setting**: One centre **Sample size:** 326 patients **Recruitment duration**: January 1999 - April 2007 **Follow-up: ?** .	(range: 45–88)	Systems. Total ablation while avoiding the neurovascular bundles (NVB) using a color Doppler system to maintain potency. TURP 1 month before HIFU if prostate volumes > 40 ml, evaluated by transrectal Ultrasonography (n=18) NADT in 214 patients (65.6%)	prostate cancer according to risk group; low, intermediate and high were 84%, 64% and 45%, respectively, at 8 years evaluated by the “Phoenix ASTRO Criteria”. **5. Adverse events** **Urinary tract** Maximum flow rate and residual urine volume were significantly impaired at 6 months (P = 0.010) after HIFU, even if they returned to baseline values at 12 or 24 months after HIFU. Grade 3 or 4 urethral stricture (16.6%) and prolonged urinary retention (>14 days) 13.2 **Potency** At 6, 12 and 24 months after HIFU, 52%, 63% and 78%, respectively, of the patients, not receiving neoadjuvant hormonal therapy, were potent.	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				6.QoL The total FACT-G score significantly improved at 24 months (P = 0.027) after HIFU.	
Sung 2012 [157] **Korea**	**Objective**: To evaluate BCR (Stuttgart definition) and AE after HIFU treatment **Design**: retrospective case series **Funding**: **?** **Setting**: University hospital **Sample size**:126/157 **Recruitment duration**:2/2004-8/2010 **Follow-up:** median FU 61.1mo (IQR: 37.2–81.0).	**Eligibility criteria:** • Clinically localized PCa classified according to NCCN as low,intermediate or high risk. • Not suited for or declined RP or RT **Exclusion criteria:** • HIFU as salvage treatment after RT failure, immediate adjuvant hormonal therapy, no follow-up, paliative care **Characteristic of the sample** median age:71 yrs (IQR:66–76) median prostate volume at the time of	• Ablatherm (EDAP-TMS) • Pre intervention MRI • FU: q 3–4 mo 1th yr, q 6 mo 1-3 yrs, q 12 mo 5-5 yrs for DRE, PSA. Imaging or biopsies if clinically indicated.	**BCR recurrence** (nadir plus 1.2 ng/ml) 59.5%, median time to BCR 13.8 mo **5-year BCR-free survival rates per risk group:** low: 66.3% (95% CI: 41.0–91.5), intermediate: 40.2% (26.7–53.7), high:21.0% (5.5–38.4) **Disease progression (=residual tumor on biopsy or imaging studies or any kind of additional treatment):** at 5 year: 48,4 %, time to disease progression:17.9 mo (IQR:10.4-26) The Disease progression free survival rate =73.5 for low risk, 46.0 for intermediate and 29.2 for high risk.	**Patient selection:** Well described **Patient flow:** Well described **Other:** • 12 patients with extracapsular invasion

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
		surgery: 31.2 ml (IQR: 24.2–38.7). Average preoperative PSA :8.7 ng/ml - percentage of patients with a PSA of 10–20: 24.6%, 20 or greater:16.4% Neoadjuvant hormone therapy, for a median duration of 3 mo (IQR:3–4) in 40.5% Preoperative MRI (n=108, 85.7%): extracapsular invasion in 9.5%, n=12) and seminal vesicle invasion (6.3%, n= 8) NCCN:intermediate: 51.6%,n =65 – high: 33.3%, n =42 TURP in 89.1% (n = 114)		**Significant prognostic factors for BCR and disease progression:** age, PSA nadir, time to PSA nadir and the NCCN,risk classification **Additional significant prognostic factor for disease progression:** BMI **Complications:** Complication % (n) Grade (n) *During the first 3-mth postoperative period* Pain 7.9% (10) GII (10)a Blood transfusion 0 Wound problem 0 Cardiovascular events 0.8% (1) GI (1)b Cerebrovascular events 0 Deep vein thrombosis 0 Bowel dysfunction 0 *During the whole follow-up period* Acute urinary retention 19.1% (24) GI (1), GII (23) Obstruction (urethra,	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				bladder neck) 15.9% (20) GI (1), GII (5), GIII (14)c UTI 3.2% (4) Epididymitis 2.4% (3) GII (3) Incontinence 30.9% (39) At the final evaluation 6.3% (8) GI (6), GII (1), GIII (1)e Impotence post HIFU 63.7%	

4.2. Hormone therapy in monotherapy

4.2.1. Evidence tables of systematic reviews on hormone therapy

None of the retrieved reviews fulfilled our criteria for inclusion. Therefore no systematic reviews were used for the description on the efficacy of hormone therapy.

4.2.2. Evidence tables of primary studies on hormone therapy

The lay-out of the evidence tables is slightly different compared to the evidence tables on HIFU, but no change was made in the content of the evidence tables and all subtitles were kept.

Table 14 – Evidence tables of primary studies on hormone therapy

Akaza (Japanese Prostate Cancer Study Group)[371-373](Akaza 2000, Akaza 2003, Akaza 2006) [371-373]	
Methods	
• **Design**	Prospective RCT
• **Source of funding and competing interest**	Not mentioned, but participating institutes listed.
• **Setting**	List of participating institutes (n=104), all located in Japan
• **Sample size**	N=178 enrolled in de study, n=151 used for analysis (group I n= 73, group II n=78)
• **Duration and follow-up**	Enrollment between February 1993 and March 1995, follow-up analysis at 2y, at 5y and at 10y
• **Statistical analysis**	Patient characteristics: Student's t-test or the Mann-Whitney U test (sign. 5%) Antitumor effects between groups: Mann-Whitney U-test (sign. 5%) Survival and progression-free survival: Kaplan-Meier method + log rank test and generalised Wilcoxon test (sign. 5%)
Patient characteristics	
• **Eligibility criteria**	Cancer stage: T1b, T1c, T2a, T2b, T3 + not scheduled for prostatectomy Serum testosterone level: at least 1 ng/ml Performance status: grade 0-3
• **Exclusion criteria**	Not clearly reported
• **Patient & disease characteristics**	• Follow-up at 5 years (median+ range) for both groups: 78 months (63-87)[372] (Akaza 2003) • Duration of hormone therapy (median + range) for both groups: 4.3y (0.1-11.0) (Akaza 2006) • Follow-up at 10 years (median+range) for both groups: 10.4y

	Group I (n=73)	**Group B (n=78)**
Age in years, mean	76.1 ±6.7	75.2±6.4
Clinical stage T1b,c T2a T2b T3	 9 13 20 31	 11 14 16 37
Histological differentiation Well Moderate Poor	 26 39 8	 27 38 13 (slightly more poorly differentiated tumors in group II)

	Pretreatment PSA level (ng/ml) Mean+SD Median (range)	 52.4±103.5 22.7(0.6-711)	 51.5±742.4 22.4 (0.8-6350)
Interventions			
• **Intervention group (Group I)**	LH-RH agonist monotherapy (leuprorelin acetate depot, 3.75mg monthly) Treatment after 2-year follow-up was subject to change according to physician or patient preference.		
• **Control group (Group II)**	LH-RH agonist (leuprorelin acetate depot, 3.75mg monthly) + steroidal antiandrogenic agent chlormadinone acetate (CMA) (100mg/day) Treatment after 2-year follow-up was subject to change according to physician or patient preference.		
Results			
• **Antitumor effects** = evaluated according to the 'General Rules for Clinical and Pathological Studies on Prostatic Cancer (2nd edition). Complete response: abnormal pretreatment PSA level returned to normal level (<1.98 ng/ml). Partial response: ≥50% improvement of abnormal pretreatment PSA level but not decreased to normal level. No change: <50% improvement or <25% aggravation of abnormal pretreatment PSA level. Progressive disease: ≥25% increase of abnormal pretreatment PSA level or normal pretreatment PSA level became abnormal level. Recurrence: identification of any of three clinical features, i.e. imaging findings confirming distant metastasis, an increase of PSA level by ≥25% of nadir values, or an indrease in prostate size by ≥25% of nadir values from bidimensional	• After 12 weeks of treatment (group I n=73 vs group II n=78)[371] o Complete response: 49.3% vs 49.3% o Partial response: 50.7% vs 49.3% o No significant differences between both groups • After 1 year of treatment in patn with complete response at 12 weeks (group I n=34 vs group II n=34)[371]: o Complete response: 28 (82.4%) vs 30 (88.2%) o Partial response: 1 vs 0 o Progressive disease: 0 vs 0 o Dropout: 5 vs 4 o No sign diff for complete response between both groups • After 1 year of treatment in patient with partial response at 12 weeks (group I n=35 vs group II n=34): (Akaza 2000) o Complete response: 9 (25.7%) vs 18 (52.9%) o Partial response: 19 vs 6 o Progressive disease: 0 vs 1 o Dropout: 7 vs 9 o Sign higher rate of improvement to complete response in group II (p<0.05) • After 2 years of treatment in patn with complete response at 12 weeks (group I n=34 vs group II n=34): (Akaza 2000) o Complete response: 21 (61.8%) vs 23 (67.6%) o Partial response: 0 vs 1	

measurements.	o Progressive disease: 0 vs 0 o Dropout: 13 vs 10 o No sign diff for complete response between both groups • After 2 years of treatment in patient with partial response at 12 weeks (group I n=35 vs group II n=34): (Akaza 2000) o Complete response: 4 (11.4%) vs 16 (47.1%) o Partial response: 12 vs 1 o Progressive disease: 0 vs 1 o Dropout: 19 vs 16 o Sign higher rate of improvement to complete response in group II (p<0.05) • At 5-year follow-up (group I n=73 vs group II n=78) (Akaza 2003) o Recurrence: 39 vs 23 with distant metastasis in 12 vs 11
• **Progression-free survival** = ?	• At 2-year follow-up (Akaza 2000) o Overall : Logrank test : p=0.0242; Wilcoxon test: p=0.1006; sign lower rate of recurrence in group II o Stratification by pretreatment clinical stage (Akaza 2000) ▪ T1b,c: 87% vs 87% ▪ T2a: 66% vs 57% ▪ T2b: 62% vs 91% ▪ T3: 43% vs 70% ➔ Sign lower rate of recurrence in group II for T2b patients • At 5-year follow-up (Akaza 2003) o Overall: 47% vs 68%; Sign better survival rate in group II (p<0.05)
• **Survival**	• At 2-year follow-up: (Akaza 2000) o Mortality in 5/73 vs 7/78 during study but no sign diff between both groups for cause-specific survival • At 5-year follow-up (Akaza 2003): 72% vs 64% o Mortality in 24/73 vs 26/78: prostate cancer death in 4 vs 6, other cancer death in 7 vs 3, not cancer death in 13 vs 17 o No sign diff with normal Japanese population • At 10-year follow-up (Akaza 2006): 41% (31-52)

	○ No distinction made between groups
• **Cause-specific survival rate**	• At 2-year follow-up: not mentioned • At 5-year follow-up: (Akaza 2003): 93% vs 89% • At 10-year follow-up: (Akaza 2006): 78% (67-88) ○ No distinction made between groups ○ Stratified per risk group: 86% (67-100) in low-intermediate-risk group, 91% (82-100) in high-risk group, 69% (52-85) in very-high-risk group ○ Stratified per age group: 73% (55-91) in <70y, 79% (65-93) in ≥70y ○ Metastasis-free survival rate: 58% (45-71) of which 83% (65-100) in low-intermediate risk group, 68% (42-95) in high-risk group and 44% (27-61) in very-high-risk group
• **Adverse events**	• At 2-year follow-up: (Akaza 2000) ○ Mild adverse drugs reactions (elevation of serum transaminase level, feeling hot or fatigue): 23/73 vs 21/78 ○ Severe adverse drug reactions: none • At 5-year follow-up: not mentioned • At 10-year follow-up: (Akaza 2006) ○ In 35 (23%): abnormal liver function tests in 6 (8.2%) vs 6 (7.7%), hot flashes in 3 (4.1%) vs 3 (3.8%), sweating in 4 (5.5%) vs 0, sexual dysfunction in 3 (4.1%) vs 1 (1.3%) ○ Mostly grade 1-2 (mild) adverse events
Limitations and other comments	
• **Limitations**	**Authors'conclusion**: (Akaza 2000) Treatment with LH-RH agonist produced a rapid improvement in PSA level but this improvement was maximized relatively early with monotherapy (group I) whereas long-term concomitant treatment with CMA (group II) yielded further PSA improvement. Also significantly fewer recurrences in group II patients were noticed, suggesting that concomitant use of CMA and LH-RH provides local control of prostate cancer. **Authors'conclusion**: (Akaza 2003) The present results suggest that primary hormonal therapy is useful in patients with T1b-T3 prostate cancer who are unsuitable for radical therapy. The combination of LH-RH agonist and CMA might have a more potent effect in decreasing testosterone than LHRH agonist monotherapy. **Limitations** (Akaza 2000, 2003) • Less results presented compared to 2-year follow-up • No stratification per cancer stage

- No info on number of patients at 5-year follow-up
- No info on choice of treatment after 2 years
- No info on drop-outs and reason for drop-outs
- No info on adverse events

Authors'conclusion: (Akaza 2006)

These results suggested that men on primary hormone therapy have a life expectancy similar to that of the normal population. However it is difficult to clearly conclude that life expectancy can be improved by primary hormone therapy. Men with localized prostate, treated with primary hormone therapy, who do not die from prostate cancer within 5 years of treatment, are likely not to die from prostate cancer in the subsequent 5 years. The present results suggest that, at least for older men, primary hormone therapy is a valid therapeutic option for localized or locally advanced prostate cancer.

Limitations (Akaza 2006)

- Comparison with another study (prostatectomy and neoadjuvant hormone therapy)
- Not all results are presented per study group
- No info on treatment after 2y of hormone therapy

Anderson 1980[395]	
Methods	
• **Design**	Prospective randomized controlled, open multicenters study
• **Source of funding and competing interest**	No information
• **Setting**	4 urology departments and 1 private practitioner in the Stockholm
• **Sample size**	Included patients: 263 but only 182 in this publication because observed for 2 years or longer
• **Duration and follow-up**	2 years or longer
• **Statistical analysis**	
Patient characteristics	
• **Eligibility criteria**	Biopsy proven highly or moderately differentiated PCa, stage II to IV (VACURG) Treatment was considered necessary
• **Exclusion criteria**	Poorly differentiated PCa (because involved in another trial) Other malignancies Severe liver damage Platelet count <100 000/mm³ Severe urinary tract infection
• **Patient & disease characteristics**	Mean age: no information

	Group A (n=88)	**Group B (n=94)**
Grade, %		
1	13.6	21.3
2	86.4	78.7
Stage		
II	46.6	44.7
III	22.7	22.3
IV	30.7	33.0

Interventions	
• **Intervention group**	Estramutine phosphate 840 mg/d orally, divided in 2 doses
• **Control group**	Polyestradiol phosphate 80 mg IM 1X/mo + 17-α-ethinylestradiol 2 mg/d for 2 weeks, then 150 µg/d.

Results	
• **Tumor regression**	• Reduction of the primary tumor estimated by rectal palpation, observed after 2 months in 64% in the estramustine group vs 53% in the estrogen group. • No stastitical difference between the 2 groups, neither with repect to frequency or rate of remission nor to the duration of remission. • No stastitical difference between the 2 groups, neither with repect to normalisation of PSA nor to later escape from normal values.
• **Adverse events**	• Withdrawal for adverse events in 27% in the estramustine group vs 21% in the estrogen group. • Approximately same pattern of adverse reaction in the 2 groups
Limitations and other comments	
• **Limitations**	Lack of many information **Authors' conclusion**: Estramustine offers no advantage over conventional type of estrogenic therapy.

Axcrona 2012 (Axcrona 2012, Axcrona 2012 (EUS) [393, 394]	
Methods	
• **Design**	Randomized, parallel-arm, active-controlled, open-label, multicentre study (GnRH antagonist degarelix vs LHRH agonist goserelin)
• **Source of funding and competing interest**	The principal author obtained a research grant from Ferring, Other authors are employees of the sponsor.
• **Setting**	Not mentioned
• **Sample size**	N= 201 enrolled in de study, n= 179 used for analysis (group I n= 82, group II n= 97)
• **Duration and follow-up**	Enrollment period not mentioned, follow-up analysis during 12 weeks
• **Statistical analysis**	Reduction in prostate volume reduction: ANCOVA Analyses per population: ITT, per protocol, full analysis set Non-inferiority if treatment difference in adjusted mean % reduction sign greater dan Δ=-10 points in both FAS en PP analysis (p=0.05) IPSS score: ANCOVA Responder rates: Wilcoxon two-sample test + logistic regression model QoL: polytomous regression analysis
Patient characteristics	
• **Eligibility criteria**	age >18years histological confirmed PCa (all stages) Patients suitable for ADT with a serum PSA level at screening >2 ng/mL; TPV >30 mL; a bone scan in the past 12 weeks; and an estimated life expectancy of at least 12 months. Patients who received at least one dose of the investigated drug and had at least one efficacy assessment after dosing were included in the full analysis set (FAS). The per-protocol (PP) population was obtained by excluding major protocol violators.
• **Exclusion criteria**	Previously received treatments for PCa, use of a urinary bladder catheter, treatment with a 5- α reductase inhibitor or botulinum toxin in the past 6 months, treatment with alpha-adrenoceptor blocker in the past 4 weeks, or planned radiotherapy during the trial.
• **Patient & disease characteristics**	• No sign difference in baseline variables between groups

	Group I (n=82)	**Group II (n=97)**	
Age in years, mean (SD)	71.9 (7.71)	73 (7.1)	p=0.30

Tumour stage, % Localised	 29	 33	 p=0.28
T-stage, % (n) T1-T2 T3-T4	 42,7 (35) 57.3 (47)	 43.3 (42) 56.7 (55)	 p=0.63
PSA level (ng/ml) Mean Median	 277 (937) 27.8 (1.9-6206)	 148 (438) 15.6 (3-2829)	 p=0.25
Testosterone level (ng/ml) Mean Median	 4.25 (1.88) 4.08 (0.32-10.8)	 4.43 (1.64) 4.33 (0.13-9.61)	 p=0.48
IPSS IPSS QoL	14.3 (6.91) 2.85 (1.62)	13.4 (7.36) 2.73 (1.66)	p=0.40 p=0.62
BPH Impact Index	5.06 (3.39)	4.58 (3.58)	p=0.36

Interventions	
• **Intervention group (group I)**	Starting dose of 240mg Degarelix (40mg/ml) (2x3ml injections)→ on day 28: 80mg Degarelix (20mg/ml, 1x4ml injection)→ on day 56: 80mg Degarelix (20mg/ml, 1x4ml injection)
• **Intervention group (group II)**	Goserelin implants (3.6mg) every 28th day On day 0: 50mg once-daily oral bicalutamide (flare protection) during first 28days
Results	
• **Testosterone level**	• Change in serum testosterone level over time: o Median level at week 4 (ng/ml): 0.05 (group I) vs 0.12 (group II) o Median level at week 8 (ng/ml): 0.05 (group I) vs 0.05 (group II) o Median level at week 12 (ng/ml): 0.05 (group I) vs 0.05 (group II) ➔ No sign diff between groups at each scheduled visit (weeks 4, 8, 12)
• **PSA level**	• Change in PSA level over time: o Decrease from baseline at week 4 (ng/ml): -80.6% (group I) vs -85.2% (group II) o Decrease from baseline at week 8 (ng/ml): -89.7% (group I) vs -96.6% (group II) o Decrease from baseline at week 12 (ng/ml): -92.0% (group I) vs -97.3% (group II) ➔ No sign diff between groups at each scheduled visit (weeks 4, 8, 12)
• **IPSS** = International Prostate Symptom Score questionnaire Mild LUTS: IPSS 1-7	• Change in IPSS over time o At baseline: IPSS score no inclusion criteria→ great variety (22.9% mild, 62.6% moderate, 14.5% severe LUTS) o Mean change over time: -4.4±0.7 (group I) vs -2.7±0.6 (group II)

Moderate LUTS: IPSS 8-19 Severe LUTS: IPSS 20-35 Clinically meaningful response: ≥3 points from baseline	➔ Progressive decreases from baseline in both groups ➔ Group I (degarelix) exceeded 3-points clinical threshold ➔ No sign difference in adjusted mean difference between groups (-1.2, 95%CI -2.9-0.4)(p=0.15) • Individual patient's benefit: o At week 4: 37.8% vs 23.7% (p=0.04) o At week 12: 61.0% vs 44.3% (p=0.02) ➔ sign more patn with clinically meaningful benefit (LUTS relief) in group I (degarelix) at week 4 and 12 • Independent predictors of clinically meaningful LUTS relief at week 4: o Age: advanced age associated with decreased probability of clinically meaningful IPSS response: OR 0.92, 95%CI: 0.89-0.95 (p<0.001) o BMI: High BMI associated with increased probability of clinically meaningful IPSS response: OR 1.15, 95%CI: 1.06-1.24 (p=0.001) o Log PSA: High log PSA associated with increased probability of clinically meaningful IPSS response: OR 1.23, 95%CI: 1.00-1.52 (p=0.05) • Independent predictors of clinically meaningful LUTS relief at week 12: o Degarelix use associated with increased probability of clinically meaningful IPSS response: OR 2.09, 95%CI: 1.11-3.96 (p=0.02) o High log PSA at baseline associated with increased probability of clinically meaningful IPSS response: OR 1.25, 95%CI: 1.03-1.52 (p=0.02) • IPSS score per LUTS group (no, mild, severe) o No to mild LUTS:-0.81±1.29 vs -0.40±0.71 (p=0.51) o Moderate LUTS:-4.52±0.79 vs -2.10±0.66 (p=0.028) o IPSS ≥13:-6.73±0.84 vs -4.02±0.97 (p=0.023) o Severe LUTS: -10.80±1.93 vs -9.57±2.70 (p=0.60) ➔ No sign between groups for no to mild LUTS ➔ In mild en ≥13: sign diff between groups + exceeded the 3-point threshold for clinical significance
• **QoL (related to urinary symptoms)** = separate 8th question of IPSS	• Change over time: (no crude data presented) o Sign improvement from baseline in both groups (p<0.001) o Relative decrease in reporting unhappy/terrible from baseline to week 12: similar in both groups o At week 12: increased (not sign) reporting of delighted or pleased in group I (degarelix) whereas group II reported more mostly satisfied/mixed/mostly dissatisfied

• **BPH Index** = Benign Prostate Hyperplasia Impact Index	• Change over time (from baseline to week 12): -1.28 vs -1.16 ➔ No sign differences between both groups
• **Adverse events**	• Treatment-emergent AEs: 39% vs 48% o Mild: 31% vs 35% o Moderate:20% vs 17% o Severe: 11% vs 2% ➔ No sign diff between groups for mild and moderate AEs ➔ Incidence severe greater in group II ➔ 35% of patn experienced AE possibly/probably related to drug • Most reported adverse drug reactions: o injection site reactions ➔ Only reported in group I o Hot flushes:10% vs 17% o Erectile dysfunction: 5% vs 4% o Hyperhidrosis: 4% vs 5%
Limitations and other comments	
• **Limitations**	**Authors' conclusion (**Axcrona 2012**)**: Prostate volume reduction was achieved to the same degree in both groups, but more pronounced effects on LUTS in degarelix group. **Limitations** o No sub- analyses per cancer stage or baseline PSA level **Abstracts**: Axcrona 2012 (summary of same results)

CS 21 (A) (Klotz 2008, Tombal 2010, Boccon-Gibod 2008, Crawford 2010, Damber 2009, Klotz 2010, Tombal 2009, Tombal 2009 (EUS), Tombal 2010 (RO), de la Rosette 2011, Crawford 2011, Crawford 2011, Crawford 2010, de la Rosette 2010, Iversen 2010, Persson 2010, Plekhanov 2010, Shore 2010, Shore 2011, Tombal 2011) [374-385, 387-392, 451, 452]	
Methods	
• **Design**	Three-armed, comparative, open-label, parallel-group phase III RCT of 12 months' duration (CS 21) After 12 months the participants from the leuprolide group were re-randomized to Degarelix 80mg or 160mg (CS 21A)
• **Source of funding and competing interest**	Ferring Pharmaceuticals, GlaxoSmithKline, Sanofi-Aventis, Johnson & Johnson, Amgen, Large Urology Group Practice Association, Society of Urologic Oncology, American Urological Association, AstraZeneca
• **Setting**	?
• **Sample size**	N= 807 enrolled in de study, n= 610 used for analysis (group I n= 207 , group II n= 202, group III= 201) (CS 21) N= 172 completed main trail and n= 134 were re-randomized to degarelix in extension trial (CS 21A) (group I CS 21A n= 65, group II CS 21A n=69)
• **Duration and follow-up**	Enrollment between February 2006 and October 2007, follow-up analysis during first 12 months (CS 21) After 1y, re-randomization in March 2007 and follow-up analysis during 3 months (CS 21 A)
• **Statistical analysis**	Effectiveness of degarelix: lower limit of the 95% CI for cumulative probability of testosterone being ≤0.5 ng/ml from 28 to 365days for degarelix was ≥90% + degarelix was not inferior to leuprolide for cumulative probability of testosterone levels being ≥0.5 ng/ml from 28 to 364 days. The non-inferiority margin for the difference between treatments was -10%. Endpoints were assessed in both intent-to treat and per protocol populations. Treatment response rate: based on the time to reach a testosterone level of ≤0.5 ng/ml from 28 to 364 days, estimated by Kaplan-Meier method. Response rate and 95% CI were calculated by log-log transformation of the survivor function. Differences between groups were assessed using a 97.5% CI calculated by normal approximation using pooled standard error. Power of study: detection with 90% power that lower limit of the 95% CI was no lower than 90% (effectiveness criterion 1) + with 200 patients per treatment group it was possible to show that degarelix was not inferior to leuprolide with >90% power. PSA progression-free survival rate: Kaplan-Meier method Overall survival: Kaplan-Meier method PSA recurrence: analysed by baseline disease stage and PSA level, Cox proportional hazards analysis adjusted for baseline disease stage and PSA level and log-rank test (unadjusted analysis)
Patient characteristics	
• **Eligibility criteria**	Men aged ≥18y with histologically confirmed adenocarcinoma of the prostate (all stages) for whom endocrine treatment was indicated Also patient included with an increasing PSA level after treatment with an curative intent (i.e. those with biochemical failure and with metastatic diseases (hormone-sensitive)

	Cancer stage: any stage Serum testosterone level: >1.5 ng/ml Eastern Cooperative Oncology Group score ≤2 PSA level ≥ 2 ng/ml
• **Exclusion criteria**	Neoadjuvant hormonal therapy Previous or current hormonal management of prostate cancer (at least discontinued >6 months for inclusion) Candidates for curative therapy
• **Patient & disease characteristics**	• CS 21 group I n= 207 vs group II n= 202 vs group III n= 201 o Age (median+ range): 72y (51-89) vs 72y (50-88) vs 74y (52-98) o PSA ng/ml (median+ 25-75 percentile) : 19.8 (9.4-46) vs 19.9 (8.2-68) vs 17.4 (8.4-56) o Stage of disease: localized n=69 (33%) vs n=59 (29%) vs n=63 (31%) • CS 21 A group I n= 69 vs group II n= 65 o Age (median+ range): 74.0y (52-98) vs 73.0y (52-92) o PSA ng/ml (median+ 25-75 percentile) : 0.4 (0.1-6.2) vs 0.4 (0.1-1.1) o Stage of disease: localized n=20 (29%) vs n=19 (29%)
Interventions	
• **Intervention group (Group I)**	Starting dose of Degarelix (240mg, 2x3ml injections)→ maintenance dose every 28days of 80mg Degarelix (1x4ml injection of 20mg/ml), n= 207
• **Intervention group (Group II)**	Starting dose of Degarelix (240mg, 2x3ml injections)→ maintenance dose every 28days of 160mg Degarelix (1x4ml injection of 40mg/ml), n= 202
• **Control group (Group III)**	Starting dose of Leuprolide (7.5mg, 1x1ml injection, TAP Pharmaceuticals)→ maintenance dose every 28days of 7.5mg Leuprolide (1x1ml injection, TAP Pharmaceuticals), n= 201 Bicalutamide (50mg tablet, once daily) could be administered at start of treatment for clinical flare protection (at discretion of investigator). After 1 year, patients were re-randomized to treatment with degarelix: (CS 21 A) - Starting dose of Degarelix (240mg, 2x3ml injections)→ maintenance dose every 28days of 80mg Degarelix (1x4ml injection of 20mg/ml), n= 69 - Starting dose of Degarelix (240mg, 2x3ml injections)→ maintenance dose every 28days of 160mg Degarelix (1x4ml injection of 40mg/ml), n= 65
Results	
• **Treatment response rate** = testosterone suppression, lower	ITT analysis (Klotz 2008) (group I n= 207, n= 202 responders; group II n= 202, n= 199 responders; group III n=201, n=194 responders) (% + 95% CI): 97.2% (95% CI 93.5-98.8) vs 98.3% (95% CI 94.8-99.4) vs 96.4% (95% CI 92.5-

limit of 95% CI of testosterone ≤0.5 ng/ml for degarelix was ≥90% from 28 to 364 days	98.2) PP population (Klotz 2008) (group I n= 207; group II n= 202; group III n=201): 97% vs 99.4% vs 96.3% (no 95% CI mentioned) o Predefined success criterion met: degarelix is not inferior to leuprolide Insufficient response rate (1x testosterone value of >1.0 ng/ml or 2 consecutive values of >0.5 ng/ml from 28 to 364 days) (Klotz 2008): in 12 patients (1.9% in group 1 vs 1.0% in group II vs 3.0% in group III)
• **PSA levels**	• **Change in median PSA levels over time** (Klotz 2008, Boccon-Gibod 2008, Crawford 2010, Damber 2009) o After 14days: declined from baseline by 64% (group I) vs 65% (group II) vs 18% (group III) o Sign decline in all groups between baseline and PSA level at 14 days (p<0.001) o After 28days: declined from baseline by 85% (group I) vs 83% (group II) vs 68% (group III) o At day 28: Proportion of patients with PSA <4 ng/ml was 59% (both degarelix groups) vs 34% (leuprolide group) (p<0.0001) o Sign decline in all groups between baseline and PSA level at 28 days (p<0.001) o At day 364: Proportion of patients with PSA <4 ng/ml was 83% (both degarelix groups) vs 78% (leuprolide group) (p=0.339) o Proportion of patients achieving PSA <4 ng/ml over time was similar in bot treatment groups but faster in degarelix groups • **PSA failure** (PSA increase of ≥50% from nadir and ≥5 ng/ml on 2 consecutive occasions at least 2 weeks apart) (Klotz 2008) o No differences between the three groups: 8.9% (group I) vs 14.2% (group II) vs 14.1% (group III) • **PSA recurrence** (Tombal 2010, Tombal 2009, Tombal 2009 (EUS), Tombal 2010 (RO)) - Incidence of PSA recurrence (n, %): 16 (7.7% (group I) vs 26 (12.9%) (group II) vs 26 (12.9%) (group III) o More frequently in leuprolide group (III) (p=0.05) - Probalibility of PSA recurrence (%, 95% CI): 8.9% (95% CI 5.5-14.1) (group I) vs 14.2% (95% CI 9.9-20.2) (group II) vs 14.1% (95% CI 9.8-20.1) (group III) - Subgroup analysis per baseline disease stage (degarelix 240/80 (I) mg vs leuprolide 7.5mg (III)) (n): 0 (group I) vs 2 (group III) for localized, 7 (group I) vs 6 (group III) for localized advanced, 8 (21.6%)(group I) vs 17 (36.2%)(group III) for metastatic o Mainly in patn with locally advanced or metastatic disease, but no difference between groups (p=0.156) - Subgroup analysis per PSA level (degarelix 240/80 (I) mg vs leuprolide 7.5mg (III)) (n): 0 (group I) vs 0 (group III) in PSA <10ng/ml, 0 (group I) vs 0 (group III) in PSA 10-20ng/ml, 2 (group I) vs 4 (group III) in PSA >20-50ng/ml, 14 (group I) vs 22 (group III) in PSA >50ng/ml

	o More frequently in patn with higher baseline PSA levels in both treatment groups o In patn with baseline PSA >20 ng/ml risk of PSA recurrence significantly lower in degarelix groups (p=0.04) but no difference in patn with baseline PSA >50ng/ml (29.2% vs 40.0%, p=0.10) • **Change in median PSA levels over time after switching from leuprolide to degarelix** (de la Rosette 2011, Crawford 2011, de la Rosette 2010, Persson 2010, Plekhanov 2010) Between day 3 and day 28: median PSA level of 0.5ng/ml or less o The ≥95% median reduction was maintained after switch and during first 84 days
• **Overall survival**	• Incidence of death (n,%) (Klotz 2008, Tombal 2010): 5 (2% (group I) vs 5 (2%) (group II) vs 9 (4%) (group III) o More frequently in leuprolide group (III) • Probability of death (%, 95% CI): 2.6% (95% CI 1.1-6.2) (group I) vs 2.9% (95% CI 1.2-6.8) (group II) vs 4.9% (95% CI 2.6-9.3) (group III)
• **PSA progression-free survival rate**	• After adjustment for baseline disease stage and PSA (CS 21)(Tombal 2010): hazard ratio of 0.664 (95% CI 0.385-1.146) • At median follow-up of 27.5months the PSA PFS hazard ratio had decreased significantly from 0.20 events annually in year 1 to 0.08 events annually after the switch (CS 21A) (chi-square test p=0.003) (Crawford 2011, Crawford 2011 abstract, Crawford 2010, Shore 2010, Shore 2011, Tombal 2011) o Comparable hazard ratio in continuous degarelix group (group I): 0.11 with 0.14 events annually (p=0.464) o Consistent effects of degarelix over time o Subgroup analysis per PSA level: (Crawford 2011) - in patients with baseline PSA level >20ng/ml PSA PFS hazard ratio from 0.38 events annually in y1 to 0.19 events annually after switch (chi-square test p=0.031) - Comparable hazard ratio in continuous degarelix group (group I): 0.23 with 0.23 events annually (p=0.988)
• **Adverse events**	• Treatment-emergent AEs in 79% (group I) vs 83% (group II) vs 78% (group III) (CS 21) (Klotz 2008, Boccon-Gibod 2008) o Mostly mild to moderate intensity, most reported was hot flushes (26% (group I) vs 26% (group II) vs 21% (group III)), musculoskeletal and connective tissue AEs sign higher in leuprolide group (26% vs 17% (both degarelix groups) p<0.05) o Comparable incidence and intensity of hot flushes in degarelix (240/80mg) vs leuprolide + switching from agonist to antagonist is not associated with increased rates of hot flushes (Iversen 2010) o Serious AEs in 21 (10% (group I) vs 24 (12%) (group II) vs 28 (14%) (group III) o Death in 5 (2%) (group I) vs 5 (2%) (group II) vs 9 (4%) in group III. None of death were considered

	related to study treatment. o Cardiovascular safety (Klotz 2010, Albertsen 2013): cardiac disorders in 9% (degarelix) vs 13% (group III) (p=0.089), no difference between groups for most frequently reported AEs (supraventricual arrhythmias (2 vs 4%), acute coronary syndromes (<1 vs 3%), coronary artery disease (2 vs 2%), cardiomyopathy (2 vs 2%) and atriocentricular conduction disturbances (<1 vs 1%) o Fatal CV-related events occurred in 1% vs 2% o Rates of CV adverse events were los and similar for degarelix and leuprolide • Treatment-emergent AEs in 86 (64%) in both switched-to-degarelix groups (CS 21 A) (de la Rosette 2011, de la Rosette 2010) o Most frequently reported were the injection site reactions (pain and eythema); n=40 (30%) vs none in main trial but incidence decreased in year 3 and 4 with similar levels in 2 groups o (first time reported) musculoskeletal and connective tissue AEs similar between degarelix and switched group (17% vs 20%, p=0.532) (Crawford 2011, Crawford 2010, Shore 2010) o Most reported ADT-related AEs (overall n=52, 39%) were hot flushes in n= 19 (14%) and weight increase in n=21 (16%) o No difference in ADT-related AEs between main trail (CS 21) and extension trial (CS21A) o Serious AEs in 7% (group I CS 21 A) and 8% (group II CS 21A) o At 4y follow-up: incidence of individual AEs was low in each group with no major differences between groups (Crawford 2011)
Limitations and other comments	
• **Limitations**	**Authors'conclusion (Klotz 2008)**: Both degarelix dose regimens achieved sustained testosterone suppression. Moreover both degarelix doses were at least as effective as leuprolide at inducing and sustaining testosterone suppression to castrate levels (≤0.5 ng/ml) throughout treatment period. The degarelix regimens induced a more rapid reduction of testosterone and PSA levels than leuprolide. Degarelix represents a new effective therapy for inducing and maintaining AD for 1 year in patients with prostate cancer. **Limitations** o Open-label: patn not blinded to treatment, could hamper the interpretation of reported AEs o Leuprolide dosage of 7.5 mg is standard in USA but in Europe lower dosage used o Administration of bicalutamide not standard care o Conflict of interest of authors (employees of sponsor) **Authors'conclusion (Tombal 2010)**: in the exploratory analyses, degarelix patients generally achieved more rapid PSA control compared with leuprolide, irrespective of baseline disease stage and PSA level. The difference in the 1-y study was most marked in those with metastatic prostate cancer of high baseline PSA levels.

Limitations

- Not all results clearly presented (mix of data and graphs)

Abstracts related to trial CS 21: Boccon-Gibod 2008, Crawford 2010, Damber 2009, Klotz 2010, Tombal 2009, Tombal 2009 (EUS), Tombal 2010 (RO)

*Damber 2012: subgorup analysis per baseline serum testosterone level, outcomes: PSA suppression, change in testosterone level and occurence of testosterone surges

Authors'conclusion (de la Rosette 2011): The 3-month analysis indicates that patients with prostate cancer can be safely switched from leuprolide to degarelix treatment. After switching effective suppression of testosterone (at castrate levels) and PSA are all maintained.

Limitations:

- No results per treatment group for all outcomes
- No data presented of continued degarelix treatment in group I and II (CS 21)

Authors'conclusion (Crawford 2011): Effective suppression of testosterone and PSA can be maintained for greate that 3 years in patients with prostate cancer receiving degarelix 240/80mg. In patients switched from leuprolide to degraleix testosterone and PSA suppresions were also maintained at consistent levels after 1 year. After switching from leuprolide to degarelix the PSA PFS hazard rate decreased significantly and the patient risk of progression in 1 year was more than halved (similar trend in patients with PSA >20 ng/ml). There was no significant change in hazard rate in patients who continued degarelix. These results support degarelix as first line ADT as an alternative to an GnRH agonist.

Limitations:

- Both groups after switch presented as one group→ no info on difference bewteen groups due to different dosage of degarelix
- Results presented in graphes not useful for ET, lack of all reported date in text

Abstracts related to trial CS 21A: Crawford 2011, Crawford 2010, de la Rosette 2010, Iversen 2010, Persson 2010, Plekhanov 2010, Shore 2010, Shore 2011, Tombal 2011

EORTC 30891 (Studer 2006, 2008, 2011 and 2013)[366-369]	
Methods	
• **Design**	Randomized controlled study, multicenters
• **Source of funding and competing interest**	Hoechst Company (now Sanofi). Publication supported by Fonds Cancer (FOCA) of Belgium.
• **Setting**	2 centers
• **Sample size**	**Recruitment target**: **Included patients:** 985
• **Duration and follow-up**	Recruitment period: Between February 1990 and January 1999 Follow-up: 12.8 y
• **Statistical analysis**	Intent-to-treat; The primary objective of the trial was to demonstrate noninferior overall survival with deferred ADT compared with immediate ADT; The initial design assumed a 5-year survival rate of 55% with immediate treatment. This assumption appeared overly pessimistic and in June 1997, an independent data monitoring Committee recommended increasing the sample size to 900 patients to provide 80% power (450 events) to rule out a ≥7% decrease from an assumed 65% 5-year survival rate (hazard ratio, 1.26) using a one-sided 5% significance level Log rank test for noninferiority. Kaplan-Meier or cumulative incidence; Cox or Fine and Gray models.
Patient characteristics	
• **Eligibility criteria**	Men ≤80y Recently (<105d) confirmed (histologically or cytologically) PCa, T0–4, N0–2 M0 Without previous local or systemic treatment (because refused by patient or because patient deemed unsuitable due to too far advanced local tumor or short life expectancy and/or severe comorbidities)
• **Exclusion criteria**	>80y Other malignancies (except adequately treated basal cell carcinoma of the skin Pain or ureteric obstruction caused by the prostate cancer, or proven iuxtaregional metastatic lymph nodes
• **Patient & disease characteristics**	Mean age: 73 years (range 52-81) Median PSA level (ng/ml):16

	Group A (n=492)	**Group B (n=493)**
Age in years, range (mean)	52-81 (73.0)	54-81 (73.0)
Associated chronic disease, % Cardiovascular	57.5 39.8	57.8 35.9

Respiratory	12.4	14.8
Other	24.6	26.0
Stage of disease, %		
T0	9.1	7.9
T1	9.3	8.5
T2	34.1	36.9
T3	41.1	41.2
T4	5.9	5.5
TX	0.4	0.0
Nodal status, %		
NO	78.7	76.9
N1	1.2	1.8
N2	4.5	3.9
NX/unknown	15.7	17.4
G category, %		
G0	0.0	0.2
G1	27.4	28.0
G2	51.4	46.5
G3	20.3	24.1
GX/unknown	0.8	1.2

Interventions	
• **Intervention group**	Immediate subcapsular orchiectomy (52%) or 2-monthly subcutaneous injections of a depot LHRH analog Buserelin 6.3 mg combined with an initial 2-wk antiandrogen treatment (50mg cyproterone acetate 3X/d)
• **Control group**	Same treatment but deferred until time progression (= new symptomatic metastases; increase in pain score; deterioration of WHO performance status; ureteric obstruction); only 34% patients were orchiectomied in the deferred group because LHRH treatment became more popular over time. Of the 493 patients in the deferred ADT arm, 8 (2%) received immediate ADT, 267 (54%) began deferred ADT after a median of 2.8 yr after entry into the study, and the remaining 267 patients (44%) never started ADT. After 7.8 yr only 50% of patients in the deferred ADT arm had initiated ADT treatment[369].
Results	

• **Time to objective progression**
= metastases or ureteric obstruction caused by PCa documented on imaging
	• At median FU 12.8y[369]:
	  • Time shorter in the deferred ADT arm: HR 1.62; 95%CI 1.32-1.99; p<0.0001
	  • Objective progression at 10y in 42% in the deferred group vs 30% in the immediate (>13%; 95%CI 6.5-18.7)

• **Overall survival**	• At median FU 7.8[453]: 54.9% died, with 35.7% from PCa
	  • 57.6% died in the deferred group vs 52.2% in the immediate group
	  • Mortality HR deferred vs immediate group 1.25; 95%CI 1.05-1.48
	  • **Survival benefit on immediate treatment remains significant** (HR 1.29; 95%CI 1.09-1.53) **when adjusting for baseline risk factors** (age, performance status, voiding symptoms, T-stage, tumor grade, PSA≥20 ng/mL, TURP, and associated chronic disease).
	• At median FU 12.8y[369]: 78% died, with 27% from PCa
	  • 80% died in the deferred group vs 76% in the immediate group
	  • Lower OS in the deferred group: HR: 1.21; 95%CI 1.05–1.39; p = 0.0085 (noninferiority test failed with p = 0.72)
	  • Largest difference at 10 yr when the excess mortality with deferred ADT amounted to 10% (overall mortality: 74%; 95%CI 69–78) in deferred ADT vs 64%; 95% CI 59–68 in the immediate ADT arm).

• **PCa mortality**	• At median FU 7.8[453]:
	  • No significant difference between the 2 groups due to limited statistical power.
	• At median FU 12.8y[369]:
	  • No statistical difference in PCA mortality between the 2 groups: HR: 1.05; 95%CI 0.83–1.33; p = 0.70) with 10-yr rates of 25% (95% CI 21–29) versus 23% (95%CI 21–29) for the deferred versus immediate ADT arms, respectively.

• **Time to castration-resistant progression after randomisation**	• At median FU 12.8y[369]: • No difference between the 2 groups
Limitations and other comments	
• **Limitations**	Not blinding No subgroup analyses according to T stage. Morbid population; competing causes of death PSA measurement often infrequent or irregular Deferred ATD started sometimes earlier than mandated by the protocol (with short difference in time between the start of immediate and deferred ADT and thus masked additional possible differences between the two treatment arms.) **Authors' conclusion** at median FU 12.8y[369,368]: Immediate ADT resulted in a modest but statistically significant increase in overall survival but no significant difference

	in prostate cancer mortality or symptom free survival. This must be weighed against the side-effects of lifelong androgen deprivation on an individual basis with the option of deferred treatment in a substantial number of patients.[368] **Immediate ADT benefits mainly the high-risk patients** who die from aggressive PCa within 5 yr after its diagnosis. For the other PCa patients, deferred treatment is safe and reduces significantly the time on ADT, if indeed required at all.[369]

EPC 3 trials (See 2001, See 2002, Wirth 2002, Wirth 2004, Fourcade 2003, Fourcade 2006, Iversen 2010, McLeod 2006) [352-359]

Methods

• **Design**	The bicalutamide EPC program comprises three randomized, double-blind, placebo-controlled, parallel-group, multicenter trials of an identical design to permit a planned pooled analysis (See 2001). Treatment randomization was conducted separately for each center. The blind was broken due to statistically significant differences in time to objective progression in the combined data and in Trials 24 and 25(Wirth 2002)
• **Source of funding and competing interest**	Astra-Zeneca
• **Setting**	See number of centres and countries involved below. No information available on the healthcare setting.
• **Sample size**	Recruitment target: 7500 patients (assuming a median time to progression and death of 7 and 10 years, respectively, for placebo-treated patients, it was calculated that the program will have 90%power to detect a 15–20% reduction in the rate of progression and overall survival with bicalutamide compared to placebo.) Included patients: 8113

Study	Recruitment target	Countries	Number of centers	Final recruitment
North American (Trial 23)	3000	USA, Canada	96	3292
CAPRx1 = (Trial 24)	3500	CAPRx1 3500 Australia, Austria, Belgium, Czech Republic, Eire, France, Germany, Holland, Hungary, Israel, Italy, Mexico, Poland, Portugal, S. Africa, Spain, UK	196	3603

	Scandinavian (Trial 25)	1000	Denmark, Finland, Norway, Sweden	61	1218
	Overall	7500	World-wide	353	8113

• **Duration and follow-up**	Recruitment period: Between August 1995 and July 1998 Follow-up: end analysis= 9.7 (0-12.87) and lost patients= 8.7% • At median FU 3y[353]: withdrawal from randomized treatment or death in 38.1% in bicalutamide group and 31.8% in the standard care alone group
• **Statistical analysis**	Intent-to-treat (See 2001) For Time-to-event data, Cox proportional hazards regression model, using covariates for trial, randomized treatment, primary treatment of curative intent, baseline PSA level, and tumour grade and stage. Each trial was designed and powered to detect a 15% reduction in the rate of progression for bicalutamide 150 mg compared with placebo (i.e. HR 0.85; 90% power; 5% two-sided significance) (Wirth EuroUroSup2002) The timing of the second analysis (FU 5.4 With 2004) was based on the accrual of sufficient deaths across the program to allow detection of a 15% decrease in the overall mortality rate (80% power, 5% 2-sided significance).
Patient characteristics	
• **Eligibility criteria**	Men > 18y (upper limit in Scandinavian study =75 years old) Histologically or cytologically confirmed non-metastatic (T1b-4M0) prostate cancer Absence of bony metastases confirmed by bone scan In the North American study, no lymph node metastases (N0) In the North American study, patients must have undergone therapy of primary curative intent (radical prostatectomy or radiotherapy), whereas in the other two studies, patients who were previously untreated and engaged in “watchful waiting” were also eligible. In all studies, it was specified that patients treated with curative intent had their radical prostatectomy or final session of radiotherapy within 16 weeks of randomization
• **Exclusion criteria**	Prior systemic therapy for prostate cancer with the exception of 5 a-reductase inhibitors. In the Scandinavian trial only, neoadjuvant hormonal therapy Patients with a serum bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 2.5 times the upper limit of normal, serious concomitant disease or a history of invasive malignancy In the Scandinavian study, if long-term therapy was considered inappropriate (i.e., if a patient had negative surgical margins and undetectable PSA following surgery).
• **Patient & disease characteristics**	Mean age: 66.9 years Stage tumor: T1-T2 (67.4%), T3 (31%) and T4 (1.5%), well balanced between the groups A & B Gleason score: <6 (66.4%) with a similar proportion in the 2 groups

N: N0 for the majority in the 2 groups (only 3.1% in two of the trials and none in the third trials had N1 disease confirmed)

Initial therapy: radical prostatectomy (54.9%), radiotherapy (17.7%), conservative therapy (28.2%), brachytherapy (0.6%) and other therapies (0.1%). The percentages of patients add up to more than 100% as a few patients had more than one therapy of primary curative intent.

Median PSA level (ng/ml): 7.1 in Trial 0.23, 11.7 in Trial 0.24, 16.1 in Trial 0.25

	Group A n=4052	**Group B n=4061**
Age in years, range (mean)	38-93 (66.9)	38-93 (66.9)
Initial therapy, %		
Radical prostatectomy	55.2	54.6
Radiotherapy	18.0	17.3
Brachytherapy	0.6	0.5
Other	0.1	0
None	27.5	28.9
Stage of disease, %		
T1/T2	67	68
T3	32	30
T4	2	2
Nodal status, %		
NO	60	59
Nx	38	39
N+	2	2
Tumour grade (Gleason score), %		
Well differentiated (2-4)	22	22
Moderately differentiated (5-6)	44	45
Poorly differentiated (7-10)	33	32

Interventions

- **Intervention group**

Bicalutamide 150 mg 1/d

Patients were assigned in a 1:1 ratio to receive either bicalutamide 150 mg tablets once daily or matching placebo tablets. Treatment commenced within 2 weeks of randomization. Patients were instructed to take the treatment once daily at approximately the same time each day.

Patients will continue to receive randomized therapy until completion of the treatment period (2 years in the North American study, otherwise >5 years) or until treatment failure (defined as death, adverse event requiring treatment cessation, clinical progression or need for additional systemic therapy or radiotherapy for prostate cancer). In the event of clinical progression, it is recommended that randomized therapy is discontinued and that patients are treated with appropriate therapy at the investigators' discretion.

• **Control group**	Placebo 1/d
Results	
• **Time to objective progression** **=number of days between the date of randomisation and the earliest sign of objective confirmed progression or death of any cause.** Based on symptomatic progression diagnosed by clinical criteria (presence of ureteric obstruction, lymphedema of the lower extremities, or recurrent vesical obstruction, bleeding or pain due to prostate cancer) and objective confirmation (by computed tomography, magnetic resonance imaging, etc.). Serum PSA levels are measured at each clinic visit, but PSA changes alone are not considered evidence of progression.	*Objective PFS reflects not only disease progression events but also deaths without evidence of disease progression. An aging population, as in the EPC, would be expected to be increasingly at risk from competing causes of death, and such deaths could tend to dilute the treatment effect for disease progression*[355]*.* • At median FU 3 y[354, 357]: o Risk of objective progression with bicalutamide vs placebo: 9.0% vs 13.8% for all stages, all trials o Reduction of the risk of progression: 42% for all stages, all trials (HR 0.58; 95%CI 0.51-0.66; p<<0.0001) ▪ For localised PCa T1-T2: HR 0.72; 95%CI 0.60-0.86; p<0.001 ▪ For localy advanced PCa T3-T4: HR 0.46; 95%CI 0.38-0.56; p<0.001 ▪ With WW: HR 0.53; 95%CI 0.44-0.64; p<0.0001 (but no statistical result for the subgroups PSA ≤4 and PSA 4-10 ng/ml). ▪ After RP: HR 0.63; 95%CI 0.50-0.80; p=0.001 ▪ After RT: HR 0.63; 95%CI 0.46-0.85; p=0.0024 o Reduction of the risk of developing bone metastases or dying within 2 years of randomisation[6,353]: 33%; RR 0.67; 95%CI 0.56-0.79; p<0.0001 • At median FU 5.4 y[355]: o Risk of objective progression with bicalutamide vs placebo: 19.7% vs 21.6% for all stages, all trials o Reduction of the risk of progression: 27% for all stages, all trials (HR 0.73; 95%CI 0.66-0.80; p<0.0001) ▪ With WW: HR 0.68; 95% 0.60-0.78; p<0.0001 • For localised PCa: HR 0.81; 95%CI 0.68-0.96; p=0.018 • For locally advanced PCa: HR 0.53; 95%CI 0.42-0.65; p<0.0001 ▪ After RP or RT: HR 0.77; 95%CI 0.67-0.87; p=0.00007 • For localised PCa T1-T2: HR 0.86; 95%CI 0.72-1.03; p=0.0971 • For localy advanced PCa T3-T4: HR 0.67; 95%CI 0.56-0.82; p=0.00005 o Relative increase in time to objective progression (ETR) ▪ With WW: HR 1.31; 95% 1.19-1.45; p<0.05 • For localised PCa: HR 1.16; 95%CI 1.03-1.32; p<0.05 • For locally advanced PCa: HR 1.58; 95%CI 1.35-1.86; p<0.05 ▪ After RP or RT: HR 1.22; 95%CI 1.11-1.35; p<0.05

	• For localised PCa T1-T2: HR 1.11; 95%CI 0.98-1.26; p<0.05 • For localy advanced PCa T3-T4: HR 1.37; 95%CI 1.18-1.61; p<0.05 • At median FU 7.4 y[356, 454]: o Risk of objective progression with bicalutamide vs placebo: 27.4% vs 30.7% for all stages, all trials o Reduction of the risk of progression: 27% for all stages, all trials (HR 0.79; 95%CI 0.73-0.85; p<0.001) ▪ With WW: • For localised PCa: no significant difference • For locally advanced PCa: HR 0.60; 95%CI 0.49-0.73; p<0.001) ▪ After RP or RT: • For localised PCa T1-T2: no significant difference • For localy advanced PCa T3-T4: significant difference showed in figure • At median FU 9.7y[358]: o Risk of objective progression with bicalutamide vs placebo: 37.4% vs 38.1% for all stages, all trials o Reduction of the risk of progression: 15.3% for all stages, all trials (HR 0.85; 95%CI 0.79-0.91; p=0.001) ▪ With WW: • For localised PCa: no significant difference: HR 0.93; 95%CI 0.82-1.06; p=0.261 • For locally advanced PCa: HR 0.67; 95%CI 0.56-0.80; p<0.001 ▪ After Adjuvant therapy (RP-RT): • For localised PCa: no significant difference HR 0.92; 95%CI 0.81-1.05; p=0.215 • For localy advanced PCa: HR 0.78; 95%CI 0.67-0.91; p=0.001; the improvement was significant for RT (p=0.001) but not for RP (p=0.065)
• **Overall survival**	• At median FU 3y[354, 357]: 6% died, with <2% due to PCa o No difference between the 2 groups because of few number of events: HR 0.93; 95%CI 0.79-1.11; p=0.43) • At median FU 5.4 y[355]: o No significant difference between the 2 groups: HR 1.03; 95%CI 0.92-1.15; p=0.58 ▪ With WW: HR 1.04; 95% 0.89-1.22; p=0.634 • For localised PCa T1-T2: HR 1.23; 95%CI 1.00-1.50; p=0.05 *(= reduction of survival, appearing to be due to an increase in nonprostate cancer deaths, without specific cause identified !)*

	• For locally advanced PCa T3-T4: HR 0.81; 95%CI 0.63-1.04; p=0.097 ▪ After RP or RT: HR 1.01; 95%CI 0.8-1.19; p=0.860 (no statistical result according to the PCa stage) • At median FU 7.4 y[356, 454]: 23% died, with 6.9% due to PCa o For localised PCa, no difference between the 2 groups, all or WW or after RP or RT o For locally advanced PCa, difference for RT only: HR 0.65; 95%CI 0.44-0.95; p=0.03; trend for WW:HR 0.81; 95%CI 0.66-1.01; p=0.06 • At median FU 9.7y[358]: 31% died, with 9% due to PCa o No significant difference between the 2 groups: HR 1.01; 95%CI 0.94-1.09; p=0.765 ▪ With WW: • For localised PCa: HR 1.15; 95%CI 1.00-1.32; p=0.054 • For locally advanced PCa: no significant difference: HR 0.89; 95%CI 0.74-1.07; p=0.206 ▪ After RP or RT: • For localised PCa: no significant difference HR 1.01; 95%CI 0.87-1.16; p=0.943 • For localy advanced PCa: no significant difference HR 0.93; 95%CI 0.78-1.10; p=0.386
• **PSA PFS**	• At median FU 3y[353]: o Reduction of PSA risk progression: HR 0.41; 95%CI 0.38-0.45; p<<0.0001
• **Adverse events** Details on adverse events are elicited using open questions at each clinic visit during randomized treatment and at 28 days after the cessation of randomized treatment.	Frequently reported with bicalutamide 150 mg vs placebo • At median FU 3y[354, 357]: o Gynecomastia (68% vs 8.3%) o Breast pain (74% vs 7.6%) o Impotence (9.0% vs 6.1%); Decreased libido (3.6% vs 1.9%) o Withdrawals due to adverse events (25.8% vs 8.1%) • At median FU 5.4 y[355]: o Gynecomastia (66% vs 7.8%) o Breast pain (73% vs 7.2%) o Impotence (9.2% vs 6.5%); o Urinary incontinence (7.1% vs 6.4%) o Withdrawal rates due to adverse events (28.7% vs 9.8%); overall withdrawal rates (51.5% vs 49.1%) with 100% in Trial 23 because randomized therapy was scheduled for 2 years only but patients are still being

	followed for objective progression and death. • At median FU 7.4 y[356, 454]: o Gynecomastia (69% vs 8.3%) o Breast pain (74% vs 7.6%) o Impotence (9.3% vs 6.5%); Decreased libido (3.6% vs 1.2%) o Withdrawals due to adverse events (29.3% vs 10.0%) • At median FU 9.7y[358]: idem than at median FU 7.4y.
Limitations and other comments	
• **Limitations**	In trial 23, patients with relative good prognosis and low tumour burden (no N+, no WW) **Authors' conclusion** at 9.7y[358]: "Bicalutamide 250 mg reduces the risk of disease progression in patients with locally advanced prostate cancer when compared with placebo, irrespective of the standard of care. **There is no benefit for PFS in patients with localised PCa treated with bicalutamide, compared with placebo."** **Authors' conclusion** at 9.7y[358]: "**There is no benefit for OS in patients with localised PCa treated with bicalutamide, compared with placebo; there is a survival trend in favour of placebo in the WW group**. A similar lack of efficacy was reported for other antiandrogens, including nilutamide 150 mg and flutamide 250 mg in patients with localised disease, suggesting that antiandrogen therapy might be an inappropriate treatment for patient with localised PCa".

EPC: SPCG-6 or Trial 25 (Iversen 2002, Iversen 2004, Iversen 2006) [360-362]	
Methods	
• **Design**	Randomized study, Double-blind, placebo-controlled, parallel-group, multicenter trials (Norway, Denmark, Sweden and Finland) The blind was broken due to statistically significant differences in time to objective progression in Trials 24 and 25. In the Trial 25, 3% of the population elected to break.
• **Source of funding and competing interest**	Astra-Zeneca (grant + statistical analysis)
• **Setting**	62 centres, in Norway, Denmark, Sweden and Finland. No information available on the healthcare setting.
• **Sample size**	1218
• **Duration and follow-up**	Recruitment period: Between October 1995 and July 1998 FU: minimum after 2 y, after 4.5y and after 6.7y at which a 22% mortality rate was anticipated • At median FU 3y[362]: withdrawal from randomized treatment or death in 31.9% in bicalutamide group and 47% in the standard care alone group • At median FU 5.3y[361]: withdrawal from randomized treatment or death in 52.6% in bicalutamide group and 69.3% in the standard care alone group • At median FU 7.1y[360]: withdrawal from randomized treatment or death = 100%
• **Statistical analysis**	The study was designed to have 80% power (5% two-sided significance) to detect a 30% reduction in the rate of progression for bicalutamide 150 mg compared with standard care alone (i.e. HR 0.70).
Patient characteristics	
• **Eligibility criteria**	Men 18-75 years old Clinical or pathological confirmed non-metastatic (T1b-4, any N, M0) prostate cancer Absence of bony metastases confirmed by bone scan Watchful waiting or previous curative treatment (radical prostatectomy or final session of radiotherapy within 16 weeks of randomization) Detectable PSA levels and/or positive margins if curative therapy
• **Exclusion criteria**	Prior systemic therapy for prostate cancer with the exception of 5 a-reductase inhibitors. Neoadjuvant hormonal therapy *(different from 2 other trials of the EPC)* If long-term therapy was considered inappropriate (i.e., if a patient had negative surgical margins and undetectable PSA following surgery) *(different from 2 other trials of the EPC)* Previous history or presence of malignancy other than PCa, or treated squamous/basal cell carcinoma of the skin within the past 10y Patients with a serum bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 2.5 times the upper limit of normal

	Any serious concomitant disease Treatment with a new chemical entity within the previous 3 months Patients at risk of transmitting any infection through the blood or other bodily fluids
• **Patient & disease characteristics**	Median Age: 68.5y Tumor stage: majority have T2-T3 (76.9%) and a Gleason score<7 (87.4%) Previous treatment: less than 20% have received therapy of primary curative intent.

	Group A n=607	**Group B n=611**
Age in years, range (mean)	46-87 (68.5)	52-77 (68.5)
Initial therapy, %		
Radical prostatectomy	12.7	12.4
Radiotherapy/brachytherapy	6.4	4.3
Watchful waiting	80.1	82.7
Other	0.8	0.7
Stage of disease, %		
T1	19.8	22.4
T2	39.7	38.1
T3	38.9	37.0
T4	1.5	2.3
Unknown	0.2	0.2
Nodal status, %		
NO	21.7	20.0
N+	4.6	4.3
Unknown	73.6	75.8
Tumour grade (Gleason score), %		
Well differentiated (2-4)	42.7	43.2
Moderately differentiated (5-6)	43.7	45.2
Poorly differentiated (7-10)	11.9	11.1
Unknown	1.8	0.5

Interventions	
• **Intervention group**	Bicalutamide 150 mg 1/d Patients were assigned in a 1:1 ratio to receive either bicalutamide 150 mg tablets once daily or matching placebo tablets. Treatment commenced within 2 weeks of randomization and continued until a treatment failure endpoint occured. Choice of second-line therapy was at the investigators' discretion.
• **Control group**	Placebo 1/d
Results	
• **Time to progression =number of days between the date**	Summary of the critical and important outcomes within and between groups: effect size (absolute risk reduction, relative risk (reduction), odds ratio) and its precision (p value, CI)

of randomisation and the earliest sign of objective confirmed progression or death of any cause. Using appropriate imaging techniques or time to death without prior progression. Changes in PSA level alone or clinical examination findings were not evidence of objective progression.	• At median FU 3y[362]: o Risk of objective progression with bicalutamide vs placebo: 16.3% vs 29.3% for all stages (majority based on bone scan findings (68%) o Reduction of the risk of progression: 57% for all stages (HR 0.43; 95%CI 0.34-0.55; p<<0.0001) o Withdrawal for disease progression (7.9% vs 27.6%) • At median FU 5.3y[361]: o Reduction of the risk of progression: 43% for all stages (HR 0.57; 95%CI 0.48-0.68; p<<0.0001) ▪ For localised PCa: HR 0.78; 95%CI 0.61-1.00; ▪ For locally advanced PCa: HR 0.40; 95%CI 0.31-0.52; o Withdrawal for disease progression (17.5% vs 38.8%) • At median FU 7.1y[360]: o Risk of objective progression with bicalutamide vs placebo: 48.3% vs 56.3% for all stages o Reduction of the risk of progression: 35% for all stages (HR 0.65; 95%CI 0.55-0.76; p<0.001) ▪ For localised PCa: no significant difference HR 0.85; 95%CI 0.69-1.06; p=0.15 ▪ For locally advanced PCa: HR 0.47; 95%CI 0.37-0.59; p<0.001
• **Overall survival**	• At median FU 3y[362]: 11.4% died, with 4.7% due to PCa o No difference between the 2 groups because of few number of events • At median FU 5.3y[361]: 26% died o No significant difference between the 2 groups: HR 0.99; 95%CI 0.79-1.23; p=0.93 ▪ For localised PCa: 21.7% died all causes: 25.6% vs 17.8% (HR 1.47; 95%CI 1.06-2.03); 8.8% vs 8.1% died from Pca ▪ For locally advanced PCa: 33.1% died all causes: 28.6% vs 37.6% (HR 0.68; 95%CI 0.50-0.92); 18.6% vs 24.5% died from Pca • At median FU 7.1y[360]: 39% died, with 19.8% vs 22.2% from PCa o No significant difference between the 2 groups: HR 0.91; 95%CI 0.76-1.09; p=0.31 ▪ For localised PCa: death all causes: 37.3% vs 31.4% (HR 1.23; 95%CI 0.96-1.58; p=0.11) 15.7% vs 13.4% died from Pca ▪ For locally advanced PCa: death all causes: 41.2% vs 52.4% (HR 0.65; 95%CI 0.50-0.85; p=0.001) 25.5% vs 34.9% died from Pca o For the subgroup of patients with WW (81.4% of the total trial population and 85.6% of the 480 deaths

	observed) ▪ For localised PCa: death all causes: HR 1.18; 95%CI 0.91-1.54; p=0.22 ▪ For locally advanced PCa: death all causes: HR 0.67; 95%CI 0.50-0.90; p=0.007 • At median FU 9.7y[358]: o For the subgroup of patients with WW ▪ For localised PCa: death all causes: HR 1.24; 95%CI 1.00-1.54; p=0.056 ▪ For locally advanced PCa: death all causes: HR 0. 76; 95%CI 0.59-0.98; p=0.031
• **PSA Doubling Time**	• At median FU 3y[362]: o Reduction of the risk of PSA doubling: 76% (HR 0.24; 95%CI 0.20-0.30; p<<0.0001)
• **Adverse events**	Frequently reported with bicalutamide 150 mg vs placebo • At median FU 3y[362]: o Gynecomastia (53.9% vs 2.6%) o Breast pain (61.3% vs 3.8%) o Impotence (16.0% vs 6.4%) o Withdrawal rates due to adverse events (15.7% vs 6.7%) • At median FU 5.3y[361]: o Gynecomastia (57.5% vs 3.1%) o Breast pain (63.3% vs 4.1%) o Impotence (16.9% vs 7.1%) o Withdrawal rates due to adverse events (19.7% vs 8.9%) • At median FU 7.1y[360]: o Gynecomastia (58.5% vs 3.1%) o Breast pain (63.6% vs 4.1%) o Impotence (17.4% vs 7.2%); decreased libido (3.8% vs 1.3%) o Withdrawal rates due to adverse events (20.7% vs 9.2%)
Limitations and other comments	
• **Limitations**	WW commonly recommended to a wide spectrum of patients (difference with trial 24 see below) **Authors' conclusion** at 7.1[360]: For patients with localised disease, the addition of bicalutamide to standard care results in **no difference in PFS.** For patients with locally advanced disease, bicalutamide in addition to standard care

	improved objective PFS." **Authors' conclusion** at 7.1[360]: For patients with localised disease, the addition of bicalutamide to standard care results in a trend towards decreased OS compared with standard care alone. The increased number of deaths in these patients appeared to be due to a number of small imbalances rather than a specific cause. In addition, no direct toxic effect on any organ system could be identified. **Bicalutamide should not be recommended in patients with localised disease.** For patients with locally advanced disease, bicalutamide in addition to standard care improved OS. "

EPC: Trial 24 (Wirth 2001, 2004 et 2007) [363-365]	
Methods	
• **Design**	Randomized study, Double-blind, placebo-controlled, parallel-group, multicenter trials (Europe, South Africa, Australia, and Mexico) A total of 12% of patients broke their blind. At median FU 7y[364], no patients were still receiving randomized therapy
• **Source of funding and competing interest**	Astra-Zeneca
• **Setting**	191 centres in non-Scandinavian Europe (n=2925), South Africa (n=394), Israel (n=193), Mexico (n=77) and Australia (n=14)
• **Sample size**	Recruitment target: On the basis of a minimum FU of 2y and an expected median PFS of 7y, the required sample size was 3500 patients (90% power; 5% two-sided significance). Included patients: 3603
• **Duration and follow-up**	Min FU of 2y. • At median FU 2.6y[365]: withdrawal from randomized treatment or death in 40.3% in bicalutamide group and 37.2% in the placebo group • At median FU 5.1y[363]: withdrawal from randomized treatment or death in 64.5% in bicalutamide group and 69.0% in the placebo group • At median FU 7y[364]
• **Statistical analysis**	Intent-to-treat. The trial was designed and powered to detect a 20% reduction in the rate of progression (i.e.hazard ratio 0.80) for bicalutamide compared with placebo.
Patient characteristics	
• **Eligibility criteria**	Men > 18y Clinical or pathological confirmed non-metastatic (T1b-4, any N, M0) prostate cancer Absence of bony metastases confirmed by bone scan Watchful waiting or previous curative treatment (radical prostatectomy or final session of radiotherapy within 16 weeks of randomization;)

- **Exclusion criteria**

Prior systemic therapy for prostate cancer with the exception of 5 a-reductase inhibitors.
Previous history or presence of malignancy other than PCa, or treated squamous/basal cell carcinoma of the skin within the past 10y
Patients with a serum bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 2.5 times the upper limit of normal
Any serious concomitant disease

- **Patient & disease characteristics**

Mean age: 69y

	Group A n=1798	**Group B n=1805**
Age in years, range (mean)	42-93 (68.6)	46-93 (68.7)
Initial therapy, %		
Radical prostatectomy	44.9	43.4
Radiotherapy	18.6	18.0
RP + RT	1.6	1.6
Watchful waiting	34.9	36.9
Stage of disease, %		
T1/T2	64.3	66.3
T3	33.2	31.2
T4	2.6	2.5
Nodal status, %		
NO	61.3	60.4
Nx	36.0	36.9
N+	2.6	2.7
Tumour grade (Gleason score), %		
Well differentiated (2-4)	31.0	31.2
Moderately differentiated (5-6)	40.5	41.1
Poorly differentiated (7-10)	26.7	26.1

Interventions

- **Intervention group**

Bicalutamide 150 mg 1/d
Patients were assigned in a 1:1 ratio to receive either bicalutamide 150 mg tablets once daily or matching placebo tablets. Treatment commenced within 2 weeks of randomization and continued until 5 years or until disease progression in patients with treatment of curative intent and until disease progression with no maximum duration in patients with WW.

- **Control group**

Placebo 1/d

Results

- **Time to progression**

=number of days between the date of randomisation and the earliest

- At median FU 2.6y[365]:
  - Risk of objective progression with bicalutamide vs placebo: 10.1% vs 16.2% for all stages
  - Reduction of the risk of progression: 43% for all stages (HR 0.57; 95%CI 0.48-0.69; p<<0.0001)

sign of objective confirmed progression or death of any cause.	▪ This benefit was numerically consistent of whether bicalutamide was given as adjuvant therapy of after WW and regardless of disease stage. • At median FU 5.1y[363]: o Risk of objective progression with bicalutamide vs placebo: 22.5% vs 28.1% for all stages o Reduction of the risk of progression: 27% for all stages (HR 0.73; 95%CI 0.64-0.83; p<0.0001) ▪ With WW: 32.0% vs 34.8% (HR 0.82; 95%CI 0.67-0.99; p=0.03) ▪ After RT or RP: 17.4% vs 24.2% (HR 0.66; 95%CI 0.55-0.79; p<0.0001) Authors' conclusion at median FU 5.1y[363]: The addition of bicalutamide 150 mg/day improves objective and PSA PFS, irrespectively of wther patient undergone WW or had adjuvant therapy. • At median FU 7y[364]: o Risk of objective progression with bicalutamide vs placebo: 31.4% vs 36.1% for all stages o Reduction of the risk of progression: 22% for all stages (HR 0.78; 95%CI 0.70-0.88; p<0.001) ▪ For localised PCa: HR 0.88; 95%CI 0.76-1.03; p=0.104 ▪ For locally advanced PCa: HR 0.66; 95%CI 0.55-0.79; p<0.001
• **Overall survival**	• At median FU 2.6y[365]: 7.2% died, with less than 2% from PCa; data too immature • At median FU 5.1y[363]: 18% died, 4.2% from PCa in group bicalutamide vs 5.6% in placebo group. • No difference between the 2 groups: HR 1.03 95%CI 0.88-1.20; p=0.75 • At median FU 7y[364]: 27% died, with 6.3% from PCa in bicalutamide group and 8.5% in placebo group • No difference between the 2 groups: HR 1.00 95%CI 0.88-1.24; p=0.95 • No significant difference between the treatment group for patient with localised PCa (25.7% vs 24.5% died) or locally advanced PCa (27.7% vs 30.8% died) Authors' conclusion: There was **no difference in OS** between bicalutamide and standard care alone.
• **PSA Doubling Time**	• At median FU 2.6y[365]: o Reduction of the risk of PSA doubling: HR 0.37; 95%CI 0.32-0.43; p<<0.001
• **PSA PFS**	• At median FU 5.1y[363]: • Reduction of the risk of PSA progression: HR 0.43; 95%CI 0.39-0.48; p<0.0001 ▪ With WW: HR 0.37; 95%CI 0.32-0.43; p<0.0001 ▪ After RT or RP: HR 0.48; 95%CI 0.41-0.55; p<0.0001 • At median FU 7y[364]:

	• Reduction of the risk of PSA progression: HR 0.51; 95%CI 0.46-0.56; p<0.001 ▪ For localised PCa: HR 0.55; 95%CI 0.49-0.62; p<0.001 ▪ For locally advanced PCa: HR 0.45; 95%CI 0.39-0.53; p<0.001)
• **Adverse events**	Frequently reported with bicalutamide 150 mg vs placebo • At median FU 2.6y[365]: o Gynecomastia (64.9% vs 7.4%) o Breast pain (65.1% vs 5.2%) o Impotence (8.0% vs 5.3%) o Withdrawal rates due to adverse events (24.5% vs 7.7%) • At median FU 5.1y[363]: o Gynecomastia (67.9% vs 8.4%) o Breast pain (66.3% vs 6.0%) o Impotence (8.4% vs 6.0%) o Withdrawal rates due to adverse events (29.4% vs 10.9%) • At median FU 7y[364]: o Gynecomastia (68.7% vs 8.4%) o Breast pain (66.3% vs 6.1%) o Impotence (8.4% vs 6.1%) o Withdrawal rates due to adverse events (30.6% vs 11.3%)
Limitations and other comments	
• **Limitations**	No analysis according the tumour stage but >64% T1-T2 and statistical interaction test suggesting that baseline prognostic factors, such as disease stage, did not influence the relative effect of bicalutamide on overall survival. WW reserved for patients with severe comorbidites, which is reflected in higher mortality from causes other than prostate cancer compared with the trial 25 and lead to a lower absolute risk of PCa mortality in Trial 24. The patients in the Trial 24 had a better PCa prognosis than in Trial 25 (lower median PSA level before randomisation). **Authors' conclusion** at median FU 7y[364]: **In the subgroup of localised PCa,** addition of bicalutamide to standard care provides **no significant benefit in terms of objective PFS or overall survival.** In the subgroup of locally advanced PCa, addition of bicalutamide to standard care improves objective PFS and PSA FPS but no overall survival.

Ishizuka 2013[396]	
Methods	
• **Design**	Multicenter, randomized, controlled study with an open-label, parallel group design to compare different doses of LH-RH agonists (goserelin)
• **Source of funding and competing interest**	Source of funding not mentioned, no conflict of interest declared.
• **Setting**	Hospitals in Japan (list available in appendix)
• **Sample size**	N= 120 enrolled in de study, n= 101 used for analysis (Switch group n= 47, Direct group n=54)
• **Duration and follow-up**	Enrollment between June 2007 and December 2010, follow-up analysis during 6 months (at 4, 8, 12 and 24 weeks)
• **Statistical analysis**	Suppression of serum testosterone: Student's t test to compare both groups PSA level: Student's t test to compare both groups Adverse events: chi square or Fisher's exact test to compare proportion of AEs between groups, incidence at 0-4 weeks, 5-8 weeks, 9-12 weeks, 13-24 weeks.
Patient characteristics	
• **Eligibility criteria**	Cancer stage: T3-4, NX, MX advanced prostate cancer or T1-2, N0 or M0 prostate cancer for whom other therapies were not selected Performance status: Eastern Cooperative Oncology Group Performance status of 0 or 1 Hematological parameters: white blood cell count of at least 3000/mm3, hemoglobin of more than 10.0 g/dL, platelet count of more than 7.5 9 104/mm3, aspartate aminotransferase (AST) of\2.5 9 upper limit of normal(ULN), alanine aminotransferase (ALT) of\2.5 9 ULN, alkaline phosphatase (ALP) of\2.5 9 ULN, and creatinine of\1.5 9 ULN at study entry
• **Exclusion criteria**	History of hormonal therapy (surgical and medical castration), chemotherapy, operative therapy or radiation therapy. Patient with following criteria were withdrawn from study: disease progression, any adverse event that, in the opinion of the physicians, justified the discontinuation of treatment; toxicity of Grade; or withdrawal of consent for participation by the patient.
• **Patient & disease characteristics**	Switch group(n=47) vs Direct group (n=54) o Age: 76.3 ±6.87y vs 75.0±5.97y (p=0.318) o Testosterone (ng/ml): 4.98±1.62 vs 5.07±1.76 (p=0.798) o PSA (ng/ml) (mean): 46.72 ±123.26 vs 52.37±85.62 (p=0.793) o Cancer stage (n): 34 (72.3%) vs 35 (64.8%) for T1-2; 12 (25.5%) vs 15 (27.8%) for T3; 1 (2.1%) vs 3 (5.6%) for T4; 0 (0%) vs 1 (1.9%) for TX (p=0.609) o Clinical stage (N) (n): 39 (83.0%) vs 45 (83.3%) for N0; 6 (12.8%) vs 6 (11.1%) for N1; 2 (4.3%) vs 3 (5.6%)

	for NX (p=0.817) o Clinical stage (M) (n): 35 (74.5%) vs 41 (75.9%) for M0; 10 (21.3%) vs 13 (24.1%) for M1; 2 (4.3%) vs 0 (0%) for MX (p=0.828) o Performance status ECOG (n): 44 (93.6%) vs 48 (88.9%) for score 0; 2 (4.3%) vs 6 (11.1%) for score 1; 1 (2.1% vs 0 (0%) unknown score (p=0.282) ➔ Small but not significant difference between groups
Interventions	
• **Intervention group (Switch group)**	The Switch Group was initially treated monthly with injections of a 1-month depot of goserelin acetate (LHRH agonist) (Zoladex 3.6 mg depot; AstraZeneca, Osaka, Japan) for 3 months →then switched to a 3-month depot (Zoladex LA 10.8 mg depot). (n=47) Supplemented with orally administered anti-androgen agent bicalutamide (Casodex 80mg; AstraZeneca) once daily during treatment period.
• **Intervention group (Direct group)**	In the Direct Group, the 3-month depot of goserelin acetate (LHRH agonist) (Zoladex LA 10.8 mg depot) was administered at the start of the treatment and then again 3 months later. (n=54) Supplemented with orally administered anti-androgen agent bicalutamide (Casodex 80mg; AstraZeneca) once daily during treatment period.
Results	
• **Suppression of serum testosterone to castration level** = serum testosterone level of ≤0.5 ng/ml	• At week 4 (compared to baseline) o Switch group: from 4.98±1.62 ng/ml to 0.13±0.08 ng/ml (p<0.001) o Direct group: from 5.07±1.76 ng/ml to 0.17±0.19 ng/ml (p<0.001) ➔ Sign drop in both groups (compared to baseline levels) ➔ No sign difference between groups (p=0.189) • At week 8 o Switch group: 0.08±0.04 ng/ml o Direct group: 0.09±0.06 ng/ml ➔ Testosterone levels remained ≤0.2 ng/ml in both groups ➔ No sign difference between groups (p=.262) • At week 12 o Switch group: 0.08±0.04 ng/ml o Direct group: 0.11±0.11 ng/ml ➔ Testosterone levels remained ≤0.5 ng/ml in both groups ➔ No sign difference between groups (p=.056)

	• At week 24 o Switch group: 0.11±0.06 ng/ml o Direct group: 0.10±0.06 ng/ml ➔ Testosterone levels remained ≤0.5 ng/ml in both groups ➔ No sign difference between groups (p=.668)
• **PSA levels & normalization rate** = PSA levels <4.0ng/ml	• At week 4 (compared to baseline) o Switch group (n=46): from 46.72±123.26 ng/ml to 8.99±34.19 ng/ml o Direct group (n=49): from 52.37±85.62 ng/ml to 8.53±20.62 ng/ml ➔ No sign difference between groups at 4 weeks (p=0.937) • At week 8 o Switch group (n=46): 4.60±21.99 ng/ml o Direct group (n=50): 2.18±5.99 ng/ml ➔ No sign difference between groups at 8 weeks (p=0.454) • At week 12 o Switch group (n=46): 2.26±8.97 ng/ml o Direct group (n=48): 1.34±4.38 ng/ml ➔ No sign difference between groups at 12 weeks (p=0.528) ➔ % of patn with PSA level <4.0ng/ml: 93.5% (43/46) vs 95.8% (46/48) • At week 24 o Switch group (n=40): 1.01±4.44 ng/ml o Direct group (n=48): 0.91±3.02 ng/ml ➔ No sign difference between groups at 24 weeks (p=0.902) ➔ % of patn with PSA level <4.0ng/ml: 95.0% (38/40) vs 95.8% (46/48)
• **Adverse events** = evaluated by National Cancer Institute Commonn Terminology Criteria for Adverse Events (all grade 1 or greater were reported)	• At week 0-4 o Switch group (n, %): 25/47 (53.2%) o Direct group (n=50): 31/54 (57.4%) ➔ No sign difference between groups at 0-4 weeks (p=0.671) • At week 5-8 o Switch group (n, %): 9/47 (19.1%)

	o Direct group (n=50): 5/54 (9.3%) ➔ No sign difference between groups at 5-8 weeks (p=0.151) • At week 9-12 o Switch group (n, %): 3/47 (6.4%) o Direct group (n=50): 4/51 (7.8%) ➔ No sign difference between groups at 9-12 weeks (p=0.999) • At week 13-24 o Switch group (n, %): 0/42 (0.0%) o Direct group (n=50): 2/51 (3.9%) ➔ No sign difference between groups at 13-24 weeks (p=0.499) ➔ More adverse events in weeks 0-4 than in any other period, from week 5 gradually decrease in both groups ➔ Majority were grade 1-2 adverse events
Limitations and other comments	
• **Limitations**	**Authors' conclusion (**Ishizuka 2013**)**: This study has shown that the efficacy and safety of the 3-month depot of goserelin acetate are comparable with that of the 1-month depot. The adverse events leading to treatment discontinuation were considered to be associated with bicalutamide. Immediately after treatment initiation, patients should be monitored for adverse events. The benefit of reduced hospital visits using 3-month depot will be lost due to the closer monitoring for adverse events. **Limitations** o No blinding of participants and assessors o No subgroup analysis per baseline PSA level or cancer stage (bur majority are T1-2)

Lundgren 1995[370]	
Methods	
• **Design**	Randomized controlled, open multicenters study
• **Source of funding and competing interest**	No information
• **Setting**	5 urological or surgical clinics in the southern part of Sweden
• **Sample size**	Included patients: 285
• **Duration and follow-up**	Start in November 1978 and end of randomization in July 1984 Follow-up until August 1993 (180mo)
• **Statistical analysis**	Kaplan-Meier; Cox.
Patient characteristics	
• **Eligibility criteria**	Well or moderately well differentiated PCa, stage I to III (VACURG), T0a-T3, NX, M0 Previoulsy untreated PCa
• **Exclusion criteria**	Other malignancies Previous or present cardiovascular disease
• **Patient & disease characteristics**	Mean age: 70 years (range 52-90)

	Group A (n=66)	Group B (n=74)	Group C (n=88)
Age in years,			
<65	25.7	17.6	22.7
65-70	16.7	27.0	26.1
71-75	33.3	32.4	30.7
>75	24.2	22.9	20.5
Tumor differentiation, %			
Well	69.7	71.6	68.2
Moderately well	30.3	28.4	31.8
Stage of disease, %			
T0a	27.3	22.9	20.5
T0b	18.2	17.6	18.2
T0x	3.0	1.3	1.1
T1	18.2	9.5	15.9
T2	27.3	35.1	35.2
T3	6.1	13.5	9.1

Interventions	
• **Intervention group**	Polyestradiol phosphate IM 80 mg every 4 weeks + ethinyloestradiol 50 µg 3X/d (Group A); stop in 1983 because of a high frequency of cardiovascular disease; instead Polyestradiol phosphate IM 80 mg every 4 weeks alone (Group D) but with only 13 patients and not considered in the calculations. Or Estramustine phosphate 280 mg 2X/d (Group B)
• **Control group**	Deferred endocrine treatment at progression to symptomatic or metastatic disease (Group C)
Results	
• **Time to objective progression** = metastases or poorly differientiated PCa, local progression with occurences of severe local pains and/or ureteral dilatation remaining after TURP or indwelling catheterization.	• Time shorter in the estramustine phosphate and the polyestradiol phosphate + ethinylestradiol groups compared to the deferred treatment group: p<0.0001
• **Metastasis-free survival** = interval from randomisation to appearence of metastatic disease, diagnosed by a skeletal scintigram or, in addition after withdrawal from the study, by a significant increase of PSA (>80 µg/l)	• No significant difference among the 3 groups in interval to development of metastases (p=0.07)

• **Causes of death and survival time**	• 56% patients died, with 20% from PCa
	  • Significantly more patients died from PCA in the deferred group (28%) than in the estramutine phosphate (18%) and the polyestradiol phosphate + ethinylestradiol groups (12%)
	  • In patients with well differentiated cancer, polyestradiol phosphate + ethinylestradiol groups seemed better than estramustine phosphate: risk ratio=0.54, p=0.07
	  • In patients with moderately well differentiated cancer, estramustine phosphate seemed to be related to a lower risk of dying of PCa compared to polyestradiol phosphate + ethinylestradiol groups: risk ratio=1.93; p=0.14
	  • No difference in overall survival (p=0.48)

Limitations and other comments	
• **Limitations**	Not blinding Imbalance in T stage between groups Low power of the study due to the low number of events (a total of 700 to 1500 patients is needed to achieve a power of 80%) Exclusion of patients with cardiovascular disease and thus more risk of dying of PCa **Authors' conclusion**: "Patients with moderately well differentiated cancer (stage>T0a) who received early treatment with estramustine phosphate had the lowest risk of metastases or death from PCa, while those with well differentiated cancer (stage>T0a) did best on early polyestradiol phosphate + ethinylestradiol treatment.

SPCG-7[401, 402]	
Methods	
• **Design**	Open randomized study, multicenters
• **Source of funding and competing interest**	Grants from Schering-Plough and Abbott Scandinavia. Funding has also been provided from the Nordic Cancer Union, Swedish Cancer Society (070604), Norwegian Cancer Society, Lions Cancer Foundation, and Umeå University.
• **Setting**	47 centres (Norway, Sweden, and Denmark). No information available on the healthcare setting.
• **Sample size**	**Recruitment target**: 660 patients (to provide a statistical power of 80% to detect an increased cause-specific survival of 10% after 7 years of FU in the endocrine+radiotherapy group compared with 65% in the endocrine group. In a blinded analysis of 716 enrolled patients by an independent Committee in February, 2002, the overall mortality was lower than anticipated. Therefore, the study steering board decided to extend the target sample size to 880 patients to achieve a total of 198 PCa deaths after 7 years of FU. In February, 2008, after a median follow-up of 7·6 years, the total number of PCa deaths was 116) **Included and analysed patients: 875** **Side study on 120 patients[401]**
• **Duration and follow-up**	Recruitment period: Between February 1996 and December 2002 Median FU: 7.6y (range 0.2-11.9)[402]
• **Statistical analysis**	Intent-to-treat; cumulative incidence for each point; Gray's test; RR based on Cox proportional-hazards model.
Patient characteristics	
• **Eligibility criteria**	Men <76y Good performance status Life expectancy >10 years Histological-proven prostate cancer, categorised as clinical T1b–T2, G2–G3, or T3 (TNM-classification 1992), any

WHO Grade 1–3
PSA ≤ 70 ng/mL
No evidence of metastases as determined by bone scanning and pulmonary radiography.

- **Exclusion criteria**: N+
- **Patient & disease characteristics**: Baseline demographics and clinical characteristics balanced between the groups[402]

	Group A (n=439)	Group B (n=436)
Age in years, mean (SD)	66.2 (5.1)	65.7 (5.5)
Initial therapy, %		
Radical prostatectomy	55.2	54.6
Radiotherapy	18.0	17.3
Brachytherapy	0.6	0.5
Other	0.1	0
None	27.5	28.9
Stage of disease, %		
T1b	0.2	0.5
T1c	1.6	2.1
T2	18.9	19.7
T3	79	76.8
Unknown	0.2	0.9
WHO grade, %		
I	15	14.9
II	64.5	66.3
III	19.1	18.3
Unknown	1.4	0.5

Interventions

- **Intervention group**: Total androgen blockade with Leuprorelin (3.75 mg a month or 11.25 mg every 3 months), for 3 months + simultaneously, flutamide 250 mg 3X/d.

  After 3 mo of total androgen blockade, continued flutamide until progression or death.

  When antiandrogen treatment side-effects were evident, flutamide was stopped and then reinstituted with stepwise increased dose to at least 500 mg. If this treatment failed, antiandrogen was changed to bicalutamide (150 mg once a day). 80% of all patients received breast irradiation to prevent gynecomastia. After the first publication of the SPCG-6 data in 2002, the addition of leuprorelin was allowed before clinical progress when the PSA level was more than 10 µg/mL.

- **Control group**: After 3 months of the same treatment as above, patients in the endocrine plus radiotherapy group started radiotherapy (total dose minimum 70 Gy).

Results

• **Cancer specific survival**
= time from randomisation to death from PCa or death from another cause with PCa as a signifi cantly contributing factor; deaths from other causes = censoring events.
	• At 7y[402]:
	  • 18.0% vs 8.5% patients died of PCa
	  • Cumulative incidence for cancer-specific mortality: 9.9% (95%CI 7.1-12.8) vs 6.3% (3.9-8.6); difference 3.7% (0.0-7.4)
	• At 10y[402]:
	  • Cumulative incidence for cancer-specific mortality: 23.9% (95%CI 18.4-29.4) vs 11.9% (95%CI 7.4-16.5); significant difference 12.0% (4.9-19.1); RR 0.44 (0.30-0.66); p<0.001 in favour of endocrine+RT group
	  • **Subgroup analyse stratified by T stage**, PSA level, and inclusion age uniformly revealed decreased 10-year cumulative incidence of prostate-cancer-specific mortality in the radiotherapy group. In particular, this decrease was evident in patients with T1b–T2 tumours, where the mean absolute risk reduction was 16·0% (95% CI 3·7–28·2)

• **Overall mortality**
= time from randomisation to death irrespective of cause
	• At 7y[402]:
	  • Cumulative incidence for overall mortality: 20.1% (95%CI 16.2-23.9) vs 16.5% (12.9-20.1); difference 3.6% (-1.7-8.8)
	• At 10y[402]:
	  • Cumulative incidence for overall mortality: 39.4% (95%CI 33.0-45.7) vs 29.6% (95%CI 23.3-36.0); significant difference 9.8% (0.8-18.8); RR 0.68 (0.52-0.89); p=0.004 in favour of endocrine+RT group.
	Authors' conclusion: The endocrine treatment plus radiotherapy resulted in a substantial reduction in prostate cancer mortality. This significant difference, which at 10 years reached 12%, also translated into improved diff erence in OS (9·8%).

• **PSA recurrence**
= the time from randomisation to first occurrence of a PSA recurrence or death from prostate cancer; PSA progression = untill 2006, an increase in PSA on 2 consecutive measurements with at least 1 month between them. After 2006= an increase of PSA of 2 ng/ml or more above nadir.
	• At 7y[402]:
	  • Cumulative incidence of PSA recurrence: 71.1% (95%CI 66.3-75.9) vs 17.6% (13.6-21.5); difference 53.5% (47.3-59.7)
	• At 10y[402]:
	  • Cumulative incidence of PSA recurrence: 74.7% (95%CI 69.6-79.8) vs 25.9% (95%CI 19.3-32.6); significant difference 48.8% (40.4-57.2); RR 0.16 (0.12-0.20); p<0.001 in favour of endocrine+RT group

• **Quality of life** **= EORTC QLQ-C30 questionnaire**	• According to the doctor-assessed moderate and severe side-effects at 5-year follow-up compared with baseline: Significantly more patients in the endocrine + RT group had urinary incontinence, urgency, urethral stricture, and erectile dysfunction[402]

	• No significant difference in global health and quality of life score was seen 4 years posttreatment.

• **Biopsy result in 117 patients (side study)**	• After FU of 101.5 mo[401]:
	  • Residual cancer in 66% vs 22% (p<0.0001); mainly poorly differenciated (Gleason score ≥8)
	  • In logitic regression analysis, significant predictors of residual PCa= endocrine therapy alone (OR 7.49; 95%CI 3.18-17.7; p<0.0001), and baseline PSA (OR 1.03; 95%CI 1.0-1.07; p=0.044)
	Authors' conclusion: Patients receiving endocrine therapy alone had a threee times higher incidence of local residual PCa (biopsie-verified) than dit patients receiving combined therapy[401]

Limitations and other comments	
• **Limitations**	No blinding Few localised PCa No high dose of radiotherapy, as now Change in PSA measure during the study period. **Authors' conclusion**: "Compared with endocrine treatment alone, the addition of definitive prostate radiotherapy reduces the 10-year cancer-specific and overall mortality by 12·0% and 9·8%, respectively, in non-metastatic prostate cancer patients with locally advanced tumours or tumours that are prostate-confined but with aggressive histology. The quality of life and adverse effect profile is acceptable. We therefore suggest that endocrine treatment plus radiotherapy should be the new standard of care for these patients"[402]

Tunn 2009[397]	
Methods	
• **Design**	Randomized, open-label, European multicentre, three-armed study (LHRH agonist leuprorelin)
• **Source of funding and competing interest**	Not mentioned
• **Setting**	42 centres in Germany, Austria and Poland
• **Sample size**	N= 296 enrolled in de study, n= 296 used for analysis (group I n= 58, group II n= 118?, group III n= 120)
• **Duration and follow-up**	Enrollment between and, follow-up analysis during 12 months
• **Statistical analysis**	Demographic and baseline characteristics: descriptive statistics Progression: chi squared test. No adjustment for multiple tests and tests were not pre-specified. Clinical assessment: intention-to-treat population (all patn with at least one injection of study medication and at least one efficacy assessment after the first injection)

Patient characteristics	
• **Eligibility criteria**	Men with newly diagnosed prostate cancer or PSA relapse after radiotherapy or radical prostatectomy Patn aged 18-85y with histologically confirmed prostate cancer of any grade and stage requiring endocrinological castration with a life expectancy of >12 months and WHO performance status 0-3 For patients who had not received prior hormonal therapy, testosterone and PSA levels at screening were required to be ≥150ng per 100 ml and ≥1ngml^{-1}, respectively. For patients who had received an LHRHa for <3 months, testosterone level was to be <80 ng per 100 ml before randomization.
• **Exclusion criteria**	Prior orchiectomy, cytostatic treatment or prostate cancer or any other cancer within 6 months before study entry, prior hormonal treatment of prostate cancer for >3 months and hormone refractory prostate cancer.
• **Patient & disease characteristics**	Group I (n=58) vs group III (n= 120) - Age (mean): 72.9±5.6 vs 73.6±6.2 - PSA level (ng/ml) (median): 1.5 vs 1.1 - WHO performance scale: 63.8% vs 60.8% for scale 0; 31.0% vs 30.8% for scale 1; 5.2% vs 7.5% for scale 2; 0% vs 0.8% for scale 3 - Tumour stage at study entry: 82.8% vs 85.8% newly diagnosed; 12.1% vs 10.0% PSA relapse post-radical prostatectomy; 3.4% vs 1.7% PSA relapse after radiotherapy; 1.7% vs 2.5% others - Time since first tumour diagnosis in patn with PSA relapse (months, median): 25.8 (2-160) vs 47.9 (1-148) - Cancer stage: not reported ➔ Well balanced with regard to WHO performance status (majority scale 0-1), 21% of patn had previously received treatment with LHRH
Interventions	
• **Control group (group I)**	Four injections of the 3M depot of 11.25mg leuprorelin acetate at intervals of 3 months (baseline, months 3, 6 and 9);
• **Intervention group (group II)**	Two injections of a 6M depot containing 22.5mg leuprorelin acetate at baseline and month 6→ will not be reported, only 6M 30mg depot selected for submission for approval in European countries
• **Intervention group (group III)**	Two injections of a 6M depot of 30mg leuprorelin acetate at baseline and month 6
Results	
• **Progression** = objective response based on EORTC criteria	EORTC response criteria: o Complete remission: not seen in either group o Partial remission: 46.6% (group I) vs 50.8% (group III) o Objective stabilization: 46.6% (group I) vs 34.2% (group III) o Objective progression: 3.4% vs 9.2% at any point during study conduct o No data for 3.4% (group I) and 5.8% (group III) ➔ No difference between groups in terms of EORTC response criteria

	➔ No statistically sign difference in progression rate between groups (p=0.1570) ➔ At 12 months: more than 90% of patn in both groups had not progressed
• **Suppression of serum testosterone to castration level** = serum testosterone level of ≤0.5 ng/ml on 2 consecutive occasions (EORTC response criteria)	Median testosterone level (ng/ml) over time (between 1 month and 12 months) (range): 0.12 to 0.15 (group I) vs 0.12 to 0.15 (group III) ➔ no sign differences between both groups (p-value not mentioned) Response rate by time point at month 12 (=response at month 12 if testosterone levels were ≤0.5 ng/ml): - 42/42 (100%) (group I) vs 96/98 (98%) (group III) - If all measured testosterone levels from month 1 to 12, response rate by time point at month 12: 1257/1310 (96%) (group I) vs 565/602 (94%) (group III) Serum testosterone levels (≤0.2 ng/ml): 81% (group I) vs 90% (group III)
• **PSA levels & normalization rate** = PSA levels <4.0ng/ml	Median PSA level (ng/ml) - At baseline: 1.5 (group I) vs 1.1 (group III) - At month 12: decrease of 88% (group I) vs 89% (group III) ➔ No sign differences between both groups (p-value not mentioned) - Range from month 1 to month 12: 1.0 to 0.2 ng/ml (group I) vs 1.1 to 0.3 ng/ml (group III)
• **Performance status** = Eastern Cooperative Oncology Group/World Health Organization performance status	• At baseline: 63.8% (group I) vs 60.8% (group III) for grade 0; 31.0% (group I) vs 30.8% (group III) for grade 1 ➔ No sign difference between groups (p-values not mentioned) • At 12 months: 56.9% (group I) vs 58.3% (group III) for grade 0; 36.2% (group I) vs 28.3% (group III) for grade 1 ➔ No difference between groups (p-values not mentioned)
• **Adverse events** = definition not reported	• Adverse events (at 12 months) o No. of patn (%) experiencing AEs: 45 (77.6%) (group I) vs 95 (79.2%) (group III) o No. of patn (%) with AEs leading to withdrawal: 2 (3.4%) (group I) vs 5 (4.2%) (group III) • Serious adverse events: (at 12 months) o No. of patn (%) experiencing serious AEs: 7 (12.1%) (group I) vs 19 (15.8%) (group III) o No. of patn (%) with serious AEs leading to withdrawal: 2 (3.4%) (group I) vs 3 (2.5%) (group III) o No. of deaths: 2 (group I) vs 4 (group III) ➔ All deaths were unrelated to study drug • Incidence of most common adverse drug reactions: (at 12 months) o Flushing: 25 (43.1%) (group I) vs 41 (34.2%) (group III) o Increased sweating: 6 (10.3%) (group I) vs 7 (5.8%) (group III) o Injection-site induration: 2 (3.4%) (group I) vs 7 (5.8%) (group III)

	o Fatigue: 1 (1.7%) (group I) vs 2 (1.7%) (group III) ➔ Number of injection-site reactions increased with higher dose (2% group I vs 11.8% group III) ➔ No differences between groups for adverse events and adverse drug reactions
Limitations and other comments	
• **Limitations**	**Authors' conclusion (**Tunn 2009**)**: Overall, there was no observed difference in terms of safety between 6M depot (group III) and the well-established 3M depot (group I) except for local reactions which were assessed as mild in severity and were considered not clinically relevant. Objective response rates (EORTC criteria) did not show relevant differences between treatment groups. A 6M 30mg depot formulation of leuprorelin acetate has been shown to be as safe and effective as the established 3M 11.25mg depot. **Limitations** o Results of group II not reported o Testosterone levels at baseline not reported o No info on cancer stages o No sub- analyses per cancer stage or baseline PSA level

Warde 2011 (Warde 2011, Warde 2010, Gospodarowicz 2012) [398-400]	
Methods	
• **Design**	Unmasked, randomized phase 3 trial (collaboration with Eastern Cooperative Oncology Group and Southwest Oncology Group)
• **Source of funding and competing interest**	Canadian Cancer Society Research Institute, US National Cancer Institute, UK Medical Research Council No conflict of interest
• **Setting**	Centres in UK and North America
• **Sample size**	N= 1205 enrolled in de study, n= 1205 used for analysis (group I n= 602, group II n= 603)
• **Duration and follow-up**	Enrollment between March 1995 and August 2005, median follow-up 6.0y (IQR 4.4-8.0) with maximum of 13.3y
• **Statistical analysis**	Overall survival: Kaplan-Meier product limit method, comparison with log-rank test stratified by minimizing factors at randomization Hazard ratios and CIs: Cox model Event rates: Kaplan-Meier or cumulative incidence estimates, Gray test to test differences in cumulative cause-specific incidence Efficacy analyses: intention-to-treat HrQoL: EORTC core questionnaire and PR13 prostate-cancer module, Functional Assessment of Chronic Illness

	Therapy Standards
Patient characteristics	
• **Eligibility criteria**	Histologically confirmed prostate adenocarcinoma with locally advanced disease (T3-T4, N0 or NX or M0) + patn with clinical T2 tumours with either PSA >40ng/ml or both T2 and PSA >20ng/ml with a Gleason score >8 Esatern Cooperative Oncology Group Performance status: 0-2 Age <80years Pelvic lymph nodes were not imaged unless planned radiation area was to the prostate only and was negative for nodal involvement. Surgical staging was allowed but if done pelvic nodes had to be histologically confirmed free of disease
• **Exclusion criteria**	Previous treatment for prostate cancer, with exception of neoadjuvant ADT in the 12 weeks before randomization.
• **Patient & disease characteristics**	Group I (n= 602) vs group II (N= 603) o Age at allocation(median, IQR): 69.7y (65.5-73.5) vs 69.7y (65.5-74.0) o Performance status (ECOG): 474 (79%) vs 469 (78%) for score 0; 119 (20%) vs 126 (21%) for score 1; 9 (1% vs 8 (1%) for score 2 o Clinical stage: 76 (13%) vs 70 (12%) T2; 499 (83%) vs 501 (83%) T3; 27 (4%) vs 30 (5%) T4; 0 (0%) vs 2 (<1%) missing o Lymph node staging : 477 (79%) vs 475 (79%) clinical or radiological ; 113 (19%) vs 111 (18%) not done ; 12 (2%) vs 17 (3%) surgical o PSA: 224 (37%) vs 220 (36%) for <20 ng/ml; 228 (38%) vs 228 (38%) for 20-50ng/ml; 150 (25%) vs 155 (26%) for >50ng/ml; median (IQR) 28 (13.9-49.8) vs 27 (14.1-51.3) o ADT of choice: 92% LHRH agonist vs 8% orchiectomy (similar pattern in both treatment groups)
Interventions	
• **Intervention group (group I)**	Lifelong ADT (choice between bilateral orchiectomy or LHRH agonist (initially given with 2 weeks of anti-androgens which could be continued at investigator's discretion) (n=602)
• **Intervention group (group II)**	Lifelong ADT (choice between bilateral orchiectomy or LHRH agonist (initially given with 2 weeks of anti-androgens which could be continued at investigator's discretion) + radiotherapy (started within 8 weeks of randomization, 4-field box technique) (n=603) The pelvic target volume (45Gy given in 25 fractions over 5 weeks): whole pelvis, prostate, seminal vesicles, external and internal iliac lymph nodoes The prostate target volume (20-24 Gy given in 10-12 fractions over 2-2.5 weeks): prostate gland with known periprostatic tumour extension
Results	
• **Overall survival** = survival from time of randomisation to date of death from any cause or	• Overall survival at 7y o 66% (60-70) (group I) vs 74% (95% CI 70-78) (group II)

censored at the date of last follow-up	o Number of deaths : 175 (group I) vs 145 (group II) o Number of deaths at 8y follow-up (Gospodarowicz 2012): 260 (group I) vs 205 (group II) ➔ The addition of RT to ADT resulted in significantly improved survival (HR 0.77, 95% CI 0.61-0.98, p=0.03) ➔ At follow-up of 8y (Gospodarowicz 2012): HR 0.70, 95% CI 0.57-0.85, p=0.0003
• **Disease-specific survival** = risk of death from PC	• Risk of death from prostate cancer (also mentioned in Warde 2010) o N=89 (51%) (group I) vs n=51 (35%) (group II) ➔ The addition of RT to ADT reduced the risk of death from prostate cancer (HR 0.54, 95% CI 0.27-0.78, p=0.0001) ➔ At follow-up of 8y (Gospodarowicz 2012): HR 0.46, 95% CI 0.34-0.61, p<0.0001 o 7-year cumulative disease-specific deaths: 19% (group I) vs 9% (group II) (p=0.001) ➔ The incidence from other causes did not differ sign between both groups (p=0.734)
• **Disease progression** = biochemical relapse (= PSA >10ng/ml in 2 consecutive samples if minimum PSA <4ng/ml reached at any time or if serum PSA never >4ng/ml, PSA of both >10ng/ml and 20% higher than minimum value), local progression (= ureteral onstruction or progressive disease accompanied by biopsy sample showing tumour), distant metastatic spread or death from prostate cancer	• Disease progression: n=251 (group I) vs n=95 (group II) • Time to disease progression (median): 6.8y (IQR 3.4-not reached) (group I) vs not reached (IQR 8.2-not reached) (group II) ➔ Estimated HR 0.30, 95%CI 0.23-0.39, p=0.0001 • Biochemical relapse (=first reported evidence of relapse): n=119 (group I) vs n=41 (group II) • Local progression (=first reported type of relapse): o n= 97 (group I) vs n= 14 (group II) o n= 58 in group I whose local disease progressed were given RT at time of relapse
• **Adverse events** = National Cancer Institute of Canada Clinical Trials Group expanded common toxicity criteria	• Gastrointestinal toxicity: (group I vs group II) o Diarrhoea (grade 1-2): 47 (8%) vs 81 (13%); grade >3 4(<1%) vs 8 (1%) o Rectal bleeding grade 1-2 30 (5%) vs 75 (12%); grade >3 3(1%) vs 2 (<1%) o Genitourinary grade 1-2 252 (2%) vs 262 (43%); grade >3 14 (2%) vs 14 (2%) ➔ Majority of mild adverse events, higher incidence in group II (ADT+RT)
• **QoL** = EORTC and FACT-P	• Overall health-related QoL scores at baseline (group I vs group II) o FACT-P (n=844): 55.3 (1.4) vs 58.1 (1.4) o EORTC (n=179): 77.8 (1.9) vs 77.4 (1.9) ➔ No sign differences between groups

	• Overall health-related QoL scores at 6 months (group I vs group II) o FACT-P (n=716): 4.3 (1.5) vs -3.0 (1.6)→ sign diff between both groups (p=0.002) o EORTC (n=148): -1.74 (1.7) vs -8.98 (2.5)→ sign diff between both groups (p=0.04) • Overall health-related QoL scores at 36 months (group I vs group II) o FACT-P (n=538): 2.5 (2.0) vs -1.1 (1.8)→ no sign diff between both groups (p=0.2) o EORTC (n=123): -9.4 (2.1) vs -11.4 (2.4)→ no sign diff between both groups (p=0..96) ➔ Overall QoL and physical function scores show a general deterioration of physical function in both groups, consistent with ADT suppression
Limitations and other comments	
• **Limitations**	**Authors' conclusion (**Warde 2011**)**: This trials show a greater benefit of combined modality therapy (ADT+RT) than of ADT treatment alone in the management of patients with locally advanced prostate cancer, resulting in a reduction in overall mortality and disease-specific mortality, reduced disease progression and reduced rate at which local disease progression presented. The adverse events of RT were modest clinically and frequency of serious toxicity was low. The use of anti-androgen monotherapy would not be judged an adequate ADT by modern standards. **Limitations** o Large sample size o Cause of death assessed by local investigator o Possible bias in disease-specific survival due to unmasked treatment allocation o Data on skeletal adverse events not assessed o Change in dose of RT over time (not adapted in this trial), rather low dose **Abstracts**: Warde 2010, Gospodarowicz 2012

5. EXTERNAL REVIEW

5.1. Evaluation of the recommendations GDG2

		DEM		DHO		SCA		TOM		SCH	
		1		2		3		4		5	
NICE 2014 RECOMMENDATIONS	NICE's LEVEL of EVIDENCE	SCORE	SoR	SCORE	SoR	SCORE	SoR	SCORE	SoR	SCORE	SoR
Offer radical prostatectomy or radical radiotherapy to men with intermediate-risk localised prostate cancer. [2008]	NA	5	S	5	S	5	S	5	S	4	W
Offer radical prostatectomy or radical radiotherapy to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control. [2008]	NA	5	W	4	S	5	S	5	S	4	S
Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer. [2014]	very low	NA		3	W	NA		1	W	1	W
Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are based in centres that perform at least 150 radical prostatectomies per year. [2014]	very low	NA		4	W	NA		1	W	1	W
Do not offer adjuvant hormonal therapy in addition to radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial. [2008]	NA	5	S	5	S	4	S	5	S	4	S
For men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage. [2008]	NA	5	S	5	S	5	S	5	W	5	W

Offer men undergoing radical external beam radiotherapy for localised prostate cancer a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction. [2008]	NA	4	S	5	S	4	S	5	W	4	W
Do not offer brachytherapy alone to men with high-risk localised prostate cancer. [2008]	NA	5	S	5	S	5	S	5	W	4	W
Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. [2014]	moderate	3	W	4	W	3	W	3	W	3	W
Offer men with intermediate- and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone. [2014]	very low to low	5	S	3	W	5	S	5	S	4	S
Offer men with intermediate- and high-risk localised prostate cancer 6 months of androgen deprivation therapy given before, during or after radical external beam radiotherapy. [2014]	low to moderate	1	S	3	W	2	S	5	S	5	S
Consider extending the period of androgen deprivation therapy to 3 years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them. [2014]	low to moderate	4	S	3	W	5	S	5	S	4	S

		REN		DEN		JUN		SPI	
		6		7		8		9	
NICE 2014 RECOMMENDATIONS	NICE's LEVEL of EVIDENCE	SCORE	SoR	SCORE	SoR	SCORE	SoR	SCORE	SoR
Offer radical prostatectomy or radical radiotherapy to men with intermediate-risk localised prostate cancer. [2008]	NA	5	S	4	S	5	S	NA	
Offer radical prostatectomy or radical radiotherapy to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control. [2008]	NA	5	S	4	S	5	W	NA	
Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer. [2014]	very low	NA		4	W	NA		1	
Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are based in centres that perform at least 150 radical prostatectomies per year. [2014]	very low	NA		3	W	NA		1	
Do not offer adjuvant hormonal therapy in addition to radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial. [2008]	NA	5	S	5	S	5	S	NA	
For men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage. [2008]	NA	5	S	5	S	5	S	NA	
Offer men undergoing radical external beam radiotherapy for localised prostate cancer a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction. [2008]	NA	5	S	4	S	3	S	NA	

Do not offer brachytherapy alone to men with high-risk localised prostate cancer. [2008]	NA	5	S	5	S	5	S	NA
Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer. [2014]	moderate	3	W	4	W	4	W	NA
Offer men with intermediate- and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone. [2014]	very low to low	4	S	5	S	5	S	NA
Offer men with intermediate- and high-risk localised prostate cancer 6 months of androgen deprivation therapy given before, during or after radical external beam radiotherapy. [2014]	low to moderate	4	S	3	W	1	S	NA
Consider extending the period of androgen deprivation therapy to 3 years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them. [2014]	low to moderate	4	S	4	W	4	S	NA

NA = not applicable

SCORE
1 completely disagree
2 somewhat disagree
3 unsure
4 somewhat agree
5 completely agree
NA not applicable to me

SoR: Strength of recommendation
Strong
Weak

5.2. Evaluation of the recommendations GDG3

	RECOMMENDATION	LoE	DHO 1 SCORE	DHO 1 SoR	SCHR 2 SCORE	SCHR 2 SoR	SPI 3 SCORE	SPI 3 SoR	REN 4 SCORE	REN 4 SoR	FEY 5 SCORE	FEY 5 SoR
	NICE 2014 Recommendations											
	Modification to decisions made on Febr 4th - to be re-discussed March 18th											
1	**Consider radical treatment in men with intermediate-risk localised prostate cancer.**	**NA**	5	S	2	W	4	S	3	S	5	S
2	**Consider brachytherapy in men with low-risk localised prostate cancer who prefer radical treatment above active surveillance.**	**NA**	(4)	(S)	2	W	4	S	5	S	4	S
	Recommendations on patient information - to be discussed March 18th											
3	**Prior to radical treatment, warn men and, if they wish, their partner, that radical treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function. [2008]**	**NA**	5	S	5	W	5	S	5	S	5	S
4	**Warn men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with radical treatment for prostate cancer. Offer sperm storage. [2008]**	**NA**	5	S	2	W	5	S	5	S	5	S
5	**Warn men undergoing radical treatment for prostate cancer of the likely effects of the treatment on their urinary function. [2008]**	**NA**	5	S	5	W	5	S	5	S	5	S
6	**Offer men experiencing troublesome urinary symptoms before treatment a urological assessment. [2008]**	**NA**	5	S	5	W	4	S	5	S	5	S
7	**Tell men that there is a small increase in the risk of colorectal cancer after radical external beam radiotherapy for prostate cancer. [2014]**	**very low**	5	S	4	W	5	S	3	W	4	S
	De novo Belgian recommendations - to be discussed March 18th (HIFU already discussed Sep 18th, 2013)											

8	**Consider HIFU as a treatment option in men with localised prostate cancer only in the context of controlled clinical trials.**	**very low**	(1)	(S)	3	W		W		NA		5	S
9	**Do not offer hormones in mono-therapy in men with localised prostate cancer (any risk level).**	**moderate**	5	S	4	W	5	S	5	S	5	S	

	RECOMMENDATION	LoE	TOM 6		DEM 7		VANVEL 8		SCHA 9		OYE 10		JON 11	
			SCORE	SoR	SCORE	SoR	SCORE	SoR	SCORE	SoR	SCORE	SoR	SCORE	SoR
	NICE 2014 Recommendations													
	Modification to decisions made on Febr 4th - to be re-discussed March 18th													
1	**Consider radical treatment in men with intermediate-risk localised prostate cancer.**	**NA**	5	W	5	S	5	S	5	S	4	S	5	S
2	**Consider brachytherapy in men with low-risk localised prostate cancer who prefer radical treatment above active surveillance.**	**NA**	3	W	4	W	3		4	S	3	W	4	W
	Recommendations on patient information - to be discussed March 18th													
3	**Prior to radical treatment, warn men and, if they wish, their partner, that radical treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function. [2008]**	**NA**	5	S	5	S	4		5	S	5	S	5	S
4	**Warn men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with radical treatment for prostate cancer. Offer sperm storage. [2008]**	**NA**	5	W	4	S	5	S	5	S	2	S	2	W

5	**Warn men undergoing radical treatment for prostate cancer of the likely effects of the treatment on their urinary function. [2008]**	**NA**	5	S	4	S	2		5	S	5	S	5	S
6	**Offer men experiencing troublesome urinary symptoms before treatment a urological assessment. [2008]**	**NA**	5	S	5	S	4		5	S	5	S	4	W
7	**Tell men that there is a small increase in the risk of colorectal cancer after radical external beam radiotherapy for prostate cancer. [2014]**	**very low**	2	W	3	W	4		3	W	2	W	3	W
	De novo Belgian recommendations - to be discussed March 18th (HIFU already discussed Sep 18th, 2013)													
8	**Consider HIFU as a treatment option in men with localised prostate cancer only in the context of controlled clinical trials.**	**very low**	5	W	5	W	5	S	4	W	4	S	4	W
9	**Do not offer hormones in mono-therapy in men with localised prostate cancer (any risk level).**	**moderate**	5	S	5	S	5	S	4	S	5	S	5	S

NA = not applicable	**SCORE**	1 completely disagree
		2 somewhat disagree
		3 unsure
		4 somewhat agree
		5 completely agree
		NA not applicable to me

SoR: Strength of recommendation	Strong
	Weak

5.3. Evaluation of the recommendations STAKEHOLDERS and GDG4

		STAKEHOLDERS											GDG MEMBERS					
		CUY	DUM	HAU	LUM	ROM	GOV	MOR	AME	DEJ	JUN	DHO	SCHR	DENI	DEME	FEY	SPI	REN
1	**Prior to prostate cancer treatment, inform men and, if they wish, their partner, that any active treatment may result in an alteration of sexual experience and may result in loss of sexual function.**	5	5	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5
2	**Inform men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with active treatment for prostate cancer. Discuss the possibility of sperm storage.**	4	4	4	3	5	5	5	4	5	5	5	4	4	3	4	5	5
3	**Inform men and if they wish, their partner, of the potential effects on urinary and gastro-intestinal functions associated with active treatment for prostate cancer.**	5	5	4	4	5	5	5	5	5	5	5	5	5	4	5	5	5
4	**Discuss the socio-economical impact of radical treatment, including potential professional disability and out-of pocket expenses related to the management of adverse treatment effects.**	5	4	3	5	4	4	2	2	5	4	4	4	5	3	3	5	3
5	**Offer a urological assessment**	5	5	4	5	5	5	2	5	5	5	4	5	5	5	5	5	5

	to men who experience urinary symptoms before treatment.																	
6	**Consider radical treatment with curative intent in men with localised prostate cancer who decline active surveillance.**	5	5	NA	5	NA	5	5	5	3	5	5	3	5	5	4	5	5
7	**Consider radical treatment with curative intent in men with intermediate-risk localised prostate cancer.**	5	5	NA	3	NA	5	5	4	4	4	5	4	4	5	5	5	5
8	**Offer radical treatment with curative intent to men with high-risk localised prostate cancer.**	5	5	NA	5	NA	5	5	5	5	5	5	4	5	5	5	5	5
9	**Do not offer adjuvant hormonal therapy in addition to radical prostatectomy to men with pN0, even to those with margin-positive disease.**	3	5	4	5	NA	5	5	5	4	5	5	5	5	5	5	NA	5
10	**In men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage.**	5	5	4	5	NA	5	5	5	5	5	5	5	5	5	4	5	5
11	**In men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer a minimum dose of 74 Gy to the prostate.**	5	5	3	5	NA	4	5	5	3	4	5	4	5	5	5	NA	5

12	**Do not offer brachytherapy to men with high-risk localised prostate cancer.**	5	5	1	5	NA	4	5	5	3	3	5	4	5	5	5	NA	5
13	**In men with intermediate risk localised prostate cancer treated with radical external beam radiotherapy, consider concomitant androgen deprivation therapy (ADT). The duration of ADT should not exceed 6 months.**	4	4	3	4	NA	5	5	5	3	4	5	5	5	4	5	NA	5
14	**In men with high risk localised prostate cancer treated with radical external beam radiotherapy, offer concomitant androgen deprivation therapy (ADT). ADT should be continued beyond 6 months and for a maximum of 3 years.**	5	5	4	2	NA	5	4	5	3	5	5	4	4	3	5	NA	5
15	**Do not offer hormones in mono-therapy to men with localised prostate cancer (any risk level).**	2	5	5	5	NA	4	5	5	4	5	5	4	5	5	5	5	5
16	**Consider HIFU as a treatment option in men with localised prostate cancer only in the context of controlled clinical trials.**	3	5	5	4	NA	5	4	5	3	5	4	3	4	3	3	5	NA

5.4. Final version of the Belgian recommendations as compared with NICE's guideline

#	NICE 2014 RECOMMENDATIONS	FINAL BELGIAN RECOMMENDATION, i.e. after GDG4 and STAKEHOLDERS MEETING
1	Prior to radical treatment, warn men and, if they wish, their partner, that radical treatment for prostate cancer will result in an alteration of sexual experience, and may result in loss of sexual function.	Prior to prostate cancer treatment, inform men and, if they wish, their partner that any active treatment may result in an alteration of sexual experience and may result in loss of sexual function.
2	Warn men and, if they wish, their partner, about the potential loss of ejaculation and fertility associated with radical treatment for prostate cancer. Offer sperm storage.	Inform men and, if they wish, their partner about the potential loss of ejaculation and fertility associated with active treatment for prostate cancer. Discuss the possibility of sperm storage.
3	Warn men undergoing radical treatment for prostate cancer of the likely effects of the treatment on their urinary function.	Inform men and if they wish, their partner of the potential effects on urinary function, particularly the risk of incontinence, and digestive function associated with active treatment for prostate cancer.
4	Offer men experiencing troublesome urinary symptoms before treatment a urological assessment.	Offer a urological assessment to men who experience urinary symptoms before treatment of their prostate cancer.
5	NA	Discuss the socio-economical impact of radical treatment, including potential professional disability and out-of pocket expenses, related to the management of adverse treatment effects.
	Tell men that there is a small increase in the risk of colorectal cancer after radical external beam radiotherapy for prostate cancer.	incorporated in Belgian recommendation #3
6	NA	In men with localised prostate cancer to whom AS has been proposed, but who decline, consider standard radical treatment with curative intent (i.e. radical prostatectomy, external beam radiotherapy or brachytherapy).
7	Offer radical prostatectomy or radical radiotherapy to men with intermediate-risk localised prostate cancer.	In men with intermediate risk localised prostate cancer, consider standard radical treatment with curative intent (i.e. radical prostatectomy, external beam radiotherapy or brachytherapy).
8	Offer radical prostatectomy or radical radiotherapy to men with high-risk localised prostate cancer when there is a realistic prospect of long-term disease control.	In men with high risk localised prostate cancer, offer radical treatment with standard curative intent (i.e. radical prostatectomy or external beam radiotherapy).
	Commissioners of urology services should consider providing robotic surgery to treat localised prostate cancer.	deleted
	Commissioners should ensure that robotic systems for the surgical treatment of localised prostate cancer are cost effective by basing them in	deleted

#	NICE 2014 RECOMMENDATIONS	FINAL BELGIAN RECOMMENDATION, i.e. after GDG4 and STAKEHOLDERS MEETING
	centres that perform at least 150 radical prostatectomies per year.	
9	Do not offer adjuvant hormonal therapy in addition to radical prostatectomy, even to men with margin-positive disease, other than in the context of a clinical trial.	Do not offer adjuvant hormonal therapy in addition to radical prostatectomy to men with pN0, even to those with margin-positive disease.
10	For men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer planned treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage.	In men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer treatment techniques that optimise the dose to the tumour while minimising the risks of normal tissue damage.
11	Offer men undergoing radical external beam radiotherapy for localised prostate cancer a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction.	In men with localised prostate cancer receiving radical external beam radiotherapy with curative intent, offer a minimum dose equivalent to 74 Gy, delivered over 7-8 weeks.
12	Do not offer brachytherapy alone to men with high-risk localised prostate cancer.	Do not offer brachytherapy as a unique radiotherapy modality to men with high-risk localised prostate cancer.
	Consider high-dose rate brachytherapy in combination with external beam radiotherapy for men with intermediate- and high-risk localised prostate cancer.	incorporated in Belgian recommendation #12
13	Offer men with intermediate- and high-risk localised prostate cancer 6 months of androgen deprivation therapy given before, during or after radical external beam radiotherapy.	In men with intermediate risk localised prostate cancer treated with radical external beam radiotherapy, consider concomitant androgen deprivation therapy (ADT). Consider to give ADT for 6 months.
14	Consider continuing androgen deprivation therapy for up to 3 years for men with high-risk localised prostate cancer and discuss the benefits and risks of this option with them.	In men with high risk localised prostate cancer treated with radical external beam radiotherapy, offer concomitant androgen deprivation therapy (ADT). ADT should be continued beyond 6 months and for a maximum of 3 years.
	Offer men with intermediate- and high-risk localised prostate cancer a combination of radical radiotherapy and androgen deprivation therapy, rather than radical radiotherapy or androgen deprivation therapy alone.	split over recommendations #13,14,15
15	Do not offer high-intensity focused ultrasound and cryotherapy to men with localised prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions.	Consider HIFU as a treatment option in men with localised prostate cancer only in the context of controlled clinical trials.
16	NA	Do not offer hormonal therapy as a unique treatment modality to men with localised prostate cancer (any risk level).

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